Rationale and design of a study assessing treatment strategies of atrial fibrillation in patients with heart failure: The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial

The AF-CHF Trial Investigators*

Background Nonrandomized studies suggest that atrial fibrillation is independently associated with increased mortality in patients with heart failure. Whether restoring and maintaining sinus rhythm will have a beneficial impact on cardiovascular mortality in patients with heart failure has never been tested in an adequately powered randomized trial.

Objective The primary objective of the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial is to determine whether restoring and maintaining sinus rhythm significantly reduces cardiovascular mortality compared with a rate-control strategy in patients with atrial fibrillation and CHF.

Methods AF-CHF is a prospective multicenter trial (109 centers in Canada, United States, South America, Europe, and Israel), that will randomize 1450 patients with CHF with left ventricular ejection fraction ≤35% and atrial fibrillation to 1 of 2 treatment strategies: (1) rhythm control with the use of electrical cardioversion combined with antiarrhythmic drugs (amiodarone or other class III agents), (2) rate control with the use of β-blockers, digoxin, or pacemaker and AV nodal ablation. Cardiovascular mortality is the primary end point and the intention-to-treat approach the primary method of analysis. We anticipate an 18.75% 2-year cardiovascular mortality in the rate control arm with a 25% mortality reduction in the rhythm control group.

Results As of August 13, 2002, 334 patients have been enrolled from 68 participating centers. Enrollment is expected to be concluded in May 2003 with a minimum follow-up of 2 years.

Conclusion The results of this trial should provide definitive information concerning 2 widely applicable treatment strategies of atrial fibrillation in a large cohort of patients with CHF. (Am Heart J 2002;144:597-607.)

Background and rationale
Importance of atrial fibrillation and congestive heart failure
Congestive heart failure (CHF) is a major complication of virtually all forms of heart disease and is a leading cause of morbidity and mortality in industrialized nations. It is estimated that >2.5 million North Americans are afflicted with CHF and that it develops in 400,000 patients each year.4 Atrial fibrillation (AF) is also a major health problem. It is the most frequent cardiac arrhythmia, affecting 5% of individuals aged >65 years, and it is associated with an increased risk of stroke and a doubling of all-cause mortality.5,8 The number of hospital discharges for AF has more than doubled, from 110,000 in 1984 to 270,000 in 1994.9 CHF promotes AF and AF aggravates CHF.10,11 Recent advances in therapeutic interventions have resulted in impressive age-adjusted declines in the incidence and hospital mortality of cardiovascular disease; however, the prognosis of CHF patients remains grim, with a 5-year survival rate usually <50%.1,12,13 Currently, the management of AF has become more aggressive with prompt cardioversion and an increase in the use of either newer drugs or nonpharmacologic therapies. This change has occurred mainly because of the awareness that AF may be self-perpetuating14-16 and that it is associated with an increased risk of stroke and with the onset or exacerbation of CHF.17-23

Prognostic significance of AF in CHF
The incidence of AF in CHF ranges from 10% to 50%, with the highest incidence in those with the most severe symptoms.1,24-29 The association between
AF and CHF is well documented, but the impact of AF on survival remains controversial. In older and smaller studies of patients with CHF, AF has been reported as an adverse, nonsignificant, and even beneficial predictor of outcome. More recently, larger reports that evaluate the impact of AF on mortality have been published (Table I). Three reports showed no increase in mortality, whereas 5 showed AF to be an independent risk factor. Prior studies of AF and CHF were all nonrandomized comparisons and most were retrospective analyses. Some studies suggested that AF has no effect on survival, but in most recent large CHF reports, AF has been shown to be an independent risk factor for mortality or major morbidity. Moreover, previous investigators, whether they reported positive or negative relationships between AF and survival, concluded that a prospective randomized trial was warranted to clarify the influence of AF and the role of therapy to maintain sinus rhythm on prognosis. Recently, Wyse et al indicated that AF was an independent risk factor for increased mortality among the patients in the registry of the Antiarrhythmics Versus Implantable Defibrillators study.

Consequences of AF in CHF patients

Excessive ventricular rate, irregularity of ventricular response, and loss of atrial contraction are all associated with adverse hemodynamic consequences that influence prognosis in patients with AF. Restoration of sinus rhythm is associated with improvement in cardiac output, exercise capacity, and maximal oxygen consumption. Moreover, the results of the Pharmacological Intervention in Atrial Fibrillation trial indicated that patients randomized to rhythm control had a better exercise tolerance than those undergoing rate control. Recent prospective data show that the onset of AF in patients with CHF is associated with clinical and hemodynamic deterioration. Increased mortality also occurs and is attributed to embolic complications of AF and to detrimental effects associated with the use of antiarrhythmic drugs.

### Table I. Prognostic significance-nonrandomized studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients in atrial fibrillation</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carson et al</td>
<td>24 patients, follow-up 2 years</td>
<td>107</td>
</tr>
<tr>
<td>Mahoney et al</td>
<td>345 patients, advanced CHF, follow-up 1 year</td>
<td>62</td>
</tr>
<tr>
<td>Crijns et al</td>
<td>PRIME II trial, 409 patients, NYHA class III-IV, follow-up 3-4 years</td>
<td>84</td>
</tr>
<tr>
<td>Middlekauf et al</td>
<td>390 patients, NYHA class III-IV, follow-up 1 year</td>
<td>75</td>
</tr>
<tr>
<td>Bourassa et al</td>
<td>SOLVD registry, 6273 patients, follow-up 1 year</td>
<td>31</td>
</tr>
<tr>
<td>Dries et al</td>
<td>SOLVD trials, 6517 patients, follow-up 2.5 years</td>
<td>419</td>
</tr>
<tr>
<td>Maggioni et al</td>
<td>Italian CHF network, 2086 patients, follow-up 2.5 years</td>
<td>23%</td>
</tr>
<tr>
<td>Mathew et al</td>
<td>DIG trial, 7788 patients, follow-up 3 years</td>
<td>866</td>
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</tbody>
</table>

Antiarrhythmic drug therapy in patients with AF and CHF

Antiarrhythmic drugs are frequently used to help maintain sinus rhythm. However, long-term use of quinidine and other class I agents for AF control may have substantial risks, particularly in patients with CHF, as retrospective analyses suggest that they increase mortality. Deedwania et al evaluated the long-term effects of amiodarone on morbidity and mortality in patients with AF/CHF from the Veterans Affairs Congestive Heart Failure Survival Trials of Antiarrhythmic Therapy (CHF-STAT) and reported a lower mortality rate in patients in AF at baseline who subsequently converted to sinus rhythm on amiodarone than in those who did not. Among the available antiarrhythmic medications, only amiodarone has been reported to have a beneficial impact on survival in patients with CHF. The Canadian Trial of Atrial Fibrillation (CTAF) has recently demonstrated that amiodarone is much more effective than sotalol or propafenone at maintaining sinus rhythm in patients.
with either paroxysmal or persistent AF. The Danish Investigations of Arrhythmia and Mortality ON Dofetilide in Congestive Heart Failure (DIAMOND) study evaluated 1518 patients with symptomatic CHF. Dofetilide had no effect on mortality; however, the drug was effective in converting AF to sinus rhythm and in preventing its recurrence. Treatment with dofetilide significantly reduced the risk of hospitalization for CHF, and in a subsequent report by Camm et al., this benefit was found to be the result of the effect of dofetilide in patients with AF.

Thus, the available evidence suggests that (1) it is possible to restore and maintain sinus rhythm in the majority of patients with AF/CHF, (2) therapy with a class I antiarrhythmic drug worsens prognosis in patients with CHF, (3) maintaining sinus rhythm, at least with amiodarone, in patients with CHF may reduce mortality, (4) antiarrhythmic therapy may prevent new-onset AF and may reduce hospitalizations in CHF patients. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study of the National Heart, Lung, and Blood Institute evaluated mortality after various approaches to AF management in patients with risk factors for stroke. However, this trial was not designed to, and will not have the power to establish optimal management of AF in patients with CHF. Indeed, of the 4060 patients recruited into the Atrial Fibrillation Follow-up Investigation of Rhythm Management study, <10% have significant left ventricular dysfunction. Therefore, the results of AFFIRM (which were reported at the 51st Annual Scientific Session of the American College of Cardiology) are not applicable to the AF-CHF population, which will have a higher onset AF and may reduce hospitalizations in CHF patients. The primary hypothesis of the AF-CHF trial is that restoring and maintaining sinus rhythm significantly reduces cardiovascular mortality compared with a rate-control treatment strategy in patients with AF and CHF.

Alternatives to antiarrhythmic drug therapy for rhythm control

Pacing is indicated in patients with AF with symptomatic bradycardia or after AV nodal ablation. The concept of pacing to prevent or to suppress AF is more recent. Physiologic pacing reduced the annual rate of development of chronic AF in the Canadian Trial of Physiologic Pacing. Multisite atrial pacing and new pacing algorithms are also under development. The atrial implantable defibrillator may be of benefit in a selected subset of patients with refractory AF. The MAZE procedure has been reported to restore sinus rhythm with a relatively low (2%) operative mortality in selected patients and institutions. Increasing attention is now being focused on developing catheter ablation techniques to treat AF. Encouraging results have been obtained with this new technique, although it has not been extensively studied in patients with CHF.

Therapies for ventricular rate control

Control of ventricular response as primary therapy of AF is widely used in clinical practice. The optimal or adequate ventricular rate remains undefined, and long-term evaluation of heart rate control by standard drug regimens has not been systematically investigated. The combination of digoxin and β-blockers produces a synergistic effect on the AV node and is an effective rate-control regimen. Both digoxin and β-blocking agents have been shown to favorably influence prognosis in patients with CHF. In the Digitalis Investigation Group (DIG) trial, digoxin reduced the rate of both overall and CHF-related hospitalizations. β-Blockers, primarily carvedilol, metoprolol, and bisoprolol, improve left ventricular function and survival and reduce hospitalizations in patients with CHF. Verapamil and diltiazem are effective in controlling ventricular response. However, calcium antagonists can adversely affect prognosis in patients with CHF. AV nodal catheter ablation with permanent pacemaker implantation is an alternative therapy for patients with AF not controlled by drug therapy. The technique is effective, complications occur infrequently, and it allows good rate control without the need for drugs. Furthermore, AV nodal ablation is associated with improvement in ventricular function and in quality of life and does not adversely affect long-term survival.

Research design and methods

The AF-CHF study (Figure 1) is being conducted in 90 cardiology centers throughout Canada, the United States, South America, and Europe. The investigational review board of each institution approved the study, and all patients will give written informed consent. Recruitment began in May 2001, randomization is expected to be concluded in May 2003, and follow-up will terminate in May 2005. This trial is fully funded by a grant from the Canadian Institutes of Health Research.

Hypothesis, patient selection, and randomization

The primary hypothesis of the AF-CHF trial is that restoring and maintaining sinus rhythm significantly reduces cardiovascular mortality compared with a rate-control treatment strategy in patients with AF and CHF.

To be eligible, patients must meet all of the following criteria: (1) left ventricular ejection fraction ≤35% as measured by nuclear imaging, echocardiography, or cardiac angiography within 6 months preceding enrollment, (2) history of CHF defined as either (a) symp-
AF occurring and not persisting beyond 10 days of surgery or myocardial infarction, (4) reversible cause of CHF such as severe aortic or mitral stenosis and tachycardia-induced cardiomyopathy, (5) decompensated CHF within 48 hours before randomization, (6) antiarrhythmic drugs other than calcium-channel blockers, β-blockers, or digoxin required for other arrhythmias or indications, (7) second or third degree AV block, sinus pause >3 seconds, resting heart rate <50 beats per minute without a permanent pacemaker, (8) history of drug-induced torsades de pointes or congenital long QT syndrome, (9) prior AV nodal ablation or MAZE surgery, (10) probable cardiac transplantation in the next 6 months, (11) chronic renal failure requiring dialysis, (12) women of child-bearing potential not using a reliable method of birth control, (13) geographic or social factors, drug or alcohol abuse making follow-up or compliance difficult, (14) other noncardiovascular medical condition (such as cancer) making 1-year survival unlikely, (15) age <18 years.

Written informed consent will be obtained from patients who fulfill eligibility criteria. Patients are randomized in an open-label fashion to the rhythm control or rate control arm. Randomization is accomplished at the coordinating center by an automated randomization service. To randomize a patient, the clinical site must have available the completed eligibility forms, the signed patient consent form, the sequential patient number, the center number, and the authorization code. Randomization is stratified according to study center. Random permuted blocks of various sizes are used and the block sizes are varied randomly.

Therapies for rhythm control

Therapies for rhythm control are shown in Figure 2. Aggressive therapy to prevent AF recurrences is recommended for patients assigned to the rhythm control arm (including electrical cardioversions, antiarrhythmic drug dose adjustment, use of intravenous drugs such as ibutilide, and nonpharmacologic therapies).

Electrical direct current cardioversion will be performed within 6 weeks of randomization in those patients with AF who do not convert to sinus rhythm after antiarrhythmic therapy, and if necessary, a second cardioversion will be performed within 3 months of enrollment. Cardioversion will be deemed unsuccessful only after 2 shocks are delivered at the maximum energy of the device. Patients who fail standard external cardioversion should be referred for innovative techniques, such as double-paddle cardioversion and internal catheter cardioversion. Patients who fail cardioversion will continue to be followed up in the rhythm control arm and therapy will be adjusted for adequate rate control.
The initial drug of choice for patients assigned to the rhythm control strategy is amiodarone. The recommended loading dose is 10 mg/kg/day for 14 days as an outpatient, followed by 300 mg/day for 4 weeks and then a maintenance dose of 200 mg/day. The use of amiodarone will be strongly recommended, but it will not be mandatory that it be prescribed for any individual patient. The following antiarrhythmic drugs can be considered whenever a patient fails amiodarone therapy or is unable to tolerate a minimal dose: diltiazem may be given to a patient with an implantable cardioverter defibrillator or, if clinically appropriate, to men with normal renal function. Dosing should start at 240 mg daily (in 2 or 3 divided doses) for patients aged 70 years and weight ≥70 kg; 160 mg daily for patients aged >70 years or weight <70 kg. Dofetilide is a reasonable alternative to amiodarone and may be the initial drug for patients in the United States. Inhospital initiation of dofetilide is required, and dosing will be performed according to the package insert. Azimilide and dronedarone are currently undergoing extensive clinical review and may become additional options to maintain sinus rhythm during the course of this trial.

Patients refractory to antiarrhythmic drug therapy may be referred for additional nonpharmacologic therapy designed to maintain sinus rhythm. This therapy is at the discretion of the investigator and may include the surgical MAZE procedure or atrial catheter ablation, new permanent pacemaker techniques, and implantable atrial defibrillators. Permanent pacemakers will be implanted to control bradyarrhythmia by use of the American College of Cardiology and the American Heart Association guidelines for cardiac pacing. Patients in whom significant bradycardia develops during antiarrhythmic drug therapy should receive a permanent pacemaker to allow continued antiarrhythmic drug administration. Physiologic atrial or dual-chamber pacing will be recommended for patients in the rhythm control group who undergo pacemaker implantation.

Therapies for rate control

Therapies for rate control are shown in Figure 2. Appropriate doses of β-blockers, digoxin, or both are recommended to achieve adequate rate control. The doses are titrated based on a target heart rate to be assessed both at rest and during a 6-minute walk test and according to tolerance. The guidelines for target heart rate during AF are <80 beats per minute during a resting 12-lead echocardiogram and <110 beats per minute during a 6-minute walk test. Evaluation of heart rate control and the need for AV nodal ablation and pacemaker implantation will be performed within 3 weeks of randomization. The following β-blockers are recommended: metoprolol (starting dose 6.25-25 mg twice a day, maximum 50-100 mg twice a day), carvedilol (starting dose 3.125 mg twice a day, maximum 25-50 mg twice a day), and bisoprolol (starting dose 1.25 mg/day, maximum 10 mg/day). Pacemaker ther-
therapy is strongly recommended if bradycardia limits adequate medical rate control. AV nodal catheter ablation will be considered in symptomatic patients with inadequate rate control or if side effects limit the use of drug therapy. In the latter patients, a permanent (VVIR or DDDR) pacemaker will be implanted. The use of amiodarone for the purpose of controlling ventricular rate is not recommended.

CHF management

Both groups will receive optimal CHF management. A 6-minute walk test is performed at baseline and will be used to assess functional capacity objectively. All patients in this study will require treatment with an ACE inhibitor, if tolerated at enrollment. If an ACE inhibitor is not tolerated, a combination of hydralazine and nitrates, or an angiotensin-II receptor antagonist should be used. Spironolactone (12.5-50 mg/day) is recommended in patients receiving a loop diuretic with NYHA functional class III or IV who have a serum creatinine concentration of ≤220 μmol/L (2.5 mg/dL) and serum potassium ≤5.0 mEq/L.65 Unless contraindicated, β-blockers are started within 3 months of randomization in any patient not already receiving this therapy. Investigators are asked to ensure that the highest tolerated dose be attained and maintained for the duration of the trial. The use of carvedilol is recommended in NYHA functional class IV patients.73 Ventricular resynchronization with biventricular pacing may be considered for NYHA class III to IV patients with an intraventricular conduction delay.86 Anticoagulation is recommended and will be prescribed according to published guidelines for antithrombotic therapy in atrial fibrillation.87

Follow-up and outcome events

All patients will be evaluated at 3 weeks, 4 months, and every 4 months thereafter. Clinical variables, medications, characterization of hospitalizations, and major clinical events are assessed at each follow-up visit by a nurse coordinator in consultation with a physician and are documented on specially designed case report forms.

The primary end point of this study is cardiovascular death, defined as a death that is not clearly the result of a noncardiovascular cause (such as cancer, trauma, sepsis, suicide, and noncardiac surgery). Secondary end points are total mortality; stroke; hospitalization; quality of life; cost of therapy; composite end point of cardiovascular death and stroke; and composite end point of cardiovascular death, stroke, and hospitalization. Assessment of quality of life will be performed before randomization and at the 4-month visit, with measures selected from the following questionnaires that are available in English and French: The Medical Outcomes Study Form-36, the Symptoms Checklist for Arrhythmia-related Symptom Frequency and Severity, the University of Toronto Atrial Fibrillation Severity Scale, and the University of Minnesota (1986) Living With Heart Failure Questionnaire. Psychological factors of known prognostic importance will also be assessed: depression (the Beck Depression Inventory-II) and anxiety (the Anxiety Sensitivity Index). An estimate of the cost of each treatment strategy will be obtained by recording the number of days of relevant hospitalizations, the number of major cardiac procedures and device implantations, and the number of emergency room visits.

Sample size

We estimate that total mortality over 2 years in patients with symptomatic CHF and ejection fraction of ≤35% will be at least 25%. This expected event rate is based on the data from the DIG,13 Vasodilator in Heart Failure trials (V-HeFT) II,24 Studies Of Left Ventricular Dysfunction (SOLVD),26 Cooperative North Scandinavian Enalapril Survival Study,27 Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina,28 Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy,29 and Danish Investigations of Arrhythmia and Mortality ON Dofetilide in Congestive Heart Failure trials.30 We chose different NYHA entrance criteria for patients with CHF because there is a relationship between functional class and prognosis. Indeed, patients in the SOLVD prevention trial had about half the mortality of patients in the SOLVD treatment trial, so if we were to consider including NYHA class I patients in the study, we needed to identify a high-risk subgroup. We chose prior hospitalization for heart failure, which has been identified as a marker of worse prognosis, and left ventricular ejection fraction, which is an objective measurement that is inversely related to survival; the choice of left ventricular ejection fraction ≤25% assures that we will include a population with a high event rate.

Cardiovascular death rather than total mortality was chosen as the primary end point for this trial because 15% to 20% of deaths will be noncardiovascular, and the study interventions are unlikely to affect these deaths. However, total mortality will remain the most important secondary outcome event. The sample size calculations were performed with the estimate of an 18.75% 2-year cardiovascular mortality in the rate control arm. Assuming a 2% loss to follow-up, a 2-sided alpha level of 0.05, and an annual accrual rate of 750 patients, we calculate that with 722 patients per group (rounded total number of 1450 patients), the study will have >80% power to detect a 25% reduction in cardiovascular mortality. Conservative estimates in expected event rates and risk reduction were chosen so that the sample size will preserve excellent power,
even if factors such as noncompliance or cross-over to therapy occur frequently, as these are difficult to predict in a trial designed as an initial treatment strategy comparison. The number of planned participating sites is 100. To enroll 750 patients per year, each site will need to randomize an average of 0.625 patients per month. At this rate, the actual accrual period will be 1.9 years and the total study duration will be 3.9 years.

Statistical analysis

The primary analysis will be a comparison of time to cardiovascular death: survival curves will be estimated by the Kaplan-Meier method and the difference between treatment arms will be assessed by use of the log rank test. The analyses will be performed according to the intention-to-treat principle. Censoring will occur if the patient is lost to follow-up or reaches the end of the follow-up period. Patients will remain in their assigned treatment arm for treatment comparison regardless of cross-over or noncompliance. The Cox proportional hazards model will be used to investigate important covariates. Different methods of statistical analyses will be used for secondary outcomes. Continuous outcomes (eg, quality of life, cost of therapy) will be studied by covariance analysis. Prognostic factors, baseline values, and treatment-covariate interactions will be studied. Subgroup analysis for age, use of β-blockers, left ventricular ejection fraction, and NYHA functional class will be performed. An interim analysis will be performed when half of the anticipated total deaths have been observed. The O’Brien-Fleming stopping boundary will be used as a guideline for early termination because of its requirement of strongly convincing evidence (critical P value of .0054).

Conclusions

The results of this trial should provide definitive information concerning 2 widely applicable treatment strategies of AF in a large cohort of CHF patients. Clinical decision-making will be improved regardless of outcome. If the study hypothesis is borne out, the data will support a compelling indication for aggressive treatment of AF with prompt cardioversion and long-term antiarrhythmic therapy. Given the frequent occurrence of CHF and AF and the high mortality and hospitalization rates associated with them, we postulate that even a modest improvement could prevent thousands of hospitalizations and deaths each year. It would also provide a strong incentive to search for new and improved methods to maintain sinus rhythm. On the other hand, if the trial yields negative results, it will indicate that adequate rate control is sufficient therapy for AF in CHF and will eliminate the need for cardioversion and hospitalization in otherwise stable patients. The trial will also provide up-to-date cost effectiveness and quality of life measures that will be useful to health care organizations. In addition, fundamental data will be obtained that will improve our understanding of the natural history of AF and of modes of death in patients with CHF.

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Hospital, Hvidovre, Denmark; Leonardo Reisin, MD, Barzilai Medical Centre, Ashkelon, Israel; Angel Rodríguez-Santiago, MD, Bayamón, Puerto Rico; Jens Rokkedal, MD, KAS Glostrup, Glostrup, Denmark; Tiberio Rozenfeld, MD, Haemek Medical Centre, Afula, Israel; Joseph Rozennman, MD, Wolfson Medical Centre, Holon, Israel; Denis Roy, MD, Institut de Cardiologie de Montréal, Montreal, Quebec, Canada; Andrew Rubin, MD, Eisenhower Medical Centre, Rancho Mirage, Calif; Monique Ruef, MD, CHUM – Hôpital Saint-Luc, Montreal, Quebec, Canada; Dennis Rupka, MD, Keary Medical Centre, New Westminster, British Columbia, Canada; Joseph Sacco, MD, Stratton VA Medical Center, Albany, NY; Michel Samson, MD, CHU – Pavillon CHUL, Sainte-Foy, Quebec, Canada; Franco Sandrin, MD, Lakeshore General Hospital, Pointe-Claire, Quebec, Canada; Richard Schuld, MD, Internal Medicine, Lethbridge, Alberta, Canada; Monohara Senaratne, MD, Grey Nuns Community Hospital & Health Centre, Edmonton, Alberta, Canada; Jorge A. Salerno, MD, Ospedale di Circolo e Fondazione Macchi, Varese Italy; Nawal Sharma, MD, Midtown Medical Centre, Saskatoon, Saskatchewan, Canada; Igor Singer, MD, University of Louisville, Louisville, Ken; Bramah N. Singh, MD, VA Medical Center of Los Angeles, Los Angeles, Calif; Narendra Singh, MD, Scarborough Cardiology Research, Scarborough, Ontario, Canada; Nassar Smiley, MD, Northwest Ohio Cardiology Consultants, Toledo, Ohio; Eduardo Sosa, MD, Instituto de Coração, Sao Paulo, Brazil; Bruce Stambler, MD, Albert Waldo, MD, Cleveland VA Medical Centre, Cleveland, Ohio; Jonathan Steinberg, MD, St. Luke’s-Roosevelt Hospital Center, New York, NY; Laurence Sterns, MD, Fort Royal Medical Building, Victoria, British Columbia, Canada; Randle Storm, MD, Geisinger Health System, Danville, Pa; Gérald Tremblay, MD, Complexe hospitalier de la Sagamie, Chicoutimi, Quebec, Canada; Dan Tzivoni, MD, Shaare Zedek Medical Centre, Jerusalem, Israel; Tarik Vakani, MD, Halton Heart Institute, Burlington, Ontario, Canada; Govindaraj Venkatesh, St. Catharines, Ontario, Canada; Zvi Vered, MD, Assaf HaRofeh Hospital, Beer Yaacov, Israel; Elizari Marcelo Victor, MD, Hospital Ramos Mejia, Buenos Aires, Argentina; Saul Vizel, MD, Cambridge General Hospital, Cambridge, Ontario, Canada; Humberto Vidalillet, MD, Marshfield Clinic, Marshall, Wis; Michael Weigel, MD, Medicine Hat, Alberta, Canada; Ted Weiss, MD, Hadassah Medical Centre, Jerusalem, Israel; Zaev Wulfhart, MD, The Newmarket Cardiology Research Group, Newmarket, Ontario, Canada; George Wyse, MD, University of California, Medical Clinic, Calgary, Alberta, Canada; Leandro Zimmermann, MD, Porto Alegre, Brazil; Jorge Gonzalez Zuelgaray, MD, Hospital Universitario de la Universidad Austral, Buenos Aires, Argentina.

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Coordinating and Methods Centre
Montreal Heart Institute, Faculty of Medicine, University of Montreal, Montreal; Dominique Johnson, PhD (Director), Stéphane Bourque, MSc, Marie-Claude Guertin, PhD, Mary Morello, Manon Provencher, RN, Magali Morin, RN, Marcio Stürmer, MD, Felix Ayala Parades, MD, Sarah Timmermans, MSc, Geneviève Brassard.

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Coordinating and Methods Centre
Montreal Heart Institute, Faculty of Medicine, University of Montreal, Montreal; Dominique Johnson, PhD (Director), Stéphane Bourque, MSc, Marie-Claude Guertin, PhD, Mary Morello, Manon Provencher, RN, Magali Morin, RN, Marcio Stürmer, MD, Felix Ayala Parades, MD, Sarah Timmermans, MSc, Geneviève Brassard.