Prevention of Syncope Trial (POST)
A Randomized, Placebo-Controlled Study of Metoprolol in the Prevention of Vasovagal Syncope

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Background—Previous studies that assessed the effects of β-blockers in preventing vasovagal syncope provided mixed results. Our goal was to determine whether treatment with metoprolol reduces the risk of syncope in patients with vasovagal syncope.

Methods and Results—The multicenter Prevention of Syncope Trial (POST) was a randomized, placebo-controlled, double-blind, trial designed to assess the effects of metoprolol in vasovagal syncope over a 1-year treatment period. Two prespecified analyses included the relationships of age and initial tilt-test results to any benefit from metoprolol. All patients had >2 syncopal spells and a positive tilt test. Randomization was stratified according to ages <42 and ≥42 years. Patients received either metoprolol or matching placebo at highest-tolerated doses from 25 to 200 mg daily. The main outcome measure was the first recurrence of syncope. A total of 208 patients (mean age 42±18 years) with a median of 9 syncopal spells over a median of 11 years were randomized, 108 to receive metoprolol and 100 to the placebo group. There were 75 patients with ≥1 recurrence of syncope. The likelihood of recurrent syncope was not significantly different between groups. Neither the age of the patient nor the need for isoproterenol to produce a positive tilt test predicted subsequent significant benefit from metoprolol.

Conclusions—Metoprolol was not effective in preventing vasovagal syncope in the study population. (Circulation. 2006;113:1164-1170.)

Key Words: syncope ■ vasovagal ■ randomized trial ■ beta-blocker

Vasovagal syncope is a common problem that reduces quality of life1,2 and can be difficult to treat. Although β-adrenergic blockers are frequently prescribed to prevent syncope, clinical studies have provided conflicting results with regard to their effectiveness. Cox et al3 reported in an observational study that patients receiving β-blockers had a marked reduction in the likelihood of syncope, but we and others could not confirm this.4-5 Similarly, other small or short-duration randomized trials provided conflicting evidence about efficacy or effectiveness.5-9

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Part of the explanation for the discrepant conclusions about a β-blocker effect may relate to patient selection. Two nonrandomized studies suggested that the response to β-blockers may be age dependent.10,11 Metoprolol appeared to decrease recurrences in patients ≥42 years old, whereas those <42 years old had an increased frequency of syncope. The authors also suggested that patients who do not faint during passive drug-free tilt tests but do so during an isoproterenol infusion are more likely to benefit from β-blockers.10,11

We therefore performed a multicenter, double-blind, placebo-controlled, randomized clinical trial of metoprolol to assess its benefit in preventing vasovagal syncope. We also assessed the ability of tilt-test results and age to predict this potential benefit.

Methods

Patient Eligibility
The study12 was approved by ethics review committees in all centers. Patients were eligible if they had a positive response to any currently used tilt-test protocol and 1 or both of ≥3 lifetime syncopal spells preceding the tilt test13 (n=206), or ≥1 syncope recurrence within 6 months of a positive tilt test14 (n=2). All centers used passive head-up tilt with or without subsequent isoproterenol infusion if the first stage was negative. Patients were excluded if they had other...
causes of syncope, could not give informed consent, had important noncardiovascular or cardiovascular diseases, had a permanent pacemaker, had a pressing need for or contraindication to \( \beta \)-blockers, had a diagnosis of carotid sinus hypersensitivity, or had previously used \( \beta \)-blockers at a dose greater than the equivalent of metoprolol 25 mg BID for the purpose of suppressing the symptoms of vasovagal presyncope or syncope. In the isoproterenol substudy, 151 patients in 9 participating centers underwent a prespecified, uniform tilt-test protocol that involved a 30-minute head-up tilt at an angle of 80°, followed if necessary by an infusion of isoproterenol 30 mg \( \cdot \) kg\(^{-1}\) \( \cdot \) min\(^{-1}\) for 10 minutes at 80°. This substudy was initially planned to include all study centers, but due to local practices, several centers were unable to participate in it. Centers that participated in this substudy enrolled all their study subjects in it.

Counseling and Advice

All patients were given an overview of the causes of vasovagal syncope, were reassured about its overall benign outcome, were provided advice about increasing dietary salt and fluid intake unless contraindicated, and were coached on how to avoid situations that might provoke syncope and how to handle them if unavoidable. They received information about other treatment options and a perspective about the degree of evidence that supported their use.

Randomization and Study Treatment

Patients were stratified according to whether they were <42 or \( \geq \)42 years old and randomized separately within each center in blocks of 4. Patients were not stratified on tilt-test result because we were uncertain of the effect of incomplete center participation on subject numbers. They were allocated randomly and equally in a double-blinded fashion to receive metoprolol or a matching placebo from coded, numbered containers. The study coordinators started dosing with 50 mg of study drug twice daily with the intent to increase to 100 mg twice daily after 3 to 5 days if tolerated. Patients who were intolerant of the study medication had it reduced to a level that permitted remission of their side effects to a minimum dose of 25 mg/d. If intolerable symptoms persisted, the medication was discontinued and the patient released from the study. Patients received either active treatment or placebo for a prespecified period of 1 year. Unless unavoidable, patients were not permitted to receive permanent pacemakers, \( \alpha \)-adrenergic agonists or antagonists, antidepressants, scopolamine, theophylline, or fludrocortisone until after the primary outcome event. The use of nonstudy \( \beta \)-blockers was forbidden. Metoprolol was chosen for the study because the extant pathophysiological model involved \( \beta \)-, myocardial receptors; because \( \beta \)-selective blockers such as metoprolol and atenolol prevented syncope during isoproterenol tilt-table tests; and because metoprolol was reported in nonrandomized trials to prevent syncope in doses of 50 to 200 mg daily.

Power Calculations and Analysis

The Prevention of Syncope Trial (POST) was designed to have an 80% power to detect a 50% relative reduction in the risk of recurrent syncope from a rate of 40% in the control group to 20% in the treatment group. The composite published data in 1998 suggested a relative risk reduction by \( \beta \)-blockers of the likelihood of syncope of 70%. The entry criteria assumed an average risk of syncope in the control population of 40% in the first year of follow-up. A study population of 182 patients with 1 year of follow-up was increased to 208 to allow for anticipated dropout. A study population of 182 patients with 1 year of follow-up was increased to 208 to allow for anticipated dropout. Planned interim analyses were performed by a blinded data safety and monitoring committee when 33% and 67% of the total patient enrollment occurred, with the intention of stopping the study if the analysis reached a \( P < 0.001 \) for benefit or \( P < 0.01 \) for harm. The overall experimental type I error (\( \alpha \)) was maintained at 5% by using the O’Brien-Fleming design\(^{13} \) for a total of 3 tests with 2-sided significance levels of 0.0006, 0.0151, and 0.0472 to detect benefit. In addition, for safety, it was agreed to stop the trial if metoprolol appeared to adversely affect the outcome at \( P < 0.01 \).

Analysis

The University of Calgary Syncope Clinic coordinated the trial and managed data storage and analysis. The primary analysis was on intention-to-treat. In the intention-to-treat analysis, patients who fainted while taking study medication, discontinued their allocated treatment, dropped out of the study, or were withdrawn by their physician were considered to have treatment failures at that time. The timing of the first recurrence of syncope was used because it correlates well with the frequency of syncope, which in turn correlates with the diminution of quality of life in syncope patients.\(^{2} \)

The verification of syncope within 1 week was done by recording the nature of the syncopal spell, by collateral history from bystander witnesses, and by examination of the patient for signs of physical trauma such as abrasions, contusions, and fractures. Outcomes were adjudicated by a blinded outcomes adjudication committee. In a second, on-treatment analysis, the first faint while the subject was taking study medication was the primary outcome, and dropouts and withdrawals were censored. Presyncope was measured with a questionnaire that captured presyncope frequency (spells per day), presyncope duration (minutes), and presyncope intensity (scale of 1 to 10).

Statistical Methods

All reported levels of significance are 2 sided. Differences between variables were examined with either the Fisher exact test for categorical variables or a \( t \) test or nonparametric analysis for continuous variables. The times to treatment failure for both the intention-to-treat and on-treatment analyses were depicted with the Kaplan-Meier estimate of the survival function. Baseline event rates differed markedly by centers, and therefore, we performed secondary stratified analyses to control for the confounding due to the different baseline rates. Differences between the survival curves were tested with both unstratified and stratified log-rank statistics, as appropriate. When the survivor functions crossed, we used the Fisher exact test to compare the simple proportions. A prespecified stratified analysis was done for patients <42 years and \( \geq 42 \) years. In a subset of 151 patients (see above), we assessed the predictive effect of the requirement of isoproterenol for a positive baseline tilt test on subsequent benefit from metoprolol. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Patient Characteristics

There were 337 patients who met the inclusion criteria and had no exclusion criteria. Between October 1998 and April 2003, we randomized 208 consenting patients from 14 university hospitals in Canada, Columbia, Germany, the United States, and Australia (Table 1). The mean age was 42 ± 18 years, and 134 (64%) were women. Before randomization, these patients had experienced a median of 9 syncope spells (interquartile range [IQR] 5 to 20) over a median of 11 years (IQR 3 to 24), with a median frequency of 1.2 (IQR 0.5 to 4.0) syncopal spells per year. They had had a median of 3 syncopal spells in the year before randomization (IQR 1 to 6). Twenty-six patients had suffered physical trauma due to syncope. There were few patients with comorbidities, and only a minority of patients had received prior medical therapy for syncope. The proportion of patients with positive drug-free tilt tests was 44%.

Study Participation and Compliance

With Medication

The average dose of study medications at the time of first syncopal spell was similar in the metoprolol and placebo
Females, n 66 68
Patients with comorbidities, n

TABLE 1. Baseline Characteristics of Study Populations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Metoprolol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. randomized (sample size)</td>
<td>108</td>
<td>100</td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>43±18</td>
<td>41±18</td>
</tr>
<tr>
<td>Syncope history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime No. of spells, median (IQR)</td>
<td>8 (4–20)</td>
<td>9 (5–20)</td>
</tr>
<tr>
<td>No. of spells in previous year, median (IQR)</td>
<td>3 (2–5)</td>
<td>3 (1–6)</td>
</tr>
<tr>
<td>Duration of symptoms, y, median (IQR)</td>
<td>125 (3.3–30.1)</td>
<td>101.1 (3.2–20.3)</td>
</tr>
<tr>
<td>Syncope frequency, spells/year, median (IQR)</td>
<td>1.2 (0.3–3.9)</td>
<td>1.2 (0.6–4.4)</td>
</tr>
<tr>
<td>Trauma due to syncope, n</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Patients with comorbidities, n</td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>5</td>
<td>3</td>
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<tr>
<td>Non–insulin-dependent diabetes</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Pulmonary disease</td>
<td>0</td>
<td>4</td>
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<tr>
<td>Other</td>
<td>38</td>
<td>28</td>
</tr>
<tr>
<td>Provocative factors (≥25% spells), n</td>
<td></td>
<td></td>
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<tr>
<td>Emotional stress</td>
<td>57</td>
<td>57</td>
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<tr>
<td>Physical pain</td>
<td>26</td>
<td>35</td>
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<tr>
<td>Venipuncture</td>
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<td>22</td>
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<tr>
<td>Fatigue</td>
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<td>56</td>
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<tr>
<td>Exercise</td>
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<td>39</td>
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<tr>
<td>Warm environment</td>
<td>59</td>
<td>66</td>
</tr>
<tr>
<td>Previous medical therapy for syncope, n</td>
<td>2</td>
<td>5</td>
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<tr>
<td>Fluorocortisone</td>
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<td></td>
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<tr>
<td>Midodrine</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Serotonin reuptake inhibitor</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Baseline positive tilt test, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive drug-free test</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>Positive isoproterenol tilt test</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>Supine blood pressure, mm Hg</td>
<td>129±21</td>
<td>123±18</td>
</tr>
<tr>
<td>Supine heart rate, bpm</td>
<td>70±11</td>
<td>72±11</td>
</tr>
</tbody>
</table>

The significance of any differences between randomization arms is not reported, in accordance with CONSORT guidelines.6

arms (122±61 versus 128±51 mg/d, respectively; P=0.54; Table 2). The doses of study medication at the time of the termination of subject participation in the study were lower in the metoprolol arm than in the placebo arm (118±62 versus 139±57 mg/d, P=0.012; Table 2). Only 3 subjects took either fluorocortisone or midodrine as concomitant medications. The proportion of subjects taking serotonin-specific reuptake inhibitors was 11% in each study arm.

Not all patients completed the study: 24 patients in the metoprolol group and 22 in the placebo group withdrew from the study before fainting or the end of the prespecified observation period (Figure 1; Table 2). The reasons for premature termination in the study by patients in the placebo group were fatigue (5), presyncope (2), and nausea and depression (1 each). The reasons for premature termination in the study by patients in the metoprolol group were fatigue (5), presyncope (3), insomnia (2), and depression and edema (1 each). In the metoprolol group, there were no significant differences between patients who withdrew before a syncope spell or study outcome and those who completed the study in age (mean 41 versus 44 years, P=0.39), duration of syncope history (mean 16 versus 20 years, P=0.36), or number of historical syncope spells (median 8 versus 10, P=0.38). In the placebo group, there were no significant differences between patients who withdrew before a syncope spell or study outcome and those who completed the study in age (mean 43 versus 40 years, P=0.89) or number of historical syncope spells (median 12 versus 16 years, P=0.09). Patients who withdrew prematurely from the placebo group had fewer historical syncope spells (median 6 versus 12, P=0.0035).

Effect of Metoprolol in Total Population

In the intention-to-treat analysis, there were 63 of 108 subjects with treatment failure while taking metoprolol (39 with syncope and 24 who withdrew from the study) compared with 58 of 100 with treatment failure (36 with syncope and 22 withdrawals) while taking placebo (P=0.87). In the on-treatment analysis, the numbers of subjects with syncope were 38 of 107 with metoprolol and 35 of 97 with placebo (P=0.99). This is depicted in the survival curves in Figure 2. In the intent-to-treat analysis, the hazard ratio for patients taking metoprolol compared with those taking placebo was 0.89 (95% CI 0.63 to 1.25, P=0.49) for the unstratified analysis and 0.99 (95% CI 0.69 to 1.43, P=0.97) when the analysis was stratified by center. In the on-treatment analysis, the hazard ratio for patients taking metoprolol compared with those taking placebo was 0.94 (95% CI 0.60 to 1.49, P=0.80) for the unstratified analysis and 1.00 (95% CI 0.62 to 1.62, P=0.99) in the stratified analysis. Therefore, treatment with metoprolol did not benefit the population as a whole.

Predictive Accuracy of Tilt Tests

A subset of 151 patients participated in a substudy to assess whether the need for isoproterenol to produce a positive response would predict a subsequent clinical benefit from metoprolol. Figure 3 shows that baseline tilt-test conditions did not predict subsequent benefit from metoprolol for the on-treatment analysis. Similarly, outcome-free survival could
not be predicted by tilt-test conditions in the intent-to-treat analysis. Because the survivor functions crossed, we performed Fisher exact analyses. In the intent-to-treat analysis of subjects who had a positive drug-free tilt test, the number with treatment failure (syncope or withdrawal from the study) was 28 of 48 taking metoprolol and 27 of 45 taking placebo ($P=1.00$). In a similar analysis of subjects who had a positive isoproterenol tilt test, the number with treatment failure was 20 of 34 taking metoprolol and 17 of 26 taking placebo ($P=0.84$). In the on-treatment analysis of subjects who had a positive drug-free tilt test, the number with syncope was 18 of 45 taking metoprolol and 13 of 42 taking placebo ($P=0.69$). In a similar analysis of subjects who had a positive isoproterenol tilt test, the number with syncope was 13 of 34 taking metoprolol and 11 of 26 taking placebo ($P=1.00$). Stratified analyses did not detect any significant predictive effects. Therefore, baseline tilt-test conditions did not predict clinical benefit from metoprolol.

**Effect of Age**

In the intent-to-treat analysis of subjects aged $<42$ years, the number with treatment failure (syncope or withdrawal from the study) was 40 of 57 taking metoprolol and 36 of 57 taking placebo ($P=0.55$). In a similar analysis of subjects aged $\geq 42$ years, the number with treatment failure was 25 of 51 taking metoprolol and 27 of 43 taking placebo ($P=0.21$). In the on-treatment analysis of subjects aged $<42$ years, the number with syncope was 22 of 57 taking metoprolol and 20 of 55 taking placebo ($P=0.85$). In a similar analysis of subjects aged $\geq 42$ years, the number with syncope was 16 of 50 taking metoprolol and 15 of 42 taking placebo ($P=0.83$).

Figure 3 shows on-treatment survival analysis of the effect of age on syncope or withdrawal from the study. For patients aged $<42$ years, the hazard ratio for those taking metoprolol compared with placebo was $1.22$ (95% CI 0.66 to 2.24, $P=0.52$), and for patients aged $\geq 42$ years, the hazard ratio for those taking metoprolol compared with placebo was 0.69 (95% CI 0.34 to 1.39, $P=0.30$). In the intent-to-treat analy-
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In this randomized, double-blind, placebo-controlled clinical trial, we demonstrated that metoprolol does not benefit patients with vasovagal syncope as a group. We were not able to demonstrate that age influenced the effect of treatment. Furthermore, the need for isoproterenol to induce vasovagal syncope in the baseline tilt test does not predict a favorable response to the drug.

Previous clinical studies provided conflicting results about the effectiveness of β-blockade in vasovagal syncope. Cox et al. gave a variety of β-blockers or no treatment in a nonrandomized trial to 137 syncope patients with recurrent syncope and a positive tilt test. After 28±11 months, the proportion of patients with a recurrence was significantly lower in persistently treated patients than in the partially or completely untreated patients. We studied a cohort of 153 syncope patients with positive tilt tests and a historical median of 7 syncopal spells. The actuarial probability of remaining free of syncope after 1 year was the same in both the treated and control subjects. Alegria et al. also observed the apparent inefficacy of β-blockers in a similar observational study. Mahanonda et al. randomized 42 patients to treatment with atenolol or placebo for 1 month. Fully 71% of patients receiving atenolol and only 29% of patients receiving placebo reported feeling better. Patients receiving atenolol reported fewer combined presyncope and syncopal spells. Three recent, small, randomized studies (at least 1 of which was unblinded) of 30 to 56 patients each provided conflicting evidence for benefit from β-blockers. In fact, Flevari et al. reported in 2002 that patients in both active and control arms improved similarly, in agreement with the present findings. Their observed improvement presumably was a placebo effect. Therefore, the potential benefit of β-blockers remained uncertain, because studies reported to date were either observational or underpowered to detect even a 50% relative risk reduction.

**Impact on Presyncope**

There was no significant difference between patients taking metoprolol and placebo in median intensity of spells (3.46 [IQR 2.56 to 4.49] versus 3.75 [IQR 3.15 to 5.01], respectively; P=0.30). There was no significant difference between patients taking metoprolol and placebo in median duration of spells (6.8 minutes [IQR 2.3 to 71.3 minutes] versus 15.0 minutes [IQR 4.5 to 25.0 minutes], respectively; P=0.87). There was no significant difference between patients taking metoprolol and placebo in median frequency of spells (1.1/d [IQR 1 to 1.76] versus 1.1/d [IQR 1 to 1.32], respectively; P=0.35).

**Discussion**

In this randomized, double-blind, placebo-controlled clinical trial, we demonstrated that metoprolol does not benefit...
Clinical Implications
Proven, effective treatments for vasovagal syncope remain elusive. Increased salt and fluid intake is commonly advised, but this strategy has not been validated by clinical trials.17 Counterpressure maneuvers are effective in preventing syncope during tilt tests but have not been reported to be more effective than placebo in clinical situations.18,19 Fludrocortisone has not been studied in adults in a randomized clinical trial.20–21 Midodrine was effective in 3 small studies, but its use is limited by side effects, including supine hypertension.22–24 Paroxetine was effective in small, randomized clinical trials.25 Permanent pacing is unlikely to be effective in more than a small minority of patients.26 The results of the present study disappointingly add metoprolol to the list of generally ineffective treatments for vasovagal syncope.

Study Limitations
We used metoprolol, which is both hydrophilic and β1 selective, and it is possible that either a more hydrophobic or nonselective β-blocker would have been more effective. There is evidence that this may be so, at least for the effect of β-blockers in preventing syncope in tilt-table tests.27 Another possible limitation is that we included only patients who had positive tilt tests. Although this provided internal validity by restricting patient entry to a fairly homogeneous group, it does raise the issue of the diagnostic accuracy of tilt tests. Their usefulness has not been tested adequately in “gold standard” groups; a plethora of protocols has detected patient populations that do not overlap completely; and patients with negative and positive tilt tests have similar histories and outcomes.28–30 Therefore, although the test is widely accepted, and was used in this study, there are concerns about its external validity and generalizability. Finally, the inverse correlation between the time of first syncope recurrence was noted in observational studies and may not be true for randomized studies, in which patients have an expectation of some form of treatment. Indeed, the true end points that are needed are quality of life and syncope frequency.

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Disclosures
None.

References


### CLINICAL PERSPECTIVE

Reflex-mediated vasovagal syncope is very common. Many patients’ conditions can be managed with education about the syndrome, avoidance of provocative factors, and attention to adequate hydration, but frequent episodes persist in some patients. A role for β-adrenergic stimulation in initiating the reflex is supported by studies of β-agonists and antagonists on vasovagal syncope provoked by tilt testing. Consequently, β-adrenergic blockade was one of the first pharmacological therapies proposed to prevent recurrences, but previous trials have provided mixed results. Accordingly, we performed a randomized, placebo-controlled trial to determine whether chronic therapy with oral metoprolol prevented recurrent syncope in patients followed up for up to 1 year. Disappointingly, there was no evidence of benefit from metoprolol. Even the need for isoproterenol to provoke syncope during tilt testing and age of the patient did not identify subgroups that benefited from β-blockade. This study has 2 major implications. First, metoprolol—and possibly other β-adrenergic blockers—has no role as first-line therapy in the large majority of patients with vasovagal syncope. Second, the role of β-adrenergic stimulation in the physiology of vasovagal syncope warrants reevaluation.
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