Cardiovascular Effects of Incretin Therapy in Diabetes Care

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Abstract

Diabetes patients are at high risk for development of cardiovascular disease. The cardiovascular safety of antidiabetic medications is a concern. Incretin therapies, including glucagon-like peptide 1 receptor (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors, have recently been introduced to clinical practice and are widely used. Data from phase 2 and 3 trials and retrospective analyses of clinical databases have shown favorable changes in cardiovascular risk factors and outcomes. However, only a few prospective trials have been designed with cardiovascular outcomes as a primary end point. From current data, alogliptin and saxagliptin do not change cardiovascular risk in type 2 diabetes mellitus (T2DM) patients. Vildagliptin does not alter myocardial function in T2DM patients with systolic dysfunction. However, the possibility of an increase in clinical heart failure and worsened outcomes in patients with existing heart failure is suggested by current data. Clinicians need to follow patients on DPP-4 inhibitors carefully for this possibility until more prospective randomized controlled data are available.

Introduction

CARDIOVASCULAR DISEASE (CVD) IS A main cause of morbidity and mortality in diabetes patients.¹ Diabetes patients have an increased risk of atherosclerotic disease (including coronary artery disease, ischemic stroke, and peripheral vascular disease), congestive heart failure, and cardiovascular death.² Furthermore, because of the increasing prevalence of diabetes,³ the contribution of diabetes to the burden of CVD is increasing.⁴

Optimal glycemic management of diabetes patients with CVD or cardiovascular risk factors is unknown. Several large randomized controlled trials failed to show the benefits of intensive glucose control.^{5–7} Hypoglycemia, commonly accompanying intensive therapy, is strongly associated with increased cardiovascular events and mortality.⁸ Furthermore, some agents seem to be more harmful or beneficial than others. For example, some sulfonylureas may intensify ischemic damage because of interference with ischemic preconditioning.⁹ Although metformin¹⁰ and pioglitazone¹¹ have been associated with improved cardiovascular outcomes, a meta-analysis suggested that rosiglitazone could increase the risk of myocardial infarction and cardiovascular mortality.¹² Because of such concerns, the Food and Drug Administration (FDA) now requires preapproval or postapproval cardiovascular studies for all new antidiabetic medications.¹³

Incretins are gut-derived hormones that enhance insulin secretion in a glucose-dependent manner. There are two

known incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). The incretin effect is somewhat impaired in type 2 diabetes mellitus (T2DM) patients, partly because of resistance to the insulinotropic action of GIP and defective secretion of GLP-1. However, the response to GLP-1 is relatively preserved in T2DM patients. Therefore, GLP-1 has been a target of pharmacologic interventions. Endogenous GLP-1 is rapidly degraded from GLP-1(7–36)amide to GLP-1(9–36)amide by dipeptidyl peptidase-4 (DPP-4). To overcome this limitation, GLP-1 receptor agonists (GLP-1RA), which are resistant to DPP-4, and DPP-4 inhibitors, which prolong action of endogenous GLP-1, have been developed.^{14,15} Many GLP-1RAs and DPP-4 inhibitors are now used in clinical practice.

GLP-1 receptors exist in the vasculature as well as the myocardium.^{16,17} Many preclinical studies have shown beneficial effects of GLP-1 (Fig. 1) on endothelial function, survival of cardiomyocytes, myocardial metabolism and function, and protection against ischemic and reperfusion injury.^{17,18} In addition, DPP-4 inhibitors increase the levels of other substrates of DPP-4, including stromal cell–derived factor 1 α (SDF-1 α), which can recruit possibly regenerative progenitor/stem cells to the injured vasculature and myocardium.¹⁹ Therefore, possible direct beneficial effects combined with a lower risk of hypoglycemia due to their glucose-dependent insulinotropic action suggest that incretin therapies may be an ideal antidiabetic agent for

FIG. 1. Summary of proposed cardioprotective mechanisms of incretin therapies.

diabetes patients with or at risk of CVD. Phase 2 and 3 clinical trials showed cardiovascular safety and apparent beneficial effects of incretin therapy, but these parameters were outside of predefined primary and secondary end points.^{20–25} However, long-term cardiovascular outcomes of high-risk patients on incretin therapies are unknown.

In this review, we will discuss the cardiovascular effects reported in clinical studies. First, we will review the effects of incretin therapy on cardiovascular risk factors and cardiovascular outcomes on the basis of meta-analyses of phase 2 and phase 3 trials. Second, we will review small clinical trials that have examined the effects of a short course of incretin therapy on coronary artery disease and cardiomyopathy. Third, we will review large randomized controlled studies designed specifically to determine cardiovascular outcomes of incretin therapy in diabetes patients.

Effects on Cardiovascular Risk Factors

Many of the phase 2 and phase 3 trials aimed at evaluating the glucose-lowering effects of incretin therapies have also revealed favorable changes in cardiovascular risk factors in T2DM patients. GLP-1RAs have beneficial effects on body weight,^{20,23,26–29} blood pressure,^{23,26–30} and lipid profiles.^{23,26} DPP-4 inhibitors have weaker effects, and decreases in body weight, blood pressure, and lipids were inconsistent.^{20,24,31} Because weight loss improves variety of cardiovascular risk factors, it is not clear whether improvements in blood pressure or lipid profile are a direct effect or are secondary to weight loss. Outside of the setting of clinical trials, weight loss and improvements in blood pressure and lipid profiles also were found in a retrospective analysis of a large database of patients on incretin therapies.³²

Incretin therapy also reduces postprandial hypertriglyceridemia, which is recognized as a risk factor for CVD.³³ Recombinant GLP-1 (rGLP-1) infusion³⁴ and a single dose of exenatide³⁵ can decrease the postprandial excursion of plasma triglycerides. Similar findings have been observed after a short course of exenatide,³⁶ liraglutide,³⁷ or sitagliptin.^{36,38} Reduction of postprandial hypertriglyceridemia was not necessarily associated with delayed

gastric emptying.^{36,37} Notably, the effect of the DPP-4 inhibitor sitagliptin was smaller than that of exenatide.³⁶

Incretin therapy also has anti-inflammatory actions that may be of benefit for reduction of cardiovascular risk. Both exenatide³⁹ and sitagliptin⁴⁰ reduced inflammatory markers in plasma and circulating mononuclear cells after 12 weeks, as compared with placebo. However, exenatide and sitagliptin treatment resulted in improved glycemic control in these studies, and resolution of hyperglycemia-mediated inflammation may have contributed to the anti-inflammatory effects. Another study compared the anti-inflammatory effects of vildagliptin and sitagliptin.⁴¹ Both treatments had similar abilities to lower fasting and postprandial glucose as well as glycated hemoglobin (HbA1c). After 12 weeks, vildagliptin led to a greater decrease in oxidative stress and inflammatory markers in the plasma than sitagliptin. Notably, increases in GLP-1 levels and a reduction of mean amplitude of glycemic excursions were greater after vildagliptin than sitagliptin. Therefore, whether antioxidative and anti-inflammatory effects are mediated by GLP-1 or a secondary reduction of glycemic excursions is not clear.

In addition, incretin therapy improves subclinical markers of CVD. Infusion of rGLP-1 has been shown to increase endothelium-mediated vasodilatation in healthy individuals.⁴² Although a single dose of exenatide does not increase baseline endothelium-mediated vasodilatation, it did prevent endothelial dysfunction after ischemia–reperfusion injury in healthy individuals⁴³ and the postprandial endothelial dysfunction that is associated with hypertriglyceridemia in T2DM patients.⁴⁴ Liraglutide has been shown to decrease intima media thickness of the carotid artery (cIMT) independent of changes in glucose metabolism and weight.^{45,46} From data on DPP-4 inhibitors, vildagliptin decreased cIMT greater than sitagliptin,⁴⁷ but it is not clear whether this was due to higher GLP-1 levels or reduced glycemic excursions with vildagliptin or additional effects of DPP-4 inhibitors.⁴⁸

Neither exenatide⁴⁹ nor liraglutide⁵⁰ causes meaningful QT interval prolongation. However, a very small increase in heart rate (about 2 beats/min) was observed with use of GLP-1RAs.^{23,27–29} When acutely administered to healthy volunteers, rGLP-1 infusion did not change heart rate or

TABLE 1. CARDIOPROTECTIVE EFFECTS OF INCRETIN THERAPY IN SHORT CLINICAL TRIALS

<i>Author</i>	<i>Design</i>	<i>Subjects</i>	<i>Medications</i>	<i>Outcome</i>
Thrainsdottir et al. ⁷³ (2004)	No control	Diabetes and CHF	rGLP1 (<i>n</i> = 6) × 72 hr	Trend for improved systolic and diastolic function
Nikolaidis et al. ⁵⁸ (2004)	Nonrandomized, controlled	AMI with LV EF < 40% after successful PCI	rGLP1 (<i>n</i> = 10) vs. none (<i>n</i> = 11) × 72 hr	Improved global and regional LV function independent of diabetes
Sokos et al. ⁵⁹ (2006)	Nonrandomized, controlled	CHF	rGLP1 (<i>n</i> = 12) vs. none (<i>n</i> = 9) × 5 weeks	Improved LV function and functional capacity
Sokos et al. ⁶⁰ (2007)	Randomized controlled, double blinded	CAD with preserved LV function undergoing elective CABG	rGLP1 (<i>n</i> = 10) vs. saline (<i>n</i> = 10) starting 12 hr before CABG × 48 hr	No difference in hemodynamic recovery but less use of pharmacologic/mechanical intervention and fewer arrhythmias; better glycemic control with less hypoglycemia
Halbirk et al. ⁶¹ (2010)	Randomized crossover study, double blinded	Stable CHF, nondiabetic	rGLP1 vs. saline and albumin (total <i>n</i> = 15)	No difference in LV function or exercise capacity ↓
Read et al. ⁶² (2010)	Randomized crossover (blinded analysis of echocardiography)	CAD with preserved LV undergoing DSE	100 mg of sitagliptin vs. none (total <i>n</i> = 14) × 1 dose	Improved global and regional LV function, mitigated post-ischemic stunning
Read et al. ⁶³ (2011)	Randomized controlled, double blinded	CAD with preserved LV function undergoing elective PCI	rGLP1 (<i>n</i> = 10) vs. saline (<i>n</i> = 10) immediately after the first balloon occlusion	Reduced ischemic LV dysfunction, improved recovery of LV function, mitigated LV stunning
Read et al. ⁶⁴ (2012)	Randomized crossover (blinded analysis of echocardiography)	CAD with preserved LV function undergoing DSE	rGLP1 vs. saline starting 30 min before DSE (total <i>n</i> = 14)	Improved global, regional (including ischemic area) LV function, mitigated postischemic stunning
Lønborg et al. ⁶⁶ (2012)	Randomized controlled, double blinded	STEMI prior to PCI	Exenatide with albumin (<i>n</i> = 85) vs. saline and albumin (<i>n</i> = 87) starting 15 min before PCI × 6 hr	Increased myocardial salvage but no difference in infarct size and LV function or 30-day events; decreased infarct size if presented early on <i>post hoc</i> analysis ⁶⁸
Woo et al. ⁶⁷ (2013)	Randomized controlled (blinded analysis of echocardiography)	STEMI prior to PCI	Exenatide (<i>n</i> = 18) vs. saline (<i>n</i> = 40) × 5 min before PCI and next 2 days	Reduced infarct size and improved subclinical LV function
Rahmi et al. ⁶⁵ (2013)	Nonrandomized	Diabetes, CAD with preserved LV function	Repaglinide (<i>n</i> = 42) vs. Vildagliptin (<i>n</i> = 54)	Preserved ischemic preconditioning

CHF, congestive heart failure; rGLP-1, recombinant GLP-1; AMI, acute myocardial infarction; LV, left ventricle; EF, ejection fraction; CAD, coronary artery disease; CABG, coronary artery bypass graft; DSE, dobutamine stress echocardiography; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.

blood pressure,⁵¹ whereas exenatide induced vasodilatory and natriuretic effects associated with a mild increase in heart rate but without a change in blood pressure.⁵² The mechanism of the heart rate increase is poorly understood, as is its clinical significance. Nonetheless, this needs to be addressed because of the known association of heart rate and poorer cardiovascular outcomes. Increased heart rate is associated with increased risk of all-cause and cardiovascular mortality in coronary artery disease patients⁵³ as well as in the general population.⁵⁴ In patients with coronary artery disease and left ventricular dysfunction, even a heart rate of 70 beats/min was associated with worse cardiovascular outcomes.⁵⁵

Cardiovascular Outcomes in Studies Not Designed for Cardiovascular Outcomes

Meta-analyses of phase 2 and 3 trials showed an absence of increased cardiovascular risk and hinted at possible cardiovascular benefits of incretin therapy. Exenatide did not significantly reduce major cardiovascular events, defined as cardiovascular death, myocardial infarction, stroke, acute coronary syndrome, and revascularization on a patient-level pooled analysis of those followed for 12–52 weeks.²¹ Similarly, liraglutide did not significantly reduce cardiovascular death, myocardial infarction, and stroke from a pooled analysis of data from patients who were followed for 26–52 weeks.²² A trial-level meta-analysis combining exenatide and liraglutide with a mean follow-up of 42 weeks also showed no significant reduction of cardiovascular death, myocardial infarction, stroke, acute coronary syndrome, and heart failure; GLP-1RAs did significantly reduce these same end points when compared with placebo and pioglitazone.²³ Likewise, a meta-analysis of data from trials of DPP-4 inhibitors showed reduced cardiovascular death, myocardial infarction, stroke, acute coronary syndrome, and heart failure when followed for a mean of 44.1 weeks.²⁴ The effect of individual DPP-4 inhibitors, however, is not consistent among different studies.^{24,25}

The results of clinical trials are supported by a retrospective database analysis reflecting common clinical practice. Data were gleaned from a medical and pharmaceutical insurance claim database looking at exenatide prescriptions and cardiovascular events (myocardial infarct, ischemic stroke, coronary revascularization) based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Exenatide was associated with a significantly lower risk of

cardiovascular events⁵⁶ and heart failure,⁵⁷ but the association was not fully adjusted for cardiovascular risk factors due to the limitations of the claim data.

Notably, these trials were not designed to evaluate cardiovascular outcomes. There was no standardized diagnosis or adjudication of cardiovascular outcomes. Also, the follow-up period was short (most less than a year). The results of meta-analyses are further limited because of comparison with both placebo and active antidiabetes agents of heterogeneous cardiovascular risk. Therefore, cardiovascular efficacy and safety of incretin therapies need to be confirmed by appropriately designed trials.

Cardiovascular Effects in Short Clinical Studies

Preclinical studies have suggested that there are many potential beneficial effects of incretins on the cardiovascular system.¹⁸ To translate preclinical findings to humans, small clinical studies have been performed involving participants with coronary artery disease and congestive heart failure. These studies examined the effects of incretin therapy on myocardial function, postischemic stunning, ischemic preconditioning, and infarct size (Table 1).

Early nonrandomized studies showed improved left ventricular function after infusion of rGLP-1.^{58,59} However, subsequent double-blind, randomized controlled trials failed to show myocardial benefit of rGLP-1 in patients after coronary artery bypass surgery or patients with stable congestive heart failure.^{60,61} Instead, increases in heart rate and diastolic blood pressure and more hypoglycemic episodes were observed after rGLP-1 infusion, raising a safety concern for incretin therapy in congestive heart failure.⁶¹

In patients with stable coronary artery disease without left ventricular dysfunction, rGLP-1 and sitagliptin administration resulted in improved left ventricular function against ischemic stunning during stress testing or percutaneous coronary intervention.^{62–64} Furthermore, there were improvements in ischemic tolerance/threshold between two consecutive exercise tests. Ischemic preconditioning was better preserved after a short course of vildagliptin versus repaglinide in diabetic patients with multivessel coronary artery disease without left ventricular dysfunction.⁶⁵ In patients with ST elevation myocardial infarction, a short course of exenatide prior to revascularization improved myocardial salvage⁶⁶ and reduced infarct size and subclinical left ventricular function.⁶⁷

TABLE 2. RANDOMIZED CONTROLLED TRIALS OF INCRETIN THERAPY FOR CARDIOVASCULAR OUTCOMES

Medication	Completion	Enrollment	Comparator	Subjects	Primary CV end point
Alogliptin ⁶⁸ (EXAMINE)	2013	5380	Placebo	T2DM; ACS within 15–90 days	CV death, nonfatal MI, or nonfatal stroke
Saxagliptin ⁶⁹ (SAVOR-TIMI 53)	2013	16,492	Placebo	T2DM; >40 years old with atherosclerosis or male >55 years old/female >60 years old with CV risk factor(s)	CV death, nonfatal MI, or ischemic stroke
Vildagliptin ⁷² (VIVID)	2012	254	Placebo	T2DM; CHF NYHA I–III, LV EF <40%	LV function

CV, cardiovascular; T2DM, type 2 diabetes mellitus; ACS, acute coronary syndrome; MI, myocardial infarction; CHF, congestive heart failure; NYHA, New York Heart Association; LV, left ventricle; EF, ejection fraction.

TABLE 3. ONGOING RANDOMIZED CONTROLLED TRIALS OF INCRETIN THERAPY FOR CARDIOVASCULAR OUTCOMES

<i>Medication</i>	<i>Completion (estimated)</i>	<i>Enrollment (estimated)</i>	<i>Comparator</i>	<i>Subjects</i>	<i>Primary CV end point</i>
DPP-4 inhibitors					
Linagliptin (CAROLINA)	2018	6,000	Glimepiride	T2DM; CVD <i>or</i> end organ damage <i>or</i> >70 years old <i>or</i> ≥2 CV risk factors	CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA
Sitagliptin (TECOS)	2014	14,000	Placebo	T2DM with CVD	CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA
GLP-1RA					
Exenatide (EXSCEL)	2018	14,000	Placebo	T2DM	CV death, nonfatal MI, or nonfatal stroke
Dulaglutide (REWIND)	2019	9,622	Placebo	T2DM; >50 years old and clinical CVD <i>or</i> >55 years old and subclinical vascular disease <i>or</i> >60 years old and ≥2 CV risk factors	CV death, nonfatal MI, or nonfatal stroke
Liraglutide (LEADER)	2015	9,340	Placebo	T2DM; >50 years old and CVD or chronic renal failure or chronic heart failure <i>or</i> >60 years old and risk factor(s)	CV death, nonfatal MI, or nonfatal stroke
Lixasenatide (ELIXA)	2015	6,000	Placebo	T2DM; ACS within 180 days	CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA
Semaglutide (SUSTAIN 6)	2016	3,260	Placebo	T2DM; >50 years old and clinical CVD <i>or</i> >60 years old and subclinical CVD	CV death, nonfatal MI, or nonfatal stroke
Taspoglutide	2014	2,118	Placebo	T2DM; established CVD	CV composite endpoint

CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; T2DM, type 2 diabetes; CVD, cardiovascular disease; MI, myocardial infarction; ACS, acute coronary syndrome; UA, unstable angina; GLP-1RA, glucagon-like peptide 1 receptor agonist.

Although a small number of patients including both diabetics and nondiabetics were treated for a short duration in these studies, they do suggest that there may be cardioprotective effects of incretin therapies in the right setting.

Cardiovascular Effects in Randomized Controlled Trials Designed for Cardiovascular Outcomes

The cardiovascular effects of several GLP-1RAs and DPP-4 inhibitors are under investigation at present (Tables 2 and 3). The outcomes of trials involving alogliptin and saxagliptin have been published, and data from a trial involving vildagliptin were presented recently at an international meeting.

The EXAMINE study⁶⁸ was designed to prove noninferiority of alogliptin in T2DM patients with recent acute coronary syndrome within the past 15–90 days. A total of 5390 patients were randomized to either alogliptin (dose adjusted according to estimated glomerular filtration rate) or placebo and followed for up to 40 months with a median of 18 months. The primary end point—a composite of car-

diovascular death, nonfatal myocardial infarction, or nonfatal stroke—occurred in 11.3% of the alogliptin and 11.8% of the placebo group [hazard ratio (HR) 0.96, $P < 0.001$ for noninferiority at margin of HR 1.3, $P = 0.32$ for superiority]. The effect of alogliptin on each single component of the primary end point, the secondary end point (a composite of primary end point along with urgent revascularization for unstable angina), and death from any cause or from cardiovascular causes was not significantly different from placebo. In subgroup analysis, there was mild heterogeneity of the interaction with treatment group for former smokers, no use of metformin at baseline, and duration of diabetes greater than 10 years, as well as for those on insulin at baseline, those with moderate to severe renal impairment, and those residing in North America or Western Europe, Australia, New Zealand, and the Middle East (all favored placebo).

The SAVOR-TIMI 53⁶⁹ looked at noninferiority followed by superiority of saxagliptin versus placebo in T2DM patients with or at risk of CVD. There were 16,492 patients randomly assigned to saxagliptin (dose adjusted based on estimated glomerular filtration rate) or placebo and followed for a median of 2.1 years. The primary end point, a

composite of cardiovascular death, myocardial infarction, or ischemic stroke, occurred in 7.3% and 7.2%, respectively, in the saxagliptin and the placebo group (HR 1.00, $P < 0.001$ for noninferiority at margin of HR 1.3, $P = 0.99$ for superiority). The saxagliptin group had similar risk compared to the placebo group for each component of the primary end point, all-cause death, and hospitalization for unstable angina or coronary revascularization. There was a trend toward a higher risk of the primary end point if multiple risk factors were present versus established atherosclerosis, and a trend toward lower risk if the patients were on thiazolidinediones at baseline, a contradictory result compared to the subgroup analysis of the EXAMINE study. Unexpectedly, hospitalization for heart failure occurred more frequently in the saxagliptin group compared with the placebo group (3.5% vs. 2.8%, HR 1.27; 95% CI 1.07–1.51). Saxagliptin increased the risk of heart failure similarly regardless of baseline history of heart failure, which already was present in 12.8% of the subjects.⁷⁰ In contrast, alogliptin did not induce new-onset heart failure or worsen existing heart failure.⁷¹ Myocardial structural and functional details related to clinical heart failure, such as ejection fraction, ventricular hypertrophy, and diastolic dysfunction, are not available, and the mechanism behind the increased risk of heart failure with saxagliptin is unknown.

The VIVID study⁷² examined noninferiority of vildagliptin with regard to left ventricular ejection fraction in T2DM patients with congestive heart failure and left ventricular dysfunction. Patients ($n = 254$) were assigned to vildagliptin or placebo and followed for up to 52 weeks. Decreased left ventricular ejection fraction and cardiovascular events, including the worsening of heart failure, occurred similarly between the two groups. Brain natriuretic peptide, which also is degraded by DPP-4, actually decreased more in the vildagliptin group. However, vildagliptin increased left ventricular end diastolic diameter significantly, a finding usually associated with reduced systolic function, but may be suggestive of improved myocardial compliance. Furthermore, there was a nonsignificant increase in all-cause death ($n = 11$ vs. 4) and cardiovascular death ($n = 7$ vs. 4) for vildagliptin and placebo, respectively. The number of deaths was small so the clinical significance of this finding is not clear.

In summary, on the basis of current prospective data, DPP-4 inhibitors seem to be neither harmful nor beneficial for overall cardiovascular outcomes. However, at this juncture, there is some data supporting caution for the use of DPP-4 inhibitors in patients with congestive heart failure. In addition, there is possible heterogeneity in the effects of DPP-4 inhibitors on cardiovascular end points, depending on past medical history and baseline medications.

Conclusion

Incretin therapy is widely used because of antidiabetic efficacy and lower risk of hypoglycemia. Many phase 2 and 3 trials and retrospective analyses showed improvement in cardiovascular risk factors and outcomes. However, there are data only from a few prospective trials designed to examine cardiovascular outcomes that provide reliable information about cardiovascular effects of incretin therapy. At present, it appears that DPP-4 inhibitors may be used safely, but without improvement in cardiovascular outcomes in T2DM. DPP-4 inhibitors should be used cautiously in

patients with heart failure, and patients on DPP-4 inhibitors may need careful monitoring for heart failure. We await the prospective data from cardiovascular trials using GLP-1RAs. Further studies should give clearer answers regarding risks and benefits of incretin therapy in general and according to patient-specific characteristics.

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Author Disclosure Statement

The authors declare there is no conflict of interest.

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