TURKISH SOCIETY OF CARDIOLOGY

December 2026
Volume 30, Issue 12

THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Residual Cholesterol Inflammatory Index and CKM Syndrome
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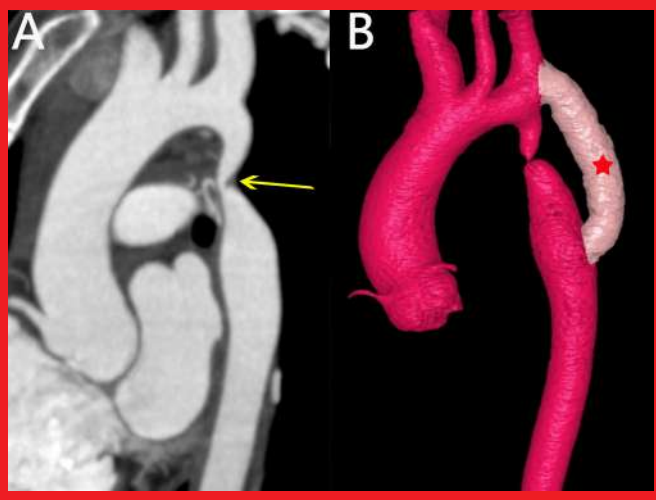
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TMAO Levels and Prognosis in Acute MI
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ISSN - 2149-2263 eISSN 2149-2271
www.anatoljcardiol.com

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

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- **Editorial comment**
- **Review**
- **Education**
- **Scientific letter**
- **Case report**
- **Original image**
- **Letter to the editor**
- **Publication ethics**
- **Scientific puzzle**
- **Miscellaneous articles**

B. References

C. Special Terms and Conditions

A. Manuscript types

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Aviation Guidelines

EDITORIAL

Aeromedical cardiovascular assessment requires a lower threshold for acceptable risk than routine clinical cardiology because even a low annual probability of sudden or subtle incapacitation may have major operational consequences. Fitness decisions should integrate contemporary cardiovascular guidelines with authority-specific standards from ICAO, EASA, FAA, and the Turkish DGCA rather than relying on diagnosis alone.So it is my pleasure to introduce for the first time a guidelines on this topic. Congratulations all the authors (Aydın et al from Türkiye) and the reviewers for their great efforts. I hope it will be a useful contribution to the literature.

Distal left main coronary artery bifurcation lesions are associated with a worse prognosis than other coronary bifurcation lesions. Although coronary artery bypass grafting remains a safe and effective treatment option in this patient population, percutaneous coronary intervention has been increasingly adopted in patients with low-to-intermediate anatomical complexity due to its less invasive nature and the favorable long-term outcomes demonstrated in major randomized clinical trials. Esenboğa and Özerdem from Türkiye reviewed this importatnt issue.

The development or progression of tricuspid regurgitation (TR) following the implantation of cardiovascular implantable electronic devices represents a significant concern. Although the link between transvalvular lead placement and TR is well established, the patient-related and lead-related factors that predispose patients to develop TR remain unclear. Kuru Görgülü et al from Türkiye evaluated the effect of additional pacing/sensing leads or Implantable Cardioverter Defibrillator leads on tricuspid valve function in patients with lead failure.

Zhang et al from China focused to scrutinize the utility of the residual cholesterol inflammatory index as a potential biomarker for cardiorenal-metabolic risk determination in their study.

Atrial fibrillation (AF) catheter ablation is a cornerstone rhythm-control intervention in symptomatic patients. Despite technological improvements, recurrence remains a critical determinant of long-term success, particularly in persistent AF. Uslu et al from Türkiye aimed to evaluate the two-year clinical outcomes of high-power radiofrequency (RF) ablation performed in a high-volume single center and to identify predictors of AF recurrence in patients undergoing catheter ablation.

Comparative data on ultrasound-assisted catheter-directed thrombolysis (USAT) and systemic low-dose tissue-type plasminogen activator (tPA) for intermediatehigh-risk (IHR) pulmonary embolism (PE) remain limited. Kaymaz et al from Türkiye evaluated the efficacy and safety outcomes of USAT versus intravenous (IV) low-dose tPA in this population. Another new, well done manuscript from the team.

Jiang et al from China examined the relationship of plasma trimethylamine N-oxide (TMAO), a gut microbiota-derived metabolite, with both disease severity and short-term prognosis in acute myocardial infarction (AMI) patients.

Çetin Erol

Editor-in-Chief, Ankara, Türkiye

DOI: 10.14744/AnatolJCardiol.2026.12

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Patients with heart failure and reduced ejection fraction presenting with acute heart failure (HFrEF-AHF) carry a high in-hospital mortality. Conventional predictors do not fully capture the interplay between hepatic dysfunction, systemic inflammation, and nutritional decline.

The platelet–albumin–bilirubin (PALBI) score, originally developed in hepatology, may offer incremental prognostic information in this setting. Is it so? Read the Hekimsoy et al study.

Dogsom et al from Mongolia investigated the association between apolipoprotein E (APOE) gene polymorphisms and coronary heart disease risk within a localized Mongolian clinical cohort. And Meral Kayıkçıoğlu as an expert on this topic wrote an editoril about this manuscript. Thanks all.

Long-term (>5-year) durability data from Turkish TAVI cohorts are scarce. Seven-year single-center cohort outcomes of early-generation SAPIEN XT valves are presented by Konuş et al from Türkiye.

And a new case report, letters, e-page original....

I hope this new issue of our journal will be interest of our readers.

Çetin Erol

THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Aviation Medicine and Cardiovascular Assessment of Aircrew: A European Society of Cardiology–Aligned Review of Integrating International Civil Aviation Organization, European Union Aviation Safety Agency, Federal Aviation Administration, and Turkish Directorate General of Civil Aviation Aeromedical Standards

ABSTRACT

Aeromedical certification is based on a safety-first principle: a pilot or other aircrew member must not have a medical disorder that creates an unacceptable risk of sudden or subtle incapacitation during flight. Cardiovascular disease remains one of the most important determinants of flight fitness, as it may impair consciousness, judgment, rhythm stability, exercise capacity, and hemodynamic reserve. Modern aeromedical decision-making therefore requires the integration of aviation law, operational risk, contemporary cardiology guidelines, advanced imaging, biomarkers, and long-term surveillance. The International Civil Aviation Organization (ICAO) Annex 1 provides the global licensing framework; the European Union Aviation Safety Agency (EASA) Part-MED, together with its Acceptable Means of Compliance and Guidance Material, defines detailed operational standards in Europe; and the Federal Aviation Administration (FAA) employs a protocol- and special issuance–based system for many cardiovascular and metabolic disorders. This review summarizes the aeromedical assessment of hypertension, diabetes mellitus, chronic and acute coronary syndromes, heart failure, cardiomyopathies, arrhythmias and conduction disorders, pacemakers and implantable cardiac devices, valvular heart disease, aortic disease, congenital heart disease, venous thromboembolism, cardiovascular pharmacotherapy, and major respiratory conditions relevant to flight certification. The manuscript is aligned with current European Society of Cardiology cardiovascular guidance and with the operational aeromedical principles applied by ICAO, EASA, FAA, and the Turkish Directorate General of Civil Aviation. In general, preserved ventricular function, absence of significant symptoms, low thromboembolic and arrhythmic risk, stable treatment, and adequate exercise capacity support certification or restricted certification. In contrast, uncontrolled hypertension, unstable diabetes, significant residual myocardial ischemia, reduced ejection fraction, malignant ventricular arrhythmias, implantable defibrillator therapy, severe valvular disease, significant aortic pathology, major congenital hemodynamic lesions, or poorly controlled sleep apnea usually preclude certification. Final decisions remain individualized and depend on license class, operational role, treatment burden, surveillance data, and the judgment of the aeromedical authority.

Keywords: Aerospace cardiology, arrhythmia, aviation medicine, chronic coronary syndromes, diabetes mellitus, fitness to fly, heart failure, hypertension

INTRODUCTION

Aviation medicine differs fundamentally from routine clinical practice because the threshold for acceptable risk is substantially lower. In everyday clinical settings, patients may continue their professional and social activities despite moderate symptoms or partially controlled risk factors. In contrast, within the aviation environment, even a transient episode of chest pain, syncope, severe hypoglycemia, embolic stroke, arrhythmic instability, or acute dyspnea may pose a direct threat to flight safety and operational integrity.[1,2] For this reason, the International Civil

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Aviation Organization (ICAO) established medical provisions within Annex 1, forming the global regulatory framework for aeromedical certification, while national and regional authorities have developed structured assessment systems based on operational safety, recurrence risk, and the probability of sudden or subtle incapacitation.[1-3] From a cardiovascular perspective, aeromedical evaluation extends beyond conventional diagnostic assessment. It is inherently prognostic and operational. In addition to hypobaric hypoxia and operational stress, aviation-related environmental exposures such as aircraft noise may contribute to cardiovascular stress through autonomic activation, oxidative stress, inflammation, endothelial dysfunction, and sleep disturbance.[4] The central question is not solely whether a pilot has conditions such as coronary artery disease (CAD), atrial fibrillation (AF), diabetes mellitus, or an implanted cardiac device, but whether these conditions—or their treatments—may lead to sudden or insidious incapacitation, impair cognitive or physical performance, or generate an unacceptable level of residual risk relative to the privileges of the intended licence.[2,3,5] This review summarizes the fundamental principles for evaluating cardiovascular fitness in pilots in accordance with contemporary aviation medicine standards. Both pilot applicants and licensed aircrew are required to undergo medical fitness assessments conducted by authorized aeromedical examiners and competent regulatory authorities. Table 1 presents the standardized color-coded classification system for flight fitness, while Table 2 summarizes major international aviation authorities, aeromedical centers, and certification classes.

REGULATORY AND AEROMEDICAL FRAMEWORK

The international legal foundation of aeromedical licensing is ICAO Annex 1—Personnel Licensing, which sets the minimum standards for medical fitness of license applicants and holders.[1] The broader interpretive and practical framework is supported by the ICAO Manual of Civil Aviation Medicine (Doc 8984), which is explicitly intended to assist medical examiners and licensing authorities in decisions related to fitness for licensing.[6]

In Europe, detailed implementation is provided by European Union Aviation Safety Agency (EASA) Part-MED and its Acceptable Means of Compliance and Guidance Material (AMC/GM).[2] These documents define how cardiovascular, metabolic, respiratory, neurological, and other conditions should be approached for Class 1, Class 2, Light Aircraft Pilot Licence (LAPL), and related aeromedical certificates.[2,5] In Türkiye, Directorate General of Civil Aviation (DGCA) practice is broadly aligned with this EASA-based aeromedical framework.[7] The Federal Aviation Administration (FAA) uses a different but conceptually similar system in which some disorders are directly issuable, some require deferment, and others may be handled under Special Issuance or AME-Assisted Special Issuance pathways.[8]

Aeromedical Risk Assessment and the "1% Rule"

Aeromedical risk assessment frequently incorporates the "1% rule," according to which license privileges may be restricted or suspended when the estimated annual risk of sudden pilot incapacitation exceeds approximately 1%, particularly in multi-crew commercial aviation operations. This principle is derived primarily from operational aviation safety calculations rather than from purely clinical considerations and provides an important conceptual framework for aeromedical decision-making. It emphasizes that certification depends not only on the presence or severity of a medical condition, but also on the probability that the condition may cause sudden or subtle incapacitation during flight.[6]

Three practical consequences arise from this framework. First, "fit" is not binary: a pilot may be fit, fit with limitation, temporarily unfit, or unfit.[3,8] Second, license class matters: what may be acceptable for a private pilot or Class 2 certificate may still be unacceptable for a commercial, multi-crew, or Class 1 operational role.[2] Third, follow-up is dynamic:

Table 1. Aerospace Cardiology—Flight Fitness Color Codes

Color	Explanation
Green	Fit—Eligible to fly, fully fit.
Yellow	Conditionally Fit—May fly under certain conditions.
Orange	Restricted Flight Privileges – Requires close monitoring, may not fly if adverse health issues arise.
Red	Unfit—Not eligible for flying duties.

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Received: September 25, 2026
Accepted: September 29, 2026
Available Online Date: October 26, 2026

Cite this article as: Aydın S, Ekici B, Yalçın M, et al. Aviation medicine and cardiovascular assessment of aircrew: an European Society of Cardiology-aligned review of integrating International Civil Aviation Organization, European Union Aviation Safety Agency, Federal Aviation Administration, and Turkish Directorate General of Civil Aviation aeromedical standards. *Anatol J Cardiol*. 2026;30(12):845-873.

DOI: 10.14744/AnatolJCardiol.2026.6446

Table 2. Aviation Medicine Authorities, Centers, and Certification Levels

Unit	Role/Explanation
ICAO	Global standard-setting body for civil aviation safety and medical regulations.
EASA	Responsible for civil aviation safety and medical certification in the EU.
FAA	Responsible for aviation safety and aeromedical certification in the USA.
JAA	Former European aviation authority; responsibilities transferred to EASA in 2009.
CAA	National aviation authority; in the UK, responsible for aviation safety and medical certification.
SHGM	Turkish Directorate General of Civil Aviation, national authority aligned with ICAO and EASA standards.
AME	Authorized by the aviation authority to perform medical examinations for flight personnel.
AeMC	Specialized center for advanced aeromedical examinations, required for some Class 1, 2, 3 and LAPL certificates.
AMS	Division within the aviation authority that reviews AME/AeMC reports.
AMAS	Provides online and telephone-based aeromedical consultation and FAA medical certification assistance to pilots and aviation professionals.
Medical Assessor	Physician within AMS who reviews reports and makes the final decision (Fit/Unfit/Restricted).
Class 1 Certificate	Commercial Pilots (ATPL and CPL)
Class 2 Certificate	Private Pilots (PPL)
LAPL Medical Certificate	Light Aircraft Pilot Licence (LAPL)
Class 3 Certificate	Air Traffic Controllers (ATCO)

AME, Aviation Medical Examiner, AeMC, Aeromedical Center, AMAS, Aviation Medicine Advisory Service, AMS, Aeromedical Section, ATCO, Air Traffic Controller, ATPL, Airline Transport Licence, CPL, Commercial Pilot Licence, CAA, Civil Aviation Authority, DGCA, Directorate General of Civil Aviation (Türkiye), EASA, European Union Aviation Safety Agency, FAA, Federal Aviation Administration, ICAO, International Civil Aviation Organization, JAA, Joint Aviation Authorities, LAPL, Light Aircraft Pilot Licence, PPL, Private Pilot Licence.

an aeromedical decision is never final in the same way as a routine clinic note; it must be revalidated against time, treatment changes, recurrent symptoms, and new tests.[5,8]

AEROMEDICAL CERTIFICATION CLASSES AND LIMITATION CODES

For the purposes of practical flight medicine, the most important certification classes are Class 1 for commercial pilots, Class 2 for private pilots, Class 3 for air traffic controllers, and LAPL for light aircraft pilot licensing.[2,5] The EASA and associated authorities also use limitation codes to mitigate risk rather than simply deny certification.[2] EASA Medical Certificate Limitation Codes with abbreviations and explanations are summarized in Table 3.

Relevant examples include OML (operational multi-crew limitation), OSL (operational safety pilot limitation), ORL, SSL, TML, and vision-related limitations such as VDL/VCL.[2,5] Operational limitations are especially important in cardiovascular disease. An applicant with a history of AF, coronary intervention, valve surgery, pacemaker implantation, or stable medication-controlled metabolic disease may not be unrestrictedly fit, but may still be certifiable under OML or another safety-reducing limitation if the aeromedical authority is satisfied that residual risk is sufficiently controlled.[2,5] EASA explicitly uses this logic in multiple cardiovascular sections.[2,5]

GENERAL CARDIOVASCULAR EVALUATION IN AIRCREW

Any aircrew member with known or suspected cardiovascular disease requires a structured assessment built around 5 pillars: clinical symptoms, hemodynamic impact, arrhythmic risk, structural heart disease, and treatment effects. The EASA's cardiovascular guidance requires that when a formal cardiovascular assessment is indicated, exercise electrocardiogram (ECG) should be symptom-limited and completed to at least Bruce Stage IV or equivalent. This threshold is operationally important because it helps to identify both ischemic burden and functional reserve.[2]

In practice, the baseline work-up usually includes history, physical examination, resting ECG, echocardiography, ambulatory rhythm monitoring when indicated, laboratory testing, and disease-specific advanced imaging such as stress imaging, coronary computed tomography angiography (CTA), invasive coronary angiography, or vascular imaging. In selected disorders, biomarkers such as brain natriuretic peptide / N-terminal pro-brain natriuretic peptide (BNP/NT-proBNP), troponin, hemoglobin A1C (HbA1c), renal function, and lipid profile are central to risk interpretation. Aeromedical evaluation is therefore a multidisciplinary process, not a single examination.[9]

HYPERTENSION AND FITNESS TO FLY

Hypertension is one of the most common findings in aeromedical practice. EASA states clearly that the diagnosis of hypertension should trigger cardiovascular evaluation including potential vascular risk factors.[2] This principle mirrors modern European Society of Cardiology (ESC) hypertension guidance, which treats hypertension not as an isolated number but as a disease integrated with total cardiovascular risk, organ damage, obesity, renal function, diabetes, and overall vascular burden. The current recommendations are based on ESC hypertension guidelines published in 2024.[10]

From an aeromedical standpoint, the key questions are: Is blood pressure controlled? Is there left ventricular

Table 3. EASA Medical Certificate Limitation Codes

Code	Expansion	Meaning	Example Situations
SIC	Specific regular medical examination(s)	AME or AeMC cannot conduct the examination without consulting the licensing authority's medical assessor. Additional tests/follow-up required.	Kidney stones story, prediabetes, suspected heart disease, etc.
OML	Operational Multi-crew Limitation	Pilot cannot fly alone, only allowed in multi-crew operations.	Arrhythmia, coronary artery disease, Kidney stones, diabetes controlled epilepsy risk
ORL	Valid only with a safety pilot if passengers are carried	Valid only with a safety pilot if passengers are carried and in aircraft with dual controls	This limitation applies to holders of a class 2 or LAPL medical certificate with a medical condition that may lead to an increased level of risk to flight safety when exercising the privileges of the licence. The safety pilot, if carried, should be made aware of the type(s) of possible incapacity that the pilot whose medical certificate has been issued with this limitation may suffer and should be prepared to take over the aircraft controls during flight.
OSL	Operational Safety Pilot Limitation	Pilot cannot fly without a second pilot (safety pilot).	Vision impairment, temporary neurological conditions
SSL	Special restriction(s) as specified	This limitation may be considered when an individually specified limitation, not defined in this AMC, is appropriate to mitigate an increased level of risk to flight safety.	The description of the SSL should be entered on the medical certificate or in a separate document to be carried with the medical certificate. medical stabilization period
VDL	Valid only with corrective lenses	Pilot must wear glasses or contact lenses during flight.	Myopia, hypermetropia, astigmatism
VCL	Valid by day only	holders of a medical certificate with varying degrees of colour deficiency, to exercise the privileges of their licence by daytime only.	Mild vision defects
TML	Time Limitation	Certificate validity is shorter than usual, frequent checks required.	Newly diagnosed illness, medication initiation period
CML	Colour perception Limitation	Pilots with color blindness may face operational restrictions.	Color blindness (failure in Ishihara test)

hypertrophy, renal disease, cerebrovascular disease, or coronary disease? Is the treatment compatible with safe flying? And is the applicant in a category where sudden stroke, acute hypertensive destabilization, or treatment-related hypotension could compromise safety? Uncontrolled hypertension generally leads to temporary unfitness until evaluation and treatment are completed. Borderline hypertension without other major risk factors may allow short-interval review, but persistent elevation requires a formal decision pathway.[2]

Medication compatibility matters. The EASA's AMC/GM identifies acceptable classes such as non-loop diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, calcium-channel blockers, and selected hydrophilic beta-blockers. By contrast, medications with substantial CNS effects or orthostatic burden are less desirable in flight personnel.[2] The FAA materials also treat hypertension in a structured certification framework, with emphasis on acceptable therapy, tolerability, and absence of aeromedically significant side effects.[8]

Aircrew with controlled blood pressure, no symptoms, no hypertension-mediated organ damage, and well-tolerated acceptable therapy may be considered fit or fit with an operational limitation, depending on license class. By contrast, uncontrolled hypertension, major comorbidity, medication intolerance, or hypertension-mediated organ

Table 4. Flight Fitness in Hypertensive Individuals

Hypertension Status	Flight Fitness	Possible Limitations
Uncontrolled hypertension	Unfit	—
Untreated but borderline hypertension (and no additional risk factor)	Conditionally fit	Follow-up required
Stable and well-controlled hypertension with appropriate medication (Class 1)	Fit	OML may apply
Stable and well-controlled hypertension with appropriate medication (Class 2)	Fit	OSL may apply
Renal disease or hypertension-related organ damage	Requires individual assessment	—

OML, operational multi-crew limitation; OSL, operational safety pilot limitation.

damage warrants temporary unfitness or unfitness until adequate clinical stability has been documented.[2] Serial lipid assessment and comprehensive cardiovascular risk-factor management remain important, particularly after the age of 40.[2,10] The regulations regarding hypertensive aircrew are presented in Table 4.

DIABETES MELLITUS AND FITNESS TO FLY

Diabetes is highly relevant to aeromedical certification because it may impair safety in 2 distinct ways: acutely, through hypoglycemia and cognitive dysfunction; and chronically, through accelerated atherosclerosis, autonomic dysfunction, retinopathy, nephropathy, and cerebrovascular disease. European Union Aviation Safety Agency's rule text is explicit: applicants with diabetes mellitus requiring insulin shall be assessed as unfit, while applicants with diabetes not requiring insulin are unfit unless stable blood sugar control can be demonstrated.[2] The EASA further states that applicants not requiring medication may be assessed as fit and that antidiabetic medications not likely to cause hypoglycemia may be acceptable, often with an OML.[2] Applicants with body mass index (BMI) ≥35 may be assessed as fit only after satisfactory risk assessment including cardiovascular review and evaluation of possible sleep apnea.[2]

The FAA is more protocol-driven and, importantly, more nuanced in current practice. Its diabetes disposition tables and protocol pages show that medication-controlled non-insulin diabetes may be considered under special issuance pathways and that even some insulin-treated applicants may be considered under structured protocols, especially with defined monitoring requirements.[8] Insulin therapy should not be regarded as an absolute and universal bar to aeromedical certification. Under EASA provisions, applicants with insulin-treated diabetes are generally assessed as unfit, whereas the FAA may consider selected applicants through a special issuance pathway after documented metabolic stability and compliance with the required monitoring protocol.[2,8] Clinically, the aeromedical assessment of diabetes should include HbA1c, hypoglycemia history, treatment class, renal function, retinal status, neuropathy, coronary risk, obesity, and coexistence of hypertension or dyslipidemia. Modern ESC diabetes guidance emphasizes cardiovascular risk assessment and intensive preventive management in diabetic patients, reinforcing why diabetes in pilots should never be viewed as a purely metabolic issue.[11] It is a cardiovascular disease modifier and often a multiplier of aeromedical risk.

Accordingly, aircrew with diet-controlled diabetes or treatment with agents carrying a low risk of hypoglycemia, stable glycemic control, and no clinically relevant target-organ damage may be considered fit or conditionally fit following specialist assessment. Recurrent hypoglycemia, unstable glycemic control, advanced diabetic complications, or major cardiovascular comorbidity warrants deferment and may preclude higher-class certification. Fitness to fly in individuals with diabetes is assessed according to their clinical status, treatment regimen, and risk of hypoglycemia (Table 5).

ISCHEMIC HEART DISEASE, CHRONIC CORONARY SYNDROMES, AND ACUTE CORONARY SYNDROMES

Coronary artery disease is central to aeromedical cardiology because it can produce angina, myocardial infarction, ventricular dysfunction, malignant arrhythmia, and sudden death. The current ESC chronic coronary syndromes guideline is the 2024 version, and the current ACC/AHA acute coronary syndromes guideline is the 2025 version. Together, these define the contemporary cardiology framework for diagnosis, risk assessment, imaging, and treatment.[12,13]

In aviation medicine, the problem is not only the diagnosis of coronary disease, but the annual risk of incapacitation associated with that disease. The ICAO's risk-based philosophy has historically been expressed through the "1% rule" concept in operational aeromedicine: flight duties are not considered acceptable when the residual annual risk of acute incapacitation is too high for the role. Although exact thresholds and applications vary by authority, the principle remains foundational.[6,14]

Diagnostic evaluation should follow an ESC-style stepped framework: pre-test probability, resting assessment, anatomical or functional confirmation, and ischemic risk stratification. In pilots, the threshold for reassurance is higher than that in ordinary clinical practice. Exercise ECG, stress imaging, coronary CTA, and invasive angiography are used not only to diagnose but to document stability and operational safety. EASA specifically requires Bruce Stage IV or equivalent when exercise ECG forms part of the cardiovascular assessment.[2,12]

Table 5. Flight Fitness in Diabetic Patients

Diabetes Status (Class 1-2)	Flight Fitness	Possible Limitations
Insulin-treated diabetes	Generally unfit under EASA; selected applicants may be considered under an FAA special issuance pathway	Authority-specific assessment and intensive glucose-monitoring protocol required
Diabetes controlled with OAD	Conditionally fit	Regular follow-up required, low risk of hypoglycemia
Diabetes controlled with diet	Conditionally fit	Regular follow-up required
BMI > 35 kg/m^2	Conditionally fit	Cardiovascular risk assessment required
Additional risk (smoking, HT, obesity, etc.)	Further examination required	Regular monitoring of blood lipids and cholesterol

BMI, body mass index; HT, hypertension; OAD, oral antidiabetics.

As a practical aeromedical principle, preserved EF, complete revascularization when indicated, absence of residual ischemia, good exercise capacity, and stable clinical course are the minimum conditions for possible recertification. A pilot with residual angina, reduced EF, significant unrevascularized stenosis, abnormal functional testing, recurrent acute coronary syndrome (ACS), or complex multivessel disease should be considered unfit until a higher authority determines otherwise. The FAA materials also continue to treat coronary heart disease as a structured special issuance category rather than a routine issue condition.[2,8]

In percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and post-myocardial infarction certification, return to flight should require an adequate waiting period, documented recovery, negative or acceptable stress imaging findings, satisfactory echocardiographic evaluation, and the absence of high-risk rhythm or hemodynamic abnormalities. Although timelines may vary slightly among regulatory authorities, none permits immediate unrestricted return to flight following coronary intervention.[2,8,12-14] Table 6 summarizes the aeromedical evaluation of ischemic heart disease across various clinical scenarios.

.HEART FAILURE AND FITNESS TO FLY

Heart failure is a major aeromedical concern because it reduces hemodynamic reserve and exercise performance while increasing the risks of arrhythmia, syncope, pulmonary congestion, and sudden deterioration. The current ESC basis is the 2021 heart failure guideline together with the 2023 focused update, which incorporated newer trial evidence ahead of the next full guideline cycle.[15,16]

Aeromedically, heart failure should be stratified by phenotype, EF, New York Heart Association (NYHA) class, natriuretic peptides, exercise capacity, pulmonary pressures, rhythm status, and device therapy. Only a narrow subgroup—typically those with preserved EF, asymptomatic or minimally symptomatic status, and durable stability—can be considered for possible certification. Patients with reduced EF, recent decompensation, pulmonary hypertension, recurrent hospitalization, or any meaningful risk of sudden deterioration are generally unfit.[2,8]

Guideline-directed medical therapy must be optimized, but treatment alone does not restore flight fitness. An applicant taking ARNI, beta-blocker, MRA, and SGLT2 inhibitor may be well treated from a cardiology perspective, yet still remain

Table 6. Ischemic Heart Diseases and Flight Fitness Based on Clinical Scenarios

Clinical Status	Flight Fitness (Class 1)	Flight Fitness (Class 2/3/LAPL)	Possible Limitations
All cases with EF <50%	Unfit for flight	Individual assessment/ OSL (rare cases)	EF <50% is a disqualifying criterion for flight fitness.
Complete revascularization, EF ≥50%	OML	ORL/SSL	Exercise test and myocardial perfusion scan (MPS) must be negative; anatomical suitability is required.
Non-revascularized, EF ≥50%	Unfit for flight	Individual assessment/ OSL	High-risk coronary anatomy—flight fitness may be granted only in rare individual cases.
Normal coronary angiography or CCS-CT <100, EF ≥50%	Fit for flight	Fit for flight	All cardiovascular risk factors must be optimally controlled; periodic follow-up is mandatory.
Post-STEMI PCI, ≥6 months, EF ≥50%	OML	ORL	Stable, completely revascularized cases with negative functional tests may be considered fit.
Elective PCI, ≥3 months, EF ≥50%	OML	ORL	Single-vessel lesion with FDA-approved stent and no symptoms—may be accepted as fit.
Post-CABG, ≥6 months, EF ≥50%	OML	ORL	Negative functional tests; MPS mandatory at the fifth year of follow-up.
Single-vessel disease, EF ≥50%, asymptomatic	OML	ORL	Stenosis <50%, LAD or left main <30%; CCS-CT) <400 is acceptable.
Two-vessel disease with <50% stenosis, EF ≥50%, asymptomatic	OML	ORL	Stenosis <50%, LAD or left main <30%; CCS-CT) <400 is acceptable.
More than 2 stenoses between 30% and 50%, or left main/proximal LAD >30% stenosis, or single-vessel stenosis >50%	Unfit for flight	Unfit for flight	A maximum of 2 vessels may have 30%-50% stenosis; if 3 vessels are involved, flight fitness must be denied.

CABG, coronary artery bypass grafting; CCS-CT, coronary calcium score computed tomography; EF, ejection fraction; FDA, Food and Drug Administration; LAD, left anterior descending; LAPL, Light Aircraft Pilot Licence; MPS, myocardial perfusion scintigraphy; OML, operational multi-crew limitation; ORL, operational pilot restriction limitation; OSL, operational safety pilot limitation; PCI, percutaneous coronary intervention; SIC, specific regular medical examination(s); SSL, specific safety pilot limitation.

unfit aeromedically if exercise capacity is inadequate, EF is reduced, or arrhythmic substrate persists. Likewise, implantable cardioverter-defibrillator (ICD) implantation is usually incompatible with active flying because it signals both serious underlying risk and the possibility of device shocks or pre-shock incapacitation. Selected CRT-P recipients may be considered on an exceptional basis if ventricular function, rhythm stability, and follow-up data are very favorable.[2,8,14-16] Flight fitness in heart failure is summarized in Table 7.

CARDIOMYOPATHIES

Cardiomyopathies are highly relevant in aviation medicine because they represent a heterogeneous group of diseases associated with variable but potentially significant risks of ventricular arrhythmias, heart failure progression, thromboembolic events, and sudden cardiac death.[2,7,17] The recommendations discussed in this review are based on the most up-to-date international cardiology and aviation medicine guidelines available at the time of manuscript preparation.

Cardiomyopathies require phenotype-specific aeromedical assessment because their hemodynamic, arrhythmic, and sudden-incapacitation risks differ substantially. Dilated cardiomyopathy raises concerns about reduced EF and ventricular tachyarrhythmia. Hypertrophic cardiomyopathy raises concerns about syncope, dynamic obstruction, AF, ventricular tachyarrhythmia, and sudden death risk.[7,17,18] Restrictive cardiomyopathies raise concerns about filling instability, pulmonary hypertension, and embolic/arrhythmic burden.[17] Arrhythmogenic right ventricular cardiomyopathy is particularly concerning because of its strong association with malignant ventricular arrhythmias and exercise-related sudden death.[17,19] Beyond structural and functional parameters, the 2023 ESC Guidelines for the management of cardiomyopathies identify a group of high-risk arrhythmic genes, including *PLN*, *FLNC*, *RBM20*, *DSP*, and *LMNA*, which confer a risk of malignant ventricular arrhythmias that may be disproportionate to the degree of ventricular dysfunction across both the dilated and arrhythmogenic cardiomyopathy spectrum. Gene-specific risk calculators should be considered where available. Applicants carrying a high-risk genotype require individualized arrhythmic risk assessment independent of ejection fraction, and preserved systolic function alone should not be interpreted as reassuring in this subgroup. Takotsubo syndrome and transient secondary cardiomyopathies may be reconsidered only after complete recovery and prolonged stability.[2,17]

As an aeromedical rule, the combination of structural cardiomyopathy plus reduced EF, prior sustained ventricular arrhythmia, unexplained syncope, ICD implantation, or high-risk imaging/genetic profile should be considered incompatible with certification.[2,7,17] A very small subset of asymptomatic, preserved EF, stable patients without arrhythmic burden may qualify for individualized restricted certification, but this is the exception rather than the rule.[2,7,17] Various cardiomyopathy conditions and their corresponding flight fitness requirements are summarized in Table 8.

ARRHYTHMIAS, CONDUCTION DISEASE, AND PACEMAKERS

European Union Aviation Safety Agency specifically identifies AF/flutter, major supraventricular rhythm disturbance, complete left bundle branch block, and several conduction disorders as conditions requiring referral and specialist cardiovascular evaluation.[2,7] Applicants with supraventricular rhythm disorders may be assessed as fit if cardiological evaluation is satisfactory and stroke risk is sufficiently low; where anticoagulation is required, ORL or OSL may be considered after a stable anticoagulation period.[2,7] European Union Aviation Safety Agency also states that asymptomatic pre-excitation may be acceptable if electrophysiologic criteria are favorable and that pacemaker recipients may be considered no sooner than 3 months after implantation if they are not pacemaker-dependent, have a bipolar lead system, and undergo regular follow-up.[2,7,20]

The current ESC arrhythmia framework is derived primarily from the 2024 AF guideline, the 2022 ventricular arrhythmia and sudden cardiac death guideline, the 2021 pacing guideline, and the 2019 supraventricular tachycardia guideline, which together constitute the most comprehensive contemporary ESC-aligned basis for aeromedical rhythm assessment.[20-23] This combination is the best contemporary ESC-aligned base for an aviation review. In practical terms, benign sinus bradycardia or sinus tachycardia in the absence of structural heart disease may be compatible with medical certification following appropriate cardiovascular evaluation.[2,22,23] Atrial fibrillation/flutter

Table 7. Heart Failure Types and Fitness for Flight

Clinical Status	Flight Fitness	Possible Limitations
EF < 50% (all classes)	Unfit	Disqualified
EF ≥ 50% (HFpEF), NYHA I, ≥6 months stable, exercise ≥ 7 METs	Fit	None
EF ≥ 50%, NYHA II	Conditionally fit	OML and follow-up required (SIC or TML for monitoring)
EF ≥ 50%, PASP > 50 mm Hg	Unfit	Disqualified
CRT-P present, EF ≥ 50%, stable rhythm ≥ 6 months	Conditionally fit	Individual assessment
Presence of ICD or VAD	Unfit	Disqualified

CRT-P, cardiac resynchronization therapy with pacemaker; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter-defibrillator; OML, operational multi-crew limitation; PASP, pulmonary artery systolic pressure, estimated by Doppler echocardiography; SIC, specific regular medical examination; TML, time limitation; VAD, ventricular assist device; NYHA, New York Heart Association.

Table 8. Cardiomyopathies and Aeromedical Fitness

Clinical Condition	Flight Fitness	Possible Limitations
EF <50%	Unfit	Disqualified
EF ≥50%, NYHA I, ≥6 months stable, exercise ≥ 7 METs	Fit	None
EF ≥50%, NYHA II	Conditionally fit	OML and follow-up
HCMP, EF ≥50%, septum <25 mm, asymptomatic, no arrhythmia	Conditionally fit	OML/ORL/SSL—annual follow-up required
HCMP + VT / septum ≥25 mm / unexplained syncope	Unfit	Disqualified
Diagnosed ARVC	Unfit	Disqualified
Takotsubo/transient CMP (EF ≥50%, ≥6 months stable)	Restricted flight privileges	Individual assessment
Presence of ICD or VAD	Unfit	Disqualified
A group of high-risk arrhythmic genes, including *PLN*, *FLNC*, *RBM20*, *DSP*, and *LMNA*	Unfit	Disqualified

ARVC, arrhythmogenic right ventricular cardiomyopathy; CRT-P, cardiac resynchronization therapy pacemaker; EF, ejection fraction; HCMP, hypertrophic cardiomyopathy; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; OML, operational multi-crew limitation; ORL, operational restriction limitation; SSL, special safety pilot limitation; VAD, ventricular assist device; VT, ventricular tachycardia.

may be considered compatible with certification after satisfactory cardiological evaluation if ventricular rate and rhythm control are adequate, thromboembolic risk is low or appropriately mitigated, and the applicant is clinically stable on therapy.[2,8,21] Under EASA Part-MED, revalidation may be possible when stroke risk is sufficiently controlled and anticoagulation is stable; for vitamin K antagonist therapy, stability generally requires at least 5 international normalized ratio (INR) measurements within the previous 6 months with at least 4 values within the therapeutic range, whereas direct oral anticoagulants (DOACs) may be acceptable after a stabilization period of approximately 3 months.[2] Following catheter ablation, temporary unfitness is recommended, with possible return to flying duties after successful evaluation, often with an operational multi-pilot limitation (OML) for at least 1 year unless electrophysiological testing demonstrates satisfactory early results.[2] Federal Aviation Administration guidance similarly allows AME-Assisted Special Issuance for AF when there is no evidence of thromboembolic complications, ventricular rate control is satisfactory on monitoring, symptoms are well controlled, and anticoagulation management is acceptable; cases with poor rate control, interval embolic events, unstable anticoagulation, significant bleeding, or associated structural cardiac disease generally require FAA deferral and specialist review.[8] Following successful catheter ablation of atrioventricular nodal re-entrant tachycardia (AVNRT) or atrioventricular re-entrant tachycardia (AVRT), aeromedical recertification should balance the small but clinically relevant risk of recurrence against the occupational consequences of disproportionate restriction. Current regulatory approaches differ. European Union Aviation Safety Agency generally requires an operational multi-pilot limitation (OML) for at least 1 year unless an electrophysiological study (EPS), performed no earlier than 2 months after ablation, demonstrates satisfactory results.[2] The FAA permits reconsideration after a 3-month observation period, provided that a 24-hour Holter recording shows no evidence of recurrent arrhythmia.[8] Similarly, the Turkish DGCA, in its Algorithms and Guidance Document within the Scope of SHT-MED, requires an initial 2-month period of unfitness following catheter ablation for Wolff–Parkinson–White (WPW) syndrome or AVNRT, followed by a cardiological evaluation including exercise electrocardiography, 24-hour ambulatory ECG monitoring, and transthoracic echocardiography. The DGCA guidance recommends a follow-up EPS with pharmacological provocation after successful ablation of inducible arrhythmias, including AVNRT and AVRT, and permits unrestricted certification when the post-ablation EPS findings are satisfactory. If EPS is not performed, Class 1 recertification is generally subject to an OML for 1 year, together with appropriate cardiological follow-up. When follow-up EPS is not considered necessary, fitness may be granted if Holter monitoring performed 3 months after successful ablation demonstrates no recurrent arrhythmia.[7] No comparative evidence has established that any of these strategies provides superior flight-safety outcomes. Although 24-hour Holter monitoring has limited sensitivity for detecting infrequent paroxysmal supraventricular tachycardia, routine repeat invasive EPS in every asymptomatic aircrew member is not supported by contemporary clinical guidelines or practice. Furthermore, residual dual AV-nodal physiology or isolated AV-nodal echo beats should not, in isolation, be regarded as recurrence of clinical AVNRT.[23] Accordingly, recertification should comply with the requirements of the applicable aviation authority and should confirm an appropriate procedural endpoint at the index ablation, absence of pre-excitation and clinically relevant symptoms, discontinuation of antiarrhythmic medication where appropriate, and absence of recurrence during the prescribed observation period. Extended ambulatory ECG monitoring may provide greater reassurance than a conventional 24-hour Holter recording, particularly when symptoms are infrequent. Repeat EPS with pharmacological provocation is most appropriately reserved for cases in which it is required by the applicable regulation or guidance, or in which the procedural endpoint, symptoms, arrhythmic mechanism, or risk of recurrence remains uncertain. Inducibility of sustained clinical AVNRT or

AVRT should prompt further electrophysiological evaluation; however, isolated and non-specific electrophysiological findings should not automatically result in a determination of aeromedical unfitness.[2,7,8,23]

Ventricular tachycardia, symptomatic broad-complex tachycardia, dangerous pre-excitation, high-grade AV block without appropriate treatment, or recurrent syncope are usually disqualifying.[2,20,22] Pacemaker implantation may permit restricted return to flight under authority supervision; ICD implantation does not.[2,7,20] Federal Aviation Administration materials likewise treat AF, pacemakers, bundle branch block, and other arrhythmias through structured disposition tables and FAA decision pathways rather than unrestricted routine issuance.[7,8]

The aeromedical assessment of aircrew with suspected or documented cardiac arrhythmias requires a structured and comprehensive cardiological evaluation, as rhythm disturbances may lead to syncope, impaired consciousness, hemodynamic instability, or sudden incapacitation during flight. Therefore, the initial evaluation must be sufficiently detailed to identify the type of arrhythmia, its underlying mechanism, the presence of structural heart disease, and the potential risk of recurrence.[2,8,22] During the initial assessment, a comprehensive cardiologist's report is mandatory. The diagnostic work-up should include, at minimum, a 12-lead ECG, symptom-limited exercise stress testing, 24-hour Holter rhythm monitoring, and transthoracic echocardiography to evaluate structural cardiac abnormalities and ventricular function. These examinations are essential for determining the hemodynamic significance of the arrhythmia and for identifying any associated structural heart disease. When clinically indicated, EPS or other advanced diagnostic investigations—such as extended rhythm monitoring, stress imaging, or cardiac magnetic resonance imaging—may be required to clarify the arrhythmic substrate and guide aeromedical decision-making.[2,8,22] Aircrew with documented arrhythmias or those who have undergone implantation of a permanent pacemaker require structured periodic follow-up, as both the arrhythmia itself and device-related factors may influence long-term flight safety. During the first year after diagnosis or device implantation, cardiological evaluations should generally be performed at 3- to 6-month intervals to ensure rhythm stability, adequate device function, and absence of hemodynamic compromise. After this initial period of stabilization, annual follow-up examinations are typically considered sufficient in individuals who remain clinically stable.[2,8,20] Follow-up assessment should include clinical review, electrocardiographic monitoring, device interrogation in pacemaker recipients, and additional investigations when clinically indicated.[2,8,20] If clinical deterioration, recurrence of significant arrhythmia, worsening ventricular function, or device malfunction is identified, the individual's fitness for flight must be reassessed immediately, and temporary suspension of flight duties may be required until the condition is adequately evaluated and stabilized.[2,8,20] Given the potentially serious consequences of arrhythmic events during flight operations, fitness-to-fly decisions in various arrhythmic conditions must be made with particular caution and should be individualized according to the specific arrhythmia type, underlying cardiac condition, treatment status, and long-term risk profile.[2,8,20,22] A structured summary of aeromedical decision pathways for different arrhythmic conditions is presented in Table 9.

Table 9. Arrhythmias and Flight Fitness

Clinical Condition	Flight Fitness	Possible Limitations
Sinus bradycardia/tachycardia	Fit (if asymptomatic)	None
AF (single episode)	Conditionally fit	OML restriction following AMS assessment
AF (with anticoagulant use)	Conditionally fit	OML, following a 3- to 6-month stabilization period
Wolff–Parkinson–White (WPW) Syndrome	Conditionally fit	if no tachycardia induced during EPS, OML may be applied after evaluation
Catheter ablation	Conditionally fit	1-year OML after a 2- to 3-month post-ablation waiting period
First-degree AV block	Fit	None
Mobitz type I AV block	Fit	Follow-up recommended
Mobitz type II/complete AV block	Unfit (if untreated)	OML (if pacemaker implanted)
Monomorphic ventricular extrasystole	Fit (if asymptomatic)	None
Wide/narrow QRS tachycardias	Unfit	Disqualified
Ventricular pre-excitation	Unfit	Disqualified unless proven safe by EPS
Incomplete right bundle branch block	Fit (if no structural heart disease)	None
Complete right bundle branch block	Conditionally fit	Following AMS assessment, OML may be applied
Complete left bundle branch block	Conditionally fit	Coronary artery evaluation required; OML applied for 3 years, which may be lifted if the condition remains stable
Pacemaker	Conditionally fit	First 3 months flight restriction, followed by re-evaluation; OML may be applied for Class 1, while generally no restriction is required for Class 2.

AF, atrial fibrillation; AMS, Aeromedical Section; EPS, electrophysiological study; OML, operational multi-crew limitation.

VALVULAR HEART DISEASE

Valve disease remains operationally important because stenosis, regurgitation, chamber remodeling, pulmonary hypertension, embolic risk, anticoagulation, and postoperative valve status may all affect flight safety.[2,8,24] The current ESC/EACTS valvular guideline is the 2025 update, replacing the 2021 version as the latest ESC/EACTS reference.[24] The EASA also provides explicit valvular aeromedical rules.[2] EASA states that previously unrecognized cardiac murmurs require cardiological evaluation and that minor valvular abnormalities may be assessed as fit, whereas significant abnormalities of any valve should be assessed as unfit.[2] For aortic valve disease, bicuspid aortic valve may be acceptable if no other cardiac or aortic abnormality is present.[2] EASA further states that applicants with left ventricular volume overload or systolic impairment due to valve disease should be assessed as unfit.[2]

After valve surgery, Class 1 applicants may be reconsidered only after at least 6 months, with satisfactory exercise ECG and 2D Doppler echocardiography; when anticoagulation is needed, stable INR documentation is required and OML may be considered.[2] Accordingly, it should be stated that mild asymptomatic valve disease with preserved ventricular response may be compatible with certification, but moderate-to-severe disease, symptomatic valve disease, progressive chamber enlargement, pulmonary hypertension, or unstable postoperative status usually preclude unrestricted licensing.[2,24] Mechanical valves and anticoagulation do not automatically prohibit all licensing, but they substantially raise the threshold for acceptable Class 1 certification. All individuals with valvular heart disease must undergo comprehensive cardiologic assessment.[2,8,24]

Previously undiagnosed cardiac murmurs or murmurs whose acoustic characteristics have changed during follow-up require prompt cardiological evaluation, as they may represent previously unrecognized structural heart disease or progressive valvular pathology. From an aeromedical perspective, the presence of a murmur is not itself disqualifying; however, the underlying cause must be clearly identified and its hemodynamic significance carefully assessed before certification can be considered.[2,24-26] In Class 1 and Class 3 license holders, evaluation of an undiagnosed murmur requires mandatory review by the AMS following specialist cardiology assessment. For Class 2 and LAPL applicants, initial evaluation may be performed by the AME, but consultation with the AMS is recommended whenever uncertainty exists regarding the hemodynamic significance of the murmur or its potential operational implications.[2,25] Diagnostic evaluation must include transthoracic echocardiography with 2-dimensional imaging and Doppler assessment or an equivalent advanced imaging modality capable of accurately defining valvular anatomy, transvalvular gradients, ventricular dimensions, and hemodynamic consequences. Minor valvular abnormalities without functional impairment may be compatible with certification. In contrast, significant valvular dysfunction, progressive chamber enlargement, or evidence of hemodynamic compromise should lead to a determination of unfitness until full evaluation and stabilization are achieved.[2,24-26] The flight fitness criteria for specific valvular diseases are summarized separately below under the headings of aortic valve disease, mitral valve disease, valve surgery, and fitness for flying.

Aortic Valve Diseases in Aeromedical Assessment

Bicuspid Aortic Valve

Bicuspid aortic valve (BAV) is the most common congenital cardiac anomaly and is frequently detected incidentally during echocardiographic evaluation performed after auscultation of a cardiac murmur.[24,27] Although many individuals with BAV remain asymptomatic for long periods, the condition is clinically important because it may be associated with progressive aortic stenosis, aortic regurgitation, and dilatation of the aortic root or ascending aorta.[24,27] In the aeromedical context, applicants with BAV may be considered fit for certification when no associated structural abnormalities are present, ventricular function is normal, and there is no clinically significant aortic dilatation.[2] Regular echocardiographic surveillance is required because progressive aortic enlargement or valve dysfunction may occur over time.[2,24,28] The frequency of echocardiographic follow-up should be determined by the AMS according to valve morphology, aortic dimensions, and clinical stability.[2,24] Certification may become impossible when significant aortic root or ascending aortic dilatation develops, as this condition carries an increased risk of progressive enlargement, dissection, or rupture—events that would represent unacceptable aeromedical risk.[2,28]

Aortic Stenosis

Aortic stenosis is particularly relevant to aviation medicine because progressive obstruction of left ventricular outflow may lead to reduced exercise tolerance, syncope, heart failure, arrhythmias, and sudden cardiac death.[2,24] Aeromedical assessment must therefore consider the severity of the stenosis, ventricular function, symptom status, and hemodynamic response to exercise.[2,24] Applicants with mild aortic stenosis, defined by a mean transvalvular gradient ≤20 mmHg with preserved left ventricular function, may generally be considered eligible for unrestricted certification, provided that they remain asymptomatic and undergo periodic cardiological follow-up.[2,24]

Moderate aortic stenosis, typically defined by a mean gradient between 20 and 40 mm Hg with an aortic valve area >1 cm^2 or indexed valve area >0.6 cm^2/m^2, may allow certification with operational limitations if the individual remains asymptomatic and ventricular function is preserved. In such cases, exercise testing and serial echocardiographic surveillance are essential components of aeromedical follow-up.[2,24]

In selected individuals with mean gradients between 40 and 50 mm Hg, certification may occasionally be considered at the discretion of the AMS, provided that a symptom-limited exercise test demonstrates normal functional capacity without hemodynamic instability and that no abnormal

increase in biomarkers such as BNP or NT-proBNP is detected. However, gradients exceeding this range generally indicate advanced disease and are considered incompatible with flight duties because of the risk of sudden hemodynamic deterioration.[2,24]

Regular cardiological follow-up and periodic echocardiography are required in all individuals with aortic stenosis.[2,24] A history of systemic embolism or marked dilation of the thoracic aorta is considered disqualifying for all license classes, as these conditions substantially increase the risk of in-flight incapacitation.[2]

Aortic Regurgitation

Aortic regurgitation may be compatible with aviation duties when the regurgitation is mild and ventricular size and function remain normal. Trivial aortic regurgitation, particularly when detected incidentally during echocardiography, may allow certification provided that regular cardiological and echocardiographic follow-up is maintained.[2,24] In some cases, a slight increase in left ventricular end-diastolic diameter (LVEDD) may still be considered acceptable for Class 1 licence holders, particularly when ventricular systolic function remains preserved and the individual remains asymptomatic. In such situations, certification is generally granted with OML (operational multi-crew limitation) in order to minimize operational risk.[2] However, when LVEDD exceeds 6.0 cm, the degree of ventricular dilatation reflects excessive volume loading and indicates significant hemodynamic impact of the regurgitant lesion. In this situation, the applicant should be considered unfit for certification, as progressive ventricular dilatation and deterioration of ventricular function may occur and could compromise flight safety.[2,24] Flight fitness criteria for aortic valve diseases are presented in Table 10.

Mitral Valve Diseases in Aeromedical Assessment

Rheumatic Mitral Disease

Aircrew presenting with mitral valve disease must be evaluated according to specified aeromedical criteria.[2] In the context of rheumatic mitral valve disease, the presence of rheumatic mitral stenosis and/or regurgitation constitutes an aeromedically significant condition and applicants are generally considered unfit for certification.[2,29] However, individuals exhibiting minor mitral leaflet tethering may be considered for Class 1 certification with an operational multi-crew limitation (OML), provided they remain in sinus rhythm and show no evidence of left atrial enlargement.[25] Furthermore, mild mitral stenosis, characterized by a valve area greater than 2 cm^2, may permit Class 2 certification with

Table 10. Aortic Valve Diseases and Flight

Clinical Condition	Flight Fitness	Possible Limitations
Bicuspid aortic valve	Fit (If there is no other cardiac or aortic abnormality. Follow-up with echocardiography as determined by AMS.)	None
Aortic stenosis		
Mean pressure gradient up to 20 mm Hg	May be considered fit	Unrestricted certification if asymptomatic with preserved LV function.
Mean pressure gradient 20-40 mmHg and valve area >1 cm^2 or AVAI >0.6 cm^2/m^2	Conditionally fit	Requires regular exercise testing and echocardiographic follow-up. OML, SSL (Class 1), ORL, OSL, OPL, (Class 2, LAPL), SSL (Class 3)
Mean pressure gradient 40-50 mmHg	Conditionally fit	Restricted certification may be considered by AMS if exercise test and biomarkers are normal.
Mean pressure gradient >50 mmHg	Unfit	Disqualified
Valve area ≤1 cm^2	Unfit	Disqualified
History of systemic embolism or significant thoracic aortic dilatation	Unfit	Disqualified
Aortic regurgitation		
Mild aortic regurgitation with normal ascending aorta	Fit	For mild or trivial AR with normal LV size and function, with regular follow-up.
Mild increase in LVEDD	Conditionally fit	If LV size/function are normal, with follow-up. Class 1 OML.
More marked increase in LVEDD without an increase in LVESD (>4.1 cm)	Conditionally fit	If LV size/function are normal, with follow-up. Class 2 OSL.
Aortic root dilatation (>4.0 cm)	Conditionally fit	If LV size/function are normal, with annual cardiac follow-up. Class 1 OML, Class 2 OSL.
Aortic root dilatation (>5.0 cm)	Unfit	Disqualified
LVEDD >6.0 cm	Unfit	Disqualified

AME, aeromedical examiner; AMS, Aeromedical Section; AVAI, aortic valve area index; BNP, brain natriuretic peptide; EF, ejection fraction; LAPL, Light Aircraft Pilot Licence; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; OML, operational multi-crew limitation; OPL, operational pilot limitation; ORL, operational restriction limitation; OSL, operational safety limitation; SSL, special skill limitation.

an operational safety limitation (OSL) following specialist cardiological assessment.[25,29]

Mitral Regurgitation

Regarding mitral regurgitation and mitral valve prolapse, an isolated mid-systolic click is considered benign and warrants an unrestricted fit assessment.[2,25] Minor mitral regurgitation is also compatible with unrestricted fitness, contingent upon the absence of thickened leaflets or flail chordae and a left atrial diameter of 4 cm or less.[25] Moderate mitral regurgitation necessitates operational restrictions, specifically an OML for Class 1 applicants and an ORL or OSL for Class 2 applicants.[25] Certification for this condition requires the absence of left ventricular enlargement, satisfactory exercise stress testing, and periodic cardiological follow-up including echocardiography, exercise testing, and Holter monitoring.[2,25] Conversely, ischemic mitral regurgitation and severe mitral regurgitation are considered incompatible with certification.[2,25] Applicants should also be considered unfit if progressive chamber remodeling is present, including LV end-diastolic diameter >6.0 cm, LV end-systolic diameter >4.1 cm, or left atrial diameter >4.5 cm.[25] Likewise, the presence of AF, previous transient ischemic attack (TIA), systemic embolism, or documented left ventricular dysfunction precludes unrestricted certification.[2,25,29] Aircrew with mitral valve disease must be evaluated according to these specified criteria (Table 11).

Fitness After Valve Surgery

Aeromedical assessment after valve repair or replacement must be especially cautious because postoperative patients may remain at risk of prosthetic dysfunction, residual regurgitation or stenosis, thromboembolism, bleeding complications related to anticoagulation, ventricular dysfunction, arrhythmias, and progressive chamber enlargement. Accordingly, return to flight should never be based solely on the elapsed time after surgery, but rather on a comprehensive demonstration of clinical stability, satisfactory imaging findings, acceptable functional capacity, and low procedural or pharmacological risk.[2,7,24]

For Class 1 licence holders, applicants are considered initially unfit after valve repair or valve replacement. Reconsideration for certification should generally not occur before 6 months after surgery, and only if the individual is asymptomatic and all relevant cardiological and aeromedical criteria are satisfied.[2,6] After mitral valve prolapse repair, return to flight may be considered only when left ventricular size and systolic function are normal, there is no relevant chamber dilatation, and any residual mitral regurgitation is no more than trivial.[2,7,24]

In individuals with tissue or mechanical prosthetic valves, return to flight may be considered at ≥6 months postoperatively if there is no significant prosthetic valve dysfunction, ventricular size and function are normal, and no relevant cardioactive medication is required beyond treatment judged compatible with aviation safety.[2,7,24] If anticoagulation is required, certification may still be possible with OML (Operational Multi-crew Limitation), provided that hemorrhagic risk is considered acceptable and anticoagulation is demonstrably stable. A practical stability definition is that at least 4 of the last 5 INR

Table 11. Mitral Valve Diseases and Flight Fitness

Clinical Condition	Flight Fitness	Possible Limitations
Rheumatic mitral valve		
Rheumatic mitral stenosis and/or regurgitation	Unfit	Disqualified
Minor mitral leaflet tethering	Conditionally fit	Class 1 with OML if in sinus rhythm and without LA enlargement.
Mild mitral stenosis (valve area >2 cm^2)	Conditionally fit	Class 2 with OSL limitation
Mitral regurgitation/mitral valve prolapse		
Isolated mid-systolic click	Fit	None
Ischemic mitral regurgitation	Unfit	Disqualified
Minor mitral regurgitation	Fit	If no thickened leaflets or flail chordae are present and LA diameter is ≤4 cm.
Moderate mitral regurgitation	Conditionally fit	Class 1 (OML) or Class 2 (ORL/OSL) if there is no LV enlargement, exercise test is normal, and annual follow-up with echocardiography, stress testing, and Holter monitoring is maintained.
Severe mitral regurgitation	Unfit	Disqualified
LVEDD >6 cm)	Unfit	Disqualified
LVESD >4.1 cm	Unfit	Disqualified
Left atrial inner diameter >4.5 cm	Unfit	Disqualified
Atrial fibrillation	Unfit	Disqualified
History of TIA	Unfit	Disqualified
LV dysfunction	Unfit	Disqualified

AMS, Aeromedical Section; Echo, echocardiography; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; OML, operational multi-crew limitation; ORL, operational restriction limitation; OSL, operational safety limitation; TIA, transient ischemic attack.

measurements must have remained within the therapeutic target range over a 6-month period.[2,7] Exercise capacity should be documented by a symptom-limited exercise test; when exercise ECG is non-diagnostic or abnormal, stress imaging should be used instead. A 2D Doppler echocardiographic examination must confirm the absence of significant chamber enlargement and show only minimal or acceptable prosthetic valve-related changes.[2,7,24] The frequency and extent of further follow-up should be determined by the AMS according to valve type, anticoagulation status, ventricular function, and overall clinical course.[2,7]

For Class 2 license holders, the postoperative approach is somewhat more flexible. If there is no ongoing need for anticoagulation, certification may be granted without limitation after satisfactory cardiological and aeromedical evaluation.[2,7] If anticoagulation is required, and bleeding risk is judged acceptable with documented treatment stability, ORL/OSL limitations may be applied.[2,7] In selected cases, near-patient INR testing performed within 12 hours before flight, together with flight only when INR is within the therapeutic range, may support certification without those limitations.[2,7] For anticoagulants that do not require INR monitoring, certification may be considered after a 3-month stabilization period, provided consultation with the AMS confirms acceptable safety and absence of treatment-related complications.[2,7]

Situations Incompatible with Flight Clearance After Valve Surgery

Patients with mechanical valve replacement should be regarded as unfit for flight within the first 3-6 months after surgery, in the presence of symptoms, when left ventricular ejection fraction is below 50%, when there is a history of thromboembolic complications, when echocardiographically determined pulmonary hypertension is present, or when stable and adequate anticoagulation cannot be maintained and regular INR monitoring is not feasible.[2,7,24] Likewise, flight clearance should not be granted in cases of uncorrected prosthetic valve dysfunction, including significant prosthetic stenosis, regurgitation, paravalvular leak, or prosthetic thrombosis.[7,24] These considerations are particularly important in Class 1 operational settings, where the aeromedical tolerance for hemodynamic instability or embolic/hemorrhagic risk is especially low.[2,7]

Practical Aeromedical Interpretation

From an aeromedical standpoint, postoperative valve patients may be considered for certification only when the following conditions are met: durable symptom-free status, preserved ventricular function, satisfactory prosthetic or repaired valve performance, acceptable exercise tolerance, absence of major arrhythmia, and stable anticoagulation when required.[2,7,24] Mechanical prostheses and anticoagulation do not automatically preclude certification, but they substantially increase the scrutiny required and usually necessitate an operational limitation in higher-risk licence classes.[2,7] Conversely, symptomatic postoperative status, depressed ventricular function, persistent pulmonary hypertension, embolic history, unstable anticoagulation, or unresolved prosthetic dysfunction should be regarded as disqualifying findings.[2,7,24] Specific conditions related to valve surgery are presented in Table 12.

AORTIC DISEASE AND ANEURYSMS

Aeromedical assessment of applicants with thoracic or abdominal aortic aneurysms should follow the principles

Table 12. Valve Surgery and Fitness for Flying

Clinical Condition	Flight Fitness	Possible Limitations
Mitral valve repair	Conditionally fit	Class 1, OML, if LV function is normal, without systolic or diastolic dilatation, and residual MR is no more than mild.
	Fit	Class 2, None, If anticoagulation is not required and evaluation is satisfactory.
Tissue or mechanical valve	Conditionally fit	Class 1 OML, Class 2 ORL/OSL if off cardioactive medication, with normal valve function and normal ventricular function/ configuration.
	Fit	Class 2, no restriction if anticoagulation is not required
Those requiring anticoagulation	Conditionally fit	Class 1 OML, Class 2 ORL/OSL if hemorrhagic risk is acceptable and anticoagulation is stable.
	Fit	Class 2, no restriction may be needed if near-patient testing is used.
<6 months post-surgery, symptoms, LVEF <50%, prosthetic valve dysfunction, thromboembolism, pulmonary hypertension, unstable anticoagulation/INR, significant ventricular dysfunction or chamber enlargement, or clinically significant arrhythmias.	Unfit	Disqualified

INR, international normalized ratio; LV, left ventricle; LVEF, left ventricular ejection fraction; OML, operational multi-crew limitation; ORL, operational restriction limitation; OSL, operational safety limitation.

outlined in the 2024 ESC Guidelines for the Management of Peripheral Arterial and Aortic Diseases, which, for the first time, integrate peripheral arterial and aortic diseases within a single guideline framework.[30] In addition, certification decisions should comply with the EASA, Easy Access Rules for Aircrew (Part-MED), which provide specific recommendations regarding aeromedical certification of applicants with aortic aneurysms.[2] Aeromedical certification should be based primarily on maximal aortic diameter, aneurysm location (thoracic, supra-renal, or infra-renal abdominal), growth rate, repair status, blood-pressure control, clinical stability, and the presence of associated valvular or connective tissue disorders, as acute aortic dissection or rupture during flight represents an unacceptable catastrophic risk.[2,30] According to EASA, infra-renal abdominal aortic aneurysms <5 cm may be considered fit before surgery for Class 1 applicants with an OML, provided serial imaging and cardiological follow-up are satisfactory, whereas thoracic or supra-renal abdominal aneurysms <5 cm may be considered for lower license classes with appropriate operational restrictions such as ORL or OSL following satisfactory cardiovascular assessment.[2] Applicants with an aortic diameter <40 mm are generally considered fit for all license classes. At diameters of 40-44 mm, certification becomes conditional, with Class 1 applicants requiring a SIC and Class 2, LAPL, and Class 3 applicants generally requiring a TML and periodic cardiological reassessment. When the aortic diameter reaches 45-49 mm, more stringent operational restrictions are required because of the increased risk of progressive dilatation and acute aortic events.[2,30] Class 1 applicants may only be considered conditionally fit with OML, TML, and SSL, whereas Class 2 and LAPL applicants require OSL, ORL, OPL, TML, and SSL. Class 3 applicants may be considered conditionally fit with TML and SSL. Applicants with an aortic diameter ≥50 mm, rapidly enlarging, symptomatic, or otherwise high-risk aneurysms should be considered unfit for all certification classes because the risk of dissection or rupture is incompatible with safe flight operations.[2,30] Following successful surgical repair of thoracic or abdominal aortic aneurysms, recertification may be considered after comprehensive cardiological and aeromedical evaluation. In such cases, applicants may be assessed as conditionally fit, generally with OML and SSL, provided postoperative recovery is complete, imaging confirms a stable repair without significant residual pathology, ventricular function is preserved, blood pressure is adequately controlled, and long-term surveillance demonstrates sustained clinical stability.[2,30] Table 13 presents the general rules for the assessment of aircrew with aortic aneurysms.

CONGENITAL HEART DISEASE

In aviation medicine, congenital heart disease cannot be assessed solely according to the anatomical diagnosis. Instead, aeromedical certification should be based on a comprehensive assessment of hemodynamic significance, ventricular size and function, pulmonary artery pressure, residual shunting, arrhythmia burden, thromboembolic risk, exercise capacity, and the long-term outcome following surgical or transcatheter repair.[2,6,31] Accordingly, simple congenital defects that are completely repaired or remain hemodynamically insignificant may be compatible with medical certification, whereas cyanotic congenital heart disease, Eisenmenger syndrome, pulmonary hypertension, significant residual shunts, ventricular dysfunction, heart failure, or clinically significant atrial or ventricular arrhythmias generally represent conditions incompatible with aviation duties because of their potential to cause progressive cardiovascular deterioration or sudden in-flight incapacitation (Table 14).[2,6,31]

Applicants with isolated atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), selected repaired coarctation of the aorta, or asymptomatic patent foramen ovale (PFO) may be considered individually when

Table 13. Assessment of Aircrew with Thoracic and Abdominal Aortic Aneurysms

Clinical Condition	Flight Fitness	Possible Limitations
Thoracic or abdominal aorta <40 mm	Fit	Certification in all classes if asymptomatic, blood pressure is well controlled, and serial imaging demonstrates stability.
Thoracic or abdominal aorta 40-44 mm	Conditionally fit	TML or SIC depending on licence class. Requires regular imaging surveillance, strict blood-pressure control, and no evidence of rapid enlargement.
Thoracic or abdominal aorta 45-49 mm	Conditionally fit	Class 1: OML + TML + SSL. Class 2/LAPL: OSL/ORL/OPL + TML + SSL. Class 3: TML + SSL. Certification only if stable, asymptomatic, and without rapid aneurysm growth.
Thoracic or abdominal aorta ≥50 mm	Unfit	Disqualified
After successful surgical repair	Conditionally fit	May be reconsidered following satisfactory cardiovascular and aeromedical evaluation. OML/SSL generally appropriate for Class 1; restrictions depend on postoperative imaging, ventricular function, blood-pressure control, and absence of complications.

OML, operational multi-crew limitation; OPL, operational pilot limitation; ORL, operational restriction limitation; OSL, operational safety pilot limitation; SIC, specific regular medical examination(s); SSL, special safety pilot limitation (requires presence of a safety pilot); TML, time-limited medical certificate.

Table 14. Congenital Heart Diseases and Fitness for Flight

Clinical Condition	Flight Fitness	Possible Limitations
Isolated ASD		
Small secundum ASD	Fit	No restriction if Qp/Qs <1.5, normal RV/PA pressures, normal Holter, no associated anomaly, and periodic cardiac follow-up.
Early closed secundum ASD	Fit	
Late closed secundum ASD	Conditionally fit	Class 1 OML
Small or corrected ostium primum type ASD	Conditionally fit	Class 1 OML
Sinus venosus type ASD (very small or corrected)	Conditionally fit	Class 1 OML
Uncorrected large ASD	Unfit	Disqualified
Presence of atrial fibrillation	Unfit	Disqualified
Isolated ventricular septal defect (VSD)		
Small VSD (Qp/Qs < 1.5:1)	Fit	No restriction if no cardiomegaly, no pulmonary hypertension, and periodic cardiac evaluation is maintained.
Early closed VSD	Fit	
Spontaneously closed VSD	Fit	
VSD, that are large and unrepaired, associated with significant arrhythmias, or persisting with complications after surgery	Unfit	Disqualified
Isolated pulmonary stenosis		
Pulmonary valvular stenosis (gradient <20 mm Hg)	Fit	No restriction if no right ventricular hypertrophy, tricuspid velocity <2.5 m/s and annual cardiac evaluation maintained.
Pulmonary valvular stenosis (gradient: 20–30 mm Hg)	Conditionally fit	Class 1 OML
Corrected infundibular stenosis	Individual assessment	
Supravalvular stenosis	Unfit	Disqualified
Isolated PDA		
Closed PDA	Fit	No restriction if no pulmonary hypertension and periodic cardiac evaluation is maintained.
Unclosed small PDA	Conditionally fit	Class 1 OML
Isolated aortic coarctation		
Early corrected aortic coarctation (<12 years)	Fit	No restrictions if normotensive with periodic follow-up.
Late corrected coarctation	Conditionally fit	Class 1 certification may be considered with OML if hypertension is controlled and periodic follow-up is maintained.
TOF		
Early operated TOF	Conditionally fit	Class 1 certification with OML may be considered if there is no residual right ventricular hypertrophy, no significant pulmonary regurgitation, no complex ventricular arrhythmia, and periodic cardiac evaluation is maintained.
PFO		
Asymptomatic PFO	Fit	None
PFO closed after TIA	Fit	Unrestricted certification may be considered 1 year after successful closure.

AME, aeromedical examiner; AMS, Aeromedical Section; ASD, atrial septal defect; EF, ejection fraction; OML, operational multi-crew limitation; PDA, patent ductus arteriosus; PFO, patent foramen ovale; Qp/Qs, pulmonary-to-systemic flow ratio; TIA, transient ischemic attack; TOF, Tetralogy of Fallot; VSD, ventricular septal defect.

complete anatomical correction has been achieved and no residual hemodynamic or electrophysiological abnormalities are present. In contrast, complex congenital heart disease—including repaired Tetralogy of Fallot with residual lesions, Fontan circulation, systemic right ventricle, Eisenmenger physiology, or congenital lesions associated with persistent right ventricular volume or pressure overload—usually requires a more restrictive aeromedical assessment because of the increased lifetime risk of arrhythmia, ventricular dysfunction, heart failure, and thromboembolic complications.[2,6,31] Aeromedical evaluation should be individualized and performed by a cardiologist experienced in adult congenital heart disease in collaboration with the aeromedical medical examiner (AME) or Aeromedical Centre (AeMC). Standard investigations include transthoracic Doppler echocardiography, maximal symptom-limited exercise

testing, and 24-hour ambulatory ECG monitoring. Cardiac magnetic resonance imaging, computed tomography, cardiopulmonary exercise testing, or additional investigations should be performed whenever structural complexity or residual hemodynamic abnormalities cannot be adequately characterized by routine assessment.[2,6,31]

Certification may be considered only in applicants with complete repair or hemodynamically insignificant lesions, preserved biventricular function, normal pulmonary artery pressure, absence of clinically significant arrhythmias, no requirement for cardioactive medication, and satisfactory exercise capacity without evidence of myocardial ischemia or hemodynamic limitation.[2,6,31,32] Periodic cardiological surveillance, including serial echocardiography and ambulatory rhythm monitoring, is recommended because late complications may develop even after apparently successful repair.[2,6,31]

Applicants with cyanosis, pulmonary hypertension, significant residual shunts, ventricular dysfunction, recurrent supraventricular or ventricular arrhythmias, heart failure, or other complex congenital physiology should generally be considered unfit for unrestricted aviation duties.[2,6] For Class 1 applicants, assessment by the licensing authority or AMS is required, whereas Class 2 applicants should undergo specialist cardiological evaluation in consultation with the AMS before certification is considered.[2]

Although many congenital cardiac conditions are compatible with long-term survival and good functional capacity, flight certification is generally reserved for individuals with the most favorable hemodynamic profiles and the lowest predicted risk of sudden incapacitation.

Atrial Septal Defect

Atrial septal defect is among the most frequently encountered congenital lesions in adult aeromedical evaluation. Small isolated secundum ASDs with a pulmonary-to-systemic flow ratio (Qp/Qs) below 1.5 may allow unrestricted certification provided that right ventricular size and pulmonary artery pressures remain normal. Similarly, defects closed early in life with no residual hemodynamic consequences may permit unrestricted certification.[8,31]

When ASD closure occurs later in life, Class 1 certification may still be considered but generally requires an OML because of the potential long-term risk of atrial arrhythmias. Elevated right ventricular or pulmonary artery pressures and the presence of atrial arrhythmias such as AF or flutter represent disqualifying findings.[2,8,31]

Less common ASD variants require careful evaluation. Ostium primum defects may permit certification with OML when mitral regurgitation is minimal or absent, pulmonary pressures are normal, and ambulatory rhythm monitoring shows no clinically significant arrhythmia. Sinus venosus defects may also permit Class 1 certification with OML when rhythm monitoring is normal, although annual echocardiographic and Holter monitoring follow-up is required.[2,8,31]

Ventricular Septal Defect

Isolated small VSDs without evidence of cardiomegaly or pulmonary hypertension are usually compatible with aviation duties. Individuals with Qp/Qs ratios below 1.5:1, normal cardiac chamber dimensions, and normal pulmonary artery pressures may receive unrestricted certification. Similarly, defects that were successfully closed in early childhood without residual hemodynamic consequences may permit certification without limitation.[2,8,31]

Pulmonary Stenosis

Mild valvular pulmonary stenosis is generally compatible with aviation duties provided that right ventricular hypertrophy is absent and the peak-to-peak transvalvular gradient remains below approximately 20 mmHg. Gradients between 20 and 30 mmHg may still permit Class 1 certification with OML, depending on overall hemodynamic stability and absence of right ventricular dysfunction.[2,8,31] Individuals who have undergone surgical correction of subvalvular pulmonary stenosis may also be considered for certification following satisfactory cardiological evaluation. In contrast, supravalvular pulmonary stenosis involving the pulmonary trunk or branch pulmonary arteries, particularly when associated with multiple structural abnormalities, is generally considered disqualifying because of the potential for progressive hemodynamic compromise.[2,8,31]

Patent Ductus Arteriosus

Following successful closure of an isolated PDA, certification may be granted if the original shunt was not hemodynamically significant and pulmonary hypertension is absent. Individuals with a small unrepaired isolated PDA may occasionally receive Class 1 certification with OML, provided that there is no evidence of ventricular enlargement, pulmonary hypertension, or arrhythmia.[2,8,31]

Coarctation of the Aorta

Individuals with coarctation of the aorta repaired before the age of 12 years may be considered fit for aviation duties if they remain normotensive both at rest and during exercise. Late repair may be associated with persistent hypertension, and in such cases, limited certification may be possible only with careful blood-pressure monitoring and regular cardiological follow-up.[2,8,31] Because BAV frequently coexists with coarctation, echocardiographic surveillance of the aortic root and ascending aorta is essential. Ascending aortic dilation is incompatible with aviation certification due to the potential risk of progressive enlargement or dissection.[2,8,31]

Tetralogy of Fallot

Individuals with Tetralogy of Fallot repaired in early childhood, particularly before the age of 12 years, may be considered for limited certification when no significant residual right ventricular hypertrophy, pulmonary regurgitation, or clinically relevant ventricular arrhythmias are present. Regular cardiological follow-up is essential because late complications such as right ventricular dilation, pulmonary regurgitation, and ventricular tachyarrhythmias are well recognized in adult survivors of TOF repair.[2,7,30] Outcomes tend to be less favorable when repair occurs later

in life, and the risk of arrhythmias and sudden cardiac death is correspondingly higher.[31]

Patent Foramen Ovale

An asymptomatic PFO is generally considered compatible with unrestricted aviation duties. However, when a transient ischemic attack or cryptogenic stroke has occurred, certification may only be reconsidered after successful closure of the defect and a stable follow-up period of approximately 1 year, provided that no recurrent neurological or cardiovascular complications are identified.[2,8,31,33]

VENOUS THROMBOEMBOLISM AND PREVENTION OF DEEP VEIN THROMBOSIS/PULMONARY EMBOLISM IN AIRCREW

Long-duration travel is a recognized VTE risk amplifier, and pilots or cabin crew may be exposed to prolonged sitting, dehydration, circadian disruption, and interacting risk factors such as age, obesity, recent surgery, thrombophilia, cancer, estrogen exposure, or prior VTE. The current ESC pulmonary embolism reference in force is the 2019 PE guideline.

Non-pharmacological measures form the basis of VTE prevention during long-duration flights and include regular ambulation, adequate hydration, avoidance of prolonged immobility, and the use of compression stockings in selected high-risk individuals. Individuals with recent DVT or PE should not fly until diagnosis, treatment, hemodynamic recovery, anticoagulation stability, and specialist clearance are complete. This is especially important because post-PE dyspnea, recurrence risk, and anticoagulant-related bleeding all have operational relevance. The FAA anticoagulation materials also underscore that the underlying condition and stability of therapy determine certification. Table 15 summarizes practical recommendations for the prevention of travel-related VTE and the aeromedical management of aircrew at increased thromboembolic risk.

CARDIOVASCULAR DRUG USE IN AIRCREW

Medication use in aircrew represents a critical component of aeromedical evaluation because pharmacological therapy itself may influence operational safety (Table 16). Although many cardiovascular conditions can be effectively treated with modern medical therapy, certain medications may impair cognitive performance, hemodynamic stability, or reaction time and thereby limit an individual's ability to safely perform flight duties. Consequently, aeromedical drug assessment is considered as important as the evaluation of the underlying disease.[2,8] A medication that is therapeutically appropriate in routine cardiology practice may still be operationally unacceptable in aviation if it produces sedation, orthostatic hypotension, cognitive slowing, urinary urgency, visual disturbance, or unpredictable metabolic effects, including fluctuations in blood glucose levels. Therefore, aviation medicine authorities require careful assessment of the pharmacodynamic and side-effect profile of cardiovascular medications, in addition to evaluating the stability of the treated condition.[2,8] Aeromedical regulatory frameworks such as EASA Part-MED and FAA

Table 15. Deep Vein Thrombosis and Pulmonary Thromboembolism: Aeromedical Recommendations for Aircrew

Category	Recommendation/Explanation	Target Group
Flight duration and position	For flights longer than 4 hours, it is recommended to move for at least 5 minutes every hour. Cockpit crew should take a short walk every 2 hours.	Pilots
Cabin mobility	Cabin crew are naturally mobile; however, they should avoid sitting for long periods during off-duty.	Cabin crew
Risk factor screening	During annual health checkups, personal or family history of VTE should be questioned. D-dimer testing and venous Doppler ultrasonography may be considered when clinically indicated.	All aircrew
Hydration	Adequate fluid intake should be ensured before and during flight. Caffeine and alcohol should be avoided.	All aircrew
Clothing and equipment	Avoid tight belts or garments compressing below the knee. On the day of flight, compression stockings are recommended especially for at-risk individuals.	Age >50/at-risk individuals
Medication (prophylaxis)	Pharmacological prophylaxis should not be used routinely. LMWH may be considered in selected individuals at very high thromboembolic risk following individualized medical assessment. Aspirin should not be prescribed solely for the prevention of travel-related VTE.	Selected aircrew
Hypobaric hypoxia risk	In conditions such as heart failure/COPD, oxygen saturation should be checked before flight. Hypoxia simulation should be performed if necessary.	Individuals with chronic diseases
Education and awareness	Aircrew should receive VTE awareness training at least once a year. Training on early symptom recognition should be provided.	All aircrew
Pre-flight checklist additions	"Leg swelling, pain, shortness of breath" symptoms should be added to the pre-flight health checklist.	All aircrew
Flight suspension conditions	Aircrew with acute DVT/PTE should refrain from flying for at least 6 weeks. Return to flight requires approval from hematology/cardiology.	Aircrew with acute VTE

ACCP, American College of Chest Physicians; ASA, acetylsalicylic acid; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; EASA, European Union Aviation Safety Agency; ESC, European Society of Cardiology; LMWH, low-molecular-weight heparin; PTE, pulmonary thromboembolism; VTE, venous thromboembolism.

Table 16. Evaluation of Aircrew Using Cardiovascular Drugs

Antihypertensives	Beta-blockers	Fit (metoprolol, carvedilol, bisoprolol, atenolol, pindolol, propranolol, labetalol)
	Calcium-channel blockers	Fit (amlodipine, nifedipine, nicardipine, benidipine, felodipine, lacidipine, diltiazem, verapamil)
	Angiotensin receptor blockers	Fit (valsartan, losartan, irbesartan, olmesartan, candesartan, telmisartan)
	ACE inhibitors	Fit (ramipril, lisinopril, captopril, perindopril, zofenopril, trandolapril, quinapril)
	Alpha blockers	Fit (doxazosin, prazosin)
	Diuretics	Fit (hydrochlorothiazide, furosemide, torasemide, bumetanide, triamterene, amiloride)
	Mineralocorticoid Inhibitors	Fit (spironolactone, eplerenone)
	Centrally acting agents	Unfit (clonidine, methyldopa)
Heart failure drugs	ARNI	After specialist review sacubitril
	SGLT-2 inhibitors	After specialist review (dapagliflozin, empagliflozin)
	Digitalis	After specialist review (digoxin)
Coronary artery disease treatment	Antiplatelet therapy	Fit (aspirin, clopidogrel)
		After specialist review (prasugrel, ticagrelor)
	Coronary vasodilators/anti-ischemic drugs	Unfit (nitrates and ranolazine)
Arrhythmia treatment	Antiarrhythmic drugs	After specialist review (disopyramide, procainamide, mexiletine, flecainide, propafenone, sotalol, dronedarone, amiodarone [max 200 mg])
	Anticoagulants	After specialist review (warfarin, apixaban, rivaroxaban, edoxaban)
Hyperlipidemia treatment	Statins	Fit (atorvastatin, rosuvastatin, pitavastatin, simvastatin, fluvastatin)
	Fibrates	Fit (fenofibrate, gemfibrozil)

ACE, angiotensin-converting enzyme; ARNI, angiotensin receptor–neprilysin inhibitor; SGLT-2, sodium–glucose cotransporter-2.

aeromedical guidance emphasize that pharmacological treatment must always be interpreted within the context of the underlying cardiovascular disorder. For example, antihypertensive therapy may be acceptable when blood pressure is well controlled and medication is well tolerated, whereas treatment for unstable heart failure or active ischemia generally indicates a disease state incompatible with flight duties.[2,8] A practical aeromedical principle is that initiation of a new cardiovascular medication or any dose adjustment should result in a temporary grounding period until tolerability and hemodynamic stability are documented. This observation period allows detection of potential side effects such as hypotension, bradycardia, dizziness, or cognitive impairment that may interfere with flight performance. The required observation period varies according to the regulatory authority. Current FAA guidance requires a 7-day no-fly/ground trial following initiation of a new antihypertensive medication to verify the absence of adverse effects, whereas EASA guidance recommends that applicants initiating antihypertensive therapy be assessed as unfit until the absence of significant side effects has been established.[2,8] In general, ACE inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium-channel blockers, thiazide diuretics, statins, and selected antiplatelet agents are frequently compatible with aeromedical certification when the underlying cardiovascular condition is stable and medication is well tolerated.[2,8]

Federal Aviation Administration guidance identifies several antihypertensive drug classes—including ACE inhibitors, angiotensin II receptor blockers (ARBs), beta-adrenergic blockers, calcium-channel blockers, diuretics, alpha-adrenergic blockers, direct renin inhibitors, and direct vasodilators—as acceptable when certification criteria are met. In contrast, clonidine, guanabenz, guanfacine, methyldopa, reserpine, and nitrates are specifically listed as unacceptable for the treatment of hypertension.[8] FAA aeromedical policies similarly address medication acceptability within structured disease-disposition frameworks. Conditions such as CAD, AF, anticoagulation therapy, and diabetes mellitus are evaluated through dedicated aeromedical decision pathways, often involving special issuance certification when the treated condition demonstrates long-term stability.[8]

Antihypertensive Therapy

Antihypertensive therapy is one of the most commonly encountered pharmacological treatments among aircrew. Initiation of antihypertensive medication or a clinically relevant modification of therapy requires a period of temporary grounding to assess tolerability and exclude adverse effects that may compromise flight safety. Current

FAA guidance requires a 7-day no-fly/ground trial after initiation of a new antihypertensive medication, while EASA guidance recommends that applicants initiating blood-pressure–lowering medication be assessed as unfit until the absence of significant side effects has been established. Return to flight duties should therefore be considered only after satisfactory aeromedical evaluation and confirmation that blood-pressure control is stable and treatment is well tolerated.[2,8]

Major Antihypertensive Drug Classes

Several antihypertensive drug classes are generally considered compatible with aviation duties when well tolerated and when the underlying hypertension remains adequately controlled.[2,8,34]

Beta-blockers may be acceptable in appropriately selected aircrew provided that excessive bradycardia, fatigue, hypotension, or exercise intolerance does not occur. European Union Aviation Safety Agency guidance specifically recognizes certain, generally hydrophilic, beta-blocking agents as acceptable options, while FAA guidance also includes beta-adrenergic blockers among acceptable antihypertensive drug classes when certification criteria are met.[2,8]

Calcium-channel blockers are similarly accepted by both EASA and FAA as potential antihypertensive therapy in aircrew, provided that treatment is effective and does not produce clinically significant adverse effects.[2,8]

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ARBs) are explicitly included among acceptable antihypertensive drug classes in both EASA and FAA aeromedical guidance.[2,8]

Alpha-adrenergic blockers may also be acceptable under FAA guidance, provided that treatment is well tolerated and certification criteria are fulfilled. Particular attention should be paid to orthostatic hypotension and related symptoms that could impair operational performance.[8]

Diuretics are considered acceptable within FAA guidance, whereas EASA specifically identifies non-loop diuretic agents as acceptable antihypertensive therapy. In all cases, adequate hydration, electrolyte balance, renal function, and the absence of clinically significant adverse effects should be established.[2,8]

By contrast, several centrally acting antihypertensive agents are considered aeromedically problematic. FAA guidance specifically lists clonidine, guanabenz, guanfacine, methyldopa, and reserpine, as well as nitrates used for the treatment of hypertension, as unacceptable medications for medical certification.[8] Aircrew starting any antihypertensive therapy should undergo an appropriate period of aeromedical observation to confirm efficacy and the absence of significant adverse effects before returning to flight duties.[2,8,34]

Pharmacological Therapy in Heart Failure

Most individuals with symptomatic congestive heart failure are considered unfit for aviation duties because of the risk of hemodynamic instability and arrhythmia. Nevertheless, when heart failure is mild, well controlled, and stable under specialist supervision, pharmacological therapy may be compatible with restricted certification following comprehensive cardiological assessment.[2,8]

Major Heart Failure Medications

Angiotensin receptor–neprilysin inhibitors (ARNIs), particularly sacubitril/valsartan, constitute an established component of guideline-directed medical therapy for heart failure with reduced ejection fraction.[35] From an aeromedical perspective, their use should be evaluated individually, with particular attention to blood pressure, renal function, electrolyte balance, functional capacity, and the stability of the underlying cardiac disease.[2,8,35]

Sodium–glucose cotransporter-2 (SGLT2) inhibitors, including dapagliflozin and empagliflozin, are established components of contemporary heart failure therapy and reduce the risk of heart failure hospitalization and cardiovascular events in appropriately selected patients.[34] In aircrew, their use requires individualized aeromedical assessment, including evaluation for volume depletion, hypotension, renal dysfunction, and metabolic adverse effects that could potentially affect operational safety.[2,8,35]

Digoxin may be used in selected patients with heart failure or for ventricular rate control in AF according to clinical indications.[35] In an aeromedical setting, particular consideration should be given to renal function, serum drug concentrations when clinically indicated, cardiac rhythm, conduction abnormalities, and the potential for toxicity.[2,8,35]

Importantly, the requirement for advanced heart failure pharmacotherapy may indicate significant underlying structural or functional cardiac disease. Aeromedical fitness should therefore be determined primarily by the severity and stability of the cardiovascular disorder, ventricular function, arrhythmic risk, exercise capacity, and treatment tolerability rather than by medication use alone.[2,8]

Pharmacological Therapy in Coronary Artery Disease

Pharmacological therapy is a central component of the long-term management of CAD in aircrew. From an aeromedical perspective, however, cardiovascular medication should not be assessed solely according to whether a particular drug is considered acceptable or unacceptable for flight duties. The indication for treatment, the stability of the underlying coronary disease, the presence or absence of myocardial ischemia, residual coronary atherosclerotic burden, ventricular function, exercise capacity, treatment efficacy, adverse effects, bleeding risk, and the probability of future acute coronary events must all be considered together. The principal pharmacological objectives in aircrew with established CAD are prevention of coronary thrombosis, stabilization of atherosclerotic plaque, reduction of recurrent cardiovascular events, optimization of blood pressure and ventricular workload, and control of other modifiable cardiovascular risk factors. In contrast, medication that is required primarily to suppress ongoing myocardial ischemia or anginal symptoms has substantially different aeromedical implications because dependence on

chronic anti-anginal treatment may indicate persistence of clinically relevant coronary disease.[2,8,36]

Accordingly, CAD medications can be considered aeromedically within 2 broad categories: secondary-prevention therapies, which reduce future cardiovascular risk, and symptom-controlling anti-ischemic therapies, which may indicate continuing active disease. This distinction is especially important in aviation medicine because successful suppression of symptoms does not necessarily indicate that the underlying coronary substrate has become sufficiently low risk for unrestricted flight duties.[2,36]

Antiplatelet Therapy

Antiplatelet therapy is a cornerstone of secondary prevention in patients with established CAD, previous myocardial infarction, and following coronary revascularization. Aspirin, and where clinically indicated additional antiplatelet therapy, reduces the risk of recurrent coronary thrombosis and forms part of standard secondary-prevention treatment following coronary events or PCI.[2,8] From an aeromedical perspective, antiplatelet therapy itself should generally be interpreted as a marker of the underlying cardiovascular condition rather than as an isolated reason for disqualification. The aeromedical assessment should therefore establish why antiplatelet treatment is required, whether the coronary disease is clinically stable, whether myocardial ischemia has been adequately excluded, whether ventricular function is preserved, and whether there has been any clinically significant hemorrhagic complication.[2,8] The bleeding risk associated with antiplatelet therapy is particularly relevant in aircrew because even relatively minor hemorrhagic events may have operational consequences in certain flight environments. Nevertheless, the presence of antiplatelet therapy does not by itself imply unacceptable aeromedical risk when treatment is stable and well tolerated. Conversely, recurrent gastrointestinal bleeding, intracranial hemorrhage, significant anemia, or any bleeding episode requiring medical intervention should prompt reconsideration of fitness and further aeromedical review.[8] Following PCI, the requirement for dual antiplatelet therapy should be considered in the context of the indication for intervention, the time elapsed since revascularization, treatment stability, absence of recurrent ischemia, and overall bleeding risk. The completion of a clinically appropriate antiplatelet regimen does not in itself establish fitness to fly; return to duties remains dependent on satisfactory clinical, anatomical, and functional reassessment.[2,8] Thus, in aircrew receiving antiplatelet agents, the critical aeromedical questions are not simply whether aspirin or another antiplatelet drug is being used, but whether treatment is effective, stable, free of clinically significant adverse effects, and associated with a sufficiently low residual risk of coronary thrombosis or incapacitating bleeding.[2,8,36]

Lipid-Lowering Therapy

Aggressive lipid-lowering therapy is one of the most important pharmacological strategies for aircrew with established coronary atherosclerosis. Its aeromedical relevance is particularly high because the objective is not merely reduction of serum cholesterol but stabilization of coronary plaque, limitation of atherosclerotic progression, and reduction of the probability of future ACSs. Statin therapy should therefore be regarded as an important component of secondary prevention in aircrew with CAD. Davenport et al. emphasized that aggressive modification of cardiovascular risk factors is essential in aviation personnel with documented coronary atherosclerosis, including individuals with non-obstructive disease.[36] The aeromedical significance of lipid-lowering therapy is particularly important because non-obstructive coronary disease should not be regarded as benign. Acute coronary events may arise from previously non-severe plaques, and future risk relates not only to the severity of the largest individual stenosis but also to the overall atherosclerotic burden. Consequently, effective lipid-lowering therapy may contribute substantially to long-term risk reduction even in aircrew without hemodynamically significant coronary stenosis.[36] Davenport et al[36] incorporated aggressive LDL reduction into an overall strategy of cardiovascular risk optimization. In their aviation cardiology framework, an LDL cholesterol level below approximately 2 mmol/L, together with excellent aerobic fitness and control of other modifiable risk factors, represented a favorable risk profile in selected aircrew with established CAD. These values should be interpreted within the context of comprehensive cardiovascular risk reduction rather than as an isolated licensing threshold. When statins are insufficient to achieve appropriate lipid control, additional lipid-lowering agents may be clinically indicated. From an aeromedical perspective, such therapies should be evaluated according to treatment indication, pharmacological stability, absence of significant adverse effects, and effectiveness in achieving adequate cardiovascular risk-factor control. The 2019 aviation cardiology consensus noted limited aircrew-specific experience with newer lipid-lowering agents such as PCSK9 inhibitors and therefore recommended individualized assessment.[36]

The FAA likewise places considerable emphasis on cardiovascular risk-factor control during follow-up of pilots with established CAD. Appropriate guideline-directed medical therapy, satisfactory LDL-C control, adequate blood-pressure management, and glycemic control where relevant form part of the overall cardiovascular reassessment.[8] Therefore, lipid-lowering treatment in aircrew should generally be viewed positively when clinically appropriate, effective, and well tolerated. The need for intensive lipid-lowering therapy should not itself be interpreted as evidence of aeromedical unfitness; rather, it reflects appropriate secondary prevention in an individual whose residual anatomical and functional cardiovascular risk must be assessed independently.[2,8,36]

Anti-anginal and Anti-ischemic Therapy

Anti-anginal medication requires a fundamentally different aeromedical interpretation from preventive cardiovascular treatment. Drugs used to suppress ongoing myocardial ischemia or anginal symptoms may indicate that clinically significant coronary disease remains active, even if symptoms are pharmacologically controlled. The EASA

specifically states that applicants with angina pectoris should be assessed as unfit irrespective of whether the symptoms are relieved by medication.[2] Consequently, the ability of nitrates, beta-blockers, calcium-channel blockers, or other anti-anginal agents to prevent chest discomfort should not be interpreted as evidence that the individual is aeromedically safe. The central issue is the underlying ischemic substrate. If an aircrew member requires chronic medication specifically to prevent or suppress anginal symptoms, this suggests that myocardial oxygen supply-demand imbalance may persist. Such a situation requires reassessment of coronary anatomy, ventricular function, and evidence of inducible myocardial ischemia rather than simple consideration of drug tolerability.[2,36]

Long-acting nitrates are particularly important from an aeromedical standpoint. Federal Aviation Administration guidance indicates that the use of a long-acting nitrate in an individual being followed under a coronary heart disease special issuance pathway requires deferral for further FAA review rather than routine recertification by the AME.[8] Thus, chronic nitrate treatment should generally be regarded as an important marker of active or potentially active coronary disease. The medication itself is not the only concern; rather, its requirement suggests that the underlying coronary condition may not meet the expected level of clinical stability for unrestricted flight duties.[2,8] The same conceptual approach applies to other chronic anti-anginal therapies. Where beta-blockers or calcium-channel blockers are prescribed primarily for hypertension or another stable cardiovascular indication, their aeromedical interpretation may differ substantially from their use specifically to suppress anginal symptoms. Therefore, the indication for every cardiovascular medication must be clearly documented.[2,8]

Beta-blockers and Heart-Rate Modulating Therapy

Beta-blockers may be used in patients with CAD for several indications, including post-myocardial infarction management, hypertension, ventricular dysfunction, arrhythmia control, or angina. Their aeromedical implications therefore depend heavily on the reason for treatment. When used as part of secondary prevention or for control of hypertension in an otherwise stable and asymptomatic individual, beta-blocker therapy may be compatible with flight duties provided that the medication is well tolerated and does not produce excessive bradycardia, hypotension, fatigue, dizziness, impaired exercise tolerance, or cognitive impairment.[2,8] In contrast, when a beta-blocker is required primarily to suppress exercise-induced angina or myocardial ischemia, the underlying coronary disease becomes the principal aeromedical concern. Pharmacological suppression of symptoms should not be considered equivalent to elimination of ischemic risk.[2] Beta-blockers may also attenuate the heart-rate response to exercise. This is relevant when interpreting exercise testing in aircrew, because achievement of adequate workload and evaluation of functional capacity remain important components of cardiovascular risk assessment. Exercise capacity should therefore be interpreted together with the individual's medication regimen.[2,36] New initiation or significant dose adjustment of a beta-blocker should also prompt an appropriate period of observation until hemodynamic and operational tolerability are demonstrated, particularly because bradycardia, postural symptoms, and impaired exercise performance may have direct flight-safety implications.[2,8]

Angiotensin-converting Enzyme Inhibitors, Angiotensin Receptor Blockers, and Other Cardioprotective Therapy

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may form part of cardiovascular risk reduction in patients with CAD, especially in the presence of hypertension, diabetes mellitus, ventricular dysfunction, or other appropriate clinical indications. These drugs are generally assessed favorably from an aeromedical perspective when blood pressure is adequately controlled and no significant adverse effects are present. Particular attention should be paid to symptomatic hypotension, orthostatic intolerance, dizziness, renal dysfunction, electrolyte disturbances, and any effect that could impair performance during flight operations.[2,8] As with other cardiovascular medications, their use should not be interpreted in isolation. An aircrew member taking an ACE inhibitor or ARB because of well-controlled hypertension may have a very different aeromedical risk profile from an individual receiving the same medication because of significant left ventricular dysfunction following a large myocardial infarction. Thus, the indication for therapy and the underlying cardiovascular substrate remain more important than the pharmacological class itself.[2,8]

Blood-Pressure Control and Multiple Cardiovascular Medications

Hypertension commonly coexists with CAD and constitutes an important modifiable determinant of future cardiovascular events. Effective blood-pressure treatment therefore forms part of secondary prevention in aircrew with established coronary disease. ACE inhibitors, ARBs, selected beta-blockers, calcium-channel blockers, and diuretics may all be clinically appropriate depending on the individual situation. However, treatment should result in stable blood-pressure control without hypotension, orthostatic symptoms, excessive fatigue, or other adverse effects that could impair flight performance.[2,8] Particular attention should be given to aircrew receiving multiple cardiovascular medications because combined therapy may increase the probability of bradycardia, hypotension, electrolyte abnormalities, or reduced exercise tolerance. Polypharmacy should not automatically result in aeromedical disqualification, but the cumulative physiological effects of treatment must be considered. Following initiation of a new cardiovascular medication or significant dosage adjustment, temporary grounding may be appropriate until clinical stability and absence of operationally significant adverse effects have been demonstrated.[2,8]

Pharmacological Therapy Following Myocardial Infarction or Coronary Revascularization

Following myocardial infarction, PCI or CABG, medication is an essential component of secondary prevention. Typical

management may include antiplatelet therapy, intensive lipid-lowering treatment, blood-pressure control and other guideline-directed cardiovascular therapies according to the patient's clinical condition. From an aeromedical perspective, however, successful pharmacological treatment cannot substitute for objective demonstration that the residual cardiovascular risk has become acceptably low. European Union Aviation Safety Agency requires comprehensive reassessment following an ischemic event or coronary revascularization. Appropriate secondary-prevention medication should continue, but medication required specifically to control cardiac symptoms is not considered acceptable as a basis for fitness.[2] For Class 1 assessment, satisfactory coronary anatomy should be demonstrated. European Union Aviation Safety Agency guidance specifies that there should generally be no stenosis exceeding 50% in a major untreated vessel, graft or angioplasty/stent site. Particular attention should be paid to multiple stenoses and repeated revascularization procedures. Untreated disease involving the left main stem or proximal left anterior descending artery carries particular significance. Functional reassessment is also essential. After an appropriate recovery period, exercise testing should demonstrate satisfactory functional capacity without evidence of myocardial ischemia or clinically significant rhythm or conduction disturbance. Ventricular function should remain satisfactory, with a left ventricular ejection fraction of at least approximately 50% under the relevant EASA assessment framework.[2] Following angioplasty or stenting, appropriate stress imaging may be required to demonstrate absence of reversible myocardial ischemia. Additional investigations, including ambulatory ECG monitoring, may be appropriate when arrhythmic risk is suspected.[2]

These anatomical and functional criteria are important specifically because they determine whether pharmacologically treated CAD has reached an acceptably stable state. In other words, aspirin, statins, antihypertensive drugs, or other secondary-prevention therapies may be entirely appropriate, but they cannot compensate aeromedically for residual hemodynamically significant disease, inducible ischemia, or impaired ventricular function.

Residual Coronary Disease and the Role of Medical Therapy

Medical therapy becomes particularly important in aircrew with residual non-obstructive coronary atherosclerosis following investigation or revascularization. Revascularization treats selected stenotic lesions but does not eliminate the systemic atherosclerotic process. Davenport et al[36] emphasized that coronary risk should not be determined solely by the severity of a single stenosis. Overall plaque burden, aggregate stenosis, multivessel involvement, and lesion location are relevant to future cardiovascular event risk. This is important when interpreting pharmacological therapy. Aggressive lipid lowering, antiplatelet therapy where indicated, blood-pressure optimization, smoking cessation, glycemic control, and maintenance of excellent physical fitness may reduce future risk substantially, but they do not eliminate the need for continued surveillance of residual coronary disease.[36] For lesions greater than approximately 50%, functional assessment becomes particularly relevant. Fractional flow reserve or stress imaging may be used when appropriate to determine whether a lesion is hemodynamically significant. In the aviation cardiology consensus described by Davenport et al,[36] an FFR below 0.80 represented evidence of hemodynamic significance. The same consensus proposed assessment of cumulative coronary disease burden through aggregate stenosis. A high cumulative burden, particularly aggregate stenosis exceeding approximately 120%, was considered inconsistent with continued unrestricted professional flying even when individual lesions were not necessarily critically obstructive. These anatomical thresholds are not themselves pharmacological recommendations; rather, they demonstrate the limit beyond which optimal medical therapy alone may not reduce aeromedical risk sufficiently for unrestricted flight duties.

Monitoring Treatment Effectiveness and Adverse Effects

Long-term pharmacological treatment in aircrew requires structured surveillance. The effectiveness of therapy should be assessed through control of cardiovascular risk factors, absence of recurrent angina or acute coronary events, maintenance of satisfactory ventricular function, and preservation of adequate exercise capacity. Laboratory monitoring should be tailored to the medications being used and may include lipid profile, renal function, electrolytes, glucose control, and other clinically relevant parameters. Medication adverse effects have particular importance in aviation. Symptoms such as dizziness, orthostatic intolerance, excessive bradycardia, hypotension, fatigue, muscle weakness, cognitive slowing, or clinically important bleeding may be acceptable inconveniences in ordinary clinical practice but may represent unacceptable operational hazards in professional aircrew. Medication tolerance should therefore be demonstrated not only at rest but also under conditions relevant to operational performance, including exercise and prolonged duty where appropriate.[2,8]

Federal Aviation Administration follow-up of individuals with established coronary disease places emphasis on continued guideline-directed medical therapy, control of LDL-C, blood pressure and glycemic risk factors, absence of new cardiovascular symptoms, stable functional status and absence of clinically significant medication-related bleeding. New chest pain, recurrent myocardial infarction, restenosis requiring intervention, a new coronary procedure, clinically significant bleeding or use of a long-acting nitrate are among the findings that require further FAA review rather than routine aeromedical recertification.[8]

Aeromedical Interpretation of Medical Therapy

The presence of medication should therefore never be considered independently from the coronary disease that prompted its prescription. Preventive therapy such as antiplatelet agents, statins, and appropriate blood-pressure treatment may be compatible with flight duties and should generally be considered an essential component of risk reduction when clinically indicated.[2,8,36]

Conversely, dependence on medication to suppress angina or myocardial ischemia is fundamentally different. EASA specifically considers angina pectoris incompatible with fitness regardless of whether symptoms are relieved pharmacologically.[2]

A useful aeromedical distinction is therefore:

Secondary-prevention medication may support return to flight by reducing future cardiovascular risk, whereas symptom-controlling anti-ischemic medication may indicate persistence of disease that remains incompatible with unrestricted flight operations.[2,8,36]

- The final aeromedical decision should therefore integrate:the indication for each medication;
- clinical stability of coronary disease;
- absence of angina or other ischemic symptoms;
- absence of inducible myocardial ischemia;
- residual coronary anatomy and overall atherosclerotic burden;
- ventricular function;
- functional and exercise capacity;
- LDL-C and other cardiovascular risk-factor control;
- bleeding risk associated with antithrombotic therapy;
- hemodynamic effects of medication;
- absence of operationally significant adverse effects;
- adherence to guideline-directed secondary prevention; and
- estimated risk of recurrent acute coronary events.[2,735]

Overall, pharmacological management of CAD in aircrew should be viewed primarily as a strategy for secondary prevention and long-term cardiovascular risk reduction, rather than simply as treatment of coronary symptoms. Aspirin and other appropriate antiplatelet agents, intensive lipid-lowering therapy, optimal blood-pressure management, and other guideline-directed cardiovascular treatments may be compatible with aviation duties when the individual is clinically stable and medication is well tolerated. In contrast, continuing myocardial ischemia, recurrent anginal symptoms, hemodynamically significant coronary disease, excessive residual coronary burden, impaired ventricular function, recurrent coronary events, clinically important medication adverse effects, or dependence on chronic anti-anginal treatment should prompt grounding, restriction, or further specialist aeromedical evaluation. Thus, aeromedical fitness in pharmacologically treated CAD should ultimately be determined not by the mere presence or absence of cardiovascular medication, but by whether medical therapy has achieved a sufficiently stable, asymptomatic, and low-risk cardiovascular state to meet the safety requirements of aviation operations

Pharmacological Therapy in Cardiac Arrhythmias

Pharmacological therapy for cardiac arrhythmias requires particularly careful aeromedical evaluation because both the underlying rhythm disorder and the treatment itself may influence flight safety. From an aeromedical perspective, the principal concerns include recurrence of a clinically significant arrhythmia, syncope or presyncope, rapid ventricular rates, clinically relevant bradycardia, atrioventricular or intraventricular conduction disturbances, impaired ventricular function, drug-induced proarrhythmia, QT prolongation, and treatment-related neurological, visual, hemodynamic, or systemic adverse effects that could impair operational performance.[2,8,37]

A significant disturbance of cardiac rhythm or conduction should therefore prompt comprehensive cardiological assessment before aeromedical fitness is considered. The assessment should define the type and burden of the arrhythmia, symptom status, recurrence pattern, ventricular rate, presence of pauses or conduction abnormalities, ventricular function, underlying structural or ischemic heart disease, exercise response, and the effectiveness and tolerability of therapy. Depending on the clinical setting, investigations may include a resting 12-lead ECG, ambulatory ECG monitoring, transthoracic echocardiography, exercise testing, and additional imaging or EPSs when clinically indicated. Current aeromedical literature emphasizes that the presence or absence of symptoms and the predicted natural history of the arrhythmia are central elements in determining operational risk.[2,8]

Particular attention is required in AF and atrial flutter because aeromedical risk is determined not only by the arrhythmia itself but also by ventricular rate, symptom burden, recurrence, associated structural heart disease, thromboembolic risk, and the treatment required to maintain adequate rate or rhythm control.[1-3,9] EASA permits consideration of fitness in selected applicants with AF/flutter when cardiological assessment is satisfactory and stroke risk is sufficiently low; when anticoagulation is required, certification is dependent on stable anticoagulation, acceptable hemorrhagic risk, and the applicable medical-certificate class and operational limitation.[2]

Federal Aviation Administration assessment similarly focuses on the functional and clinical consequences of AF rather than on the diagnosis or medication alone. Under the FAA AF AASI pathway, continuing certification requires cardiovascular documentation, a minimum 24-hour cardiac monitor performed within the preceding 90 days, and a cardiology assessment addressing rate or rhythm control, symptoms, treatment, thromboembolic events, CHA_2DS_2-VA score, and embolic-risk mitigation when indicated. Poor rate control, functionally important symptoms, significant pauses, inadequate embolic-risk mitigation, or bleeding requiring medical intervention may require deferral for further FAA review.[8]

Aeromedical fitness should therefore not be determined solely by the presence or absence of antiarrhythmic medication. The indication for treatment, the underlying electrophysiological and structural cardiac substrate, risk of recurrence, probability of sudden or subtle incapacitation, ventricular function, treatment efficacy, and potential adverse effects of therapy should all be incorporated into the decision. A medication that is clinically appropriate may still require aeromedical restriction if it causes bradycardia, hypotension, impaired exercise capacity, visual disturbance,

dizziness, cognitive impairment, or clinically relevant proarrhythmia.[2,37]

Catheter ablation may represent an alternative to chronic antiarrhythmic drug therapy in appropriately selected aircrew, particularly for recurrent supraventricular arrhythmias or AF. Successful ablation, however, does not automatically restore unrestricted certification. Demonstration of procedural success, freedom from clinically significant recurrent arrhythmia, appropriate post-procedural rhythm monitoring, and satisfactory aeromedical reassessment are required; the observation period and operational restrictions depend on the arrhythmia, certification class, and regulatory authority.[1,2,9] EASA and FAA both provide specific post-ablation assessment pathways rather than treating ablation itself as evidence of immediate fitness.[2,8]

Major Antiarrhythmic and Antithrombotic Agents

Antiarrhythmic drugs should be evaluated according to their electrophysiological effects, indication, underlying cardiac substrate, potential for proarrhythmia, hemodynamic consequences, and extracardiac toxicity rather than being regarded as universally acceptable or unacceptable for aviation duties. Importantly, neither EASA nor FAA provides a universal drug-by-drug list stating that all commonly used Class I or Class III antiarrhythmic agents are compatible with unrestricted flying. Aeromedical assessment must therefore remain individualized.[2,8]

According to the conventional Vaughan–Williams classification, Class I sodium-channel blockers include Class IA agents such as disopyramide and procainamide, Class IB agents such as mexiletine, and Class IC agents such as flecainide and propafenone. Sotalol combines beta-adrenergic blocking activity with Class III potassium-channel-blocking effects, while amiodarone and dronedarone are multichannel agents conventionally classified predominantly within Class III. Modern electrophysiological guidance emphasizes that drug choice must account for structural heart disease, ventricular function, conduction status, renal and hepatic function where relevant, QT interval, drug interactions, and proarrhythmic risk.[37]

Class IA agents such as disopyramide and procainamide warrant particular caution because of their potential to prolong ventricular repolarization and provoke clinically important ventricular arrhythmias in susceptible patients. Class IB agents such as mexiletine are generally used in specific ventricular arrhythmia settings; in such cases, the underlying ventricular arrhythmia and structural cardiac substrate may be of greater aeromedical importance than the medication itself. Class IC agents such as flecainide and propafenone can produce conduction slowing and proarrhythmic effects, particularly in inappropriate cardiac substrates, and therefore require careful assessment of QRS duration, ventricular function, structural heart disease, and arrhythmia control.[37]

Flecainide illustrates why the aeromedical significance of an antiarrhythmic drug depends strongly on its indication. UK Civil Aviation Authority guidance specifically states that flecainide used for AF may be acceptable in selected applicants. However, the same guidance considers flecainide unacceptable for certification when it is being used to treat ventricular arrhythmias, even in a structurally normal heart.[6] Visual or vestibular symptoms should also be specifically questioned because blurred vision and related disturbances may have operational relevance even when conventional ophthalmological function is otherwise preserved.[38]

Sotalol requires consideration of both its beta-blocking effects and its Class III electrophysiological properties. Clinically relevant bradycardia, hypotension, impaired exercise tolerance, QT prolongation, and the risk of torsades de pointes should be excluded before favorable aeromedical consideration. Dronedarone likewise requires individualized assessment, with attention to rhythm control, bradycardia, QT effects, drug interactions, and the clinical condition for which treatment is required. Neither agent should be described as universally aeromedically acceptable solely on the basis of drug class.[2,37]

Amiodarone deserves particularly cautious aeromedical consideration because of its long elimination half-life and broad extracardiac toxicity profile, including potential pulmonary, thyroid, hepatic, neurological, ocular, and bradyarrhythmic effects. A universal aeromedical maintenance-dose threshold—such as 200 mg/day—should therefore not be used as a general criterion for fitness.[37,38] UK CAA guidance explicitly considers amiodarone unacceptable for Class 1 medical certification. For Class 2 certification, treatment usually requires a VCL restricting privileges to daytime flying; unrestricted Class 2 certification may only be considered in selected applicants without relevant night-time glare and following satisfactory ophthalmological review. Consequently, any aeromedical decision concerning amiodarone must remain authority- and license-class-specific rather than being based on dose alone.[38]

The same general principle applies to all antiarrhythmic therapy: successful suppression of an arrhythmia does not automatically establish aeromedical fitness. The possibility of proarrhythmia, excessive bradycardia, conduction disease, QT prolongation, hemodynamic intolerance, interaction with other cardiovascular drugs, and neurological or visual adverse effects should be considered together with the severity and natural history of the underlying arrhythmia.[2,37]

Antithrombotic therapy constitutes a separate but closely related component of arrhythmia management, particularly in AF and atrial flutter. The requirement for oral anticoagulation does not necessarily result in permanent disqualification from aviation duties. Certification may be possible in appropriately selected individuals when the underlying condition is sufficiently stable, anticoagulation is reliably controlled, treatment is well tolerated, and the combined thromboembolic and hemorrhagic risks are acceptable for the level of certification sought.[2,39,40]

For vitamin K antagonist therapy, particularly warfarin, stability of anticoagulation must be demonstrated. Under EASA guidance, anticoagulation is considered stable when at least 5 INR measurements have been documented during the preceding 6 months and at least 4 are within the prescribed therapeutic target range; hemorrhagic risk must also be

acceptable. The applicable operational limitation differs according to medical-certificate class and the underlying indication for anticoagulation. EASA additionally requires ongoing review of INR results during aeromedical follow-up.[2]

The FAA applies a different, indication-specific framework. For non-valvular AF, when the CHA_2DS_2-VA score is 2 or higher, acceptable embolic-risk mitigation strategies for FAA medical certification purposes include warfarin, a NOAC, or left atrial appendage closure. For applicants newly starting warfarin, the FAA requires a minimum 6-week observation period, completion of any additional observation period required for the underlying condition, and 6 INR measurements obtained no more frequently than once weekly. For non-valvular AF, at least 80% of these INR values should be within the 2.0-3.0 range; other therapeutic INR ranges may apply to different indications such as prosthetic valves.[39]

For applicants already established on warfarin therapy, FAA guidance requires documentation of the dosing history, medication tolerance, and adverse effects, together with at least monthly INR results for the preceding 6 months as part of the aeromedical review. Thus, the use of warfarin is not itself an automatic prohibition, but certification depends on the indication for anticoagulation, stability of treatment, bleeding history, and the aeromedical status of the underlying cardiovascular disorder.[7,39]

Direct oral anticoagulants are increasingly relevant to aeromedical assessment. EASA does not identify individual DOACs by name in its general Part-MED anticoagulation provisions; instead, it refers to anticoagulant medication that does not require INR monitoring. Under EASA guidance, a fit assessment may be considered following a stabilization period of 3 months, subject to the relevant medical-assessor review and certificate-class requirements.[2]

UK CAA guidance is more drug-specific and explicitly identifies dabigatran, rivaroxaban, edoxaban, and apixaban as acceptable DOACs for aeromedical consideration. Applicants receiving DOAC therapy should be free of treatment-related adverse effects for 3 months before fitness reassessment and should have satisfactory appropriate blood monitoring. Under the UK CAA framework, certification on anticoagulation may be possible at Class 1 OML level and, in appropriate cases, at unrestricted Class 2 level, provided that the underlying condition is stable and the overall incapacitation and hemorrhagic risks are acceptable.[40]

Federal Aviation Administration guidance also permits NOAC/DOAC therapy in appropriately selected applicants. For applicants newly starting a NOAC/DOAC, a minimum observation period of 2 weeks is required, in addition to any observation period imposed by the underlying cardiovascular condition.[5,6] In the FAA AF pathway, treatment must be tolerated without significant adverse effects or bleeding complications and must form part of an adequate embolic-risk mitigation strategy when the CHA_2DS_2-VA score requires such treatment.[8,39]

Bleeding risk is a critical aeromedical consideration with all forms of anticoagulation. The evaluation should include previous spontaneous or clinically important bleeding, renal and hepatic function as appropriate for the selected anticoagulant, adherence, drug interactions, concomitant antiplatelet therapy when present, and the operational consequences of trauma-associated bleeding. Importantly, the presence of anticoagulation should always be interpreted together with the condition necessitating anticoagulation rather than treated as an isolated medication issue.[2,39,40]

Overall, pharmacological treatment of cardiac arrhythmias in aircrew requires an individualized, risk-based approach. Neither successful rhythm suppression nor stable anticoagulation alone is sufficient to establish aeromedical fitness. The final decision should integrate the underlying arrhythmia, symptom burden, risk of recurrence and sudden or subtle incapacitation, ventricular and structural cardiac function, thromboembolic risk, bleeding risk, treatment efficacy, medication tolerability, and the specific certification class sought. Depending on the regulatory framework and clinical circumstances, multi-crew or other operational limitations may remain necessary even when pharmacological therapy is otherwise compatible with certification.[2,8]

Pharmacological Therapy in Hyperlipidemia

As discussed in detail in the section on pharmacological therapy in CAD, lipid-lowering therapy represents an important component of cardiovascular risk reduction and secondary prevention in aircrew.[2,8,36] Dyslipidemia is common among aviation populations and is usually managed according to standard cardiovascular prevention guidelines.

Major Lipid-Lowering Agents

Statins, including atorvastatin, rosuvastatin, pitavastatin, simvastatin, and fluvastatin, are widely accepted because of their strong cardiovascular risk-reduction benefits and favorable safety profile.[2,8,36] Fibrates, such as fenofibrate and gemfibrozil, may also be acceptable when tolerated and when metabolic stability is maintained.[2,8]

Practical Recommendations

Appropriate pharmacological management allows many cardiovascular conditions to be treated without necessarily resulting in loss of occupational capability. Nevertheless, drug selection in aircrew must always consider both therapeutic efficacy and operational safety. Aircrew members who initiate new cardiovascular therapy or undergo dose adjustments must notify their flight physician or AME, and temporary grounding may be required until treatment tolerability is confirmed. In clinical practice, resources such as the Aviation Medicine Advisory Service database may assist physicians in verifying whether proposed pharmacological therapies are compatible with aviation duties.[41]

RESPIRATORY DISEASE AND FITNESS TO FLY

Although the present review primarily focuses on cardiovascular disease, respiratory fitness remains an important component of aeromedical certification because pulmonary disorders may impair oxygenation, ventilation, exercise tolerance, vigilance, and operational performance. Respiratory conditions of particular aeromedical relevance include chronic airflow limitation, asthma, active inflammatory respiratory

Table 17. Flight Fitness in Respiratory System Diseases

Disease/Condition	Class 1 Fitness
Chronic obstructive pulmonary disease (COPD)	Unfit
Asthma (recurrent attacks)	Unfit
Asthma (stable, appropriate medication use)	Fit with AMS assessment
Active respiratory infections	Temporarily unfit
Sarcoidosis (active)	Unfit
Sarcoidosis (limited, inactive, no medication)	Fit with AMS assessment
Spontaneous pneumothorax (single, healed, after 1 year)	Fit
Spontaneous pneumothorax (single, healed, after 6 weeks)	Fit with OML restriction
Spontaneous pneumothorax (recurrent, after surgery)	Fit with AMS assessment
Spontaneous pneumothorax (recurrent, without surgery)	Unfit
Pneumonectomy (complete lung removal)	Unfit
Chest surgery (minor interventions, fully healed)	Fit with AMS assessment (OML restriction possible)
Sleep apnea (untreated)	Unfit
Sleep apnea (after successful treatment)	Fit
Initial Class 1 Examination (FEV1/FVC <70%)	Pulmonologist assessment required

AME, aviation medical examiner; AMS, Aeromedical Section; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; OML, operational multi-crew limitation; OSL, operational safety pilot limitation.

disease, sarcoidosis, pneumothorax, major thoracic surgery, and obstructive sleep apnea syndrome.[2,6] According to EASA Part-MED, applicants with asthma requiring medication, active inflammatory respiratory disease, active sarcoidosis, pneumothorax, sleep apnea syndrome, major thoracic surgery, pneumonectomy, or chronic obstructive pulmonary disease (COPD) require satisfactory respiratory evaluation before a fit assessment can be considered. Class 1 applicants with these conditions require referral to the medical assessor of the licensing authority, whereas Class 2 applicants are assessed in consultation with the medical assessor.[2] Respiratory assessment is particularly relevant in aerospace cardiology because respiratory and sleep-related disorders frequently interact with cardiovascular and metabolic disease. Their combined effects on oxygenation, exercise capacity, alertness, and cardiovascular risk may materially influence aeromedical fitness.[6,42] The principal aeromedical considerations and fitness-to-fly recommendations for common respiratory system diseases are summarized in Table 17.

Chronic Obstructive Pulmonary Disease

Applicants with clinically significant COPD should generally be assessed as unfit because impaired pulmonary function and gas exchange may compromise physiological reserve. However, applicants with only minor and stable impairment of pulmonary function may be considered fit following satisfactory respiratory evaluation.[2]

Asthma

Asthma may be compatible with certification when the disease is stable, pulmonary function is satisfactory, and the required medication is compatible with flight safety. Recurrent or inadequately controlled asthma requires further assessment. Applicants requiring systemic corticosteroid therapy should be assessed as unfit for active flight duties. For Class 1 applicants, aeromedical assessment should involve the medical assessor of the licensing authority when asthma requires medication. Class 2 applicants may be assessed in consultation with the medical assessor when satisfactory disease control and pulmonary function are demonstrated.[2]

Acute Respiratory Infections

Active inflammatory or infectious respiratory disease should result in temporary unfitness while clinically significant symptoms persist. A fit assessment may be reconsidered after resolution of the condition, particularly when pulmonary function has returned to an acceptable level and no significant sequelae remain.[2,6]

Sarcoidosis

Active sarcoidosis should be assessed as unfit because of the possibility of systemic involvement, particularly cardiac involvement. A fit assessment may be considered when the disease is inactive, requires no continuing medication, and has been shown to be limited to hilar lymphadenopathy. Cardiac or neurological sarcoidosis is incompatible with a favorable aeromedical assessment. The possibility of cardiac involvement is particularly important in aviation medicine because cardiac sarcoidosis may be associated with conduction abnormalities, ventricular arrhythmias, and potential incapacitation. Accordingly, EASA requires satisfactory cardiological evaluation in applicants with established sarcoidosis before certification is reconsidered.[2]

Spontaneous Pneumothorax

Spontaneous pneumothorax is initially incompatible with flight duties because recurrence at altitude may produce significant respiratory compromise. For Class 1 applicants, a fit assessment may be considered 1 year after full recovery from a single spontaneous pneumothorax. At revalidation, an earlier assessment may be considered 6 weeks after full recovery with an OML maintained for at least 1 year after recovery. Recurrent spontaneous pneumothorax is generally incompatible with certification unless successful surgical treatment has been performed and recovery is satisfactory.

For Class 2 applicants, a fit assessment may be considered 6 weeks after full recovery from a single spontaneous pneumothorax when respiratory evaluation is satisfactory. Following surgery for recurrent pneumothorax, certification may also be reconsidered after satisfactory recovery.[2]

Thoracic Surgery and Pulmonary Operations

Applicants undergoing major thoracic surgery should be considered unfit until recovery is complete, they are asymptomatic, and the risk of secondary complications is minimal. Following lesser thoracic procedures, certification may be reconsidered after satisfactory recovery and pulmonary evaluation. Pneumonectomy requires particular consideration because of the permanent reduction in pulmonary reserve. Under EASA Part-MED, Class 1 applicants who have undergone pneumonectomy are assessed as unfit.[2]

Obstructive Sleep Apnea Syndrome

Untreated or inadequately treated obstructive sleep apnea syndrome is incompatible with flight duties because excessive daytime sleepiness and impaired vigilance may compromise operational safety. European Union Aviation Safety Agency specifically requires applicants with unsatisfactorily treated sleep apnea syndrome to be assessed as unfit.[2] Certification may be reconsidered when effective treatment, most commonly continuous positive airway pressure where clinically indicated, has been established and satisfactory treatment adherence and control of symptoms have been demonstrated.[2,42] OSA management should include continued follow-up because treatment effectiveness and compliance are central to maintaining adequate daytime alertness.[42] Beyond its implications for daytime vigilance, OSA is also relevant to cardiovascular risk assessment, particularly in the presence of hypertension; recent data have highlighted the additional burden associated with comorbid insomnia and sleep apnea in hypertensive patients.[43]

Spirometry in the Initial Class 1 Medical Examination

Spirometry is required as part of the initial Class 1 aeromedical examination and should subsequently be repeated when clinically indicated. Applicants with an forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio below 70% should undergo further evaluation by a respiratory specialist to determine the presence, severity, and functional significance of airflow limitation. The assessment should consider whether any identified respiratory impairment may adversely affect exercise capacity, oxygenation, or operational performance during flight. For Class 2 applicants, pulmonary function testing should be performed when clinically indicated.[2]

FOLLOW-UP, SURVEILLANCE, AND REVALIDATION

One of the most important principles of aviation medicine is that certification is a process, not a one-time event. Hypertension, diabetes, CAD, valve disease, arrhythmia, device therapy, aneurysm, and congenital heart disease all require periodic revalidation. European Union Aviation Safety Agency repeatedly links certification to satisfactory specialist review, repeat imaging, stable anticoagulation, pacemaker checks, or serial cardiovascular evaluation depending on the diagnosis.

Surveillance should be disease-specific while following a consistent, risk-based framework. Blood-pressure disorders need repeated blood pressure and risk-factor review; diabetes requires HbA1c and complication surveillance; coronary disease requires clinical review plus periodic functional/anatomical reassessment when indicated; heart failure and cardiomyopathy require echocardiography, rhythm surveillance, and biomarker/exercise re-evaluation; pacemakers require annual device checks at minimum; post-valve surgery needs imaging and anticoagulation review; aortic disease needs serial imaging; respiratory disease needs PFT-anchored reassessment when appropriate. Any clinical deterioration, therapy change, or new symptom complex should trigger immediate reconsideration of fitness.

CONCLUSION

Aeromedical cardiovascular assessment is a high-consequence application of clinical cardiology. The essential principle is not whether a disease can be treated, but whether the residual risk of sudden or subtle incapacitation is compatible with the license privileges being exercised. Current aeromedical standards under ICAO, EASA, FAA, and DGCA converge on this point even when operational details differ.

Aeromedical cardiovascular assessment should follow a structured hierarchy based on diagnosis, disease severity, ventricular function, arrhythmic and thromboembolic risk, treatment compatibility, and the required intensity of surveillance. Under this framework, controlled hypertension, stable non-hypoglycemic diabetes therapy, successfully treated coronary disease, selected low-risk arrhythmias, minor valvular abnormalities, small stable aneurysms, and simple repaired congenital lesions may remain certifiable in some applicants. Conversely, unstable metabolic disease, significant residual ischemia, reduced EF, malignant arrhythmia, ICD therapy, severe valvular or aortic pathology, complex congenital disease, active pulmonary sarcoid, recurrent pneumothorax, and untreated sleep apnea generally preclude safe certification.

This review integrates contemporary cardiovascular guidance with the aeromedical standards applied by ICAO, EASA, FAA, and Turkish DGCA. It is intended to serve as a practical clinical reference rather than a formal ESC guideline. Certification decisions should remain individualized and should account for residual incapacitation risk, treatment-related effects, license class, and the operational demands of the specific aviation role.

Author Contributions: Concept – S.A., B.E.; Design – S.A., B.E.; Supervision – S.A., B.E.; Resources – Not applicable; Materials – Not applicable; Data Collection and/or Processing – Not applicable; Analysis and/or Interpretation – Not applicable; Literature Search –All authors; Writing – All authors.; Critical Review – L.C., E.N., K.E., A.Y.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Approach to Distal Left Main Coronary Artery Bifurcation Lesions

ABSTRACT

Distal left main coronary artery (LMCA) bifurcation lesions are associated with a worse prognosis than other coronary bifurcation lesions. Although coronary artery bypass grafting remains a safe and effective treatment option in this patient population, percutaneous coronary intervention (PCI) has been increasingly adopted in patients with low-to-intermediate anatomical complexity due to its less invasive nature and the favorable long-term outcomes demonstrated in major randomized clinical trials. Given the substantial impact of LMCA revascularization on patient prognosis, meticulous procedural planning and optimization are of paramount importance. The use of intravascular imaging has proven to be of significant value both in making revascularization decisions and in optimizing PCI outcomes. Since the side branch in distal LMCA bifurcation lesions is the left circumflex artery, which supplies a significant portion of the myocardium, accurately predicting and preventing damage to this side branch is of vital importance. Intravascular imaging plays a key role in predicting side branch compromise and in determining the most appropriate stenting strategy, including provisional stenting or an upfront 2-stent approach. Regardless of the stenting strategy employed, achieving optimal minimal stent area targets is essential for improving long-term clinical outcomes. Adverse events following distal LMCA PCI most frequently occur at the left circumflex ostium, highlighting the importance of maintaining long-term side branch patency. Drug-coated balloons, which have demonstrated favorable results in bifurcation interventions, may represent a promising adjunctive therapy for side branch treatment during provisional stenting. However, further large-scale randomized studies are required to establish their role in distal LMCA bifurcation.

Keywords: Drug-coated balloons, intravascular imaging, left main bifurcation lesions, provisional stenting

REVIEW

INTRODUCTION

Assessment of left main coronary artery (LMCA) lesions and decision-making regarding revascularization have always represented a critical challenge for interventional cardiologists. In clinical practice, LMCA disease is encountered in approximately 4%-9% of patients undergoing coronary angiography.[1] In 70% of patients with LMCA lesions, the lesion affects the distal bifurcation. The prognosis for distal lesions is worse than that for ostial-mid LMCA lesions. [2] Intravascular imaging studies have demonstrated that only a small proportion of atherosclerotic plaques involving the LMCA are confined to the left main (LM) segment alone, whereas the majority extend distally into the bifurcation, involving the ostia of the left anterior descending (LAD) and/or left circumflex (LCx) arteries.[3]

The distal left main bifurcation differs from other coronary bifurcations in terms of its unique anatomical and hemodynamic characteristics. The LMCA has a significantly larger diameter than other epicardial coronary arteries, and its diameter typically exceeds 5 mm. Furthermore, a wider bifurcation angle, combined with turbulent blood flow and low endothelial shear stress, contributes to accelerated atherosclerotic plaque formation in this region. Additionally, since the side branch involved in distal LMCA interventions is typically LCx, which supplies a significant myocardial region, the loss of this side branch may have vital clinical consequences.[4,5]

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Received: June 23, 2026
Accepted: August 26, 2026
Available Online Date: September 21, 2026

Cite this article as: Esenboğa K, Özerdem ME. Approach to distal left main coronary artery bifurcation lesions. *Anatol J Cardiol.* 2026;30(12):874-882.

DOI: 10.14744/AnatolJCardiol.2026.6808

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One of the most critical challenges encountered in the treatment of distal LMCA lesions is the variability in bifurcation geometry and the risk of side-branch occlusion. [5] Therefore, careful assessment of lesion morphology, appropriate selection of the stenting strategy, and the use of a 2-stent technique when necessary are essential for the optimal management of distal LMCA bifurcation lesions. In contemporary practice, a provisional single-stent strategy is generally preferred whenever feasible; however, a planned 2-stent approach is recommended in the presence of complex anatomy or significant side branch involvement.[4,6]

In this review, the evaluation of distal LMCA bifurcation lesions, intravascular imaging methods, interventional treatment strategies, and current technical approaches will be discussed in view of the literature.

INTRAVASCULAR IMAGING METHODS FOR LEFT MAIN CORONARY LESIONS

Conventional angiography has important limitations in the evaluation of LMCA disease, particularly with respect to the assessment of lesion severity, disease distribution, and plaque morphology. The complex anatomy of the LMCA, characterized by vessel angulation, distal branch overlap, foreshortening, calcification, and the difficulty in obtaining true orthogonal views of the bifurcation, makes it difficult to accurately measure the degree of stenosis, which leads to significant variability among observers and potentially inadequate treatment outcomes.[7]

In contrast, intravascular imaging methods such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) provide high-resolution imaging of vascular wall morphology, lumen structure, and atherosclerotic plaque characteristics, which facilitates a more accurate assessment of lesions and optimizes the interventional decision-making process.[8] These techniques help optimize the procedure by determining the appropriate stent diameter and length, selecting the optimal segments for stent placement, and ensuring that the stent achieves full apposition to the vessel wall with adequate expansion. They also enable early detection and prevention of stent-related procedural complications, such as edge dissection and intramural hematoma.[8,9] Each method has its own advantages. Intravascular ultrasound offers a wider field of view and is superior for assessing plaque burden and aorto-ostial lesions. Optical coherence tomography, on the other hand, is better suited for evaluating calcification, stent malposition, deformation, and edge dissection. Although OCT provides higher resolution (10-20 μm vs. 30-40 μm with contemporary high-definition IVUS systems), its tissue penetration is more limited, making IVUS more suitable for the assessment of large-caliber vessels such as the LMCA.[4] In addition, OCT requires contrast injection to clear blood from the imaging field, whereas IVUS does not require additional contrast administration. Therefore, IVUS may offer a distinct advantage in patients with advanced chronic kidney disease or in clinical scenarios where minimizing contrast volume is desirable.[4,8]

Recent meta-analyses, including the RENOVATE-COMPLEX-PCI, ILUMIEN IV, and OCTOBER studies, have shown that intravascular imaging guidance during LM coronary interventions leads to improvements in clinical outcomes such as mortality and target vessel failure.[10] Nevertheless, the results of the OPTIMAL trial, published in 2026, have raised important questions regarding the clinical benefit of intravascular imaging guidance. In this international, multicenter, randomized study, 806 patients with LM coronary artery disease were assigned to undergo percutaneous coronary intervention (PCI) under either IVUS guidance or angiographic guidance. During follow-up, no significant differences were observed between the 2 groups with respect to the incidence of death, myocardial infarction (MI), or repeat revascularization.[11] However, when interpreting the results of the OPTIMAL trial, several important methodological differences compared with previous studies should be taken into consideration. The trial was conducted in high-volume, experienced centers, and the vast majority of procedures in both groups were completed with post-dilatation and proximal optimization technique (POT). Furthermore, additional optimization based on post-procedural IVUS findings was required in only approximately 30% of patients in the IVUS-guided group, suggesting an overall high procedural

HIGHLIGHTS

- In meta-analyses, incorporating long-term outcomes from major randomized trials such as Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) and Nordic-Baltic-British Left Main Revascularization Study (NOBLE) in left main coronary artery (LMCA) stenosis, no significant difference in mortality has been demonstrated between coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) in selected patient populations.
- The findings of the OPtimal Therapy for Left Main Coronary Artery Disease (OPTIMAL) trial appear insufficient to conclude that intravascular ultrasound (IVUS) provides limited benefit in LMCA. Intracoronary imaging modalities continue to play an important role in left main interventions.
- According to the latest European Association of Percutaneous Cardiovascular Interventions/European Bifurcation Club (EAPCI/EBC) consensus recommendations, optimal post-PCI expansion targets in distal left main (LM) bifurcation interventions are an LM minimal stent area (MSA) of 10-12 mm^2 and an left anterior descending (LAD MSA) of 7-8 mm^2, with an LCx minimal lumen area (MLA) > 4 mm^2 after provisional stenting, and LM, LAD, and LCx MSA targets of 10-12 mm^2, 7-8 mm^2, and 6-7 mm^2, respectively, after planned 2-stent treatment.
- Hybrid approaches using drug-coated balloons (DCB) in provisional stenting for distal LMCA lesions appear to have the potential to improve long-term outcomes of side-branch ostial patency; however, large randomized controlled trials are needed.

quality. Consistent with this, the minimal stent area (MSA) values achieved in the IVUS arm were 14.3 mm^2 in the proximal LMCA, 12.3 mm^2 at the polygon of confluence, 8.02 mm^2 in the LAD, and 6.71 mm^2 in the left circumflex artery, all of which were in line with or exceeded the currently recommended optimization targets.[11]

Along with the findings reported by Hong et al, the results of the OPTIMAL trial may indicate that the incremental value of IVUS guidance becomes less evident when complex PCI procedures are performed by highly experienced operators under optimal technical conditions. Notably, Choi et al[12] demonstrated that the clinical benefit associated with IVUS guidance was particularly pronounced among operators with less than 5 years of PCI experience and in the setting of complex coronary interventions.

However, in light of current evidence, the use of intracoronary imaging techniques in the evaluation and treatment of LMCA disease remains a Class I recommendation in current European guidelines.[13] The European Bifurcation Club (EBC) supports the use of IVUS or OCT in main coronary interventions and recommends that operators choose the imaging technique in which they have the most experience and confidence in interpretation, or which they believe is most appropriate for the patient, lesion anatomy, and procedural characteristics.[4]

INTRAVASCULAR ULTRASOUND–BASED ASSESSMENT AND OPTIMIZATION CRITERIA FOR LESIONS IN THE LEFT MAIN CORONARY ARTERY

Minimal lumen area (MLA) is the principal intravascular imaging parameter used for the assessment of lesion severity. In the evaluation of LMCA disease, MLA measurements should be obtained from pullbacks performed in both the LAD and LCx arteries, with the lowest measured value considered for clinical decision-making. An IVUS-derived MLA cutoff of 6 mm^2 remains the most commonly accepted threshold for determining the functional significance of LM lesions.[14] However, findings from studies conducted in Asian populations have highlighted the limitations of applying a single absolute cutoff value irrespective of patient size, leading to the proposal of a lower MLA threshold of 4.5 mm^2.[15] It is recommended that physiological assessment be used for lesions ranging from 4.5 to 6 mm^2.[4]

According to the latest joint consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and EBC, revascularization decisions should not rely solely on MLA measurements but should also incorporate plaque morphological characteristics. The presence of high-risk plaque features, including plaque disruption (rupture or erosion), with or without intraluminal thrombus, as well as intraplaque hemorrhage, may favor proceeding with revascularization.[4]

Intravascular ultrasound plays a crucial role in both making treatment decisions and optimizing treatment. In 2 stent strategies, the "5-6-7-8 rule" was previously defined, defining optimal MSA criteria for LCx, LAD, bifurcation, and distal LM, respectively.[16] However, recent studies involving Western populations have called into question the classic 5-6-7-8 criteria, which were originally identified in the Korean population and predict angiographic restenosis at 9 months. In the IVUS subgroup analyses of the EXCEL and NOBLE studies, the mean MSA values within the LM were found to be 9.9 ± 2.3 mm^2 (n = 504) and 12.5 ± 3.0 mm^2 (n = 224), respectively.[17,18] For this reason, there has been debate over whether there are significant differences between Eastern and Western populations.

Subsequently, Kang and colleagues proposed target MSA cutoff values of 11.8 mm^2 for the distal LMCA, 8.3 mm^2 for the LAD ostium, and 5.7 mm^2 for the LCx ostium.[19] These threshold values appear to align more closely with data derived from Western populations. Nevertheless, the prognostic value of IVUS-derived MSA criteria for long-term clinical outcomes remains imperfect. In the study by Kang et al[16], MSA measurements at the LAD and LCx ostia were predictive of adverse clinical events, whereas the distal LM MSA was not significantly associated with outcomes. Likewise, the 9.8 mm^2 distal LM MSA threshold identified in the EXCEL trial demonstrated only limited predictive performance.[16,18]

In 2023, Bangalore and Maehara introduced the concept of "magic numbers" for IVUS-guided LM PCI optimization, proposing target MSA thresholds of >6-8-10 mm^2 and optimal MSA values of >7-9-12 mm^2.[7] They also suggested that, in patients with smaller coronary vessel dimensions, relative MSA may be more appropriate than absolute cutoff values. Relative MSA is defined as the ratio of the MSA to the reference vessel area within the same segment, and a threshold exceeding 40% was proposed as a reliable surrogate that closely approximates the conventional absolute MSA targets.[7]

In a study aimed at identifying optimal MSA areas in PS, the MSA threshold values were determined as ≥11.4 mm^2 for the proximal LMCA, ≥8.4 mm^2 for the distal LMCA, and ≥8.1 mm^2 for the LAD ostium. An MSA value of <11.4 mm^2 in the proximal LMCA doubled the 5-year risk of MACE. The presence of under-expansion in both the distal LMCA and the LAD ostium was also found to be associated with high rates of major adverse cardiovascular events (MACE).[20]

Building on these observational data, the most recent joint EAPCI/EBC consensus provides a contemporary framework for IVUS-guided LM PCI optimization. Rather than replacing the previously proposed "magic numbers," the consensus integrates the available evidence into practical recommendations according to the revascularization strategy. [4] The consensus recommends MSA values of 10-12 mm^2 for the LMCA and 7-8 mm^2 for the LAD, with MLA > 4 mm^2 for the LCx, in the provisional approach; and 10-12 mm^2 for the LMCA, 7-8 mm^2 for the LAD, and 6-7 mm^2 for the LCx in the dual-stent strategy. The latest EAPCI/EBC consensus statement suggests that IVUS-guided optimization should incorporate not only absolute MSA targets but also relative stent expansion indices based on the reference vessel area. A relative stent expansion of approximately 80%-90% is considered an appropriate optimization criterion, with a target of 90% for normal LM anatomy and 80% for tapering

LM segments to reduce the risk of overexpansion and vessel perforation. Importantly, the consensus emphasizes that relative expansion indices should be interpreted alongside absolute MSA targets and that excessive stent expansion, particularly in the LM, should be avoided.[4]

PHYSIOLOGICAL ASSESSMENT OF LEFT MAIN CORONARY ARTERY STENOSES

Physiological assessment of LMCA disease has several limitations compared with intravascular imaging modalities. During fractional flow reserve (FFR) measurement, the guiding catheter should be disengaged from the LM ostium to avoid interference from an ostial lesion, and pressure measurements are recommended to be obtained separately in both the LAD and LCx arteries. However, in the presence of diffuse atherosclerotic disease involving the distal LAD and LCx, FFR values may be falsely increased, potentially leading to an underestimation of LM lesion severity. An FFR value >0.80 in both the LAD and LCx is generally considered indicative of a hemodynamically non-significant LM lesion.[21]

In the provisional stenting strategy, FFR can be used to assess the function of a side branch. Supporting this, it has been shown that an FFR value >0.80 measured in the LCx following LMCA–LAD crossover stenting is associated with a better prognosis in terms of long-term clinical outcomes (particularly at 5-year follow-up).[22]

CORONARY ARTERY BYPASS RAFTING VERSUS PERCUTANEOUS CORONARY INTERVENTION IN THE MANAGEMENT OF DISTAL LEFT MAIN CORONARY ARTERY DISEASE

Determining the revascularization strategy for LMCA disease requires a multidisciplinary approach that considers anatomical, clinical, and functional parameters. In this process, the decision should be made using the "heart team" approach, while considering patient preference and the experience of the center and the operator.[13]

In patients with high surgical risk, as assessed by the EuroSCORE II or Society of Thoracic Surgeons (STS) score, PCI may be favored, whereas coronary artery bypass grafting (CABG) remains the preferred strategy in those with a low operative risk. Factors supporting a CABG-based approach include a high SYNTAX score, the presence of diabetes mellitus, reduced left ventricular ejection fraction (LVEF ≤ 35%), contraindications to dual antiplatelet therapy, recurrent in-stent restenosis, and the need for concomitant cardiac surgery. Conversely, PCI may be preferred in patients with low-to-intermediate SYNTAX scores, isolated LM disease, advanced frailty or significant comorbidities, a history of thoracic radiotherapy, porcelain aorta, previous cardiac surgery, or presentation with ST-segment elevation myocardial infarction (STEMI).[8,23]

Apart from these, determining the most appropriate revascularization strategy for patients who are suitable for both methods has been a subject of intense debate and a key research area in large-scale, multicenter studies over the past 2 decades.

Although CABG remains the standard of care for treating LMCA lesions, advances in stent technology and intravascular imaging have improved the outcomes of PCI. Data from large-scale clinical trials and meta-analyses support the emerging evidence for the use of PCI in the treatment of LMCA disease.[23]

A meta-analysis incorporating the 4 major randomized trials comparing PCI and CABG for LM disease (Synergy Between PCI With Taxus and Cardiac Surgery [SYNTAX], Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease [PRECOMBAT], NOBLE, and EXCEL) demonstrated no significant difference in all-cause mortality between the 2 revascularization strategies.[24] Among these studies, EXCEL and NOBLE are the most contemporary, both utilizing second-generation drug-eluting stents (DES). Approximately 80% of the LM lesions included in these 2 trials involved distal bifurcation disease. While no difference was observed in the primary endpoints in the 5-year results of the EXCEL trial, all-cause mortality and MI were found to be higher in the PCI arm. Differences in the definition of periprocedural MI in the EXCEL trial and the fact that the difference in mortality rates was largely attributable to non-cardiovascular deaths have raised questions.[25]

In 2025, the 10-year follow-up data from the NOBLE trial were published, confirming the absence of a significant difference in all-cause mortality between PCI and CABG. Interestingly, this finding was observed irrespective of SYNTAX score. However, the relatively limited number of patients with high SYNTAX scores included in the study raises questions regarding the robustness of this subgroup analysis. Another notable observation was that, among patients presenting with LMCA acute coronary syndrome (ACS), PCI was associated with a lower rate of all-cause mortality than CABG.[26]

In fact, all these findings demonstrate that both approaches can be used as treatment strategies and highlight the importance of a patient-centered approach to treatment rather than relying solely on a single scoring system. According to current myocardial revascularization guidelines, PCI is indicated as Class I for cases with significant LM disease and a low SYNTAX score, and as Class 2a for lesions of moderate complexity (SYNTAX 23-32).[13,27]

STENTING STRATEGY FOR LEFT MAIN CORONARY ARTERY BIFURCATION LESIONS

One of the most commonly used classifications for evaluating the complexity of bifurcation lesions is the DEFINITION (Definitions and impact of complEx biFurcation leslons on clinical outcomes after percutaNeous coronary IntervenTIOn using drug-eluting steNts) criteria. Based on this classification, a complex bifurcation lesion is defined by the presence of at least 1 major criterion and 2 accompanying minor criteria. For LM bifurcations, a side-branch lesion length of >10 mm and a side-branch stenosis of more than 70% are among the major criteria (Table 1).[28]

In the DEFINITION II trial, which compared provisional single-stent and planned 2-stent strategies in patients with

Table 1. Definition Criteria for a Complex Coronary Bifurcation

Major Criteria	
For left main bifurcation (Major 1)	SB lesion length ≥10 mm, and
	SB diameter stenosis ≥70%
For non-left main bifurcation (Major 2)	SB lesion length ≥10 mm, and
	SB diameter stenosis ≥90%
Minor Criteria	Moderate or severe calcification
	Multiple lesions
	Bifurcation angle <45° or >70°
	MV-RVD <2.5 mm
	MV lesion length ≥25 mm
	Thrombus-containing lesions
A complex coronary bifurcation lesion is defined by the presence of one applicable major criterion and at least two minor criteria.	

LM, left main; MV, main vessel; RVD, reference vessel diameter; SB, side branch.

complex coronary bifurcation lesions (CBL), the use of a 2-stent approach was associated with a significant reduction in target lesion failure (TLF) at 12 months. Notably, distal LM bifurcation lesions accounted for approximately 29% of the study population, and the double kissing (DK)-crush technique was the predominant 2-stent strategy, being used in 77.8% of patients assigned to the dual-stent arm.[28]

There are 2 important randomized studies comparing provisional stent strategies with dual stent approaches in distal LMCA bifurcation lesions. The first of these is the DKCRUSH-V study. In this trial, 484 patients with Medina 1,1,1 or 0,1,1 distal LM bifurcation lesions were randomized to undergo either provisional stenting (PS) or DK-crush stenting and were assessed for the primary endpoint of 1-year TLF. Among patients with true distal LM bifurcation disease, the DK-crush strategy achieved a comparable relative reduction in TLF across both simple and complex lesion subsets compared with provisional stenting ($P = .65$). Nevertheless, the absolute clinical benefit was greater in the complex lesion subgroup (11.2% vs. 4.1%). The superiority of the DK-crush strategy even in patients with simple lesions further suggests that the study cohort largely consisted of anatomically true bifurcation lesions.[29]

The use of IVUS in the study was about 40% and was left to the operator's discretion. In angiographic evaluations, restenosis in the provisional stent group was most frequently observed at the side branch (SB) ostium. This finding demonstrates that one of the primary challenges in distal LM bifurcation procedures is the optimal treatment of the side branch ostium. In 2019, the 3-year results of this study showed that the dual-stent strategy maintained its benefit in terms of primary endpoints. The DKCRUSH-V results contribute to the evidence that, when performed by experienced operators, the antegrade 2-stent strategy may be the most appropriate approach in selected patients with complex underlying anatomy.[30]

Another landmark study comparing provisional stenting with an upfront 2-stent strategy for the treatment of distal LMCA bifurcation lesions is the EBC Left Main (EBC MAIN) trial. In the study, the primary endpoint was defined as a composite of all-cause mortality, MI, and target lesion revascularization (TLR) within 12 months. The primary endpoint occurred in 34 patients (14.7%) in the provisional stenting group (n = 230) and in 42 patients (17.7%) in the planned 2-stent group, with no significant difference observed between the treatment strategies (hazard ratio [HR] ≈ 0.80, $P = .34$). Analysis of the secondary endpoints similarly demonstrated no significant between-group differences. In the PS arm, the rates of MI, TLR, and stent thrombosis were 10.0%, 6.1%, and 1.7%, respectively, compared with 10.1%, 9.3%, and 1.3% in the planned 2-stent arm.[31,32]

The 1-year results of the EBC MAIN study show that the provisional stenting approach in patients with true left main bifurcation lesions yields clinical outcomes similar to those of the planned dual-stent strategy. In the 3-year follow-up results, no significant differences were observed for most endpoints; however, a significant advantage in favor of provisional stenting was reported in terms of target vessel revascularization.[31,32]

On the other hand, when the EBC MAIN and DKCRUSH-V studies are evaluated together, it becomes apparent that many factors—such as the patient characteristics, lesion complexity, operator experience, and the techniques used—play a role in the differing results. In the DKCRUSH-V study, higher operator experience, patients exhibiting more complex characteristics (higher SYNTAX scores and longer side-branch lesions), and a higher frequency of dual-stent requirements (47% vs. 22%) stand out as key factors influencing the results. Moreover, the fact that the culotte technique was the predominant 2-stent strategy in the EBC MAIN trial (53%), whereas crush-based techniques were used in only a small proportion of cases (5%), raises the possibility that differences in stenting technique may, at least in part, have influenced the study outcomes.[29,31]

When all these data are evaluated together, it becomes clear that the optimal approach to distal LMCA bifurcation lesions must be tailored to the complexity of the lesion. In complex bifurcation lesions, planned dual-stent strategies—particularly the DK crush technique—may be a more appropriate option, whereas in simpler lesions, the provisional stent approach remains a rational and effective treatment option.[8]

PREDICTORS OF SIDE BRANCH COMPROMISE IN LEFT MAIN CORONARY INTERVENTIONS

In left main coronary procedures, whether a direct, planned dual-stent strategy or a provisional approach is used, it appears that a significant proportion of MACE is attributable to side branches.[33] The EAPCI and EBC recommend current guidelines that combine IVUS and coronary angiography to identify predictors of side-branch loss and, if necessary, to initiate treatment of the side branch from the outset. According to this consensus:

- Angiographic LCx diameter stenosis ≥ 70%
- LCx minimal lumen area (MLA) < 4 mm² or plaque burden > 55% as assessed by intravascular imaging
- LCx lesion length > 10 mm
- In the presence of moderate-to-severe LCx calcification, intravascular imaging is recommended; lesions with a calcium arc > 180°, calcium length > 5 mm, and calcium thickness > 0.5 mm are considered to be at particularly high risk.
- Evidence of plaque instability, with or without the presence of intraluminal thrombus, is also considered a predictor of side branch compromise.[4]

PROVISIONAL STENTING TECHNIQUE FOR LEFT MAIN CORONARY ARTERY BIFURCATION LESIONS

In its latest recommendations, the EBC, based on the EBC MAIN study results, recommends provisional stenting regardless of lesion complexity. Provisional stenting of the LM differs from that of other bifurcations in that the side branch is the LCx artery, which already has clinical significance.[34]

Initially, guidewires should be advanced into both the LAD and LCx. A crossover stent is then implanted from the LM into the LAD, with stent sizing determined according to the diameter of the distal main vessel. After stent deployment, POT should be systematically performed using a short non-compliant (NC) balloon sized to the proximal main vessel, ensuring complete apposition of the proximal stent segment.

Proximal optimization technique is a key component of the provisional stenting strategy. Properly performed POT can correct carina shift induced by main vessel stenting, optimize expansion of the side branch ostium, and minimize the risk of suboptimal rewiring through a proximal stent cell during subsequent side branch access. As a result, POT facilitates easier and more accurate distal side branch rewiring, thereby improving the efficacy of any further bifurcation optimization maneuvers.[34,35]

The benefit of routinely performing kissing balloon inflation (KBI) after POT is unclear, and data are limited. Studies on non-LM bifurcation lesions have shown that not performing KBI slightly increases the risk of stenosis and thrombosis

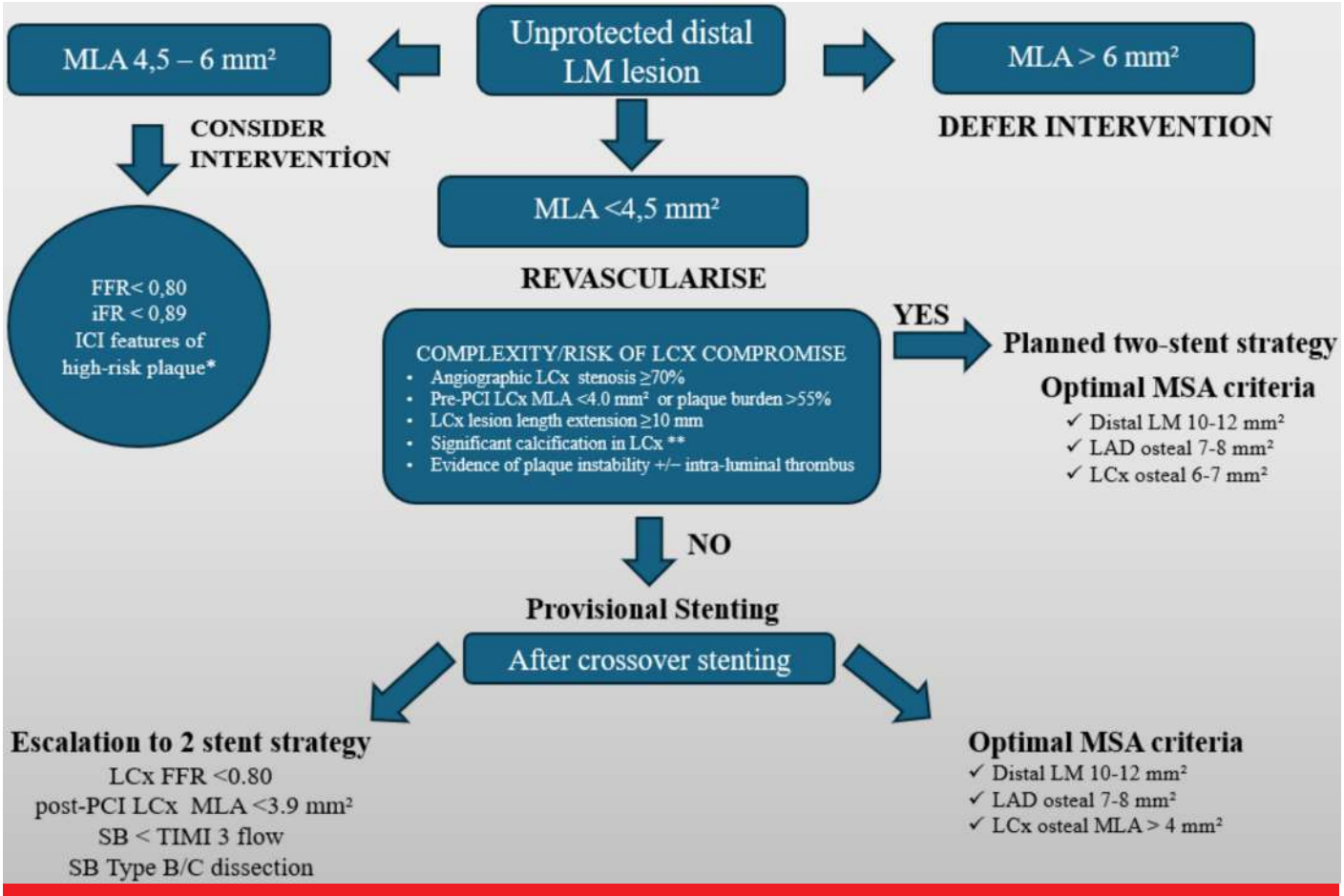


Figure 1. Management algorithm for unprotected distal left main coronary artery lesions. FFR, fractional flow reserve; ICI, intracoronary imaging; iFR, instantaneous wave-free ratio; LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main coronary artery; MLA, minimal lumen area; MSA, minimal stent area; PCI, percutaneous coronary intervention; SB, side branch. *Plaque disruption - with or without luminal thrombus, or intra-plaque hemorrhage. **ICI-defined calcification with arc > 180°, >5 mm in length, and >0.5 mm thickness.

during follow-up; however, this risk generally does not lead to clinically significant outcomes.[36]

In 2022, Yoon et al[37] argued that performing routine KBI following a provisional strategy in 255 LMCA patients could have adverse outcomes. The 15th EBC Consensus Report emphasized that, while the absence of KBI in provisional LMCA procedures does not make a difference in terms of MACE, there are concerns regarding fenestrated restenosis.[38]

It should be noted that, in addition to all this data, KBI is also routinely applied in the EBC-MAIN study.[31] The ongoing IKISS-LM (Impact of Kissing Balloon Inflation in Provisional Left Main Coronary Bifurcation PCI) trial, a prospective, multicenter, randomized controlled study, is expected to provide further insight into this issue.[39]

Following KBI, elliptical deformation of the main vessel stent may occur, characterized by loss of its circular geometry. Therefore, repeat proximal optimization technique (re-POT) should be performed to restore the optimal stent configuration within the main vessel. After re-POT, the side branch should be carefully reassessed. Conversion to a 2-stent strategy should be considered in the presence of significant side branch compromise, including >90% ostial stenosis, TIMI 1-2 flow, type B/C dissection, or evidence of ischemia and/or angina. The choice of 2-stent technique should be guided by bifurcation anatomy, including bifurcation angle and side branch diameter, with T-stenting/T and small protrusion (T/TAP) generally favored for bifurcation angles > 70°, and culotte or reverse crush techniques considered for angles < 70°.[38,40] The contemporary approach to unprotected left main coronary artery bifurcation lesions, based on current evidence, is schematically illustrated in Figure 1.

ROLE OF DRUG-COATED BALLOONS IN LEFT MAIN CORONARY ARTERY BIFURCATION LESIONS

Evidence from clinical trials has shown that drug-coated balloons (DCBs), when compared with conventional balloon angioplasty, significantly reduce late lumen loss and restenosis in the SB. In addition, DCB-based strategies may simplify PCI procedures by reducing the need for extensive stent implantation. Furthermore, hybrid approaches combining DCBs with DES have been reported to provide superior clinical and angiographic outcomes compared with DES-only strategies in patients with true CBL.[40]

Given that most events in LM interventions occur in side branches, this suggests that DCB may be useful in ensuring side-branch patency, particularly in provisional procedures without increasing the metal burden.

The DCB-BIF trial (Drug-Coated Balloon Angioplasty of the Side Branch During Provisional Stenting: The Multicenter Randomized DCB-BIF Trial) evaluated the use of DCBs versus non-compliant (NC) balloons angioplasty in compromised SB following provisional stenting of true CBL. Drug-coated balloons treatment was associated with lower rates of MI and a reduction in the primary composite endpoint. Nevertheless, the generalizability of these findings to distal LMCA bifurcation disease remains limited, as complex bifurcation lesions were excluded and only 10%-15% of the study population consisted of distal LMCA lesions.[41]

A retrospective study comparing a hybrid DES + DCB approach with upfront dual stent strategies in distal LMCA bifurcation lesions demonstrated no significant difference in MACE between these groups. Double kissing-crush was the predominant 2-stent technique employed. However, elective angiographic follow-up revealed a significantly larger MLA at the LCx ostium and lower late lumen loss (LLL) in the DES + DCB group ($P < .05$). Despite these encouraging angiographic findings, the small study population and the limited use of intravascular imaging warrant cautious interpretation, and larger prospective studies are required to confirm these results.[42]

In real-world data involving 597 patients, the DES + DCB combination was associated with lower rates of clinical TLR (2.91% vs. 9.42%; $P = .007$), TLF (9.60% vs. 17.14%; $P = .026$), and stent thrombosis (0.00% vs. 2.89%; $P = .030$) at 2-year follow-up compared to a strategy using DES alone (provisional or dual-stent).[43]

The use of DCBs in bifurcation lesions has been described using 2 distinct strategies based on the timing of DCB use relative to main vessel stenting. In the first strategy, lesion preparation and DCB treatment of the SB are performed before main vessel stenting, followed by POT. In cases where the SB result remains suboptimal, additional optimization with KBI and re-POT may be required. Nevertheless, it has been hypothesized that these additional balloon inflations could alter the distribution of the antiproliferative drug previously delivered to the side branch, thereby potentially attenuating its therapeutic effect.[40]

In the other method, MV stent implantation involves rewiring the SB after POT, performing a KBI, followed by DCB in the side branch, and concluding the procedure with POT. The disadvantages of this method are thought to include the possibility that interaction between the DCB and the stent struts during DCB advancement into the SB may lead to drug loss and suboptimal drug distribution, as well as inadequate preparation of the SB lesion. In studies conducted to date on LMCA lesions, DCB has been administered primarily after main vessel stenting.[40]

CONCLUSION

In summary, PCI has become an increasingly utilized revascularization strategy for distal LMCA disease. Intravascular imaging appears to be essential for optimizing procedural outcomes and improving long-term prognosis, supporting its routine use during both pre- and post-procedural assessment. While the EBC recommends a provisional stenting strategy regardless of bifurcation complexity, the DK-crush technique has emerged as the preferred planned 2-stent approach in patients at high risk for side branch compromise. Hybrid strategies combining provisional stenting with DCB treatment of the LCx ostium represent a promising approach for maintaining long-term side branch patency. However, the available evidence in distal LMCA bifurcation PCI remains limited, as only approximately 10%-15% of patients enrolled

in the DIF-BIF and DCB studies had distal LMCA lesions. Therefore, their role in distal LMCA bifurcation PCI requires confirmation in adequately powered randomized clinical trials specifically designed for this lesion subset.

Informed Consent: Not applicable.

Peer-review: Internally peer-reviewed.

Author Contributions: Concept – K.E., M.E.O.; Design – M.E.O.; Supervision – K.E.; Resources – K.E., M.E.O.; Analysis and/or Interpretation – K.E., M.E.O.; Literature Search – K.E., M.E.O.; Writing – K.E., M.E.O.; Critical Review – K.E., M.E.O.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Tricuspid Valve Function After Add-On Pacing/Sensing Lead vs ICD Lead Implantation for Failed IS-1/DF-1 ICD Leads: A Single-Center Experience

ABSTRACT

Background: The development or progression of tricuspid regurgitation (TR) following the implantation of cardiac implantable electronic devices (CIED) represents a significant concern. Although the link between transvalvular lead placement and TR is well established, the patient-related and lead-related factors that predispose patients to develop TR remain unclear. This study aimed to evaluate the effect of additional pacing/sensing leads (PSL) or implantable cardioverter defibrillator (ICD) leads on tricuspid valve function in patients with lead failure.

Methods: In this retrospective, single-center, case-control study, all ICD implantation patients, in cases performed by one of these authors, presenting with lead failure were screened. The degree of TR on pre- and post-procedural echocardiograms of patients who underwent additional PSL or ICD lead implantation is compared.

Results: The study comprised a total of 52 patients; 28 patients received PSL, and 24 patients received ICD electrodes. A non-significant increase in the degree of TR was observed in patients who underwent new ICD lead implantation ($P = .059$). The degree of TR observed in patients who underwent new PSL implantation was found to be comparable to the pre-procedure levels ($P = .180$). However, no statistically significant differences were observed between the 2 groups with respect to change in TR degree ($P = .123$).

Conclusion: This study is the first analysis comparing the effect of ICD electrode addition with PSL addition without lead extraction on right ventricular and tricuspid valve function in patients with lead failure. This study provides the first comparative analysis of PSL versus ICD lead addition in patients with lead failure. The findings suggest that additional leads, whether PSL or ICD, do not significantly worsen tricuspid valve function. The addition of PSL to the IS-1/DF-1 ICD lead with standard high-voltage leads may be a viable treatment option, as it yields similar results to a new ICD lead implantation in terms of right heart function.

Keywords: Implantable cardioverter defibrillator, lead failure, tricuspid regurgitation

ORIGINAL INVESTIGATION

INTRODUCTION

The implantation of cardiac implantable electronic devices (CIEDs), including permanent pacemakers, implantable cardiac defibrillators (ICDs), and cardiac resynchronization therapy (CRTs), has increased significantly in recent years.[1] The development or progression of tricuspid valve dysfunction after implantation of CIED represents a significant concern.[2] Following CIED implantation, tricuspid valve dysfunction is more commonly associated with tricuspid regurgitation (TR) and less commonly associated with tricuspid stenosis. The crossing of CIED electrodes over the tricuspid valve can result in the development of acute or chronic TR for a few reasons, including valve impingement, inflammation, and fibrosis of subvalvular structures and valve surfaces, damage to the right ventricular wall, leading to systolic dysfunction, and electrode-induced endocarditis.[3-5] The number, thickness, stiffness, and course of the electrodes placed across the valve are factors that affect the likelihood of valve damage or dysfunction occurring during and after electrode placement.[1,3,6] While the link between transvalvular lead placement and TR is well established, further research is required to elucidate the

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Received: October 6, 2025
Accepted: May 13, 2026
Available Online Date: July 7, 2026

Cite this article as: Kuru Görgülü B, Akbulut Ö, Altın AT, Dinçer İ, Baskovski E. Tricuspid valve function after add-on pacing/sensing lead vs ICD lead implantation for failed IS-1/DF-1 ICD leads: A single-center experience. *Anatol J Cardiol.* 2026;30(12):883-889.

DOI: 10.14744/AnatolJCardiol.2026.5878

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underlying conditions that predispose patients to develop associated and electrode-induced TR.

There are also studies showing more TR development with ICD lead than with pacemaker lead.[3,7] The ICD lead comprises a flexible silicone cylinder that can be coated with 1 or more copolymer materials to accommodate multiple conductors. Of particular significance is the inclusion of at least 1 distal right ventricle (RV) shock coil, which adds weight and stiffness to the transvalvular apparatus. In comparison, the pacemaker leads are typically thinner and lack a shock coil. These differences in size and material composition may influence the development of lead-related TR.[8]

To the knowledge, no study has investigated the effect of additional lead placement in the RV and the type of lead on tricuspid dysfunction. The study's objective was to investigate the effect of increasing the number of leads passing through the tricuspid valve and the type of lead on tricuspid valve dysfunction.

METHODS

Study Design and Patient Selection

This retrospective, single-center, case-control study was conducted in accordance with the Declaration of Helsinki and received approval from the Local Ethics Committee (Approval date: 05/05/2025, decision number: İ04-358-25). Each participant provided informed consent. Artificial intelligence assisted technologies were not used in the production of this study.

All ICD-implanted patients who presented with pacing/sensing component failure between 2010 and 2024 were screened for inclusion in the study. The flow chart for patient inclusion in the study is shown in Figure 1. Pacing/sensing failure was defined as intermittent or constant pacing impedance rise above manufacturer specified threshold, increase in pacing threshold > 5 mV, R wave drop < 4 mV, or oversensing (not caused by electromagnetic interference or T wave oversensing). If patients were to be included in the PSL arm, the high-voltage circuit of the faulty electrode had to be intact (defined by shock coil impedances within the ranges specified by the manufacturer and the absence of faulty cardioversion/defibrillation). Patients who underwent electrode revision based on the manufacturer's recommendation and patients with LF due to a loose connector screw were excluded from the study. Patients who underwent PSL implantation for other indications (such as His or left bundle branch pacing) were not included in the study.

Patients with IS-1/DF-1 ICD leads with intact high-voltage conductors were included in the new PSL implantation group. Patients undergoing PSL implantation for other indications (such as His or left bundle pacing) were not included. In patients with DF4 connectors, a new ICD lead was added, and the old lead was capped.

Patients with baseline or follow-up transthoracic echocardiography (TTE) of insufficient quality for TR evaluation were excluded. Patients who underwent lead extraction were not included in the study. Three patients were lost during follow-up, and 1 patient was excluded from the study because lead extraction was performed due to axillary vein occlusion.

Implantation Procedure

All patients were taken to the electrophysiology laboratory in a fasting state. The procedures were performed under conscious sedation by a total of 3 different electrophysiologists. Patency of the venous system was confirmed by venography. The appropriate lead (PSL and ICD lead) was advanced to the RV and implanted according to current guidelines. If appropriate indications were available, additional coronary sinus and/or right atrial leads were implanted. In the study group, the IS-1 pin of the old ICD cable was switched off, while the DF-1 high-voltage connectors were reconnected to the appropriate sites on the ICD generator. The PSL pin was connected to the IS-1 connection slot on the generator. In patients with DF4 lead, the old DF4 lead was switched off and the new lead was connected to the system. If coronary sinus or atrial leads were implanted or the old device had an end-of-service warning, the generator was replaced or upgraded for CRT, as appropriate. The device was then fixed in the generator pocket, and the pocket was closed with sutures. Post-implantation fluoroscopic recordings of patients with PSL or ICD leads are shown in Video 1 and 2. The device was interrogated, and electrical parameters (threshold, pacing impedance, sensing) were checked. Patients were removed from the laboratory if all measurements were within the specified range.

Echocardiographic Studies

The primary outcome parameter was TR severity at follow-up. Two-dimensional, color flow, continuous pulse-wave, and tissue Doppler TTE were performed using a Vivid E9 imaging system (GE Medical Systems, Chicago, USA). Measurements were obtained in the standard manner recommended by the American Society of Echocardiography. Tricuspid regurgitation evaluation was based on the regurgitant jet area in the right atrium and the size of the vena contracta by color Doppler in the apical 4-chamber view. Mitral regurgitation evaluation was based on the color flow jet area in the left atrium and vena contracta by color Doppler. The degree of atrioventricular valve regurgitation was divided into 4 categories: None TR/MR; mild TR/MR (small, narrow, central jet

HIGHLIGHTS

- The valvular consequences of separate transvalvular shock and left bundle area pacing (LBAP) leads remain unclear, and an additional RV lead may further increase the risk of tricuspid regurgitation in the LBAP era.
- Our findings indicate that additional leads, whether pacing/sensing leads or implantable cardioverter defibrillator, do not significantly worsen tricuspid valve function.
- In patients with normal high-voltage IS-1/DF-1 ICD leads, PSL supplementation appears to be a viable alternative, providing comparable right heart functional outcomes to new ICD lead implantation.

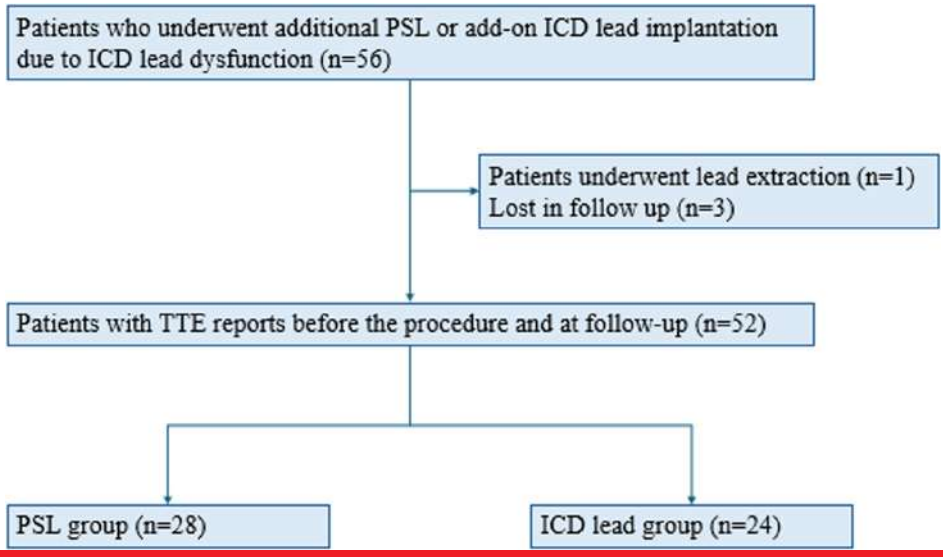


Figure 1. Patient inclusion flowchart for the study.

area; vena contracta < 3 mm); moderate TR/MR (moderate central jet area; vena contracta 3-7 mm); severe TR/MR (large central jet or jet compressing the eccentric wall of variable size; vena contracta > 7 mm). The transtricuspid pressure gradient was measured by continuous wave Doppler of the regurgitant tricuspid jet in the apical 4-chamber view. The right ventricular systolic pressure was calculated as the sum of the maximal transtricuspid pressure gradient and an estimate of the right atrial pressure based on inferior vena cava dimension and collapsibility.

The echocardiographic imaging and analysis, as well as the follow-up, were performed by cardiology residents, specialists, and professors.

Clinical Follow-Up and Data Collection

All patients underwent predetermined clinical follow-up: after echocardiographic evaluation before and after the procedure, routine annual follow-up was planned unless the clinical condition required more frequent visits. Echocardiographic reports of the patients were retrospectively reviewed. The echocardiographic evaluations of the patients before and after the procedure were analyzed.

Statistical Analysis

A Statistical Package for Social Sciences (SPSS Inc., Chicago, IL) version 26 was used for statistical analysis. The normal distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Categorical variables are expressed as frequencies (%). Differences between categorical variables were analyzed using the χ^2 test with Yates continuity correction or the Fisher's exact test, as appropriate. Continuous variables were presented as means ± SD for normally distributed data and compared using the Student's t-test, while non-normally distributed data were expressed as medians and interquartile ranges (IQR) and compared using the Mann–Whitney *U*-test. The Wilcoxon signed-rank test was used for the comparison of paired non-normally distributed continuous variables. A *P*-value of <.05 was considered statistically significant. The marginal homogeneity test was applied to compare the degree of TR before and after the lead implantation procedure.

RESULTS

Patient Characteristics

A total of 52 patients were included in the study. A new pace sense lead was implanted in 28 patients, and a new ICD lead was implanted in 24 patients. Most of the patients in both groups were male. The median echocardiographic follow-up time (months) after intervention was similar in PSL and ICD groups (respectively; 14 (IQR: 28) vs. ICD group: 13.5 (IQR: 17) $P = .92$). There was no significant difference between groups regarding types; other basic features and baseline echocardiographic parameters are listed in Table 1. Information regarding implanted patients is also provided in Table 1. No statistically significant difference was found between the degree of tricuspid valve regurgitation and the diameter of the tricuspid regurgitant jet in the vena contracta before the procedure (respectively; $P = .055$ and $P = .613$). Patients' right heart function and systolic pulmonary artery pressures obtained by echocardiography were also similar.

Post-procedure echocardiographic and electrical parameters of patients are presented in Table 2. There was no significant difference in ejection fraction between groups after the procedure. No differences were detected between the groups in terms of mitral regurgitation grades and mitral valve regurgitant jet vena contracta diameter. Similarly, tricuspid valve regurgitation grade and tricuspid valve regurgitant jet vena contracta diameter were similar between the 2 groups after the procedure. No differences were detected between the groups in the other echocardiographic findings evaluated in patients. Median R wave at the end of the procedure was similar between the 2 groups (10 (IQR: 9.0), 14 (IQR: 12.0), $P = .194$). Median pacing impedances and shock impedances were also similar.

Baseline and post-implantation echocardiographic parameters are summarized in Table 3. In the PSL group, there were

Table 1. Baseline Demographic and Echocardiographic Characteristics

		Total n (%)	PSL Group n = 28 (%)	ICD Lead Group n = 24 (%)	*P*
Etiology	Ischemic	32	18 (64.3)	14 (58.3)	.87[a]
	Non-ischemic	20	10 (35.7)	10 (41.7)	
Sex	Female	10 (19.2)	5 (17.9)	5 (20.8)	1.00 [b]
	Male	42 (80.8)	23 (82.1)	19 (79.2)	
Age (years)		62.8 ± 11.7	65.5 ± 11.4	59.79 ± 11.4	.08[c]
ICD type					.32[b]
VR-ICD		20 (38.5)	10 (35.7)	10 (41.7)	
DR- ICD		14 (26.9)	6 (21.4)	8 (33.3)	
BIV-ICD		18 (34.6)	12 (42.9)	6 (25.0)	
CRT upgrade		1	1	0	
Primary prophylaxis		38 (73.1)	24 (85.7)	14 (58.3)	.057[a]
Secondary prophylaxis		14 (26.9)	4 (14.3)	10 (41.7)	
Follow-up duration, -months		48 (IQR: 24)	48 (IQR: 24)	48 (IQR: 34)	.87[d]
Follow-up echocardiography time after procedure (month)		14 (IQR: 18)	14 (IQR: 28)	13.5 (IQR: 17)	.92[d]
Indication for lead revision					
Impedance rise/pacing threshold rise/R wave decrease		37 (72.5)	18 (66.7)	19 (79.2)	
Oversensing		28 (53.8)	15 (53.6)	13 (54.2)	
Implanted leads					
Pacing/sensing leads					
Medtronic 5076			18 (64.2)	–	
Boston scientific INGEVITY			5 (17.8)	–	
Biotronik solia S60			3 (10.7)	–	
SJM tendril			2 (7.1)	–	
Defibrillation leads					
Medtronic 6947			–	16 (66.6)	
Boston scientific endotak			–	7 (29.1)	
SJM durata			–	1 (4.1)	
Ejection fraction (%)		35 (IQR: 5)	35 (IQR: 6)	30 (IQR: 5)	.68[d]
Baseline MR					.971[b]
None		3 (5.8)	2 (7.1)	1 (4.1)	
Mild (VC < 3.0 mm)		17 (32.7)	8 (28.6)	9 (37.5)	
Moderate (VC = 3.0-6.9 mm)		23 (44.2)	13 (46.4)	10 (41.6)	
Severe (VC ≥ 7.0 mm)		9 (17.3)	5 (17.8)	4 (16.6)	
Vena contracta of MR (mm)		3.50 (IQR: 2.25)	3.50 (IQR: 2.25)	3.55 (IQR: 2.5)	.84[d]
Baseline TR					.055[b]
None		3 (5.8)	0 (0)	3 (12.5)	
Mild (VC < 3.0 mm)		28 (57.7)	15 (53.6)	15 (62.5)	
Moderate (VC = 3.0-6.9 mm)		18 (30.8)	11 (39.3)	5 (20.8)	
Severe (VC ≥ 7.0 mm)		3 (5.8)	2 (7.1)	1 (4.2)	
Vena contracta of TR (mm)		2.55 (IQR: 2.65)	2.55 (IQR: 2.85)	2.55 (IQR: 1.88)	.613[d]
Pre-implantation sPAP (mmHg)		38 (IQR: 15)	38 (IQR: 15)	37.5 (IQR: 12)	.10[d]
TR vmax (m/sec)		3.18 (IQR: 1.1)	3.20 (IQR: 1.2)	3.15 (IQR: 1.0)	.14[d]
TAPSE (mm)		20 (IQR: 4)	20.0 (IQR: 4)	20.5 (IQR: 5)	.87[d]
TAPSE/sPAP		0.47 (IQR: 0.08)	0.45 (IQR: 0.09)	0.50 (IQR: 0.08)	.68[d]

[a]Yates Continuity Correction chi-square test; [b]Exact test; [c]Student *T*-Test; [d]Mann–Whitney *U*-test.TAPSE, Tricuspid Annular Plane Systolic Excursion

no statistically significant changes in vena contracta of mitral regurgitation (3.50 [IQR 2.25] vs. 3.50 [IQR 2.25], *P* = .21) or TR (2.55 [IQR 2.85] vs. 2.55 [IQR 2.15], *P* = .42). Similarly, no significant differences were observed in sPAP (38 [IQR 15] vs. 40 [IQR 15], *P* = .27), TR Vmax (3.20 [IQR 1.20] vs. 3.31 [IQR 1.20], *P* = .48), or TAPSE (20.0 [IQR 4] vs. 20.1 [IQR 4], *P* = .87) after implantation. In the ICD lead group, vena contracta of mitral regurgitation remained unchanged after implantation

Table 2. Post-procedural Echocardiographic and Electrical Parameters of Patients

	Total n (%)	PSL Group n = 28 (%)	ICD Lead Group n = 24 (%)	*P*
Ejection fraction (%)	35 (IQR: 7.5)	35 (IQR: 7.5)	30.0 (IQR: 5)	.68[c]
Follow-up MR				.581[b]
None	4 (7.6)	3 (10.7)	1 (4.1)	
Mild (VC < 3.0 mm)	15 (28.8)	7 (25.0)	10 (41.6)	
Moderate (VC = 3.0-6.9 mm)	24 (46.1)	13 (46.4)	9 (37.5)	
Severe (VC ≥ 7.0 mm)	9 (17.3)	5 (17.8)	4 (16.6)	
Vena contracta of MR (mm)	3.50 (IQR: 2.25)	3.50 (IQR: 2.25)	3.55 (IQR: 2.5)	.56[c]
Follow-up TR				.324[b]
None	3 (5.8)	0	3 (12.5)	
Mild (VC < 3.0 mm)	26 (50.0)	14 (50.0)	12 (50)	
Moderate (VC = 3.0-6.9 mm)	16 (26.9)	10 (35.7)	6 (250)	
Severe (VC ≥ 7.0 mm)	7 (13.4)	4 (14.2)	3 (12.5)	
Vena contracta of TR (mm)	2.60 (IQR: 2.45)	2.55 (IQR: 2.15)	3.0 (IQR: 2.78)	.202[c]
Post-implantation sPAP (mmHg)	37.5 (IQR: 16.5)	40.0 (IQR: 15)	35.0 (IQR: 15)	.29[c]
TR vmax (m/sec)	3.25 (IQR: 1.2)	3.31 (IQR: 1.2)	3.18 (IQR: 1.2)	.16[c]
TAPSE (mm)	20.0 (IQR:4)	20.1 (IQR: 4)	20.4 (IQR: 4)	.88[c]
TAPSE/sPAP	0.45 (IQR: 0.08)	0.42 (IQR: 0.07)	0.48 (IQR: 0.08)	.42[c]
R wave at the end of the procedure	13.0 (IQR: 11.1)	10 (IQR: 9.0)	14 (IQR: 12.0)	.194[c]
RV coil Shock impedance at the end of the procedure	51 (IQR: 14)	50 (IQR: 21)	52 (IQR: 9.0)	.744[c]
Pacing impedance at the end of the procedure	620 (IQR: 308)	660 (IQR: 224)	565 (IQR: 328)	.307[c]

[a]Yates Continuity Correction Chi-Square Test; [b]Exact test; [c]Mann–Whitney *U*-test.

(3.55 [IQR 2.50] vs. 3.55 [IQR 2.50], *P* = .35). A non-significant increase in TR vena contracta was observed (2.55 [IQR 1.88] vs. 3.00 [IQR 2.78], *P* = .22). No significant changes were detected in sPAP (37.5 [IQR 12] vs. 35 [IQR 15], *P* = .36), TR Vmax (3.15 [IQR 1.00] vs. 3.18 [IQR 1.20], *P* = .62), or TAPSE (20.5 [IQR 5] vs. 20.4 [IQR 4], *P* = .88). Overall, implantation was not associated with statistically significant changes in left- or right-sided echocardiographic functional parameters in either group. Table 4 summarizes changes in the degree of tricuspid and mitral regurgitation in patients. The numbers in the table represent the number of patients. In the 4 patients who received PSL implantation, at least a 1-degree increase in TR grade was observed. In the 6 patients who received a new ICD electrode implantation, at least a 1-degree increase in TR grade was observed. The addition of PSL did not result in a statistically significant change in TR grade (*P* = .180). In the ICD lead group, a trend toward an increase in TR grade was observed; however, this did not reach statistical significance (*P* = .059). The change in TR grade (ΔTR) demonstrated minimal variation in both groups. Median ΔTR grade was 0 (IQR: 0-0.5) in the PSL group and 0 (IQR: 0-0.75) in the ICD lead group. There was no statistically significant difference in ΔTR change between groups (*P* = .123, Mann–Whitney *U*-test). Overall, neither PSL addition nor ICD lead implantation was associated with a statistically significant worsening in TR severity.

During follow-up there were no episodes signaling lead-lead interaction and no patients were diagnosed with venous obstruction or superior vena cava syndrome.

DISCUSSION

The importance of the potential pro-regurgitant effect of an additional transvalvular (RV) lead is probably even more critical in the era of left bundle area pacing (LBAP). Mounting evidence suggests that in selected patients undergoing CRT, favorable clinical outcomes may be achieved via this pacing modality.[9-11] However, the question of potential valvular

Table 3. Pre- and Post-Implantation Echocardiographic Parameters in PSL and ICD Lead Groups

	PSL Group			ICD Lead Group		
Variables	**Pre-implantation**	**Post-implantation**	***P***	**Pre-implantation**	**Post-implantation**	***P***
Vena contracta of MR (mm)	3.50 (2.25)	3.50 (2.25)	.21	3.55 (2.50)	3.55 (2.50)	.35
Vena contracta of TR (mm)	2.55 (2.85)	2.55 (2.15)	.42	2.55 (1.88)	3.00 (2.78)	.22
sPAP (mm Hg)	38 (15)	40 (15)	.27	37.5 (12)	35 (15)	.36
TR Vmax (m/s)	3.20 (1.20)	3.31 (1.20)	.48	3.15 (1.00)	3.18 (1.20)	.62
TAPSE (mm)	20.0 (4)	20.1 (4)	.87	20.5 (5)	20.4 (4)	.88

Wilcoxon signed-rank test.

Table 4. Change in the Degree of Mitral and Tricuspid Regurgitation in Patients

			Mild	Severe	*P*	ΔMR Grade (Post–Pre)	*P*
PSL group n = 28	Pre-implantation MR degree	Post-implantation MR degree					
		None	0	0	.317[a]	0 (IQR: 0.5)	.85[b]
		Mild	7	0			
		Moderate	0	0			
		Severe	0	5			
ICD lead group n = 24		None	0	0	1.00[a]	0 (IQR: 0.0)	
		Mild	8	0			
		Moderate	1	0			
		Severe	0	4			
PSL group n = 28	Pre-implantation TR degree	Post-implantation TR degree					
		None	0	0	.180[a]	0 (IQR: 0.5)	.123[b]
		Mild	13	0			
		Moderate	1	2			
		Severe	0	2			
ICD lead group n = 24		None	0	0	.059[a]	0 (IQR: 0.75)	
		Mild	11	0			
		Moderate	1	2			
		Severe	0	1			

[a]Marginal homogeneity test; [b]Mann–Whitney *U*-test.

dysfunction that may occur due to separate shock and LBAP leads that are both transvalvular is still unanswered. Most (but not all) studies attribute the higher incidence of TR worsening to ICD leads and the presence of multiple transvalvular (RV) leads.[3,7,12-16] In a previously published observational study, De Cock et al[6] investigated the complications of patients with 3 or more leads and suggested that the presence of more than 1 lead in the RV may increase TR. Çeliker et al[15] found no difference in the degree of TR with 1 or 2 lead implantations, whereas Al-Bawardy et al[13] also found no correlation between the number of leads and the worsening of TR.[1,15] In the study, findings suggest that additional leads, whether PSL or ICD, do not significantly worsen tricuspid valve function. When compared with the patient's preoperative echocardiogram, no statistically significant difference was found between the 2 groups in terms of TAPSE, vena contracta diameter, and changes in tricuspid valve insufficiency grade and right heart function in the postoperative echocardiogram. Although no statistically significant difference was observed in TR progression between groups, a borderline *P*-value was noted in the ICD lead group ($P = .059$), suggesting a potential trend toward greater TR worsening in this subgroup. Previous studies have suggested that ICD leads are typically thicker and less flexible than Pacemaker leads (PPM), causing more interference with TV closure or more damage to the valve.[3,7] While Kim et al[7] observed a higher prevalence of TR in patients with ICDs compared to PPMs, Leibowitz et al[14] and Al-Bawardy et al[13] reported no correlation. Patients in the groups were also similar in terms of the type of previously implanted device. Since most patients with ICDs exhibit moderate or severe left ventricular dysfunction and a predisposition to secondary (functional) TR, comparing CIED-related TR may be particularly biased in patients undergoing CRT. The strength of the study is that both PSL and ICD lead groups were compared in a relatively homogeneous population with similar left ventricular function in both groups with previous ICD implantation. It is noteworthy that the groups exhibited comparable characteristics with respect to the potential for a diminution in the evolution of secondary TR, attributable to the anticipated enhancement in left heart function in patients who have undergone implantation of a BIV-ICD.

Limitations of the Study

There was no selection bias in terms of referral of the patients for echocardiographic follow-up. However, simultaneous control echocardiographic measurements were not performed in patients after implantation is one of the limitations of the study. A total of 3 patients were excluded from the study because they did not undergo post-procedure echocardiography, and a further patient was excluded due to lead extraction performed. In order to avoid confounding the study results with tricuspid valve insufficiency due to additional valve trauma that may occur during electrode removal procedures and to evaluate the effect of multiple leads in patients, patients who underwent electrode removal procedures were not included in the study.

Although no statistically significant difference was observed in TR progression between groups, a borderline *P*-value was noted in the ICD lead group. Future prospective studies with larger patient populations and longer follow-up periods are needed to clarify whether ICD lead–associated mechanical interaction with the tricuspid valve contributes to clinically relevant TR progression.

Since the study was a retrospective observational study, the echocardiographic evaluation of the patients did not specifically include the evaluation of TV function. In routine follow-ups in the clinic, the degree of TR is mostly evaluated by measuring the regurgitation of the jet area and vena contracta with color flow imaging. This qualitative and semi-quantitative assessment may be inaccurate compared to quantitative measurements. Furthermore, the presence of an eccentric TR results in the loss of this Doppler-colored flow signal (Coanda effect) and thus underestimation of regurgitation. A prospective study including quantitative measurements such as proximal isovelocity surface area method and volumetric methods and examination of the hepatic vein flow model will provide a more objective view. 3D echocardiography may provide information on the mechanism by better characterizing the interaction between the lead and the valve or valve apparatus. The study is not mainly aimed at explaining the mechanism but provides an idea about the effect of increasing lead number and lead type on tricuspid valve function in a relatively homogeneous population.

CONCLUSION

This study provides the first comparative analysis of PSL versus ICD lead addition in patients with lead failure. The findings suggest that additional leads, whether PSL or ICD, do not significantly worsen tricuspid valve function.

Ethics Committee Approval: This study was approved by the Ethics Committee of Ankara University Faculty of Medicine (Approval date: 05/05/2025, decision number: İ04-358-25).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.K.G., E.B.; Design - E.B., B.K.G.; Resources: A.T.A., Ö.A., İ.D., E.B.; Data Collection and Processing - B.K.G., E.B.; Analyses and Interpretation - B.K.G., Literature Search - B.K.G., E.B.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

Video 1: Post-implantation fluoroscopic recordings of patients with PSL.

Video 2: Post-implantation fluoroscopic recordings of patients with ICD lead addition.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Residual Cholesterol Inflammatory Index: A Predictor of Cardiovascular–Kidney–Metabolic Syndrome; Insights from NHANES and CHARLS Cohorts

ABSTRACT

Background: Cardiovascular–kidney–metabolic syndrome (CKM) is a multi-organ metabolic disorder with an increased risk of morbidity and mortality among populations worldwide. Identifying effective biomarkers for early risk assessment is important. The residual cholesterol (RC) inflammatory index (RCII), which is derived from the combination of RC and C-reactive protein (CRP), represents a novel biomarker that captures the interplay between dyslipidemia and systemic inflammation. The interaction between RCII and CKM risk in the general populations of the US and China and evaluated its dose-response pattern, nonlinear relationship, and subgroup variations were evaluated.

Methods: Data were retrieved by accessing 2 nationally representative cohorts: the US National Health and Nutrition Examination Survey (NHANES, n = 10,669) and the China Health and Retirement Longitudinal Study (CHARLS, n = 9,496). Multivariate logistic regression models (Model 1-3) were constructed to determine the relationship between RCII (as a continuous and quartile-categorized variable) and CKM. Progressive adjustments were made for demographic, socioeconomic, lifestyle, and anthropometric factors. In addition, a restricted cubic spline (RCS) analysis was conducted to examine nonlinearity and stratified analyses to assess effect modification across subgroups.

Results: Increased RCII was significantly linked with increased CKM risk in both models. In fully adjusted models, each 1-unit increment in RCII was associated with a 4% increase in CKM risk in NHANES (odds ratio (OR) = 1.04, 95% CI: 1.03-1.06, $P < .001$) and a 3% increase in CHARLS (OR = 1.03, 95% CI: 1.02-1.05, $P < .001$). Quartile analysis revealed a strong dose-response pattern. In CHARLS, individuals in the highest quartile (Q4) exhibited a 9.60-fold higher CKM risk compared with that in Q1 (95% CI: 7.83-11.80). RCS models confirmed a nonlinear, upward-sloping relationship between RCII and CKM risk in both datasets. Subgroup analysis revealed robust associations across most strata, with a significant interaction by race in NHANES and by hypertension, diabetes, stroke, and smoking status in CHARLS.

Conclusion: RCII exhibited an independent and positive association with CKM risk in the US and Chinese populations, with consistent dose-response and nonlinear trends. This index may be a practical and integrative biomarker for identifying individuals with an increased CKM risk, particularly during the early stages of metabolic dysregulation. Prospective studies are warranted to validate their predictive performance and establish clinically relevant thresholds for risk stratification.

Keywords: CHARLS, CKM, inflammation index, inflammation interaction, lipid, NHANES, residual cholesterol, restricted cubic spline

INTRODUCTION

Cardiovascular–kidney–metabolic syndrome (CKM) caused several physiological actions including adiposity, type 2 diabetes mellitus, cardiovascular impairment, and chronic kidney complications.[1,2] These pathophysiological changes are interconnected through metabolic abnormalities that trigger the cascade of dyslipidemia and inflammatory responses for individuals by damaging the endothelial cells, which ultimately cause the blockage that induces atherosclerosis, plaque

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Received: April 29, 2026
Accepted: May 14, 2026
Available Online Date: July 7, 2026

Cite this article as: Zhang M, Huang L, Zhang T, *et al*. Residual cholesterol inflammatory index: A predictor of cardiovascular–kidney–metabolic syndrome; insights from NHANES and CHARLS cohorts. *Anatol J Cardiol*. 2026;30(12):890-900.

DOI: 10.14744/AnatolJCardiol.2026.6609

formation, and cardiovascular dysfunctions. The inflammatory response-related 2 biomarkers have been reported in the literature for the evaluation of CKM: one works on the basis of Systemic Inflammation Response Index (SIRI)[3] and the second works by recording chronic low-grade inflammation, particularly effective for patients suffering from T2DM and CKM.[4]

Residual cholesterol (RC) is basically the cholesterol ester in the form of triglycerides which, upon lipolysis, is converted to low-density lipoproteins and glycerin derivatives.

Residual cholesterol due to its triglyceride content has dominant arterial wall accumulation efficacy, which triggers cardiovascular risk, plaque development, and atherosclerosis related complications.[5,6] During the progression of atherosclerosis, the role of RC is pronounced. It penetrates the arterial intima and binds to the extracellular matrix to promote smooth muscle cell proliferation and macrophage activation, which accelerates atherogenesis.[7] Once infiltrated into the arterial wall, RC accumulates within the intima, inducing endothelial dysfunction, vascular inflammation, and cholesterol deposition.

Systemic inflammation is a key mechanism underlying multiple chronic disorders that affect the cardiovascular, renal, and metabolic systems. This process is important in atherosclerosis initiation and progression, which is a chronic, progressive vascular inflammatory condition defined by lipid deposition, plaque formation, endothelial dysfunction, and aberrant immune activation.[8] Endothelial inflammatory responses are particularly important to this process and are typified by increased levels of C-reactive protein (CRP), a pro-inflammatory cytokine.[9] These mediators exacerbate endothelial malfunction, atherosclerosis, and vascular stiffness, which promote the progression of hypertension (HTN), chronic kidney disease (CKD), insulin resistance, and heart failure. As an acute-phase reactant, CRP is a marker of inflammation and an independent cardiovascular disease (CVD) risk factor. C-reactive protein is involved in multiple stages of atherogenesis, from leukocyte recruitment to the rupture of unstable plaques.[10] CKD patients frequently exhibit systemic and vascular inflammation, which is closely associated with increased levels of CRP and other inflammatory cytokines.

The conventional methods for the lipid profile assessment primarily focused on low-density lipoprotein. This approach may overlook the residual risk factors from the RC level, which can implement considerable cardiovascular and renal risk.[11]

The RC-Inflammation Index (RCII), which is derived from RC and CRP levels, has not been extensively examined relative to CKM. Data from the US National Health and Nutrition Examination Survey (NHANES, 1999-2010) and the China Health and Retirement Longitudinal Study (CHARLS, 2011-2012) were used to determine the interaction between RCII and CKM. The results highlight the effect of RC and inflammation on CKM development and support the potential RCII value as a novel indicator for CKM risk assessment.

HIGHLIGHTS

- Early and precise detection of cardiovascular–kidney–metabolic syndrome (CKM) is highly desirable.
- Small molecule–based biomarkers help in the early diagnosis and reduce the mortality risk.
- The present study focused on scrutinizing the utility of the residual cholesterol inflammatory index (RCII) as a potential biomarker for cardiorenal-metabolic risk determination.
- The relationship between RCII and CKM risk was determined through multivariate logistic regression models, with RCII analyzed as a continuous variable and across quartile categories.
- The results illustrated the consistent alignment between higher RCII levels and enhanced risk of CKM in both cohorts.

METHODS

Study Design

This study used data from 2 nationally representative datasets: the China CHARLS and the US NHANES. Baseline data were obtained from the 2011-2012 cycle of CHARLS, a longitudinal survey of middle-aged and older adults in China.[12] NHANES data were pooled across 10 cycles (1999-2010), which consisted of biennial cross-sectional surveys of the noninstitutionalized civilian population in the US, conducted using a stratified multistage probability sampling design.

Both surveys collected comprehensive observations on the population characteristics, physiological conditions, medication use, and laboratory test results. National Health and Nutrition Examination Survey and CHARLS received ethical approval from their respective review boards, with NHANES authorized by the National Center for Health Statistics (NCHS) Ethics Review Board. Appropriate sampling weights were applied to ensure that the estimates could be generalized to the national populations of each country. The study was conducted in accordance with the Declaration of Helsinki.

Flowcharts for participant selection are presented in Figures 1 and 2.

CKM Definition

A universally accepted CKM diagnostic criterion has not been established. In the present study, CKM represented the coexistence of cardiometabolic syndrome (CMS) and CKD.[13,14] The CMS diagnostic criteria relied upon the NCEP-ATP III guidelines.[15] A CMS diagnosis was established when 3 or more of the following criteria were met:

1. Central obesity: Waist circumference (WC) of at least 102 cm for men and 88 cm for women
2. Hypertriglyceridemia: Serum triglycerides (TG) $\geq$ 150 mg/dL
3. Low high-density lipoprotein (HDL): HDL $<$ 40 mg/dL in men or $<$ 50 mg/dL in women

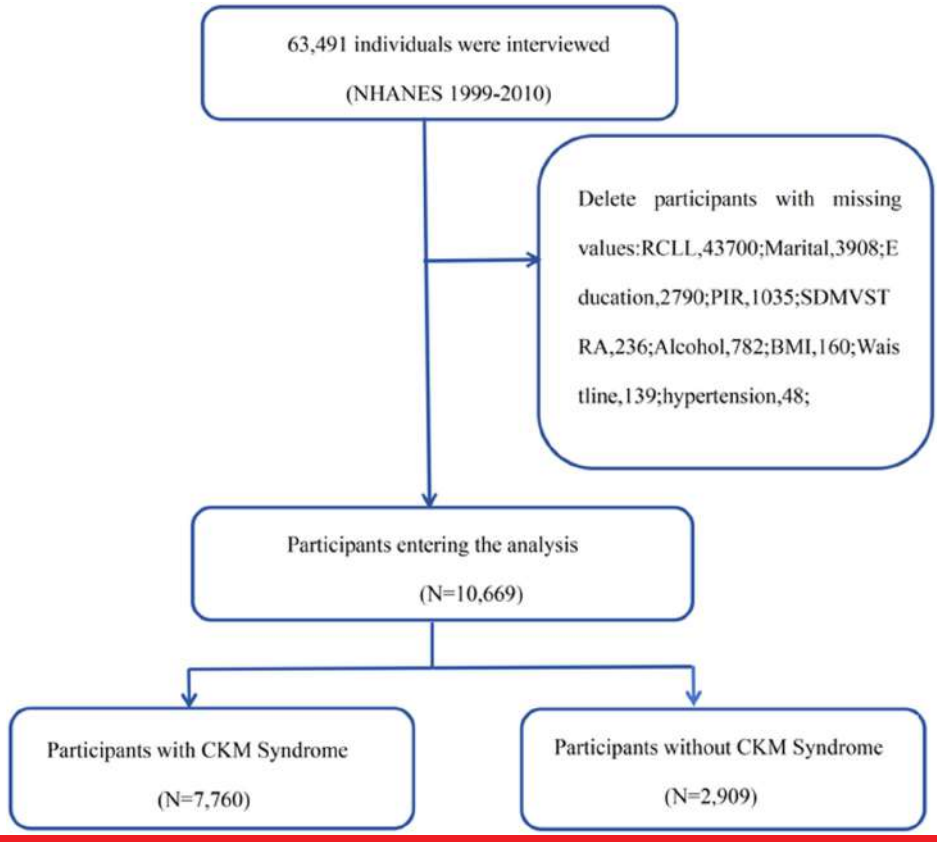


Figure 1. Screening process in the National Health and Nutrition Examination Survey (NHANES).

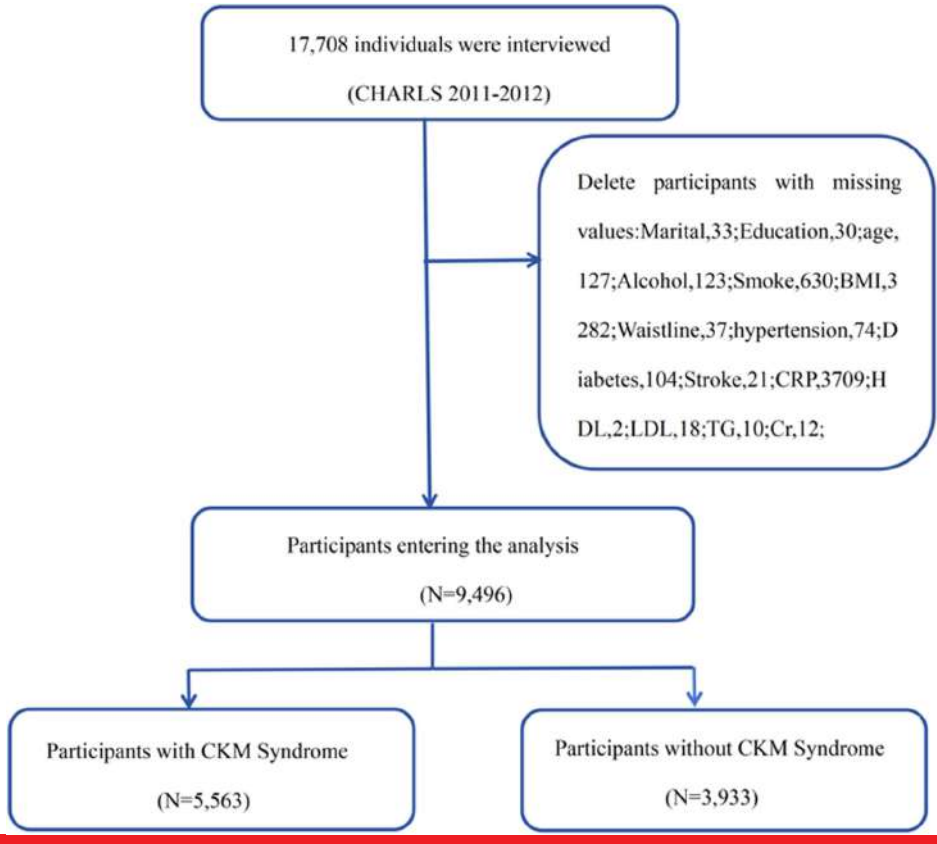


Figure 2. Screening flow of respondents in the China Health and Retirement Longitudinal Study (CHARLS).

4. Elevated blood pressure: Systolic pressure ≥ 130 mm Hg, diastolic pressure ≥ 85 mm Hg, or using antihypertensive medication
5. Hyperglycemia: Fasting plasma glucose (FPG) ≥ 100 mg/dL or currently using antidiabetic medication

Anthropometric measurements (WC, weight, and height) were obtained using standardized protocols and blood pressure measurement was done on the average of 4 measurements. Certified laboratories measured serum TG and HDL levels, as well as plasma FPG levels. CKD was defined by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 or a urine albumin-creatinine ratio of >30 mg/g.[16,17] The eGFR calculation was done using the CKD-EPI 2009 creatinine (Cr) equation.[18,19] Individuals with CKM stage ≥ 2 were classified as having CKM, based on previous evidence indicating that stage ≥ 2 is associated with more pronounced metabolic disturbances and greater cardiorenal risk.[20,21]

RC and RCII Calculation

RC (mg/dL) was determined by subtracting HDL and low density lipoprotein (LDL) sum from total cholesterol (TC). For the CHARLS cohort, based on the study by Chen et al[22] RCII was calculated as:

RCII = (RC × hsCRP [mg/L])/10

In the NHANES cohort, because CRP was measured in mg/dL rather than hsCRP in mg/L, the formula was:

RCII = RC × CRP [mg/dL]

Statistical Analysis

This study used data from NHANES and CHARLS. Initial descriptive analyses were conducted to summarize the baseline attributes of the study participants. Group differences were assessed using a chi-square test for categorical variables and an independent-sample *t*-test for continuous variables. Regression, subgroup, and restricted cubic spline (RCS) analyses were performed to determine the associations of interest, with the results displayed in forest plots. Three regression models with increasing adjustments were established: Model 1 was unadjusted; Model 2 included adjustments for race, marital status, educational level, sex, and age; and Model 3 incorporated subsequent adjustments for behavioral functions including nicotine addiction status, ethanol intake, poverty income ratio (PIR), and body mass index (BMI). Statistical analyses were conducted using R software (v4.5.1), with a 2-sided $P < .05$ indicating significance.

RESULTS

Baseline Characteristics

Baseline characteristics of participants from NHANES and CHARLS were stratified by the presence or absence of CKM (Tables 1 and 2). In the NHANES cohort (n = 10,669), participants with CKM were older (50.35 vs. 37.58 yr, $P < .001$), more likely to be male (52% vs. 41%, $P < .001$), displayed lower education (≥high school: 24% vs. 33%, $P < .001$), higher smoking prevalence (51% vs. 44%, $P < .001$), and lower alcohol consumption (73% vs. 79%, $P < .001$). Clinically, they exhibited significantly higher BMI, WC, blood pressure, FBG, uric acid (UA), Cr, TG, and CRP levels, along with decreased HDL levels (all $P < .001$). Interestingly, the CKM group (RC: 29.98 vs. 16.43 mg/dL, RCII: 14.55 vs. 4.91; $P < .001$) was found to exhibit the higher level of RC and RCII. Cardiovascular–kidney–metabolic participants were older (61.15 vs. 56.57 years, $P < .001$), with lower alcohol consumption rates (30% vs. 36%, $P < .001$) and tobacco use (27% vs. 31%, $P = .004$). They also exhibited significantly higher WC, CRP, TG, UA, and RCII values (all $P < .001$).

Interaction Between RCII and CKM

Three logistic regression models were constructed to evaluate the RCII–CKM association in both cohorts:

Model 1: Unadjusted

Model 2: Adjusted for demographic variables

NHANES: age, sex, race, education level, marital status

CHARLS: age, sex, education level, marital status

Model 3: Additionally adjusted for socioeconomic and lifestyle variables

NHANES: Model 2 + PIR, smoking, alcohol use, and BMI

CHARLS: Model 2 + smoking, alcohol use, and BMI

NHANES Findings (Table 3)

RCII showed a significant association with CKM. As a continuous variable, each 1-unit increment in RCII was associated with a 4% increase in CKM risk (Model 3: OR = 1.04, 95% CI: 1.03-1.06, $P < .001$). In a quartile-based analysis, unlike Q1, the OR for CKM in Q2, Q3, and Q4 were 0.55 (0.39-0.71), 1.00 (0.86-1.20), and 1.80 (1.60-2.00), respectively (P for trend < 0.001), indicating a nonlinear dose-response relationship.

CHARLS Findings (Table 4)

There were similar associations in the CHARLS data. Each 1-unit increment in RCII was related to a 3% escalation in CKM risk (Model 3: OR = 1.03, 95% CI: 1.02-1.05, $P < .001$). Unlike Q1, the ORs in Q2-4 were 2.26 (1.91-2.67), 5.08 (4.18-6.18), and 9.60 (7.83-11.80), respectively (P for trend < .001), which indicates a strong and consistent dose-response effect across increasing RCII levels.

Subgroup Analysis and Interaction Effects

Subgroup analyses (Figures 3 and 4) were done to determine whether the interaction between RCII and CKM varied across demographic and clinical subpopulations. For NHANES, the positive association remained robust across sex, age groups, BMI categories, nicotine intake level, ethanol intake, HTN, and diabetes mellitus (DM) subgroups. No notable interaction was evident in these strata (all interaction $P > .05$), suggesting consistent effects across the populations. The only significant heterogeneity was observed in race/ethnicity (interaction $P = .000$). This association was significant among Mexican Americans, Non-Hispanic Whites/Blacks, and multi-racial participants (OR range: 1.02-1.07), but not among other Hispanics (OR = 1.01).

For CHARLS, no prominent interaction was found across sex, education, or alcohol consumption (interaction $P > .05$); however, significant heterogeneity was detected in subgroups of HTN ($P = .000$), DM ($P = .000$), stroke ($P = .002$), and smoking

Table 1. Baseline Attributes of NHANES Participants Categorized by Their Cardiovascular–kidney–metabolic Syndrome (CKM) Status

Characteristic	n	Overall (%)	Non-CKM (%)	CKM (%)	*P*
Age (years)	10 669	46.18 ± (16.39)	37.58 ± (12.64)	50.35 ± (16.38)	<.001
Sex, n (%)	10 669				<.001
Male		5,171 ± (48)	1,212 ± (41)	3,959 ± (52)	
Female		5,498 ± (52)	1,697 ± (59)	3,801 ± (48)	
PIR	10 669	3.10 ± (1.61)	3.20 ± (1.60)	3.04 ± (1.61)	<.001
Race, n (%)	10 669				.11
Mexican American		2,155 ± (7.6)	602 ± (8.4)	1,553 ± (7.2)	
Other Hispanic		607 ± (3.9)	179 ± (4.4)	428 ± (3.6)	
Non-Hispanic White		5,588 ± (74)	1,480 ± (73)	4,108 ± (74)	
Non-Hispanic Black		1,907 ± (10.0)	539 ± (10)	1,368 ± (9.9)	
Other Race - Including Multi-Racial		412 ± (5.0)	109 ± (4.5)	303 ± (5.3)	
Marital Status, n (%)	10 669				<.001
Married		6,002 ± (60)	1,521 ± (56)	4,481 ± (61)	
Widowed		920 ± (5.3)	44 ± (1.0)	876 ± (7.4)	
Divorced		1,055 ± (9.6)	245 ± (8.5)	810 ± (10)	
Separated		312 ± (2.4)	77 ± (2.1)	235 ± (2.5)	
Never married		1,594 ± (16)	740 ± (23)	854 ± (12)	
Living with a partner		786 ± (7.5)	282 ± (8.8)	504 ± (6.8)	
Education level, n (%)	10 669				<.001
<9th grade		1,342 ± (6.0)	206 ± (3.5)	1,136 ± (7.1)	
9th–11th grade (Includes 12th grade with no diploma)		1,676 ± (12)	410 ± (10)	1,266 ± (13)	
High school graduate/GED or equivalent		2,519 ± (25)	617 ± (22)	1,902 ± (27)	
Some college or AA degree		2,925 ± (30)	909 ± (32)	2,016 ± (30)	
College graduate or above		2,197 ± (27)	766 ± (33)	1,431 ± (24)	
Alcohol, n (%)	10 669				<.001
Yes		7,523 ± (75)	2,176 ± (79)	5,347 ± (73)	
No		3,146 ± (25)	733 ± (21)	2,413 ± (27)	
Smoke, n (%)	10 669				<.001
Yes		5,151 ± (49)	1,217 ± (44)	3,934 ± (51)	
No		5,518 ± (51)	1,692 ± (56)	3,826 ± (49)	
BMI, kg/m^2	10 669	28.35 ± (6.38)	25.62 ± (5.00)	29.68 ± (6.56)	<.001
WC, cm	10 669	97.37 ± (15.91)	88.84 ± (12.80)	101.51 ± (15.63)	<.001
HTN, n (%)	10 669				<.001
Yes		3,589 ± (29)	0 ± (0)	3,589 ± (44)	
No		7,068 ± (70)	2,906 ± (100)	4,162 ± (56)	
DM, n (%)	10 669				<.001
Yes		1,025 ± (6.7)	0 ± (0)	1,025 ± (10.0)	
No		9,470 ± (92)	2,892 ± (99)	6,578 ± (88)	
Borderline		168 ± (1.4)	16 ± (0.6)	152 ± (1.8)	
Stroke, n (%)	10 669				<.001
Yes		358 ± (2.4)	0 ± (0)	358 ± (3.6)	
No		10,298 ± (97)	2,909 ± (100)	7,389 ± (96)	
CRP, mg/dL	10 669	4.15 ± (8.34)	2.79 ± (6.26)	4.82 ± (9.11)	<.001
HDL, mg/dL	10 669	53.79 ± (15.59)	58.47 ± (14.80)	51.51 ± (15.45)	<.001
TC, mg/dL	10 669	197.52 ± (39.73)	186.74 ± (35.20)	202.76 ± (40.74)	<.001
LDL, mg/dL	10 669	118.19 ± (35.13)	111.84 ± (32.02)	121.28 ± (36.14)	<.001
TG, mg/dL	10 669	127.74 ± (67.50)	82.16 ± (25.63)	149.90 ± (70.36)	<.001
RCII	10 669	11.39 ± (24.66)	4.91 ± (12.22)	14.55 ± (28.30)	<.001
RC	10 669	25.55 ± (13.50)	16.43 ± (5.13)	29.98 ± (14.08)	<.001
UA, mg/dL	10 669	5.44 ± (1.39)	4.90 ± (1.22)	5.71 ± (1.39)	<.001
Cr, μmol/L	10 669	0.87 ± (0.34)	0.82 ± (0.17)	0.90 ± (0.39)	<.001

Continuous data: Mean ± SE; weighted *T*-test-calculated *P*-values. Categorical data: n (%); weighted chi-square test-calculated *P*-value.
BMI, body mass index; CKM, cardiovascular–kidney–metabolic syndrome; Cr, Creatinine; CRP, C-reactive protein; DM, diabetes mellitus; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; Model 1, No adjustment; Model 2, Adjusted for age, sex, race, education level, and marital status; Model 3, Further adjusted for PIR, smoking status, alcohol consumption, and BMI; PIR, poverty income ratio; RC, remnant cholesterol; RCII, residual cholesterol inflammatory index.

Table 2. Baseline Attributes of CHARLS Participants Categorized by CKM Status

Characteristic	n	Overall (%)	Non-CKM (%)	CKM (%)	*P*
Age (years)	9 496	59.27 ± (10.04)	56.57 ± (9.18)	61.15 ± (10.19)	<.001
Sex, n (%)	9 496				.131
Male		5 157 ± (55)	2 096 ± (54)	3 061 ± (55)	
Female		4 339 ± (45)	1 837 ± (46)	2 502 ± (45)	
Marital Status, n (%)	9 496				<.001
Married		1161 ± (14)	382 ± (9.9)	779 ± (16)	
Unmarried		8 335 ± (86)	3 551 ± (90)	4,784 ± (84)	
Education level, n (%)	9 496				.082
Illiteracy		4 581 ± (46)	1 871 ± (46)	2 710 ± (47)	
Completed primary education		2 100 ± (22)	851 ± (21)	1 249 ± (23)	
Middle school		1 902 ± (21)	827 ± (23)	1 075 ± (20)	
High school and above		913 ± (10)	384 ± (10)	529 ± (10)	
Drinking	9 496	3 063 ± (32)	1 401 ± (36)	1 662 ± (30)	<.001
Smoking	9 496	2 830 ± (29)	1 249 ± (31)	1 581 ± (27)	.004
BMI, kg/m^2	9 496	24.69 ± (45.62)	24.80 ± (69.99)	24.61 ± (10.91)	<.001
WC, cm	9 496	84.43 ± (12.73)	80.53 ± (11.92)	87.14 ± (12.57)	<.001
HTN, n (%)	9 496				<.001
No		6 998 ± (73)	3,933 ± (100)	3,065 ± (55)	
Yes		2 498 ± (27)	0 ± (0)	2,498 ± (45)	
DM, n (%)	9 496				<.001
No		8 911 ± (94)	3,933 ± (100)	4,978 ± (89)	
Yes		585 ± (6.3)	0 ± (0)	585 ± (11)	
Stroke, n (%)	9 496				<.001
No		9,254 ± (97)	3,933 ± (100)	5,321 ± (95)	
Yes		242 ± (2.7)	0 ± (0)	242 ± (4.7)	
CRP, mg/L	9 496	2.73 ± (7.48)	2.35 ± (7.61)	3.00 ± (7.38)	<.001
HDL, mg/dL	9 496	50.49 ± (15.04)	55.75 ± (14.17)	46.82 ± (14.54)	<.001
LDL, mg/dL	9 496	115.74 ± (34.71)	114.80 ± (31.39)	116.40 ± (36.83)	.129
TC, m/dL	9 496	132.17 ± (94.61)	87.78 ± (28.93)	163.10 ± (110.80)	<.001
RCII	9 496	7.61 ± (43.50)	3.74 ± (14.34)	10.31 ± (55.23)	<.001
RC	9 496	26.06 ± (24.48)	15.63 ± (9.46)	33.34 ± (28.74)	<.001
UA, mg/dL	9 496	4.51 ± (1.30)	4.20 ± (1.12)	4.73 ± (1.37)	<.001
Cr, μmol/L	9 496	0.79 ± (0.25)	0.75 ± (0.18)	0.82 ± (0.28)	<.001

(*P* = .030). In individuals without these comorbidities, RCII exhibited a positive association with CKM (OR range: 1.01-1.04), whereas the association was attenuated or became nonsignificant in those with existing metabolic or vascular disease (OR ≈ 1.00).

Taken together, the predictive RCII value may be more pronounced in metabolically "at-risk but not yet overtly diseased" individuals, underscoring the importance of considering clinical context and population heterogeneity in risk interpretation.

Table 3. Multivariate Logistic Regression Analysis of the RCII–CKM Relationship in the NHANES Cohort

	Models					
	1		2		3	
Characteristic	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Continuous RCII	0.07 (0.05, 0.08)	<.001	1.07 (1.05, 1.09)	<.001	1.04 (1.03, 1.06)	<.001
RCII-Q1	Ref		Ref		Ref	
RCII-Q2	0.97 (0.82, 1.1)	<.001	0.74 (0.58, 0.90)	<.001	0.55 (0.39, 0.71)	<.001
RCII-Q3	1.5 (1.4, 1.7)	<.001	1.4 (1.2, 1.5)	<.001	1.0 (0.86, 1.2)	<.001
RCII-Q4	2.4 (2.2, 2.5)	<.001	2.4 (2.2, 2.6)	<.001	1.8 (1.6, 2.0)	<.001
P for trend		<.001		<.001		<.001

Table 4. Multivariate Logistic Regression Analysis of RCII–CKM Relationship in the CHARLS Cohort

	Models					
	1		2		3	
Characteristic	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Continuous RCII	1.05 (1.03, 1.06)	<.001	1.04 (1.03, 1.06)	<.001	1.03 (1.02, 1.05)	<.001
RCII-Q1	Ref		Ref		Ref	
RCII-Q2	1.95 (1.69, 2.25)	<.001	1.93 (1.68, 2.23)	<.001	2.26 (1.91, 2.67)	<.001
RCII-Q3	4.35 (3.70, 5.12)	<.001	4.24 (3.63, 4.96)	<.001	5.08 (4.18, 6.18)	<.001
RCII-Q4	8.40 (6.97, 10.1)	<.001	8.19 (6.83, 9.81)	<.001	9.60 (7.83, 11.8)	<.001
P for trend		<.001		<.001		<.001

Nonlinear Association: RCS Analysis

The RCS models have been demonstrated Figure 5 and 6 which displayed the non-linear relationship between the RCII and CKM values obtained from both cohorts. The graphical curves showed the progressive increment in the CKM risk factor at low levels of RCII, followed by a steeper rise at higher RCII values without any noticeable plateau or inflection point. These results exhibited the continuous and accelerating risk elevations which support the biomarker capability of RCII for CKM risk sensation.

Summary

The present investigation focused on the link assessment between RCII and CKM utilizing 2 extensive nationally representative cohorts. The results indicate that RCII independently contributes to CKM risk and shows a significant dose-response correlation. Furthermore, the consistent association across various population subgroups indicates the potential of RCII as a novel inflammatory biomarker for cardiorenal-metabolic risk stratification.

Table 1-4 & Figure 3-6.

DISCUSSION

In the present study, 2 extensive, nationally representative population databases, China's CHARLS and the US NHANES, were analyzed enabling the first systematic assessment of the relationship between RCII and CKM. The results were consistent across both cohorts and indicated that increased RCII levels markedly increased the risk of CKM. Overall, RCII may be a sensitive and universal marker for assessing multisystem metabolic impairment.

The present revealed several important findings. First, previous studies on RCII primarily focused on predicting cardiovascular event risk. Residual cholesterol is an independent risk factor for CVD and correlates with systemic inflammation. For instance, in the EPIC-Norfolk study, each 1 mmol/L increment in RC corresponded to a 29.5% increase in hsCRP levels, underscoring the strong linkage between RC and systemic inflammation.[22,23] The elevated RC levels are directly linked to major cardiovascular events.[24] The establishment of RC as an independent predictor of cardiovascular death has been recognized by the NHANES-based analysis, which exhibited the linear correlation between RC and cardiovascular mortality.[25] RCII is a composite index of RC and hsCRP and shows higher prognostic value for cardiovascular risk prediction. Residual cholesterol inflammatory index was used to evaluate stroke risk in the CHARLS cohort, and higher stroke incidence was associated with increased RCII levels.[26] The present investigation extended this framework to CKM with particular emphasis on the identification of RCII for investigation of comorbidity risk in the heart, kidney, and metabolic system by the CKM.

The outcome generalizability was magnanimously enhanced by the broad population coverage through incorporation of CHARLS and NHANES in the investigation. The meticulous analytical model adjustment was carried out on broad spectrum variables including demographic, socioeconomic, lifestyle, and BMI confounders. The non-linear associations and dose-dependent relationships were validated through quartile analysis and RCS modeling. The sysregulated lipid metabolism and systemic inflammation exhibited dependency on the 2 major variables including RC and hsCRP. Their levels were associated with the extent of coronary artery disease even for individuals having normal LDL level.[26] These factors into a single composite index offers a tool for evaluating cardiovascular risk and disease severity. C-reactive protein contributes to atherosclerotic progression by promoting oxidative stress and plaque instability as well as associated with lipoprotein metabolism, particularly under hypertriglyceridemic and low HDL conditions, and exhibits an interactive role in CKM pathogenesis.[27,28] RC exacerbates atherosclerosis[23,24] by accumulating within macrophages, which promotes foam cell generation and endothelial dysfunction, which in turn intensifies vascular inflammation.[29-32] Further amplification of vascular inflammation can be triggered by the RC crystal upon activation of the NLRP3 inflammasome.[33] The increment in the level of RC and CRP in the CKM group with noticeably higher RCII values compared with the non-CKM group (NHANES: 14.55 vs. 4.91; CHARLS: 10.31 vs. 3.74; all $P < .001$) suggests the synergistic activation of lipid-inflammatory imbalance by the RCII.[26,34] The non-linear RCII–CKM risk interaction by the RCS analysis with a rapid risk escalation at higher RCII levels indicates the potential clinical "acceleration threshold" for risk stratification. Subgroup analyses indicated that, in NHANES, the RCII–CKM association remained consistent across age, sex, smoking, alcohol use, HTN, and DM subgroups, except for notable heterogeneity across racial groups, which suggests broad population applicability. In contrast, within CHARLS, HTN, DM, stroke, and smoking appeared to modulate the

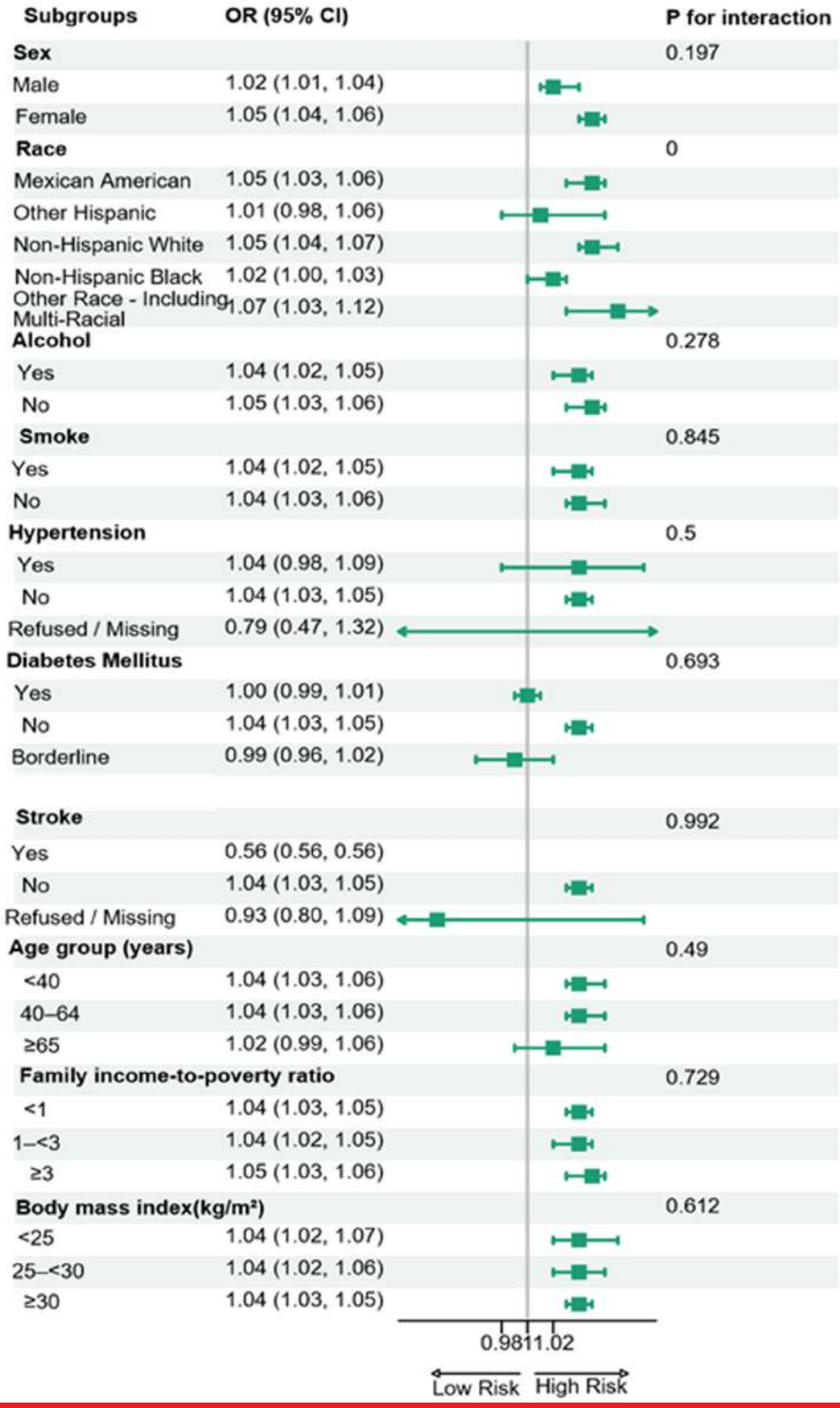


Figure 3. Forest plots: Subgroup analyses of the RCII–CKM relationship in the NHANES study

strength of the RCII–CKM relationship, suggesting that underlying disease states may affect the biomarker's predictive magnitude. Previous studies have indicated that cholesterol deposition within atherosclerotic plaques drives disease progression and correlates with plaque vulnerability,[35] which warrants clinical attention in risk management.

Despite several outcome-based results of the present investigation, it also carries some limitations. The first one includes that the cross-sectional design did not permit causal inference. Second, CHARLS lacked detailed data on diet, medication use, and renal function parameters (e.g., eGFR, proteinuria, etc.), introducing potential residual

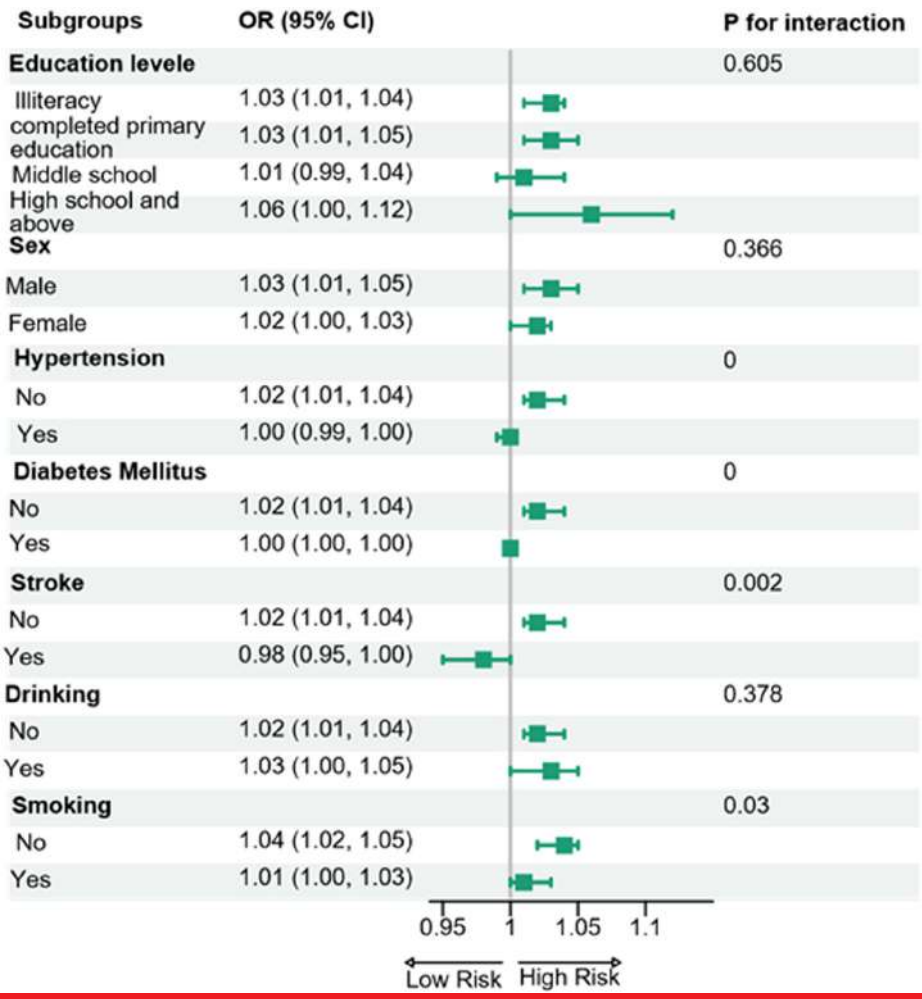


Figure 4. Forest plots: Subgroup analyses of the RCII–CKM relationship in CHRALS

confounding. Lifestyle factors were primarily self-reported, which may have resulted in information bias. Finally, although 3 progressively adjusted models were constructed, the effects of unmeasured confounders cannot be entirely excluded. Future investigations are required to clarify the causal mechanism by examining the temporal dynamics of

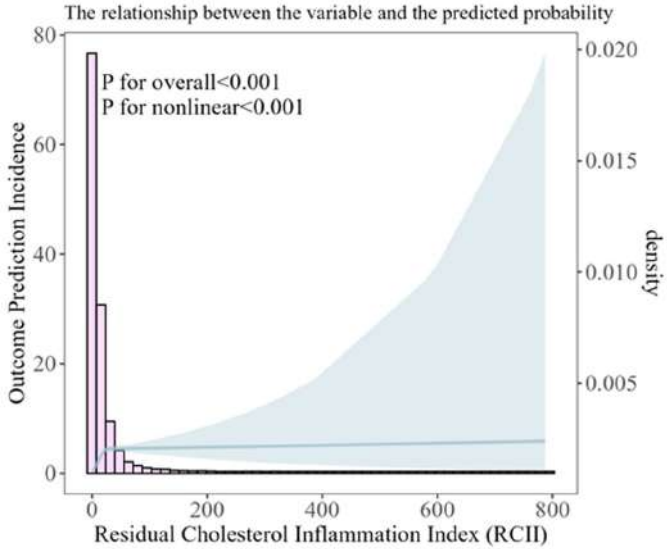


Figure 5. Nonlinear relationship of RCII with cardiorenal-metabolic syndrome incidence (NHANES data).

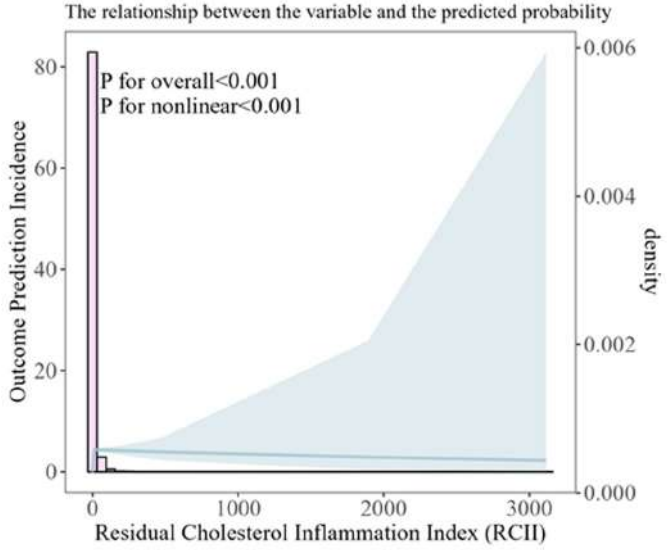


Figure 6. Nonlinear relationship of RCII index with cardiorenal-metabolic syndrome incidence (CHRALS data).

RCII relative to CKM onset and progression through prospective cohorts or interventional analysis.

CONCLUSION

The present investigation represents the significant interaction between increased RCII levels and elevated CKM risk, which has been established by utilizing 2 large national cohorts from China and the US that represent the dose-responsive relationship and model stability among the variables. Residual cholesterol inflammatory index potentially serves as an integrative biomarker that bridges inflammatory and lipid-metabolic pathways, offering a potential indicator for preliminary risk recognition and assessment of metabolic comorbidities. Although the cross-sectional design constrains causal inference, the results suggest that maintaining lower RCII levels might help mitigate CKM risk. Future studies should examine its predictive performance, mechanistic pathways, and response to interventions, offering novel tools and perspectives for preventing and managing CKM.

Data Availability Statement: The data used in this study were obtained from publicly accessible repositories. Data from the National Health and Nutrition Examination Survey (NHANES), provided by the US Centers for Disease Control and Prevention (CDC; https://www.cdc.gov/nchs/nhanes/), are openly available to the public. Data from the China Health and Retirement Longitudinal Study (CHARLS), conducted (http://charls.pku.edu.cn/), can be accessed upon registration and approval through the official data portal. No additional data were generated or used during the current study.

Ethics Committee Approval: National Health and Nutrition Examination Survey and CHARLS received ethical approval from their respective review boards, with NHANES authorized by the National Center for Health Statistics (NCHS) Ethics Review Board. Appropriate sampling weights were applied to ensure that the estimates could be generalized to the national populations of each country. The study was conducted in accordance with the Declaration of Helsinki.

Artificial Intelligence Usage Statement: During the preparation of this work, the author(s) used [CHATGPT] in order of GRAMMATICAL CORRECTION. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Informed Consent: Informed consent was obtained from all participants in the original CHARLS and NHANES studies. The present study used publicly available, de-identified data; therefore, no additional informed consent was required.

Peer-review: Internally peer-reviewed.

Author Contributions: Concept – M.Z.; Design – M.Z.; Supervision – T.Z., G.S., X.R., L.Z., L.H.; Resources – A.H., M.Z.; Materials – G.S., X.R.; Data Collection and/or Processing – L.Z., L.H.; Analysis and/or Interpretation – T.Z., G.S.; Literature Search – L.Z., L.H., G.S.; Writing – M.Z., T.Z., L.Z.; Critical Review – X.R., L.Z., M.Z.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Two-Year Outcomes and Predictors of Recurrence After High-Power Radiofrequency Ablation for Atrial Fibrillation: A Single-Center Experience With 480 Patients

ABSTRACT

Background: Atrial fibrillation (AF) catheter ablation is a cornerstone rhythm-control intervention in symptomatic patients. Despite technological improvements, recurrence remains a critical determinant of long-term success, particularly in persistent AF. This study aimed to evaluate the 2-year clinical outcomes of high-power radiofrequency (RF) ablation performed in a high-volume single center and to identify predictors of AF recurrence in patients undergoing catheter ablation.

Methods: This retrospective observational study included 480 consecutive adults who underwent RF catheter ablation for AF between January 2021 and December 2024. The patients were categorized based on AF recurrence, defined as >30-second episodes detected during 48- to 72-hour Holter at 6, 12, 24, and 36 months.

Results: The cohort had a mean age of 59.8 ± 11.5 years, 56.3% were male, and 55.2% had persistent AF. The overall recurrence rate was 14.5% over an average follow-up duration of 23.8 ± 9.2 months. The recurrence rate was 9.2% in paroxysmal AF and 20% in persistent AF. The left atrial diameter was significantly larger in recurrence-positive patients (43.1 ± 6.5 mm vs 41.4 ± 5.5 mm, $P = .023$). Additionally, mitral regurgitation (MR) was more prevalent in the recurrence-positive group, particularly in patients with ≥grade 3 MR (18.6% vs. 6.4%, $P = .004$). Independent predictors of recurrence were symptom duration (odds ratio [OR] = 1.01, $P = .006$, 95% CI: 1.00-1.02) and prior direct current cardioversion (OR = 3.12, $P < .001$, 95% CI: 2.34-4.10). The complication rate was 2.0%.

Conclusion: High-power RF ablation in an experienced center resulted in high sinus rhythm maintenance and low recurrence at 2 years. Individualized treatment strategies may have contributed to the low recurrence rates.

Keywords: Atrial fibrillation, radiofrequency ablation, high-power short duration

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and remains a major contributor to morbidity despite ongoing advances in rhythm-control strategies. Recurrent symptoms, limitations of antiarrhythmic drug therapy, and the progressive nature of atrial remodeling frequently necessitate interventional treatment. Therefore, catheter ablation has become a central component of rhythm control, and the *European Society of Cardiology* guidelines emphasize that pulmonary vein isolation (PVI) is an effective strategy after antiarrhythmic drug failure and may also be considered as a first-line treatment option in selected patients.[1]

Cryoballoon ablation is widely used as a standardized single-shot PVI technique with well-established efficacy.[2,3] Radiofrequency (RF) ablation remains the most frequently utilized alternative owing to its precision, adaptability, and compatibility with contemporary electroanatomic mapping systems.[4-6] Technological refinements, such as contact-force sensing and high-power, short-duration energy delivery, have further enhanced lesion durability and procedural outcomes.[4,5] Pulse-field ablation, a non-thermal modality with promising safety and

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Received: January 11, 2026
Accepted: May 22, 2026
Available Online Date: July 7, 2026

Cite this article as: Uslu A, Küp A, Çelik M, *et al*. Two-year outcomes and predictors of recurrence after high-power radiofrequency ablation for atrial fibrillation: A single-center experience with 480 patients. *Anatol J Cardiol*. 2026;30(12):901-908.

DOI: 10.14744/AnatolJCardiol.2026.6202

efficiency, is also rapidly gaining adoption in modern electrophysiology laboratories.[7]

Despite advancements in ablation strategies, real-world outcomes vary substantially based on AF type, atrial substrate, and operator experience. Two-year recurrence rates after RF ablation have been reported to range from 15% to 48%, being generally lower in paroxysmal AF (≈14-35%) and higher in persistent AF (≈36-60%).[8-12] Identifying predictors of recurrence, such as left atrial (LA) size, AF chronicity, valvular disease, and prior rhythm-control attempts, remains essential to optimize patient selection and procedural strategy.[10-13] Single-center studies utilizing uniform workflows and consistent operators offer valuable insight by reducing heterogeneity related to technique, experience, and procedural approach.

In this study, the center's experience with RF catheter ablation in 480 patients is presented, evaluating procedural success, recurrence rates, complications, and clinical predictors of AF recurrence in a high-volume electrophysiology setting.

Study Population

This retrospective, single-center study included consecutive patients who underwent RF ablation for AF at the center between January 2021 and December 2024. Patients aged 18-82 years who were followed up for at least 12 months with a diagnosis of paroxysmal or persistent AF were included in the study. The patients were classified into 2 groups based on the presence or absence of AF recurrence. Patients with reversible causes of AF, postoperative AF, documented intra-atrial thrombus, or cardiac tumor, myocardial infarction within the previous 3 months, or percutaneous coronary intervention within the previous 3 months were excluded.

The study protocol was approved by the local ethics committee, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Procedural Strategies and Techniques

Before the procedure, all patients underwent detailed evaluation, including laboratory tests, transthoracic echocardiography, and 12-lead electrocardiography to exclude secondary causes of AF. According to institutional workflow, all cases were discussed in a multidisciplinary cardiology-cardiovascular surgery council, and ablation was performed under general anesthesia following anesthesiology approval.

HIGHLIGHTS

- In 480 patients with atrial fibrillation (AF) who were treated with high-power radiofrequency (RF) ablation, the 2-year recurrence rate was 14.5% (9.2% for paroxysmal AF, 20% for persistent AF), and 85.5% remained in sinus rhythm.
- Procedural safety was favorable, with 2.0% complications and low fluoroscopy times in a high-volume center.
- Longer AF symptom duration and prior direct current cardioversion independently predicted recurrence.
- These data support early ablation and individualized lesion sets to improve long-term rhythm control.

Vascular access was obtained through the right femoral vein using the Seldinger technique, and 2 6-F and 1 8-F sheaths were introduced. A coronary sinus catheter was positioned first, followed by a single transseptal puncture using an SL1 sheath and a Brockenbrough needle to access the LA. High-density (HD) mapping catheters were used for electroanatomic mapping.

If a stable atrial flutter with a constant tachycardia cycle length was present at the beginning of the procedure, late activation mapping was performed and a right atrial map was generated. In patients presenting in atrial flutter or in AF at the start of the procedure, scar assessment was performed using a bipolar voltage scale of 0.1-0.3 mV. In these cases, circumferential PVI was completed after ablating the critical isthmus of the arrhythmia. In patients in sinus rhythm, a bipolar voltage scale of 0.2-0.5 mV was used.

In cases with concentric activation indicating typical cavotricuspid isthmus (CTI)-dependent flutter, entrainment was used for confirmation. Cavotricuspid isthmus ablation and restoration of sinus rhythm were performed first, followed by transseptal puncture and LA mapping.

After voltage mapping, additional ablation beyond PVI was individualized, regardless of AF type. Decisions were based on predefined parameters: AF symptom duration, AF type (paroxysmal or persistent), anterior LA scarring related to mitral regurgitation (MR), patient age, and overall LA scar burden. According to these findings, posterior wall isolation, anterior mitral line, or scar homogenization was applied when indicated.

Open-irrigated RF catheters with contact-force sensing were used (Thermocool® SmartTouch®, Biosense Webster; TactiCath™, Abbott). HD mapping was performed using PENTARAY® NAV ECO or Advisor™ HD Grid Mapping Catheters. All LA lesions were delivered using a high-power, short-duration strategy. Right atrial ablation was performed at 40 W.

Pulmonary veins were isolated using a contiguous lesion set with an approximate lesion width of 3 mm. Lesion continuity was confirmed at a 2-mm resolution, and additional "touch-up" ablation was applied even when an entrance block was present.

In patients with documented AF and concomitant typical flutter at the beginning of the procedure, CTI ablation was performed first, followed by PVI and the additional LA ablation lesions. After first-pass isolation and restoration of sinus rhythm (spontaneously or via cardioversion), the LA was remapped using a bipolar voltage scale of 0.2-0.5 mV. Residual potentials within the pulmonary veins or posterior wall (when applicable) were targeted with additional RF applications at 35-40 W, irrespective of exit block, until residual electrical activity was eliminated.

After PVI or PVI plus posterior box isolation, programmed stimulation and burst pacing were performed. Empirical anterior mitral line ablation was not routinely performed in the absence of low-voltage areas or inducible flutter. In

both paroxysmal and persistent AF, LA mapping and ablation were performed first, followed by right atrial mapping. Cavotricuspid isthmus ablation and right atrial scar homogenization were performed when indicated.

Clinical Follow-up and Study Endpoints

All patients underwent 24-hour post-procedural monitoring and transthoracic echocardiography at 24 hours. In the absence of contraindications, amiodarone was administered during the blanking period. The blanking period was defined as the first 90 days after ablation, and any documented episode of AF, atrial flutter, or atrial tachycardia lasting >30 seconds during this period was classified as recurrence for the study analysis.

Oral anticoagulation was continued for at least 4 months in all patients and for at least 1 year in those with a CHA_2DS_2-VASc score of >2. Outpatient follow-ups, including electrocardiogram, echocardiography, and laboratory testing, were performed at week 1, month 1, and month 3 after the procedure. All patients underwent 48-72 hour Holter monitoring at 6, 12, 24, and 36 months.

During the blanking period, amiodarone therapy was administered to prevent arrhythmia recurrence unless contraindicated or not tolerated. After the blanking period, amiodarone was discontinued in patients who remained in sinus rhythm, and treatment was continued with beta-blocker therapy alone according to symptom status and clinical need. In patients who experienced arrhythmia recurrence during the blanking period, amiodarone or flecainide was continued at the discretion of the treating physician.

Arrhythmia Center Characteristics and Operator Experience

The institution has a dedicated arrhythmia center within the cardiology department that performs a broad spectrum of electrophysiological procedures. The center manages more than 1,000 arrhythmia procedures annually, including AF ablation and complex arrhythmias such as endocardial and epicardial ventricular tachycardia ablation.

The arrhythmia team consists of 5 interventional electrophysiologists with an average experience of approximately 8 years in invasive electrophysiology and catheter ablation. All operators are actively involved in both basic and complex arrhythmia procedures. Each operator performs at least 100 complex arrhythmia procedures annually.

Treatment strategies, procedural workflows, and patient management algorithms are standardized within the center and applied consistently among operators to ensure uniform decision-making and procedural reproducibility.

Statistical Analysis

Statistical analyses were performed using SPSS, version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were tested for normality using the Kolmogorov–Smirnov test and for homogeneity of variance. Normally distributed continuous variables were compared using the independent-samples *t*-test, whereas non-normally distributed variables were compared using the Mann–Whitney *U*-test. Categorical variables were compared using the chi-square test. Normally distributed continuous variables are presented as mean ± SD, non-normally distributed variables as median (interquartile range, Q1-Q3), and categorical variables as counts and percentages.

To identify predictors of AF recurrence, univariate and multiple logistic regression analyses were performed. Variables significant in univariate analysis were entered into a multiple model using a stepwise selection method. Receiver operating characteristic (ROC) curve analysis was performed to determine optimal cut-off values, sensitivity, and specificity for independent predictors. A 2-tailed *P*-value of <0.05 was considered statistically significant.

RESULTS

A total of 480 patients who underwent RF ablation for AF were included in the study. The mean age of the cohort was 59.76 ± 11.51 years, with 270 patients (56.25%) being male and 210 (43.75%) being female. Of all patients, 215 had paroxysmal AF and 265 had persistent AF. Atrial flutter was observed in 31 of the 265 patients with persistent AF. In patients with paroxysmal AF who presented with ongoing AF before the procedure or developed AF during the procedure, as well as in all patients with persistent AF, sinus rhythm was successfully restored by cardioversion under sedation. Procedure-related complications occurred in 9 patients (2.0%).

The mean follow-up duration was 23.8 ± 9.2 months. During follow-up, AF recurrence was documented in 70 patients (14.5%). The overall sinus rhythm maintenance rate was 85.5%, with rates of 92.1% in the paroxysmal AF group and 80.0% in the persistent AF group. Among patients who experienced recurrence, the median time to the first documented arrhythmia was 2 months (range: 1-60 months). Twenty patients (28.6%) experienced recurrence within the first month, and 40 patients (57.1%) within the first 3 months. In the analysis excluding the blanking period, recurrence was observed in 48 patients (10%) in the entire study population, in 14 patients (6.5%) in the paroxysmal AF group, and in 34 patients (12.8%) in the persistent AF group.

Demographic characteristics and medication histories of patients with and without recurrence are presented in Table 1. There were no statistically significant differences between the groups in demographic or medication-related variables.

Laboratory and echocardiographic parameters are compared in Table 2. LA diameter and the presence of MR, particularly grade 3 MR, showed statistically significant differences between the recurrence and non-recurrence groups. No significant differences were observed in other laboratory or echocardiographic parameters.

Clinical AF-related characteristics and procedural variables are shown in Table 3. The ratio of paroxysmal to persistent AF was 0.93 in the non-recurrence group compared with 0.32 in the recurrence group ($P < .001$). AF symptom duration, history of cardioversion, time elapsed after ablation, and procedure duration were all significantly different between the

Table 1. Demographic Characteristics and Medication Use of the Study Cohort

	Patients Without AF Recurrence n = 410	Patients with AF Recurrence n = 70	*P*
Age (years)	62 (19-84)	58.5 (20-79)	.086
Sex (F/M)	184/226	26/44	.228
Body mass index (kg/m^2)	27 (19-47)	28.9 (22.4-49.3)	.194
Hypertension, n (%)	215 (44.8)	29 (41.4)	.089
Diabetes mellitus, n (%)	91 (18.9)	13 (18.5)	.723
Medical treatment			
Beta-blocker, n (%)	338 (82.4)	60 (85.7)	.501
Calcium channel blockers, n (%)	53 (12.9)	9 (12.8)	.987
Propafenone, n (%)	101 (24.6)	10 (14.2)	.058
Amiodarone, n (%)	116 (28.3)	24 (34.2)	.528
Apixaban, n (%)	57 (13.9)	14 (20)	.184
Edoxaban, n (%)	75 (18.3)	11 (15.7)	.597
Rivaroxaban, n (%)	183 (44.6)	30 (42.8)	.782

AF, atrial fibrillation; F, female; M, male.

2 groups. In the overall cohort, the median procedure duration was 104 minutes (range: 23-589 minutes; mean: 111.9 minutes), and the median fluoroscopy time was 8.75 minutes (range: 0.9-65 minutes; mean: 10.95 minutes).

Univariate and multiple logistic regression analyses evaluating predictors of AF recurrence are presented in Table 4. In univariate analysis, paroxysmal AF ($P < .001$), MR ($P = .008$), AF symptom duration ($P = .006$), history of cardioversion ($P < .001$), and LA diameter ($P = .021$) were identified as significant predictors of recurrence. In multiple regression, AF symptom duration (odds ratio [OR]= 1.01, $P = .006$, 95% CI: 1.00-1.02) and a history of cardioversion (OR = 3.12, $P < .001$, 95% CI: 2.34-4.10) remained independent predictors of AF recurrence.

ROC curve analysis showed that an LA diameter cut-off value of 41.5 mm predicted AF recurrence with an AUC = 0.597, $P = .037$, 95% CI: 0.509-0.685, a sensitivity of 57.8%, and a specificity of 57.9% (Figure 1).

DISCUSSION

In this study, approximately 24-month outcomes of 480 patients who underwent RF catheter ablation for AF were evaluated. The overall AF recurrence rate was 14.5%, which is notably lower than the recurrence rates reported in contemporary literature, where 2-year recurrence typically ranges between 15% and 48.3% (6,8). Recurrence rates in paroxysmal AF cohorts are generally reported between 14% and 34.5%,[4,5] whereas they range from 36% to 59.8% in persistent AF cohorts.[9,10] In the study, both the paroxysmal cohort (7.9%) and the persistent cohort (20%) demonstrated recurrence rates substantially below these ranges. In the study, atrial flutter was identified in 31 patients within the persistent AF group, and ablation was performed using 3-dimensional electroanatomic mapping in these cases. Macroreentrant

Table 2. Comparison of Laboratory and Echocardiographic Parameters Between the Study Groups

	Patients Without AF Recurrence (n = 410)	Patients with AF Recurrence (n = 70)	*P*
Hemoglobin (g/dL)	13.7 (8.1-20.1)	14.2 (10-17.2)	.155
White blood cell count (×10^9/L)	7.44 (3.55-62.46)	7.25 (2.86-21.62)	.979
Neutrophil count (×10^9/L)	4.42 (1.45-11.87)	4.37 (1.49-18.4)	.535
Lymphocyte count (×10^9/L)	2.14 (0.87-54.14)	2.11 (0.98-4.29)	.247
Platelet count (×10^9/L)	241 (58-515)	238 (164-454)	.937
NT-proBNP (pg/mL)	320 (5.37-6 472)	323 (16-4 408)	.486
Creatine (mg/dL)	0.89 (0.38-4.2)	0.88 (0.57-1.66)	.862
GFR	84 (10-140)	87 (42-122)	.219
Sodium (mmol/L)	140 (122-160)	140 (132-145)	.361
Potassium (mmol/L)	4.36 (2.88-6.32)	4.49 (3.3-5.76)	.152
HgA1C (%)	5.75 (4.7-9.5)	5.6 (5-9.4)	.222
LV-EF (%)	65 (15-65)	65 (20-65)	.218
LV-EDD (mm)	47 (32-69)	48 (38-70)	.421
LV-ESD (mm)	30 (16-62)	30 (22-60)	.811
IVS (mm)	11 (7-13)	11 (7-15)	.844
LA size (mm)	41.4 ± 5.5	43.1 ± 6.5	.023
sPAP (mm Hg)	30 (18-70)	30 (16-90)	.576
Tricuspid regurgitation, n (%)			.101
Absent, n (%)	69 (16.8)	5 (7.1)	.058
Grade 1	200 (48.7)	34 (48.5)	.974
Grade 2	110 (26.8)	21 (30)	.582
Grade 3	25 (6)	7 (10)	.226
Grade 4	6 (1.5)	3 (4.2)	.108
Mitral regurgitation, n (%)			.040
Absent	67 (16.3)	8 (11.4)	.295
Grade 1	211 (51.4)	28 (40)	.076
Grade 2	105 (25.6)	24 (34.2)	.130
Grade 3	25 (6)	10 (14.2)	.015
Grade 4	2 (0.4)	0 (-)	.558

AF, atrial fibrillation; GFR, glomerular filtration rate; HgA1C, hemoglobin A1C; IVS, interventricular septum; LA, left atrium; LV-EDD, left ventricular end-diastolic diameter; LV-EF, left ventricular ejection fraction; LV-ESD, left ventricular end-systolic diameter; NT-proBNP, N-terminal pro–b-type natriuretic peptide; sPAP, systolic pulmonary artery pressure.

atrial tachycardias such as atrial flutter are frequently encountered in conjunction with AF, and contemporary evidence suggests that addressing both arrhythmias during the ablation procedure may improve overall procedural success and long-term rhythm outcomes.[14]

When recurrence timing was analyzed, 28% of recurrences occurred within the first month and 57% within the first 3 months. The predominance of early recurrences suggests

Table 3. Comparison of Clinical Features and Ablation Parameters Between the Study Groups

	Patients Without AF Recurrence (n = 410)	Presence of AF Recurrence (n = 70)	*P*
Paroxysmal/persistent AF, n	198/212	17/53	<.001
AF symptom duration (months)	15 (1-236)	30 (3-129)	.001
Prior DC-CV, n (%)	144 (35.1)	52 (74.8)	<.001
Restoration of sinus rhythm via DC-CV, n (%)	134 (32.6)	46 (65.7)	<.001
Pre-procedural DC-CV, n (%)	111 (27)	23 (32.8)	.319
Duration after ablation (months)	21 (6-49)	26 (12-81)	<.001
Fluoroscopy dose (mGy)	344 (5-2,998)	456 (49-3,591)	.139
Fluoroscopy time (minutes)	8 (1-41.5)	10.9 (0.9-65)	.023
Procedure time (minutes)	101 (23-589)	116.5 (60-260)	.008

AF, atrial fibrillation; DC-CV, direct current cardioversion.

that many events occurred during the blanking period, when electrophysiological instability due to edema, inflammation, and autonomic fluctuations may result in transient arrhythmogenicity. Although arrhythmias during blanking remain controversial in terms of classification,[15,16] the high proportion of early recurrences in the cohort suggests that the true long-term recurrence rate may be even lower.

Although the analysis is limited to a single center, this design also confers methodological advantages. Previous multicenter studies have demonstrated that operator variability, including learning curves, technique heterogeneity, and procedural inconsistencies, significantly affect AF ablation outcomes.[11] In the study, all procedures were performed in a high-volume center by the same experienced operators using a uniform ablation workflow, which reduced variability related to operator-dependent factors and enhanced internal validity.

All patients in the cohort underwent RF ablation. Although cryoballoon ablation and RF ablation are the 2 most widely used PVI techniques, pulse-field ablation has recently emerged as a promising non-thermal alternative. Randomized trials and meta-analyses have shown comparable success rates between RF and cryoballoon ablation, with no clear superiority of either strategy.[3,17] However, in the previously published single-center cryoballoon AF ablation study, success rates were 85.6% for paroxysmal AF and 61.8% for persistent AF.[18] In that study, the mean procedure times for recurrence-positive and recurrence-negative patients were 116.8 and 115.8 minutes, respectively, with mean fluoroscopy times of 26.4 and 29.2 minutes. In contrast, in the present RF cohort, the mean procedure time was 111.9 minutes, and the mean fluoroscopy time was only 10.95 minutes. Thus, compared with the own cryoballoon experience, RF ablation yielded similar procedure duration but markedly lower radiation exposure, with similar complication rates.[18] Although the literature often shows shorter procedure duration but higher phrenic nerve injury rates with cryoballoon ablation,[3] the findings suggest that RF ablation performed by highly experienced operators can achieve comparable efficiency. Moreover, RF ablation offers greater flexibility for individualized lesion sets enabled by advanced 3-dimensional mapping capabilities.

Pulse-field ablation continues to gain widespread adoption, and early studies suggest that it may ultimately offer procedural and safety advantages over both RF and cryoablation.[7] However, its rapid evolution complicates direct comparison with established modalities.

Among echocardiographic parameters, LA diameter and the presence of MR, particularly grade 3, were significantly associated with recurrence. Left atrial size has long been recognized as one of the strongest predictors of AF recurrence, and this relationship has been consistently supported by meta-analyses.[12] Initially, the association between MR and AF recurrence was believed to be mediated by LA enlargement.[13] However, more recent evidence indicates that moderate-to-severe MR independently predicts AF recurrence, regardless of LA size.[19] MR leads to pressure and volume overload of the atrium, promoting structural remodeling and atrial cardiomyopathy through electromechanical alterations.[20] Consequently, in patients with clinically relevant MR, anterior LA low-voltage areas adjacent to the mitral annulus are frequently observed. In such patients, incorporation of personalized lesion sets (posterior wall isolation, anterior mitral line, or targeted homogenization of low-voltage regions) may be beneficial. In the cohort, even patients with

Table 4. Results of Univariate and Multiple Regression Analyses Showing the Relationship Between AF Recurrence and Investigated Parameters

	Univariable			Multiple		
Variables	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Paroxysmal AF, n	0.34	0.19-0.61	<.001	0.55	0.22-1.11	.442
Mitral regurgitation, n	1.50	1.11-2.02	.008	1.35	0.82-1.89	.420
AF symptom duration (months)	1.01	1.00-1.02	.006	1.01	1.00-1.02	.006
Prior DC-CV, n	5.33	3.01-9.46	<.001	3.12	2.34-4.10	<.001
LA size (mm)	1.01	1.00-1.01	.021	1.00	0.99-1.01	.396

AF, atrial fibrillation; CI, confidence interval; DC-CV, direct current cardioversion; LA, left atrium; OR, odds ratio.

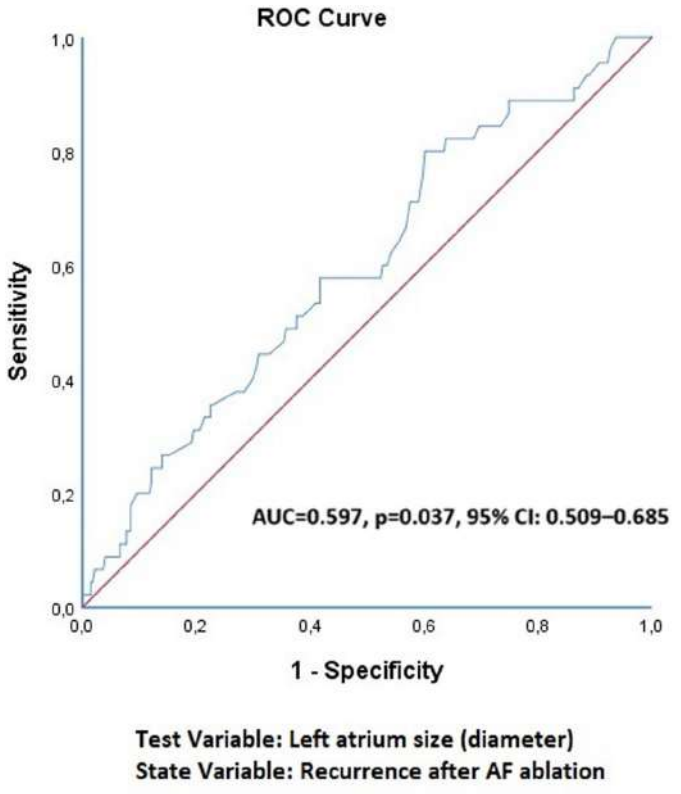


Figure 1. Receiver operating characteristic curve of left atrial size for predicting atrial fibrillation (AF) recurrence.

paroxysmal AF frequently underwent right atrial scar assessment and homogenization, which may partly explain the low recurrence rates. Larger prospective studies are needed to validate this observation.

Regarding AF type distribution, 44.8% of the patients had paroxysmal AF and 55.2% had persistent AF. Large contemporary AF ablation cohorts typically include 55-70% paroxysmal AF cases.[21] Thus, despite the cohort having a relatively high proportion of persistent AF, traditionally associated with higher recurrence, the overall recurrence rates remained lower than expected. This may reflect the detailed, standardized lesion formation strategy used in the center. This approach includes reduced lesion spacing, additional ablation applications at sites with incomplete isolation identified during post-ablation assessment with a HD catheter, and individualized adjunctive lesions (posterior wall box, scar homogenization, or anterior mitral line) when appropriate. Moreover, although earlier multicenter studies suggested that additional lesions did not reduce recurrence but increased procedure and fluoroscopy time, these studies predated zero-fluoroscopy and HD mapping technologies. In the experience, right atrial scar heterogeneity assessment and homogenization were systematically performed in all patients regardless of AF type. In many patients with paroxysmal AF, atrial runs detected during programmed or burst pacing resolved after right atrial homogenization, suggesting a potential mechanistic benefit. This observation is supported by prior work showing the relevance of right atrial remodeling in paroxysmal AF recurrence.[22] These findings highlight the potential role of bi-atrial substrate modification in select patients and warrant further prospective investigation.

AF symptom duration was also significantly longer in the recurrence group and emerged as an independent predictor of recurrence in multiple analyses. This aligns with prior findings by Sairaku et al, demonstrating that longer symptom duration predicted post-ablation recurrence.[23] AF diagnosis-to-ablation time, which is closely correlated with symptom duration, has similarly been shown in multiple recent systematic reviews and meta-analyses to be strongly associated with recurrence risk.[24,25]

A history of direct current cardioversion was also significantly more common among patients with recurrence and remained an independent predictor in multiple analyses. While this may partially reflect longer AF duration or more symptomatic disease prompting repeated cardioversions, its independent association suggests that prior direct current cardioversion may serve as a clinical marker of atrial substrate vulnerability.

Although LA diameter was significantly associated with AF recurrence, ROC analysis demonstrated limited discriminatory ability (area under the curve: 0.597), indicating poor predictive performance. These findings suggest that LA size alone is insufficient for risk stratification and should be interpreted in conjunction with other clinical and procedural variables.

Limitations of the Study

This study has several limitations that must be acknowledged. First, the retrospective and single-center design inherently limits the generalizability of the findings. Second, despite structured follow-up that included 48-72 hour Holter recordings, asymptomatic subclinical AF episodes may have been missed. Continuous monitoring (e.g., implantable loop recorders) would have provided more precise measurement of AF recurrence and burden. Third, procedural decisions regarding additional lesions (posterior wall isolation, anterior mitral line, and right atrial homogenization) were individualized based on operator assessment, introducing operator-dependent variability. Fourth, subgroup analyses comparing outcomes between PVI-only and PVI plus additional ablation strategies were not performed in the present study. Future studies incorporating such subgroup data from other centers and additional clinical experience may further contribute to the literature. Finally, although multiple regression identified independent predictors of AF recurrence, residual confounding from unmeasured variables such as autonomic factors, genetic predisposition, or inflammatory processes cannot be excluded.

CONCLUSION

In this study, RF ablation for AF performed in a high-volume, experienced electrophysiology laboratory demonstrated high procedural success and low recurrence rates over approximately 24 months of follow-up. The treatment was associated with low complication rates, short fluoroscopy times, and a high rate of sinus rhythm maintenance. A high

level of operator experience combined with individualized ablation strategies may have contributed to the improved treatment outcomes.

Ethics Committee Approval: This study was approved by the Ethics Committee of Koşuyolu High Specialization Training and Research Hospital (Approval No: 2023/12/711, Date: 18.07.2023).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Acknowledgments: The authors would like to thank Professor Mehmet Kaan Kirali, MD, Chief Physician of Koşuyolu High Specialization Training and Research Hospital, for facilitating access to study data and providing institutional coordination.

Author Contributions: Concept – A.U., A.Küp, S.D., G.G.D., M.G.; Design – A.U., M.Ç., A.Ö., M.S.B., B.B., H.E., A.Kepez; Supervision – A.U., K.G., A.Ö., Ş.K., A.Kepez; Materials – A.Küp, M.Ç., A.Ö., M.S.B., D.Ş., B.B., H.E., A.Kepez; Data Collection and/or Processing – A.Küp, M.Ç., S.D., K.G., G.E., A.Ö., Ş.K., D.Ş., B.B.; Analysis and/or Interpretation – A.Ö., M.Ç., Ş.K., A.U., G.E., G.G.D., A.Kepez; Literature Search – A.Küp, K.G., S.D., G.G.D., M.S.B., D.Ş., H.E.; Writing – A.U., A.Ö., G.E.; Critical Review – A.U., S.D., G.G.D., A.Kepez.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Ultrasound-Assisted Catheter-Directed Thrombolysis vs. Low-Dose Intravenous Tissue-Type Plasminogen Activator Treatments in Acute Intermediate-High Risk Pulmonary Embolism: Insights from a Retrospective Study

ABSTRACT

Background: Comparative data on ultrasound-assisted catheter-directed thrombolysis (USAT) and systemic low-dose tissue-type plasminogen activator (tPA) for intermediate-high-risk (IHR) pulmonary embolism (PE) remain limited. The efficacy and safety outcomes of USAT vs. intravenous (IV) low-dose tPA were evaluated in this population.

Methods: This study enrolled 329 IHR PE patients treated with USAT (n = 205) or IV low-dose tPA (n = 124). Post-treatment changes in clot burden (Qanadli score), right ventricular (RV) strain, and long-term mortality (median follow-up 95.8 months) were assessed. Propensity score analysis with inverse probability weighting (IPW) was employed to adjust for confounders.

Results: Ultrasound-assisted catheter-directed thrombolysis was predominantly bilateral (82.9%), with a mean tPA dose of 38.5 ± 13.6 mg. In the IV tPA cohort, 58.9% required a second infusion to achieve stabilization. While IV tPA was associated with more pronounced early reductions in heart rate and RV/LV (left ventricle) ratio, USAT provided significantly greater thrombus resolution (all $P < .005$). After IPW adjustment, USAT demonstrated clear superiority over IV tPA in reducing residual clot burden ($P < .001$). However, improvements in oxygen saturation, tricuspid annular plane systolic excursion, and pulmonary artery systolic pressure (PASP) were comparable. No significant differences were observed in in-hospital mortality, PE recurrence, or long-term survival between cohorts. Higher PE severity indexes scores independently predicted in-hospital adverse events, whereas older age, male sex, and higher discharge PASP were predictors of shortened long-term survival.

Conclusions: In IHR PE, IV low-dose tPA relates to more pronounced early hemodynamic and RV diameter improvements, whereas USAT achieves superior thrombus resolution. Despite these divergent surrogate responses, both strategies yield comparable early and long-term clinical outcomes, supporting their roles as viable reperfusion options.

Keywords: Pulmonary embolism, ultrasound-assisted thrombolysis and systemic thrombolysis

INTRODUCTION

Acute pulmonary embolism (PE) has been reported as one of the most frequent lethal cardiovascular diseases in the world.[1,2] Acute onset hemodynamic deterioration develops following the thrombotic obstruction in 30%-50% of the pulmonary arteries (PA), resulting in right ventricular (RV) failure, and increased right ventricle to left ventricle (RV/LV) diameter ratio either assessed by echocardiography or computed tomographic pulmonary angiography predicts clinical worsening irrespective of the initial clinical status.[1-5] The aims of reperfusion strategies in acute PE are to achieve quick reversal of obstructive burden and RV pressure strain, restoration of RV to PA coupling, and hemodynamic stabilization. European Society of Cardiology/European Respiratory Society (ESC/ERS) 2019 PE Guidelines have recommended an updated risk-based treatment strategy.[2] Patients at high-risk (HR) status or initially at intermediate- or low-risk (IR or LR) status but

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Received: March, 30 2026
Accepted: June 1, 2026
Available Online Date: August 3, 2026

Cite this article as: Kaymaz C, Kültürsay B, Tokgöz HC, et al. Ultrasound-assisted catheter-directed thrombolysis vs. low-dose intravenous tissue-type plasminogen activator treatments in acute intermediate-high risk pulmonary embolism: insights from a retrospective study. *Anatol J Cardiol.* 2026;30(12):909-920.

DOI: 10.14744/AnatolJCardiol.2026.6510

developing acute hemodynamic instability has been considered for urgent reperfusion therapies.[2]

Although global trends have demonstrated an increasing incidence with a decreasing all-cause or PE-related 30-day mortality, rates of systemic thrombolytic therapies (STT), catheter-directed therapies (CDTs), or surgical reperfusion therapies have remained unsatisfactory.[6-11] This underutilization is likely driven by concerns regarding the increased risk of bleeding despite the proven benefits from STT over anticoagulants against the mortality and/or PE recurrence risks.[12,13]

Therefore, various CDTs have been developed to attain PA reperfusion quickly with minimal thrombolytic dosages or even without the need for thrombolytics in HR and intermediate-high-risk (IHR) patients.[14-36] Currently, 6 CDT systems are approved by the Food and Drug Administration Committee for interventional PE treatments, and according to their mechanisms, they can be classified as catheter-directed thrombolysis (CDL) or mechanical aspiration thrombectomy (MT) systems.[1,2,14-36] Ultrasound-assisted catheter-directed thrombolysis (USAT) represents the most frequently used CDL therapy in patients with PE at HR or IHR status.[14-28,31]

Although STT remains as the recommended therapeutic option in cases of deterioration to the higher risk status, safety concerns for bleeding risk have driven the search for reduced-dose lytic regimens.[1,2,37-40] Current evidence suggests that satisfactory PA reperfusion, improvements in RV function, and hemodynamic status may not require full-dose tissue-type plasminogen activator (tPA) regimens in IHR PE, and reduced-dose protocols may offer an efficacy comparable to those in full-dose regimens with the advantage of a lower risk of major bleeding events.[1,2,37-40]

In this single-center PE study, the IHR patients who underwent USAT or intravenous (IV) low-dose tPA therapies were retrospectively evaluated, and the post-treatment improvements in the PA thrombolysis, and pressure strain and recovery of RV function, as well as clinical efficacy and safety outcomes during the in-hospital stay period and long-term follow-up, were compared.

HIGHLIGHTS

- Ultrasound-assisted thrombolysis provides significantly greater thrombus resolution and reduction in residual clot burden compared to intravenous (IV) low-dose tissue-type plasminogen activator (tPA).
- Intravenous low-dose tPA achieves more pronounced early improvements in heart rate and right ventricular/left ventricular ratio during the initial treatment.
- Both reperfusion strategies yield comparable outcomes regarding in-hospital mortality, pulmonary embolism (PE) recurrence, and long-term survival rates.
- Higher PE severity indexes scores and discharge pulmonary artery systolic pressure serve as independent predictors for adverse events and mortality.

METHODS

Study Design and Population

In this study, 329 patients with acute PE at IHR out of the 976 patients diagnosed with acute PE in the tertiary cardiovascular center between October 2012 and April 2025 were retrospectively evaluated. The treatment regimen was USAT and systemic tPA (alteplase) infusion in 205 and 124 patients, respectively. The systematic work-up for the initial diagnosis of acute PE and risk stratification, including multidetector contrast-enhanced computed tomography (CT) angiography, echocardiography assessments, pulmonary embolism severity indexes (PESI), and biomarker evaluation, was based on the criteria recommended by the European Society of Cardiology / European Respiratory Society (ESC/ERS) 2014 and 2019 PE guidelines.[1,2] Patients at LR or ILR, and patients at HR who were treated with different CDT other than USAT, those with symptom onset longer than 14 days, and those with the following contraindications for thrombolytics were excluded: Hemorrhagic stroke or stroke of unknown cause at any time, ischemic stroke within the last 6 months, central nervous system damage or malignancy, gastrointestinal bleeding within the last month, known bleeding diathesis. The study protocol was approved by the Institutional Ethics Committee [no. 2025/06/1093, date: April 22, 2025].

Chest Computed Tomography Pulmonary Angiography and Echocardiography

Computed tomography images were acquired by using 64-slice helical CT angiography (Toshiba Aquilion 64, Toshiba Medical Systems Corp., Tokyo, Japan). A validated CT score for PA occlusion proposed by Qanadli et al [Qanadli score (QS)], RV/LV ratio, RV diameter, right atrial to left atrial diameter ratio (RA/LA ratio), and main, left, and right PA diameters were measured from CT images.[41] Pulmonary infarction is defined as a peripheral wedge-shaped pulmonary consolidation in a hypoperfused segment of the lung. Computed tomography images were evaluated at admission and 72-96 hours after the initiation of treatment.

Transthoracic echocardiogram (TTE) was performed on all patients on the first day of admission and repeated at discharge. Tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler (S') measurements were obtained to assess RV function in TTE, and estimated pulmonary artery systolic pressure (PASP) were calculated from the tricuspid regurgitation jet. All measurements and assessments were made in accordance with the American Society of Echocardiography guidelines.[42]

Right Heart Catheterization, Pulmonary Angiography, and Ultrasound-assisted Thrombolysis Procedure

All procedures were performed via the femoral vein (6-F sheath), and arterial puncture was avoided. A 6F multipurpose catheter was used for initial PA pressure measurements and selective angiograms. The EkoSonic Endovascular Device (EKOS, Bothell, Washington) was employed, which includes the Intelligent Drug Delivery Catheter and the MicroSonic Device equipped with multiple small ultrasound transducers distributed across the treatment zone. Procedural details were given in the previous papers.[24-26] The

preferred treatment approach involved operator-driven selection of tPA dose and treatment duration on an individual basis, tailored to each patient's risk status and comorbidities. Approximately 4 hours after the completion of tPA delivery, the system catheters and sheath were removed under fluoroscopic control. Intravenous heparin was started after termination of the USAT procedure with a targeted activated partial thromboplastin time (aPTT) around 60 seconds. Procedural details are summarized in Supplementary Materials.

Low-Dose Intravenous Tissue-Type Plasminogen Activator Treatment Protocol

The thrombolytic treatment strategy was implemented as part of an institutional protocol informed by expert consensus. Patients fulfilling at least one of the following criteria have been included in the study: systolic blood pressure ≤ 110 mm Hg, heart rate > 100 bpm, pulse oximetric saturation (SpO_2) < 90% on room air, respiratory rate > 20 breaths per minute, or serum lactate > 2 mmol/L. Exclusion criteria were the presence of any contraindication for STT, age <18 years, and duration from symptom onset to PE diagnosis >14 days. According to the institutional protocol, patients who met inclusion criteria and none of the exclusion criteria received initial weight-adjusted unfractionated heparin, followed by a 25 mg intravenous infusion of tPA over 4-6 hours. After this first infusion, a bedside clinical reassessment was performed. If any of the following criteria were still present—heart rate >100 bpm, SpO_2 < 90%, or signs of organ hypoperfusion—a second 25 mg tPA infusion was administered in the same manner. In case of persistent clinical deterioration, repeated infusions were given according to the same dosing strategy.

Primary Measures of Effectiveness

Baseline and post-treatment RV/LV ratio and PA obstruction severity (Qs), along with their changes from baseline, were assessed by CT imaging, and baseline and post-treatment TAPSE and its change were evaluated by TTE as measures of treatment effectiveness.

Safety Measures

For safety endpoints, major and minor bleeding events, as well as in-hospital deaths from all causes, were recorded. Major bleeding was defined as overt hemorrhage associated with a fall in the hemoglobin level ≥2.0 g/dL or with transfusion of 2 units of packed red blood cells or involvement of a critical site bleeding including airway, intra-abdominal, and intracranial and other central nervous system bleeding, pericardial tamponade, hemothorax, and retroperitoneal hematoma.[43] Clinical overt bleeding not fulfilling the criteria of major bleeding was classified as a minor bleeding complication.[43]

Statistical Analysis and Modelling

Continuous variables were presented as mean ± SD or median with interquartile range (IQR), based on normality. Categorical data were expressed as frequencies and percentages. Group comparisons were performed using the independent samples *t*-test, Mann–Whitney *U*-test, Pearson's χ^2 or Fisher's exact tests, as appropriate. Within-group changes from baseline were assessed using paired *t*-tests or Wilcoxon signed-rank tests. Missing data (up to 10% for numerical and 5% for categorical variables) were handled via the missForest imputation algorithm.

To mitigate potential selection bias and confounding inherent in the retrospective design, propensity score analysis (PSA) using inverse probability weighting (IPW) was employed. Variables for the PSA, including age, sex, baseline heart rate, oxygen saturation, PESI score, postoperative status, and comorbidities, were selected based on baseline differences and clinical relevance. Covariate balance before and after weighting was assessed using absolute standardized mean differences (Figure 1).

Following IPW adjustment, weighted multiple linear regression models were constructed to evaluate primary effectiveness outcomes (RV/LV, Qs, TAPSE, and their respective changes). Long-term mortality was analyzed using a weighted multivariable Cox regression model, adjusted for age, sex, PESI score, and discharge measurements of TAPSE and PASP. Statistical significance was defined as a 2-tailed $P < .05$. All analyses were performed using Jamovi and R software (version 4.3.2) with packages Hmisc, missForest, ipw, matchit, cobalt, survival, survminer, and rms. During the preparation of this manuscript, artificial intelligence-assisted technologies were utilized solely for grammatical refinement and linguistic clarity.

RESULTS

Baseline Demographic and Clinical Characteristics

The demographic, clinical, and laboratory characteristics of the patients who underwent USAT and those who received low-dose IV tPA are presented in Table 1. Mean and median doses were comparable between the USAT and systemic

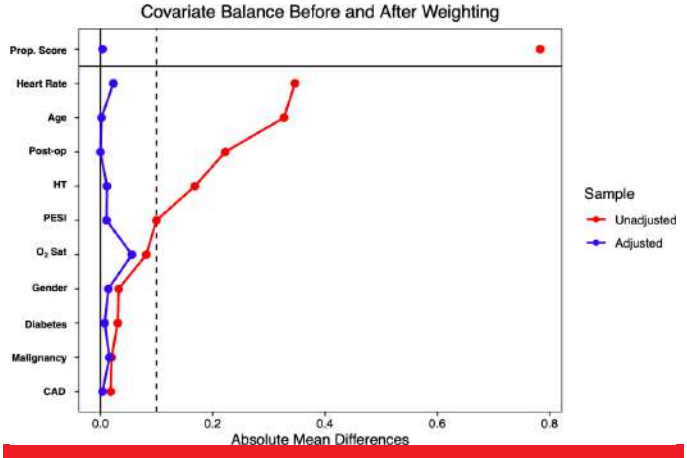


Figure 1. Assessment of covariate balance via propensity score weighting. Absolute standardized mean differences (ASMD) for baseline clinical and demographic variables before (red circles) and after (blue circles) inverse probability weighting. The vertical dashed line represents the threshold for optimal balance (ASMD < 0.1). Post-weighting, all covariates demonstrated significant balance, mitigating potential selection bias between the ultrasound-assisted thrombolysis and intravenous low-dose tissue-type plasminogen activator cohorts.

Table 1. Patients' Demographic, Clinical, and Laboratory Characteristics

	USAT (n = 205)	IV tPA (n = 124)	*P*
Age, years	64 (49.7-73)	55.5 (44-66.6)	<.003
Gender (male), n (%)	91 (44.4)	51 (41.1)	.563
Hypertension, n (%)	94 (45.9)	32 (25.8)	.001
Diabetes, n (%)	35 (17.1)	17 (13.7)	.501
CAD, n (%)	22 (10.7)	9 (7.2)	.387
Heart failure, n (%)	3 (1.5)	3 (2.4)	.669
Hyperlipidemia, n (%)	15 (7.3)	11 (8.8)	.700
COPD, n (%)	18 (8.8)	4 (3.2)	.083
Atrial fibrillation, n (%)	15 (7.3)	2 (1.6)	.104
Stroke, n (%)	5 (2.4)	0 (0)	.329
Past VTE, n (%)	10 (9.8)	15 (12.1)	.505
Acute DVT, n (%)	131 (63.9)	61 (49.2)	.029
Malignancy, n (%)	14 (6.8)	6 (4.8)	.464
Postoperative status, n (%)	77 (37.6)	19 (15.3)	<.001
Orthopedic surgery/fractures, n (%)	15 (7.3)	6 (4.8)	.373
HRT/OCS, n (%)	6 (2.9)	3 (2.4)	.701
Prolonged travelling, n (%)	18 (8.3)	6 (4.8)	.220
Thrombophilia, n (%)	3 (1.5)	1 (0.85)	.293
Syncope, n (%)	54 (26.3)	34 (27.4)	.831
Symptom duration, days	4 (2-7)	3 (2-7)	.14
SBP, mm Hg	120 (109-133)	123 (110-140)	.11
DBP, mm Hg	76 (70-85)	80 (65-90)	.76
Heart rate, /min	108 (95-115)	113 (98.4-125)	<.001
Oxygen saturation, %	89 (87-92)	89 (85-93)	.46
PESI	98 (80.7-117.3)	96.5 (72.8-115.6)	.42
PESI Class	3 (2-4)	3 (2-4)	.50
sPESI	1 (1-2)	1 (1-2)	73
d-Dimer, mg/L	8.1 (4.7-15)	9.8 (5.1-18.9)	.47
Troponin, ng/mL	0.1 (0-0.2)	0.1 (0-0.3)	.39
CRP, mg/L	3.5 (2-8.5)	8.5 (2.2-26)	<.001

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DBP, diastolic blood pressure; DVT, deep vein thrombosis; HRT/OCS, hormone replacement therapy/oral contraceptive drug; IV, intravenous; PESI, Pulmonary Embolism Severity Index; SBP, systolic blood pressure; tPA, tissue-type plasminogen activator; USAT, ultrasound-assisted thrombolysis; VTE, venous thromboembolism.

tPA groups (36.6 ± 13.8 mg - 35 (IQR 30-45) mg, and 47.6 ± 24.8 mg - 50 (IQR 25-50) mg, respectively). Patients in the USAT cohort were significantly older ($P = .003$) and had a higher prevalence of hypertension ($P = .001$) and acute deep vein thrombosis ($P = .029$). No significant baseline differences were observed regarding other comorbidities, symptom duration, or oxygen saturation. Notably, heart rate was lower in the USAT group at admission ($P < .001$). No significant differences were observed regarding PESI scores or sPESI between the groups.

Baseline Echocardiographic and Tomographic Findings

Baseline echocardiographic and tomographic assessments are summarized in Table 2. Although RV function parameters TAPSE and S' were similar between groups, PASP and thrombus burden quantified by Qs were significantly higher in the USAT group ($P < .001$ for both). Right ventricular diameter and RV/LV ratio at admission were higher in the IV tPA group ($P < .001$ for both), while no significant difference was found in RA/LA ratio, PA diameters, or presence of pulmonary infarction ($P =$ NS).

Procedural Characteristics

As illustrated in Figure 2, most USAT procedures (82.9%) were bilateral, with a mean tPA dose of 38.5 ± 13.6 mg and an average infusion duration of 25.2 ± 6.6 hours. Ultrasound-assisted thrombolysis resulted in significant acute reductions in systolic, diastolic, and mean pulmonary artery pressures (Figure 2). In the low-dose IV tPA group, the mean and median total tPA dose was 47.6 ± 24.8 - 50 mg (IQR: 25-50 mg), with an infusion duration of 6 hours (IQR: 4-10 hours). 58.9% of patients required a second infusion, and 11.3% received up to 4 infusions to achieve clinical stabilization (Figure 2) (Detailed data provided in Supplementary Materials).

Post-Treatment Clinical and Imaging Outcomes

Table 3 demonstrates post-treatment clinical, echocardiographic, and tomographic measurements. While systolic and diastolic blood pressures remained similar between groups at discharge, oxygen saturation was modestly higher in the IV tPA group ($P = .004$). No difference between groups was observed in TAPSE, S', RV/LV ratio, or PA diameters at discharge. However, PASP remained significantly lower in the

Table 2. Echocardiographic and Tomographic Measures

	USAT (n = 205)	IV tPA (n = 124)	*P*
TAPSE, mm	1.8 (1.5-2.1)	1.8 (1.5-2.1)	.75
S′, cm/s	11 (9.5-12.1)	12 (8.9-13)	.56
PASP, mm Hg	55 (50-65)	50 (40-60)	<.001
Qanadli score	24 (20-28.1)	20 (18-23.1)	<.001
RV/LV_1 ratio	1.17 (1.1-1.3)	1.28 (1.1-1.4)	<.001
RV diameter, mm	43.8 (40-47)	47.3 (41.9-50)	<.001
RA/LA_1 ratio	1.32 (1.1-1.5)	1.29 (1.1-1.5)	.47
Main PA diameter, mm	30.5 (28.2-34)	30.4 (27.9-32.1)	.24
Left PA diameter, mm	22.8 (21-25.6)	22.7 (20-24.6)	.22
Right PA diameter, mm	23.8 (21.5-26)	22.9 (20.3-25)	.12
Main PA/Aorta ratio	0.9 (0.8-1.0)	0.9 (0.8-1.0)	.42
Pleural effusion, n (%)	26 (12.7)	20 (16.1)	.524
Pulmonary infarction, n (%)	41 (20)	26 (21)	.881

IV, intravenous; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PASP, systolic pulmonary artery pressure; RA, right atrium; RV, right ventricle; S′, right ventricle tissue Doppler; TAPSE, tricuspid annular plane systolic excursion; tPA, tissue-type plasminogen activator.
$_1$Measurement at admission.

IV tPA group ($P = .014$), whereas the post-treatment RA/LA ratio was higher in the USAT group ($P < .001$). Pleural effusion and pulmonary infarction were more prevalent among USAT-treated patients ($P = .002$ and $P = .031$, respectively). Changes in clinical and imaging parameters from baseline are summarized in Table 4. The reduction in heart rate was greater in the IV tPA group ($P = .023$), whereas improvements in oxygen saturation and TAPSE were comparable between groups. The decrease in thrombus burden (Qs) was significantly higher among USAT-treated patients ($P < .001$). Conversely, the reduction in RV/LV ratio was more pronounced in the IV tPA group ($P < .001$), while PASP improvement did not differ significantly between groups (Figure 3).

Adjusted Treatment Effects

After adjustment for confounders using IPW, USAT demonstrated superiority in thrombus resolution over IV tPA. Systemic low-dose IV tPA was associated with a significantly higher residual thrombus burden (Qs_2) (Estimate = 1.92; 95% CI = 0.77-3.07; $P = .001$) and a markedly lower overall

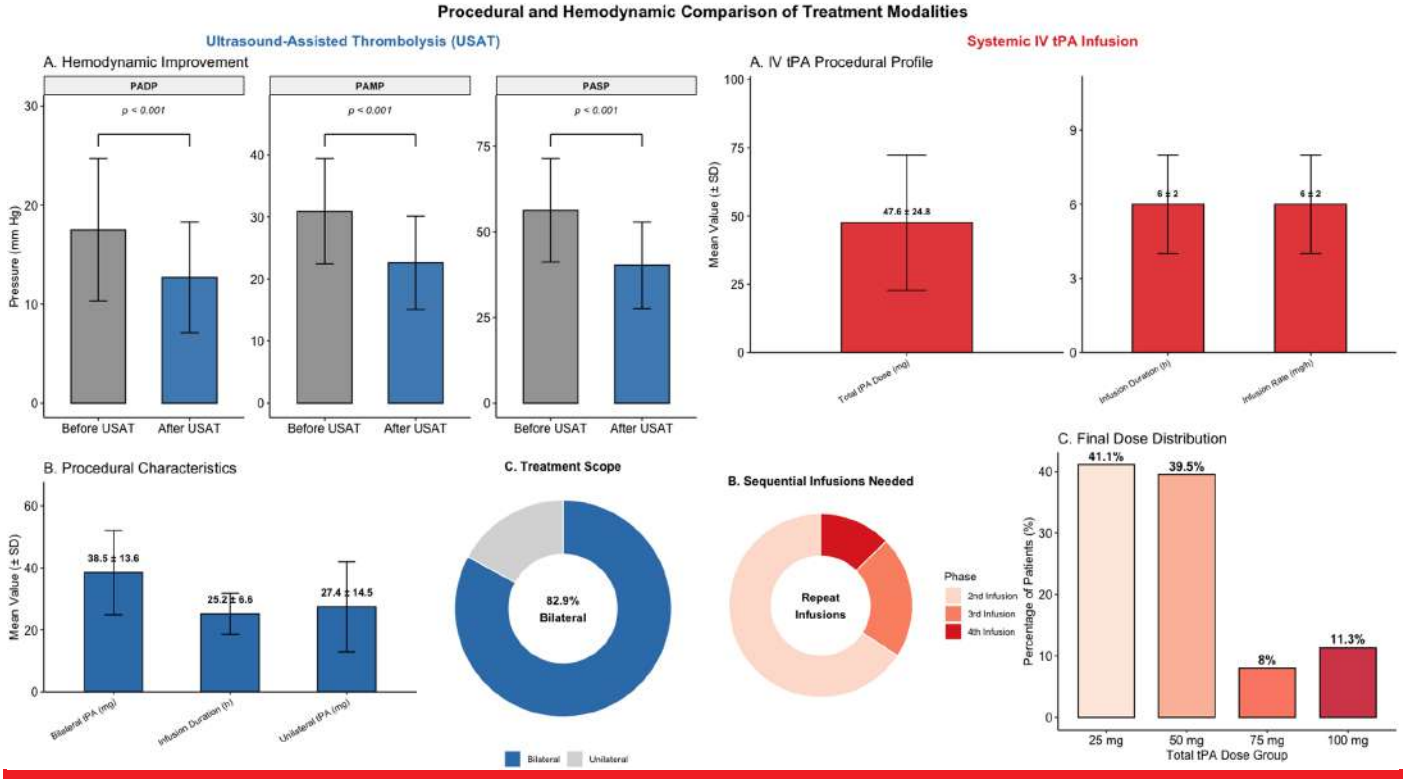


Figure 2. Procedural and hemodynamic profiles of treatment modalities. A head-to-head comparison of procedural characteristics and acute responses.

Table 3. Post-treatment Clinical, Echocardiographic, and Tomographic Measurements

	USAT (n = 205)	IV tPA (n = 124)	*P*
SBP, mm Hg	124 ± 17.2	123 ± 14.9	.848
DBP, mm Hg	75.5 ± 10.5	76 ± 10.5	.776
Heart rate, /min	81.7 ± 12.7	82.2 ± 11.3	.706
Oxygen saturation, %	95 (93-97)	96 (94-97.3)	.004
TAPSE, cm	2.29 ± 0.4	23 ± 0.3	.872
S′, cm/s	14.2 ± 2.4	14.1 ± 2.5	.648
PASP, mm Hg	35 (30-40)	30 (29.5-35.8)	.014
Qanadli score	8 (5-13)	9 (6.75-13)	.169
RV/LV$_2$ ratio	0.91 ± 0.11	0.90 ± 0.13	.275
RA/LA$_2$ ratio	1.14 ± 0.22	1.02 ± 0.18	<.001
Main PA diameter, mm	28 ± 4.6	27.8 ± 4	.718
Left PA diameter, mm	21.3 ± 3.3	20.8 ± 2.9	.243
Right PA diameter, mm	21.8 ± 3.5	21.6 ± 3.45	.623
Main PA/Aorta ratio	0.82 ± 0.13	0.86 ± 0.12	.053
Pleural effusion, n (%)	90 (43.9)	26 (20.9)	.002
Pulmonary infarction, n (%)	71 (34.6)	25 (20.1)	.031
Major bleeding, n (%)	12 (5.9)	6 (4.8)	.695
Minor bleeding, n (%)	19 (9.4)	4 (3.2)	.027
In-hospital mortality, n (%)	10 (4.9)	6 (4.8)	.987

IV, intravenous; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; RA, right atrium; RV, right ventricle; S′, right ventricle tissue Doppler; TAPSE, tricuspid annular plane systolic excursion; tPA, tissue-type plasminogen activator.
$_2$Measurement after treatment.

reduction in clot load (ΔQs, Estimate = −3.31; 95% CI = −4.63 to −1.99; *P* < .001) (Figure 4). No significant associations were observed between treatment modality and post-treatment RV/LV ratio or TAPSE changes. The results of the weighted models assessing the treatment effect are summarized in Table 5 and Supplementary Tables.

In-Hospital Outcomes and Long-Term Mortality

Weighted logistic regression analysis revealed no significant difference between groups regarding in-hospital mortality or PE recurrence (*P* = .694) (Table 6). Among covariates, higher PESI scores were independently associated with increased risk of in-hospital death or PE recurrence (*P* = .003).

Table 4. Changes in Clinical and Imaging Measurements of Patients

	Mean Change from Baseline (Standard Error)		
	USAT	IV tPA	*P*
Heart rate, /min	24.5 (1.4)	29.6 (1.7)	.023
Oxygen saturation, %	5.1 (0.6)	5.4 (0.8)	.788
TAPSE, cm	0.46 (0.03)	0.46 (0.04)	.995
Qs	14.5 (0.4)	10.1 (0.6)	<.001
RV/LV ratio	0.28 (0.01)	0.37 (0.02)	<.001
PASP, mm Hg	19.1 (0.9)	17.6 (1.4)	.394

IV, intravenous; LV, left ventricle; PASP, pulmonary artery systolic pressure; Qs, Qanadli score; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; tPA, tissue-type plasminogen activator.

The median follow-up period was 95.8 months (IQR: 76.6-104.3). One-year survival rates were comparable between the USAT and IV tPA groups (89.1% vs. 89.5%, respectively) (Figure 5). Weighted Cox regression confirmed no significant difference in long-term mortality between the 2 treatment arms (Table 7). Older age and higher PASP at discharge emerged as independent predictors of mortality, while female sex was associated with lower risk. Notably, neither PESI scores nor discharge TAPSE values were significantly associated with long-term survival.

DISCUSSION

This single-center study retrospectively evaluated the USAT vs. IV low-dose tPA in acute PE patients at IHR status. The reductions in heart rate and in RV/LV ratio were more pronounced with IV tPA, whereas the lysis of thrombi was significantly higher with USAT. However, improvements in the oxygen saturation, TAPSE, and PASP were comparable. After adjustment for confounders, the superiority of USAT over IV tPA in terms of clot resolution was significant, while in-hospital mortality, PE recurrence and long-term mortality were similar between the 2 arms. A higher PESI score independently associated with the risk of in-hospital death or PE recurrence, whereas an older age, male sex and a higher PASP at discharge were independent predictors for shortened long-term survival.

The decisions for urgent reperfusion strategies in acute PE seem to require innovative risk algorithms that consider the changes in cardiorespiratory, metabolic, renal, and cerebrovascular parameters under initial therapies as the

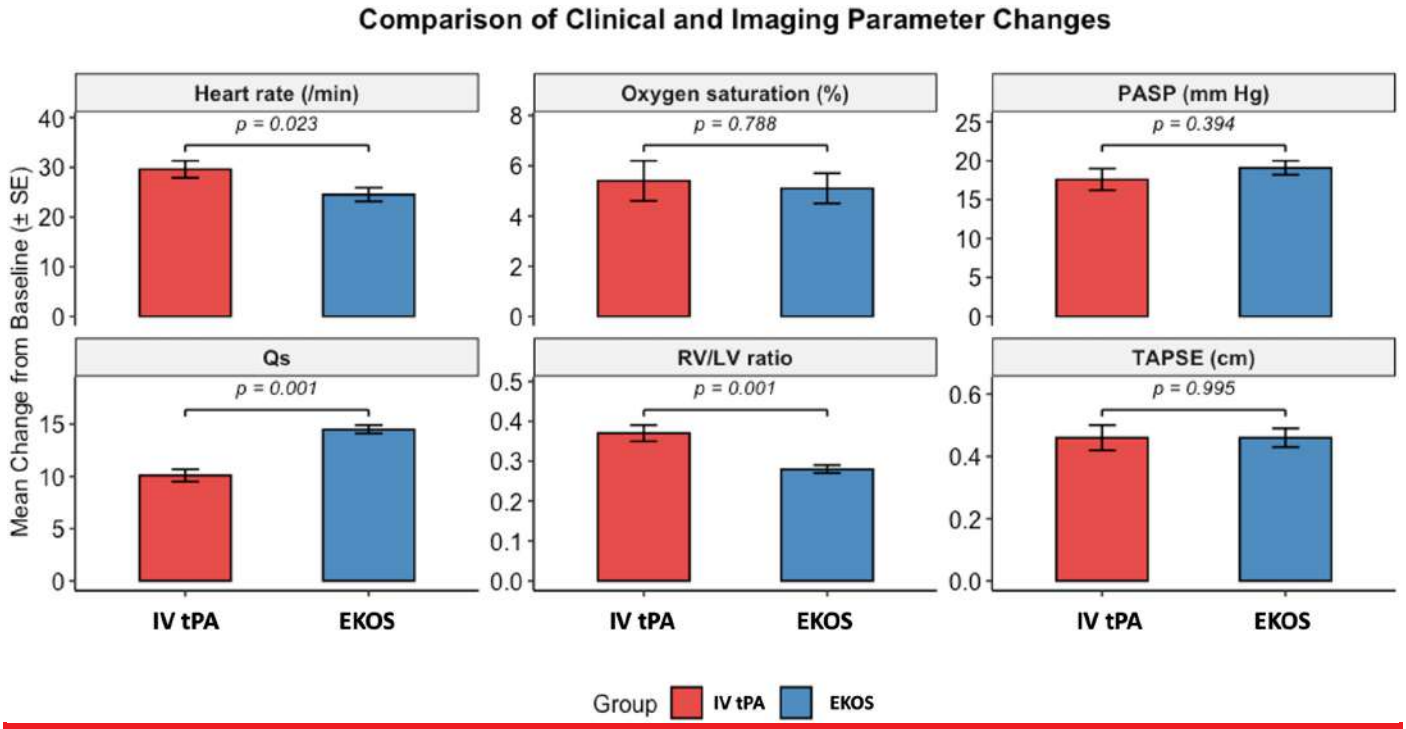


Figure 3. Comparison of acute clinical and imaging response metrics. Bar plots representing the absolute changes from baseline to discharge in key parameters. While ultrasound-assisted thrombolysis (blue) demonstrated significantly greater reductions in thrombus burden (Qanadli score), intravenous low-dose tissue-type plasminogen activator (red) was associated with more pronounced early improvements in heart rate and right ventricle (RV)/left ventricle ratio. Improvements in oxygen saturation and RV functional markers were comparable between the 2 reperfusion strategies.

benefit, failure or deterioration, and tendency for major bleedings.[1,2,14-16,44] Moreover, treatment goals of CDTs and STT are also different between HR and IHR statuses.[1,2,14-16,44] Therefore definitions of treatment success or failure need to be tailored, and comorbidities should also be taken into the account.[1,2,14-16,44] In the clinical consensus statement of the ESC for percutaneous treatments for acute PE, CDT is proposed for HR and IHR patients in the absence of stabilization in vital parameters under initial unfractionated or low-molecular-weight heparin therapies and the presence

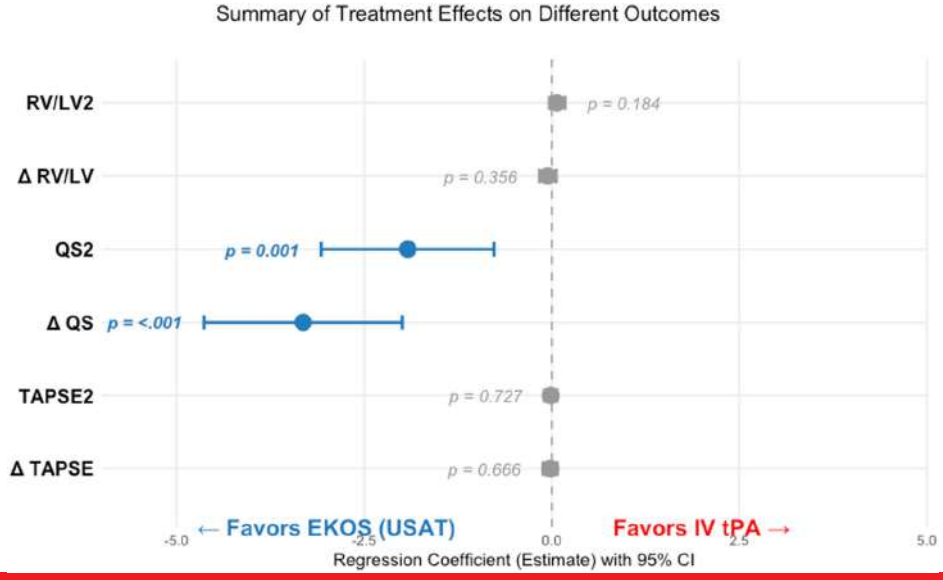


Figure 4. Forest plot of adjusted treatment effects (intravenous (IV) tissue-type plasminogen activator (tPA) vs. ultrasound-assisted thrombolysis (USAT)). Weighted linear regression analysis following inverse probability weighting adjustment. Estimates represent the independent association of IV low-dose tPA with clinical outcomes relative to USAT (Reference).

Table 5. Summary of IV tPA Effects on Different Clinical Outcomes (Weighted Linear Regression)

Outcomes	Estimate (IV tPA)	95% CI Lower	95% CI Upper	*P*
RV/LV_2	0.071	−0.033	0.175	.184
Δ RV/LV	−0.053	−0.164	0.058	.356
QS_2	1.920	0.768	3.072	.001
Δ QS	−3.314	−4.634	−1.994	<.001
$TAPSE_2$	−0.014	−0.094	0.066	.727
Δ TAPSE	−0.021	−0.113	0.071	.666

USAT (EKOS) is the reference group. Positive estimates indicate higher values in the IV tPA group; negative estimates indicate lower values in the IV tPA group compared to USAT. $_2$Measurement after treatment. IV, intravenous; LV, left ventricle; Qs, Qanadli score; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; tPA, tissue-type plasminogen activator; USAT, ultrasound-assisted thrombolysis.

Table 6. Weighted Logistic Regression for in-Hospital Death and Re-embolism

Variables	Estimate (log-odds)	Standard Error	*z*	*P*
IV tPA	−0.226	0.575	−0.393	.694
PESI	0.038	0.013	2.991	.003
Age (per year)	−0.015	0.021	−0.717	.474
Gender (female)	0.469	0.583	0.805	.421

IV, intravenous; PESI, pulmonary embolism severity indexes; tPA, tissue-type plasminogen activator.

of contraindications for STT.[15] In the further decision-making for the selection of optimal CDT devices in PE, location, extension, and age of clot, and risk of bleeding are regarded as major determinants.[14-16,44] A more distal and acute thrombus is considered to favor USAT or other CDL systems, whereas MT seems to be the first treatment of choice in cases of more proximal and subacute thrombus, and there is a need to avoid bleeding. [45,46]

The USAT system produces high frequency and low power pulses of varying waveforms facilitating the penetrance of tPA to deeper layers of clot without disruption of fibrin crosslinks.[17] The efficacy and safety of USAT with adjunctive reduced-dose t-PA regimens have been confirmed by 2 RCTs, retrospective and prospective studies, and meta-analyses.[17-31] In the previously reported series, USAT therapy was associated with significant improvements in the measures of PA thrombotic obstruction, RV/LV and RA/LA ratios, TAPSE, PA diameters, and PA pressures in patients with PE at HR or IHR.[17-31] Thirty-day mortality rate was related to HR status whereas long-term mortality was predicted by aging over 65 years.[46] The OPTALYSE-PE RCT provided the first evidence for low-dose/short-duration t-PA regimen in USAT, and long-term follow-up over a 1-year period revealed sustained benefit in terms of RV function, functional status, and quality of life.[19-21] Thereafter, KNOCOUT-PE multicenter registry also provided the robust evidence for the efficacy and safety of USAT with low-dose/short-duration tPA regimen in real-life settings.[22] Most recently, the HI-PEITHO trial demonstrated that USAT plus anticoagulation significantly reduced the composite risk of PE-related death, cardiorespiratory decompensation, or recurrence within 7 days compared

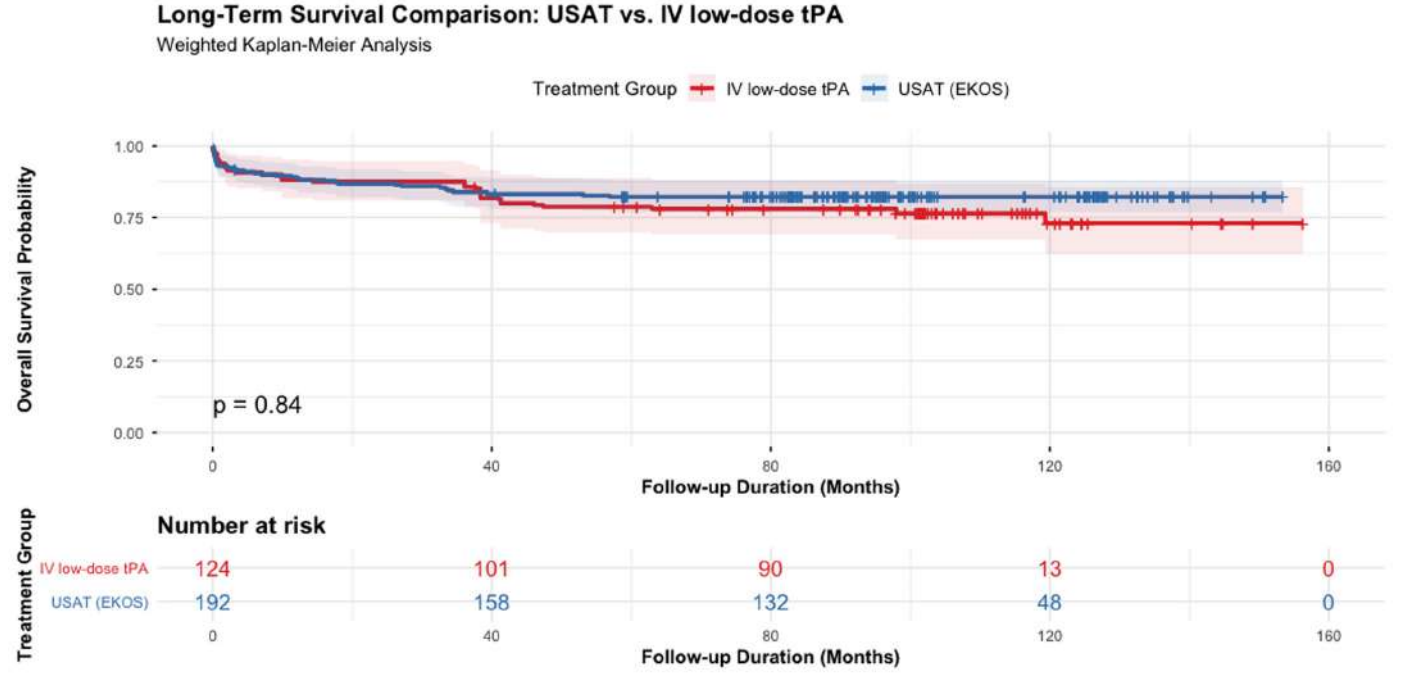


Figure 5. Long-term overall survival: ultrasound-assisted thrombolysis (USAT) vs. intravenous low-dose tissue-type plasminogen activator (tPA). Inverse probability weighted Kaplan–Meier survival curves demonstrating long-term prognosis. The USAT (blue line) and IV low-dose tPA (red line) cohorts exhibited comparable survival probabilities (*P* = NS). The risk table (bottom) displays the number of patients at risk at specific time points throughout the follow-up period.

Table 7. Weighted Cox Regression Results for Long-term Mortality

Variables	HR	95% CI Lower	95% CI Upper	*P*
Age (per year)	1.04	1.01	1.07	.004
Gender (female)	0.51	0.30	0.86	.012
IV tPA	1.42	0.83	2.41	.200
PESI	1.01	1.00	1.02	.133
$TAPSE_2$ (cm)	1.30	0.67	2.53	.444
$PASP_2$ (mm Hg)	1.03	1.00	1.05	.017

HR, hazard ratio; IV, intravenous; PASP, pulmonary artery systolic pressure; PESI, pulmonary embolism severity indexes; TAPSE, tricuspid annular plane systolic excursion; tPA, tissue-type plasminogen activator. $_2$Measurement after treatment.

to anticoagulation alone (4.0% vs. 10.3%, *P* = .005), without increasing major bleeding.[47]

A systematic review and meta-analysis comparing the safety and efficacy of USAT vs. standard CDL with low-dose lytics showed no statistically significant difference between the 2 treatments for odds of in-hospital mortality, intracranial hemorrhage, major bleeding, and for means of hospital or intensive care unit length of stay, or reduction in PA pressures.[48]

On the other hand, dosing of the IV tPA in IHR PE represents another challenging issue.[1,2,37-40] Although STT remains as the recommended therapeutic option in cases of deterioration to the higher risk status, current evidence suggests that satisfactory resolution of PA thrombotic obstruction, improvements in RV pressure strain and hemodynamic status may not require full-dose tPA regimens in IHR PE, and reduced doses may also offer similar efficacy as compared to those in full-dose regimens with the lower risks of bleeding events.[1,2,37-40] In the previously published study, reduced-dose tPA therapies were found to be associated with significant improvements in PASP, RV/LV and RA/LA ratios, and TAPSE in PE patients at IHR.[40] Moreover, the present study demonstrated that the mean and median tPA dose was 47.6 ± 24.8 mg and 50 mg (IQR: 25-50 mg), with an infusion duration of 6 hours (IQR: 4-10 hours) in the low-dose IV tPA cohort. A distinctive finding was the high requirement for repeated infusions; nearly 59% of patients required a second 25 mg dose, suggesting that a single bolus may be insufficient for a significant portion of IHR PE patients. The Pulmonary Embolism Response Team (PERT) algorithm in acute PE related to reductions in all-cause mortality, major or clinically relevant bleeding, length of hospital stay, but higher utilization rates of advanced therapies.[10] In the PERT Consortium Registry between the years 2028 and 2024, trends for utilization of CDT, STT, surgical embolectomy, and extracorporeal membrane oxygenation (ECMO) in large series of patients with acute PE enrolled at 51 sites were analyzed, and an age-, sex-, and PE risk-matched population from the US Nationwide Inpatient Sample was also used for comparison. The HR and IR status were documented in 13.7% and 62.5% of patients respectively. The CDTs were utilized in 23.1% of overall PE patients, and CDL with USAT, MT and CDL without USAT were documented in 32.2%, 58.1% and 5.3% of those, respectively. Surgical embolectomy, STT and ECMO were also noted in 1.1%, 5.6% and 1.1% of patients, respectively. There were significant trends of increase in CDT over time, with an increase in MT and a decrease in CDL. In comparison to the US Nationwide Inpatient Sample population, patients enrolled in the PERT Consortium registry had a lower in-hospital mortality and a shorter hospital length of stay.[6] Similarly, Medicare records confirmed the increase in the rate of CDT over time, and this was mainly related to increases in MT.[7] Time trends of PE treatments from Germany also demonstrated an increase in the utilization of CDT for HR patients. Although utilization of CDT decreased with aging, in-hospital case-fatality rates showed a higher benefit from CDT in octogenarians.[8]

In the ERASE PE (Bern Acute Pulmonary Embolism Registry) single-center cohort study investigating the safety and effectiveness of USAT with low-dose tPA according to the decision of the local PE response team in IHR and HR patients, RV overload and pulmonary artery mean pressure was reduced in 88% of patients. Mortality, embolic stroke, bleeding, and recurrent PE rates were 3.2%, 0.3%, 7.9%, and 1.0%, respectively.[9]

Comparisons of MT and CDL in a systematic review and meta-analysis showed comparable all-cause mortality, in-hospital stay, re-hospitalizations, and bleeding rate in PE.[49] In a nationwide analysis on patients with HR PE, in-hospital mortality, major bleeding, and 30-day urgent readmission rates were not different among the CDL, MT, or both CDL and MT cohorts.[50] A meta-analysis on patients with IR and HR PE revealed that CDT vs. STT was associated with a 60% reduction in in-hospital mortality, a 49% reduction in 30-day mortality, a 54% reduction in 1-year mortality, a 57% reduction in stroke, a 29% reduction in 30-day readmission, a 39% reduction in major bleeding, but a 2.5 times higher rate of hemoptysis and 2.52 times higher rates of ECMO utilization.[51] Another systematic review and network meta-analysis on patients with IR or HR PE, CDT vs. STT was associated with a 57% reduction in all-cause mortality, a 39% reduction in major bleeding, and a 56% reduction in intracranial hemorrhage.[52] The last systematic review and meta-analysis on patients with PE at IR to HR confirmed the superiority of CDT over STT in terms of reductions in major bleeding, in-hospital mortality, and recurrent PE rates.[53] Earlier vs. delayed CDTs was also associated with a significantly higher 90-day survival in IR and HR PE cohorts.[54]

In the study, the majority of USAT procedures were performed bilaterally, and the mean adjuvant tPA dose range was higher, and the infusion duration was also longer than those in currently available other low-dose/slow-infusion USAT trials.

In an emulated target trial analysis on in-hospital mortality prediction adjusted for all non-modifiable risk factors according to treatment strategy in patients with HR PE, the mortality risk ratios were largely in favor of any advanced recanalization strategy including STT, CDT, and surgical thrombectomy over veno-arterial ECMO alone.[55]

In the study, post-treatment systemic arterial pressures, RV function, RV/LV ratio, and PA diameters were similar between 2 treatment groups, but PASP and RA/LA ratio were significantly higher, and pleural effusion and pulmonary infarction were more frequent after USAT treatment. Low-dose IV t-PA was related to more marked reductions in heart rate and in RV/LV ratio, while USAT showed superiority in thrombus resolution. However, both treatment cohorts showed similar improvements in the oxygen saturation, TAPSE, and PASP. Adjustment for confounders also confirmed the superiority of USAT over IV tPA in the dissolution of clot but not for in-hospital mortality, PE recurrence and long-term mortality. These results seem to differ from the results of some meta-analyses favoring the CDT over STT in terms of all-cause mortality and bleeding outcomes. However, the low doses of tPA in STT and moderate-dose/slow-infusion tPA regimen in USAT cohorts might be associated with the absence of the difference in mortality and bleeding outcomes in the study. But, regardless of the selected reperfusion treatments, a higher PESI score independent predictor for in-hospital death or PE recurrence risks, whereas older age, male sex and a higher PASP at discharge predicted long-term survival.

In the recently published retrospective study, using unsupervised machine learning, 2 phenotypes were identified in IHR PE patients.[56] Cluster 1 (RV-failure phenotype) exhibited a younger age, lower systolic blood pressure, more severe RV dysfunction, higher thrombotic burden, and lower baseline TAPSE/PASP ratios, while Cluster 2 (comorbidity-dominant phenotype) comprised older patients with more cardiovascular/metabolic comorbidities but relatively preserved hemodynamics. Cluster 1 demonstrated a higher improvement in RV function after reperfusion therapies, while Cluster 2 was independently associated with a lower early mortality. However, the CDT-cluster interaction term was not statistically significant, and long-term survival was comparable between clusters.[56]These findings suggest that unsupervised machine learning may refine initial risk stratification and help guide tailored management decisions in patients at IHR.

With further validations regarding the efficacy and safety outcomes of low-dose IV tPA protocols, this approach might transform the care for IHR PE. Three ongoing trials in patients at IHR; reduced-dose intravenous thrombolysis for acute intermediate-high-risk pulmonary embolism: rationale and design of the pulmonary embolism international thrombolysis (PEITHO)-3, and low dose thrombolysis, USAT or heparin for intermediate high risk pulmonary embolism (STRATIFY) have been designed to assess the efficacy and safety of reduced-dose tPA regimen compared with standard anticoagulant therapy, and the USAT with low-dose, rapid-infusion tPA strategy vs. standard anticoagulation, respectively.[46,57]

Limitations, Clinical Implications, and Future Directions

This study has several limitations inherent to its retrospective, single-center design. Although IPW adjustment was employed to mitigate selection bias, unmeasured confounders may still influence the results. However, the relatively large sample size for a single-center study and the long-term follow-up provide robust real-world data on these competing reperfusion strategies. Innovative risk stratification algorithms taking into account obstructive burden, RV adaptive response to pressure strain, hemodynamic status, and bleeding risks may provide further insights regarding the tailored PE treatments in IHR. Prospective trial designs that permit comparisons among risk-based anticoagulant and full-dose or reduced-dose STT therapies, different doses and infusion regimens of tPA with USAT, and USAT vs. other CDTs might provide more relevant data for efficacy and safety concerns in this setting.

CONCLUSION

In patients with acute IHR PE, systemic low-dose IV tPA was associated with more pronounced early improvements in heart rate and RV/LV ratio, whereas USAT demonstrated clear superiority in thrombus resolution. After adjusting for confounders, these responses did not translate into differences in early or late clinical outcomes, including in-hospital mortality, PE recurrence, or long-term survival. The comparable safety and efficacy profiles suggest that both USAT and low-dose systemic regimens are viable reperfusion strategies in this setting. Ongoing randomized trials are expected to further refine the optimal selection of reperfusion strategies for this vulnerable patient population.

Ethics Committee Approval: This study was approved by the Ethics Committee of Kartal Kosuyolu Research and Education Hospital, Istanbul, Türkiye (Approval No: 2025/06/1093, Date: April 22, 2025).

Informed Consent: Due to the retrospective nature of the study, informed consent was not obtained from the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.K., B.K., N.Ö.; Design – C.K., B.K., H.C.T., H.I.T.; Supervision – C.K., Ç.E.Ç., H.I.T., N.Ö.; Resources – C.K., B.K., B.K. (Berhan Keskin), Ç.B., D.M., S.E.; Materials – S.T., Ç.B., D.M., F.A., R.B., A.H., Ş.K.; Data Collection and/or Processing – B.K., H.C.T., S.T., B.K. (Berhan Keskin), Ç.B., S.E., F.A., R.B., A.H., Ş.K.; Analysis and/or Interpretation – C.K., B.K., H.I.T.; Literature Search – H.C.T., S.T., Ç.B., D.M., S.E., F.A., R.B., A.H., Ş.K.; Writing – C.K., B.K., H.C.T.; Critical Review – C.K., Ç.E.Ç., H.I.T., N.Ö.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declare that this study received no financial support.

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SUPPLEMENTARY MATERIAL

Procedural characteristics of USAT.

	USAT n = 205		
Bilateral, n (%)	170 (82.9%)		
tPA dose, mg Unilateral Bilateral	27.4 ± 14.5 38.5 ± 13.6		
Infusion duration, hours	25.2 ± 6.6		
Pulmonary pressures before USAT		Pulmonary pressures after USAT	
PASP, mm Hg	56.2 ± 15.1	PASP, mm Hg	40.2 ± 12.6
PADP, mm Hg	17.5 ± 7.2	PADP, mm Hg	12.7 ± 5.6
PAMP, mm Hg	30.9 ± 8.5	PAMP, mm Hg	22.6 ± 7.5

Abbreviations: tPA: Tissue plasminogen activator, PASP: Pulmonary artery systolic pressure PADP: Pulmonary artery diastolic pressure, PAMP: Pulmonary artery mean pressure

Thrombolytic dosing regimens.

	All, n = 124
tPA dose, mg	50 (25-50), 47.6 ± 24.8
tPA infusion duration, hours	6 (4-10)
tPA infusion rate, mg/hours	6 (4-10)
Requirement following the 1st infusion 2nd Infusion (50 mg) 3rd Infusion (75 mg) 4th Infusion (100 mg)	 73 (58.9%) 24 (19.3%) 14 (11.3%)
tPA dose groups 25mg 50mg 75mg 100mg	 51 (41.1%) 49 (39.5%) 10 (8%) 14 (11.3)

Supplementary Table 1. Weighted Linear Regression for RV/LV_2.

Variables	Estimate	95% CI	*P*
IV tPA	0.071	(−0.033 – 0.175)	0.184
PESI	0.001	(−0.001 – 0.004)	0.220
Age (per year)	−0.000	(−0.004 – 0.003)	0.814
Gender (female)	−0.052	(−0.158 – 0.054)	0.334
RV/LV_1	0.039	(−0.230 – 0.308)	0.778

Supplementary Table 2. Weighted Linear Regression for ΔRV/LV.

Variables	Estimate	95% CI	*P*
IV tPA	**−0.053**	**(−0.164 – 0.058)**	**0.356**
PESI	**−0.001**	**(−0.003 – 0.002)**	**0.460**
Age (per year)	**0.001**	**(−0.003 – 0.005)**	**0.666**
Gender (female)	**0.094**	**(−0.019 – 0.206)**	**0.103**

Supplementary Table 3. Weighted Linear Regression for QS_2.

Variables	Estimate	95% CI	*P*
IV tPA	**1.920**	**0.768 – 3.072**	**0.0012**
PESI	**−0.013**	**(−0.037 – 0.012)**	**0.323**
Age (per year)	**−0.045**	**(−0.087 – −0.003)**	**0.038**
Gender (female)	**−0.180**	**(−1.311 – 0.951)**	**0.755**
QS_1	**0.498**	**0.410 – 0.586**	**<0.001**

Supplementary Table 4. Weighted Linear Regression for ΔQS

Variables	Estimate	95% CI	*P*
IV tPA	**−3.314**	**−4.634 – −1.994**	**<0.001**
PESI	**0.015**	**−0.015 – 0.045**	**0.310**
Age (per year)	**0.070**	**0.020 – 0.120**	**0.006**
Gender (female)	**0.666**	**−0.659 – 1.990**	**0.325**

Supplementary Table 5. Weighted Linear Regression for $TAPSE_2$.

Variables	Estimate	95% CI	*P*
IV tPA	**−0.014**	**−0.094 – 0.066**	**0.727**
PESI	**−0.001**	**−0.003 – 0.001**	**0.443**
Age (per year)	**0.000**	**−0.003 – 0.004**	**0.779**
Gender (female)	**−0.040**	**−0.120 – 0.041**	**0.335**
$TAPSE_1$ (cm)	**0.420**	**0.318 – 0.521**	**<0.001**

Supplementary Table 6. Weighted Linear Regression for ΔTAPSE

Variables	Estimate	95% CI	*P*
IV tPA	**−0.021**	**−0.113 – 0.071**	**0.666**
PESI	**0.001**	**−0.001 – 0.004**	**0.268**
Age (per year)	**0.001**	**−0.003 – 0.005**	**0.773**
Gender (female)	**−0.020**	**−0.133 – 0.093**	**0.685**

THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

The Level of Gut Microbiota–Derived TMAO in Acute Myocardial Infarction and Its Prognostic Value

ORIGINAL INVESTIGATION

ABSTRACT

Objective: This study examined the relationship of plasma trimethylamine N-oxide (TMAO), a gut microbiota-derived metabolite, with both disease severity and short-term prognosis in acute myocardial infarction (AMI) patients.

Methods: This retrospective observational study was performed at a single center and comprised 60 AMI patients along with 30 controls with angiographically normal or near-normal coronary arteries (stenosis <20% in all major epicardial vessels). Plasma TMAO levels were measured at admission via high-performance liquid chromatography-tandem mass spectrometry. The severity of coronary artery disease was graded according to the Gensini score. Patients were followed up for 6 months after discharge, and the occurrence of major adverse cardiovascular events (MACEs) within this period was ascertained retrospectively from hospital electronic medical records and routine cardiology follow-up documentation.

Results: Compared to controls, AMI patients had significantly higher plasma TMAO levels (median 5.80 vs. 2.10 μmol/L, $P < .001$). Consistent with its elevation, TMAO demonstrated a strong positive correlation with the Gensini score (rs = 0.998, $P < .001$) and peak troponin I (rs = 0.996, $P < .001$). A high TMAO level (>5.80 μmol/L) was independently associated with an increased risk of 6-month MACE (hazard ratio = 2.45, 95% CI: 1.38-4.35, $P = .002$). Furthermore, incorporating TMAO into traditional clinical models enhanced their predictive performance, yielding a modest yet statistically significant improvement in the area under the curve from 0.880 to 0.884 ($P = .012$).

Conclusion: Elevated plasma TMAO is associated with more severe coronary artery disease, greater myocardial injury, and worse short-term prognosis in AMI patients, offering incremental prognostic value beyond conventional risk factors.

Keywords: Acute myocardial infarction, Gensini score, gut microbiota, major adverse cardiovascular events, prognosis, trimethylamine N-oxide

INTRODUCTION

Acute myocardial infarction (AMI) stands as a primary cardiovascular emergency responsible for global mortality and disability. Its pathological essence lies in the unstable rupture of coronary atherosclerotic plaques and subsequent thrombus formation, leading to a sudden cessation of myocardial blood flow. Despite substantial advancements in percutaneous coronary intervention (PCI) and pharmacological management that have markedly enhanced early survival rates among AMI patients, the enduring risk of major adverse cardiovascular events (MACEs) remains persistently elevated, posing a significant challenge for long-term prognostic management.[1] Consequently, delving into novel mechanisms underpinning AMI pathogenesis and progression, and subsequently identifying new biomarkers capable of precisely discerning high-risk individuals, holds paramount clinical significance for refining personalized therapeutic strategies and improving long-term outcomes.[2]

Traditionally, atherogenesis has been viewed as a pathological process intimately linked to dyslipidemia, endothelial dysfunction, inflammatory responses, and oxidative stress.[3] However, emerging data in recent years indicate that the

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Received: February 3, 2026
Accepted: June 2, 2026

Cite this article as: Jiang M, Xu S, Zhou Y, Liu M. The level of gut microbiota–derived TMAO in acute myocardial infarction and its prognostic value. *Anatol J Cardiol.* 2026;30(12):921-931.

DOI: 10.14744/AnatolJCardiol.2026.6143

once-overlooked gut microbiota exerts a significant influence on the development and advancement of cardiometabolic diseases.[4,5] The gut microbiota constitutes a complex micro-ecosystem that orchestrates host nutrient metabolism and immune function, while also directly or indirectly modulating host physiology and pathology through its metabolic products. In this context, trimethylamine N-oxide (TMAO), a metabolite yielded from gut microbial processing of dietary precursors like phosphatidylcholine and L-carnitine, has progressively moved to the forefront of cardiovascular research.[6]

Investigations into the pathogenic mechanisms of TMAO have begun to delineate its multifaceted pathways in promoting atherosclerosis. Foundational studies indicate that TMAO can disrupt reverse cholesterol transport, promote macrophage foam cell formation, thereby accelerating atherosclerotic plaque development.[7] Recent experimental evidence further supports the role of gut microbiota modulation in cardiovascular health, demonstrating that probiotic intervention can significantly improve aortic parameters, including aortic systolic and diastolic diameters and aortic strain, in a rat model.[8]

More critically, TMAO may exacerbate local vascular inflammation and enhance platelet aggregability by activating signaling pathways such as the NLRP3 (NOD-like receptor family pyrin domain-containing 3) inflammasome, providing a theoretical basis for its role in plaque instability and acute thrombogenesis.[9] Clinical data from observational studies consistently demonstrate that high circulating TMAO levels are correlated with not only the presence and severity of coronary artery disease but also an elevated risk of long-term cardiovascular events,[10,11] suggesting its potential as a novel risk predictor independent of traditional factors.

Nevertheless, gaps remain in the current body of research. Most evidence derives from Western populations or mixed cohorts encompassing various cardiovascular conditions.[12] Data from prospective or high-quality retrospective studies specifically targeting Chinese AMI populations, particularly those undergoing emergency PCI, remain limited.[13] A recent large-scale prospective study in a Chinese AMI cohort (n = 1203) evaluated changes in TMAO-related metabolites and their association with clinical outcomes;[12] however, that work did not include an angiographically normal control group and did not specifically focus on the quantitative relationship between admission TMAO levels and the anatomical severity of coronary artery disease (e.g., assessed by the Gensini score). Furthermore, 2 key questions remain to be systematically validated in Chinese clinical cohorts: first, the relationship between TMAO levels and the anatomical severity of coronary artery disease (e.g., assessed by the Gensini score); and second, its incremental utility for short-term prognosis in AMI patients.[14,15]

Based on this context, the present study aims to leverage the resources of the hospital's standardized biobank and clinical database through a rigorously designed retrospective cohort study.[16] This study aims to systematically examine, in Chinese AMI patients, the relationship between admission plasma TMAO levels and both coronary artery disease severity and the 6-month post-discharge risk of MACE. It was postulated that elevated TMAO plays a dual role, correlating with more severe coronary lesions and acting as an independent predictor of adverse outcomes. The anticipated findings are expected to furnish novel insights for AMI risk stratification and yield pivotal evidence for developing "gut-heart axis"–targeted interventions.

HIGHLIGHTS

- Plasma trimethylamine N-oxide (TMAO) levels were significantly elevated in patients with acute myocardial infarction (AMI) and showed a near-perfect positive correlation with coronary lesion severity (Gensini score) and myocardial injury extent (peak troponin 1).
- Elevated TMAO (>5.80 μmol/L) was an independent predictor of 6-month major adverse cardiovascular events and provided significant incremental prognostic value beyond conventional clinical and imaging risk factors.
- The findings provide clinical evidence from a Chinese AMI cohort supporting the role of the gut microbiota–derived metabolite TMAO in acute cardiovascular events, highlighting its potential as a novel biomarker for risk stratification.

METHODS

Study Design and Participants

A retrospective cohort design was adopted for this single-center observational study. In the institution, venous blood is routinely drawn at admission into EDTA tubes for standard biochemical and hematological testing in patients undergoing coronary angiography and/or PCI, and surplus plasma from these routine samples has been prospectively processed and stored in a hospital-wide −80°C biobank according to predefined protocols, independent of the present study. The study population was derived from a consecutive cohort of patients admitted to the Department of Cardiology at the hospital who underwent coronary angiography between July 1, 2022, and June 30, 2024. Through a systematic review of the Electronic Medical Record system, all cases were initially screened with a first-time diagnosis of AMI who received emergency PCI. To construct a control cohort, this study concurrently screened patients admitted for chest pain whose coronary angiography confirmed stenosis of less than 20% in all major epicardial vessels and who did not undergo revascularization therapy. These patients did not meet the diagnostic criteria for AMI or unstable angina and, after completion of the clinical and diagnostic work-up, were ultimately categorized as having non-ischemic chest pain or nonobstructive coronary artery disease; therefore, they served as an angiographically normal or near-normal control group rather than a cohort with unstable or stable angina.

Inclusion criteria for the AMI group: (1) fulfillment of the Chinese guideline diagnostic criteria for ST-segment elevation myocardial infarction or non-ST-segment elevation acute coronary syndrome, as evidenced by typical chest pain,

dynamic electrocardiographic changes, and a definitive rise and fall of myocardial necrosis biomarkers (troponin I/T); (2) hospital admission and receipt of emergency PCI within 24 hours of symptom onset; and (3) availability, as part of routine clinical care, of an EDTA-anticoagulated venous blood sample drawn within 24 hours of admission, from which surplus plasma had been processed and stored in accordance with the hospital's −80°C standardized biobank procedures. The clinical AMI cohort was first defined according to the above diagnostic and angiographic criteria, and biobank samples were then retrieved secondarily from these eligible patients to measure TMAO. Inclusion criteria for the Control group: (1) presence of chest pain symptoms with normal or near-normal coronary angiography (stenosis <20% in all major epicardial vessels); and (2) availability of a contemporaneous frozen plasma sample meeting the testing requirements. Common exclusion criteria for both groups: (1) a history of confirmed infection, major trauma, surgical procedure, or use of antibiotics/probiotics/prebiotics within 1 month prior to admission, to avoid short-term disturbances to gut microbiota stability; (2) co-existing end-stage liver disease (Child-Pugh class C), end-stage renal disease (on maintenance dialysis), or an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2, to exclude severe organ dysfunction significantly affecting TMAO metabolism and excretion; (3) diagnosed active malignancy, autoimmune disease, or chronic inflammatory bowel disease; and (4) severe deficiencies in clinical data or follow-up information precluding endpoint assessment.

Following the above procedures, the study ultimately enrolled 60 AMI patients meeting all criteria (AMI group) and 30 control subjects with angiographically normal or near-normal coronary arteries (stenosis <20% in all major epicardial vessels and no revascularization) (Control group), totaling 90 participants. The complete screening and selection process, including the numbers of patients excluded for each reason, is summarized in the patient flowchart (Supplementary Figure 1). This study received approval from the hospital's Institutional Medical Ethics Committee. Because it was a retrospective analysis that used only anonymized samples and clinical data obtained as part of routine care, the Ethics Committee waived the need for individual informed consent.

Data Collection and Definitions

All clinical data were independently extracted from the hospital information system by 2 uniformly trained researchers using a standardized electronic data collection form. Data entries were cross-checked, and any discrepancies were resolved by consulting the original medical records or through arbitration by a third senior cardiologist.

Follow-up and endpoint ascertainment were conducted retrospectively. For each patient, the inpatient and outpatient electronic medical records, rehospitalization data, and documentation from the routine telephone follow-up program run by the cardiology department to determine vital status and cardiovascular events within 6 months after the index discharge were reviewed. The primary endpoint was the first occurrence of a MACE within 6 months after discharge, and only patients whose discharge date allowed at least 6 months of observation and for whom endpoint status could be reliably ascertained were included in the final analysis.

Collected data spanned the following dimensions: Demographics and Baseline Characteristics: including age, sex, height, weight (for calculating body mass index, body mass index), and vital signs upon admission (systolic blood pressure, diastolic blood pressure, heart rate). Past Medical and Personal History: documented history of hypertension, type 2 diabetes, hyperlipidemia (based on prior medical records or long-term medication use), and smoking history (defined as continuous or cumulative smoking for ≥6 months). Admission Laboratory Tests: recorded the first or the most abnormal results within 24 hours of admission, including lipid profile (total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol), renal function [serum creatinine, eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula], liver function (alanine aminotransferase, aspartate aminotransferase), fasting blood glucose, high-sensitivity C-reactive protein (hs-CRP), and key complete blood count indicators. Cardiac Structure and Function Assessment: left ventricular ejection fraction (LVEF) reported on transthoracic echocardiography performed during hospitalization. Coronary Artery Disease Assessment: 2 interventional cardiologists, blinded to patients' TMAO levels and study group allocation, independently analyzed coronary angiography images. The internationally recognized Gensini score system[17] was used to quantitatively assess disease severity. This scoring system assigns points based on stenosis location (e.g., highest weight for left main) and degree of stenosis (1%-99%), with the final sum representing the patient's score. Inter-rater reliability (intraclass correlation coefficient) was excellent (>0.90). Treatment Information: recorded key in-hospital treatments, specifically details of emergency PCI, stent implantation, and use of secondary prevention medications. Endpoint Events: The primary endpoint was the occurrence of a MACE within 6 months after discharge, defined as a composite of cardiac death, recurrent myocardial infarction, rehospitalization for new or worsening heart failure, or unplanned target vessel revascularization [PCI or coronary artery bypass grafting (CABG)]. Endpoint adjudication was performed via telephone follow-up combined with review of re-admission records. All events were independently adjudicated by 2 investigators according to predefined criteria.

Plasma Sample Processing and Trimethylamine N-Oxide Measurement

Plasma samples for TMAO measurement were obtained from surplus EDTA-anticoagulated venous blood that had been drawn within 24 hours of admission as part of routine clinical care and, according to the pre-existing biobank protocol, were centrifuged, aliquoted, and stored long-term at −80°C until assay, avoiding freeze−thaw cycles. Plasma TMAO concentration was measured using the currently accepted gold standard method—high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). Specific steps were as follows: 100 μL of plasma sample

was mixed with 400 µL of ice-cold methanol containing the stable isotope internal standard (d9-TMAO) for protein precipitation. After vortexing, the mixture underwent high-speed centrifugation at 4°C. The supernatant was dried under a stream of nitrogen and reconstituted in 100 µL of mobile phase. Chromatographic separation was achieved using a hydrophilic interaction chromatography column with a gradient elution of methanol and an aqueous ammonium formate (0.1%) solution. Mass spectrometric detection employed multiple reaction monitoring mode, with the transition m/z 76→59 for TMAO quantification and m/z 85→68 for the internal standard d9-TMAO. The standard curve constructed using the internal standard method demonstrated excellent linearity ($R^2 > 0.999$), with a lower limit of detection of 0.1 µmol/L. All samples were analyzed in a single batch by laboratory personnel blinded to clinical information. To ensure data quality, each analytical batch included quality control samples, with both intra- and inter-assay coefficients of variation maintained below 5%.

Statistical Analysis

The authors employed SPSS software (version 27.0; IBM Corp., Armonk, NY, USA) for primary statistical computations and hypothesis testing, and GraphPad Prism (version 9.0; GraphPad Software, San Diego, CA, USA) for creating graphical representations and conducting designated comparative analyses. The distribution of continuous variables was evaluated using the Shapiro–Wilk test. Accordingly, data conforming to a normal distribution are presented as mean ± SD and analyzed with the independent samples *t*-test; non-normally distributed data are presented as median (interquartile range) and analyzed with the Mann–Whitney *U*-test. Categorical data are presented as number (percentage) and analyzed using the chi-square test or Fisher's exact test, as appropriate.

Advanced statistical analyses were conducted to explore variable relationships, model prognosis, and validate findings. To assess associations, Spearman's rank correlation (rs) was used to evaluate TMAO against the Gensini score and peak troponin I. For prognostic modeling, patients were dichotomized by median TMAO into high/low groups. Kaplan–Meier curves with log-rank tests compared MACE-free survival. To identify independent predictors, a Cox proportional hazards model was built. All candidate variables first underwent univariate screening; a conservative entry threshold of $P < .10$ was used to avoid omitting potentially important confounders. Variables meeting this criterion were then entered into a forward stepwise (likelihood ratio) multivariate Cox model. In the final multivariate model, as well as in all correlation analyses and receiver operating characteristic curve (ROC) comparisons, a 2-sided $P < .05$ was considered statistically significant. All tests were 2-sided, with $P < .05$ deemed significant.

RESULTS

Comparison of Basic Clinical Characteristics of the Study Population

This study ultimately enrolled 90 participants, comprising 60 patients in the AMI group and 30 individuals in the control group with angiographically normal or near-normal coronary arteries (stenosis <20% in all major epicardial vessels). The detailed baseline clinical characteristics of the 2 groups are presented in Table 1. Regarding demographic data, no statistically significant differences were observed between the AMI and control groups in age (65.8 ± 10.2 years vs. 63.1 ± 8.9 years, $P = .215$), sex distribution (70.0% male vs. 60.0% male, $P = .340$), or body mass index (25.3 ± 3.4 kg/m^2 vs. 24.1 ± 2.8 kg/m^2, $P = .085$), indicating good baseline comparability between the cohorts. However, indicators reflecting acute cardiovascular stress showed that systolic blood pressure (141.8 ± 13.0 mmHg vs. 129.6 ± 9.4 mmHg, $P < .001$), diastolic blood pressure (86.4 ± 8.2 mmHg vs. 78.9 ± 5.2 mmHg, $P < .001$), and heart rate (88.3 ± 9.4 beats/min vs. 73.2 ± 5.5 beats/min, $P < .001$) were all significantly higher in the AMI group compared to the control group. Among traditional cardiovascular risk factors, the proportion of patients with a smoking history was significantly greater in the AMI group (58.3% vs. 33.3%, $P = .022$), whereas the prevalence of hypertension, diabetes, and hyperlipidemia did not differ significantly between the groups. Laboratory examinations revealed that the AMI group had significantly elevated levels of low-density lipoprotein cholesterol (2.73 ± 0.40 mmol/L vs. 2.44 ± 0.35 mmol/L, $P < .001$), serum creatinine (85.6 ± 12.8 µmol/L vs. 76.2 ± 9.1 µmol/L, $P < .001$), fasting blood glucose (7.2 ± 1.5 mmol/L vs. 6.1 ± 0.8 mmol/L, $P < .001$), and high-sensitivity C-reactive protein (9.5 (4.1, 19.1) mg/L vs. 1.6 (0.9, 2.8) mg/L, $P < .001$). Conversely, estimated glomerular filtration rate (78.5 ± 9.6 mL/min/1.73m^2 vs. 85.3 ± 7.9 mL/min/1.73m^2, $P < .001$) and LVEF (52.4 ± 6.8% vs. 62.1 ± 3.7%, $P < .001$) were significantly lower in the AMI group. These characteristics align with the typical clinical manifestations of AMI in the acute phase, including metabolic disturbances, systemic inflammatory response, and impaired cardiac function, thereby confirming the clinical authenticity of the data in this cohort.

Distribution Differences of Plasma Trimethylamine N-Oxide Levels Across Groups

As the core variable of interest in this study, plasma TMAO levels exhibited a highly significant distribution difference between the AMI and control groups (Figure 1). The median TMAO level in AMI patients was 5.80 µmol/L, with an interquartile range of 4.12-7.65 µmol/L, whereas the control group had a median of only 2.10 µmol/L and an interquartile range of 1.58-2.85 µmol/L (Mann–Whitney *U*-test, $P < .001$). This finding initially suggests that TMAO levels are substantially higher in AMI patients compared to individuals with angiographically normal or near-normal coronary arteries (stenosis <20% in all major epicardial vessels). Further stratification within the AMI group, based on the median Gensini score (48 points), which reflects the anatomical severity of coronary artery disease, revealed that the plasma TMAO level in the high Gensini score subgroup (≥48 points) [7.01 (5.20, 8.95) µmol/L] was significantly greater than that in the low-score subgroup [4.55 (3.60, 5.85) µmol/L] ($P < .001$, Figure 2).

Correlation Analysis Between Trimethylamine N-Oxide and Severity of Coronary Artery Disease and Myocardial Injury

To quantify the relationship between TMAO levels and indicators of disease severity, Spearman's rank correlation analysis

was performed. The results demonstrated that among AMI patients, plasma TMAO levels showed a significant positive correlation with the Gensini score (rs = 0.998, $P < .001$), with the scatter plot illustrating data points distributed along a positive trend (Figure 3). This indicates a tendency for the degree of coronary atherosclerotic lesions to increase with rising plasma TMAO concentrations. Furthermore, TMAO levels also exhibited a significant positive correlation with the core biomarker of myocardial necrosis extent - peak troponin I levels (rs = 0.996, $P < .001$, Figure 4). Since the release of troponin I is closely related to the area of infarcted myocardium, this correlation further links TMAO to a more direct measure of myocardial injury severity. These 2 findings of strong correlation jointly construct a clinical evidence chain for TMAO's involvement in the severe pathophysiological process of AMI from the dual dimensions of "coronary lesion" and "myocardial injury," providing support for understanding its biological plausibility as a risk marker.

Predictive Value of Trimethylamine N-Oxide Levels for Short-Term Prognosis in Acute Myocardial Infarction Patients: Survival Analysis and Multivariate Model

During the 6-month follow-up period, MACEs occurred in 22 out of the 60 AMI patients (36.7%). To assess the prognostic impact of TMAO, patients were divided into a high-TMAO group (n = 34) and a low-TMAO group (n = 26) based on the median TMAO level (5.80 μmol/L) among AMI patients. Kaplan–Meier survival curve analysis revealed that the MACE-free survival rate was significantly lower in the high-TMAO group compared to the low-TMAO group (Log-rank $\chi^2 = 25.729$, $P < .001$), indicating a significant association between elevated TMAO levels and worse clinical outcomes (Figure 5). To further clarify the independent predictive role of TMAO, a Cox proportional hazards regression model was constructed. Univariate analysis identified age, diabetes, LVEF, Gensini score, and TMAO level as being associated with MACE risk ($P < .1$). After incorporating these variables into the multivariate analysis, the results showed that even after adjusting for the influences of age, diabetes, LVEF, and Gensini score, a high TMAO level (>5.80 μmol/L) remained an independent risk factor for MACE occurrence in AMI patients, with a hazard ratio (HR) as high as 2.45 (95% CI: 1.38-4.35, $P = .002$). Detailed results are presented in a forest plot (Figure 6 and Table 2). This finding strongly suggests that TMAO provides additional prognostic information beyond traditional clinical and imaging risk factors.

Performance Evaluation and Incremental Value of Trimethylamine N-Oxide in Predicting Major Adverse Cardiovascular Events

To objectively evaluate the discriminatory ability of TMAO as a predictive tool, ROC curves were plotted, and the area under the curve (AUC) was calculated. The AUC for TMAO alone in predicting 6-month MACE was 0.852 (95% CI: 0.737-0.966). To assess its incremental value, it was compared with a traditional clinical prediction model containing age,

Table 1. Baseline Characteristics of the Study Population

Variables	AMI Group (n = 60)	Control Group (n = 30)	$t/\chi^2/z$	*P*
Demographics				
Age, years	65.8 ± 10.2	63.1 ± 8.9	$t = 1.25$	.215
Male, n (%)	42 (70.0)	18 (60.0)	$\chi^2 = 0.91$	.340
BMI, kg/m²	25.3 ± 3.4	24.1 ± 2.8	$t = 1.74$	.085
Vital signs				
SBP, mm Hg	141.8 ± 13.0	129.6 ± 9.4	$t = 4.55$	**<.001**
DBP, mm Hg	86.4 ± 8.2	78.9 ± 5.2	$t = 4.60$	**<.001**
Heart rate, bpm	88.3 ± 9.4	73.2 ± 5.5	$t = 8.31$	**<.001**
Medical history, n (%)				
Hypertension	38 (63.3)	14 (46.7)	$\chi^2 = 2.29$	.130
Diabetes	22 (36.7)	6 (20.0)	$\chi^2 = 2.58$	.108
Hyperlipidemia	36 (60.0)	18 (60.0)	$\chi^2 = 0.00$	1.000
Smoking	35 (58.3)	10 (33.3)	$\chi^2 = 5.24$	**.022**
Laboratory tests				
LDL-C, mmol/L	2.73 ± 0.40	2.44 ± 0.35	$t = 3.33$	**.001**
Cr, μmol/L	85.6 ± 12.8	76.2 ± 9.1	$t = 3.57$	**<.001**
eGFR, mL/min/1.73 m²	78.5 ± 9.6	85.3 ± 7.9	$t = -3.36$	**.001**
FBG, mmol/L	7.2 ± 1.5	6.1 ± 0.8	$t = 3.80$	**<.001**
hs-CRP, mg/L⁰	9.5 (4.1, 19.1)	1.6 (0.9, 2.8)	$Z = 7.12$	**<.001**
Cardiac structure and function				
LVEF, %	52.4 ± 6.8	62.1 ± 3.7	$t = -7.58$	**<.001**

Data presented as median (interquartile range), analyzed by Mann-Whitney *U*-test (*Z* value).
AMI, acute myocardial infarction; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction, DBP, diastolic blood pressure; FBG, fasting blood glucose; Cr, serum creatinine; SBP, systolic blood pressure. Bold values indicate statistically significant between-group differences ($P < .05$).

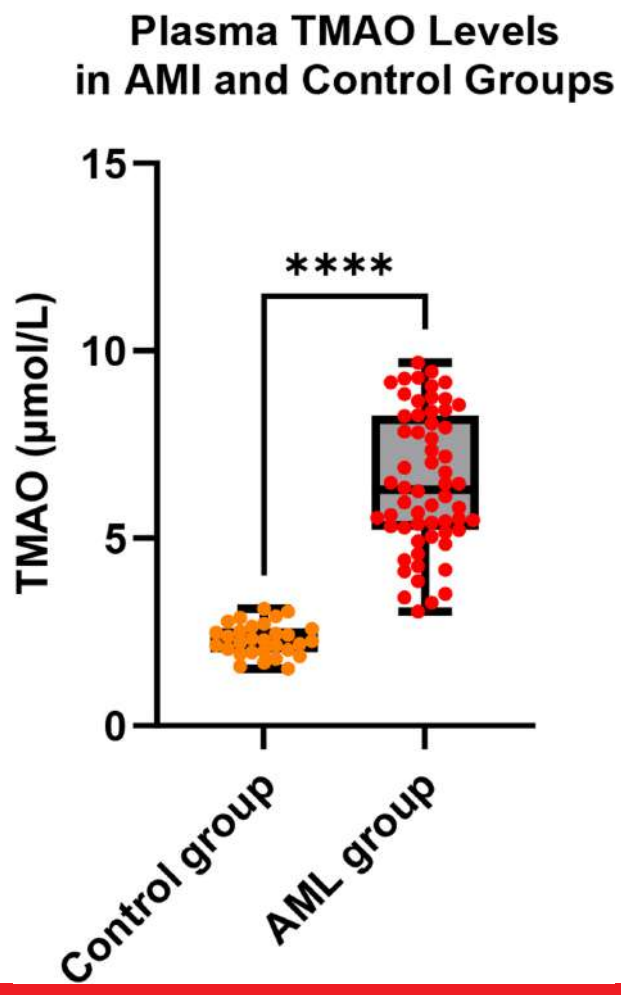


Figure 1. Comparison of plasma trimethylamine N-oxide levels between acute myocardial infarction and control groups (median [interquartile range]: 5.80 [4.12-7.65] vs. 2.10 [1.58-2.85] µmol/L, $P < .001$).

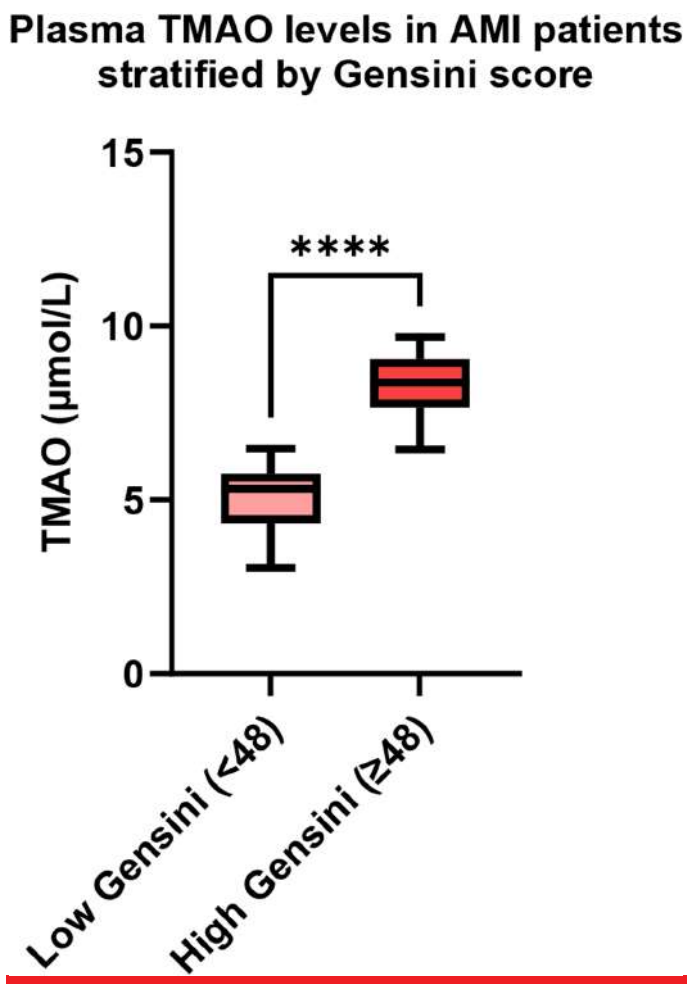


Figure 2. Plasma trimethylamine N-oxide levels in acute myocardial infarction patients stratified by Gensini score (high-score vs. low-score subgroup: 7.01 [5.20-8.95] vs. 4.55 [3.60-5.85] µmol/L, $P < .001$).

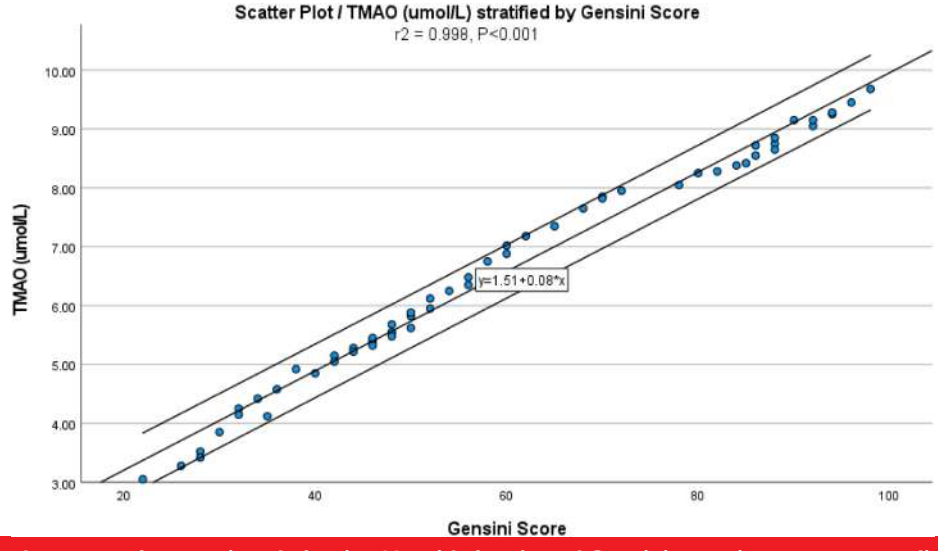


Figure 3. Correlation between plasma trimethylamine N-oxide levels and Gensini score in acute myocardial infarction patients (rs = 0.998, $P < .001$).

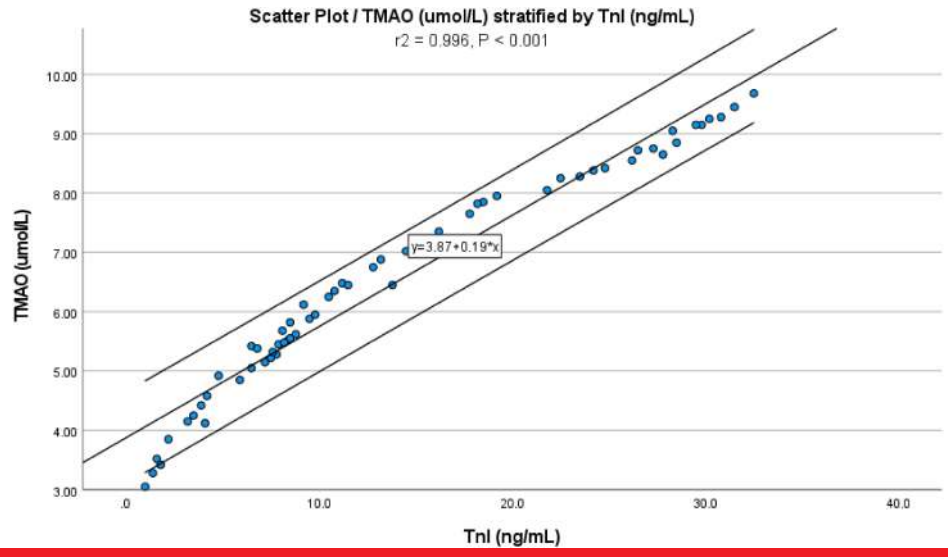


Figure 4. Correlation between plasma trimethylamine N-oxide levels and peak troponin 1 in acute myocardial infarction patients (rs = 0.996, *P* < .001).

diabetes, and LVEF. The traditional model had an AUC of 0.880 (95% CI: 0.780-0.981). When TMAO was added to the traditional model, the predictive performance of the combined model improved significantly, with the AUC increasing to 0.884 (95% CI: 0.781-0.987). The DeLong test confirmed that the AUC of the combined model was significantly higher than that of the traditional model alone (*P* = .012). A comparison of the ROC curves is clearly presented in Figure 7. This analysis demonstrates that plasma TMAO level has good predictive capability for MACE and provides significant incremental value to risk assessment based on conventional clinical indicators, suggesting that incorporating it into existing evaluation systems could potentially enhance the accuracy of identifying high-risk patients.

Subgroup Analysis to Verify the Robustness of Results

To ensure the consistency and reliability of the main study findings, exploratory analyses were conducted in different pre-specified subgroups to examine the robustness of the association between high TMAO levels (>median) and MACE risk. The subgroup analysis encompassed key stratifications including sex (male/female), age (≤65 years/>65 years), and the presence or absence of diabetes (Table 3). The results showed that across all subgroups, high TMAO levels consistently demonstrated a trend toward increased MACE risk, with all point estimates of the HR being greater than 1. Interaction tests did not reveal statistically significant interactions (all *P* for interaction >.05), indicating that the adverse prognostic impact of TMAO may be universally

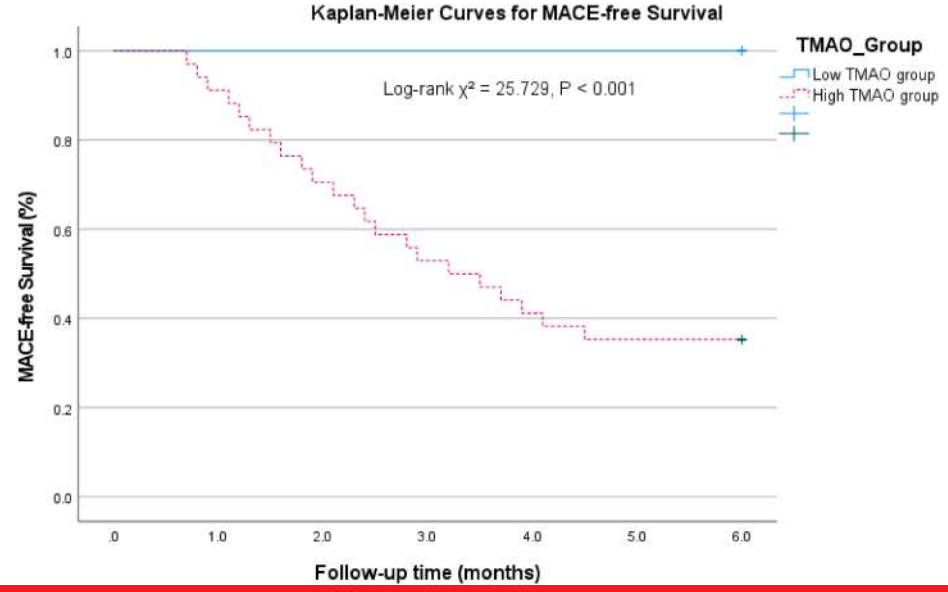


Figure 5. Major adverse cardiovascular event–free survival curves in acute myocardial infarction patients stratified by trimethylamine N-oxide levels (Log-rank χ^2 = 25.729, *P* < .001).

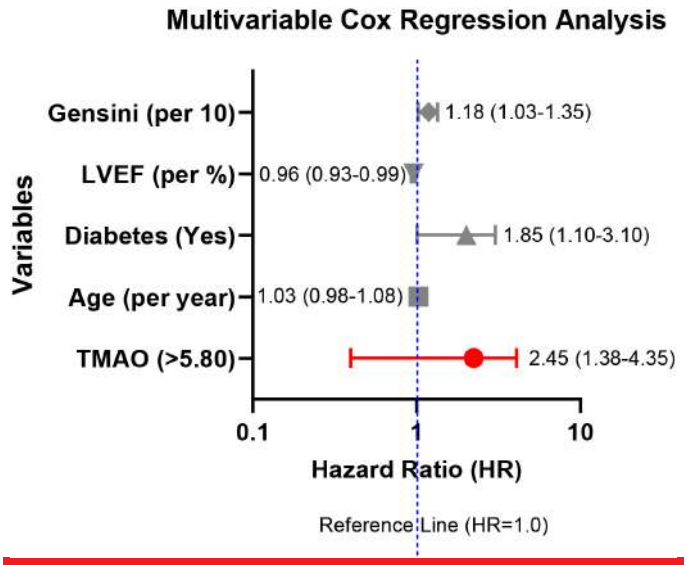


Figure 6. Forest plot of multivariate Cox regression analysis for major adverse cardiovascular events in acute myocardial infarction patients.

present across patient populations with different characteristics. Although the sample size of this study limits the statistical power of the subgroup analyses, this consistent trend enhances the credibility of TMAO as a universal risk marker and provides preliminary support for its potential application across diverse clinical contexts.

DISCUSSION

The core findings can be summarized into 3 points. First, plasma TMAO levels were significantly higher in AMI patients compared to controls with angiographically normal or near-normal coronary arteries (stenosis <20% in all major epicardial vessels), and within the AMI group, TMAO levels showed a strong positive correlation with the anatomical severity of coronary atherosclerosis (Gensini score). Taken together, these findings suggest that TMAO levels are not merely associated with the presence of AMI, but also reflect the severity of coronary artery lesions, such that higher TMAO concentrations may signify a more extensive and severe atherosclerotic burden in the coronary tree. Second, TMAO levels were significantly correlated with the peak concentration of the myocardial necrosis marker (troponin I), suggesting a potential link to more extensive myocardial injury. Finally, and most clinically significant, a high TMAO level was an independent predictor of MACEs within 6 months after discharge in AMI patients and provided significant incremental value to traditional clinical risk prediction models. Collectively, these results indicate that TMAO is not merely a "bystander" marker of AMI disease severity but likely an active mediator involved in disease progression with important prognostic stratification value.

Consistent with a growing body of evidence, elevated plasma TMAO has been identified as a risk marker for cardiovascular events in population-based and stable coronary disease cohorts. This study's data contribute to the existing literature by extending this association to the acute, high-risk setting of AMI.[18,19] However, evidence specifically within the acute, high-risk context of AMI, and particularly from Chinese populations, has been insufficient.[20] The present research addresses this gap and further links TMAO to a more precise quantitative indicator of coronary artery disease (Gensini score).[21] This strong correlation (rs = 0.998) surpasses the simple association between TMAO and the "presence or absence of coronary heart disease" observed in prior studies, providing more robust clinical anatomical evidence for the "gut-heart axis" theory.[22] The underlying pathophysiological mechanisms warrant in-depth exploration. Trimethylamine N-oxide may exacerbate the pathological process of AMI through several pathways.[23] First, TMAO has been shown to promote macrophage polarization toward a pro-inflammatory M1 phenotype and activate the NLRP3 inflammasome, thereby amplifying local plaque inflammation, leading to plaque instability and rupture—the initiating event in AMI.[24] Second, TMAO can enhance platelet calcium release and

Table 2. Cox Proportional Hazards Regression Analysis for Major Adverse Cardiovascular Event Prediction

Variables	Reference Category	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*
TMAO (>5.80 μmol/L)	≤5.80 μmol/L	3.82 (2.31-6.32)	<.001	**2.45 (1.38-4.35)**	**.002**
Age (per 1-year increase)	–	1.05 (1.01-1.09)	.018	1.03 (0.98-1.08)	.210
Diabetes (yes)	No	2.35 (1.48-3.73)	<.001	**1.85 (1.10-3.10)**	**.020**
LVEF (per 1% increase)	–	0.94 (0.91-0.97)	<.001	**0.96 (0.93-0.99)**	**.015**
Gensini score (per 10-point increase)	–	1.32 (1.16-1.50)	<.001	**1.18 (1.03-1.35)**	**.018**
Sex (female)	Male	1.18 (0.87-1.60)	.285	–	–
Hypertension (yes)	No	1.28 (0.97-1.69)	.085	–	–
Smoking (yes)	No	1.85 (1.33-2.57)	<.001	–	–
Peak Troponin 1 (per 1 ng/mL)	–	1.09 (1.04-1.14)	<.001	–	–
eGFR (per 1 mL/min/1.73 m^2)	–	0.98 (0.96-1.00)	.120	–	–
hs-CRP (per 1 mg/L)	–	1.03 (1.01-1.05)	.002	–	–

Variables with $P < .10$ in univariate analysis were included in the multivariate Cox proportional hazards model (forward stepwise method). Bold indicates statistical significance ($P < .05$) in the final multivariate model.
eGFR, estimated glomerular filtration rate; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; TMAO, trimethylamine N-oxide.

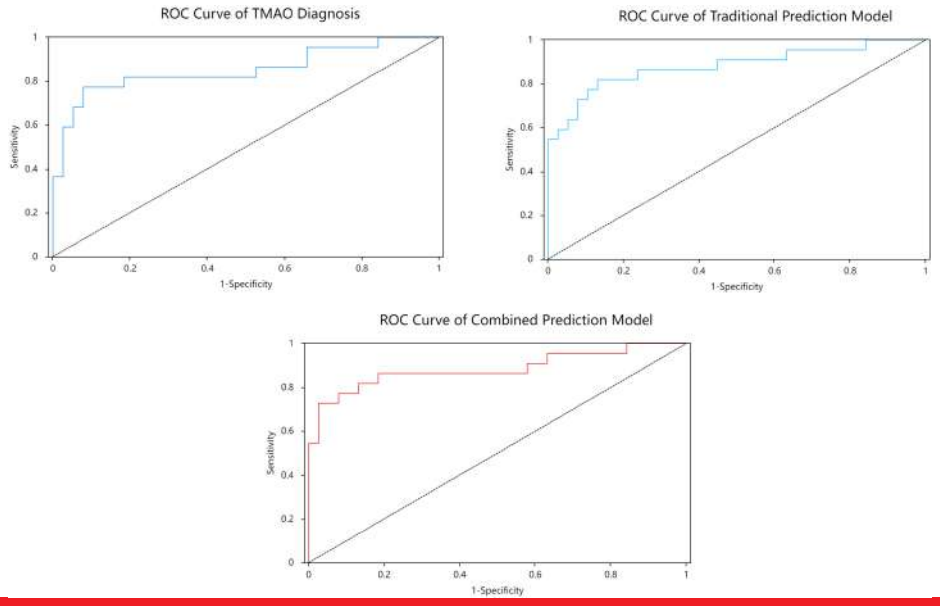


Figure 7. Receiver operating characteristic curves of different prediction models for 6-month major adverse cardiovascular events.

hyper-reactivity, increasing thrombotic risk, which may directly influence the burden and stability of intracoronary thrombi during the acute phase of AMI.[25] Third, the positive correlation between TMAO and the extent of myocardial injury (troponin I) found in this study may suggest that, beyond influencing coronary events, TMAO could directly aggravate myocardial damage through mechanisms such as exacerbating ischemia-reperfusion injury or affecting cardiomyocyte metabolism.[26] These mechanisms collectively outline a potential pathway from "gut microbiota dysbiosis → elevated TMAO → exacerbated inflammation and thrombosis → promotion of plaque rupture and myocardial injury → adverse prognosis."[27]

From a clinical translation perspective, the findings of this study hold dual significance. In terms of risk prediction, TMAO demonstrated predictive performance (AUC = 0.852) superior to traditional inflammatory markers like hs-CRP.[28] This aligns with emerging evidence that novel biomarkers derived from routine laboratory parameters, such as the prognostic nutritional index, can independently predict the functional significance of coronary artery stenosis, highlighting the expanding role of accessible biomarkers in coronary artery disease assessment.[29] Its prognostic value, independent of strong predictors such as age, cardiac function, and severity of coronary lesions, is particularly notable. Incorporating TMAO into existing risk assessment frameworks could significantly enhance the identification of high-risk patients,[30] providing clinicians with a potential new tool for more precisely selecting individuals requiring intensive management and follow-up after the acute phase of AMI. At the level of therapeutic intervention, TMAO, as a modifiable metabolite, opens up a novel "gut-heart axis" target for the secondary prevention of AMI.[31] Future research

Table 3. Subgroup Analysis of the Association Between High Trimethylamine N-Oxide Level and Major Adverse Cardiovascular Events Risk

Characteristic	Subgroup	Reference Category	N	Events	HR (95% CI)	*P*	*P* for Interaction
Overall	–	–	60	18	**3.82 (2.31-6.32)**	<.001	–
Gender	Male	(reference)	40	13	**3.65 (2.05-6.50)**	<.001	.452
	Female		20	5	**4.25 (1.85-9.75)**	.001	
Age (years)	≤65	(reference)	32	10	**3.40 (1.75-6.60)**	<.001	.318
	>65		28	8	**4.10 (2.05-8.20)**	<.001	
Diabetes	No	(reference)	30	8	**3.90 (1.95-7.80)**	<.001	.521
	Yes		30	10	**3.75 (1.88-7.50)**	<.001	

High TMAO was defined as >5.80 μmol/L. Cox proportional hazards models were performed in each subgroup. Hazard ratios are for high vs. low TMAO level. Reference categories are indicated in the third column; *P*-values for reference categories have been omitted as requested. The *P* for interaction values were obtained from separate Cox proportional hazards models that included the stratification factor (gender, age, or diabetes), the TMAO group (high vs. low), and their product term (TMAO group × stratification factor). The *P* for interaction corresponds to the Wald test for the product term, testing whether the effect of TMAO on MACE differs across levels of the stratification factor. Bold values indicate statistically significant associations between high TMAO levels and MACE risk ($P < .05$).
HR, hazards ratio.

directions may include exploring dietary modifications (e.g., reducing intake of foods rich in choline and L-carnitine like red meat and egg yolks), using prebiotics/probiotics to modulate gut microbiota composition,[32] or developing small-molecule drugs specifically inhibiting trimethylamine (TMA)-generating enzymes to lower TMAO levels, followed by prospective validation of whether these interventions ultimately translate into a reduction in cardiovascular events.[33]

It is, of course, essential to view the limitations of this study with caution. First, the retrospective design precludes establishing a causal relationship between TMAO and AMI prognosis; the observed associations may be influenced by unknown confounding factors. Second, the single-center nature and moderate sample size limit the generalizability of the conclusions, necessitating validation in larger-scale, multicenter prospective cohorts. Third, the control group consisted of symptomatic patients with angiographically normal or near-normal coronary arteries, rather than community-based healthy volunteers; consequently, the between-group difference in TMAO may be attenuated, and extrapolation of the present findings to truly healthy populations should be made with caution. Fourth, although admission blood sampling was standardized within 24 hours of hospitalization, TMAO was measured only once; levels may fluctuate during the acute coronary syndrome phase because of hemodynamic, metabolic, and treatment-related changes, and dynamic patterns over time could not be captured in this study. Fifth, because inclusion required the availability of a stored EDTA-anticoagulated plasma sample, a certain degree of selection bias related to biobank coverage and pre-analytic handling cannot be completely ruled out. Sixth, although multiple confounding factors were adjusted for statistically, detailed dietary history or previous antibiotic exposure were not systematically collected; key information potentially influencing TMAO levels, such as habitual intake of TMAO-rich foods, recent dietary changes, antibiotic use, and the resulting gut microbiota composition, was therefore not included in the analysis, and residual confounding from these unmeasured factors cannot be excluded. ded in the analysis, and residual confounding from these unmeasured factors cannot be excluded. Future prospective studies should incorporate comprehensive data collection on potential confounders and consider emerging therapeutic approaches in cardiovascular disease management, as the field continues to evolve with novel interventional strategies.

CONCLUSION

This study confirms within a Chinese AMI cohort that elevated plasma TMAO is not only associated with greater coronary disease severity and myocardial injury but also independently predicts worse short-term prognosis, adding incremental value to conventional risk models. These findings substantiate the relevance of the gut-heart axis in acute cardiovascular events and position TMAO as a promising prognostic biomarker. Future large-scale prospective and interventional studies are warranted to establish causality and explore therapeutic modulation of this pathway.

Artificial intelligence (AI) assistance declaration: The authors did not use any AI-assisted technologies in the creation of this manuscript.

Ethics Committee Approval: This study was approved by the Ethics Committee of Huzhou Traditional Chinese Medicine Hospital (Approval No.: 2026 Research No. 002-01; Date: January 28, 2026).

Informed Consent: Informed consent was waived by the Institutional Medical Ethics Committee because this was a retrospective study involving only anonymized clinical data and stored biological samples obtained during routine clinical care.

Peer-review: Internally peer-reviewed.

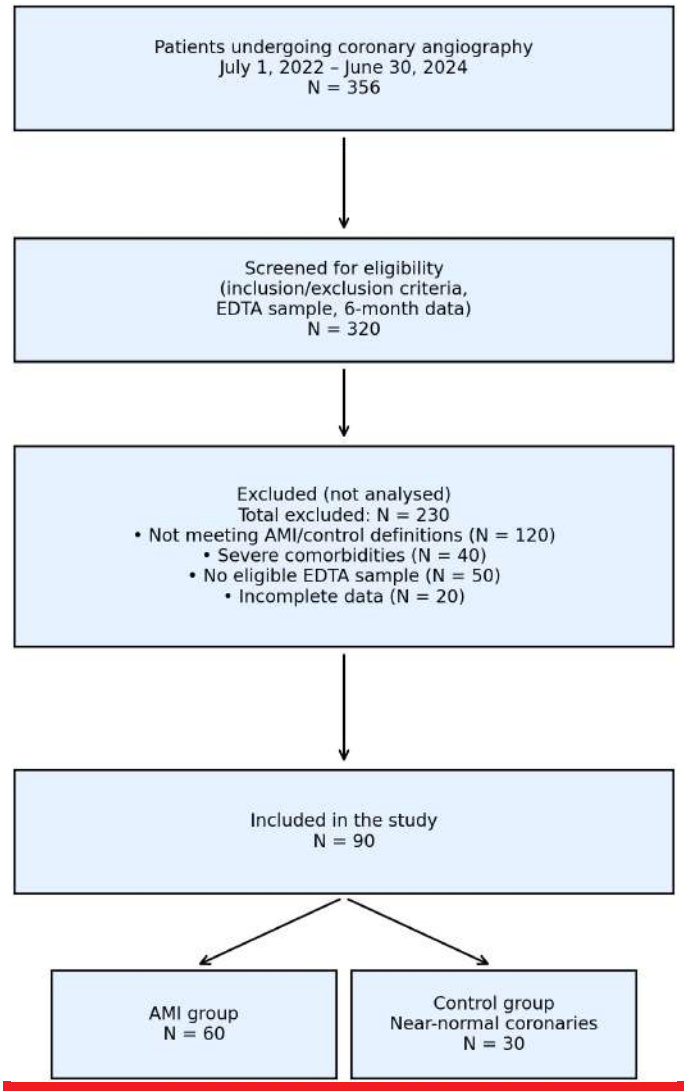
Author Contributions: Concept – M.J., M.L.; Design – M.J., S.X.; Supervision – M.L.; Resources – Y.Z.; Materials – Y.Z.; Data Collection and/or Processing – M.J., Y.Z.; Analysis and/or Interpretation – M.J., S.X.; Literature Search – M.J.; Writing – M.J.; Critical Review – M.L.Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declare that this study received no financial support.

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Supplementary Figure 1. Flowchart of participant screening and enrollment.

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Platelet–Albumin–Bilirubin Score Predicts In-Hospital Mortality in Patients with HFrEF Presenting with Acute Heart Failure

ABSTRACT

Background: Patients with heart failure and reduced ejection fraction presenting with acute heart failure (HFrEF-AHF) carry a high in-hospital mortality. Conventional predictors do not fully capture the interplay between hepatic dysfunction, systemic inflammation, and nutritional decline. The platelet–albumin–bilirubin (PALBI) score, originally developed in hepatology, may offer incremental prognostic information in this setting.

Methods: A total of 401 patients hospitalized with HFrEF-AHF were retrospectively studied. Baseline demographic, clinical, and laboratory data were collected. Platelet–albumin–bilirubin and albumin–bilirubin (ALBI) scores were calculated. The primary endpoint was all-cause in-hospital mortality.

Results: In-hospital mortality occurred in 47 patients (11.7%). Non-survivors were older, more frequently had chronic kidney disease (CKD), and showed lower albumin but higher bilirubin and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Both PALBI and ALBI were significantly higher in non-survivors. In multivariable Cox analysis, PALBI independently predicted mortality (hazard ratio = 2.638, 95% CI: 1.177-4.099, $P < .001$), along with age, CKD, and NT-proBNP. Receiver operating characteristic analysis showed that PALBI demonstrated slightly better performance than conventional predictors and, compared with ALBI (area under the curve = 0.737 vs. 0.708), yielded a modest but significant net reclassification improvement (~10%). Kaplan–Meier curves demonstrated clear separation in survival across PALBI strata (log-rank, $P < .001$), and restricted cubic spline analysis confirmed a graded, continuous association with risk.

Conclusion: The PALBI score independently predicts in-hospital mortality in patients with HFrEF-AHF and may represent a simple and clinically useful tool for early risk stratification. External validation in larger, multicenter cohorts is warranted.

Keywords: Acute heart failure, in-hospital mortality, PALBI score, prognosis, risk assessment

INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) is a major global health problem, accounting for substantial morbidity, frequent hospitalizations, and high rates of in-hospital mortality.[1,2] Patients with HFrEF presenting with acute heart failure (HFrEF-AHF) represent one of the most severe clinical presentations, often requiring urgent hospitalization and intensive management.[3,4] Despite advances in guideline-directed therapies, the short-term prognosis of these patients remains unfavorable,[5] underscoring the importance of accurate, early risk stratification. Identifying reliable prognostic markers at admission is crucial for guiding therapeutic decision-making, allocating healthcare resources efficiently, and improving clinical outcomes.

Traditional risk predictors, such as age, comorbidities, renal function, and serum sodium, have long been recognized as important prognostic factors.[6] However, recent studies have emphasized the role of systemic inflammation, hepatic dysfunction, and nutritional status in the pathophysiology of HFrEF-AHF.[7-9] Congestion and impaired forward flow frequently result in hepatic venous hypertension and hypoperfusion, leading to cholestasis, hyperbilirubinemia, impaired

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Received: December 6, 2025
Accepted: June 4, 2026
Available Online Date: July 21, 2026

Cite this article as: Hekimsoy V, Tanık VO, Akbuğa K, et al. Platelet–albumin–bilirubin score predicts in-hospital mortality in patients with HFrEF presenting with acute heart failure. *Anatol J Cardiol.* 2026;30(12):932-942.

DOI: 10.14744/AnatolJCardiol.2026.6089

albumin synthesis, and thrombocytopenia.[10] At the same time, neurohormonal activation and systemic inflammation drive endothelial dysfunction and oxidative stress, further aggravating multi-organ impairment.[11] These complex pathophysiological processes link cardiac dysfunction with hepatic and hematologic abnormalities, suggesting that biomarkers reflecting this interplay may provide incremental prognostic value.

Among liver-derived indices, the albumin–bilirubin (ALBI) score has been increasingly studied in AHF and shown to carry prognostic significance.[12] Building on this concept, the platelet–albumin–bilirubin (PALBI) score incorporates platelet count, in addition to albumin and bilirubin, thereby embedding a hematologic dimension into the assessment of cardiohepatic interactions. Although originally applied in hepatology,[13] recent evidence suggests that the PALBI score may also be beneficial in cardiovascular disorders. To date, only 1 study has evaluated the prognostic impact of the PALBI score in cardiovascular disease, demonstrating that a higher PALBI score was independently associated with all-cause mortality following transcatheter aortic valve replacement.[14] However, data regarding its role in HFrEF-AHF remain scarce, and its predictive utility for in-hospital mortality has not been clearly established.

Given this background, the present study was designed to evaluate the prognostic significance of the PALBI score in patients hospitalized with HFrEF-AHF. Specifically, this study aimed to determine whether the PALBI score could serve as an independent predictor of in-hospital mortality, thereby providing clinicians with an additional, easily obtainable tool for early risk stratification in this high-risk population.

METHODS

Study Population

This single-center, retrospective cohort study included patients diagnosed with HFrEF (left ventricular ejection fraction [LVEF] of 40% or less) according to the European Society of Cardiology guidelines for heart failure[15] who were hospitalized with a primary diagnosis of HFrEF-AHF, encompassing the full clinical spectrum of AHF, including acutely decompensated heart failure, acute pulmonary edema, and cardiogenic shock, in order to reflect routine clinical practice and derive real-world data. All consecutive patients admitted to the tertiary cardiology clinic between January 2024 and December 2024 were screened for eligibility. Patients were eligible for inclusion if they were 18 years of age or older, had a confirmed diagnosis of HFrEF prior to or during admission, and had complete laboratory data necessary for calculating the PALBI score at the time of admission. Patients admitted with a diagnosis of acute coronary syndrome, with a history of chronic liver disease or cirrhosis, chronic inflammatory disease, active malignancy or hematological disease, prior liver transplantation, or those receiving immunosuppressive therapy were excluded. Additionally, patients with missing data for any parameter required for PALBI calculation, as well as those who were transferred to another institution or were lost to follow-up during their hospitalization, were excluded from the final analysis. After applying the inclusion and exclusion criteria, 401 patients with HFrEF-AHF were included in the final study cohort. All clinical and laboratory data of the patients were obtained retrospectively from electronic medical records and institutional databases. The study was approved by the Local Ethics Committee of the Ankara Etlik City Hospital, approval date and number: 22 July 2025 – AEŞH-BADEK2-2025-278 and was conducted in accordance with the Declaration of Helsinki. The Local Ethics Committee waived the requirement for informed consent because the research was retrospective.

Data Collection

Baseline demographic and clinical characteristics, including age, sex, active smoking status, history of hypertension, diabetes mellitus, peripheral artery disease, atrial fibrillation, coronary artery disease, chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD), were recorded for each patient. In addition, baseline medications at the time of index hospitalization, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, sodium-glucose cotransporter 2 inhibitors, antiplatelet agents, and anticoagulants, were documented.

Laboratory data were collected from venous blood samples obtained within the first 24 hours of hospital admission. These included complete blood count (platelet count, white blood cells, neutrophils, lymphocytes, hemoglobin), liver function parameters (total bilirubin, serum albumin), renal function tests (urea, creatinine), electrolytes (sodium, potassium, chloride), lipid profile, C-reactive protein (CRP), and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2, in accordance with the Kidney Disease: Improving Global Outcomes guidelines.[16]

Transthoracic echocardiography was performed on all patients during hospitalization by experienced cardiologists to evaluate left ventricular function. Left ventricular ejection fraction was measured according to the recommendations of the American Society of Echocardiography[17] using the biplane Simpson's method.

Platelet–albumin–bilirubin score was calculated using the following formula:[13]

HIGHLIGHTS

- Patients with HFrEF presenting with acute heart failure (HFrEF-AHF) still carry a high in-hospital mortality.
- Platelet–albumin–bilirubin combines platelet count, serum albumin, and bilirubin into one index.
- Platelet–albumin–bilirubin independently predicted mortality.
- Kaplan–Meier and spline analyses confirmed acceptable prognostic performance.
- Simple lab-based indices may guide early risk stratification in HFrEF-AHF.

PALBI score = 2.02 × $\log_{10}$ [bilirubin (μmol/L)] − 0.37 × ($\log_{10}$ bilirubin)^2 − 0.04 × albumin (g/L) − 3.48 × $\log_{10}$ [platelet count (×10^9/L)] + 1.01 × ($\log_{10}$ platelet count)^2.

Albumin–bilirubin score was calculated as follows:[13]

ALBI score = (0.66 × $\log_{10}$ bilirubin [μmol/L]) + (−0.085 × albumin [g/L]).

Study Endpoint

The outcome of the study was all-cause in-hospital mortality, defined as death occurring during the index hospitalization. Survival status was determined from hospital medical records and, when necessary, verified through the national death registry.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was evaluated with the Kolmogorov–Smirnov test. Normally distributed data are summarized as mean ± SD, and non-normally distributed data were expressed as median (interquartile range). Categorical variables are presented as frequencies and percentages. For comparisons between 2 groups (survivors vs. non-survivors), the independent-samples *t*-test or Mann–Whitney *U*-test was applied for continuous variables. In contrast, the chi-square test or Fisher's exact test was used for categorical variables. For comparisons across 3 groups, a 1-way ANOVA was used for normally distributed variables, with post hoc Tukey's test where appropriate. When assumptions of normality were violated, the Kruskal–Wallis test with Bonferroni-adjusted pairwise comparisons was used. To investigate prognostic factors for in-hospital mortality, univariable Cox proportional hazards regression analyses were first performed. Variables associated with the outcome in univariable analysis and considered clinically relevant were subsequently evaluated for inclusion in a multivariable Cox proportional hazards regression model. Given the limited number of mortality events (n = 47), a parsimonious multivariable model was constructed to minimize the risk of overfitting. The final model included age, CKD, CRP, NT-proBNP, and PALBI score. Variables exhibiting substantial clinical overlap or multicollinearity were not entered simultaneously into the model. Specifically, serum creatinine was not included alongside CKD because both variables reflect renal dysfunction, whereas serum albumin, total bilirubin, and ALBI score were excluded because they are components of or closely related to the PALBI score. Hazard ratios (HRs) and 95% CIs were reported. Assumptions of proportional hazards were assessed using log–log survival plots, and multicollinearity was evaluated using variance inflation factors. The discriminatory ability of the predictors was further assessed using receiver operating characteristic (ROC) curve analyses; area under the curve (AUC) values and optimal cutoffs (based on the Youden index) were calculated. Comparative ROC analyses were performed for both PALBI and ALBI scores against traditional predictors. In addition, the incremental prognostic value was evaluated using net reclassification improvement (NRI) and integrated discrimination improvement (IDI) metrics, which quantify the added reclassification and discrimination capacity of PALBI relative to ALBI. For survival analysis, patients were stratified by PALBI score, and Kaplan–Meier curves were generated; comparisons were made using the log-rank test. Two complementary stratification approaches were applied: (i) Median-based dichotomization (PALBI < −2.047 vs. ≥ −2.047); (ii) interquartile-based stratification (≤25th percentile, 25th-75th percentile, and ≥75th percentile). Finally, a restricted cubic spline model was fitted to illustrate the continuous relationship between the PALBI score and the risk of in-hospital mortality. All statistical tests were 2-sided, and P < .05 was considered statistically significant.

RESULTS

A total of 401 patients hospitalized for HFrEF-AHF were included in the study. The cohort's mean age was 62.9 ± 14.4 years, and 72.3% (n = 290) of participants were male. Baseline demographic, clinical, laboratory, and echocardiographic characteristics of survivors (n = 354) and patients who died during hospitalization (n = 47) are summarized in Table 1. Compared to survivors, non-survivors were significantly older (72.6 ± 11.1 vs. 61.5 ± 14.6 years, P < .001) and had a markedly higher prevalence of CKD (68.1 vs. 26.6%, P < .001). Laboratory analyses showed that non-survivors had lower serum albumin levels and higher CRP, NT-proBNP, and total bilirubin levels. The mean PALBI score was also significantly higher among non-survivors (−1.80 ± 0.45 vs. −2.19 ± 0.39, P < .001). Similarly, the mean ALBI score was significantly higher (less negative) among non-survivors compared to survivors (−1.93 ± 0.66 vs. −2.38 ± 0.51, P < .001). No significant differences were observed between the 2 groups with respect to other baseline comorbidities, medication use, or echocardiographic parameters.

In univariable regression analysis, age, CKD, CRP, serum creatinine, NT-proBNP, serum albumin, total bilirubin, PALBI score, and ALBI score were significantly associated with in-hospital mortality (Table 2). In the final parsimonious multivariable model, age (HR = 1.067, 95% CI: 1.031-1.105, P < .001), CKD (HR = 1.266, 95% CI: 1.120-1.591, P = .001), NT-proBNP (per 500-unit increase) (HR = 1.245, 95% CI: 1.106-1.567, P = .001), and PALBI score (HR = 2.638, 95% CI: 1.177-4.099, P < .001) remained as independent predictors of in-hospital mortality.

The ROC curve analysis demonstrated that both hepatic scores carried significant discriminatory power for in-hospital mortality. The AUC for PALBI was 0.737 (95% CI: 0.653-0.816), which was higher than that of ALBI (AUC = 0.708, 95% CI: 0.615-0.788), age, CKD, and NT-proBNP (Table 3). The optimal cutoff value for PALBI was −2.047 (sensitivity, 70%; specificity, 68%), whereas for ALBI, it was −2.010 (sensitivity, 60%; specificity, 76%). Comparative ROC curves are shown in Figure 1A. To further characterize patients according to the optimal PALBI cutoff identified by ROC analysis, baseline demographic, clinical, laboratory, and echocardiographic characteristics were compared between patients with PALBI < −2.047 and those with PALBI ≥ −2.047 (Table 4). The 2 groups were comparable with respect to age, sex, cardiovascular comorbidities, baseline medications, and LVEF. However, patients with

Table 1. Baseline Demographic, Clinical, and Laboratory Characteristics of the Study Population, Stratified by Study Outcome

Variables	Survivors (n = 354)	Deceased (n = 47)	*P*
Demographics			
Age (years)	61.5 ± 14.6	72.6 ± 11.1	<.001
Male, n (%)	254 (71.8)	36 (76.6)	.486
Comorbidities, n (%)			
Smoking, n (%)	157 (44.4)	18 (38.3)	.293
Hypertension	215 (60.7)	32 (68.1)	.330
Diabetes mellitus	119 (33.6)	14 (29.8)	.600
Atrial fibrillation	136 (38.4)	20 (42.6)	.699
Coronary artery disease	138 (39.0)	20 (42.6)	.637
Peripheral artery disease	25 (7.1)	6 (12.8)	.169
Chronic kidney disease	94 (26.6)	32 (68.1)	<.001
Chronic obstructive pulmonary disease	100 (28.2)	18 (38.3)	.155
Medications, n (%)			
Angiotensin-converting enzyme inhibitors	259 (73.2)	29 (61.7)	.101
Angiotensin II receptor blockers	50 (14.1)	10 (21.3)	.197
Beta-blockers	325 (91.8)	43 (91.5)	1.000
Mineralocorticoid receptor antagonists	258 (72.9)	29 (61.7)	.110
SGLT-2 inhibitors	114 (32.2)	14 (29.8)	.738
Asetylsalicylic acid	217 (61.3)	26 (55.3)	.430
Oral anticoagulant	115 (32.5)	21 (44.7)	.100
Statins	162 (45.8)	22 (46.8)	.892
Laboratory findings			
Hemoglobin (g/dL)	13.2 ± 2.2	12.6 ± 2.7	.398
White blood cells (×10^9/L)	7.7 (6.5-9.2)	7.6 (6.4-8.6)	.494
Neutrophil (×10^9/L)	6.1 (4.8-9.1)	6.4 (5.0-9.4)	.204
Lymphocyte (×10^9/L)	1.6 (1.1-2.1)	1.6 (1.0-2.0)	.123
Platelets (×10^9/L)	241 (190-297)	251 (177-301)	.182
C-reactive protein (mg/dL)	18.6 (8.0-42.0)	41.0 (21.0-78.4)	<.001
Serum creatinine (mg/dL)	1.2 (0.9-2.0)	2.7 (1.9-3.2)	<.001
Serum sodium (mmol/L)	138 (135-140)	134 (132-137)	.104
Serum potassium (mmol/L)	4.3 (4.0-4.6)	4.5 (4.1-4.7)	.142
Serum chloride (mmol/L)	102 (98-104)	102 (98-103)	.902
AST (U/L)	16 (13-23)	17 (13-23)	.881
ALT (U/L)	21 (10-31)	24 (12-32)	.462
Total cholesterol (mg/dL)	162 (131-200)	163 (124-222)	.887
LDL-cholesterol (mg/dL)	114 (88-161)	124 (86-200)	.283
HDL-cholesterol (mg/dL)	36 (29-44)	33 (26-42)	.163
Triglyceride (mg/dL)	114 (86-156)	123 (81-228)	.211
NT-proBNP (pg/mL)	1892 (712-5378)	2024 (589-10 276)	<.001
Serum albumin (g/L)	37.1 ± 5.9	33.9 ± 7.1	.001
Total bilirubin (μmol/L)	15 (11-19)	33 (16-43)	<.001
PALBI score	−2.19 ± 0.39	−1.80 ± 0.45	<.001
ALBI score	−2.38 ± 0.51	−1.93 ± 0.66	<.001
LVEF (%)	26.3 ± 6.3	27.8 ± 5.2	.103
Length of in-hospital stay (days)	8 (6-13)	6 (4-10)	.021

ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PALBI, platelet–albumin–bilirubin; SGLT-2, sodium-glucose cotransporter-2.

PALBI ≥ −2.047 had a higher prevalence of COPD (37.4% vs. 24.8%, *P* = .011). They also exhibited lower hemoglobin and serum albumin levels, and higher neutrophil counts, platelet counts, CRP, creatinine, alanine aminotransferase, NT-proBNP, and total bilirubin levels (all *P* < .05). Importantly, in-hospital mortality was markedly higher in

Table 2. Univariable and Multivariable Cox Proportional Hazards Regression Analyses for Predictors of In-hospital Mortality in Patients with Acute Decompensated Heart Failure with Reduced Ejection Fraction

Variables	Univariable Regression Analysis		Multivariable Regression Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years)	1.067 (1.038-1.096)	<.001	1.067 (1.031-1.105)	<.001
Chronic kidney disease	1.169 (1.088-1.327)	<.001	1.266 (1.120-1.591)	.001
C-reactive protein	1.011 (1.004-1.017)	.001	1.009 (1.000-1.019)	.054
Serum creatinine†	1.685 (1.456-1.950)	<.001	–	–
NT-proBNP, per 500-unit increase	1.169 (1.081-1.350)	<.001	1.245 (1.106-1.567)	.001
Serum albumin‡	0.933 (0.892-0.976)	.003	–	–
Total bilirubin‡	1.080 (1.058-1.102)	<.001	–	–
PALBI score	2.523 (1.285-3.761)	<.001	2.638 (1.177-4.099)	<.001
ALBI score‡	3.153 (1.955-5.084)	<.001	–	–

ALBI, albumin–bilirubin; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PALBI, platelet–albumin–bilirubin; VIF, variance inflation factor.
†Serum creatinine was not included simultaneously with chronic kidney disease due to clinical overlap and multicollinearity between these renal function markers (pairwise VIF = 6.391).
‡Serum albumin, total bilirubin, and ALBI score were not included in the multivariable model because they are components of, or closely related to, the PALBI score. When PALBI, ALBI, albumin, and bilirubin were entered together, marked multicollinearity was observed, particularly for ALBI (VIF = 200.042), albumin (VIF = 164.011), and bilirubin (VIF = 12.197). Therefore, PALBI was retained as the representative composite index in the final parsimonious model.

patients with PALBI ≥ −2.047 compared with those with PALBI < −2.047 (22.4% vs. 5.5%, $P < .001$).

Beyond AUC, PALBI provided incremental prognostic information over ALBI as reflected by an NRI (9.9%) and a small IDI (0.5%). The reclassification scatter plot (Figure 1B) shows that PALBI shifted a subset of patients—particularly those who died in the hospital—toward higher predicted-risk categories than ALBI, thereby improving bedside risk stratification.

Table 3. Receiver Operating Characteristic Curve Analysis of Age, Chronic Kidney Disease, NT-proBNP, PALBI, and ALBI Scores for Predicting In-hospital Mortality in Patients with Acute Decompensated Heart Failure with Reduced Ejection Fraction

Variables	AUC (95% CI)	Cutoff Point	*P*	Sensitivity (%)	Specificity (%)
Age (years)	0.722 (0.657-0.790)	68	<.001	68	67
Chronic kidney disease	0.708 (0.637-0.775)	–	<.001	–	–
NT-proBNP	0.702 (0.633-0.765)	982	<.001	69	68
PALBI score	0.737 (0.653-0.816)	−2.047	<.001	70	68
ALBI score	0.708 (0.615-0.788)	−2.010	<.001	60	76

ALBI, albumin–bilirubin; AUC, area under the curve; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PALBI, platelet–albumin–bilirubin.

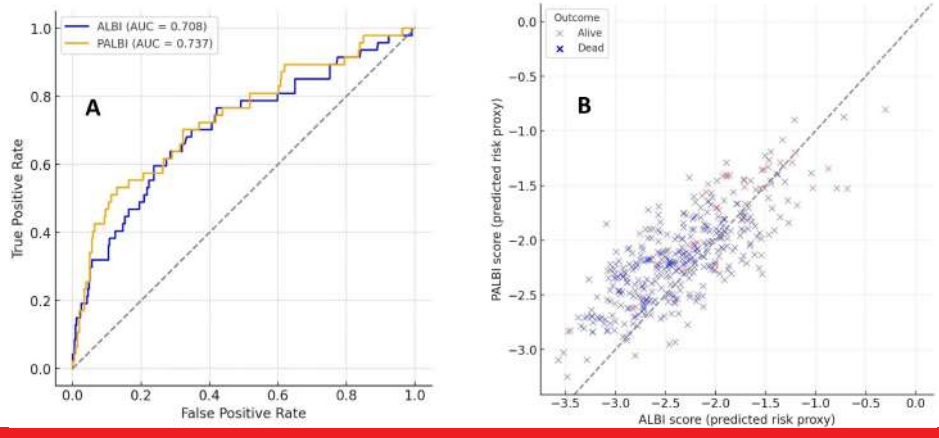


Figure 1. Prognostic performance of PALBI and ALBI in patients with heart failure and reduced ejection fraction presenting with acute heart failure: (A) Receiver operating characteristic curves comparing the discriminative ability of PALBI and ALBI for in-hospital mortality. (B) Reclassification plot illustrating the relationship between PALBI and ALBI scores, stratified by survival status. ALBI, albumin–bilirubin; PALBI, platelet–albumin–bilirubin.

Table 4. Baseline Demographic, Clinical, Laboratory, and Echocardiographic Characteristics of Patients Stratified According to the Optimal PALBI Cutoff Value (PALBI < −2.047 vs. PALBI ≥ −2.047)

Variables	PALBI < −2.047 (n = 254)	PALBI ≥ −2.047 (n = 147)	*P*
Demographics			
Age (years)	62.2 ± 14.5	63.7 ± 14.8	.317
Male, n (%)	188 (74.0)	102 (69.4)	.378
Comorbidities, n (%)			
Smoking, n (%)	112 (44.1)	63 (42.9)	.820
Hypertension	151 (59.4)	96 (65.3)	.291
Diabetes mellitus	86 (33.9)	47 (32.0)	.782
Atrial fibrillation	92 (36.2)	64 (43.4)	.146
Coronary artery disease	99 (39.0)	59 (40.1)	.902
Peripheral artery disease	20 (7.9)	11 (7.5)	1.000
Chronic kidney disease	77 (30.3)	49 (33.3)	.606
Chronic obstructive pulmonary disease	63 (24.8)	55 (37.4)	.011
Medications, n (%)			
Angiotensin-converting enzyme inhibitors	183 (72.0)	105 (71.4)	.986
Angiotensin II receptor blockers	37 (14.6)	23 (15.6)	.883
Beta-blockers	233 (91.7)	135 (91.8)	1.000
Mineralocorticoid receptor antagonists	183 (72.0)	104 (70.7)	.871
SGLT-2 inhibitors	87 (34.3)	41 (27.9)	.228
Asetylsalicylic acid	155 (61.0)	88 (59.9)	.902
Oral anticoagulant	80 (31.5)	56 (38.1)	.180
Statins	112 (44.1)	72 (49.0)	.400
Laboratory findings			
Hemoglobin (g/dL)	13.5 ± 2.2	12.5 ± 2.3	<.001
White blood cells (×10^9/L)	7.6 (6.4-8.9)	7.9 (6.6-9.2)	.186
Neutrophil (×10^9/L)	5.1 (3.9-6.8)	6.0 (4.8-8.1)	<.001
Lymphocyte (×10^9/L)	1.9 (1.3-2.4)	1.8 (1.1-2.4)	.996
Platelets (×10^9/L)	216 (174.2-268.5)	283 (241.0-334.8)	<.001
C-reactive protein (mg/dL)	18.4 (8.0-41.8)	22.0 (10.7-57.5)	.025
Serum creatinine (mg/dL)	1.2 (0.9-2.0)	1.3 (1.0-2.3)	.043
Serum sodium (mmol/L)	138 (135-140)	137 (132.5-139)	.030
Serum potassium (mmol/L)	4.3 (4.0-4.6)	4.4 (4.0-4.7)	.875
Serum chloride (mmol/L)	101.5 (98-104)	102 (98-104)	.916
AST (U/L)	16 (13-23)	16 (12-23)	.640
ALT (U/L)	20 (9-29.5)	24 (12-35)	.018
Total cholesterol (mg/dL)	167 (131-201.5)	158.5 (130-200)	.236
LDL-cholesterol (mg/dL)	116 (88-167.5)	117.5 (88-171.5)	.893
HDL-cholesterol (mg/dL)	36 (29.8-44)	34 (27.6-43)	.665
Triglyceride (mg/dL)	118 (89.2-165.8)	110 (79.5-150.5)	.088
NT-proBNP (pg/mL)	1676 (638-4899)	2736 (931-7797)	<.001
Serum albumin (g/L)	39.1 ± 5.1	32.6 ± 5.6	<.001
Total bilirubin (μmol/L)	13 (10-16)	23 (15-33)	<.001
PALBI score	−2.4 ± 0.3	−1.7 ± 0.3	<.001
LVEF (%)	26.4 ± 6.3	26.5 ± 6.0	.830
Length of in-hospital stay (days)	8 (5-12)	8 (5-15)	.587
In-hospital mortality, n (%)	14 (5.5)	33 (22.4)	<.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PALBI, platelet–albumin–bilirubin; SGLT-2, sodium-glucose cotransporter-2.

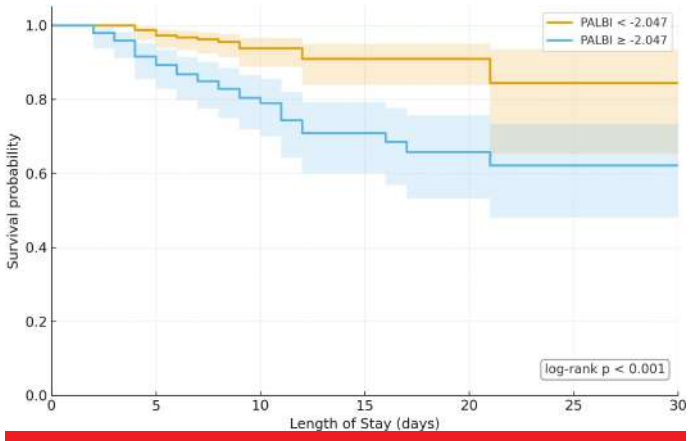


Figure 2. Kaplan–Meier survival curves stratified by PALBI score. Patients with higher PALBI values (≥ −2.047) had significantly lower in-hospital survival compared with those with lower scores (< −2.047) (log-rank *P* < .001). PALBI, platelet–albumin–bilirubin.

Kaplan–Meier survival curves showed that patients in the high-risk group (PALBI ≥ −2.047) had significantly higher in-hospital mortality than those in the low-risk group (PALBI < −2.047) (log-rank *P* < .001; Figure 2). Similarly, when patients were divided into tertiles based on PALBI scores [tertile 1 (< −2.458), tertile 2 (−2.458 to −1.896), tertile 3 (> −1.896)], survival rates declined gradually from tertile 1 to tertile 3 (log-rank *P* < .001; Figure 3).

Further stratified analyses are presented in Table 5, in which patients were categorized into 3 groups based on the PALBI score distribution (< −2.458, −2.458 to −1.896, and > −1.896). Comparisons revealed that higher PALBI scores were associated with more adverse clinical profiles, including a greater prevalence of COPD, as well as significant laboratory differences, including lower hemoglobin levels, higher neutrophil counts, and higher NT-proBNP levels. Platelet counts, serum albumin, and total bilirubin levels also differed significantly across the groups in line with the PALBI score components. Importantly, in-hospital mortality increased markedly across the groups, from 4% in the lowest PALBI group to 27% in the highest group (*P* < .001).

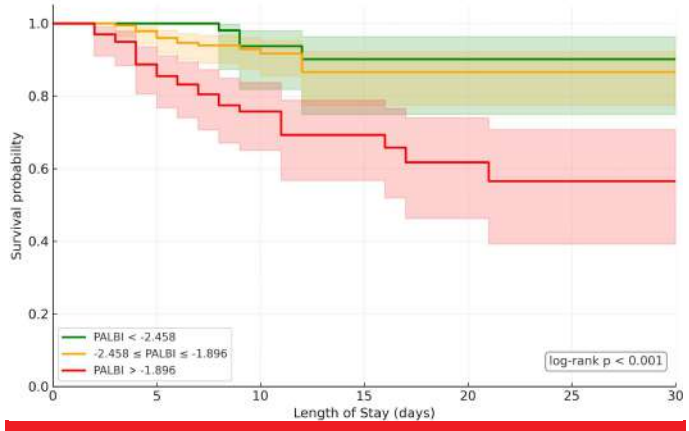


Figure 3. Kaplan–Meier survival curves stratified by PALBI tertiles. Patients with higher PALBI scores (> −1.896, red line) had significantly lower in-hospital survival compared with intermediate (−2.458 ≤ PALBI ≤ −1.896, yellow line) and lower PALBI scores (< −2.458, green line) (log-rank *P* < .001). PALBI, platelet–albumin–bilirubin.

Restricted cubic spline analysis was performed to further evaluate the relationship between PALBI score and in-hospital mortality. This analysis demonstrated a significant overall association, indicating that higher PALBI scores were associated with a higher risk of in-hospital mortality (*P* < .001). However, the test for nonlinearity was not statistically significant (*P* = .360), suggesting that the association was primarily linear rather than curvilinear. The predicted probability of in-hospital mortality increased progressively across the PALBI score spectrum, as illustrated in Figure 4.

DISCUSSION

The present study provides novel evidence that the PALBI score, a composite index traditionally used to assess hepatic functional reserve, has prognostic value in HFrEF-AHF. By systematically examining its association with short-term outcomes, this study identified PALBI as an independent predictor of in-hospital mortality. To the authors' knowledge, this is the first report to establish a direct link between PALBI and adverse prognosis in HFrEF-AHF, thereby expanding the clinical applicability of this biomarker beyond hepatology and opening a new perspective for integrated risk assessment in cardiovascular care.

The pathophysiology of HFrEF-AHF is inherently complex, involving the interplay between cardiac dysfunction, systemic inflammation, venous congestion, and multi-organ impairment.[18] Hepatic involvement is well recognized; elevated right atrial pressures and impaired forward flow lead to hepatic venous congestion, hypoperfusion, and subsequent biochemical abnormalities, including cholestasis, hyperbilirubinemia, and reduced albumin synthesis.[19] Concomitantly, systemic inflammation and neurohormonal activation promote oxidative stress, endothelial dysfunction, and bone marrow suppression, leading to thrombocytopenia and contributing to adverse outcomes.[20,21] The PALBI score integrates 3 readily available laboratory markers that mirror these pathophysiological processes. Thrombocytopenia may reflect systemic inflammation, increased platelet destruction, or impaired bone marrow function.[22] Hypoalbuminemia is a well-established surrogate of both malnutrition and impaired hepatic synthetic capacity.[23] Hyperbilirubinemia reflects cholestasis and impaired clearance due to hepatic congestion.[19] By combining these parameters into a single index, PALBI captures multiple dimensions of HFrEF-AHF pathophysiology, potentially providing a more robust assessment of overall disease burden than individual markers. The association between higher PALBI scores and mortality in HFrEF-AHF underscores the importance of systemic inflammation, nutritional decline, and hepatic dysfunction in driving adverse outcomes. These mechanisms are not merely epiphenomena but central features of the pathophysiology of AHF. Inflammatory cytokines contribute to

Table 5. Comparison of Baseline Characteristics, Comorbidities, Laboratory Results, Echocardiographic Parameters, and In-hospital Outcomes Among Patients Divided into 3 Groups Based on the Platelet–Albumin–Bilirubin Score

Variables	Group 1 (PALBI Score < −2.458, Below 25th Percentile) (n = 100)	Group 2 (PALBI Score Between −2.458 and −1.896, Inclusive, 25th-75th Percentile) (n = 201)	Group 3 (PALBI Score > −1.896, Above 75th Percentile) (n = 100)	*P*
Demographics				
Age (years)	61.4 ± 14.4	63.1 ± 14.4	63.5 ± 15.3	.524
Male, n (%)	75 (75.0)	146 (72.6)	69 (69.0)	.631
Comorbidities, n (%)				
Smoking, n (%)	44 (44.0)	91 (45.3)	40 (40.0)	.249
Hypertension	61 (61.0)	120 (59.7)	66 (66.0)	.566
Diabetes mellitus	34 (34.0)	66 (32.8)	33 (33.0)	.979
Atrial fibrillation	37 (37.0)	80 (39.8)	39 (39.0)	.986
Coronary artery disease	40 (40.0)	75 (37.3)	43 (43.0)	.684
Peripheral artery disease	11 (11.0)	11 (5.5)	9 (9.0)	.206
Chronic kidney disease	25 (25.0)	65 (32.3)	36 (36.0)	.227
Chronic obstructive pulmonary disease	21 (21.0) [a]	54 (26.9) [a]	43 (43.0) [b]	.002
Medications, n (%)				
Angiotensin-converting enzyme inhibitors	74 (74.0)	144 (71.6)	70 (70.0)	.818
Angiotensin II receptor blockers	16 (16.0)	24 (11.9)	20 (20.0)	.172
Beta-blockers	90 (90.0)	186 (92.5)	92 (92.0)	.749
Mineralocorticoid receptor antagonists	65 (65.0)	152 (75.6)	70 (70.0)	.145
SGLT-2 inhibitors	33 (33.0)	63 (32.2)	32 (32.0)	.907
Asetylsalicylic acid	60 (60.0)	124 (61.7)	59 (59.0)	.895
Oral anticoagulant	32 (32.0)	68 (33.4)	36 (36.0)	.740
Statins	47 (47.0)	87 (43.3)	50 (50.0)	.527
Laboratory findings				
Hemoglobin (g/dL)	13.8 ± 2.2 [a]	13.1 ± 2.2 [b]	12.4 ± 2.3 [b]	<.001
White blood cells (×10⁹/L)	7.7 (6.6-8.8)	7.6 (6.4-9.1)	8.0 (6.6-9.2)	.305
Neutrophil (×10⁹/L)	4.7 (3.8-7.0) [a]	5.4 (4.1-6.7) [b]	6.5 (4.9-8.9) [c]	<.001
Lymphocyte (×10⁹/L)	1.9 (1.2-2.4)	1.9 (1.3-2.5)	1.8 (1.1-2.4)	.257
Platelets (×10⁹/L)	195 (156-227) [a]	245 (198-290) [b]	303 (251-353) [c]	<.001
C-reactive protein (mg/dL)	18.1 (8.0-46.8)	20.0 (8.6-39.8)	22.0 (12.0-55.0)	.125
Serum creatinine (mg/dL)	1.1 (0.9-2.0)	1.3 (1.0-2.0)	1.3 (1.1-2.3)	.115
Serum sodium (mmol/L)	138 (136-140)	138 (135-139)	137 (132-139)	.102
Serum potassium (mmol/L)	4.3 (4.0-4.6)	4.3 (3.9-4.6)	4.4 (4.1-4.7)	.532
Serum chloride (mmol/L)	102 (98-105)	102 (98-104)	101 (98-103)	.664
Total cholesterol (mg/dL)	168 (131-201)	160 (130-196)	165 (128-209)	.730
LDL-cholesterol (mg/dL)	115 (87-160)	112 (88-153)	124 (92-190)	.248
HDL-cholesterol (mg/dL)	37 (31-46)	34 (28-43)	34 (28-43)	.071
Triglyceride (mg/dL)	128 (86-180)	110 (88-153)	118 (85-166)	.452
NT-proBNP (pg/mL)	1447 (515-4488) [a]	2001 (760-5491) [b]	2940 (915-5970) [c]	<.001
Serum albumin (g/L)	41 (38-44) [a]	37 (33-41) [b]	32 (28-35) [c]	<.001
Total bilirubin (μmol/L)	10 (8-14) [a]	15 (12-19) [b]	26 (17.8-36.5) [c]	<.001
LVEF (%)	26.5 ± 6.4	26.2 ± 6.5	26.9 ± 5.4	.697
In-hospital mortality, n (%)	4 (4.0) [a]	16 (8.0) [a]	27 (27.0) [b]	<.001

Different superscripts indicate the statistical difference between groups.
HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; N-terminal pro-B-type natriuretic peptide; SGLT-2, sodium-glucose cotransporter-2.

endothelial dysfunction, renal impairment, and myocardial injury.[24] Nutritional depletion reduces physiological reserve and impairs recovery.[25] Hepatic congestion and dysfunction perpetuate multi-organ failure.[26] Platelet–albumin–bilirubin captures these interrelated processes in a single index, offering mechanistic plausibility for its prognostic value. Moreover, the linear relationship observed in spline analysis suggests that even modest worsening of these parameters is associated with increased risk, reinforcing the need for comprehensive early assessment.

This study's results align with and extend prior evidence that liver-derived composite indices convey prognostic information in AHF. Multiple independent studies have now evaluated the ALBI score in AHF and consistently demonstrated prognostic utility. In the multicenter Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure (REALITY-AHF) registry (n = 1190), higher ALBI at emergency department presentation was associated with clinical congestion (peripheral edema, jugular venous distension, pleural effusions), added discriminative value beyond established risk factors, and independently predicted 1-year mortality.[12] These data supported ALBI as an integrated marker of liver dysfunction related to fluid overload with a genuine prognostic signal in AHF. Complementing those findings, a separate single-center study of 262 AHF admissions reported that ALBI measured at admission was independently associated with in-hospital all-cause mortality even after adjustment for the The Get With the Guidelines-Heart Failure (GWTG-HF) risk score and natriuretic peptides, and that adding ALBI improved risk classification over a clinical model.[27] Subsequent investigations have expanded the ALBI evidence base. In intensive care unit (ICU) heart failure cohorts from the Medical Information Mart for Intensive Care III (MIMIC-III) and MIMIC-IV databases, ALBI independently predicted both short-term and long-term mortality.[28] Luo et al[28] showed that combining ALBI with the GWTG-HF score (GWTG-HF-ALBI) improved discrimination compared with GWTG-HF alone. At the same time, Wang et al[29] demonstrated that each increment in ALBI tertile was associated with a ~10% increase in 1-year mortality and that a 1-unit increase conferred a 36% higher risk, reinforcing ALBI as a robust cardio-hepatic risk marker. More recently, in elderly patients hospitalized for AHF, higher ALBI identified markedly worse long-term survival, underscoring its generalizability across vulnerable age groups.[30] Collectively, these analyses indicate that a composite built from albumin and bilirubin—capturing both nutritional/inflammatory states and cholestasis from venous congestion[10]—stratifies risk across diverse AHF populations, including unselected, ICU, and elderly cohorts.

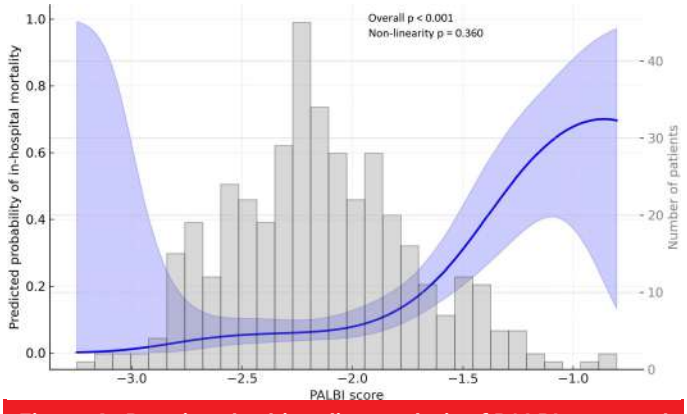


Figure 4. Restricted cubic spline analysis of PALBI score and in-hospital mortality. The plot demonstrates a graded, approximately linear association between higher PALBI scores and the probability of in-hospital mortality (overall $P < .001$; nonlinearity $P = .360$). Histogram bars represent the distribution of PALBI scores within the study population. PALBI, platelet–albumin–bilirubin.

The present work advances this literature in 3 important ways. First, whereas prior ALBI studies enrolled broad AHF cohorts with mixed ejection fraction phenotypes.[12,27-30] The present analysis focused specifically on patients with HFrEF presenting with acute decompensation—an especially high-risk subgroup in whom organ cross-talk (hepatic congestion, systemic inflammation, and catabolic/nutritional decline)[26] is pronounced. Within this population, this study confirmed the prognostic relevance of ALBI, consistent with prior reports, and found that PALBI showed modestly improved discriminatory performance. Second, by explicitly incorporating thrombocytopenia into the composite, PALBI embeds a hematologic/inflammatory dimension that ALBI does not capture. Although platelet counts alone did not differ significantly between survivors and non-survivors in this cohort, their integration into the composite with albumin and bilirubin conferred incremental discriminatory value. This suggests that PALBI reflects a broader cardio-hepatic-inflammatory axis that extends beyond individual components, and its prognostic utility derives from the synergy among these parameters rather than from isolated platelet variation. This is biologically relevant in HFrEF-AHF, where systemic inflammation and bone marrow suppression may reduce circulating platelets, and where endothelial dysfunction and oxidative stress can exacerbate multi-organ injury.[31] Taken together, the expanding external evidence on ALBI[12,27-30] and the current study's HFrEF-specific results with PALBI are convergent: simple, routinely available laboratory metrics that reflect hepatic synthetic function/cholestasis (albumin, bilirubin) as well as systemic inflammation/hematologic perturbation (platelets) carry actionable prognostic information in the acute setting.

From a practical perspective, PALBI offers several advantages for clinicians at the front line of HFrEF-AHF care, where in-hospital mortality remains substantial and early therapeutic decisions must be made amid uncertainty. Because it is derived from universally available and inexpensive laboratory tests and captures multiple pathophysiologic domains, PALBI can aid in identifying high-risk patients at admission, support decisions regarding monitoring and therapeutic escalation, and potentially enhance generalizability across diverse patient subgroups. The supportive evidence from ALBI across all-comer AHF, ICU, and elderly cohorts further strengthens the plausibility that the PALBI findings in HFrEF reflect a common cardio-hepatic-inflammatory axis, while underscoring the need for external validation and direct

head-to-head comparisons to establish whether the addition of platelets confers incremental clinical utility.

In addition to PALBI, the current analysis confirmed several well-established prognostic determinants in HFrEF-AHF, including advanced age, CKD, and NT-proBNP.[32-34] These variables have consistently been shown in prior studies to predict adverse outcomes in HFrEF-AHF,[32-34] and their emergence as significant predictors in this cohort strengthens the validity and representativeness of the study's findings. Importantly, the prognostic value of PALBI was demonstrated after adjustment for these conventional risk factors, indicating that it provides incremental information beyond these known predictors. This suggests that PALBI, when combined with established clinical and biochemical markers, could contribute to a more refined and accurate risk-stratification strategy in HFrEF-AHF. Such a multidimensional assessment may enable clinicians to better identify high-risk patients early and tailor therapeutic intensity accordingly.

Study Limitations

This study has several limitations that should be acknowledged. First, its retrospective and single-center design may limit generalizability, and residual confounding cannot be fully excluded despite comprehensive multivariable adjustment. Second, although adequate for primary analyses, the sample size was limited to 47 in-hospital deaths. This inevitably raises concern about the potential for overfitting in multivariable modeling. To mitigate this, this study pre-specified a parsimonious model, applied penalization techniques with bootstrap-based internal validation, and confirmed the robustness of the results through sensitivity analyses; inferences were directionally stable across specifications. Nevertheless, external validation in larger, multicenter cohorts is essential to confirm these findings. Third, although patients with chronic liver disease, active malignancy, or hematologic disorders were excluded, patients with concomitant active infection were not systematically excluded from the study. This may be considered a limitation, as underlying infections could have contributed not only to elevated inflammatory markers such as CRP and neutrophil counts, but also to changes in platelet and albumin levels, potentially influencing PALBI values. Furthermore, subclinical hepatic or inflammatory conditions cannot be entirely excluded and may have influenced PALBI values; moreover, although median aminotransferase levels were not markedly elevated at the cohort level, transient hepatocellular injury related to hemodynamic compromise may have been present in a small subset of patients, reflecting the heterogeneity of clinical presentations within the AHF spectrum. Fourth, the study focused exclusively on patients with HFrEF, thereby strengthening internal homogeneity but limiting extrapolation to other heart failure populations. Fifth, PALBI was assessed only at admission, and dynamic changes during hospitalization—which may provide additional prognostic information—were not evaluated. Additionally, laboratory measurements were obtained from routine clinical testing, and potential interassay or interlaboratory variability may affect reproducibility in other settings. Moreover, PALBI was not directly compared with established biomarkers such as natriuretic peptides or high-sensitivity troponin, which could have further clarified its incremental value. In addition, information on angiotensin receptor–neprilysin inhibitor use could not be reliably assessed. In Türkiye, Angiotensin Receptor-Neprilysin Inhibitors (ARNI) therapy is not reimbursed by the national health insurance system, and its use largely depends on out-of-pocket payments, resulting in inconsistent prescribing and documentation in retrospective hospital records. Therefore, ARNI use was not included in the analysis to avoid potential misclassification and reporting bias. Finally, whether PALBI-guided risk stratification influences therapeutic decision-making or improves outcomes remains to be determined in prospective interventional studies.

CONCLUSION

This study showed for the first time that the PALBI score independently predicts in-hospital mortality in patients with HFrEF-AHF. Derived from simple, widely available laboratory parameters, PALBI captures systemic inflammation, nutritional status, and hepatic dysfunction and provides prognostic information beyond conventional risk factors. By helping identify high-risk patients early, PALBI may support timely, targeted management strategies. External validation in larger and more diverse cohorts is needed to confirm its generalizability and clinical utility.

Ethics Committee Approval: This study was approved by the Ethics Committee of Ankara Etlik City Hospital (Approval No.: AEŞH-BADEK2-2025-278; Date: July 22, 2025).

Artificial Intelligence Usage Statement: The authors confirm that no artificial intelligence (AI)-assisted technologies (such as large language models, chatbots, or image generators) were used in the preparation, writing, analysis, or methodology of this manuscript. While the study itself explores an AI-related hypothesis, all aspects of the research design, data collection, analysis, and manuscript preparation were conducted entirely by the authors, without the assistance of AI tools.

Informed Consent: The Local Ethics Committee waived the requirement for informed consent because the research was retrospective.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – VH, VOT, BÖ; Design – VH VOT, KA; Supervision – VH, VOT, KA, BÖ; Resources – VH, VOT, KA, AS, ÇT, YBŞ, YT; Materials – VH, VOT, KA, AS, ÇT, YBŞ, YT; Data Collection and/or Processing – VH, VOT, KA, AS, ÇT, YBŞ, YT; Analysis and/or Interpretation – AT, BÖ; Literature Search – All authors; Writing – All authors; Critical Review – VH, VOT, BÖ.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declare that this study received no financial support.

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Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Apolipoprotein E Genotype and Coronary Heart Disease in a Mongolian Cohort: An Exploratory Case–Control Study

ABSTRACT

Background: To investigate the association between apolipoprotein E (*APOE*) gene polymorphisms and coronary heart disease (CHD) risk within a localized Mongolian clinical cohort.

Methods: This hospital-based case–control study recruited 63 patients with angiographically confirmed CHD and 61 sex-matched healthy controls. Anthropometric measurements and lipid profiles and pathways for *APOE* genotypes were strictly assessed. This exploratory hospital-based case–control study was not designed as a nationally representative population-based survey, and participant recruitment was limited to a single tertiary referral center in Mongolia.

Results: High-density lipoprotein cholesterol levels were significantly higher in the case group than in the control group (1.56 ± 0.14 vs. 1.33 ± 0.18 mmol/L, $P < .001$), while total cholesterol was significantly lower in cases than in controls (3.91 ± 0.60 vs. 5.34 ± 0.80 mmol/L, $P < .001$). The distribution of *APOE* genotypes (ε2/ε3, ε3/ε3, ε3/ε4, and ε4/ε4) differed significantly between the case and control groups ($P = .009$). Both systolic and diastolic blood pressure significantly correlated with waist circumference ($P = .026$). Multivariable logistic regression revealed that the ε2/ε3 genotype was associated with significantly lower odds of disease (odds ratio [OR] = 0.29, $P = .007$, 95% CI: 0.12-0.71), whereas ε4-related findings were highly imprecise due to sparse genotype counts and lacked statistical significance (OR = 1.07, $P = .930$, 95% CI: 0.23-5.02).

Conclusion: This study showed a significant association between the *APOE* genotype and CHD in a Mongolian population. These findings highlight the importance of considering qualitative aspects of lipid metabolism, rather than total cholesterol alone, and suggest that genetic factors, including *APOE* polymorphisms, may contribute to CHD risk independently of absolute cholesterol levels, underscoring the need for population-specific cardiovascular risk assessment.

Keywords: Apolipoprotein E, case–control study, coronary heart disease, genotype

INTRODUCTION

The coronary heart disease (CHD) is a growing health concern worldwide, with its prevalence steadily increasing across developed and developing nations.[1] Genetic factors play a crucial role in determining an individual's susceptibility to coronary artery disease, especially the apolipoprotein E (*APOE)* gene, which is a well-studied genetic marker.[2] The *APOE* gene is essential in regulating cholesterol metabolism, and its polymorphisms have been associated with varying risks of CHD across different populations.[3,4]

Located on chromosome 19q13.2, the *APOE* gene contains key single-nucleotide polymorphisms (SNPs), notably rs429358 and rs7412, which give rise to 3 primary allelic variants: ε2, ε3, and ε4.[5] These variants (ε2, ε3, and ε4) code for isoforms of apolipoprotein E that differ in their amino acid sequence, particularly at residues 112 and 158, leading to differential binding affinities for lipoprotein receptors and diverse physiological effects on lipid transport and degradation.[6] The 3 common alleles, designated ε2, ε3, and ε4, form 6 distinct genotypes (ε2/ε2, ε2/ε3, ε3/ε3, ε2/ε4, ε3/ε4, and ε4/ε4), each conferring a unique biochemical profile and

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Received: February 5, 2026
Accepted: June 19, 2026
Available Online Date: August 3, 2026

Cite this article as: Dogsom O, Punsaldulam A, Dogsom O, et al. Apolipoprotein E genotype and coronary heart disease in a Mongolian cohort: An exploratory case–control study. *Anatol J Cardiol.* 2026;30(12):943-954.

DOI: 10.14744/AnatolJCardiol.2026.6198

influencing an individual's predisposition to dyslipidemia and cardiovascular disease (CVD).[7] For instance, the ε4 allele is consistently associated with an increased risk of coronary artery disease, whereas the ε2 allele is recognized for its protective role.[8]

In Mongolia, a country experiencing rapid lifestyle changes and increasing CVD rates, it is essential to understand the relationship between *APOE* gene variants and CHD risk factors.[9] Notably, CHD manifests approximately 8-9 years earlier among Mongolians than in more developed countries.[9,10] Previous studies have shown genetic variations in *APOE* as significant contributors to the development of coronary artery disease.[3,5]

APOE polymorphisms have substantially influenced lipid metabolism, a key determinant of cardiovascular health. The *APOE* genotype is therefore of considerable interest, as it has been associated with various cardiovascular conditions, including CHD.[4,11] Although numerous studies have examined the association between *APOE* polymorphisms and CVD risk across diverse populations, evidence specific to the Mongolian ethnic group is limited, with existing literature focusing primarily on other Asian groups.[9,12,13]

The present study addresses a critical evidence gap by examining the association between *APOE* genotype polymorphisms and CHD in a population significantly underrepresented in genetic cardiovascular epidemiology literature. The vast majority of *APOE*-CHD association studies have focused on populations of European descent, with some representation of African American, Chinese, and Latino cohorts; however, Central Asian populations such as Mongolians remain poorly characterized.[13-17] This geographic and ethnic underrepresentation is concerning because population-specific variation in allele frequencies, genetic backgrounds, and environmental exposure can substantially modify the strength and direction of genetic associations with complex diseases such as CHD.[18-20]

By elucidating *APOE* genotype distributions and their relationship with CHD risk in the Mongolian population—shaped by unique genetic ancestry, dietary patterns, and environmental exposures—this study contributes to greater diversity in global genetic epidemiology literature and provides population-specific insights relevant to prevention and management strategies. This approach is crucial, given that the impact of specific allelic variations on CHD risk can significantly depend on varying genetic and environmental contexts among populations. It is especially relevant to the Mongolian population, where cardiovascular health patterns are influenced by socioeconomic determinants such as income, education, and access to health insurance, highlighting the need for tailored public health strategies.[9,21-24] Therefore, a deeper understanding of the genetic architecture of CHD in this specific demographic is paramount for the development of effective, culturally sensitive interventions. Therefore, achieving a comprehensive understanding of the genetic underpinnings of CHD in this population is essential for developing targeted and effective interventions. Accordingly, this study investigates the association between *APOE* polymorphisms and CHD susceptibility among Mongolians, elucidating the genetic and environmental factors contributing to this major public health challenge.

HIGHLIGHTS

- The *APOE* ε4 allele was significantly associated with increased coronary heart disease risk in a Mongolian population.
- Coronary heart disease cases exhibited altered lipid fraction distribution despite lower total cholesterol levels.
- ε4 carriers showed unfavorable cardiometabolic profiles, including higher body mass index and blood pressure.
- Findings underscore the importance of qualitative lipid assessment and population-specific genetic risk evaluation.

METHODS

Participants and Study Design

Cases and controls were recruited using a non-random hospital-based sampling strategy, and the findings should therefore be interpreted as exploratory rather than population representative.

This hospital-based case–control study was conducted at the Third State Central Hospital in Mongolia, in collaboration with the Mongolian National University of Medical Sciences. A total of 124 participants were enrolled, including 63 patients diagnosed with CHD and 61 healthy controls exhibiting no evidence of coronary artery disease, who served as the reference group. Participants in both the control and case groups were sex-matched and recruited from individuals visiting state and central hospitals across various provinces for routine health check-ups. Lifestyle and medical history information were obtained using a questionnaire-based interview.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the participating institution (Approval MEC No. 2018/3-09). Written informed consent was obtained from all participants, who were informed of their right to withdraw at any time.

Coronary Heart Disease Diagnosis and Severity Assessment

Coronary heart disease was diagnosed based on angiographic findings, which represent the gold standard for the detection of coronary artery disease. Coronary angiography was performed using standard techniques, and all angiograms were reviewed by experienced interventional cardiologists. The severity of CHD was assessed according to established criteria from the Coronary Artery Surgery Study.[25] The number of diseased vessels was determined based on the presence of ≥70% stenosis in the proximal, mid, or distal segments of the 3 major coronary arteries: the right coronary artery, left anterior descending artery, and left circumflex artery.[25] Patients were classified as having

single-vessel disease, double-vessel disease, or triple-vessel disease according to the number of major coronary arteries with significant stenosis.[26] In cases involving the left main coronary artery, disease severity was classified as equivalent to 2-vessel disease in right dominant circulation or 3-vessel disease in left dominant circulation.[25] This angiographic classification system has been widely validated and provides a standardized measure of disease burden that correlates with cardiovascular outcomes.[27]

All study participants, including both control and case groups, were sex-matched and recruited from individuals visiting Third State Central Hospital in Mongolia across various provinces for routine health check-ups.

Lifestyle and Medical History Assessment

Comprehensive lifestyle and medical history data were collected using standardized questionnaire-based interviews administered by trained research personnel. The following variables were assessed using operational definitions:

Smoking Status

Smoking was categorized as never, former, or current smoker. Never smokers were defined as participants who had not smoked regularly (i.e., less than 100 cigarettes in their lifetime). Current smokers were those participants who reported smoking at least 1 cigarette per day during the past year. Former smokers were those with a history of regular smoking who had quit for at least 1 year.[28,29] For current and former smokers, cumulative exposure was measured in pack-years, calculated as the average number of cigarettes smoked per day divided by 20 (1 pack), multiplied by the number of years smoked.[28,30]

Alcohol Consumption

Alcohol consumption was assessed through self-report. Participants who reported no alcohol intake in the past year were classified as non-consumers. Among consumers, alcohol intake was quantified in grams of ethanol per day based on reported drinking frequency and typical consumption amounts.[31]

Dietary Patterns

Dietary assessment was based on a food frequency questionnaire designed to capture habitual intake patterns over the past year. Intake of key food groups—including fruits, vegetables, whole grains, fish, and sources of saturated and unsaturated fats—was evaluated.[31] A diet quality index ranging from 0 to 6 was developed, with higher scores indicating greater adherence to heart-healthy dietary patterns characterized by higher intake of fruits, vegetables, fish, and polyunsaturated fats, and lower consumption of saturated fats and refined sugars.[32]

Physical Activity

Physical activity (referred to as "training" in the original questionnaire) was assessed using a validated questionnaire that captured the frequency, duration, and intensity of activities across multiple domains, including occupational, transportation, household, and leisure-time activities.[33,34] Activity intensity was classified as light (<4 metabolic equivalents [METs]), moderate (4-7 METs), or vigorous (>7 METs), where 1 MET represents the energy expenditure at rest (approximately 3.5 mL O_2/kg/min or 1 kcal/kg/hour).[33,35] Participants were asked to report the type of activities performed (e.g., walking, running, swimming, ball games, gymnastics), along with the frequency (times per week) and duration (minutes per session).[34] Total physical activity was quantified as MET-hours per week, calculated by multiplying the MET value of each activity by its frequency and duration.[35,36] This methodology aligns with World Health Organization guidelines for physical activity assessment and has been validated in large cardiovascular cohort studies.[37]

Biometric Measurements

A registered nurse or an attending physician interviewed the participants to gather medical history and measure their height and weight. Height was measured without shoes using a stadiometer, and weight was measured in light clothing using a calibrated scale. Body mass index (BMI) was calculated as the ratio of the participant's weight in kilograms to the square of their height in meters (kg/m^2).[38,39] Blood pressure was measured following standard protocols with participants at rest in a seated position for at least 5 minutes prior to measurement. Three consecutive readings were taken, and the average of the last 2 measurements was recorded as the systolic and diastolic blood pressure values.

Lipoprotein Measurements

Fasting venous blood samples were collected from participants after an overnight fast. Biochemical and lipid profiles were analyzed, including total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), using standard laboratory techniques. The analyses were conducted with automated biochemical analyzers (BA-400 and A-25), using photometric and turbidimetric methods with reagents from Biosystems (Applied Biosystems, Foster City, CA, USA). Triglyceride levels were measured photometrically using a glycerol-3-phosphate oxidase–based diagnostic kit, per the manufacturer's instructions.

Sample Collection and Processing

After overnight fasting, participants rested in a supine position for 30 minutes before blood collection. Approximately 5-8 mL of blood was drawn into tubes containing acid citrate dextrose as an anticoagulant. A portion of the sample (2-3 mL) was transferred to another vial and allowed to clot to obtain serum for biochemical parameter estimation. The remaining sample was centrifuged at 1500 rpm for 10 minutes at 4°C for plasma extraction, which was also used for biochemical parameter analyses.[40] Peripheral blood leukocytes were isolated and utilized for DNA extraction.

Determination of APOE Genotypes

Genomic DNA was extracted from leukocytes using a standard protocol and stored at 4°C. *APOE* genotypes were initially identified using an agarose gel-based method, as described by Reymer et al.[41] Briefly, polymerase chain reaction (PCR) was used to amplify the *APOE* allelic variants, which were subsequently digested using the restriction enzyme HhaI.[42] The resulting fragments were separated by agarose gel electrophoresis and visualized under ultraviolet

light to determine the participants' *APOE* genotypes. The participants' *APOE* genotypes were determined using the SNaPshot fluorescent single-base extension assay to genotype the rs429358 and rs7412. A 352 bp region of the *APOE* gene containing these SNPs was amplified by PCR using forward (5′- CTA CAA ATC GGA ACT GGA GG-3′) and reverse (5′- CAC GCG GCC CTG TTC CAC GAG-3′) primers. Each 20 µL reaction mixture contained 50 ng of DNA, 3 pmol of each primer, 1× buffer, 0.33 U of Taq DNA polymerase, and 0.2 mM deoxynucleotide triphosphates.

Polymerase chain reaction cycling conditions were as follows: initial denaturation at 95°C for 5 minutes; 38 cycles of denaturation at 95°C for 40 seconds, annealing at 56°C for 30 seconds, and extension at 72°C for 45 seconds; followed by a final extension at 72°C for 10 minutes. Polymerase chain reaction products were purified using polyethylene glycol and subsequently genotyped using the SNaPshot multiplex kit.[43]

Statistical Analysis

Normality was assessed using the Shapiro–Wilk test. Independent samples *t*-test or Mann–Whitney *U*-test were applied according to distributional assumptions, while categorical variables were compared using Pearson chi-square or Fisher's exact tests as appropriate.

Prior to group comparisons, the normality of continuous variables was assessed using the Shapiro–Wilk test, given the moderate sample size ($n < 100$ per group). Continuous variables that conformed to a normal distribution are presented as mean ± SD whereas non-normally distributed variables are reported as median with interquartile range. Group comparisons for normally distributed continuous variables were performed using 1-way ANOVA.[44] This approach was selected to allow simultaneous comparison of means across the defined subgroups (e.g., *APOE* genotype strata), thereby preserving the overall type 1 error rate relative to multiple pairwise *t*-tests. Post hoc pairwise comparisons were performed using Bonferroni correction to control the family-wise error rate across multiple comparisons. For non-normally distributed variables, the Kruskal–Wallis test was used, followed by Dunn's post hoc procedure with Bonferroni adjustment.[45] Categorical variables are expressed as frequencies and percentages. Between-group differences were evaluated using Pearson's chi-square test or Fisher's exact test, as appropriate. *APOE* allele frequencies and genotype distributions were assessed for compliance with Hardy–Weinberg equilibrium[46] using a chi-square goodness-of-fit test, performed separately for each group.

Binary logistic regression was used to estimate odds ratios (ORs) and 95% CIs for the association between *APOE* genotype and CHD risk, with the E3/E3 genotype serving as the reference category. Model 1 (unadjusted) included *APOE* genotype only. Model 2 (adjusted) additionally included age, sex, BMI, smoking status, systolic blood pressure, total cholesterol, LDL-C, HDL-C, triglycerides, family history of CVD, and physical activity as covariates. These variables were selected a priori based on established cardiovascular risk factors and those that differed significantly between groups at baseline. Odds ratios (ORs) are reported with corresponding 95% confidence intervals (CIs) and *P* values.[47]

Given the number of statistical tests performed, a Bonferroni-corrected significance threshold of $P < .003$ was applied for genotype–phenotype correlation analyses. A 2-sided *P*-value <.05 was retained as the primary threshold for prespecified comparisons. All analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Clinical Characteristics

A total of 124 participants were included in the study, comprising a case group and a control group. Among these, 63 individuals had CVD, while 61 did not. In the case group, 54% (34/63) were female, and 46% (29/63) were male. In the control group, 48% (29/61) were female, and 52% (32/61) were male. Statistical analysis revealed no significant difference in sex distribution between the 2 groups ($P = .400$).

The mean age of participants in the case and control groups was 52 ± 7 years and 53 ± 8 years, respectively ($P = .600$), indicating no statistically significant difference; however, other clinical parameters differed significantly. Body mass index was significantly higher in the case group (28.3 ± 3.0 kg/m^2) than in the control group (23.0 ± 3.0 kg/m^2; $P < .001$). Table 1 shows the clinical characteristics of the study participants.

Age distribution was consistent across study groups and genotypes. However, BMI was significantly higher among ε4/ε4 genotype carriers, particularly in the case group, indicating an association with increased metabolic risk. Individuals carrying the ε4 allele, especially those with the ε4/ε4 genotype, exhibited elevated diastolic blood pressure, suggesting a potential association with hypertension. Similarly, cases with the ε4/ε4 genotype showed higher systolic blood pressure, indicating increased cardiovascular risk. Total cholesterol levels varied significantly by genotype, with ε4 allele carriers in the case group exhibiting higher levels, consistent with the established role of the *APOE* ε4 allele in lipid metabolism disorders. Triglyceride levels were also significantly elevated among ε4/ε4 carriers in the case group, further highlighting the metabolic impact of this allele. High-density lipoprotein cholesterol levels showed only marginal variation, while LDL-C levels did not differ significantly across genotypes.

Biochemical Analysis

Table 1 summarizes the biochemical markers studied. Serum triglyceride levels were significantly lower in the case group than in the control group (1.00 ± 0.30 vs. 1.56 ± 0.74 mmol/L, $P < .001$). Serum HDL-C levels were higher in the case group than in the control group (1.56 ± 0.14 vs. 1.33 ± 0.18 mmol/L, $P < .001$). Serum LDL-C levels were also higher in the case group than in the control group (3.39 ± 0.60 vs. 2.62 ± 0.76 mmol/L, $P = .027$). Total cholesterol levels differed significantly between the 2 groups and were lower in the case group than in the control group (3.91 ± 0.60 vs. 5.34 ± 0.80 mmol/L, $P < .001$).

Table 1. Clinical Characteristics of Studied Participants

Parameters	Study Group: Case n = 63 (51%)[a]	Study Group: Control n = 61 (49%)[a]	*P* value[b]
Sex, n (%)			.400
Female	34 (54)	29 (48)	
Male	29 (46)	32 (52)	
Clinical characteristics			
Age (years)	52 ± 7 (40, 64)	53 ± 8 (40, 71)	.600
BMI (kg/m^2)	28 ± 3 (23, 37)	23 ± 3 (19, 35)	<.001
Systolic BP (mm Hg)	115.87 ± 3.6	137.27 ± 15.4	<.001
Diastolic BP (mm Hg)	77.17 ± 3.9	84.97 ± 7.8	<.001
Waist circumference (cm)	74.97 ± 6.5	92.8 ± 8.9	<.001
Lipids			
Cholesterol (mmol/L)	3.912 ± 0.6	5.34 ± 0.8	<.001
Triglycerides (mmol/L)	1.00 ± 0.3	1.56 ± 0.74	<.001
HDL (mmol/L)	1.56 ± 0.14	1.33 ± 0.18	<.001
LDL (mmol/L)	3.39 ± 0.6	2.62 ± 0.76	.027
Lifestyle/history, n (%)			
Family history of CVD			.001
Yes	24 (38)	5 (8.2)	
No	39 (62)	56 (92)	
Smoking status			.003
Yes	28 (44)	12 (20)	
No	35 (56)	49 (80)	
Alcohol consumption			.200
Yes	4 (6.3)	8 (13)	
No	59 (94)	53 (87)	
Stress			.800
Yes	15 (28)	14 (25)	
No	39 (72)	41 (75)	
Physical activity			.001
Yes	5 (7.9)	21 (34)	
No	58 (92)	40 (66)	
Dietary patterns			.090
Yes	14 (22)	22 (36)	
No	49 (78)	39 (64)	

BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]n (%): The percentage of individuals in that category relative to the total sample size.
[b]Pearson's chi-squared test; Wilcoxon rank sum test; Fisher's exact test.

The overall distribution of *APOE* genotypes differed significantly between the case and control groups ($\chi^2 = 9.08$, df = 3, $P = .009$; Table 2). Descriptively, the ε4/ε4 genotype was more frequent among cases than controls (15.9% vs 4.9%), whereas the ε2/ε3 genotype was less frequent among cases (12.7% vs 36.1%) (Table 2).

Genetical Analysis

APOE genotyping was performed on samples from 61 healthy participants and 63 patients with CHD. The identified genotypes in both groups were ε2/ε3, ε3/ε3, ε3/ε4, and ε4/ε4.

Table 2. ApoE Genotypes in Control and Case Groups

Genotype	Control n	Control n (%)	Case n	Case n (%)	χ^2	*P*
ε2/ε3	22	36.1	8	12.7		
ε3/ε3	33	54.1	41	65.1		
ε3/ε4	3	4.9	4	6.3		
ε4/ε4	3	4.9	10	15.9		
Total	61	100	63	100	9.08	.009

Genotype distributions were compared between groups using the chi-square (χ^2) test with 3 *df*.

Analysis of genotype frequencies for the *APOE* gene polymorphisms rs429358 and rs7412, in 124 individuals, showed that the control group had the following frequencies: ε2/ε3 (36.1%), ε3/ε3 (54.1%), and ε3/ε4 (4.9%). In the case group, the frequencies were as follows: ε2/ε3 (12.7%), ε3/ε3 (65.1%), ε3/ε4 (6.3%), and ε4/ε4 (15.9%). The distribution of APOE genotypes differed significantly between the case and control groups ($\chi^2 = 9.08$, $P = .009$) (Table 3).

Logistic regression analysis was conducted to evaluate the association between APOE genotypes and CHD risk. Using the ε3/ε3 genotype as the reference category, the ε2/ε3 genotype was associated with significantly lower odds of CHD (OR = 0.29, $P = .007$, 95% CI: 0.12-0.71), indicating a protective association. In contrast, no statistically significant associations were observed for the ε3/ε4 genotype (OR = 1.07, $P = .930$, 95% CI: 0.23-5.02) or the ε4/ε4 genotype (OR = 2.68, $P = .160$, 95% CI: 0.68-10.55). The wide CIs for the ε3/ε4 and ε4/ε4 genotypes reflect limited statistical precision due to the small number of carriers, particularly ε4/ε4 homozygotes.

No significant correlations were observed between *APOE* polymorphisms and demographic variables, including age ($r = -0.192$, $P = .090$) and sex ($r = 0.000$, $P = 1.000$), as shown in Table 4, suggesting that these factors did not confound the genotype–phenotype associations observed in this cohort.

Correlation Among Biomarkers

Serum cholesterol levels showed a significant positive correlation with waist circumference ($r = 0.348$, $P = .002$) and triglyceride levels ($r = 0.322$, $P = .004$). Triglycerides were also significantly associated with BMI ($r = 0.297$, $P = .008$), smoking status ($r = 0.288$, $P = .010$), and alcohol consumption ($r =$

Table 3. Frequency of *ApoE* Genotypes in Control (n = 61) and Case (n = 63) Groups and Calculated Odds Ratio

ApoE Genotype	Study Group: Control (%)	Study Group: Case	OR (95% CI)	*P*
ε3/ε3	33 (54.1)	41 (65.1)	Reference	–
ε2/ε3	22 (36.1)	8 (12.7)	0.29 (0.12-0.71)	.007
ε3/ε4	3 (4.9)	4 (6.3)	1.07 (0.23-5.02)	.930
ε4/ε4	3 (4.9)	10 (15.9)	2.68 (0.68-10.55)	.160

Odds ratios calculated using logistic regression with ε3/ε3 as the reference genotype.
OR, odds ratio.

Table 4. Correlation Analysis Among Biomarkers and Coronary Heart Disease Risk Factors

Variable 1	Variable 2	Correlation (*r*)	Adjusted *P*
Serum cholesterol	Waist circumference	0.348	.002
Serum cholesterol	Triglycerides	0.322	.004
Serum cholesterol	HDL	−0.360	.001
Triglycerides	BMI	0.297	.008
Triglycerides	Smoking status	0.288	.010
Triglycerides	Alcohol consumption	0.285	.011
BMI	Waist circumference	0.712	<.001
BMI	Smoking status	0.236	.036
LDL	Alcohol consumption	−0.245	.029
Alcohol consumption	Smoking status	0.317	.004
Alcohol consumption	Sex	0.236	.037
SBP/DBP	Waist circumference	0.250	.026
APOE genotype	Age	−0.192	.090
APOE genotype	Sex	0.000	1.000

r represents Spearman's rank correlation coefficient. All negative values are adjusted for multiple comparisons using the false discovery rate method.
BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

0.285, $P = .011$). A strong positive correlation was observed between BMI and waist circumference ($r = 0.712$, $P < .001$). In addition, both systolic and diastolic blood pressure showed a significant association with waist circumference ($r = 0.250$, $P = .026$) (Table 4).

Further analysis demonstrated that LDL-C was significantly associated with alcohol consumption ($r = -0.245$, $P = .029$), while HDL-C showed a significant correlation with total serum cholesterol ($r = -0.360$, $P < .001$).

Body mass index was also significantly correlated with smoking status ($r = 0.236$, $P = .036$) and waist circumference ($r = 0.712$, $P < .001$). Alcohol consumption showed a statistically significant association with smoking ($r = 0.317$, $P = .004$), sex ($r = 0.236$, $P = .037$), and triglyceride levels ($r = -0.285$, $P = .011$).

Regarding genetic factors, no significant correlations were observed between *APOE* genotype and demographic variables, including age ($r = -0.192$, $P = .090$) and sex ($r = 0.000$, $P = 1.000$), suggesting that these factors did not confound the observed genetic associations in this cohort (Table 4).

Finally, the observed age distribution did not differ significantly between the case and control groups across *APOE* genotypes, suggesting that age is not a significant confounding variable in this analysis (Table 5).

APOE Genotype–Related Differences in Metabolic and Cardiovascular Traits

Carriers of the ε4/ε4 genotype in the case group displayed significantly higher systolic and diastolic blood pressure, suggesting a strong association between this genotype and increased hypertensive risk. Overall group comparisons (Figure 1C and 1D) showed that both systolic and diastolic blood pressure were significantly elevated in cases compared with controls ($P < .001$), regardless of genotype, highlighting the elevated baseline cardiovascular risk in the CHD population.

Total Cholesterol

Total cholesterol levels varied significantly by genotype. In particular, ε4 allele carriers in the case group exhibited higher cholesterol levels than ε2 or ε3 carriers. However, at the group level (Figure 1E), total cholesterol was significantly lower in cases than in controls ($P < .001$), reflecting the influence of lipid-lowering therapy among patients.

Triglycerides

As illustrated in Figure 1F, triglyceride levels showed highly significant differences between groups ($P < .001$). The ε4/ε4 genotype was strongly associated with the highest triglyceride concentrations in the CHD group.

Lipoproteins

A statistically significant, albeit small, difference in HDL-C levels was observed between groups based on genotype and disease status (Figure 1G, $P < .005$). In contrast, LDL-C levels showed no significant difference between cases and controls ($P = .400$), irrespective of *APOE* genotype (Figure 1H).

Collectively, these findings indicate that while BMI and blood pressure are the primary distinguishing factors between CHD cases and controls, the ε4 allele—particularly in its homozygous (ε4/ε4) form—significantly exacerbates the metabolic and cardiovascular risk within the Mongolian CHD population (Figure 1B).

DISCUSSION

The current study aimed to investigate the associations between *APOE* genotypes, lipid profiles, and CHD risk factors in a Mongolian population. This work builds upon prior research characterizing *APOE* gene polymorphism in the Mongolian population, which reported an ε4 allele frequency of 1.9%,[9] and extends these findings by examining specific correlations with CVD markers.[8,48] The current findings indicate that carriers of the *APOE* ε3/4 and ε4/4 genotypes may exhibit an increased risk of CHD compared with ε3/3 carriers, consistent with findings from meta-analyses across diverse populations.[3] Specifically, the ε4 allele—especially in the homozygous ε4/ε4 state—is associated with elevated serum LDL-C levels, further solidifying its role in dyslipidemia and increased cardiovascular risk.[49]

In contrast, this study observed paradoxically lower total cholesterol levels in CHD cases compared with controls. This finding is likely attributable to the high prevalence of lipid-lowering therapy among patients with established coronary artery disease, reflecting adherence to secondary

Table 5. Correlation Analysis Between Biomarkers in the Healthy Control and Case Group

Variables	Age (Years)	Cholesterol	Sex	TGs	BMI	Smoking Status	Alcohol Consumption	SBP	DBP	Dietary Patterns	Waist Circumference	*ApoE* Genotype	Physical Activity	HDL	LDL
Age (years)	–														
Cholesterol	$r=-0.12$	–													
	$P=.290$														
Sex	$r=0.075$	$r=-0.078$	–												
	$P=.512$	$P=.497$													
TGs	$r=-0.184$	$r=0.322$	$r=-0.193$	–											
	$P=.102$	**$P=.004$**	$P=.089$												
BMI	$r=-0.082$	$r=0.307$	$r=-0.122$	$r=0.297$	–										
	$P=.472$	**$P=.006$**	$P=.286$	**$P=.008$**											
Smoking status	$r=0.219$	$r=-0.255$	$r=0.389$	$r=-0.288$	$r=-0.236$	–									
	$P=.053$	**$P=.023$**	**$P=0.001$**	**$P=.010$**	**$P=.036$**										
Alcohol consumption	$r=0.122$	$r=-0.054$	$r=0.236$	$r=-0.285$	$r=-0.006$	$r=0.317$	–								
	$P=.283$	$P=.636$	**$P=.037$**	$P=.011$	$P=.957$	**$P=.004$**									
SBP	$r=-0.039$	$r=-0.034$	$r=0.009$	$r=-0.13$	$r=0.084$	$r=0.034$	$r=0.075$	–							
	$P=.736$	$P=.763$	$P=.937$	$P=.252$	$P=.464$	$P=.763$	$P=.511$								
DBP	$r=0.226$	$r=0.068$	$r=0.09$	$r=0.092$	$r=0.121$	$r=0.183$	$r=0.047$	$r=0.247$	–						
	$P=.045$	$P=.550$	$P=.429$	$P=.419$	$P=.289$	$P=.107$	$P=.678$	**$P=.028$**							
Dietary patterns	$r=-0.002$	$r=-0.05$	$r=0.215$	$r=0.194$	$r=0.176$	$r=-0.135$	$r=-0.139$	$r=0.027$	$r=0.085$	–					
	$P=.984$	$P=.661$	$P=.057$	$P=.086$	$P=.121$	$P=.236$	$P=.221$	$P=.813$	$P=.455$						
Waist circumference	$r=-0.13$	$r=0.348$	$r=-0.381$	$r=0.203$	$r=0.712$	$r=-0.231$	$r=-0.075$	$r=0.25$	$r=0.02$	$r=0.001$	–				
	$P=.253$	**$P=.002$**	**$P=.001$**	$P=.072$	**$P<.001$**	**$P=.041$**	$P=.512$	**$P=.026$**	$P=.858$	$P=.990$					
ApoE genotype	$r=-0.192$	$r=0.177$	$r=0$	$r=0.076$	$r=-0.141$	$r=-0.251$	$r=-0.036$	$r=-0.076$	$r=-0.16$	$r=-0.025$	$r=-0.107$	–			
	$P=.090$	$P=.119$	$P=1.000$	$P=.507$	$P=.215$	**$P=.026$**	$P=.750$	$P=.508$	$P=.158$	$P=.828$	$P=.347$				
Physical activity	$r=-0.043$	$r=0.095$	$r=0.087$	$r=-0.12$	$r=0.094$	$r=-0.094$	$r=0.191$	$r=0.03$	$r=-0.01$	$r=0.061$	$r=0.099$	$r=-0.161$	–		
	$P=.707$	$P=.405$	$P=.446$	$P=.294$	$P=.410$	$P=.408$	$P=.091$	$P=.792$	$P=.928$	$P=.595$	$P=.384$	$P=.156$			
HDL	$r=-0.009$	$r=-0.36$	$r=0.126$	$r=-0.187$	$r=0.028$	$r=0.215$	$r=0.365$	$r=0.157$	$r=0.043$	$r=-0.002$	$r=0.044$	$r=-0.192$	$r=-0.017$	–	
	$P=.940$	**$P=.001$**	$P=.270$	$P=.098$	$P=.807$	$P=.057$	**$P=.001$**	$P=.167$	$P=.705$	$P=.988$	$P=.698$	$P=.089$	$P=.883$		
LDL	$r=-0.243$	$r=0.194$	$r=0.153$	$r=0.076$	$r=-0.043$	$r=-0.029$	$r=-0.245$	$r=0.037$	$r=-0.073$	$r=0.121$	$r=-0.113$	$r=0.083$	$r=0.116$	$r=-0.003$	–
	$P=.031$	$P=.086$	$P=.177$	$P=.506$	$P=.708$	$P=.799$	$P=.029$	$P=.747$	$P=.525$	$P=.290$	$P=.323$	$P=.465$	$P=.309$	$P=.976$	

Values are Pearson correlation coefficients (r) with P-values in parentheses. Significant correlations ($P < .05$) are shown in bold. Only the lower triangle is presented.
ApoE, apolipoprotein E; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TGs, triglycerides.

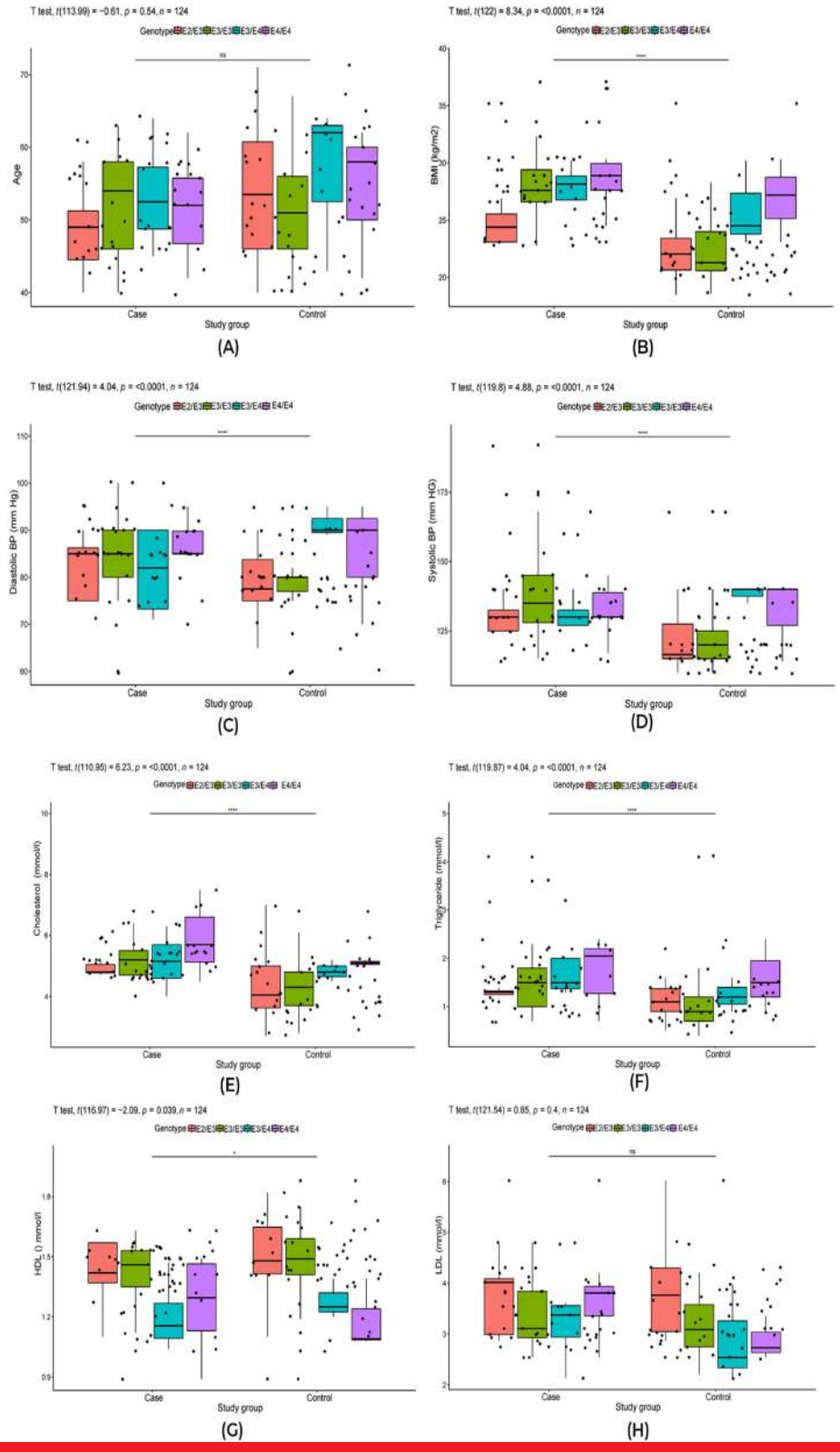


Figure 1. Distribution of clinical and biochemical parameters across study groups and *APOE* genotypes. The figure illustrates the distribution and comparison of metrics between CHD cases (63) and healthy controls (61): (A) Age (years). (B) BMI (kg/m²). (C) Diastolic blood pressure (mmHg). (D) Systolic blood pressure (mmHg). (E) Total cholesterol (mmol/L). (F) Triglycerides (mmol/L). (G) HDL cholesterol (mmol/L). (H) LDL cholesterol (mmol/L). The asterisk indicates a significant *P*-value when the case group was compared with healthy controls. All *P*-values were reformatted according to journal style requirements (*P* = .xxx or *P* < .001). BMI, body mass index; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

prevention targets in clinical practice.[37] Such pharmacological interventions often mask the underlying metabolic phenotype associated with high-risk genotypes.[27] Nevertheless, the significant association between the ε4 allele and CHD remains evident, suggesting that genetic risk factors contribute to disease susceptibility, regardless of subsequent therapeutic lipid reduction.[28,50]

The distribution of *APOE* alleles in the Mongolian population demonstrates significant variation when compared to other ethnic groups. In this study, a notably higher ε4 allele frequency was observed in CHD cases (15.9% for the ε4/ε4 genotype alone) compared with controls. This finding is consistent with that of previous research in the Mongolian population that reported an overall ε4 frequency of 15.5%, noting it as one of the highest frequencies recorded in Asia.[9]

Across Asian populations, the Mongolian ε4 allele frequency follows a prominent south to north geographic gradient. For example, southern Chinese populations (e.g., in Kunming) report relatively low ε4 frequencies (4.9%), whereas northern cohorts (e.g., in Harbin) demonstrate substantially higher prevalence (17.5%).[51] The frequency observed in this Mongolian cohort is consistent with the northern distribution pattern. Furthermore, the overall ε4 frequency in general Han Chinese populations is typically lower, approximately 7%-8.5%, compared to the levels found in the Mongolian cohort.[51,52] Japanese populations show a comparatively wide range of ε4 allele frequencies (between 11.7% and 27.8%), placing the risk profile of the Mongolian subjects within a similar range to these high-risk Japanese groups.[52,53]

Despite these observations, the current analysis did not demonstrate a statistically significant association between ε4 allele and CHD risk ($P < .945$).

While the isoform is a well-documented risk factor for atherosclerosis and neurodegeneration globally, its notable presence in the Mongolian cohort—specifically with 15.9% of the case group identified as homozygotes—provides evidence for its significant role in CHD susceptibility within this specific population.[9,54] Consequently, this interpretation has been revised to classify these ε4 findings as preliminary, emphasizing that larger multi-center studies are required to achieve the statistical power necessary to evaluate rare genetic variants in Central Asian ancestries.[55]

The findings demonstrate a robust protective association between the ε2/ε3 genotype and CHD risk (OR = 0.29), suggesting that ε2 carriers in the Mongolian population may benefit from inherently lower pro-atherogenic lipid profiles. This protective effect is biologically plausible, as the APOE2 isoform exhibits reduced binding affinity for the LDL receptor, which typically results in lower plasma LDL-C levels. These findings contrast with the ε4 allele, which, although not statistically significant in this study (OR = 1.07 for ε3/ε4), is widely recognized as a potent risk factor for atherosclerosis and late-onset Alzheimer's disease.[56,57,58]

While the ε3 isoform remains the most common "normal" variant, the differential effects of the ε2 and ε4 alleles highlight the pleiotropic nature of the *APOE* gene.[57] Although the ε2 allele is generally considered protective against CHD, it has occasionally been associated with dysbetalipoproteinemia; however, this phenotypic expression typically requires additional environmental or genetic factors.[58,59] Future studies in the Mongolian population should further explore these associations alongside neurocognitive assessments to determine whether the protective effect of ε2 extends to dementia risk within this specific ancestry.

Analysis of metabolic and cardiovascular phenotypes across *APOE* genotypes revealed significant variations, particularly among carriers of the ε4 allele. Individuals with the ε4/ε4 genotype in the CHD case group exhibited the highest metabolic risk profile, characterized by significantly elevated BMI compared with other genotypes. This pattern was consistent across the cohort, as the current results indicate that BMI was significantly higher in the CHD group than in the healthy control group ($P < .0001$), independent of specific *APOE* polymorphisms.[60]

Cardiovascular markers also demonstrated genotype-specific associations.[61,62] Specifically, the ε4 allele has been previously linked to elevated total cholesterol and LDL-C levels, as well as an increased risk of CVD and Alzheimer's disease.[63,64] However, the current analysis indicates that individuals carrying the ε2/ε3 and ε2/ε4 genotypes tend to exhibit more favorable lipid profiles, characterized by enhanced triglyceride metabolism and reduced LDL-C accumulation, suggesting a protective effect against CVD.[48] Conversely, the ε4 allele, particularly in the homozygous ε4/ε4 state, is associated with elevated very-low-density lipoprotein cholesterol and triglyceride levels, along with decreased HDL-C.[65] These findings are consistent with previous studies indicating that the ε4 allele contributes to elevated total cholesterol and LDL-C levels, whereas the ε2 allele correlates with lower triglyceride and LDL-C concentrations.[66]

Compared with European and Caucasian populations, the ε4 allele frequency observed in this study is slightly lower than the range of 14.7%-36.7% reported in various Western cohorts.[52,53] However, meta-analyses suggest that the impact of the ε4 allele on CHD risk may be more pronounced in Mongolian populations than in Caucasians, indicating that the genetic background of this population may confer increased sensitivity to the lipid-elevating effects of the allele.[3] In Turkish populations, findings have been inconsistent; while some studies report no significant association with CHD, others demonstrate that ε4 carriers exhibit significantly higher LDL-C and total cholesterol levels, mirroring the metabolic associations observed in this study.[67,68]

These findings emphasize that although the ε4 allele is a global risk factor, its prevalence and phenotypic expression in the Mongolian population appear to be distinct and may contribute significantly to the regional burden of CVD.[9]

Limitations

The modest sample size and single-center recruitment design limited statistical power and reduced the generalizability of the findings to the broader Mongolian population, including rural and nomadic communities.

This study has several limitations that require a cautious interpretation of the findings. First, the modest sample size (63 cases and 61 controls) limits the statistical power to detect associations involving less common genotypes, such as the ε2/ε4 or ε4/ε4 variants.[55,60] Second, as the study was conducted only at the Third State Central Hospital in Mongolia, its single-center, urban setting may limit the generalizability of the findings to rural or nomadic populations, which may have distinct environmental exposures and dietary patterns.[9,19] Furthermore, the case–control design prevents the determination of causal relationships; thus, longitudinal research is needed to clarify temporal associations between *APOE* genotypes and CHD in this population.[69] Finally, the current analysis was restricted to 2 canonical SNPs (rs429358 and rs7412), potentially overlooking other genetic variants or epigenetic factors that may influence CHD susceptibility in Central Asian populations.[19,70]

Future multi-regional studies are essential to validate these findings across the diverse Mongolian population. Such comprehensive investigations would facilitate a more comprehensive understanding of how genetic predisposition, environmental factors, and lifestyle choices interact to influence CVD risk. Moreover, expanding the scope of genetic markers beyond *APOE*, such as those related to lipid metabolism and inflammation, would provide a more holistic understanding of CHD susceptibility in this distinct ethnic group. Further molecular studies examining genetic polymorphisms—particularly those related to lipid processing and inflammation—are warranted to elucidate the complete genetic architecture underlying CHD risk in Mongolian populations.

CONCLUSION

Accordingly, these findings should be interpreted as preliminary and hypothesis-generating until validated in larger, multi-center Mongolian cohorts with formal power calculations and broader geographic representation. This exploratory case–control study provides the first systematic evidence linking *APOE* genotype polymorphisms to CHD risk in a Mongolian cohort, a population critically underrepresented in cardiovascular genetics research. The principal statistically supported finding is a robust protective association of the ε2/ε3 genotype against CHD, consistent with the known cardioprotective effects of the *APOE* ε2 allele, including enhanced receptor-mediated LDL clearance and favorable effects of lipoprotein metabolism. The overall *APOE* genotype distribution differed significantly between cases and controls, with the ε4/ε4 genotype more prevalent among cases; although, this difference did not reach statistical significance in logistic regression analyses, likely reflecting the limited statistical power associated with the modest sample size. A notable feature of this cohort was the paradoxically lower total cholesterol observed in CHD cases compared with controls, which is likely attributable to guideline-directed lipid-lowering therapy in patients with established disease. This finding underscores the inherent limitation of total cholesterol as a sole cardiovascular biomarker and supports the value of comprehensive lipoprotein fraction profiling, particularly in the context of *APOE* genotyping, for accurate risk stratification. Given the single-center, urban design of this study, the findings should be interpreted as exploratory and are not nationally representative of the Mongolian population.

Nevertheless, this study establishes an important evidence base for *APOE*-related cardiovascular susceptibility in Central Asian populations and identifies key priorities for future research. Multi-center, longitudinal studies involving larger and more geographically diverse Mongolian cohorts, incorporating detailed medication data and extended phenotyping characterization, are essential to validate these findings and to support the development of population-specific, genotype-informed strategies for CVD prevention.

Ethics Committee Approval: This study was approved by the Ethics Committee of Mongolian National University of Medical Sciences (Approval No.: 2025/06/1093; Date: April 22, 2025).

Informed Consent: Written informed consent was obtained from all participants before their enrollment in the study.

Peer-review: Externally peer-reviewed.

Acknowledgments: The authors are grateful to the staff of the Mongolian National University of Medical Sciences, National Center Mental Health of Mongolia, and The Third Clinical Hospital for their cooperation and assistance during the research.

Author Contributions: Concept – Ye.Ch, O.D., N.M.; Design – Ye.Ch, N.M.; Supervision – Ye.Ch.; Resources – O.D., A.P., O.D., Ts.Z.; Materials – O.D., A.P., O.D., Ts.Z., G.Z., U.G., O.N.; Data Collection and/or Processing – O.D., A.P, O.D., Ts.Z., G.Z., U.G., O.N.; Analysis and/or Interpretation – O.D., B.U., N.M., Ye.Ch.; Literature Search – O.D., A.P., O.D., Ts.Z., G.Z., U.G., O.N.; Writing – O.D., N.M., Ye.Ch; Critical Review – O.D., N.M., Ye.Ch.

Declaration of Interests: The authors declare no competing interests.

Funding: The authors declare that this study received no financial support.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Apolipoprotein E: A Genetic Bridge Between Premature Atherosclerosis and Alzheimer Disease

EDITORIAL COMMENT

Apolipoprotein E (*APOE*) represents one of the most important common genetic determinants linking coronary artery disease (CAD) and neurodegeneration. ApoE links lipid metabolism, vascular health, and brain function. The three common *APOE* alleles, ε2, ε3, and ε4, encode functionally different isoforms with important cardiovascular and neurological consequences.[1,2] Table 1 depicts the ApoE alleles and related clinical consequences.

Peripheral and brain ApoE biology should be considered separately. In the circulation, ApoE is present mainly on triglyceride-rich lipoproteins and their remnants and on a subset of high-density lipoprotein (HDL) particles. It facilitates receptor-mediated lipoprotein clearance and influences plasma lipid concentrations. Large-scale human data show a graded relationship between *APOE* genotype, low-density lipoprotein (LDL) cholesterol, and coronary risk; ε2 is generally associated with lower LDL-cholesterol and lower coronary risk, whereas ε4 is associated with higher LDL-cholesterol and a modest increase in coronary risk across the genotype spectrum.[1,2]

In this issue, Dogsom et al[3] report an exploratory hospital-based case-control study of 63 Mongolian patients with angiographically confirmed CAD and 61 controls. The study provides data from a population poorly represented in cardiovascular genetic research. The strongest finding was lower odds of CAD among individuals with the ε2/ε3 genotype (OR 0.29, 95% CI 0.12-0.71). Although ε4/ε4 was more frequent among cases, its association with CAD was not statistically significant (OR 2.68, 95% CI 0.68-10.55). Thus, the study does not establish ε4 as a CAD risk factor specifically in Mongolians, but provides hypothesis-generating data requiring confirmation.[3] The small genotype groups also limit multivariable precision and preclude important sex-specific analyses. In addition, non-HDL-cholesterol or ApoB would also have provided a more complete assessment of atherogenic lipoprotein burden.

Population-specific evaluation is particularly important for *APOE*. Allele frequencies and effect sizes vary across ancestries. In Alzheimer disease (AD), the effect associated with ε4 differs substantially across ancestry groups and is influenced by global and local genetic ancestry and gene-environment interactions.[4] This supports generating *APOE* data from Mongolian and other understudied populations.

The study also illustrates why lipid values obtained after CAD has developed require cautious interpretation. Total cholesterol and triglycerides were lower among cases, while LDL-cholesterol was higher.[3] Detailed lipid-lowering treatment data were unavailable, so these differences should not simply be attributed to therapy. More importantly, a single lipid value does not represent lifetime exposure. This is relevant in premature atherosclerosis, where cumulative atherogenic exposure and inherited susceptibility are central considerations.[5]

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Available Online Date:
September 28, 2026

Cite this article as: Kayikcioglu M. Apolipoprotein E: A genetic bridge between premature atherosclerosis and Alzheimer disease. *Anatol J Cardiol.* 2026;30(12):955-957.

DOI: 10.14744/AnatolJCardiol.2026.7025

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Table 1. Cardiovascular and Neurological Effects of Common APOE Alleles

Feature	*APOE* ε2	*APOE* ε3	*APOE* ε4
Peripheral lipid phenotype	Generally lower LDL-C; altered remnant lipoprotein metabolism	Reference phenotype	Generally higher LDL-C and total cholesterol
Coronary atherosclerosis	Generally lower coronary risk than ε3; ε2/ε2 may predispose to dysbetalipoproteinemia in susceptible individuals	Reference phenotype	Modestly higher coronary risk in large population studies
Premature CAD	Possible protective association, but evidence is limited	Reference phenotype	ε3/ε4 associated with increased premature CAD risk in a recent observational case-control study
Brain ApoE and lipid transport	ApoE-containing HDL-like particles participate in CNS cholesterol transport; isoform-specific effects differ	Reference ApoE function	Altered ApoE lipidation and cellular cholesterol handling
Alzheimer disease	Associated with lower AD risk than ε3	Reference phenotype	Strongest common genetic risk allele for late-onset AD; clear gene-dose effect
Selected brain effects	Generally associated with lower AD risk; mechanistic effects remain context dependent	Reference phenotype	Amyloid-β pathology, altered astrocyte lipid handling, microglial lipid accumulation, neuroinflammation, BBB dysfunction, and tau-related pathways
Effect of ancestry	Allele frequency and effect size vary among populations	Allele frequency varies among populations	Allele frequency varies across populations; APOE-related AD risk is strongly modified by global and local genetic ancestry, while cardiovascular associations also show population heterogeneity
Clinical interpretation	Context dependent; generally associated with lower LDL-C and AD risk, but ε2/ε2 may predispose to dysbetalipoproteinemia	Most common reference isoform	Risk allele, not a deterministic diagnosis; effect depends on ancestry and other risk factors

AD, Alzheimer disease; ApoE, apolipoprotein E protein; *APOE*, apolipoprotein E gene; BBB, blood–brain barrier; CAD, coronary artery disease; CNS, central nervous system; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol.

The relationship between *APOE* ε4 and premature CAD also deserves attention. Li et al[6] reported that ε3/ε4 was independently associated with premature CAD in a case-control study. This is consistent with broader evidence linking ε4 to higher LDL-cholesterol and coronary risk.[1,2] *APOE* genotyping is not part of routine premature CAD assessment, but unexpectedly early or severe atherosclerosis should prompt evaluation for inherited lipid disorders and other genetic contributors.[5]

Brain cholesterol metabolism is largely compartmentalized from plasma lipoprotein metabolism. Under physiological conditions, ApoE is produced predominantly by astrocytes and secreted in HDL-like lipoprotein particles that redistribute cholesterol and phospholipids among brain cells.[1,7]

The ε4 allele alters several aspects of central nervous system lipid homeostasis. Human induced pluripotent stem cell-derived astrocytes carrying ε4/ε4 show altered ApoE lipidation and reduced neurotrophic support.[8] *APOE* ε4 has also been associated with blood-brain barrier dysfunction and pericyte injury.[9] Human brain and cellular studies have identified an *APOE4*-associated microglial phenotype characterized by triglyceride-rich lipid-droplet accumulation and enhanced inflammatory and neurotoxic responses.[10] These findings connect disturbed lipid handling, inflammation, and neurodegeneration.

Clinically, *APOE* ε4 is suggested as the strongest common genetic risk allele for late-onset AD, with a clear gene-dose effect.[4] Fortea et al[11] showed that ε4 homozygotes have a highly predictable age-related pattern of AD biomarker abnormalities and proposed that ε4 homozygosity may represent a distinct genetic form of AD. This does not mean that every ε4 homozygote will inevitably develop clinical dementia.

Thus, *APOE* links cardiovascular and neurological disease through parallel, tissue-specific pathways rather than through a simple sequence in which atherosclerosis causes AD (Figure 1). For cardiologists, the practical message remains prevention. Genetic susceptibility conferred by *APOE* is lifelong, while many cardiovascular risk factors are modifiable. Early and sustained control of LDL cholesterol and other atherogenic lipoproteins, blood pressure, and diabetes, together with smoking avoidance, weight management, and regular physical activity, remains fundamental to the prevention of premature atherosclerosis. Whether these interventions specifically attenuate *APOE4*-related AD risk remains uncertain. Importantly, higher physical activity has been associated with lower AD risk across *APOE* ε4 carrier status and polygenic risk levels, suggesting that lifestyle remains relevant even with increased genetic susceptibility.[12]

The study by Dogsom et al[3] opens a broader discussion than its modest size might suggest. *APOE* is not simply another

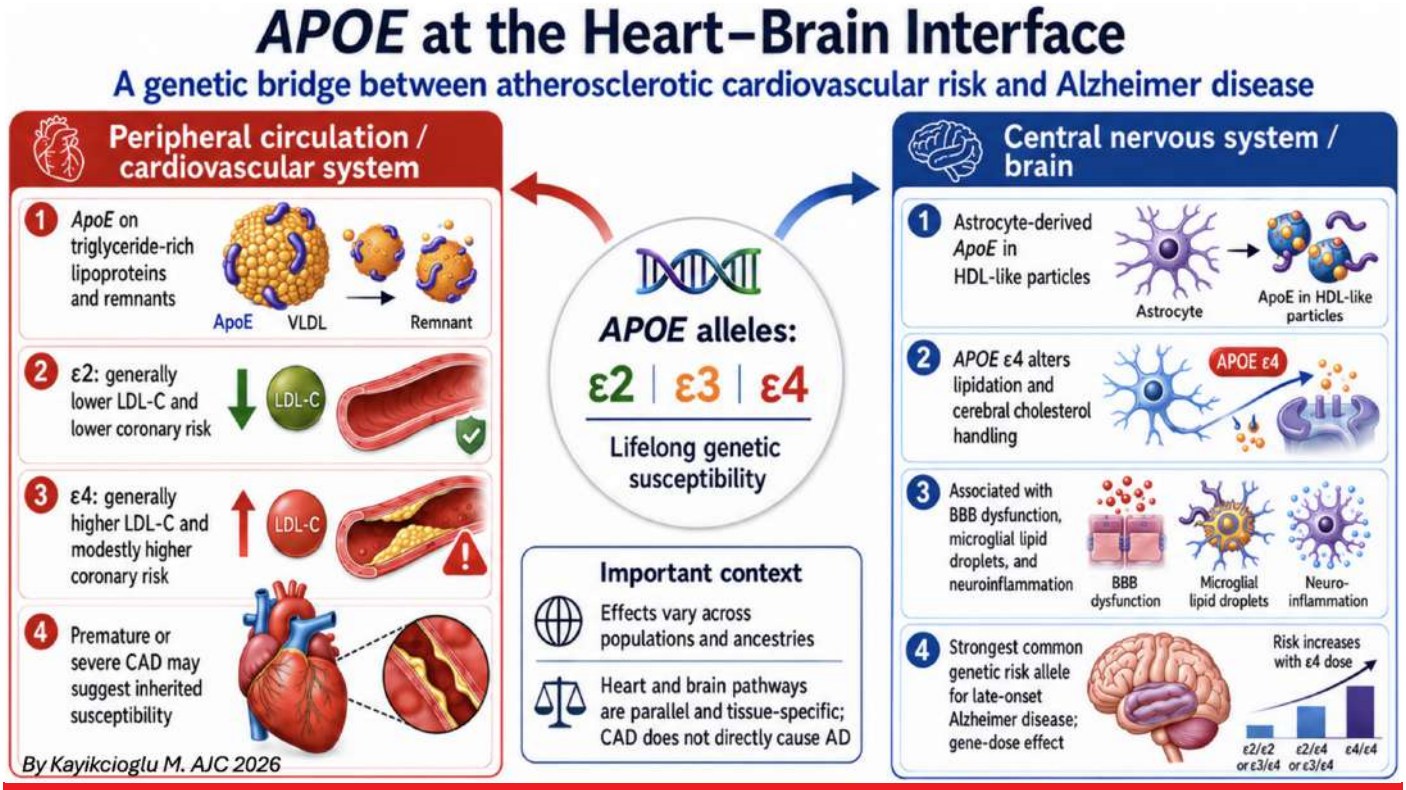


Figure 1. ***APOE*** **at the heart-brain interface. APOE influences cardiovascular and neurological risk through distinct but partly overlapping pathways. In the circulation, APOE-related differences in lipid metabolism may promote atherosclerosis and premature CAD. In the brain, APOE4 is associated with impaired lipid homeostasis, amyloid-β handling, neuroinflammation, blood-brain barrier dysfunction, and tau pathology.**

lipid-related gene; it is a biological link between lifelong lipid metabolism, premature atherosclerotic susceptibility, brain lipid homeostasis, and neurodegeneration.

Declaration of Interests: MK received research grants, honoraria for consultancy or lectures/speaker's bureau from Abbott, Abdi-Ibrahim, Amgen, Chiesi, Astra-Zeneca, Daiichi-Sankyo, Ionis pharmaceuticals, Medpace, Lib-therapeutics, Lilly, MSD, Novartis, NovoNordisk, Pfizer, Recordati, Servier, and Ultragenyx.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Seven-Year Clinical and Durability Outcomes of Balloon-Expandable Transcatheter Aortic Valve Implantation in a Turkish Single-Center Cohort

ABSTRACT

Background: Long-term durability data for early-generation balloon-expandable transcatheter aortic valve implantation (TAVI) in Turkish populations remain limited. The authors evaluated 7-year clinical outcomes and valve durability according to the Valve Academic Research Consortium (VARC-3) criteria.

Methods: In this single-center registry, 270 consecutive patients with symptomatic severe aortic stenosis treated with the early-generation balloon-expandable SAPIEN XT valve (January 2012-March 2017) were included. Clinical and echocardiographic outcomes were assessed up to 7 years. The primary endpoint was all-cause mortality. Structural valve deterioration (SVD) and bioprosthetic valve failure (BVF) were defined according to the VARC-3 criteria. Cumulative incidence was estimated using competing-risk analysis, with death from any cause treated as a competing event. Predictors of mortality were evaluated using Cox regression.

Results: At 7 years, cumulative survival was 29.6%. Cardiovascular and non-cardiovascular mortality occurred at comparable rates. In multivariable analysis, higher Katz index, reflecting better functional status, and higher body mass index were inversely associated with all-cause mortality, whereas eGFR <30 mL/min/1.73 m^2 was associated with increased mortality risk. The 5- and 7-year cumulative incidences of combined Stage 2-3 SVD were 0.74% and 3.72%, respectively; BVF rates were 1.11% and 2.23%, respectively.

Conclusion: In this Turkish single-center cohort treated during the early TAVI era, long-term outcomes reflected the advanced age and comorbidity burden of the study population. Using a competing-risk framework, the observed cumulative incidence of SVD and BVF was low at 5 and 7 years; however, these findings should be interpreted in the context of substantial competing mortality.

Keywords: Bioprosthetic valve failure, Edwards SAPIEN XT valve, long-term outcomes, structural valve deterioration, transcatheter aortic valve implantation

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Received: February 25, 2026
Accepted: June 29, 2026
Available Online Date: August 3, 2026

Cite this article as: Konuş AH, Akyüz AR, Özderya A, Yerlikaya MG, Korkmaz L. Seven-year clinical and durability outcomes of balloon-expandable transcatheter aortic valve implantation in a Turkish single-center cohort. *Anatol J Cardiol.* 2026;30(12):958-969.

DOI: 10.14744/AnatolJCardiol.2026.6352

INTRODUCTION

Transcatheter aortic valve implantation (TAVI), first performed in 2002, has now become an established treatment for severe aortic stenosis (AS) in patients with prohibitive, high, and intermediate surgical risk.[1-4]Recently, large studies comparing TAVI and surgical aortic valve replacement (SAVR) in low-risk patients have found that TAVI produces favorable clinical outcomes for short-term follow-up.[5,6] The fact that TAVI has been applied to lower-risk patients has increased the importance of long-term outcomes, including valve durability.

The Valve Academic Research Consortium (VARC) published the VARC-3 criteria in 2021. The VARC-3 criteria included some new definitions and changes. VARC-3 has been updated regarding clinical endpoints, procedural complications, and bioprosthetic valve dysfunction (BVD) and failure, and studies using these criteria are needed because limited data exist on long-term follow-up based on the updated VARC-3 criteria worldwide.[7]

In Türkiye, reimbursement policies restrict TAVI primarily to inoperable and high-surgical-risk patients, with selected intermediate-risk elderly individuals also

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eligible. Consequently, long-term outcome data in Turkish TAVI populations remain particularly relevant.

The authors aimed to investigate the long-term outcomes of patients beyond 5 years who underwent TAVI with balloon-expandable SAPIEN XT valves in the center, according to the VARC-3 criteria.

METHODS

Study Design and Procedure

This was a single-center, registry-based observational study. Between January 2012 and March 2017, 270 consecutive patients who underwent TAVI with SAPIEN XT valves (Edwards Lifesciences, Irvine, CA, USA) at the hospital due to symptomatic severe AS, which were either inoperable or had a high surgical risk, were included in the study and follow-up data were collected until April 2024. In the center, the choice of severe AS treatment method is based on the decision of the heart team. The heart team consisted of cardiologists, cardiovascular surgeons, anesthesiologists, and pulmonologists. During the study period (2012-2017), treatment decisions were based on multidisciplinary assessment, incorporating clinical status, comorbidity burden, frailty, anatomical considerations, and life expectancy, in addition to conventional surgical risk scores, including the Society of Thoracic Surgeons (STS) score and EuroSCORE II (European System for Cardiac Operative Risk Evaluation II). All procedures were performed under general anesthesia. Procedural and follow-up data of the patients were obtained from the hospital database. After discharge, clinical and echocardiographic data of the patients were recorded at 1 month, 6 months, and annually. The follow-up information of the patients who were unable to come to the institution was collected by contacting the patients, their relatives, or their physicians. Vital status was available for all patients, with follow-up extending up to 7 years after TAVI. Follow-up echocardiographic assessments and changes in functional capacity from baseline were analyzed in patients who survived the corresponding follow-up time points and had available data. The authors analyzed the 7-year clinical outcomes of these patients according to the updated Valve Academic Research Consortium (VARC-3) criteria.[7]

HIGHLIGHTS

- Long-term (>5-year) durability data from Turkish transcatheter aortic valve implantation (TAVI) cohorts are scarce.
- Seven-year single-center cohort outcomes of early-generation SAPIEN XT valves are presented.
- In a high-mortality, elderly cohort, the observed cumulative incidence of SVD and BVF was low at 5 and 7 years using VARC-3 criteria and competing-risk analysis.
- Seven-year mortality reflected advanced age and comorbidity burden.
- Provides national long-term durability data from the early TAVI era.

Measurements

Demographic and clinical characteristics included age, gender, body mass index in kg/m^2, smoking habits (recorded as current, ever, never smoked), personal medical history of hypertension, type 2 diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, chronic kidney disease and renal replacement therapy, New York Heart Association (NYHA) functional capacity score, previous thoracic surgery, previous cardiac pacemaker, prior coronary artery disease (CAD) or any other manifestations of cardiovascular disease, and family history of CAD. Society of Thoracic Surgeons (STS) score, logistic European System for Cardiac Operative Risk Evaluation (logistic EuroSCORE), and the updated EuroSCORE II, which are approved risk assessment tools for open heart surgery, were calculated.[8,9] Functional status was assessed using the Katz index, which measures independence in activities of daily living.[10]

Imaging Tools

Two-dimensional transthoracic echocardiography (TTE) and transesophageal echocardiography were used to evaluate procedural outcomes. "Low flow" was defined as indexed stroke volume (SVi) of less than 35 mL/m^2. According to the 2012 ESC valvular heart disease guidelines, high-gradient AS was defined as mean gradient ≥40 mmHg, peak velocity ≥4.0 m/s, valve area ≤1 cm^2; classical low-flow low-gradient severe AS was defined as mean gradient <40 mmHg, valve area <1.0 cm^2, and poor left ventricular systolic function (LVEF<40%).[11] The diagnosis of classical low-flow, low-gradient severe AS was confirmed by excluding pseudo-severe AS with low-dose dobutamine stress echocardiography.[11] Paradoxical low-flow, low-gradient with preserved ejection fraction (mean gradient <40 mm Hg, valve area ≤1 cm^2, LVEF ≥50%, SVi <35 mL/m^2) was considered severe AS.[11] In patients with paradoxical low-flow, low-gradient severe AS, intervention decisions were individualized by the heart team, taking into account symptomatic status and anatomical severity. In selected symptomatic patients with borderline hemodynamic parameters, a valve area ≤0.8 cm^2 (or ≤0.6 cm^2/m^2 indexed) was considered supportive of severe AS in conjunction with clinical findings. Electrocardiogram-gated multislice computed tomography (CT) was performed to assess aortic root anatomy and vascular access. Valve sizing for the balloon-expandable prosthesis was based on CT-derived annular measurements. Porcelain aorta was defined as extensive calcification of the ascending aorta or aortic arch, which can be completely or near completely circumferential.

Structural valve deterioration (SVD) and bioprosthetic valve failure (BVF) were defined according to VARC-3 recommendations. Moderate hemodynamic valve deterioration (Stage 2 SVD) was considered when the mean transvalvular gradient increased by ≥10 and <20 mmHg, resulting in a final mean gradient ≥20 mm Hg, together with a reduction in effective orifice area (EOA) of ≥0.3 cm^2 or ≥25%, and/or a decrease in Doppler velocity index (DVI) of ≥0.1 or ≥20% compared with the echocardiographic assessment performed 1-3 months after the procedure. Alternatively, new onset or worsening (≥1 grade) intraprosthetic aortic regurgitation leading to

a moderate final grade was also classified as Stage 2 SVD. Severe hemodynamic valve deterioration (Stage 3 SVD) was defined as an increase in mean gradient ≥20 mm Hg leading to a final mean gradient ≥30 mm Hg, accompanied by a decrease in EOA ≥0.6 cm^2 or ≥50%, and/or a reduction in DVI ≥0.2 or ≥40% compared with the -3-month post-procedural study. New onset or worsening (≥2 grades) intraprosthetic regurgitation resulting in severe aortic regurgitation was also considered Stage 3 SVD. Bioprosthetic valve failure was defined as any bioprosthetic valve dysfunction associated with clinical consequences, irreversible Stage 3 SVD, valve reintervention, or valve-related death. This definition includes cases of infective endocarditis with clinical consequences, even in the absence of hemodynamic SVD criteria. Structural valve deterioration and bioprosthetic valve failure events were adjudicated according to VARC-3 definitions based on available echocardiographic data. All suspected valve-related events were reviewed by experienced cardiologists, and any discrepancies were resolved by consensus.

Primary and Secondary Outcomes

The primary endpoint was all-cause mortality during the 7-year follow-up. Deaths were categorized as cardiovascular or non-cardiovascular. In accordance with VARC-3 criteria, cardiovascular death included fatalities attributable to heart failure, cardiogenic shock, bioprosthetic valve dysfunction, myocardial infarction, stroke, thromboembolism, cardiac tamponade, vascular complications, arrhythmias or conduction disturbances, and cardiovascular infections such as mediastinitis or endocarditis. Intraprocedural death, sudden death, and deaths of unknown cause were also considered cardiovascular. Deaths clearly resulting from non-cardiovascular conditions were classified as non-cardiovascular mortality. The timing of death was categorized as periprocedural, early, or late according to VARC-3 definitions.[7] Composite endpoints, including technical success, device success, and early safety, were defined in accordance with VARC-3 recommendations.[7]

Secondary endpoints of this study were periprocedural complications, changes from baseline in NYHA functional capacity score, and echocardiographic endpoints at the 7-year follow-up. Periprocedural complications include paravalvular regurgitation (PVR), major cardiac structural complication, implantation of multiple (>1) valves during the index hospitalization, valve malposition, ischemic stroke, major vascular complications, bleeding (type 2-4), acute kidney injury (stage 2-4), conduction system disturbances resulting in a new permanent pacemaker implantation (PPI). The echocardiographic endpoints include mean aortic valve gradient, LVEF. Valve durability endpoints include SVD and BVF. All endpoints were defined according to VARC-3 criteria.[7]

Statistical Analysis

Statistical analyses were performed using SPSS version 27 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate, and categorical variables as counts and percentages. Group comparisons were performed using the chi-square test for categorical variables and the Student's *t*-test or Mann–Whitney *U*-test for continuous variables, depending on data distribution.

Time-to-event outcomes, including all-cause mortality and cardiovascular mortality, were analyzed using the Kaplan–Meier method and presented as survival curves.

To identify predictors of all-cause mortality during follow-up, Cox proportional hazards regression analysis was performed. Variables for the multivariable model were selected based on pre-specified clinical relevance (including age, STS score, functional status as assessed by the Katz index, and low-flow low-gradient AS) and variables with $P < .10$ in univariate analysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported.

Collinearity among candidate variables was assessed prior to model construction. EuroSCORE II and Logistic EuroSCORE were excluded from the multivariable model due to collinearity with STS score, and STS score was retained as the primary risk stratification variable.

The proportional hazards assumption was evaluated using Schoenfeld residuals. Variables violating this assumption were retained in the model but interpreted with caution. Model discrimination was assessed using the concordance index (C-index), and overall model fit was evaluated using the likelihood ratio test.

The cumulative incidence of SVD and BVF was estimated using cumulative incidence function (CIF) analysis, with death from any cause occurring prior to the valve-related event of interest treated as a competing event. Analyses were performed using the cmprsk package in R (version 4.3.3; R Foundation for Statistical Computing, Vienna, Austria). SVD was analyzed separately for Stage 2 and Stage 3, in addition to a combined Stage 2-3 endpoint.

A two-sided P value < .05 was considered statistically significant.

RESULTS

Baseline Characteristics

The baseline characteristics of the 270 patients are summarized in Table 1. The mean age was 82.5 ± 7.1 years, and 73.3% were female. Diabetes mellitus and hypertension were present in 27.4% and 89.2% of patients, respectively, and 13.3% were current smokers. The mean STS score was 7.6% ± 2.7%. According to STS categories, 168 (62.2%) patients were high risk (STS ≥8%) and 102 (37.8%) were intermediate risk (STS 4% to <8%). The mean EuroSCORE II was 9.1% ± 3.7%, and the mean Katz index was 4.6 ± 1.

Procedural Characteristics

Procedural characteristics are shown in Table 2. The transfemoral approach was used in 99.3% of patients. Valve sizes of 23 mm, 26 mm, and 29 mm were implanted, with 26 mm being the most frequently used size. Balloon predilatation was performed in 76.7% of cases and post-dilatation in 4.4%. Three patients underwent TAVI following

Table 1. Baseline Demographic and Clinical Characteristics of the 270 Patients

Characteristics	All Patients (n = 270)
Age (years)	82.5 ± 7.1
Female, n (%)	198 (73.3)
Body mass index (kg/m^2)	30.6 ± 6.3
Body surface area (m^2)	1.8 ± 0.2
Diabetes mellitus type II, n (%)	74 (27.4)
Arterial hypertension, n (%)	241 (89.2)
Dyslipidaemia, n (%)	82 (30.3)
Family history of coronary artery disease, n (%)	12 (4.4)
Current smoking, n (%)	36 (13.3)
Percutaneous coronary intervention, n (%)	51 (18.9)
Coronary artery bypass grafting, n (%)	45 (16.7)
Myocardial infarction, n (%)	40 (14.8)
Mitral valve replacement, n (%)	3 (1.1)
Hemodialysis, n (%)	2 (0.7)
Chronic obstructive pulmonary disease, n (%)	61 (22.6)
Ischemic stroke, n (%)	21 (7.8)
STS score %	7.6 ± 2.7
STS score categories	
High (STS score ≥ 8%), n (%)	168 (62.2)
Intermediate (4% ≤ STS score < 8%), n (%)	102 (37.8)
EuroSCORE II %	9.1 ± 3.7
Logistic EuroSCORE %	24.4 ± 10.1
Left ventricular ejection fraction %	53.1 ± 10.5
Aortic valve area (cm^2)	0.7 ± 0.2
Aortic valve area index (cm^2/ m^2)	0.4 ± 0.1
Aortic mean gradient (mm Hg)	46.5 ± 13.8
Serum glucose, mg/dL	138 ± 54.1
Creatinine mg/dL	1.1 ± 0.7
Glomerular filtration rate mL/min/1.73 m^2	60.9 ± 23.3
Hemoglobin g/dL	11.7 ± 1.8
Atrial fibrillation, n (%)	52 (19.3)
Pacemaker, n (%)	8 (3)
Left bundle branch block, n (%)	30 (11.1)
Right bundle branch block, n (%)	23 (8.5)
Porcelain aorta, n (%)	2 (0.7)
Dextrocardia, n (%)	1 (0.4)
Classification of aortic stenosis n (%)	
High-gradient	235 (87)
Low-flow, low-gradient with reduced ejection fraction	24 (8.9)
Paradoxical low-flow, low-gradient with preserved ejection fraction	11 (4.1)
Stages of heart failure, n (%)	
NYHA I	0 (0)
NYHA II	108 (40)
NYHA III	136 (50.4)
NYHA IV	26 (9.6)
Katz index	4.6 ± 1

Data are presented as mean ± SD, median (interquartile range (IQR)), or n (%), as appropriate.
NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

Table 2. Procedural Characteristics and Periprocedural Complications at 30-Day Follow-Up

Procedural Characteristics	n (%)
Access site, n (%)	
Transapical	2 (0.7)
Transfemoral	268 (99.3)
Valve size (mm), n (%)	
23	91 (33.7)
26	134 (49.6)
29	45 (16.7)
Pre-dilatation, n (%)	207 (76.7)
Post-dilatation, n (%)	12 (4.4)
Simultaneous TAVI and EVAR	3 (1.1)
Periprocedural (30-day) complications	
Major cardiac structural complication[a], n (%)	3 (1.1)
Implantation of multiple valves, n (%)	1 (0.4)
Valve migration/embolization, n (%)	4 (1.5)
Ischemic stroke, n (%)	5 (1.9)
Acute kidney injury (stage 2-4), n (%)	15 (5.6)
Major vascular complication, n (%)	17 (6.3)
New permanent pacemaker[b], n (%)	26 (9.9)
≥ Moderate paravalvular regurgitation, n (%)	9 (3.3)
Bleeding (type 2-4), n (%)	37 (13.7)

EVAR, endovascular aneurysm repair; TAVI, transcatheter aortic valve implantation.
[a]Annular rupture, cardiac tamponade, coronary obstruction (left main coronary artery).
[b]Eight patients with pacemakers at baseline were not included.

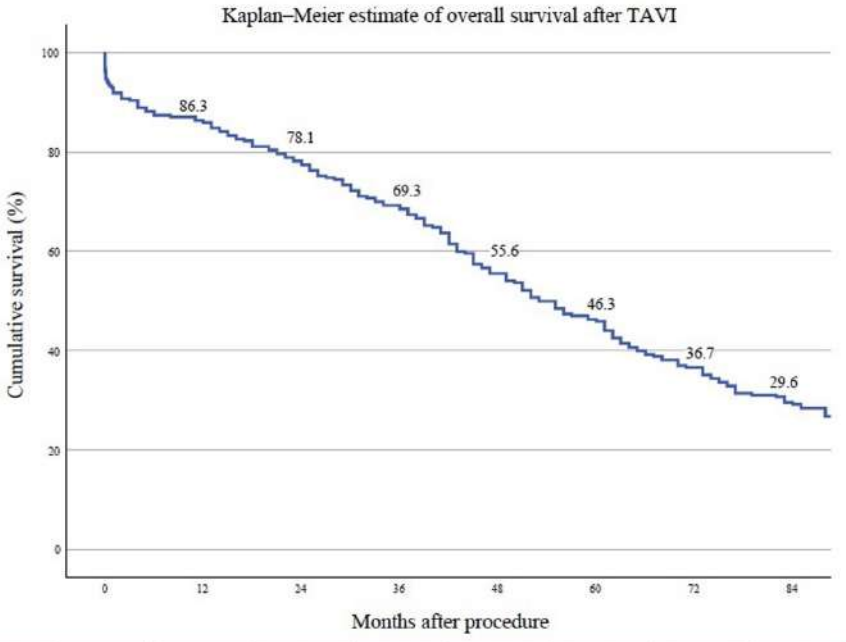
endovascular abdominal aortic aneurysm repair during the same procedure.

Primary Endpoints

The median follow-up duration was 54 months (interquartile range: 27-85), with a maximum follow-up of 147 months. Cumulative survival rates at 1, 2, 3, 4, 5, 6, and 7 years were 86.3%, 78.1%, 69.3%, 55.6%, 46.3%, 36.7%, and 29.6%, respectively (Figure 1). Freedom from cardiovascular death at 7 years was 64.8% (Figure 2).

Table 3 presents mortality data at 30-day, 1-year, 3-year, 5-year, and 7-year follow-ups. All-cause and cardiovascular mortality rates were 13.7% and 9.6% at 1 year, 30.7% and 18.9% at 3 years, 53.7% and 27.8% at 5 years, and 70.4% and 35.2% at 7 years, respectively. The distribution of causes of death is presented in Figure 3. Among cardiovascular causes, heart failure was the most frequent (19.5%), followed by acute myocardial infarction (6.8%) and stroke (5.8%). Among non-cardiovascular causes, pneumonia was the most frequent cause (13.2%).

Among the study population, 35 patients (12.9%) had low-flow, low-gradient (LFLG) AS, of whom 24 had classical (reduced LVEF) and 11 had paradoxical (preserved LVEF) LFLG AS. At 7-year follow-up, all-cause mortality was 80.0% in LFLG patients compared with 68.9% in non-LFLG patients ($P = .223$). This finding should be interpreted as exploratory given the limited sample size. Given the limited



Time (months)	0	12	24	36	48	60	72	84
No. at risk	270	233	211	187	150	125	99	80
No. of events	0	37	59	83	120	145	171	190

Figure 1. Kaplan–Meier estimate of overall survival after transcatheter aortic valve implantation. Overall survival is presented up to 7 years of follow-up. Numbers at risk and cumulative events at yearly intervals are shown in the graph.

number of patients in each subgroup, formal comparative analyses between classical and paradoxical LFLG AS were not performed.

Periprocedural mortality occurred in 19 patients (7.0%), predominantly from cardiovascular causes (78.9%). Early mortality occurred in 18 patients (6.7%), with 61.1% attributable

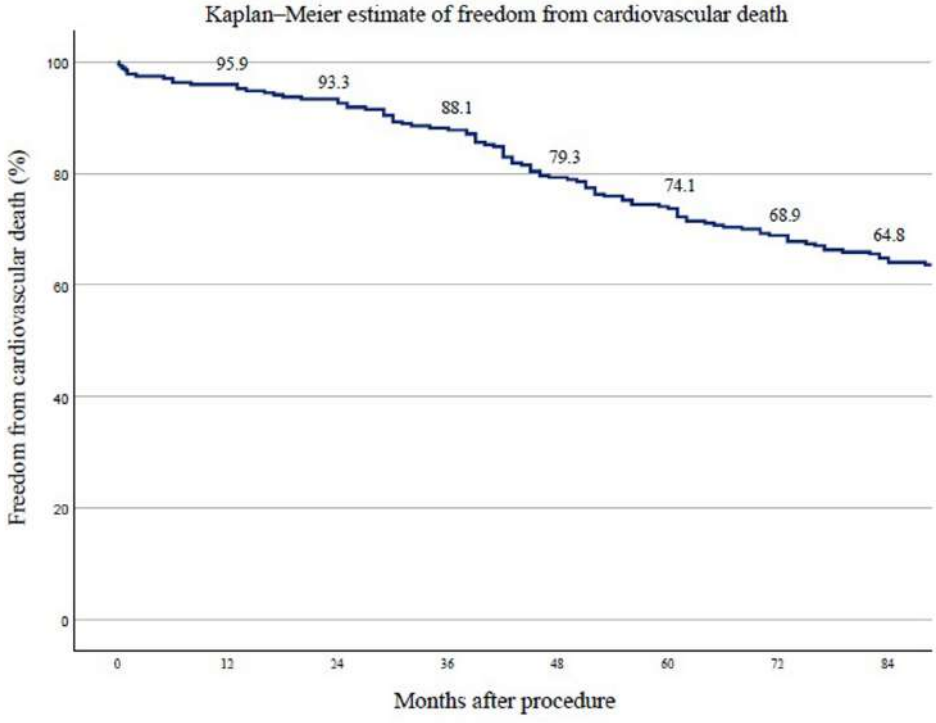


Figure 2. Kaplan–Meier estimate of freedom from cardiovascular death after transcatheter aortic valve implantation. Cardiovascular death was defined according to the Valve Academic Research Consortium-3 (VARC-3) criteria.

Table 3. Primary End Point(s) at 30-day, 1-year, 3-year, 5-year, and 7-year Follow-Up, Timing of Mortality and Composite Endpoints of the 270 Patients

Variables	30 days	1 year	3 years	5 years	7 years
All-cause mortality, yes (%)	19 (7)	37 (13.7)	83 (30.7)	145 (53.7)	190 (70.4)
Cardiovascular mortality, yes (%)	15 (5.6)	26 (9.6)	51 (18.9)	75 (27.8)	95 (35.2)
Non-cardiovascular mortality, yes (%)	4 (1.5)	11 (4.1)	32 (11.9)	70 (25.9)	95 (35.2)
Timing of mortality					
Periprocedural mortality, n (%)	19 (7)				
Early mortality, n (%)	18 (6.7)				
Late mortality, n (%)	153 (56.7)				
Composite endpoints (30-day)					
Technical success, n (%)	260 (96.3)				
Device success, n (%)	245 (90.7)				
Early safety, n (%)	195 (72.2)				

to cardiovascular causes. Late mortality occurred in 153 patients (56.7%), of whom 54.9% died from non-cardiovascular causes.

Univariate and multivariable Cox proportional hazards analyses were performed to identify factors associated with all-cause mortality during follow-up; results are presented in Supplementary Table 1. In multivariable analysis, Katz index (HR 0.698, 95% CI 0.594-0.821, $P < .001$) and higher body mass index (HR 0.959, 95% CI 0.933-0.986, $P = .003$) were inversely associated with all-cause mortality. An estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 was also associated with increased mortality risk (HR 1.737, 95% CI 1.1272.678, $P = .012$); however, this finding should be interpreted cautiously because the proportional hazards assumption was not fully satisfied for this variable. The model demonstrated moderate discriminative ability (C-index = 0.664) and was statistically significant overall (global $P < .001$).

Secondary Endpoints

Periprocedural complications are shown in Table 2. A new permanent pacemaker was implanted in 26 patients (9.9%) during the periprocedural period. The incidence of ≥ moderate PVR at 30 days was 3.3%. Ischemic stroke occurred in 5 patients (1.9%) within 30 days.

Left ventricular systolic function improved early after TAVI and partially declined over long-term follow-up (Supplementary Figure 1). New York Heart Association functional class improved significantly at 30 days after TAVI ($P <$ .001), with a reduction in the proportion of patients in NYHA

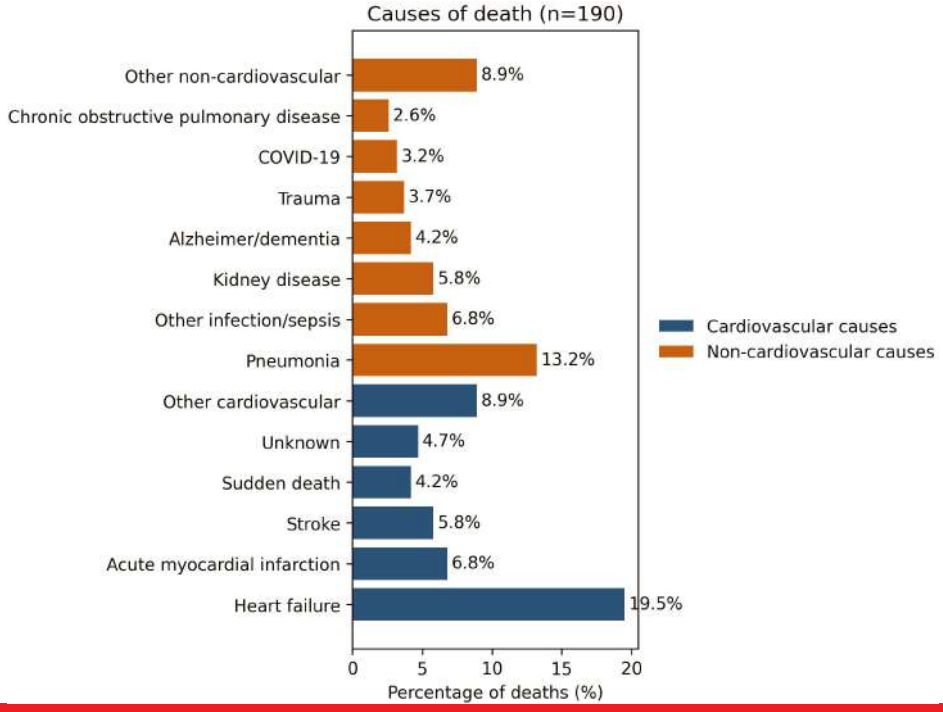


Figure 3. Causes of death during 7-year follow-up after transcatheter aortic valve implantation. Causes of death are shown as percentages of all deaths (n = 190) and grouped as cardiovascular and non-cardiovascular categories.

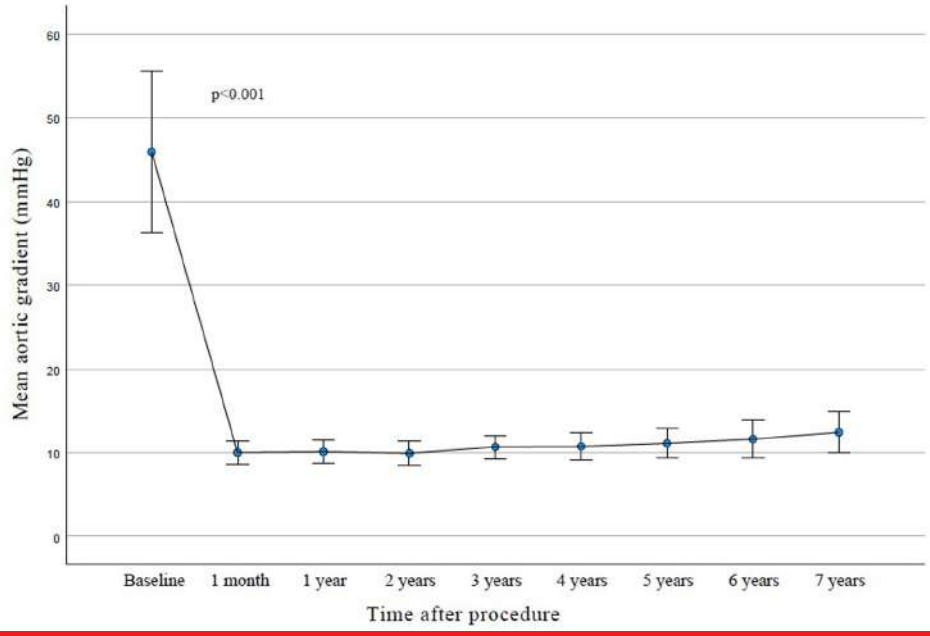


Figure 4. Change in mean aortic gradient over time after transcatheter aortic valve implantation. Values are presented as mean ± 95% confidence interval. The reduction from baseline to 1 month was statistically significant ($P < .001$).

class III-IV from 60.0% at baseline to 11.9% at 30 days. This early improvement remained stable over 7-year follow-up, with no significant change between 30 days and 7 years ($P = .641$) (Supplementary Figure 2). Pre-procedural mean aortic valve gradient decreased significantly at 30 days (46.3 vs. 10.0 mm Hg, $P < .001$). The mean gradient at 7-year follow-up remained similar to the 30-day value (12.4 vs. 10.0 mm Hg, $P = .062$), with no statistically significant change over time (Figure 4).

Echocardiographic follow-up at 7 years was available for 61 of 80 surviving patients (76.3%). During follow-up, Stage 2 SVD was observed in 6 patients and Stage 3 SVD in 4 patients (Table 4). Baseline characteristics were largely comparable between patients with and without late echocardiographic follow-up (Supplementary Table 2).

Cumulative incidence analysis, accounting for death from any cause as a competing event, demonstrated low observed cumulative incidence of SVD over long-term follow-up. The cumulative incidence of combined Stage 2-3 SVD was 0.74% at 5 years and 3.72% at 7 years (Figure 5). When analyzed separately, the 5- and 7-year cumulative incidences were 0% and 2.24% for Stage 2 SVD, and 0.74% and 1.49% for Stage 3 SVD, respectively (Figure 5). In a subset of patients, Stage 3 SVD events were observed before documented Stage 2 changes. This pattern likely reflects the small number of events and the heterogeneous mechanisms of valve deterioration, including cases without clearly documented intermediate Stage 2 progression.

Bioprosthetic valve failure occurred in 6 patients (Table 4), with cumulative incidence estimates of 1.11% at 5 years and 2.23% at 7 years. Confidence intervals widened at later time points, reflecting the diminishing number of patients remaining at risk because of high competing mortality (Figure 5).

DISCUSSION

The present study evaluated the 7-year clinical outcomes and performance of the balloon-expandable SAPIEN XT valve in patients with symptomatic severe AS in routine clinical practice using VARC-3 criteria. Long-term (>5-year) outcomes of early-generation balloon-expandable TAVI valves adjudicated according to VARC-3 definitions have been infrequently reported, particularly from Türkiye. In this context, the findings provide long-term clinical and durability data from a Turkish cohort treated during the early TAVI era. The SAPIEN XT valve demonstrated acceptable early procedural outcomes with respect to composite endpoints and periprocedural complications. In addition, an early improvement in LVEF was observed after TAVI, which partially declined over follow-up but remained higher than baseline at 7 years. Mean aortic valve gradient decreased significantly after TAVI and remained generally stable over time, while NYHA functional class improved and was maintained without significant deterioration during follow-up. The 7-year all-cause mortality reflected the advanced age, comorbidity burden, and high-risk clinical profile of the study population and was within the range reported in early-generation TAVI registries. Cardiovascular and non-cardiovascular deaths occurred at similar frequencies during follow-up. Heart failure, acute myocardial infarction, and stroke were the most common cardiovascular causes. The observed cumulative incidence of SVD and BVF was low at 7 years, as assessed using CIF analysis accounting for the competing risk of death, and was broadly consistent with previous reports of early-generation balloon-expandable valves. To the best of authors' knowledge, this study represents one of the few real-world, long-term follow-up analyses of early-generation balloon-expandable TAVI in Türkiye adjudicated according to VARC-3 criteria.

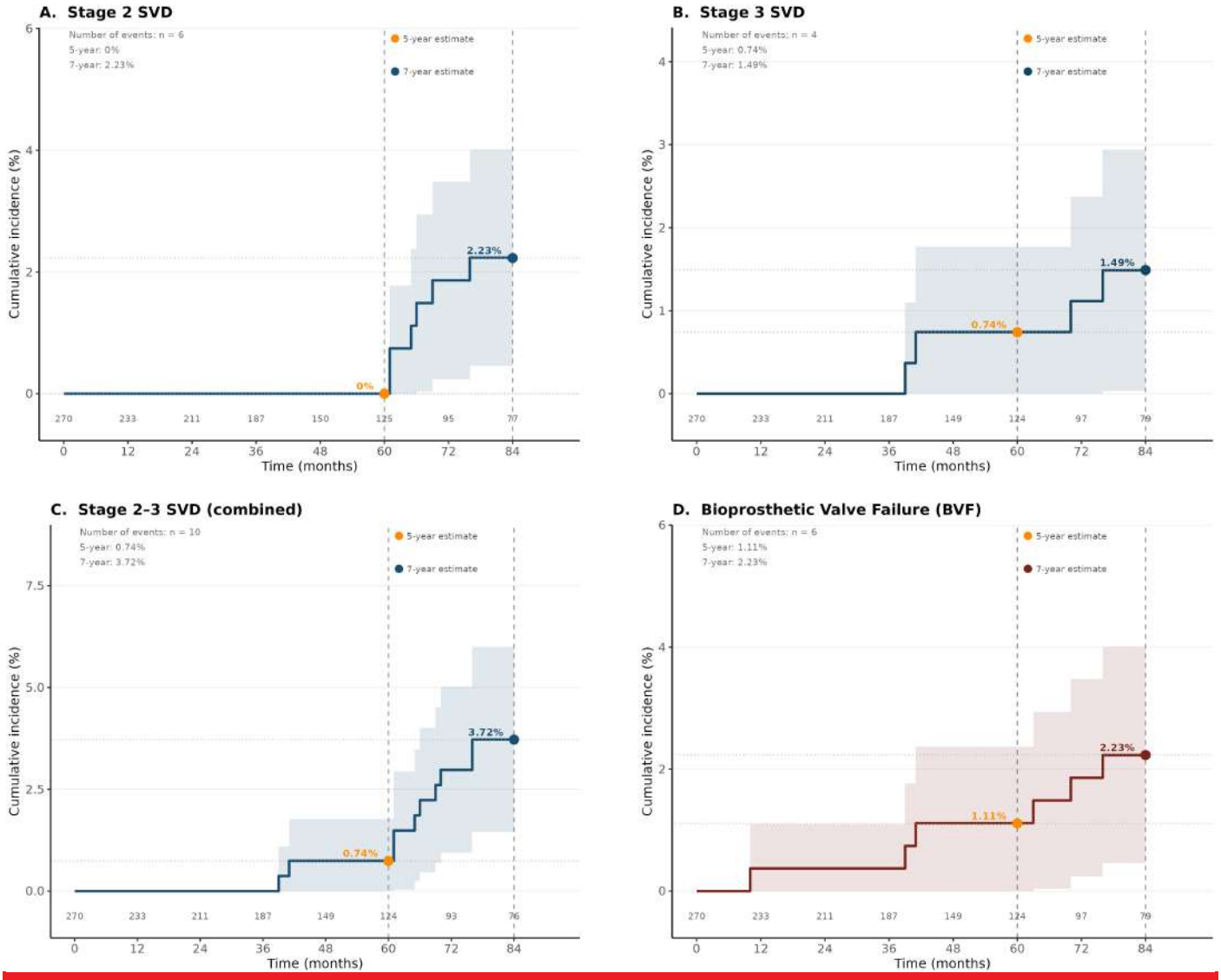


Figure 5. Cumulative incidence of structural valve deterioration (SVD) and bioprosthetic valve failure (BVF) after transcatheter aortic valve implantation using competing-risk analysis. Cumulative incidence functions (CIF) for (A) Stage 2 SVD, (B) Stage 3 SVD, (C) combined Stage 2-3 SVD, and (D) BVF over 7-year follow-up. Death from any cause occurring prior to the valve-related event of interest was treated as a competing event. Shaded areas represent 95% confidence intervals. Orange and blue markers denote the 5- and 7-year cumulative incidence estimates, respectively. Numbers at risk are displayed along the x-axis.

In this study, cumulative survival rates were 46.3% at 5 years and 29.6% at 7 years. Given the advanced age, high comorbidity burden, and surgical inoperability or high-risk profile of the study population, long-term survival was expected to be limited. Survival rates in the present cohort were broadly consistent with those reported by Şentürk et al[12] in a Turkish single-center TAVI registry using early-generation devices. In multicenter registries, Durand et al[13] reported a 7-year survival rate of 18.6%, while Deutsch et al[14] reported 5- and 7-year survival rates of 40.2% and 23.2%, respectively. Differences in survival across studies should be interpreted with caution, given variations in patient characteristics, risk profiles, and study design. Larger multicenter registries often include more heterogeneous populations and differing endpoint definitions. In contrast, the present study represents a relatively homogeneous early-generation balloon-expandable valve cohort with outcomes adjudicated according to VARC-3 criteria.

Although long-term comparative data between SAVR and TAVI from Türkiye remain limited, available Turkish surgical series in predominantly elderly and high-risk patients—including elective aortic valve replacement cohorts—report a substantial long-term mortality burden.[15] In parallel, large randomized and comparative analyses, particularly in high-risk patient populations, have demonstrated broadly similar survival outcomes between TAVI and SAVR.[16,17] These findings appear consistent with the outcomes observed in the TAVI cohort. However, given the differences in patient selection, procedural era, and study design, such comparisons should be interpreted cautiously.

Table 4. Details of Patients with Structural Valve Deterioration and Bioprosthetic Valve Failure at 7-Year Follow-Up

Patients	Age, years	Gender	Valve size, mm	SVD	BVF	Stages of SVD	Timing of SVD, years	Treatment	Death
#1	84	Male	26	Yes	Yes	Stage 3	3.4	Medication	Yes
#2	75	Female	26	Yes	No	Stage 2	5.5	Medication	Yes
#3	84	Female	23	Yes	Yes	Stage 3	5.8	Medication	Yes
#4	62	Female	23	Yes	No	Stage 2	6.3	Medication	No
#5	77	Female	23	Yes	Yes	Stage 3	3.3	ViV TAVI	Yes
#6	85	Male	29	Yes	No	Stage 2	5.4	Medication	Yes
#7	85	Male	26	Yes	Yes	Stage 2*	5.1	Medication	Yes
#8	92	Female	23	Yes	No	Stage 2	5.1	Medication	No
#9	85	Female	26	Yes	Yes	Stage 3	6.3	ViV TAVI	No
#10	78	Male	29	Yes	No	Stage 2	5.8	Medication	No
#11	78	Female	26	No	Yes	—[&]	—	Medication	Yes

BVF, bioprosthetic valve failure; SVD, structural valve deterioration; TAVI, transcatheter aortic valve implantation; ViV, valve-in-valve.
*Stage 2 SVD with valve-related death recorded as BVF.
[&]BVF due to infective endocarditis without hemodynamic SVD criteria (VARC-3: valve dysfunction with clinical consequences).

In the present study, periprocedural and early mortality were mostly due to cardiovascular causes, whereas late mortality was predominantly due to non-cardiovascular causes. The leading cause of cardiovascular death during the 7-year follow-up period was heart failure (19.5%). The shared risk profile between degenerative AS and atherosclerotic cardiovascular disease may partly explain why acute myocardial infarction (6.8%) and stroke (5.8%) were the second and third most common causes of death, respectively. In addition, the relatively high prevalence of atrial fibrillation (19.3%) may have contributed to stroke-related mortality. Among the 52 patients with atrial fibrillation, 50 (96.2%) patients were receiving oral anticoagulation therapy at baseline, including vitamin K antagonists (n=11) and direct oral anticoagulants (n=39). The rate of freedom from cardiovascular death at 5 and 7 years was 74.1% and 64.8%, respectively. In the PARTNER 1 study, 5-year freedom from cardiovascular death was 42.5% among inoperable patients and 46.9% among high-risk patients.[18] Despite differences in study design and patient characteristics, long-term cardiovascular mortality in the cohort was numerically comparable to that reported in early TAVI trials.

Beyond descriptive mortality patterns, the authors further explored factors associated with long-term outcomes using Cox proportional hazards analysis. In the present study, a higher Katz index, reflecting better functional status, was associated with lower mortality during follow-up. This finding is consistent with prior reports highlighting the prognostic importance of functional status in patients undergoing TAVI.[19,20] The Katz index may capture aspects of vulnerability that are not fully reflected by conventional risk scores such as STS score. However, given the observational design and limited sample size, these findings should be interpreted as associative rather than causal. Higher body mass index was inversely associated with mortality in the present cohort. This observation is consistent with the so-called "obesity paradox" described in elderly and high-risk cardiovascular populations. However, the underlying mechanisms remain uncertain and may reflect residual confounding, selection bias, or differences in nutritional and functional status. Therefore, this finding should be interpreted with caution rather than as evidence of a protective effect of increased body mass. Impaired renal function, as reflected by eGFR <30 mL/min/1.73 m^2, was also associated with increased mortality. However, this association should be interpreted cautiously, as the proportional hazards assumption was not fully satisfied for this variable, suggesting that its impact on mortality may vary over time. This limitation precludes definitive conclusions regarding the temporal stability of this relationship. Although STS score was associated with mortality in univariate analysis, it did not remain significant in the multivariable model. This may reflect the overlap between STS components and other variables included in the model, particularly functional status, as well as the modest number of events in the cohort. Overall, these findings underscore the multifactorial nature of long-term outcomes after TAVI, in which clinical vulnerability, comorbidity burden, and functional status appear to play a central role.

The study demonstrated technical success in 96.3% and device success in 90.7% of patients, with early safety achieved in 72.2% according to VARC-3 composite endpoints. Stroke, major vascular complications, cardiac structural complications, new permanent pacemaker implantation (PPI), VARC type 2-4 bleeding, ≥ moderate paravalvular regurgitation (PVR), and acute kidney injury grade 3 or 4 were systematically assessed. The rate of new PPI was 9.9% at 30 days. Previous studies have reported PPI rates ranging from 4% to 13% for the SAPIEN XT valve. One study reported a 12.6% PPI rate,[21] whereas another single-center Turkish study reported a rate of 6.3%.[22] The incidence of ≥ moderate PVR was 3.3%, and periprocedural stroke occurred in 1.9% of patients. These complication rates fall within the range reported in prior real-world studies of early-generation balloon-expandable TAVI.[23-28]

Structural bioprosthetic valve dysfunction (BVD), particularly structural valve deterioration (SVD), refers to permanent intrinsic changes in the prosthetic valve leading to

stenosis and/or regurgitation. Structural valve deterioration represents the principal mechanism limiting long-term durability of transcatheter bioprostheses. Historically, heterogeneity in definitions and staging of BVD has complicated interpretation of durability data. The VARC-3 criteria, introduced in 2021, provide a more standardized framework for assessing SVD and BVF. Earlier definitions, including the 2017 EAPCI/EACTS criteria, may have overestimated SVD by incorporating certain cases of prosthesis–patient mismatch or non-structural dysfunction.[29] Nevertheless, various forms of BVD—including SVD, non-structural dysfunction, thrombosis, and endocarditis—may ultimately lead to BVF and impact valve durability.

Long-term durability data for early-generation balloon-expandable valves beyond 5 years remain limited, particularly in real-world cohorts. In the study, mean transvalvular gradients remained stable between 30-day and 7-year follow-up, consistent with previously published reports.[30,31] The gradual upward trend observed in later years—particularly between years 6 and 7—warrants continued echocardiographic surveillance, as it may reflect early structural changes or the accumulation of subclinical valve deterioration in a subset of patients.

In the present study, the cumulative incidence of SVD and BVF remained low over 7 years of follow-up when analyzed using a competing-risk framework. These findings should be interpreted in the context of a high-risk, elderly population with substantial competing mortality, in whom the number of patients remaining at risk declined markedly over time. Accordingly, the observed low incidence does not necessarily reflect intrinsic valve durability but rather the combined effect of limited event occurrence and competing risk of death. In this context, the possibility that some patients died before developing SVD or BVF—thereby contributing to an underestimation of valve-related event incidence—cannot be excluded.

Stage-specific analyses demonstrated a low frequency of both Stage 2 and Stage 3 SVD, although in a subset of patients, Stage 3 events occurred without clearly documented antecedent Stage 2 changes. This observation likely reflects the heterogeneous nature of valve deterioration and the limited number of events, as well as the constraints of intermittent echocardiographic follow-up.

Cumulative incidence function analysis provides a more appropriate estimation of valve-related event rates in this setting compared with conventional Kaplan–Meier methods, which may overestimate incidence in the presence of competing risks. Overall, these findings suggest that, within the limitations of this cohort, clinically relevant valve-related events were infrequent during long-term follow-up; however, definitive conclusions regarding valve durability should be made with caution. These findings are broadly consistent with previously reported long-term outcomes of early-generation balloon-expandable transcatheter heart valves.[14,30,32] Consistent with a previous Turkish single-center study reporting low rates of SVD and BVF at long-term follow-up using early-generation devices,[12] the findings extend these observations to 7 years, using VARC-3 endpoint definitions and competing-risk analysis.

During follow-up, SVD was identified in 10 patients (6 with Stage 2 and 4 with Stage 3 hemodynamic deterioration). Among these, BVF developed in 6 patients: 4 due to irreversible Stage 3 SVD, 1 due to Stage 2 SVD accompanied by valve-related death, and 1 due to infective endocarditis without significant hemodynamic deterioration. Two patients underwent successful valve-in-valve (ViV) TAVI with post-procedural mean gradients <10 mmHg. These findings highlight that, although structural valve-related events may occur over time, reintervention with ViV TAVI was associated with favorable post-procedural hemodynamic profiles and may represent a viable management strategy for selected patients with BVF.

The present findings align with the overall pattern reported in major pivotal TAVI trials, including PARTNER 1, CoreValve/SURTAVI, and NOTION, in which valve-related events were relatively infrequent during long-term follow-up.[4,18,33] However, these observations should be interpreted with caution, given differences in patient risk profiles, valve generations, and analytical approaches, including the use of competing-risk methodology in the present study.

This study has several limitations. First, its single-center, observational design and the relatively small sample size limit generalizability and preclude causal inference. Second, the number of valve-related events was low, which restricts statistical power and necessitates cautious interpretation of stage-specific SVD analyses. Third, echocardiographic follow-up was incomplete at later time points, and SVD assessment relied on available imaging at discrete intervals; therefore, intermediate changes may have been missed and the timing of SVD onset may be imprecise. A formal comparison between patients with and without late echocardiographic follow-up did not reveal statistically significant differences; however, residual selection bias cannot be fully excluded given the limited number of patients without follow-up imaging. Fourth, although Cox proportional hazards modeling was used to explore factors associated with mortality, the proportional hazards assumption was not fully satisfied for some variables, indicating potential time-varying effects that could not be fully captured in this analysis. Finally, the high competing risk of death in this elderly, high-risk cohort reduces the number of patients remaining at risk over time and may influence the observed incidence of valve-related events, despite the use of competing-risk methodology. Furthermore, this cohort reflects early TAVI practice (2012-2017), during which procedures were performed under general anesthesia and predominantly via transfemoral access. The SAPIEN XT valve is no longer commercially available, and these procedural characteristics, together with the use of this early-generation platform, may limit the generalizability of the findings to contemporary TAVI practice, which has evolved substantially in terms of valve technology, procedural techniques, and patient selection.

Despite these limitations, the present study provides comprehensive long-term vital status follow-up and

VARC-3–based assessment of durability endpoints by experienced cardiologists in a homogeneous, early-generation, balloon-expandable valve cohort. The application of competing-risk methodology and uniform endpoint definitions strengthens the validity of durability assessment in this elderly population with substantial competing mortality risk.

CONCLUSIONS

In this TAVI cohort treated with early-generation balloon-expandable valves, early procedural outcomes were acceptable. Seven-year all-cause mortality largely reflected the advanced age, comorbidity burden, and high-risk clinical profile of the study population. Using a competing-risk framework, the observed cumulative incidence of SVD and BVF was low at 5 and 7 years; however, these findings should be interpreted in the context of substantial competing mortality. These findings contribute real-world 5- and 7-year outcome data from a Turkish TAVI cohort and may help contextualize outcomes observed with contemporary valve platforms.

Ethics Committee Approval: The study protocol was approved by the Scientific Research Ethics Committee of the University of Health Sciences, Trabzon Faculty of Medicine (approval date: 04 February 2025; approval number: 2025/160). The study was conducted in accordance with the Declaration of Helsinki.

Artificial Intelligence Usage Statement: Artificial intelligence was not used in the preparation of the article.

Informed Consent: Informed consent was not required due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Acknowledgments: The authors would like to thank all the patients participating in this study. Also, they would like to extend a special thanks to Dr. Mustafa Konuş.

Author Contributions: Concept – A.H.K., A.R.A.; Design – A.H.K., A.R.A., A.Ö.; Supervision – A.H.K., A.R.A., L.K.; Resource: A.H.K., M.G.Y.; Materials – A.H.K.; Data collection – A.H.K., A.Ö., M.G.Y.; Interpretation – A.H.K.; Literature review – A.H.K., A.R.A., A.Ö.; Writer – A.H.K., A.R.A.; Critical review – A.R.A., L.K., A.Ö.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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Supplementary Table 1. Univariate and Multivariable Cox Proportional Hazards Analyses for Predictors of 7-Year All-Cause Mortality

Variables	HR	95% CI	*P*
Part A. Univariate Cox Proportional Hazards Analysis			
Age, years	**1.027**	**1.001–1.053**	**0.045**
Female sex	0.885	0.623–1.258	0.497
Body mass index, kg/m^2	**0.968**	**0.942–0.994**	**0.017**
Diabetes mellitus	1.386	0.987–1.948	0.060
Arterial hypertension	0.891	0.572–1.388	0.608
Family history of coronary artery disease	0.773	0.362–1.650	0.506
Current smoking	0.872	0.539–1.409	0.575
Prior CABG	0.799	0.476–1.341	0.396
Prior ischemic stroke	1.246	0.740–2.097	0.408
Chronic obstructive pulmonary disease	0.984	0.699–1.385	0.927
Coronary artery disease	0.830	0.599–1.149	0.261
Atrial fibrillation	1.348	0.857–2.119	0.197
Preexisting left bundle branch block	1.272	0.624–2.594	0.508
Preexisting right bundle branch block	1.238	0.631–2.429	0.535
STS score, %	**1.095**	**1.034–1.158**	**0.002**
EuroSCORE II, %†	**1.047**	**1.003–1.093**	**0.036**
Logistic EuroSCORE, %†	**1.017**	**1.001–1.034**	**0.038**
Left ventricular ejection fraction, %	0.988	0.974–1.002	0.089
eGFR <30 mL/min/1.73 m^2	1.512	0.997–2.292	0.052
Katz index	**0.687**	**0.591–0.799**	**<0.001**
≥ Moderate paravalvular regurgitation	1.482	0.693–3.168	0.310
Permanent pacemaker implantation	0.910	0.515–1.606	0.744
Low-flow low-gradient aortic stenosis	1.359	0.885–2.087	0.092
Part B. Multivariable Cox Proportional Hazards Analysis			
Age, years	1.014	0.988–1.041	0.293
STS score, %	1.037	0.974–1.103	0.254
Katz index	**0.698**	**0.594–0.821**	**<0.001**
Low-flow low-gradient aortic stenosis	0.985	0.605–1.603	0.950
Body mass index, kg/m^2	**0.959**	**0.933–0.986**	**0.003**
Diabetes mellitus	1.190	0.829–1.710	0.346
Left ventricular ejection fraction, %	0.988	0.972–1.004	0.154
eGFR <30 mL/min/1.73 m^2‡	**1.737**	**1.127–2.678**	**0.012**

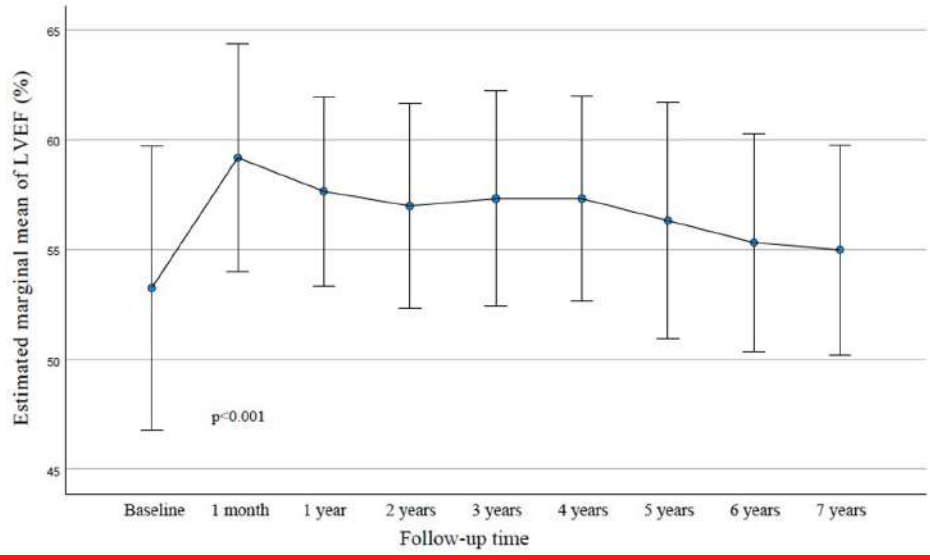
† EuroSCORE II and Logistic EuroSCORE are presented in the univariate analysis for completeness but were excluded from the multivariable model due to established collinearity with STS score; all three instruments measure operative risk from overlapping clinical variables. STS score was retained as the primary risk stratification tool. Bold red values: $p < 0.05$.

Variables entered into the multivariable model: pre-specified clinically relevant variables (age, STS score, Katz index, low-flow low-gradient AS) plus all variables with $p < 0.10$ in univariate analysis (BMI, diabetes mellitus, LVEF, eGFR <30 mL/min/1.73 m^2). EuroSCORE II and Logistic EuroSCORE were excluded due to collinearity with STS score. The model demonstrated moderate discrimination (C-index = 0.664) and was statistically significant overall ($p < 0.001$).

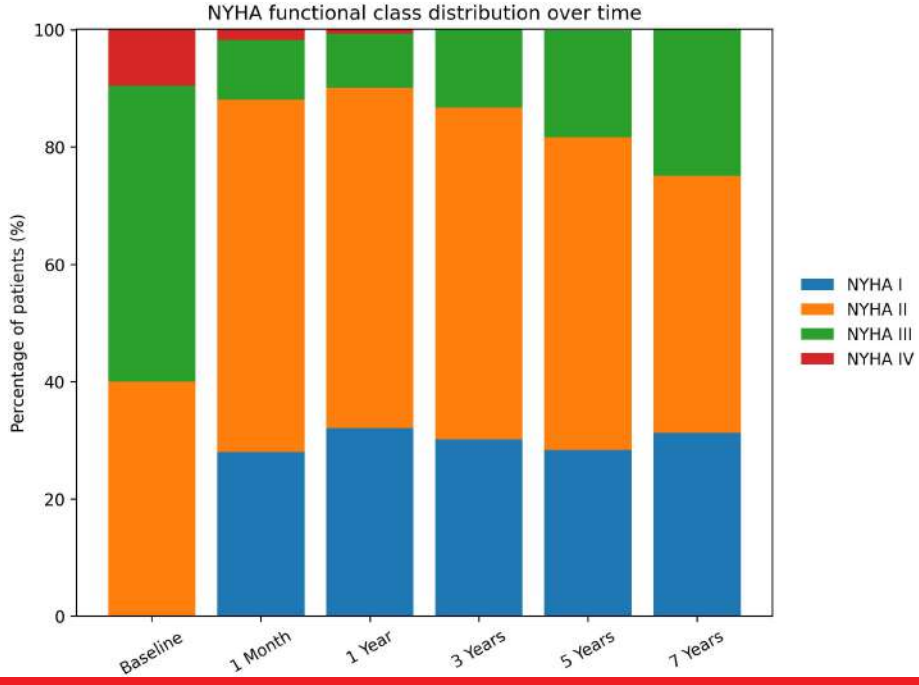
In multivariable Cox proportional hazards analysis, Katz index (HR 0.698, 95% CI 0.594–0.821, $p < 0.001$) and higher body mass index (HR 0.959, 95% CI 0.933–0.986, $p = 0.003$) were inversely associated with 7-year all-cause mortality. eGFR <30 mL/min/1.73 m^2 was also associated with increased mortality risk (HR 1.737, 95% CI 1.127–2.678, $p = 0.012$); however, this finding should be interpreted cautiously because the proportional hazards assumption was not fully satisfied for this variable‡.

‡ Proportional hazards assumption testing identified time-varying effects for diabetes mellitus and eGFR <30 mL/min/1.73 m^2, suggesting that their impact on mortality may vary over time.

AS, aortic stenosis; BMI, body mass index; CABG, coronary artery bypass grafting; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; STS, Society of Thoracic Surgeons.



Supplementary Figure 1. Change in estimated marginal mean left ventricular ejection fraction during follow-up after transcatheter aortic valve implantation.



Supplementary Figure 2. Distribution of New York Heart Association (NYHA) functional class at baseline and during follow-up.

Supplementary Table 2. Baseline Characteristics of 7-Year Survivors According to Availability of Late Echocardiographic Follow-Up

Variables	With echocardiographic follow-up (n = 61)	Without echocardiographic follow-up (n = 19)	*P*
Baseline demographics			
Age, years	79.8 ± 7.5	81.1 ± 7.3	0.555
Female sex, n (%)	47 (77.0%)	14 (73.7%)	0.751
Body mass index, kg/m^2	32.5 ± 8.0	30.2 ± 5.5	0.482
Risk stratification			
STS score, %	6.9 ± 2.5	6.5 ± 2.8	0.460
EuroSCORE II, %	8.7 ± 2.4	8.1 ± 3.7	0.197
Katz index	4.8 ± 1.0	5.2 ± 0.8	0.082
Comorbidities			
Diabetes mellitus, n (%)	3 (4.9%)	2 (10.5%)	0.421
Arterial hypertension, n (%)	49 (80.3%)	16 (84.2%)	0.678
COPD, n (%)	21 (34.4%)	4 (21.1%)	0.264
Atrial fibrillation, n (%)	7 (11.5%)	2 (10.5%)	0.913
Low-flow low-gradient AS, n (%)	3 (4.9%)	4 (21.1%)	0.141
Baseline echocardiographic parameters			
LVEF, %	51.8 ± 12.7	55.0 ± 9.6	0.410

Data are presented as mean ± standard deviation or n (%). Comparisons between groups were performed using the Mann-Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables. No statistically significant differences were observed between patients with and without late echocardiographic follow-up for any baseline characteristic examined.
AS, aortic stenosis; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; STS, Society of Thoracic Surgeons.

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Single-Session Percutaneous Left Atrial Appendage Occlusion and Atrial Septal Defect Closure Guided by Balloon Occlusion Testing in an Elderly Patient with Recurrent Gastrointestinal Bleeding Under Non-vitamin K Antagonist Oral Anticoagulants Therapy

CASE REPORT

INTRODUCTION

The coexistence of atrial fibrillation (AF) and a secundum atrial septal defect (ASD) in the elderly poses a therapeutic paradox: late closure may unmask left ventricular diastolic dysfunction (LVDD) once the shunt is abolished, making balloon occlusion testing a decisive pre-procedural step.[1-3] These patients also need lifelong anticoagulation, yet recurrent bleeding under non-vitamin K antagonist oral anticoagulants (NOACs) often necessitates percutaneous left atrial appendage occlusion (LAAO).[4] Single-session LAAO and ASD closure is feasible, but in an elderly bleeding patient with pulmonary hypertension, it has rarely been reported.[5-7] Here, such a case is presented.

CASE REPORT

A 74-year-old man presented with exertional dyspnea (New York Heart Association II–III) and peripheral edema. He had chronic AF, hypertension, non-obstructive coronary disease, and a secundum ASD diagnosed 3 years earlier. On edoxaban 30 mg daily (reduced for an estimated glomerular filtration rate of 44 mL/min/1.73 m^2), he had 2 episodes of major gastrointestinal bleeding requiring transfusion and anticoagulation withdrawal (CHA^2DS^2-VASc 4, HAS-BLED 3).

Transesophageal echocardiography (TEE) showed dilated right chambers, a 23 × 27 mm secundum ASD with prominent left-to-right shunting (Figure 1A; Supplementary Video 1), left atrial dilation (56 mm), enlarged left ventricle [left ventricular end-diastolic diameter (LVEDD) 56 mm], and reduced left ventricular ejection fraction (LVEF) (40%); pulmonary artery systolic pressure was 55 mm Hg. Cardiac computed tomography excluded intra-appendage thrombus and quantified the appendage (32.60 cm^3; Figure 1B).

Under general anesthesia with TEE guidance, catheterization confirmed a Qp/Qs of 3.1 with a pulmonary vascular resistance (PVR) of 1 Wood unit; the large shunt with preserved PVR indicated flow-related, not fixed, pulmonary hypertension, supporting operability. A 35-mm sizing balloon was inflated across the defect (Figure 1C); left ventricular end-diastolic pressure (LVEDP) rose only from 12 to 14 mm Hg and mean pulmonary artery pressure from 28 to 30 mm Hg, confirming safe accommodation of the redirected venous return.

A combined single-session strategy was undertaken. Left atrial appendage occlusion was performed first, using the native ASD as a transseptal conduit. A 31-mm Amplatzer Amulet device (Abbott Vascular, Santa Clara, CA, USA) was deployed in the chicken-wing appendage; tug test and TEE confirmed complete sealing (Figure 1D; Supplementary Video 2).

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Available Online Date: August 21, 2026

Cite this article as: Coşkun Ş, Kılıç T. Single-session percutaneous left atrial appendage occlusion and atrial septal defect closure guided by balloon occlusion testing in an elderly patient with recurrent gastrointestinal bleeding under NOAC therapy. *Anatol J Cardiol.* 2026;30(12):970-972.

DOI: 10.14744/AnatolJCardiol.2026.6723

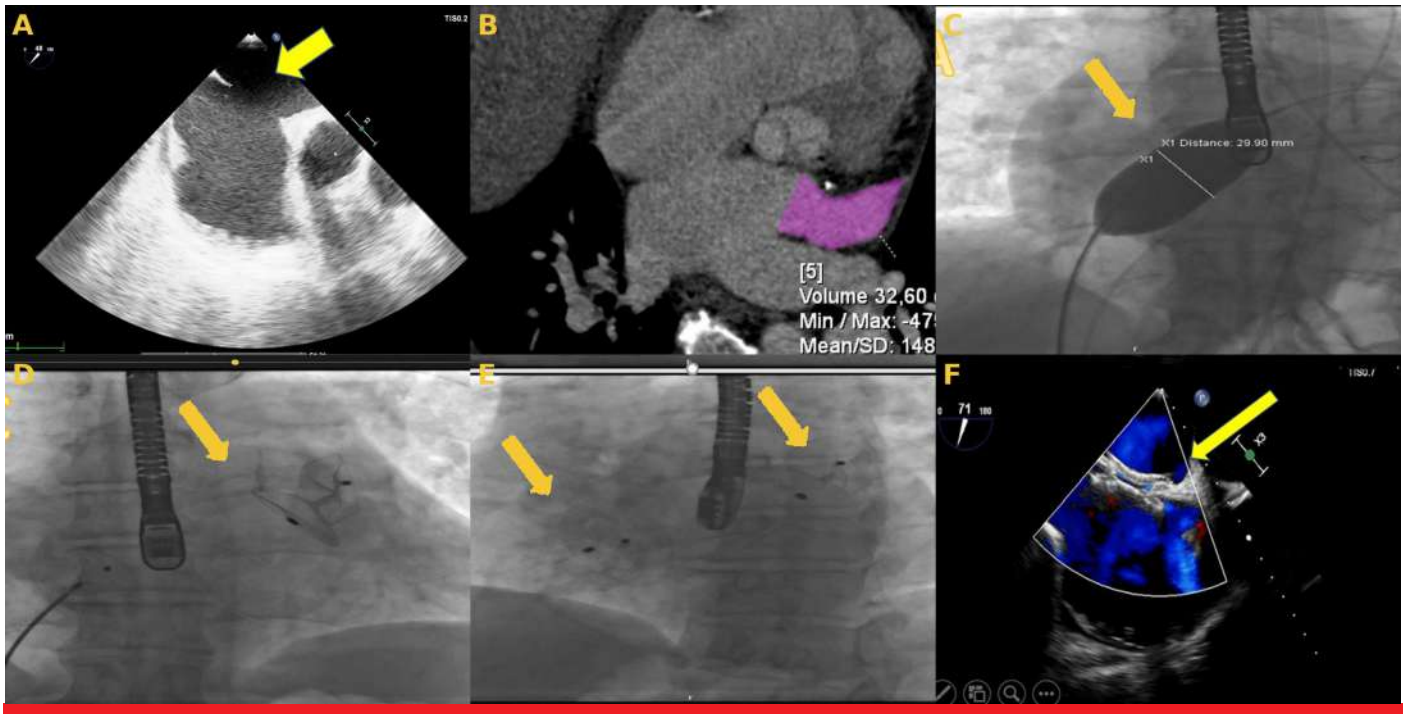


Figure 1. Diagnosis and single-session procedure. (A) Two-dimensional TEE of the secundum ASD (yellow arrow), 23 × 27 mm. (B) Cardiac CT with left atrial appendage volumetric segmentation (magenta; 32.60 cm³). (C) Fluoroscopic ASD sizing balloon, stop-flow waist 29.9 mm (yellow arrow). (D) Amplatzer Amulet device deployed in the appendage while the septal occluder is advanced (yellow arrow). (E) Final fluoroscopy after release of both devices (yellow arrows). (F) Color Doppler confirming abolition of the interatrial shunt (yellow arrow). ASD, atrial septal defect; CT, computed tomography; TEE, transesophageal echocardiography.

A 32-mm Amplatzer Septal Occluder was then advanced through the same access; a Minnesota maneuver confirmed stability, and TEE showed complete abolition of the shunt (Figure 1E, 1F). Both devices were released uneventfully. Given the high bleeding risk (2 prior major hemorrhages, advanced age, reduced renal function), dual antiplatelet therapy was avoided; the patient was discharged on clopidogrel monotherapy.

Echocardiography at 1 and 3 months showed stable devices and no residual shunt, with resolution of edema. Transesophageal echocardiography at 6 months confirmed stable devices, no peri-device leak, and no thrombus (Figure 2; Supplementary Video 3). The patient remained asymptomatic.

DISCUSSION

This case illustrates 3 points. First, sequencing LAAO before ASD closure exploited the native defect as a transseptal conduit; access after septal occluder implantation is markedly more difficult.[8] The Amulet disk-and-lobe design allowed deployment without protruding into the septum, leaving adequate margin for the occluder.[5,6]

Second, balloon occlusion testing was decisive and should be considered mandatory before ASD closure in elderly patients. The aged left ventricle is often stiff, and abrupt closure can precipitate pulmonary edema by unmasking occult LVDD.[1,2] Transient occlusion with simultaneous LVEDP and pulmonary pressure monitoring is the most reliable bedside method to confirm the left ventricle can tolerate the redirected venous return; a significant pressure rise should prompt deferral.[3] In this study's patient, pressure stability justified definitive closure.

Atrial fibrillation ablation was not pursued because advanced age, severe left atrial dilation, and reduced systolic function predict low rhythm-control success; rate control with mechanical stroke prevention was chosen.

Third, recurrent NOAC-related bleeding precluded anticoagulation, while the thromboembolic risk of AF, magnified by the ASD,[9] remained substantial; LAAO offered a definitive alternative.[4,10] To the authors' knowledge, single-session LAAO plus ASD closure guided by balloon occlusion testing in an elderly bleeding patient with pulmonary hypertension has rarely been described.[5-7]

Limitations include the single-patient design; the first TEE at 6 months rather than earlier was supported by reassuring transthoracic studies at 1 and 3 months.

CONCLUSION

Combined single-session LAAO and ASD closure, guided by balloon occlusion testing, was safe and effective in an elderly patient with concurrent thromboembolic and bleeding risk. Balloon occlusion testing should be regarded as an essential safeguard before shunt closure in this population.

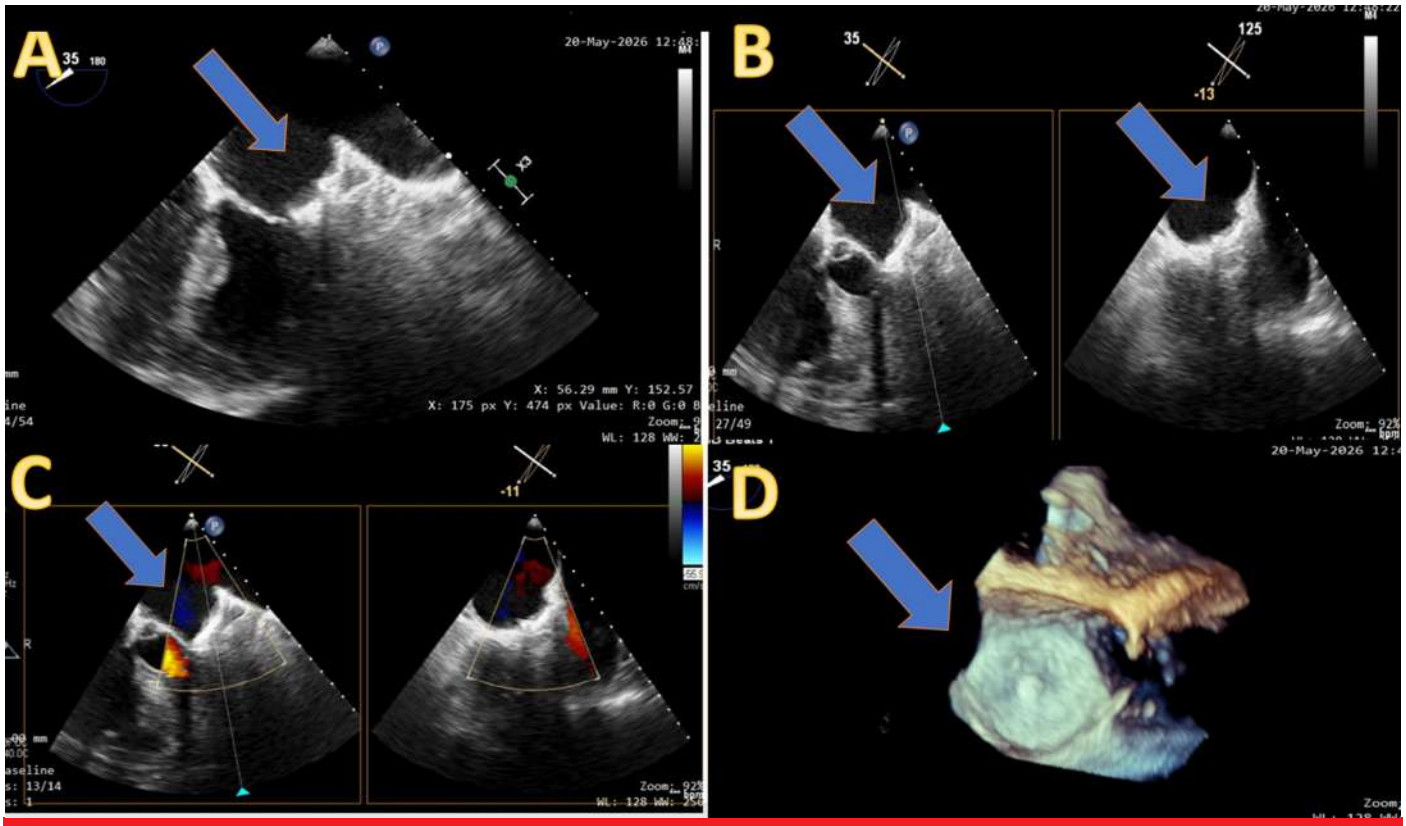


Figure 2. Six-month follow-up TEE. (A) Two-dimensional view of the Amulet device in the appendage, no leak (blue arrow). (B) Biplane imaging at 35° and 125° confirming stable position (blue arrows). (C) Color Doppler showing no peri-device flow (blue arrow). (D) Three-dimensional reconstruction of the device disc (blue arrow). TEE, transesophageal echocardiography.

Informed Consent: Written informed consent was obtained from the patient.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declare that this study received no financial support.

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Supplementary Video 1. Pre-procedural TEE of the secundum ASD: two-dimensional, three-dimensional, and color Doppler imaging of the left-to-right shunt.

Supplementary Video 2. Intraprocedural fluoroscopy: Amulet deployment in the appendage, balloon sizing of the defect, and release of the septal occluder.

Supplementary Video 3. Six-month follow-up TEE: stable position of both devices, with no peri-device leak and no device-related thrombus.

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HFpEF and BREATH2 score: From Prognostic Risk to Etiological Heterogeneity

LETTER TO THE EDITOR

To the Editor,

Risk stratification in heart failure with preserved ejection fraction (HFpEF) remains challenging because diagnostic probability and prognostic risk do not necessarily reflect the same clinical features. In this context, the study by Yalvaç et al[1] provides an interesting perspective by evaluating the BREATH2 score as a predictor of 1-year mortality in these patients . The authors found that BREATH2 was independently associated with mortality and showed greater prognostic discrimination than H_2FPEF, while its performance did not significantly differ from HFA-PEFF. These findings extend the potential utility of a score originally developed as an echocardiography-independent screening tool for HFpEF and raise the broader question of what clinical dimension BREATH2 actually captures.[2]

An interesting question arising from these results is what the prognostic performance of BREATH2 actually represents. The score incorporates age, atrial fibrillation, coronary artery disease, elevated natriuretic peptides, anemia, cardiomegaly, and electrocardiographic left ventricular high voltage.[2] Several of these variables are established markers of cardiovascular or systemic disease burden and are themselves associated with adverse outcomes. Thus, as appropriately suggested by Yalvaç et al[1], BREATH2 may perform well precisely because it captures multidimensional clinical vulnerability.

The present findings support this interpretation. Non-survivors had markedly higher NT-proBNP and creatinine and lower hemoglobin, while BREATH2 remained independently associated with mortality after adjustment for creatinine and NT-proBNP. Conversely, H_2FPEF, which was specifically developed to estimate the probability of HFpEF, showed limited discrimination for mortality.[1] This divergence between diagnostic probability and prognostic risk is conceptually relevant: the characteristics identifying a patient as likely to have HFpEF may not necessarily be those determining prognosis.

This observation also intersects with the broader challenges surrounding HFpEF classification. We previously suggested that contemporary HFpEF screening strategies may predominantly identify a phenotype characterized by exercise intolerance, cardiovascular comorbidity burden, and biomarker abnormalities rather than identifying patients prone to developing acute heart failure with overt fluid overload and congestion.[3,4] The present study provides an interesting prognostic counterpart to this concept: BREATH2 may identify a particularly vulnerable phenotype because its components capture the burden of underlying cardiovascular and systemic abnormalities.

Importantly, Yalvaç et al[1] excluded significant primary valvular heart disease and hypertrophic or restrictive cardiomyopathy, but different underlying cardiac substrates may still be represented within the HFpEF label. This distinction may be clinically relevant because patients presenting with preserved or mildly reduced ejection fraction and objectively confirmed acute congestion frequently exhibit

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Available Online Date: October 9, 2026

Cite this article as: Bellicini MG. HFpEF and BREATH2 score: From Prognostic Risk to Etiological Heterogeneity. *Anatol J Cardiol.* 2026;30(12):973-974.

DOI: 10.14744/AnatolJCardiol.2026.7063

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identifiable alternative cardiac pathologies rather than isolated diastolic dysfunction.[5]

Future studies evaluating BREATH2 according to etiological HFpEF phenotypes could therefore clarify whether its prognostic value primarily reflects HFpEF severity or, more broadly, the vulnerability of the heterogeneous population currently classified as HFpEF. Moving from diagnostic probability and risk prediction toward etiological characterization may ultimately provide information more directly relevant to individualized management.

Declaration of Interests: The author has no conflict of interest to declare.

Funding: The author declared that this study has received no financial support.

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Reply to the Letter to the Editor: "HFpEF and BREATH2 score: From Prognostic Risk to Etiological Heterogeneity"

LETTER TO THE EDITOR REPLY

To the Editor,

We thank the authors for their interest in our study and for their comments regarding the prognostic significance of the BREATH2 score in heart failure with preserved ejection fraction (HFpEF).[1,2]

First, the authors note that the components of the score (age, atrial fibrillation, coronary artery disease, elevated natriuretic peptides, anemia) are not specific to HFpEF, and that its association with mortality may therefore reflect general vulnerability rather than the severity of a single disease entity. We agree. BREATH2 was not developed to measure the degree of diastolic dysfunction but to enable rapid risk screening in primary care using readily available data; the fact that its components are not disease-specific does not undermine this purpose.[3]

Second, the persistence of the independent association between BREATH2 and mortality after adjustment for creatinine and NT-proBNP was a finding we also wished to highlight. We would add that H_2FPEF (Heavy, Hypertension, atrial Fibrillation, Pulmonary hypertension, Elder, Filling pressure), despite including age and atrial fibrillation, did not predict mortality. This suggests that BREATH2's performance may reflect not simply the number of comorbidities counted, but which variables were selected.

Third, we agree that different cardiac substrates may still be represented within the HFpEF label despite our exclusion of significant valvular disease and hypertrophic or restrictive cardiomyopathy. Our retrospective design did not allow systematic screening for infiltrative or hypertension-predominant substrates, nor exercise hemodynamic phenotyping; we noted this limitation in our manuscript.[2]

These findings suggest that BREATH2 may be a practical tool for identifying vulnerable HFpEF patients at initial clinical contact. While hypothesis-generating, we believe testing the score across etiologically defined HFpEF subgroups would help clarify the source of its prognostic value, and we are planning this in a prospective cohort.

Declaration of Interests: The author has no conflict of interest to declare.

Funding: The author declared that this study has received no financial support.

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Available Online Date: October 6, 2026

Cite this article as: Yalvaç HE. Reply to the letter to the editor: "HFpEF and BREATH2 score: From Prognostic Risk to Etiological Heterogeneity." *Anatol J Cardiol*. 2026;30(12):975.

DOI: 10.14744/AnatolJCardiol.2026.7069

THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Vericiguat in Experimental Atrial Fibrillation: Distinguishing Remodeling from Rhythm Control

LETTER TO THE EDITOR

To the Editor,

We read with great interest the experimental study by Zhang et al,[1] which examined the effects of vericiguat on atrial electrical and structural remodeling in a rat model of atrial fibrillation (AF). The authors demonstrated coherent antiremodeling signals, including reductions in left atrial enlargement, fibrosis, collagen I, and NT-proBNP, together with favorable changes in CaMKII, connexin 43, and autophagy-related proteins. These findings are biologically relevant. Nevertheless, the conclusion that vericiguat attenuates "AF progression" and the discussion of restored "electrophysiological stability" appear stronger than the rhythm and mechanistic endpoints directly assessed, raising 2 points that may refine interpretation of this important work.

First, the temporal relationship between rhythm assessment and vericiguat exposure deserves clarification. In the Methods and Results, AF frequency and duration were recorded during model establishment after ACh-$CaCl_2$ administration, and the 16 animals with AF were subsequently randomized to the AF and vericiguat groups. The reported frequency and duration values therefore appear to characterize the pre-treatment model rather than rhythm response after 4 weeks of vericiguat. No post-treatment AF burden, inducibility, atrial effective refractory period, action-potential duration, or conduction mapping is reported. Accordingly, normalization of CaMKII and connexin 43 supports molecular changes consistent with electrical remodeling, but it does not by itself demonstrate restoration of electrophysiological stability or reduction of AF burden. This distinction is particularly relevant because earlier work with vericiguat in a rabbit AF model incorporated direct electrophysiological endpoints, including atrial refractoriness and AF inducibility.[2] Demonstrating concordance between such functional endpoints and the molecular changes observed here would substantially strengthen the antiarrhythmic inference.

Second, the interpretation of autophagy merits similar caution. The endpoint pattern of increased ATG7 and LC3-II/I with reduced p62 in AF, and its reversal with vericiguat, is compatible with altered autophagy-related signaling. However, autophagy is a dynamic degradative process, and static measurements of LC3 and p62 cannot, by themselves, distinguish increased autophagosome formation from impaired downstream lysosomal clearance. Current methodological guidance therefore emphasizes assessment of autophagic flux using complementary approaches, such as lysosomal inhibition or suitable reporter systems.[3] Moreover, because autophagy was not experimentally inhibited or genetically perturbed, the present data establish association rather than mediation between autophagy-related changes and the antifibrotic effects of vericiguat. Thus, "modulation of autophagy-related markers" may be a more proportionate mechanistic description than a demonstrated autophagy-mediated pathway.

We therefore view the study as providing a compelling preclinical signal that vericiguat attenuates atrial structural remodeling, while its direct antiarrhythmic and autophagy-mediated effects remain hypothesis-generating. Future

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Available Online Date: October 6, 2026

Cite this article as: İşleyen HB, Hancıoğlu E, Yavuz ST. Vericiguat in experimental atrial fibrillation: distinguishing remodeling from rhythm control. *Anatol J Cardiol.* 2026;30(12):976-977.

DOI: 10.14744/AnatolJCardiol.2026.6998

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experiments combining posttreatment continuous rhythm phenotyping or standardized AF inducibility with direct electrophysiological measurements and autophagic-flux assessment could connect the molecular findings to rhythm outcomes and more firmly establish the proposed mechanistic pathway.

Note: The authors of the relevant article were given the opportunity to reply, but they chose not to send a response.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Postimplantation Activity Restrictions and Shoulder Dysfunction After Pacemaker Implantation

LETTER TO THE EDITOR

To the Editor,

We read with great interest the study by Ata et al[1] entitled "Comparison of Kinesiophobia, Upper Limb Function, and Grip Strength in Patients with Pacemakers and Coronary Artery Disease." The authors should be congratulated for addressing an underrecognized aspect of long-term care after pacemaker implantation. Particularly noteworthy was the selective limitation in ipsilateral shoulder internal rotation among pacemaker recipients, despite the absence of significant differences in other range-of-motion parameters, upper-limb function, or handgrip strength.[1]

As the authors emphasize, patients are often advised to limit shoulder elevation and avoid strenuous or repetitive use of the ipsilateral arm during the initial recovery period, while immobilization may also be employed.[1] However, Miracapillo et al[2] demonstrated in a randomized study that mobilization 3 hours after pacemaker implantation, compared with 24-hour immobilization, was not associated with a significant increase in lead- or pocket-related complications.

Postimplantation management may also influence subsequent shoulder function. Daniels et al[3] randomized patients undergoing cardiac rhythm device implantation to standard postimplantation instructions or a structured shoulder exercise program. At 1 month, shoulder pain or discomfort occurred in 7 of 21 patients receiving standard care compared with 1 of 23 patients in the exercise group ($P = .02$), with no activity-related complications. These findings support the possibility that post-procedural mobility and rehabilitation strategies may influence later shoulder outcomes.

In this context, an important issue in the study by Ata et al[1] is that postoperative management is not reported. Although pacemaker implantation had been performed at least 6 months before enrollment, it remains unclear whether patients were instructed to restrict ipsilateral shoulder movement, whether immobilization was used, how long such restrictions were maintained, or whether rehabilitation was recommended. This is particularly relevant because the authors themselves acknowledge that persistent avoidance of ipsilateral arm use may contribute to soft-tissue stiffness and adhesive capsulitis.[1]

The authors propose that anatomical proximity of the pacemaker pocket to the pectoralis major and subscapularis muscles may contribute to local fibrosis and altered movement patterns, potentially explaining the selective internal rotation limitation.[1] While plausible, postoperative activity restrictions and rehabilitation may also contribute to this finding. Therefore, without information on postimplantation management, distinguishing device-related effects from potentially modifiable consequences of postoperative care may be difficult. We believe this should be considered an additional limitation, and future prospective studies incorporating the type and duration of activity restrictions and rehabilitation strategies may help clarify the mechanisms underlying shoulder dysfunction after pacemaker implantation.

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Available Online Date:
November 12, 2026

Cite this article as: Çakmak AC, Sarıbıyık Çakmak B. Postimplantation activity restrictions and shoulder dysfunction after pacemaker implantation. *Anatol J Cardiol.* 2026;30(12):978-979.

DOI: 10.14744/AnatolJCardiol.2026.7074

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Reply to the Letter to the Editor: "Postimplantation Activity Restrictions and Shoulder Dysfunction After Pacemaker Implantation"

LETTER TO THE EDITOR
REPLY

To the Editor,

We thank the authors[1] for their thoughtful comments on our study[2] comparing kinesiophobia, upper-limb function, shoulder range of motion, and handgrip strength in patients with pacemakers and coronary artery disease.[2] We agree that postoperative activity restrictions, immobilization, and rehabilitation may represent important and potentially modifiable determinants of subsequent shoulder function.

As noted in our article, postoperative recommendations vary considerably among centers, and randomized evidence suggests that early mobilization can be implemented without a significant increase in lead- or pocket-related complications.[3] The study highlighted by the authors, which demonstrated a lower frequency of shoulder pain with a structured shoulder exercise program and no activity-related complications, further supports the potential importance of postoperative shoulder management.[4]

Our study protocol did not include the systematic collection of information regarding postoperative activity restrictions, immobilization, or participation in rehabilitation. Furthermore, the time elapsed since pacemaker implantation varied considerably among participants, making reliable retrospective reconstruction of early postoperative practices difficult. Therefore, the type and duration of activity restrictions, use of immobilization, adherence to movement recommendations, and participation in rehabilitation could not be included in the analyses. We agree that the absence of these data represents an additional limitation of our study.

The selective reduction in ipsilateral shoulder internal rotation observed in the pacemaker group is nevertheless clinically relevant. However, because preimplantation shoulder measurements and longitudinal postoperative data were unavailable, this cross-sectional association cannot establish a causal relationship with pacemaker implantation. The anatomical and soft-tissue mechanisms proposed in our Discussion were intended as plausible explanations rather than evidence of a device-specific causal mechanism. Postoperative movement restriction, pain-related avoidance, and differences in rehabilitation exposure may also have contributed to the observed difference.

Future prospective studies should assess shoulder function before pacemaker implantation and at standardized intervals thereafter. Postoperative instructions, the type and duration of movement restrictions, immobilization, pain, adherence to recommendations, and participation in rehabilitation should also

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Available Online Date:
November 12, 2026

Cite this article as: Ata BN, Özçete ZA, Ünal B, İnce B. Reply to the letter to the editor: "postimplantation activity restrictions and shoulder dysfunction after pacemaker implantation." *Anatol J Cardiol.* 2026;30(12):980-981.

DOI: 10.14744/AnatolJCardiol.2026.7022

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be documented. Such studies could help distinguish procedure- and device-related effects from the potentially modifiable consequences of postoperative management and contribute to the development of more standardized rehabilitation strategies.

We thank the authors for highlighting this clinically relevant issue and extending the interpretation of our findings.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declare that this study received no financial support.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Computed Tomography Angiography–Guided Bypass for Adult Long-Segment Aortic Coarctation

A 39-year-old woman presented with an 11-year history of exertional dizziness, palpitations, and chest tightness, accompanied by progressive facial edema over the preceding 5 years. Physical examination revealed a systolic blood pressure gradient of 50 mm Hg between the upper and lower extremities. A grade 3/6 systolic ejection murmur was audible at the left sternal border and a separate systolic murmur was noted over the left interscapular region. Laboratory investigations, including renal function, thyroid function, and B-type natriuretic peptide, were unremarkable, ruling out secondary causes of facial edema. Computed tomography angiography (CTA) identified severe focal isthmic coarctation (3 mm diameter, 15 mm length) (Figure 1A) with extensive collaterals, and a Sievers Type 0 bicuspid aortic valve with mild stenosis but no aortopathy. She underwent left subclavian-to-descending aorta extra-anatomic bypass using a 14-mm Dacron graft; this approach was chosen over endovascular stenting due to the coarctation's length and location. The pressure gradient resolved intraoperatively. At 12-month follow-up, CTA confirmed graft patency without stenosis or pseudoaneurysm (Figure 1B), and symptoms fully resolved (NYHA Class I).

Aortic coarctation (CoA) accounts for only 5%-8% of congenital heart defects and is rarely encountered in adult practice, as most cases are corrected in early childhood.[1] However, milder lesions may remain occult until adulthood, typically identified during evaluation of exertional intolerance or refractory hypertension.[2,3] Over 60% of affected adults harbor a bicuspid aortic valve, substantially elevating lifelong risks of aortopathy—including dilation, aneurysm, and dissection—and mandating sustained imaging surveillance.[4,5] High-resolution CTA is the cornerstone of preoperative risk stratification and procedural planning, precisely quantifying stenosis severity, lesion length, arch anatomy, and collateral burden. For long-segment coarctation unsuitable for stenting, CTA directly informs the feasibility and configuration of extra-anatomic bypass. Percutaneous interventions in adult CoA achieve favorable procedural success and low in-hospital mortality, though rare but serious complications underscore the necessity for meticulous management and lifelong follow-up.[6] Postoperatively, repaired CoA patients remain susceptible to recoarctation, pseudoaneurysm, and dissection. Computed tomography angiography enables robust surveillance of graft patency and early complication detection; guidelines recommend cross-sectional imaging at 5-year intervals in stable patients.[1] Thus, CTA remains indispensable for orchestrating individualized care and ensuring long-term prognostic surveillance in adults with congenital aortic disease.

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E-PAGE ORIGINAL IMAGE

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Available Online Date:
September 21, 2026

Cite this article as: Wang J, Qu W, Xu L, Hu P, Ma X. Computed tomography angiography–guided bypass for adult long-segment aortic coarctation. *Anatol J Cardiol.* 2026;30(12):E-28-E-29.

#Jie Wang, Wei Qu, Lin Xu, and Ping Hu contributed equally to this work and should be considered co-first authors.

DOI: 10.14744/AnatolJCardiol.2026.6964

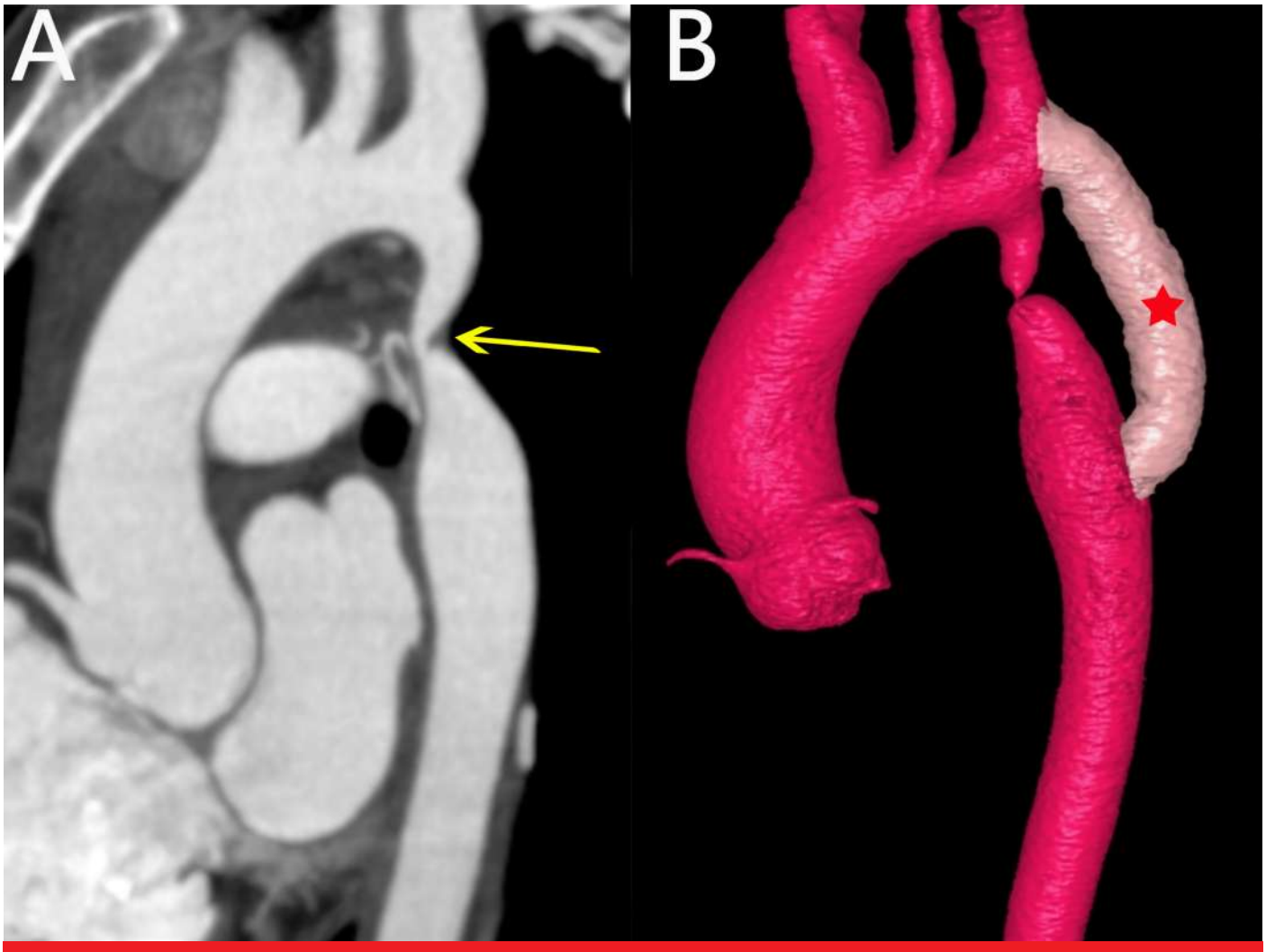


Figure 1. (A) Preoperative computed tomography angiography (CTA) demonstrating severe focal isthmic coarctation (3 mm diameter, 15 mm length; arrow) accompanied by extensive collateral circulation. (B) Twelve-month postoperative CTA confirming patency of the left subclavian-to-descending aorta Dacron graft (star), without evidence of stenosis or pseudoaneurysm.

Informed Consent: This report has obtained the patient's informed consent for the publication of their anonymized clinical data.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: This study was supported by the Wuhan Clinical Medical Research Center for Cardiomyopathy (WHCMRCC-2609) and the Wuhan Clinical Medical Research Center for Cardiovascular Imaging (CMRC202302).

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