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Modulatory Effects of Clopidogrel on Vascular Response in the Human Internal Mammary Artery: An In Vitro Study

ABSTRACT

Background: Coronary artery disease (CAD) is one of the leading causes of mortality worldwide, and coronary artery bypass grafting (CABG) is frequently preferred as a surgical approach in advanced cases. The most commonly used graft material in CABG, the left internal mammary artery (LIMA), is considered the gold standard due to its high long-term patency rates. Clopidogrel, an antithrombotic agent widely used in CABG patients that targets $P2Y_{12}$ receptors on platelets, has also been suggested to influence vascular responses due to the presence of these receptors in vascular smooth muscle cells. However, the direct vascular effects of clopidogrel on LIMA remain unknown.

Methods: In this study, isolated LIMA segments obtained from 20 patients undergoing CABG were evaluated to compare the contractile responses induced by phenylephrine (PE; 10^{-9}-10^{-4} M) and the endothelium-independent relaxation responses induced by sodium nitroprusside (SNP; 10^{-9}-10^{-4} M), before and after pretreatment with 0.1 µM clopidogrel.

Result: In clopidogrel-treated LIMA segments, all PE-induced contractile responses were significantly attenuated, whereas SNP-induced relaxation was enhanced at low and moderate concentrations; however, this relaxant effect was diminished at the highest dose.

Conclusion: This biphasic effect observed in LIMA segments suggests that clopidogrel may act not only as an antithrombotic agent, but also as a direct modulator of vascular tone. These findings indicate that the local vascular effects of clopidogrel should be considered in developing therapeutic strategies aimed at maintaining graft patency following CABG.

Keywords: Antiplatelet agents, bypass, coronary heart disease, internal mammary artery, organ bath

ORIGINAL INVESTIGATION

INTRODUCTION

Coronary heart disease (CHD), with its increasing prevalence and status as the leading cause of mortality globally, represents a critical public health challenge of worldwide significance.[1-3] Management of CHD involves a multimodal approach.[4-7] In advanced cases, invasive procedures are used to restore arterial patency, while coronary artery bypass grafting (CABG) remains the definitive treatment in severe cases.[8-11] CABG involves bypassing stenotic or occluded coronary arteries using grafts, most commonly the left internal mammary artery (LIMA) or saphenous vein grafts. Among these, LIMA is considered the gold standard, owing to its superior patency rates and long-term outcomes. Studies have demonstrated that LIMA has a 10-year patency rate exceeding 90%, significantly reducing cardiac complications and improving survival compared to other graft options.[12-14]

Despite these advancements, the long-term success of CABG is influenced by multiple factors, including graft patency and the graft's ability to maintain vasodilation and vasoconstriction responses.[15,16] One of the most critical determinants of graft failure is vasoconstriction. Arterial grafts, in particular, are prone to spasm because of their well-developed smooth muscle layer and high α-adrenergic receptor sensitivity. Surgical manipulation and endothelial injury

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further exacerbate this susceptibility, leading to decreased graft flow, thrombosis, and early occlusion.[17] Moreover, the discontinuation of antiplatelet therapy during the preoperative period may increase the risk of postoperative thrombotic events.[18,19] Following CABG, excessive vasoconstriction and thrombosis within the grafted vessels may contribute to early graft failure. Clinical data indicate that up to 20% of venous grafts may occlude within the first postoperative year.[20] Therefore, a comprehensive understanding of how antiplatelet agents (e.g., clopidogrel, ticagrelor) and anticoagulants (e.g., heparin derivatives, direct thrombin, and factor Xa inhibitors) affect vascular reactivity is of great importance in optimizing graft outcomes.[21,22]

Among the pharmacological agents used in this context, clopidogrel—a thienopyridine adenosine diphosphate (ADP) receptor antagonist—has gained widespread acceptance. Clopidogrel has become a cornerstone in preventing thrombotic events in CHD and CABG patients by irreversibly inhibiting platelet aggregation.[23,24] Clopidogrel blocks platelet $P2Y_{12}$ receptors irreversibly and may also affect vascular smooth muscle cells where these receptors are minimally expressed.[25] This suggests that clopidogrel may exert modulatory effects on vascular smooth muscle function, which may vary depending on the specific vascular bed.[26-29]

However, despite its widespread use in patients with CHD and following CABG surgery, the effect of clopidogrel on contractile responses in LIMA has not been investigated. This study aims to investigate the effects of clopidogrel on the contractile and relaxation mechanisms of human LIMA specimens, with the goal of informing the development of novel strategies to optimize postoperative management and enhance long-term graft patency and overall surgical outcomes.

METHODS

Informed consent was obtained from the patients, and the Clinical Research Ethics Committee of Fırat University Faculty of Medicine (Elazığ, Türkiye) approved the use of discarded human LIMA segments in this study (26.10.2017, number 11). This study was conducted in accordance with the principles of the Declaration of Helsinki. No artificial intelligence–assisted technologies, including Large Language Models, chatbots, or image generators, were used in the production of this manuscript.

The sample size of 20 was determined based on an a priori power analysis conducted using G*Power 3.1.9.7 software. For a repeated-measures ANOVA, the analysis was performed assuming a medium effect size ($f = 0.25$), an alpha level of 0.05, and a desired statistical power of 0.80. With 6 repeated measurements and a correlation among repeated measures set at 0.5, the required total sample size was calculated to be approximately 19. Therefore, a sample size of 20 was selected to ensure sufficient power to detect statistically significant effects while also accounting for potential data loss or variability.

Segments of the LIMA were collected from 20 patients undergoing CABG. Demographic and clinical characteristics of these patients are given in Table 1.

In accordance with standard experimental protocols in human vascular research, the distal segments of LIMA—those not utilized during grafting—were selected for evaluation. These segments are routinely obtained during CABG procedures as residual tissue and are commonly used in ex vivo studies due to their accessibility and higher smooth muscle content. While it is acknowledged that different segments of LIMA may exhibit variable anatomical and structural properties, the distal segment remains the most practical and representative choice for investigating vasomotor responses in isolated organ bath experiments.

The IMA were carefully cleaned of loose connective tissue and cut into rings (about 2-3 mm long). The preparations were placed in an isolated tissue bath containing Krebs–Henseleit (KH) solution (composition in mM: NaCl 118, KCl 4.7, $MgSO_4$ 1.2, $CaCl_2$ 1.25, KH_2PO_4 1.2, $NaHCO_3$ 25, glucose 11, EDTA 0.03) at 37°C and pH 7.4, constantly bubbled with a mixture of 95% O_2 and 5% CO_2. Contractile activities were recorded using a physiological force transducer (FDT05, Commat Ltd, Ankara, Türkiye) recorded by MP150WS for Windows (Biopac Systems Inc, CA, USA).[30,31] At the beginning of the experiments, the resting tension of the LIMA vessels was adjusted to 1 g and

Table 1. Some Clinical Features of 20 Patients Undergoing CABG

Clinical features	Mean ± SD, n (%)
Age, years	68.0 ± 4.0
Weight	78.6 ± 8.0
Body mass index	28.2 ± 2.4
Gender	
Male	11 (55)
Female	9 (45)
Smoking	8 (40)
Diseases	
Hypertension	18 (90)
Heart failure	4 (20)
Diabetes	8 (40)
Medication	
Organic nitrates	0 (0)
Aspirin	20 (100)
Beta-blockers	15 (75)
Angiotensin inhibitors	9 (45)
Calcium channel blockers	4 (20)
Hypolipidemics	14 (70)

HIGHLIGHTS

- Clopidogrel reduces PE-induced contraction in the left internal mammary artery (LIMA).
- Clopidogrel modulates sodium nitroprusside(SNP)-induced relaxation in the LIMA.
- The LIMA vascular bed is responsive to clopidogrel.

they were allowed to equilibrate under this resting tension for 120 min. Phenylephrine (PE) and SNP were obtained from Sigma (St. Louis, MO, USA), while clopidogrel was obtained from Sanofi Pharmaceuticals (Türkiye). Phenylephrine (PE) and SNP were dissolved in distilled water immediately before use to ensure stability and reproducibility of concentration–response curves.

Following the equilibration period, PE was administered to the organ bath chamber at 30-second intervals in increasing concentrations from 10^{-9} M to 10^{-4} M. The contraction induced by the highest dose (10^{-4} M) was considered as 100%, and the responses to the lower doses were recorded as percentages relative to this maximum contraction, serving as the control contraction protocol.

To assess the effect of clopidogrel on contractile responses, 0.1 μM clopidogrel was added to the organ bath.[28,32] Following clopidogrel administration, tissues were incubated for 10 minutes. After an incubation period, the PE contraction protocol was repeated with increasing concentrations of PE from 10^{-9} M to 10^{-4} M applied at 30-second intervals. To avoid any systematic influence of the solvent composition or dissolution conditions on the experimental outcomes, Krebs solution was used as the solvent for clopidogrel. This approach was chosen to ensure experimental standardization and to attribute the observed pharmacological effects solely to clopidogrel administration.

Thereafter, to allow the tissue to return to its basal tone, a 90-minute stabilization period was applied, during which the LIMA segments were washed with fresh Krebs solution at 10-minute intervals.

To evaluate the relaxation response, particularly endothelium-independent relaxation, a SNP protocol was applied. Initially, the stable isolated LIMA segment was contracted using 10^{-4} M PE. Subsequently, SNP was administered in increasing concentrations from 10^{-9} M to 10^{-4} M at 30-second intervals. The maximal relaxation observed at 10^{-4} M was accepted as 100%, and relaxation responses at lower concentrations were recorded as percentages of this maximum response.

Subsequently, 0.1 μM clopidogrel was introduced into the organ bath, followed by a 10-minute incubation period, after which the vascular segment was contracted with 10^{-4} M PE. Thereafter, the SNP-induced relaxation protocol was re-applied under identical experimental conditions.[28,30,31]

Statistical analyses were performed using GraphPad Prism version 10.4.1 (GraphPad Software, San Diego, CA, USA). Data are expressed as mean ± standard error of the mean (SEM). Contractile responses to PE were normalized to the maximal contraction. Relaxation responses to cumulative concentrations of SNP (10^{-9} to 10^{-4} M) were calculated as the percentage reduction from PE-induced precontraction. Prior to parametric analyses, the normality of all continuous variables across repeated measurements was assessed using the Kolmogorov–Smirnov test, which confirmed that the data were normally distributed in all phases ($P > .05$). Thus, the assumptions required for parametric testing were satisfied.

Comparisons between the control and clopidogrel groups across drug concentrations were conducted using 2-way analysis of variance (2-way ANOVA). When a significant interaction was detected, Türkiye's multiple comparisons test was used as a post hoc analysis to identify pairwise differences at each concentration. A P-value < .05 was considered statistically significant.

RESULTS

Cumulative concentrations of PE (10^{-9} to 10^{-4} M) induced dose-dependent contractile responses in isolated LIMA vessels. In vessels pretreated with clopidogrel, PE-induced contractions were significantly reduced at all concentrations compared to the control group. According to Türkiye's post hoc multiple comparison test, contractile responses were significantly attenuated in the clopidogrel group at concentrations of 10^{-9} ($P = .023$), 10^{-8} ($P = .022$), 10^{-7} ($P = .010$), 10^{-6} ($P < .001$), 10^{-5} ($P < .001$), and 10^{-4} M ($P < .001$) (Figure 1).

Cumulative concentrations of sodium nitroprusside (SNP) (10^{-9} to 10^{-4} M) induced dose-dependent relaxation in PE-precontracted isolated LIMA rings. In LIMA rings pretreated with clopidogrel, relaxation responses to SNP exhibited concentration-dependent alterations. According to the results of Türkiye's multiple comparison test, relaxation responses were significantly enhanced in the clopidogrel group at 10^{-8} ($P = .017$), 10^{-7} ($P = .007$), and 10^{-6} M ($P = .001$) concentrations, while no significant difference was observed at 10^{-9} ($P = .480$) and 10^{-5} M ($P = .390$) concentrations between the groups. In contrast, at the concentration of 10^{-4} M, pretreatment with clopidogrel significantly inhibited the relaxation response to SNP ($P = .018$) (Figure 2).

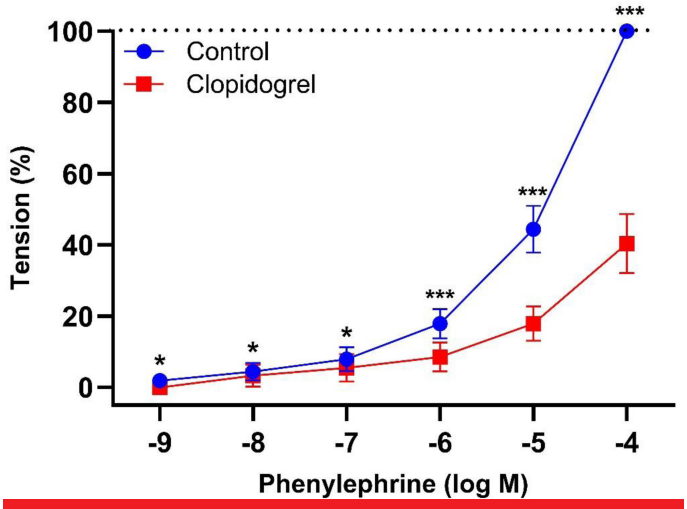


Figure 1. Effect of clopidogrel pretreatment on phenylephrine-induced contractions in isolated human left internal mammary artery (LIMA) segments. Cumulative concentration–response curves to phenylephrine (10^{-9} to 10^{-4} M) were obtained from isolated LIMA segments pretreated with clopidogrel (n = 20). Data are presented as mean ± standard error of the mean (*$P < .05$, **$P < .01$, ***$P < .001$).

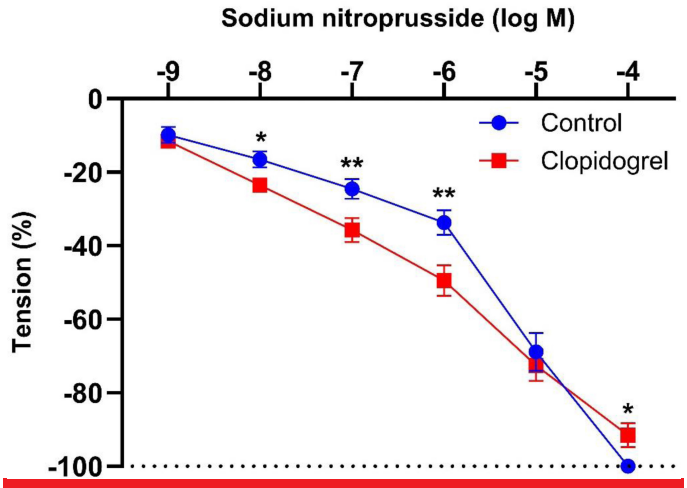


Figure 2. Effects of clopidogrel on sodium nitroprusside-induced relaxation in phenylephrine pre-contracted human left internal mammary artery (LIMA) segments. The magnitude of the relaxation response is expressed as a percentage decrease in vascular tension. Data are presented as mean ± standard error of the mean (n = 20) (*$P < .05$, **$P < .01$, ***$P < .001$).

DISCUSSION

In this study, the effects of clopidogrel on isolated human LIMA rings were investigated. Consistent with existing literature, PE induced dose-dependent contractile responses in LIMA rings. In contrast, in strips pretreated with clopidogrel, PE-induced contractions were markedly attenuated. Notably, the inhibitory effect of clopidogrel on contractile responses became more pronounced with increasing PE concentrations. As expected, SNP elicited vasorelaxation in LIMA rings. In clopidogrel-treated strips, the endothelial-independent relaxation response to low-dose SNP was significantly enhanced. However, at higher SNP doses, the vasodilatory effect was significantly diminished.

It is well established that different segments of the LIMA exhibit anatomical and histological heterogeneity. In the present study, distal segments of the LIMA were selected primarily because the proximal portion is typically used as a graft during CABG surgery, whereas the distal segments, not included in the grafting process, can be ethically and practically obtained as residual tissue. Nevertheless, distal segments are considered the most suitable for evaluating vasomotor responses in isolated organ bath experiments due to their higher smooth muscle content.[33,34]

Due to the limited viability of tissues obtained after surgery and the unavoidable impact of surgical manipulation on endothelial integrity, SNP was selected in the present study to assess endothelium-independent relaxation.[31] The observed enhancement of SNP-induced relaxation in the presence of low-dose clopidogrel suggests an increased sensitivity of vascular smooth muscle cells to nitric oxide (NO). This effect may be mediated through modulation of the NO–cyclic guanosine monophosphate (cGMP) signaling pathway and/or alterations in intracellular calcium handling, including changes in calcium influx or myofilament calcium sensitivity. In this context, previous studies have suggested that antiplatelet agents may enhance NO-mediated vasorelaxation by increasing intracellular cGMP levels and activating downstream cGMP-dependent signaling mechanisms, which can ultimately lead to reduced vascular smooth muscle contractility.[26,35-37]

The biphasic vascular response observed in the present study suggests that clopidogrel may exert its effects not merely through classical vasodilation, but rather via a broader vasomodulatory function. Importantly, this biphasic pattern also points to clinically meaningful implications. Although the in vitro concentration of clopidogrel used in this study (0.1 µM) does not directly replicate systemic plasma levels, the findings indicate that the vascular effects of clopidogrel are neither dose-independent nor unidirectional. Instead, they appear to be concentration-sensitive and bidirectional in nature. This observation underscores the potential importance of dose optimization in the context of preventing graft spasm following CABG. During the perioperative period, fluctuations in hemodynamic conditions and surgical manipulation of the vessel wall may alter local drug distribution, leading to vascular effects that differ from those observed at systemic levels. In this context, it should be considered that local drug exposure may produce variable, dose-dependent effects on vascular tone. Further translational and clinical studies are warranted to elucidate the dose–response relationship and to clarify the potential clinical implications of these findings.

Currently, antiplatelet agents play a pivotal role in preventing ischemia-related atherosclerotic and thrombotic events and are widely used in the post-CABG setting.[38] Among these agents are acetylsalicylic acid, glycoprotein IIb/IIIa receptor antagonists, and thienopyridines such as ticlopidine and clopidogrel, which block platelet ADP receptors.[39,40]

It has been demonstrated that ADP receptors are expressed not only on platelets but also on vascular smooth muscle cells, highlighting their potential role in modulating vascular responses.[27] One study reported that thienopyridines can induce in vitro vasorelaxation, independent of hepatic biotransformation, by directly affecting vascular tissues and smooth muscle cell cultures.[26] Another study suggested that this effect may not be strictly dependent on endothelial NO release, as pretreatment with the NO synthase inhibitor L-NAME did not suppress thienopyridine-induced relaxation, unlike in acetylcholine-mediated pathways.[25] These findings suggest a mechanism potentially linked to intracellular calcium modulation.[26] Several studies have reported that ticagrelor enhances adenosine-mediated vasodilation, while acetylsalicylic acid influences the prostacyclin–thromboxane balance, and that these mechanisms may collectively alter graft hemodynamics following coronary bypass surgery.[41,42]

Clopidogrel is known to undergo hepatic biotransformation to an active thiol metabolite, which irreversibly inhibits the $P2Y_{12}$ receptor. However, several studies have reported that the parent compound of clopidogrel may also exert direct regulatory

effects on various vascular and smooth muscle tissues independent of hepatic metabolism.[26,28,32] Moreover, the presence of certain esterase and CYP2C9/CYP3A4-like enzymatic activities in human vascular tissues suggests the possibility of partial local metabolic conversion.[43,44] Within this framework, the present study was designed not to replicate the in vivo pharmacokinetic process, but rather to explore the potential direct effects of the parent form of clopidogrel on contractile and relaxation mechanisms in human LIMA segments. The short plasma half-life of the active thiol metabolite and the difficulty of stabilizing it under in vitro conditions further justify the methodological rationale of this approach.[45]

Clopidogrel has been shown to reduce inflammation and preserve endothelial NO synthase expression in ischemic coronary arteries of rabbits, supporting a NO-mediated mechanism in its vascular effects.[46-48] Pre-treatment with clopidogrel has also been reported to reduce vasoconstrictive responses to serotonin (5-HT), endothelin-1, and platelet-rich plasma/arachidonic acid mixtures in rat and rabbit aortic rings.[49] Similarly, Jakubowski et al[48] demonstrated a rapid and direct endothelial effect of clopidogrel, independent of its antiplatelet action, in isolated guinea pig hearts. In contrast, other studies have reported no significant inhibition of $P2Y_{12}$ receptor-mediated vasoconstriction in patients treated with clopidogrel,[25] and even high oral doses of clopidogrel failed to inhibit this response meaningfully.[50] Nevertheless, clopidogrel has been shown to improve endothelial function in patients with stable coronary artery disease,[51] and in hypertensive rat mesenteric arteries, it normalized PE-induced vascular contraction and restored impaired acetylcholine-induced relaxation.[47] However, it remains unclear whether these effects are exclusive to the mesenteric vasculature or extend to other vascular beds. Furthermore, it is not yet established whether clopidogrel prevents structural and functional alterations in affected vessels.

Moreover, it should be noted that 90% of the patients included in the present study were hypertensive, 40% were diabetic, and all were receiving acetylsalicylic acid therapy. Each of these comorbid conditions is known to exert substantial effects on vascular reactivity.[52-54] Despite this pronounced clinical heterogeneity and high-risk profile, the observation that clopidogrel significantly attenuated PE-induced contraction may be regarded as one of the major strengths of the study.

In the literature, a study employing a hypothesis similar to that of the present research reported that clopidogrel in combination with aspirin, or clopidogrel monotherapy, may be effective in maintaining high graft patency rates in the early postoperative period following CABG. Furthermore, the same study indicated that the clopidogrel + aspirin combination did not confer a significant advantage over clopidogrel monotherapy in this context.[55] In another study, it was suggested that clopidogrel use after CABG may not improve 1-year graft patency.[56]

In this context, these collective findings underscore the importance of considering and further investigating the potential effects of clopidogrel on vascular resistance. The discrepancies reported in the literature are likely attributable to structural and functional differences among the vascular beds examined. This study serves as a pioneering investigation by demonstrating, for the first time, the potential vascular effects of clopidogrel within the LIMA vascular bed.

Future research incorporating comparative evaluations of different antiplatelet agents and translational approaches supported by clinical vascular function assessments may enable the establishment of a more comprehensive pharmacodynamic profile of these agents.

Limitations of the Study and Conclusion

Our study provides a novel perspective by demonstrating that the LIMA vascular bed is responsive to clopidogrel. In LIMA rings treated with clopidogrel, vasoconstrictor responses to PE were reduced, while vasodilator responses to SNP were enhanced at low doses and suppressed at high doses. These findings support the notion that the effects of clopidogrel are not limited to its antithrombotic properties, but may also involve a modulatory role on vascular function. This is particularly important for maintaining graft patency following CABG and underscores the need to consider the potential local vascular effects of clopidogrel. However, a major limitation of our study is the lack of advanced in vitro analyses that could provide deeper mechanistic insights into the effects of clopidogrel. This shortcoming limits our ability to fully elucidate the cellular and molecular actions of the drug on vascular smooth muscle cells. In addition, due to the limited sample size, a formal subgroup analysis comparing vascular responses between diabetic and non-diabetic patients could not be performed. Nevertheless, at an observational level, clopidogrel appeared to attenuate PE-induced contraction in both groups in a comparable manner, a finding that warrants further investigation in larger cohorts. In future studies, the use of specific inhibitors targeting NO, prostanoid, or calcium signaling pathways may provide valuable insights into the detailed mechanisms underlying the vascular effects of clopidogrel. Moreover, since the vascular tissues in the present study were obtained immediately after CABG surgery, the viability and endothelial integrity of these segments were inherently limited. Therefore, to maintain experimental consistency and minimize confounding factors related to endothelial viability, the study focused on endothelium-independent relaxation responses, as previously described in the literature.[31] Nonetheless, evaluating acetylcholine-mediated endothelium-dependent relaxation could have contributed to a more comprehensive understanding of the underlying mechanisms. Expanding this research to larger populations and exploring different clopidogrel dosing regimens would undoubtedly enhance its scientific value. In this regard, the present study provides a foundational framework for future investigations aiming to elucidate the vascular pharmacodynamics of clopidogrel in greater depth.

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Fırat University (Approval No.: 11; Date: 26.10.2017).

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: E.K., I.M.O., and L.U. designed the study. All authors performed the experimental procedures. Z.D.O. performed the statistical analyses and wrote the final version of the manuscript. All authors read and approved the final version of the manuscript.

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

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