Pacemaker Therapy for Prevention of Syncope in Patients With Recurrent Severe Vasovagal Syncope
Second Vasovagal Pacemaker Study (VPS II): A Randomized Trial

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Vasovagal Syncope, also known as neurally mediated syncope, is a common problem for which no highly effective pharmacological treatments are available. Because vasovagal syncope episodes are often associated with bradycardia, pacemakers have been proposed as a potential treatment. After some uncontrolled follow-up studies reported a benefit,1,2,3 small randomized controlled trials of pacemaker therapy were performed.3,4 All 3 trials reported a reduction in syncope recurrence with pacing. However, treatment in all 3 studies was not blinded, such that patients and their physicians knew whether the patient had received a pacemaker. It is possible that the reported benefit of pacemaker therapy was due in part to a psychological or emotional effect related to receiving a device by means of an

Context Three previous small randomized trials have reported that pacemaker therapy is beneficial for patients with severe recurrent vasovagal syncope. However, because these trials were not double blind, they may have been biased in their assessment of outcomes and had a placebo effect of surgery.

Objective To determine if pacing therapy reduces the risk of syncope in patients with vasovagal syncope.

Design, Setting, and Patients A randomized double-blind trial of pacemaker therapy in outpatients referred to syncope specialists at 15 centers from September 1998 to April 2002. In the year prior to randomization, patients had had a median of 4 episodes of syncope. Patients were followed up for up to 6 months.

Intervention After implantation of a dual chamber pacemaker, 100 patients were randomly assigned to receive dual-chamber pacing (DDD) with rate drop response or to have only sensing without pacing (ODO).

Main Outcome Measure Time to first recurrence of syncope.

Results No patients were lost to follow-up. Of the 52 patients randomized to ODO, 22 (42%) had recurrent syncope within 6 months compared with 16 (33%) of 48 patients in the DDD group. The cumulative risk of syncope at 6 months was 40% (95% confidence interval [CI], 25%-52%) for the ODO group and 31% (95% CI, 17%-43%) for the DDD group. The relative risk reduction in time to syncope with DDD pacing was 30% (95% CI, –33% to 63%; 1-sided P=.14). Lead dislodgement or repositioning occurred in 7 patients. One patient had vein thrombosis, another had pericardial tamponade leading to removal of the pacemaker system, and a third had infection involving the pacemaker generator.

Conclusions In this double-blind randomized trial, pacing therapy did not reduce the risk of recurrent syncope in patients with vasovagal syncope. Because of the weak evidence of efficacy of pacemaker therapy and the risk of complications, pacemaker therapy should not be recommended as first-line therapy for patients with recurrent vasovagal syncope.

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invasive procedure. To exclude this possibility and to provide a stronger level of evidence that prevention of bradycardia by means of pacemaker therapy reduces the risk of recurrent syncope in patients with vasovagal syncope, we conducted a randomized double-blind trial of pacing.

**METHODS**

**Patient Eligibility**

Patients were eligible for this study if they were older than 19 years and if they had a typical history of recurrent vasovagal syncope with at least 6 episodes of syncope ever, or at least 3 episodes in the 2 years prior to enrollment. In addition, patients had to have a positive head-up tilt table test result with a heart rate times blood pressure product of less than 6000/min mm Hg. Each center used its own tilt study protocol. Although there was variation in the head-up tilt table test protocols used, considerable uniformity existed between protocols at the 15 centers in Canada, Australia, the United States, and Colombia. A passive head-up tilt table test was conducted at 60° to 80° for between 15 and 30 minutes and then an isoproterenol infusion was administered at doses varying from 1 to 4 µg/min for 5 to 15 minutes. Nitroglycerine was used by some centers instead of or with isoproterenol. The protocol was approved by a research ethics board at each center and each patient provided signed informed consent. Patients were excluded from the trial if any other cause of syncope was evident. They were also excluded if they had important valvular, coronary artery, or myocardial disease; an electrocardiographic abnormality; or any major noncardiovascular disease. The trial was conducted from September 1998 to April 2002.

**Randomization and Programming**

After implantation of a dual-chamber pacemaker (Medtronic Kappa, Medtronic Inc, Minneapolis, Minn), patients were randomized by a central process to dual-chamber pacing (DDD) or sensing without pacing (ODO) (Figure 1). An unblinded nurse or physician, who had no other patient contact, did all the programming. The patients' physicians, the patients, and all other study personnel remained blinded to treatment allocation. Blinded study personnel and physicians were asked not to perform routine electrocardiograms. Patients randomized to DDD also received rate drop response pacing, a feature of the pacemaker that instituted rapid DDD pacing if the device detected a rapid decrease in heart rate. The protocol specified that the initial rate drop response parameters should be a drop size of 20 beats, a drop rate of 70/min, and an intervention rate of 100/min for 2 minutes.

**Outcomes**

The primary study outcome was syncope defined as a transient loss of consciousness with prompt spontaneous recovery. Patients were requested to report syncope episodes as soon as possible after the syncopal event occurred. Evidence of syncope was collected including signs of injury and reports from witnesses. A blinded committee of investigators adjudicated all reports of syncope. The study follow-up period was 6 months or up to the time of occurrence of the first episode of recurrent syncope.

**Statistical Analysis**

This study was designed to have 80% power to detect a 50% relative reduction in the risk of recurrent syncope from a rate of 60% in the control group to 30% in the treatment group. To achieve this, a study population of 80 patients was planned. However, after enrollment of 60 patients, the combined event rate of the 2 treatment groups was lower than anticipated, so the study target enrollment was increased to 100 patients.

The primary analysis of the study was planned as a comparison of the cumulative risk of syncope between the 2 treatment groups using a log-rank test. All randomized patients had complete data for the primary outcome (recurrence of syncope) and were analyzed according to the intent-to-treat principle. Thus, all outcomes were attributed to the randomly assigned treatment groups regardless of compliance to assigned treatment. The randomization schedule was stratified by center and used randomly varying block sizes of 2 and 4. The centers were not aware of the block sizes. The individual responsible for randomization in the center was not involved in patient recruitment. All patients received their allocated treatment assignment.
The relative risk reduction (RRR) was calculated as 1 – the hazard ratio from a Cox model. The Cox model was also used for subgroup analyses. A 1-sided test was specified for the primary analysis because it was judged that there was no conceivable interest in or plausible potential for an increase in syncope to occur with pacing. The 95% confidence intervals (CIs) are 2-sided. All statistical analyses were performed using SAS (Version 8, SAS Institute Inc, Cary, NC) and S-Plus (Version 6, Insightful Corp, Seattle, Wash) software.

RESULTS

Patient Enrollment
A total of 137 patients met the inclusion criteria (Figure 1). Two patients had exclusion criteria prohibiting enrollment (1 patient had 2 exclusions). Of the remaining 135 patients who met all eligibility criteria, 100 were enrolled in the study and randomized. There were 48 patients randomized to the DDD group and 52 to the ODO group. Baseline clinical characteristics of the patients are shown in Table 1. There were more men in the ODO group than in the DDD group, but otherwise the 2 treatment groups were well matched. Patients had many prior syncope episodes and a median of 4 in the year prior to randomization. Presyncope episodes were also common.

By protocol design, all patients had a positive head-up tilt table study result. The mean duration of the tilt test was 30 minutes in both groups. Syncope occurred during this test in 60% of the patients randomized to the DDD group and 71% in the ODO group. The mean lowest heart rate recorded was 53/min in both groups and the mean lowest systolic blood pressure was 63 mm Hg in both groups.

Many patients had previously tried medication to control syncope and presyncope. The 2 most commonly used drugs were β-blockers and fludrocortisone. Table 1 shows the associated medical conditions and the consequences of syncope in these patients. Many patients had previously sustained injuries secondary to syncope episodes, had missed time from work, or had had driving privileges restricted because of recurrent syncope.

Randomization
Patients were randomized centrally via the telephone after implantation of a dual-chamber pacemaker. The median time from implantation to randomization was 1 day (maximum 4 days) and the median duration of hospitalization for pacemaker implantation was 1 day. All patients randomized to the ODO group received ODO programming. However, 46 of 48 patients randomized to the DDD group received DDD pacing. The other 2 patients in the DDD group received dual-chamber inhibited pacing. Rate drop response was activated initially in all DDD patients. The median low rate programmed was 50/min.

Follow-up
During follow-up, no patients randomized to ODO pacing had pacing functions activated before having an outcome event. No patient was lost to follow-up. Several patients in the DDD

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### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Only Sensing Without Pacing (ODO) (n = 52)</th>
<th>Dual-Chamber Pacing (DDD) (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percent (%)</td>
<td>Percent (%)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>27 (51.9)</td>
<td>13 (27.1)</td>
</tr>
<tr>
<td><strong>Age, mean (SD), y</strong></td>
<td>47.8 (17.7)</td>
<td>50.8 (17.6)</td>
</tr>
<tr>
<td><strong>Syncope events, median (IQR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>20 (8-50)</td>
<td>15 (8-50)</td>
</tr>
<tr>
<td>Events in past year</td>
<td>4 (3-12)</td>
<td>4 (2-15)</td>
</tr>
<tr>
<td>Months since most recent event</td>
<td>1 (0-4)</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td><strong>Presyncope episodes, median (IQR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last month</td>
<td>6 (1-20)</td>
<td>5 (0-20)</td>
</tr>
<tr>
<td>Last 12 months</td>
<td>24 (5-100)</td>
<td>30 (4-112)</td>
</tr>
<tr>
<td><strong>Tilt table test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of test, mean (SD)</td>
<td>29.9 (32.2)</td>
<td>30.4 (23.2)</td>
</tr>
<tr>
<td>Syncope occurred</td>
<td>31 (59.6)</td>
<td>34 (70.8)</td>
</tr>
<tr>
<td>Isoproterenol used</td>
<td>29 (55.6)</td>
<td>21 (43.8)</td>
</tr>
<tr>
<td>Presyncope</td>
<td>40 (76.9)</td>
<td>34 (70.8)</td>
</tr>
<tr>
<td>Lowest systolic blood pressure, mean (SD)</td>
<td>62.6 (27.3)</td>
<td>62.7 (23.3)</td>
</tr>
<tr>
<td>Lowest heart rate, mean (SD)</td>
<td>53.1 (27.8)</td>
<td>56.3 (26.0)</td>
</tr>
<tr>
<td>Lowest heart rate, beats/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>29 (55.6)</td>
<td>29 (60.4)</td>
</tr>
<tr>
<td>&lt;40</td>
<td>12 (23.1)</td>
<td>7 (14.6)</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (8)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>5 (10)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Hypertension (receiving treatment)</td>
<td>12 (23)</td>
<td>13 (27)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>7 (14)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Other disease</td>
<td>14 (27)</td>
<td>10 (21)</td>
</tr>
<tr>
<td><strong>Prior therapy for syncope</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>25 (48)</td>
<td>23 (48)</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>10 (19)</td>
<td>9 (19)</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>5 (10)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Phenylinephrine</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitor</td>
<td>12 (23)</td>
<td>6 (13)</td>
</tr>
<tr>
<td><strong>Prior consequence of syncope</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor vehicle crash</td>
<td>10 (20)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Driving restrictions</td>
<td>21 (42)</td>
<td>19 (41)</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>6 (12)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>No./total of those employed with &gt;15 d of work missed in past year</td>
<td>14/34 (41)</td>
<td>9/29 (31)</td>
</tr>
</tbody>
</table>

*Values expressed as number (percentage) unless otherwise indicated.
group had programming changes. One patient had the pacemaker system removed. Two patients had their pacemakers reprogrammed to ventricular pacing due to atrial lead sensing and pacing problems. Concomitant pharmacological therapy for vasovagal syncope was used in some patients during study follow-up. Twelve percent of the patients in the ODO group compared with 19% in the DDD group received β-blockers; fludrocortisone, 10% vs 2%; and selective serotonin reuptake inhibitors, 12% vs 13%.

Recurrent Syncope
A total of 38 patients had syncope during the 6-month follow-up period. Of the 52 patients randomized to ODO, 22 had recurrent syncope within 6 months compared with 16 of 48 patients in the DDD group. The median duration of syncope reported was 2 minutes in the ODO group and 1 minute in the DDD group. Syncope resulted in injuries with bruising or bleeding in 3 patients in each group; no other injuries were reported. Syncope was witnessed in 12 patients in each group.

The Kaplan-Meier plots showing time to first episode of syncope, based on intent-to-treat analyses, are shown in Figure 2. The cumulative risk of syncope at 6 months was 40% (95% CI, 25%-52%) for the ODO group and 31% (95% CI, 17%-43%) for the DDD group. The RRR in time to syncope with DDD pacing was 30% (95% CI, −33% to 63%; log-rank \( P = .14 \)). Another treatment analysis, which excluded 1 patient who deviated from allocated therapy (this patient was randomized to the DDD group and had the pacemaker removed during the study), showed an RRR with DDD pacing of 35% (95% CI, −26% to 66%; 1-sided \( P = .10 \)).

Subgroup Analysis
To explore whether subgroups of patients benefited from a pacemaker, exploratory analyses were performed (Figure 3). Age, duration of tilt test before syncope, and minimum heart rate of less than 50/min during the tilt test did not define which patients would benefit from pacing. Patients who received isoproterenol during the tilt study were significantly more likely to benefit from pacemaker therapy than those who did not require isoproterenol during the tilt study. Sex and history of vehicular collision were also examined as potentially prognostic baseline characteristics but were not associated with an increased or decreased risk of syncope.

Presyncope
Information on presyncope was collected from patient diaries. Presyncope was defined as a feeling of impending loss of consciousness that does not result in complete syncope. Patients were instructed to record every episode of presyncope and to grade each episode on a scale of 1 to 5, in which 5 was the most severe. There were 49
Major a pacemaker or not.2 The other trial ran-
trials randomized 42 patients to receive
were also terminated early. One of these
trials of pacing for vasovagal syncope
served after enrollment of just 54 pa-
ment effect in favor of pacing was ob-
terminated early when a large treat-
maker. This pilot trial of pacing was
randomized to receive or not receive a pace-

(94%) patients with any presyncope in
the ODO group and 46 (96%) in the
DDD group (P>-.99). The median re-
ported episodes of presyncope per 100
days of follow-up were 16 in the ODO
group and 13 in the DDD group. Of
those patients who recorded any pre-
syncope, the median maximum sever-
ity of presyncope was 4 for both groups.

Complications
Pacemaker complications occurred in
several patients (TABLE 2). One patient
had infection requiring reimplantation
of the pacemaker generator and another
had pericardial tamponade leading to
removal of the pacemaker system.

COMMENT
Three previous randomized studies have
reported that pacemaker therapy re-
duces the risk of recurrent syncope in pa-
ients with vasovagal syncope. In the first
randomized trial, the Vasovagal Pacing
maker Study (VPS I),1 patients were ran-
domized to receive or not receive a pace-
maker. This pilot trial of pacing was
terminated early when a large treat-
ment effect in favor of pacing was ob-
served after enrollment of just 54 pa-
tients. Subsequently, 2 other randomized
trials of pacing for vasovagal syncope
were also terminated early. One of these
trials randomized 42 patients to receive
a pacemaker or not.2 The other trial ran-
domized 93 patients to receive a pace-
maker or to receive a β-blocker (atenol-
ol).3 All 3 studies observed statistically
significant reductions in the risk of syn-
cope in patients who received pacing.

However, all 3 of these trials were un-
blinded. Patients and physicians knew
whether pacing therapy was being used
or not. Any open-label trial has the po-
tential for bias in reporting and assess-
ment of outcomes. For trials in which
the outcomes of interest are major mor-
bid events such as stroke or death, the
risk of bias in outcome assessment is
minor. However, syncope is an out-
come that has a major subjective com-
ponent and is difficult to verify objec-
tively. It is possible in the unblinded
studies that some patients, hoping to
have received a pacemaker and disap-
pointed by being randomized not to re-
ceive one, may have been more prone
to report syncope. The double-blind
trial design removes this type of poten-
tial bias to a considerable extent.

Vasovagal syncope episodes can be
aggravated by adverse experiences such as
anxiety and fear. It is possible that the
disappointment of being randomized not
to receive a pacemaker in unblinded trials
actually increased the likelihood that pa-
tients would have recurrent syncope. On
the other hand, it is well accepted that
surgical procedures can have a placebo
effect independent of the actual surgi-
cal care received.6,8 Patients receiving a
pacemaker may have benefited from the
psychological effects of receiving a sur-
gical procedure. Although this effect is
an accepted part of medical care,6 it is im-
portant to know whether pacemaker im-
plantation is beneficial because of its
physiological effects on the heart or be-
cause of the psychological effects of sur-
gery, or both. In the 3 unblinded stud-
dies, it was not possible to determine
whether patients benefited from the ac-
tual pacing therapy.

To reduce potential for bias and con-
 founding psychological effects, we per-
formed this double-blind study. We ex-
pected that the risk of syncope in the
control group would be reduced to
some extent by the receipt of a device,
even if it was not actually pacing, and
we increased the study’s statistical
power accordingly. The VPS II is, to our
knowledge, the first double-blind ran-
domized trial of pacing, and also is the
largest of the randomized pacemaker
trials for vasovagal syncope.

The main finding of this double-
blind trial was that a statistically signifi-
cant benefit was not found for pace-
maker therapy for prevention of syncope
in patients with vasovagal syncope. The
main difference between the results of
this trial and the nonblinded VPS I is the
observed risk of syncope in the non-
paced group. Whereas in the VPS I study
almost 80% of nonpaced patients had
syncope by 6 months, in this study only
41% of ODO patients had syncope by 6
months. The 6-month rates of syncope
in the patients receiving pacing therapy
in the 2 studies were more similar; 20%
in VPS I and 31% in the present study.
Another difference between this trial and
all 3 previous trials was that the previ-
ous trials were all terminated prema-
turally. Early termination of a trial for un-
expected efficacy tends to overestimate
the treatment effect.

This study was designed to detect an
RRR with pacing of 50%. The ob-
served RRR was 30% with a wide 95%
CI. An RRR of 50% with pacing is un-
likely but still plausible. However, the
large RRRs (in the range of 80%), which
were observed in the 3 unblinded ran-
domized trials, are unlikely. These RRRs
are not included in the 95% CI of the
RRR observed in this study, the upper
limit of which was 63% RR. This trial
was designed to have reasonable power
to detect an RRR of 50%, which we be-
lieved to be the minimum effect size that
would justify this invasive treatment.
The RRR of 30% observed in this study,
if it were real, might be considered by

<table>
<thead>
<tr>
<th>Type of Complication</th>
<th>No. of Patients With Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Only Sensing Without Pacing (ODO)</td>
</tr>
<tr>
<td>Major</td>
<td>(n = 52)</td>
</tr>
<tr>
<td>Pericardial tamponade</td>
<td>0</td>
</tr>
<tr>
<td>Infection requiring reimplantation</td>
<td>1</td>
</tr>
<tr>
<td>Minor</td>
<td></td>
</tr>
<tr>
<td>Lead dislodgement or repositioning</td>
<td>3</td>
</tr>
<tr>
<td>Infection requiring antibiotics</td>
<td>2</td>
</tr>
<tr>
<td>Ven thrombosis</td>
<td>1</td>
</tr>
<tr>
<td>Wound hematoma</td>
<td>1</td>
</tr>
<tr>
<td>Pain related to pacemaker generator</td>
<td>1</td>
</tr>
</tbody>
</table>
some to be a reasonable benefit to obtain by pacing. Based on the results of this study, a benefit of this magnitude is plausible but not proven.

The rationale for the use of a pacemaker in vasovagal syncope is that bradycardia often occurs at the time of syncope. Prevention of bradycardia is the main physiological mechanism by which a pacemaker can prevent attacks of syncope. However, patients with vasovagal syncope often experience reductions in blood pressure at the beginning of a syncope episode and heart rate changes later. If profound hypotension has already occurred, pacing therapy will not help patients even if bradycardia or asystole has been demonstrated at the time of syncope. It is possible to capture the marker channel information recorded in the pacemaker at the time of syncope if the patient activates the pacemaker to do so shortly after the syncope event. Several patients made such recordings and when these data are analyzed, it may provide information to help understand how the pacemakers were functioning at the time of syncope.

Of the subgroup analyses performed, 1 was statistically significant and it suggested that patients who required isoproterenol during their tilt test were more likely to respond to pacing than those who did not receive isoproterenol. It is difficult to find a biologically plausible reason why this should be so, and it is possible that this finding is due to the play of chance.

Small differences in study design between this study and VPS I are unlikely to explain the different results, but should be noted. The VPS I study only enrolled patients with a minimum heart rate below 60/min during the tilt test and the present study did not specify any minimum heart rate during the tilt test. Both studies required a heart rate blood pressure product below 6000/ mm × mm Hg. The percentages of patients with a heart rate of less than 40/min during the tilt test were similar in both studies. In VPS I, 12 (22%) of 54 patients enrolled had a rate of less than 40/min during the tilt test compared with 19 (19%) of 100 patients in VPS II. Therefore, there were similar numbers of patients with extreme bradycardia at the time of positive tilt test results in both studies, and this minor difference in study design is not a factor in the different results observed. Moreover, our study allowed investigators to use their own institutional protocol for head-up tilt table testing. This reflects the fact that there is considerable variation in the details of the tilt test procedure. This increases the generalizability of the results of this study.

This study is unique among pacemaker and device trials because of the use of a double-blind study design, which removed the potential bias that could occur if patients and physicians knew which treatment a patient had received. Although the use of placebo-controlled surgery trials can be criticized as unethical, this was less of a concern in this study because patients receiving the pacemaker could have it activated to deliver pacing therapy once study participation had been completed.

Considering the risk of complications, the rate of recurrence of syncope in the patients receiving a pacemaker and the weak evidence for any true benefit of pacing, pacemaker therapy should not be recommended as first-line therapy for patients with vasovagal syncope.

Author Contributions: Dr Thorpe had full access to all of the data in this study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Connolly, Shelden, Roberts, Ellenbogen, Wilkoff, Morillo, Gent. Acquisition of data: Connolly, Shelden, Thorpe, Roberts, Ellenbogen, Wilkoff, Morillo, Gent. Analysis and interpretation of data: Connolly, Shelden, Thorpe, Roberts, Ellenbogen, Morillo, Gent. Drafting of the manuscript: Connolly, Shelden, Roberts, Gent. Critical revision of the manuscript for important intellectual content: Connolly, Shelden, Thorpe, Roberts, Ellenbogen, Wilkoff, Morillo, Gent. Statistical expertise: Connolly, Thorpe, Roberts, Morillo, Gent. Obtained funding: Connolly, Shelden, Gent. Administrative, technical, or material support: Connolly, Shelden, Ellenbogen. Study supervision: Connolly, Shelden, Ellenbogen, Gent.

Clinical Centers: Australia: Victorian Heart Centre, Richmond (14 patients): Angus Hamer, Graeme Soman, Sally Forsyth. Canada: St Michael’s Hospital, Toronto, Ontario (17 patients): David Newman, Paul Donavan, David Darling; Foothills Hospital, Calgary, Alberta (16 patients): Bob Sheldon, Mary-Lou Koshman; Hospital du Sacre Coeur de Montreal, Montreal, Quebec (12 patients): Teresa Kus, Ann Lang; Institut de Cardiologie Montreal, Montreal, Quebec (9 patients): Bernard Thibault, Martine Vaillancourt; Hamilton Health Sciences, Hamilton General Hospital, Hamilton, Ontario (7 patients): Stuart Connolly, Sandra Carroll; Queen Elizabeth II Health Sciences, Halifax, Nova Scotia (1 patient): Martin Gardner, Marcy Shields. Colombia: Instituto del Corazon, Flandiblanca (3 patients): Carlos Morillo, Rocio Aghon. United States: University of Maryland School of Medicine, Baltimore (7 patients): S. R. Shorofsky, Mary Ohio, Samantha Sarang; Johns Hopkins Hospital, Baltimore, Md (5 patients): Hugh Calkins, Misty Capps; Cleveland Clinic Foundation, Cleveland, Ohio (3 patients): Bruce Wilkoff, Donald Holmes; St Mary’s Hospital, Rochester, Minn (2 patients): David Hayes, Nancy Lexvold; Medical College of Virginia and McGuire VA Medical Center, Richmond (2 patients): Ken Ellenbogen, Audrey Hirsch; Columbia Presbyterian Medical Center, New York, NY (1 patient): Daniel Bloomfield, Thomas Palumbo; Loyola University Medical Center, Chicago, Ill (1 patient): Brian Olshansky, Liz Jazky. Steering Committee: Stuart Connolly, Michael Gent, Robin Roberts, Amy Brown, Jennifer Englund, Mark Erickson, Ken Ellenbogen, Bruce Wilkoff, Bob Sheldon. Coordinating and Methods Center: (Hamilton, Ontario) Lorrie Costantini, Kevin Thorpe.

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REFERENCES