Modulation of Left Ventricular Dilation Remodeling With Epicardial Restraint Devices in Postmyocardial Infarction Heart Failure

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Myocardial infarction initiates progressive changes in the biology of the myocyte and nonmyocyte components of the myocardium, as well as the geometry of the left ventricle. Despite the use of evidence-based strategies to postmyocardial infarction, heart failure supervenes and is attended by an unacceptably high mortality rate. Given that left ventricular (LV) remodeling may contribute independently to disease progression, several innovative approaches have been designed to attenuate and reverse LV remodeling. This review discusses the emerging role of epicardial restraint devices in the treatment of postmyocardial cardiac remodeling.

Introduction

Heart failure is a progressive disorder that is initiated after an "index event" that either damages the heart muscle, with a resultant loss of functioning cardiac myocytes, or alternatively disrupts the ability of the myocardium to generate force, thereby preventing the heart from contracting normally. Following the index event, heart failure progresses as a result of overexpression of biologically active molecules that can exert toxic effects on the myocardium and circulation [1]. Evidence in support of this perspective derives from several experimental models which have shown that pathophysiologically relevant concentrations of neurohormones [2] or overexpression of single components of their signal transduction cascade sufficiently mimics some aspects of the heart failure phenotype [3,4]. Moreover, clinical studies have shown that antagonizing neurohormones including the use of angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists and β-blockers leads to improved survival in patients with heart failure [5–9]. However, despite the use of these evidence-based strategies to block neurohormonal activation, in the overwhelming majority of patients, heart failure will progress, leading to adverse outcomes. Although there are many potential explanations for this attenuation or loss of effectiveness of neurohormonal antagonism, one logical reason is that our current treatment strategies do not directly address the basic pathophysiologic mechanisms that drive disease progression in heart failure; that is, current practice guidelines primarily address the consequences of heart failure (ie, neurohormonal activation) rather than its causes. Although some investigators have viewed left ventricular (LV) remodeling simply as the end-organ response after years of exposure to the toxic effects of long-term neurohormonal stimulation, increasing evidence suggests that LV remodeling may represent an important mechanism for disease progression in heart failure and, therefore, a potential target for novel therapy [10].

LV Remodeling as a Mechanism for Disease Progression in Heart Failure

Natural history studies have shown that progressive LV remodeling is directly related to future deterioration in LV performance and a less favorable clinical course in patients with heart failure [2,11,12]. Importantly, the process of LV remodeling extends to and affects the biology of the cardiac myocyte, the volume of myocyte and nonmyocyte components of the myocardium, and the geometry and architecture of the LV chamber. Although each of these various components of the remodeling process may contribute importantly to the overall development and progression of heart failure, the reversibility of heart failure is determined by whether the changes that occur at

Table 1. Mechanical disadvantages created by left ventricular remodeling

Increased wall stress (afterload)
Afterload mismatch
Episodic subendocardial hypoperfusion
Increased oxygen use
Functional mitral regurgitation
Worsening hemodynamic overloading
Worsening activation of compensatory mechanisms
Activation of maladaptive gene expression
Activation of maladaptive signal transduction pathways

Table 2. Epicardial restraint devices for postmyocardial infarction remodeling

Regional restraint devices
Marlex mesh patch (infarct stiffening)*
Mersilene† mesh wrap (left ventricular wrap)
Passive restraint devices
Acorn CorCap‡
Paracor§
Active restraint devices
Myocor Coapsys¶
CardioClasp**
Quantitative ventricular restraint device

*Marlex (New Castle, DE)
†Ethicon (Somerville, NJ)
‡Acorn Cardiovascular (St. Paul, MN)
§Paracor Medical (Sunnyvale, CA)
¶Myocor (Maple Grove, MN)
**CardioClasp (Cincinnati, OH)

the level of the myocyte, the myocardium, the extracellular matrix, and the LV chamber are reversible. In this regard, changes that occur at the level of the myocyte and the LV chamber seem at least partially reversible in some experimental and clinical models [13–16].

Several changes that occur during the process of LV remodeling may contribute to worsening heart failure. Principal among these changes is the increase in LV wall stress that occurs during LV remodeling. Indeed, one of the first observations with respect to the abnormal geometry of remodeled ventricle was the consistent finding that the remodeled heart was not only larger but was also more spherical in shape [17]. The increase in LV size and resultant change in LV geometry from the normal prolate ellipse to a more spherical shape creates de novo mechanical burdens for the failing heart, most notably an increase in LV end-diastolic wall stress (Table 1). As the load on the ventricle at end-diastole contributes importantly to the afterload that the ventricle faces at the onset of systole, it follows that LV dilation itself will increase the work of the ventricle and hence the oxygen utilization. In addition to the increase in LV end-diastolic volume, LV wall thinning also occurs as the ventricle begins to remodel. The increase in wall thinning along with the increase in afterload created by LV dilation leads to a functional "afterload mismatch" that may further contribute to a decrease in forward cardiac output [2,18–21]. Moreover, the high end-diastolic wall stress might be expected to lead to episodic hypoperfusion of the subendocardium, with resultant worsening of LV function [2], as well as increased oxidative stress, with the resultant activation of families of genes that are sensitive to free radical generation (eg, tumor necrosis factor and interleukin-1β) [22–24].

Accordingly, several innovative approaches have been evaluated to address LV remodeling, including cardiomyoplasty, partial left ventriculectomy (Batista procedure), and the endoventricular circular patch plasty (Dor procedure) [25–28]. The suggestion that epicardial restraint might prevent or reverse LV remodeling arose from studies in patients who had undergone the dynamic cardiomyoplasty procedure, in which the latissimus dorsi muscle was wrapped around the heart to provide skeletal muscle augmentation of contractile function. Observations from these studies suggested that the beneficial effects of this procedure largely depended on the external girdling effect provided by the skeletal muscle wrap, as opposed to the systolic assistance provided by the skeletal muscle contraction, which gave rise to a new generation of devices aimed at preventing and reversing progressive LV remodeling and restoring LV shape by mechanical containment of the failing left ventricle [25]. Although these devices differ in terms of biomaterial, implantation technique, and distribution of strain, they all reduce LV wall stress, thereby counteracting many deleterious changes that occur during the process of LV remodeling (Table 2).

Epicardial Restraint in Post-MI Remodeling

Regional restraint devices

Early infarct expansion initiates adverse remodeling, leads to LV dilation, and portends a poor long-term outcome [29]. The effect of epicardial restraint on remodeling after myocardial infarction (MI) was examined in several preclinical studies. Kelley et al. [30] first demonstrated that preventing infarct expansion with a Marlex (New Castle, DE) mesh patch (referred to as "infarct stiffening") prevents a decline in cardiac function after induction of anteroapical MI in an ovine model of coronary ligation. The investigators sutured a patch of Marlex mesh, which is monofilament, knitted polypropylene mesh used for hernia repair, over the precise location of the anticipated anteroapical infarction (Fig. 1A). Mesh-treated animals had preservation of LV function and geometry compared with control animals, which developed large ventricular aneurysms, increasing LV dilation, and progressive deterioration in LV function. Using an ovine model of posterolateral MI, Moainie et. al. [31] showed that placement of Marlex mesh patch reduced

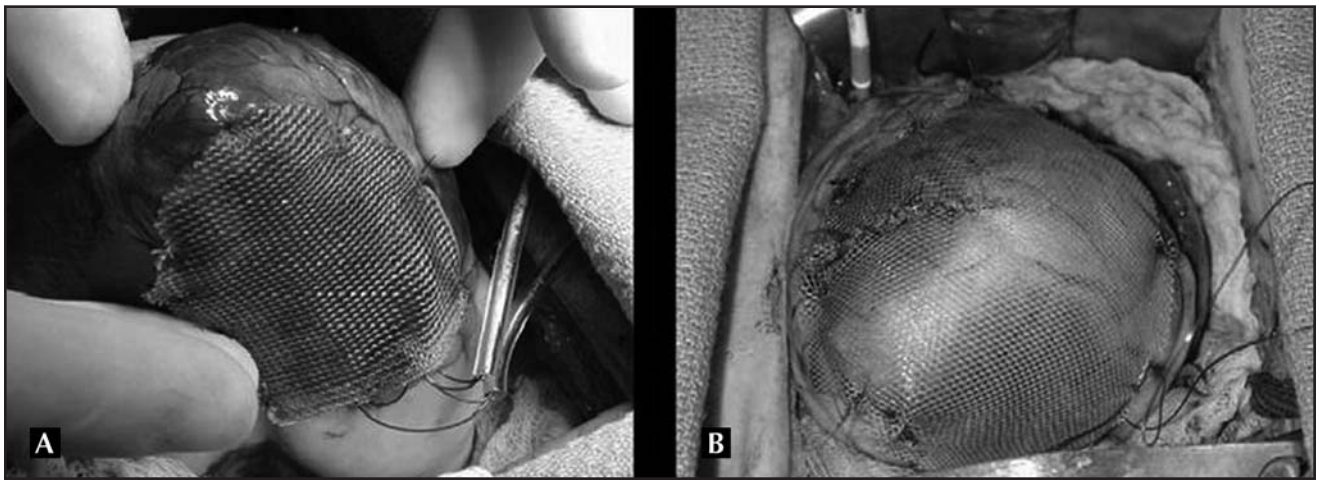

Figure 1. Regional epicardial restraint devices. **A**, Marlex mesh restraint patch over posterolateral infarct territory. **B**, Mersilene mesh ventricular wrap from the posterior view. Wrap extends from base to apex and from left anterior descending artery to posterior descending artery. (*From* Moainie et al. [31].)

ischemic mitral regurgitation (MR) 8 weeks after MI. LV end-diastolic and end-systolic volumes were also lower in mesh-treated animals; however, the differences were not significant. To determine the extent of ventricular restraint for optimum reverse remodeling, Enomoto et al. [32] compared the effects of infarct stiffening with a Marlex mesh patch over the anticipated infarct zone (infarct stiffening) with a Mersilene mesh (Ethicon; Somerville, NJ) that was wrapped over the exposed LV from the base to apex (LV Wrap) in an ovine model of acute coronary artery ligation (Fig. 1B). They demonstrated that early infarct stiffening did not significantly improve any aspect of remodeling in posterobasal infarcts, whereas an early LV Wrap significantly improved the remodeling process in both anteroapical and posterobasal infarctions, suggesting that infarct stiffening with a single patch may not be sufficient.

Passive restraint devices

CorCap Cardiac Support Device

The CorCap Cardiac Support Device (CSD; Acorn Cardiovascular, St. Paul, MN), the archetype of passive epicardial restraint devices, consists of a fabric mesh implantable device surgically positioned around the failing heart to provide diastolic support. Surgical implantation of CorCap CSD involves standard sternotomy and pericardiotomy under general anesthesia and takes about 2 hours if there is no concomitant (eg, mitral) procedure. If used as the sole therapy, the device can be implanted off-pump and the final fit is accomplished by the operating surgeon.

Mechanistic studies performed by Sabbah et al. [17] using a canine model of ischemic heart failure induced by sequential coronary microembolization provided great insight into molecular mechanisms of passive epicardial restraint on reverse remodeling and demonstrated that treatment with CorCap can attenuate and reverse various components of the remodeling process. At the myocyte level, treatment with CorCap resulted in significant reduction of myocyte hypertrophy, normalization of fetal gene expression, improvement of β-adrenergic reserve, and a significant increase in sarcoplasmic reticulum $Ca^{(2+)}$ adenosine triphosphate affinity for Ca^{2+} [16,33,34]. At the myocardial level, CorCap therapy reduced cardiomyocyte apoptosis in LV myocardium in dogs treated with the CorCap compared with untreated dogs, suggesting a possible mechanism to prevent LV wall thinning in the failing myocardium [35]. Moreover, reduction of volume fraction of interstitial fibrosis, preservation of the integrity of the collagen crosslinks between cardiomyocytes, and normalization of myocardial matrix metallopeptidase (MMP)-2 and MMP-9 expression were seen in CSD-treated animals [36,37]. At the level of the ventricle, 3 months of therapy with the CorCap significantly reduced LV end-systolic volume (LVESD), end-diastolic volume (LVEDD), and wall stress, and increased LV ejection fraction (LVEF) and end-systolic sphericity index compared with control animals [38]. Using an ovine model of MI induced by coronary ligation, investigators have demonstrated that placement of CorCap significantly reduced the area of LV akinesis that developed following acute MI. There authors speculated that the attenuation of regional wall stress with epicardial restraint result from mechanical support of the border zone in the infarct, which allows for improved recovery and decreased infarct size [39]. Using the same model of heart failure, CorCap therapy attenuated the increase in myocyte volume and improved β-adrenergic response in the cells isolated from the remote region of the MI [40]. Moreover, collagen content was increased in the peri-infarct region of the CorCap-treated myocardium, facilitating the wound healing response and maturation of the infarct scar as a potential mechanism to limit infarct expansion. CorCap placement in a sheep model of posterior MI attenuated transmural LV wall longitudinal-radial shear strain and reduced infarct-induced LV dilation and increased LV sphericity [41].

In conjunction with the preclinical work, the initial clinical experience with the CorCap CSD has been encouraging. In a safety study performed by Raman et al. [42] in six patients with ischemic cardiomyopathy undergoing concomitant coronary artery bypass grafting (CABG), placement of the CorCap resulted in a significant improvement in LVEDD, LVESD, LVEF, mitral regurgitation, and New York Heart Association (NYHA) functional class at 12 months. Repeat coronary angiography at 6 months postoperatively showed that all grafts were patent with no suggestion of the CorCap impinging on the anastomoses, grafts, or epicardial coronary arteries. A report of 48 patients who were implanted with CorCap in the initial safety and feasibility studies demonstrated preservation of coronary artery flow and no evidence of device-related adverse events or constrictive disease [43].

Based on these early preclinical and clinical studies, a randomized, prospective, controlled trial was conducted to evaluate the safety and efficacy of the CorCap CSD in patients with dilated cardiomyopathy [44••]. Given that only 10% of the patients in this study had ischemic heart disease, the results of this study will only be discussed briefly. The primary end point of the Acorn trial was a composite ordinal end point based on three outcomes: vital status, occurrence of a major cardiac procedure for progression of heart failure, and change in NYHA classification. The proportional odds ratio for the clinical composite score—the primary end point of the trial—showed that CSD-treated patients had a 73% likelihood of having a better clinical outcome relative to patients in the control arm (OR, 1.73 [95% CI, 1.07–2.79; $P = 0.02$]). Analysis of the individual components of the clinical composite score revealed a significant ($P < 0.01$) reduction in the need for major cardiac procedures in the CSD treatment arm compared with the control arm. Treatment with the CSD led to a significant decrease in LV end-diastolic ($P < 0.009$) and end-systolic volumes ($P < 0.017$), and a significant increase in the LV sphericity index ($P = 0.026$). The results of the long-term follow-up of the Acorn trial have been published recently [45]. During the entire follow-up, 41 deaths occurred in 152 patients in the control group (crude mortality rate, 27.0%) and 38 deaths in 148 patients (crude mortality rate, 25.7%) in the treatment group. This resulted in a relative risk reduction of 4.8% favoring the treatment group. Although this small difference was not statistically significant, there was no late adverse effect on mortality associated with implantation of the CorCap CSD. It bears emphasis that the Acorn study was not powered to detect a mortality benefit. Patients treated with the CorCap CSD had sustained long-term reductions in LV end-diastolic volume (average difference, 18.8 mL; $P = 0.005$) and LV end-systolic volume (average difference, 15.6 mL; $P = 0.013$) compared with the control group when followed for 3 years. Thus, the CSD appears to provide a sustained beneficial effect on remodeling when used independently, as well as incremental benefit when used with concomitant therapies such as mitral valve surgery, suggesting that this device could be used in selected patients after MI. However, at the time of this writing, the CorCap CSD is not approved by the US Food and Drug Administration for implantation in patients with ischemic heart disease or dilated cardiomyopathy.

Paracor Cardiac HeartNet Ventricular Support System

The Paracor HeartNet device (Paracor Medical; Sunnyvale, CA) is a nitinol mesh weave surgically implanted around the ventricle through a minimal access operation. Flexibility of the mesh across various sizes allows it to conform to heart size and shape without adjustment or suturing by the surgeon. The device is placed via a small invasive anterior thoracotomy under general anesthesia, without cardiopulmonary bypass, leaving the pericardium intact. If positioned correctly, the mesh covers both the left and right ventricle from base to apex and leaves the most apical part of the heart uncovered. The theoretical concepts underlying the Paracor device are similar to those of the Acorn CSD; however, the device has not been as extensively studied as the Acorn CSD.

The effect of the Paracor device on post-MI remodeling was evaluated in an ovine model of experimental MI. The device was placed immediately after ligation of the distal left anterior descending artery (LAD) and the second diagonal branch. Cardiac MRI and hemodynamic measurements were performed before and 6 weeks after MI. Animals treated with the Paracor HeartNet device received passive ventricular restraint concurrently with LV infarction, whereas the others served as controls. Treated animals had significantly less increases in the LV end-systolic and end-diastolic volume index compared with controls [46]. Moreover, the increase in LV mass was significantly lower in the Paracor group. Gross pathologic examination showed no device slippage, migration, epicardial coronary injury, or cardiac perforation. In a canine coronary embolization model, the Paracor device proved effective in reducing in LV volumes after embolization. After 8 weeks, the LV end-diastolic volume was significantly reduced by 15.5% ± 7.1% in animals treated the Paracor CSD compared with an increase of 8.1 ± 21.1% in control animals [47].

Recently, the results of a feasibility pilot trial with the Paracor HeartNet device have been reported [48•]. Given that only 20% of the patients in this study had ischemic heart disease, the results of this study will only be discussed briefly. Fifty-one patients (mean age, 52 y [range, 30–73 y]) with an EF of 35% or less, with an NYHA class II or III heart failure who were receiving optimal medical therapy for at least 3 months were enrolled at 15 sites (3 in Europe, 12 in the United States) to undergo implantation of the Paracor HeartNet device. After 6 months of follow up, significant improvement was seen in the 6-minute walk test ($P < 0.002$) and Minnesota Living with Heart Failure scores ($P < 0.002$). Echocardiographic parameters also demonstrated significant improvements in LVEDD (mean decrease, 3 mm; $P < 0.038$);

end-diastolic volume (mean decrease, 25.7 cm^3; $P < 0.025$); end-systolic volume (mean decrease, 23.5 cm^3; $P < 0.037$); and LV mass (mean decrease, 23.1 g; $P < 0.046$) at 6 months. Trend toward improvement was seen in the NYHA class at 3, 6, and 12 months, as well as a trend toward improvement in the maximal oxygen consumption by treadmill testing. Interestingly, as with the findings in the Acorn trial, major complications occurred with the patients with the largest ventricles. Currently, the Paracor HeartNet Ventricular Support System is being evaluated in the Prospective Evaluation of Elastic Restraint to Lessen the Effects of Heart Failure (PEERLESS-HF) trial, which will determine if the device benefits symptomatic stage C heart failure patients with an EF lower than 30% treated with optimal medical therapy. The primary outcome measures are peak maximum oxygen consumption and 6-minute walk at 6 months, quality of life at 6 months, and all-cause mortality at 12 months. The trial is expected to enroll 272 patients.

Active restraint devices

The Coapsys device

The Coapsys device (Myocor; Maple Grove, MN) consists of anterior and posterior epicardial-placed pads connected by a flexible, expanded polytetrafluoroethylene–coated, braided polyethylene subvalvular chord passing through the left ventricle. The device is sized by drawing the anterior and posterior pads together. The polyester-covered anterior pad is adjustable and is fixed to the subvalvular chord after sizing the device. The device can be implanted without the need for cardiopulmonary bypass or an open heart access method. The iCoapsys device (Myocor) has been developed to be implanted on a beating heart within a closed chest via a percutaneous subxiphoid approach.

Preclinical studies of the Coapsys device were performed in a canine model of dilated cardiomyopathy induced by rapid pacing. The results of these experiments indicated that placement of a Coapsys device significantly reduced MR by reducing the septal–lateral dimensions chronically at mitral annular level, as well as at midpapillary levels without any negative impact on the hemodynamic function [49,50]. The Treatment of Functional Mitral Regurgitation Without Atriotomy or Cardiopulmonary Bypass Clinical Evaluation (TRACE) trial was designed to study the effect of the Coapsys device on patients with ischemic MR (grade 2 or higher) who were referred for CABG. Mishra et. al. [51] reported on a subset of 11 patients from TRACE trial with Coapsys implantation with complete 12-month echocardiography follow-up. Researchers demonstrated that the degree of MR was significantly reduced, and that the NYHA functional class was improved significantly. In addition to a reduction in the degree of MR, implantation of the Coapsys along with CABG led to significant and progressive decrease in diastolic LV dimensions compared with CABG therapy alone [51]. The Coapsys device is currently being evaluated in the pivotal Randomized Evaluation of a Surgical Treatment for Off-pump Repair of the Mitral Valve (RESTOR-MV) trial. The ongoing (at the time of this writing) RESTOR-MV study is randomly assigning patients with coronary artery disease and functional MR to either receive an annuloplasty ring and CABG or Coapsys annuloplasty and CABG. The initial intraoperative results of the RESTOR-MV trial demonstrated significant reductions in the MR grade and ventricular dimensions at both the annular and subvalvular levels in patients who received the Coapsys annuloplasty [52].

The CardioClasp device

The CardioClasp device (CardioClasp; Cincinnati, OH) is a cardiac support device that uses two indenting bars to reshape the left ventricle as two widely communicating lobes of reduced radius. The rigid bars have a defined curvature similar to that of the heart. An adjustable tether connects the two pad-bar assemblies on either side of the left heart. The device, once implanted, was secured to the left heart by means of mechanical fixation. Once the device was fixed, the adjustment tool pulled the tether, shortening the distance between the anterior and posterior bars, thereby decreasing the LV anterior posterior (A-P) dimension. In a canine model of heart failure induced by rapid ventricular pacing, placement of CardioClasp has immediately reduced wall stress and significantly improved fractional area of contraction [53]. These effects were maintained up to 30 days [53]. However, use of the CardioClasp did not alter LV end-diastolic and peak pressure, LV dP/dt, or cardiac output. This device is no longer being actively pursued.

Quantitative ventricular restraint device

Currently available ventricular restraint devices do not allow for measurement or adjustment of the restraint level. Moreover, a standard for the wrap tightness exists and restraint is applied at the discretion of the surgeon. Once wrapped at the initial procedure, the restraint level (wrap tightness) could not be adjusted over time as the heart decreases in size as it undergoes reverse remodeling. Quantitative ventricular restraint (QVR) technique was developed to address these limitations. QVR device is a half-ellipsoidal balloon from polyurethane sheets (Polyzen; Apex, NC). Each balloon is composed of two 1-mm–thick layers. An access line is placed between the two layers to allow pressure measurement inside the balloon lumen and the addition or withdrawal of fluid. With this technique, the level of restraint can be quantified by measuring balloon luminal pressure at end-diastole and can be adjusted percutaneously by instilling or withdrawing fluid from the restraint balloon.

Ghanta et al. [54] have examined the immediate effects of QVR device in sheep after MI, using varying levels of epicardial restraint to identify the optimal restraint level. They demonstrated that a restraint level of 3 mm Hg can attenuate elevated LV end-diastolic transmural pressures with minimal adverse effects on the mean aortic pressure, suggesting that a restraint level of 3 mm Hg is the optimal

physiological restraint level for this ovine MI heart model. The authors then applied the QVR device after MI in the same ovine model for 2 months, at a restraint level of 3 mm Hg. At 2 months, QVR significantly decreased LV end-diastolic volume and improved EF from 27.3% to 43.5% ($P < 0.05$), whereas nontreated control animals had an increase of LV end-diastolic volume and a decrease of EF from 33.2% to 19.8% ($P < 0.005$) after MI. Interestingly, real-time measurement of balloon pressure throughout the study period revealed that the level of restraint (3 mm Hg) declined as the heart underwent reverse remodeling and decreased in size. Moreover, as the restraint level decreased, reverse remodeling slowed, as measured by the rate of change in LV end-diastolic volume over time.

Conclusions

Despite scarcity of clinical trials addressing the role of epicardial restraint therapy in the early post-MI period, accumulating evidence from preclinical studies suggests that epicardial restraint, applied either before or immediately after MI, has favorable effects on the LV remodeling process. Not yet established are timing, duration, and epicardial restraint level that must be applied after MI course to prevent adverse remodeling and facilitate myocardial recovery (ie, reverse remodeling). Advances in device technology combined with the development of minimally invasive approaches and tissue engineering may allow for the application of epicardial restraint devices to post-MI patients with ischemic cardiomyopathy in the foreseeable future.

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Disclosure

No potential conflicts of interest relevant to this article were reported.

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