Effects of metoclopramide on duodenal motility and flow events, glucose absorption, and incretin hormone release in response to intraduodenal glucose infusion

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Kuo P, Bellon M, Wishart J, Smout AJ, Holloway RH, Fraser RJ, Horowitz M, Jones KL, Rayner CK. Effects of metoclopramide on duodenal motility and flow events, glucose absorption, and incretin hormone release in response to intraduodenal glucose infusion. Am J Physiol Gastrointest Liver Physiol 299: G1326–G1333, 2010. First published September 9, 2010; doi:10.1152/ajpgi.00476.2009.—The contribution of small intestinal motor activity to nutrient absorption is poorly defined, partly because techniques for measuring small intestinal motor function are suboptimal. Several techniques are available for measuring motor activity in the small intestine, each with its own limitations. Manometry can provide information on the spatial and temporal arrangements of lumen-occlusive contractions, but the functional significance of manometric events in terms of chyme movement is often uncertain. Fluoroscopy generally considered the “gold standard” technique for measuring movement of intraluminal contents (16), but radiation exposure precludes prolonged use of this modality in humans. Intraluminal impedance monitoring represents an alternative method of monitoring movement of contents in the proximal small intestine. Typically, the passage of a fluid bolus results in a fall, whereas an air bolus results in an increase, in impedance (30). By detecting transient drops in impedance, recorded between serial pairs of electrodes situated along a catheter, flow patterns of intraluminal contents can be inferred. Despite the growing use of impedance recordings in the esophagus, particularly for the evaluation of gastroesophageal reflux events (40), impedance recording has not yet been adopted widely for use in the small intestine. A limited number of studies have used the technique to characterize antropyloroduodenal flow events in healthy humans (30, 35, 36) and patients with diabetic gastroparesis (29). When compared with manometry, impedance monitoring in humans shows higher concordance with fluoroscopy, for the assessment of chyme transport in the proximal small intestine (16).

“Prokinetic” drugs, commonly used to treat delayed gastric emptying, have variable effects on small intestinal motility, and little is known about their effects on glucose absorption. This is potentially important in clinical settings such as critical illness, where, in addition to disordered gastric emptying, nutrient absorption from the small intestine is frequently impaired (4). Metoclopramide has been shown to accelerate small intestinal transit and gastric emptying (6, 14, 31, 42), as measured by scintigraphy, but has uncertain effects on nutrient absorption (14); for example, one study reported that metoclopramide reduced small intestinal transit time but had little effect on the absorption of all macronutrients after the ingestion of a solid meal (14).
Exposure of the small intestine to glucose triggers the release of the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinoctopic polypeptide (GIP), from L and K cells, respectively, in the intestinal mucosa (26). K cells are located predominantly in the duodenum, whereas most L cells are situated more distally. The incretin hormones, which enhance glucose-induced insulin release from the pancreas, are important in the regulation of postprandial glycemia (27) and are of intense therapeutic interest with the development of long-acting GLP-1 analogs such as exenatide, for the treatment of type 2 diabetes. At present, there is little information about the impact of small intestinal flow events on incretin hormone secretion. Our recent study involving hyoscine butylbromide showed that the suppression of duodenal flow events by hyoscine was associated with delayed release of both GLP-1 and GIP, presumably reflecting slowing of the spread of glucose over the full length of GIP-bearing mucosa in the duodenum and proximal jejunum and postponing the arrival of glucose to the GLP-1-bearing mucosa in the more distal jejunum and ileum (3).

We hypothesized that metoclopramide would stimulate an increase in both pressure waves and flow events in the duodenum, with a corresponding increase in glucose absorption and incretin hormones.

MATERIALS AND METHODS

Subjects

Nine healthy volunteers were recruited by advertisement. No subject was taking medication known to affect gastrointestinal function. One male subject experienced agitation 5 min after receiving metoclopramide, and was withdrawn from the study, without requiring the administration of benztpine. Accordingly, eight subjects were included in the analysis (7 males and 1 female; mean age 29.8 ± 4.6 yr; mean body mass index 24.5 ± 0.9 kg/m²). The study protocol was approved by the Research Ethics Committee of the Royal Adelaide Hospital. Written, informed consent was obtained from each participant. Studies were performed in accordance to the Declaration of Helsinki.

Protocol

Each subject underwent two studies, separated by at least 3 days, in single-blinded, randomized order. Subjects attended the laboratory at 0900 after an overnight fast (12 h for solids, 10 h for liquids). A combined manometry and impedance catheter was inserted transnally in the stomach and advanced slowly in the duodenum with the combined manometry and impedance catheter was inserted transorally in the duodenum. TMPD, transmucosal potential difference; D1, first duodenal manometry channel; I1, first duodenal impedance electrode pair.

Manometric catheter was constantly perfused with degassed water and 0.9% saline (for the TMPD channels) to allow measurement of pressure waves at a rate of 0.15 ml/min in each channel.

Once the combined catheter was positioned correctly, a cannula was inserted in a forearm vein for the administration of metoclopramide or control and subsequent blood sampling. Fasting motility was observed until the onset of duodenal phase II activity. At this time (t = −5 min), 10 mg of metoclopramide hydrochloride (AstraZeneca, North Ryde, NSW, Australia), made up to 10 ml with 0.9% saline, or 10 ml 0.9% saline alone (as control), was infused intravenously as a bolus over 1 min. At t = 0 min, an intraduodenal infusion containing 45 g glucose and 111 kBq of 14C-labeled 3-O-methylglucose (3-[14C]OMG), made up to 200 ml with water, was given via the infusion channel in the manometry catheter over 60 min (i.e., 3 kcal/min and 3.3 ml/min) (t = 0–60 min). Manometry and impedance recording continued from t = 0 to 180 min.

Venous blood was sampled every 5 min from t = −5 to 60 min, and then at t = 70, 80, 90, 105, 120, 150, and 180 min, for measurement of blood glucose and plasma 3-[14C]OMG. Plasma insulin, GIP, and GLP-1 concentrations were measured on blood samples obtained every 10 min from t = 0–90 min and then at t = 105, 120, 150, and 180 min.

Measurements

Both the manometric and impedance signals were recorded at a sampling rate of 30 Hz (Insight stationary system; Sandhill Scientific) and stored on a hard disc for subsequent analysis.

Manometric analysis. Manometric data were analyzed in automated fashion using established software (3). The number of duodenal waves with amplitudes ≥10 mmHg (total number in all 6 duodenal channels/10 min) and the number of propagated sequences of duodenal waves (total number/10 min, each recorded in at least 2 channels) were analyzed, assuming a propagation velocity between 0.9 and 16 cm/s. The mean amplitudes of these waves were calculated as the average per 10 min across all six channels. Phase III-like activity was defined as pressure waves occurring at a frequency of 10–12 per minute, for ≥2 min.

Impedance analysis. Impedance recordings were analyzed by two independent observers (P. Kuo and C. K. Rayner) who were blinded
to the study conditions. A flow event was defined as a transient decrease in impedance of ≥12% from baseline in at least three sequential electrode pairs (i.e., ≥6 cm) (3) (Fig. 2). Flow events were classified as either antegrade or retrograde. The detection of flow events was compared between the two observers, and consensus was reached over discrepant observations.

**Blood glucose, plasma insulin, GIP, and GLP-1 concentrations.** Blood samples for measurement of plasma insulin, GIP, and GLP-1 concentrations were collected in ice-chilled tubes containing EDTA and 400 KIU aprotinin (Trasylol; Bayer Australia, Pymble, Australia) per liter of blood. Plasma was separated by centrifugation (1,500 g for 15 min, at 4°C) and stored at −70°C for subsequent analysis. Blood glucose concentrations were determined immediately using a portable glucometer (MediSense Optium; MediSense, Waltham, MA). Plasma total GLP-1 concentrations were measured using radioimmunoassay (RIA) (GLPIT-36HK; Linco Research, St. Charles, MO); the intra-assay coefficient of variation (CV) was 6.7% and interassay CV 7.8%, and the sensitivity was 3 pmol/l. Plasma GIP concentrations were measured by RIA; intra- and interassay CVs were both 15%, and the sensitivity was 2 pmol/l (46). Plasma insulin concentrations were measured by Enzyme-Linked Immunosorbant Assay (Diagnostics Systems Laboratories, Webster, TX); the intra-assay CV was 2.6%, interassay CV 6.2%, and sensitivity 0.26 mU/l.

**Plasma 3-14C|OMG activity.** 3-OMG is a glucose analog that is absorbed through the same mechanism as glucose but is not metabolized; plasma concentrations of 3-OMG are therefore used as an index of glucose absorption (3). Blood samples for plasma 3-[14C]OMG activity were collected in serum tubes, followed by centrifugation (1,500 g for 15 min, at 4°C) and plasma collection, and analyzed within 24 h. Results are expressed as disintegrations per minute (dpm) over the background count. We have validated this method of measuring 3-OMG absorption against chromatographic analysis of unlabeled 3-OMG concentrations in plasma (20).

**Statistical Analysis**

Data were evaluated by repeated-measures ANOVA with treatment and time as factors, with post hoc means comparisons for individual time points in the event of significant treatment-by-time interactions. Area under the curve was also calculated using the trapezoidal rule for time points in the event of significant treatment-by-time interactions.

The two observers’ independent analyses were concordant for the majority of flow events (63.2% on the metoclopramide day and 65.1% on the saline day), before reviewing the recordings together to achieve consensus.

There was a gradual decline in the number of both duodenal pressure waves and propagated pressure wave sequences over the 60 min of intraduodenal glucose infusion, on both study days. During this period, metoclopramide was associated with a greater number of duodenal pressure waves and propagated sequences than saline (treatment-by-time interaction with significant differences at the first 3 time points; \( P < 0.01 \) for both) (Fig. 3, A and B). Propagated sequences were almost all antegrade. The mean duodenal wave amplitude was not different between the two study days [25.4 ± 1.3 mmHg (metoclopramide) vs. 23.5 ± 2.0 mmHg (saline)]. There was a nonsignificant trend for more episodes of duodenal phase III-like activity during the entire study period of 180 min with metoclopramide (1.25 ± 0.27) compared with saline (0.63 ± 0.28) \( (P = 0.09) \).

**Duodenal Flow Events**

The two observers’ independent analyses were concordant for the majority of flow events (63.2% on the metoclopramide day and 65.1% on the saline day), before reviewing the recordings together to achieve consensus.

There was a gradual decrease in the number of flow events detected over the 60 min of intraduodenal glucose infusion on both study days. The number of duodenal flow events, expressed either as the total number over 60 min [31.9 ± 7.2 (metoclopramide) vs. 28.8 ± 7.6 (saline)] or as frequency of
events per 10 min over the same period, did not differ between the two study days, despite the impression of a greater number of flow events with metoclopramide during the first 10 min (Fig. 3C).

Blood Glucose Concentrations and Plasma 3-[14C]OMG Activity

Blood glucose concentrations rose rapidly during the intraduodenal glucose infusion on both days, reaching a peak at 50 min, followed by a rapid fall, returning to baseline values by 90 min. There was no difference in the area under the blood glucose curve between the two study days, during either the first 60 min [483.3 ± 12.7 mmol·l⁻¹·min⁻¹ (metoclopramide) vs. 488.5 ± 14.6 mmol·l⁻¹·min⁻¹ (saline); P = not significant (NS)] or during the entire study (0–180 min) [1,142.8 ± 33.3 mmol·l⁻¹·min⁻¹ (metoclopramide) vs. 1,152.6 ± 25.3 mmol·l⁻¹·min⁻¹ (saline); P = NS] (Fig. 4A).

Plasma 3-[14C]OMG activity also rose rapidly during the intraduodenal glucose infusion on both days, and continued to rise thereafter, reaching a peak at 80 min, followed by a gradual decline, and remained at much higher values than baseline at 180 min. There was no difference in the plasma...
3-[14C]OMG profile and area under the 3-[14C]OMG curve between the two study days, during either the first 60 min [4,247.2 ± 325.8 dpm/min (metoclopramide) vs. 3,640.3 ± 277.9 dpm/min (saline); P = NS], or during the entire study (0–180 min) [27,413.8 ± 2,123.3 dpm/min (metoclopramide) vs. 25,707.2 ± 1,514.6 dpm/min (saline); P = NS] (Fig. 4B).

Plasma Insulin, GIP, and GLP-1 Concentrations

Insulin. Plasma insulin concentrations rose rapidly after the intraduodenal glucose infusion on both days, reaching a peak at 50 min with metoclopramide, and 60 min with saline, followed by a rapid decrease, returning to baseline values by 120 min on both days. After commencement of the intraduodenal glucose infusion, metoclopramide was associated with lower concentrations of plasma insulin, compared with saline, as a treatment-by-time effect (P < 0.005). However, the area under the insulin curve did not differ significantly between the two study days, during either the first 60 min [5,423.4 ± 641.9 IU/min (metoclopramide) vs. 5,636.0 ± 933.7 IU/min (saline)], or during the entire study (0–180 min) [9,493.8 ± 940.4 IU/min (metoclopramide) vs. 12,054.3 ± 1,747.7 IU/min (saline); P = NS] (Fig. 5A).

GIP. Plasma GIP concentrations rose rapidly after the intraduodenal glucose infusion on both days, reaching a peak at 60 min, followed by a gradual decline, returning to baseline values by 180 min. Metoclopramide was associated with higher concentrations of plasma GIP, compared with saline, as a treatment-by-time effect (P < 0.001). During the first 60 min, the area under the GIP curve was higher with metoclopramide, compared with saline [3,950.8 ± 444.7 pmol·l⁻¹·min⁻¹ (metoclopramide) vs. 3,268.3 ± 232.3 pmol·l⁻¹·min⁻¹ (saline), P < 0.05], and a similar trend was observed over the entire study [8,605.2 ± 860.4 pmol·l⁻¹·min⁻¹ (metoclopramide) vs. 7,848.1 ± 539.3 pmol·l⁻¹·min⁻¹ (saline), P = 0.07] (Fig. 5B).

GLP-1. Plasma GLP-1 concentrations rose rapidly after the intraduodenal glucose infusion with metoclopramide, but more slowly with saline, with the peak concentration reached at 50 and 60 min, respectively, followed by a rapid decrease, returning to baseline values by 80 min on both days. Metoclopramide was associated with higher plasma GLP-1 concentrations, compared with saline, as a treatment-by-time effect (P < 0.01). A similar trend for area under the GLP-1 curve was also observed over the first 60 min [1,478.1 ± 290.9 pmol·l⁻¹·min⁻¹ (metoclopramide) vs. 1,060.4 ± 210.8 pmol·l⁻¹·min⁻¹ (saline); P = 0.12] but not over the entire study (0–180 min) [2,824.5 ± 517.1 pmol·l⁻¹·min⁻¹ (metoclopramide) vs. 2,483.5 ± 462.1 pmol·l⁻¹·min⁻¹ (saline); P = NS] (Fig. 5C).

Relationships Between Flow Events, Pressure Waves, Glucose Absorption, and Plasma Hormones

No correlation existed between the total number of flow events and either the total number of pressure waves or propagated pressure wave sequences during 60 min of intraduodenal glucose infusion.

There was no correlation between the total number of flow events during 60 min of intraduodenal glucose infusion and 1) the incremental blood glucose concentration at 60 min, 2) plasma 3-[14C]OMG activity at 60 min, 3) area under the plasma GIP curve (0–60 min), and 4) area under the plasma GLP-1 curve (0–60 min); however, there was a correlation between the total number of flow events during 60 min of
intraduodenal glucose infusion and area under the plasma insulin curve (0–60 min) \((r = 0.53, P < 0.05)\).

There was a good correlation between the total number of pressure waves during 60 min of intraduodenal glucose infusion and area under the curve \((0–60\) min\) of both GIP \((r = 0.59, P < 0.05)\) and GLP-1 \((r = 0.56, P < 0.05)\) and, similarly, between the total number of propagated sequences and area under the curve of GIP \((r = 0.46, P = 0.07)\) and GLP-1 \((r = 0.51, P < 0.05)\), but not with insulin, incremental blood glucose concentration at 60 min, and plasma 3-[\textsuperscript{14}C]OMG activity at 60 min.

**DISCUSSION**

In this study, the administration of metoclopramide stimulated duodenal pressure waves but did not alter the number of duodenal flow events, nor glucose absorption, in response to an intraduodenal glucose infusion. These findings are consistent with our previous observations using hyoscine butylbromide, where duodenal flow events were identified as a more important determinant of glucose absorption than pressure waves.

Multiple factors potentially influence the rate of glucose absorption from the gut, including the rate of gastric emptying, small intestinal transit, and the activity of the glucose transporters in the small intestinal mucosa. Their relative contributions in health and diabetes are currently poorly defined. The effect of gastric emptying on postprandial glycemia is well established. For example, slowing the rate of gastric emptying by administering morphine delays glucose absorption in healthy subjects and patients with type 2 diabetes (9), as indicated by changes in the postprandial glycemic excursions and area under the blood glucose curve; conversely, accelerating the rate of gastric emptying using erythromycin has the opposite effect. An impact of activity of the small intestinal glucose transporters is also apparent, at least in rodent models (18, 19). These transporters include the Na\textsuperscript{+}-glucose cotransporter SGLT-1 and the GLUT-2 transporter, with the former transporter SGLT-1 and the GLUT-2 transporter, with the former maintaining constant activity and exhibiting saturable absorptive capacity, whereas the expression of the latter on the apical membrane is upregulated within minutes of exposure to luminal glucose (19), increasing the glucose absorptive capacity of the GLUT-2 mechanism to three times that of SGLT-1 in a rodent model (18). In contrast, there is little information as to how patterns of small intestinal flow influence glucose absorption. In the current study, a combined manometry/impedance catheter was used to measure both pressure and impedance signals concurrently from the same region of the duodenum. The delivery of intraduodenal glucose (3.3 ml/min) and water/saline perfusate (1.05 ml/min) through the catheter would potentially influence the propensity for flow events to be detected, but this would be the case during gastric emptying of any orally administered drink, and our study design ensured that variations in the delivery of fluid to the small intestine between individuals, or due to the study drug, were avoided, while delivering glucose at a caloric rate similar to that of physiological gastric emptying (15). A single, intravenous dose of 10 mg metoclopramide was chosen, since this represents the usual dose used clinically as a prokinetic drug (21). A minimal impedance drop of 12% from baseline was adopted; although this differs from the figure of 50% widely used in the esophageal literature, it is based on the only fluoroscopically validated report of the technique in the small intestine (16).

For the measurement of bolus transit in the duodenum, impedance monitoring correlates more closely with the gold standard of fluoroscopy than does manometry (16). However, the length of our manometry/impedance assembly spanned only a segment of the duodenum. Sensitivity for the detection of flow events by impedance also decreases if there is incompletely cleared luminal content from a previous event (16). In addition, we only counted a flow event if impedance drops spanned at least three channels (6 cm); it is possible that shorter events, which cannot be distinguished from background “noise” by current techniques, may be of importance in the transport and absorption of duodenal contents. Thus it should be apparent that the impedance technique registers somewhat different phenomena from manometry and even from the analysis of propagated pressure sequences, many of which spread only very short distances (3 cm). This is likely to explain how our observations of the effects of metoclopramide on pressure waves and flow events could be discordant, an occurrence that we observed previously with hyoscine, which conversely suppressed flow events but not pressure waves (3).

Glucose absorption occurs predominantly in the proximal and midjejunum (2). It appears intuitive that an increased rate of transit of chyme in the duodenum will lead to increased transit in the jejunum, and will accordingly increase the rate of glucose absorption by spreading carbohydrate over a larger absorptive surface; but data to support this concept are limited. Our recent study showed that hyoscine butylbromide was associated with fewer duodenal flow events and delayed glucose absorption, compared with saline, despite having minimal impact on the frequency of duodenal pressure waves (3). This suggested that duodenal flow events, as determined by impedance analysis, correlate better with glucose absorption than the number of pressure waves and propagated sequences, perhaps by influencing the rate of transit to the jejunum. Such a concept is in keeping with observations made in the current study, where metoclopramide, despite inducing more duodenal pressure waves and propagated sequences, failed to generate more flow events, and subsequently had no impact on glucose absorption, as measured by plasma 3-[\textsuperscript{14}C]OMG activity. The marked disparity between the effects of metoclopramide on events detected by manometry and impedance further reinforces their complimentary characteristics and strengthens the rationale for using both techniques in combination.

The gradual decline in the number of duodenal pressure waves over time, during intraduodenal nutrient infusion, has been observed previously (3, 12), and in our study corresponded to a similar decline in the number of flow events; potential mechanisms include hyperglycemia, hyperinsulinemia, and increased secretion of incretin hormones, particularly GLP-1. Hyperglycemia, even in the physiological range (8 mmol/l), slows gastric emptying (8, 38), but its effect on small intestinal motor activity is uncertain. In the current study, blood glucose concentrations peaked at just below 10 mmol/l on both study days and may have influenced duodenal motor function. Hyperinsulinemia is perhaps less likely to play a role, since it has no effect on gastric motility (11). Conversely, exogenous GLP-1 slows gastric emptying (28), inhibits duodenal motility in healthy humans (37), and inhibits small intestinal motility and transit in rats (43, 44).
In our study, the lack of change in the number of flow events with metoclopramide contrasts with previous studies where metoclopramide increased small intestinal transit, as measured by scintigraphy (14, 31). However, this may be due to subject and methodological differences. For example, Holgate and Read (14) studied patients with terminal ileostomies who ingested a mixed solid meal, whereas, in the study by Prokop et al. (31), subjects ingested lactulose.

The relatively lesser impact of the frequency of duodenal pressure waves compared with flow events on glucose absorption, both in this and our previous study (3), contrasts with other reports that the frequency of small intestinal pressure waves does influence glucose absorption. In pigs, absorption of glucose (33) and xylitol (7) was increased when infused in the lumen during periods of increased motor activity (phases II and III of the migrating motor complex) when compared with periods of motor quiescence (phase I). In healthy humans, increased numbers of antegrade propagated pressure wave sequences, particularly those over short distances, were associated with increased absorption of a small intestinal glucose load, possibly by optimizing the surface area of mucosal contact with glucose (39). In type 1 diabetic patients, the small intestinal absorption of the glucose analog 3-OMG was also increased with increasing frequency of duodenal pressure waves and antegrade propagated sequences (32). In contrast, the amplitude of duodenal pressure waves has been reported not to affect 3-OMG absorption (39). Nevertheless, in none of these studies were duodenal flow events recorded directly. The lack of difference in glucose absorption observed in the current study, despite greater numbers of duodenal pressure waves and propagated sequences associated with metoclopramide, may be partly explained if glucose absorption in healthy volunteers is already optimal, making any further increase difficult to achieve. It would therefore be of interest to repeat the current study in patients with impaired baseline glucose absorption, such as those who are critically ill (10).

In our study, metoclopramide was associated with higher plasma GIP and GLP-1, but paradoxically lower plasma insulin concentrations, in response to intraduodenal glucose. The higher GIP and GLP-1 concentrations are likely to reflect the increased duodenal motility resulting in enhanced interactions between glucose and proximal small intestinal K and L cells, respectively, as evidenced by the good correlations found between the total number of pressure waves and propagated sequences, and area under the GIP and GLP-1 curves, during intraduodenal glucose infusion. Such enhanced mixing of luminal contents with the mucosa is likely to have occurred over relatively short distances, since there was no increase in flow events that could be detected by impedance. Exogenous dopamine has been consistently demonstrated to increase insulin secretion (5, 23, 24). However, the effect of the dopamine antagonist metoclopramide on insulin secretion is less consistent. During fasting, one study reported a reduction in serum insulin with the administration of intravenous metoclopramide (25), whereas other studies found metoclopramide by itself had no effect on insulin secretion but prevented the stimulation of insulin release by exogenous dopamine (23, 24). Whether metoclopramide attenuates glucose-induced secretion of insulin is, however, unknown but should be investigated further, since it is of particular relevance to patients with diabetes who are treated with metoclopramide for gastroparesis. The lack of difference in blood glucose concentrations between the two study days, despite lower insulin levels with metoclopramide, cannot be readily explained; there is currently no information regarding any potential effect of metoclopramide on peripheral glucose uptake or glucagon secretion, and glucagon concentrations were not measured in our study.

Understanding the determinants of small intestinal glucose absorption has considerable importance for the management of diabetes and is an area that has, to date, received inadequate attention. Previous studies have established the benefits of modulating the rate of gastric emptying as a therapeutic strategy to improve postprandial glycemia in type 2 diabetes; for example, this may well represent the major mechanism of action of GLP-1 analogs, such as exenatide (22). More studies are required to define the role of small intestinal chyme transport in glucose absorption, and how it affects incretin hormone release and postprandial glycemia, in health and diabetes.

GRANTS

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DISCLOSURES

The authors have no conflicts of interest to declare.

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