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Canadian Implantable Defibrillator Study (CIDS)
A Randomized Trial of the Implantable Cardioverter Defibrillator Against Amiodarone

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Background—Patients surviving ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) are at a high risk of death due to a recurrence of arrhythmia. The implantable cardioverter defibrillator (ICD) terminates VT or VF, but it is not known whether this device prolongs life in these patients compared with medical therapy with amiodarone.

Methods and Results—A total of 659 patients with resuscitated VF or VT or with unmonitored syncope were randomly assigned to treatment with the ICD or with amiodarone. The primary outcome measure was all-cause mortality, and the secondary outcome was arrhythmic death. A total of 328 patients were randomized to receive an ICD. A thoracotomy was done in 33, no ICD was implanted in 18, and the rest had a nonthoracotomy ICD. All 331 patients randomized to amiodarone received it initially. At 5 years, 85.4% of patients assigned to amiodarone were still receiving it at a mean dose of 255 mg/day, 28.1% of ICD patients were also receiving amiodarone, and 21.4% of amiodarone patients had received an ICD. A nonsignificant reduction in the risk of death was observed with the ICD, from 10.2% per year to 8.3% per year (19.7% relative risk reduction; 95% confidence interval, −7.7% to 40%; $P=0.142$). A nonsignificant reduction in the risk of arrhythmic death was observed, from 4.5% per year to 3.0% per year (32.8% relative risk reduction; 95% confidence interval, −7.2% to 57.8%; $P=0.094$).

Conclusions—A 20% relative risk reduction occurred in all-cause mortality and a 33% reduction occurred in arrhythmic mortality with ICD therapy compared with amiodarone; this reduction did not reach statistical significance. (***Circulation***. 2000;101:1297-1302.)

Key Words: heart arrest ■ tachycardia ■ amiodarone ■ defibrillators, implantable

The implantable cardioverter defibrillator (ICD) detects and rapidly terminates ventricular fibrillation (VF) and ventricular tachycardia (VT). Antiarrhythmic drug therapy has been the primary treatment for patients with a history of resuscitated VF and/or sustained VT who are at a high risk of death. However, large randomized trials have raised major concerns about the lack of efficacy and the proarrhythmic potential of Vaughan Williams Class I drugs[1] and at least one Class III drug.[2] Amiodarone, however, is still considered an effective antiarrhythmic agent that is largely free of proarrhythmic effects. Recently, a meta-analysis of randomized, controlled trials of amiodarone confirmed that this drug reduces arrhythmic death and has a modest beneficial effect on overall mortality in high-risk patients.[3] Recently, the Antiarrhythmic versus Implantable Defibrillator (AVID) study reported a reduction in mortality with the ICD com-

pared with antiarrhythmic drug therapy in patients with VF or VT.[4] The purpose of the present study was to compare the efficacy of the ICD and amiodarone for the prevention of death in patients with previous sustained ventricular arrhythmia.

Methods

Inclusion Criteria

Patients were eligible for this study if, in the absence of either recent acute myocardial infarction (≤72 hours) or electrolyte imbalance, they manifested any of the following: (1) documented VF; (2) out-of-hospital cardiac arrest requiring defibrillation or cardioversion; (3) documented, sustained VT causing syncope; (4) other documented, sustained VT at a rate ≥150 beats/min, causing presyncope or angina in a patient with a left ventricular ejection fraction ≤35%; or (5) unmonitored syncope with subsequent documentation of either spontaneous VT≥10 s or sustained (≥30 s)

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monomorphic VT induced by programmed ventricular stimulation. Patients could meet inclusion criteria 3 or 4 on the basis of a ventricular tachyarrhythmia induced in the electrophysiology laboratory if both of the following conditions were met: (1) they had prior, spontaneous, documented, sustained VT and (2) the induced arrhythmia in the electrophysiology laboratory was monomorphic, sustained VT.

Exclusion Criteria

Patients were excluded for any of the following reasons: (1) ICD or amiodarone not considered appropriate as a treatment for the tachyarrhythmia, (2) excessive perioperative risk for ICD implantation; (3) previous amiodarone therapy for ≥6 weeks; (4) nonarrhythmic medical condition making 1-year survival unlikely, and (5) long-QT syndrome. Eligible patients giving informed consent were entered into the study. The study protocol was reviewed and approved by the Institutional Review Board/Ethics Committee at each of the participating clinical centers.

Randomization

Central randomization was stratified by clinical center and by left ventricular ejection fraction (≤35% and >35%).

ICD

Patients randomized to receive the ICD were scheduled for surgery at the earliest possible date. Implant criteria were met with 3 consecutive successful defibrillations at ≥10 J below maximum device output. Either thoracotomy or nonthoracotomy lead systems were used.

Amiodarone

Patients randomized to amiodarone received it in the following manner: ≥1200 mg/day for ≥1 week in the hospital, ≥400 mg/day for ≥10 weeks, and then ≥300 mg/day. In patients who developed intolerable side effects, the dose of amiodarone could be lowered to a minimum of 200 mg/day. All patients were seen for follow-up at 2 months and 6 months after randomization and every 6 months thereafter.

Cointervention

Antiarrhythmic drugs could be used for patients in either treatment group to control supraventricular or nonsustained ventricular tachycardias that were symptomatic or that might cause discharge of the ICD.

Outcome Events

The primary outcome event was death from any cause. The secondary outcome event was arrhythmic death; this was based on the clinical classification of cardiac deaths developed by Hinkle and Thaler.[5] All deaths were adjudicated by an External Validation Committee whose members had no other affiliation to the study. Despite best efforts, it was not always possible to blind the External Validation Committee to treatment allocation. Results of ICD interrogation after death were not used to determine cause-specific mortality because this information was only available in ICD patients.

Statistical Methods

The cumulative mortality experience of each treatment group was summarized as a survival curve, which was estimated using the Kaplan-Meier method.[6] The survival curves were compared using a Mantel-Haenszel test incorporating stratification for left ventricular ejection fraction.[7] Cox's proportional hazards method was used to adjust for imbalances in baseline prognostic risk and to investigate potential subgroup effects.[8]

The study was originally designed with a primary outcome of arrhythmic death; however, in 1993, the Steering Committee decided to change the primary outcome measure to all-cause mortality because of concerns that the ICD might prevent some arrhythmic

TABLE 1. Patient Characteristics

	Amiodarone (n=331)	ICD (n=328)
Age, y, mean±SD	63.8±9.9	63.3±9.2
Male sex, %	83.7	85.4
Index arrhythmia, %		
VF or cardiac arrest	50.1	45.1
VT with syncope	10.6	15.9
Other VT	26.9	23.8
Unmonitored syncope	12.4	15.2
Cardiac history, %		
Angina pectoris	57.1	51.2
Myocardial infarction	75.8	77.1
CABG surgery	28.1	31.4
Congestive heart failure, %		
None	49.5	51.2
NYHA Class 1 or 2	39.9	37.8
NYHA Class 3 or 4	10.6	11.0
Left ventricular function		
LVEF, mean±SD	33.3±14.1	34.3±14.5
LVEF<20, %	13.3	11.3
Primary cardiac diagnosis, %		
IHD with MI	73.1	75.6
IHD without MI	9.1	7.3
Dilated cardiomyopathy	10.6	8.5
Valvular heart disease	3.0	1.2
Other heart disease	2.4	3.7
No heart disease	1.8	3.7
Medical conditions, %		
Liver disorder	2.7	1.5
Respiratory disease	17.8	17.5
Thyroid disease	3.9	5.8
Chest x-ray, %		
Interstitial abnormality*	17.6	15.5
Other abnormality	34.6	31.4
Baseline EP study, %		
Ever done	62.8	62.2
Inducible VT or VF	147/208 (70.7%)	154/204 (75.7%)
Coronary angiography, %		
Ever done	78.2	75.6
3-Vessel disease	18.9	19.0

CABG indicates coronary artery bypass grafting; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; IHD, ischemic heart disease; MI, myocardial infarction; and EP, electrophysiological.

*Interstitial abnormality was defined as having been documented on a previous standard chest x-ray report.

deaths but, due to competing risks, have little effect on overall survival. This change led to an increase in the patient enrollment target from 400 to 650 patients, which provided 90% power to detect a relative reduction in all-cause mortality of 33% by the ICD from an anticipated 3-year mortality rate of 30% on amiodarone. Crossover rates of 5% per year for both treatment groups were anticipated. The primary analysis was originally conceived of as a one-sided comparison with a clear directional hypothesis that the ICD would be superior to amiodarone. When the study was initiated, amiodarone

TABLE 2. Percentage of Patients Receiving Concomitant Antiarrhythmic Medications

	Hospital Discharge		1 Year		3 Years		5 Years	
	Amiodarone	ICD	Amiodarone	ICD	Amiodarone	ICD	Amiodarone	ICD
β-Blocker*	21.4	33.5	21.2	37.0	19.0	33.3	22.4	29.6
Sotalol	1.5	19.8	2.5	21.5	4.9	23.3	4.1	24.1
Digoxin	22.7	29.6	21.9	34.5	22.5	34.7	24.5	33.3
Class I†	2.4	5.5	2.8	8.4	2.1	10.0	2.0	9.3

*Any β-blocker other than sotalol.

†Any Vaughan Williams Class I antiarrhythmic drug.

was standard therapy, and we had no interest in proving that ICD treatment was worse than amiodarone. In response to the review process, 2-sided statistics are presented. Analysis was based on the intention-to-treat principle. An External Safety and Efficacy Monitoring Committee reviewed the unblinded study data every 6 months for safety and did 3 formal interim analyses of efficacy on the basis of an intention to stop the study early in favor of ICD if 1-sided $P \leq 0.001$.

Results

Patient Enrollment

Patient enrollment occurred between October 1990 and January 1997. The mean duration of follow-up was 2.9 and 3.0 years for amiodarone and ICD patients, respectively. The baseline demographic and clinical characteristics of the 2 treatment groups, as shown in Table 1, were well balanced.

Therapy

Among the 328 patients randomly allocated to receive an ICD, 310 (94.5%) received one. The median time to ICD implantation was 7 days, and 91.3% of patients received the ICD within 21 days of randomization. A thoracotomy was performed in 33 patients; this procedure had a 30-day mortality rate of 3.3% (1 patient). A nonthoracotomy lead system was implanted in the rest of the patients; the 30-day mortality rate for this procedure was 0.36% (1 patient). Of the 18 patients who did not receive an ICD, 7 died in the hospital while awaiting ICD surgery; in 10 patients, either the patient or his or her physician decided against an ICD after randomization; and a technical problem occurred in 1 patient. A total of 16 patients had their ICD permanently or temporarily explanted because of infection, heart transplantation, or patient preference. The total number of patient-years at risk while patients did not have an ICD in place due to cancelled or delayed implantation or ICD explantation was 72.5 years; this

represents 7.3% of total patient-years at risk for the ICD patients. The percentage of patients randomized to an ICD who were also receiving amiodarone at 1, 3, and 5 years after randomization were 17.4%, 21.7%, and 28.1%, respectively. The mean amiodarone dose in these patients at 3 years was 277 mg/day. The cumulative risk of receiving an ICD shock was 65.4% at 4 years.

The proportion of patients assigned to amiodarone who were receiving it at 2 months and 1, 3, and 5 years was 96.2%, 88.7%, 80.3%, and 85.4%, respectively, with mean doses of 390, 306, 262, and 255 mg/day, respectively. Of the 331 patients allocated to amiodarone, 52 received an ICD. The cumulative proportion of amiodarone patients receiving an ICD at 1, 3, and 5 years was 9.0%, 18.6%, and 21.4%. The median time from randomization to ICD implantation was 334 days for these patients. Patients allocated to amiodarone were also treated with an ICD for a total of 111 patient-years, which was 11.6% of the total patient-years at risk for this treatment group.

Concomitant Medications

Table 2 summarizes the use of antiarrhythmic medications other than amiodarone during follow-up. An imbalance existed between the use of each of the 4 types of antiarrhythmic drugs: significantly more drugs were used in patients randomized to ICD treatment. This imbalance was most marked for sotalol, which was taken by many more ICD patients than amiodarone patients. The imbalance in the use of either sotalol or another β-blocker was large: 22.9% for the amiodarone group and 53.3% for the ICD group.

Fatal Outcomes

Table 3 summarizes the fatal outcomes of patients in the study. A nonsignificant reduction in all-cause mortality oc-

TABLE 3. Outcome Event Rate Summary

Event Cluster	Amiodarone (n=331)		ICD (n=328)		Adjusted Treatment Effect*		
	No. of Events	Rate/y	No. of Events	Rate/y	RRR	95% CI	P
All-cause mortality	98	10.2%	83	8.3%	19.7%	−7.7% to 40.0%	0.142
Arrhythmic death	43	4.5%	30	3.0%	32.8%	−7.2% to 57.8%	0.094
Other cardiac death	40	4.2%	37	3.7%	13.5%	−35.4% to 44.7%	0.526
Noncardiac vascular death	2	0.2%	3	0.3%	−36.6%	−719.8% to 77.2%	0.732
Nonvascular death	13	1.4%	13	1.3%	4.5%	−106.1% to 55.7%	0.908

The total patient-years of follow-up for patients allocated to amiodarone and ICD were 957 and 995, respectively.

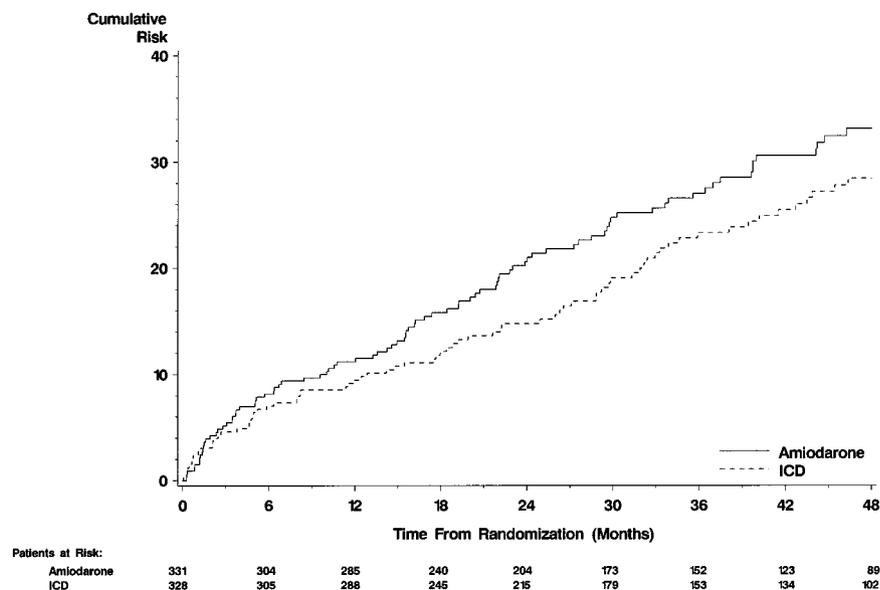*Adjusted for left ventricular ejection fraction stratification.

Figure 1. Kaplan-Meier plots depicting cumulative risk of death from any cause for treatment groups on basis of intention-to-treat analysis (*P*=0.142).

curred with the ICD compared with amiodarone, from 10.2% per year to 8.3% per year (19.7% relative risk reduction [RRR]; 95% confidence interval [CI], −7.7% to 40.0%; *P*=0.142). There was also a nonsignificant reduction in arrhythmic death with the ICD, from 4.5% per year to 3.0% per year (32.8% RRR; 95% CI, −7.2% to 57.8%; *P*=0.094). Only minor differences existed in the rates of other cardiac death, noncardiac vascular death, and nonvascular death. Total cardiac death was reduced from 8.6% per year to 6.7% per year (23.4% RRR; 95% CI, −5.7% to 44.5%; *P*=0.104). Figure 1 shows the Kaplan-Meier plots of the cumulative risk of death over 4 years for the ICD and amiodarone treatment groups. Table 4 shows the mortality rates at 1, 2, and 3 years for each treatment group, as well as the relative and absolute risk reductions. The RRR for total mortality was 15.4% at 1 year, 29.7% at 2 years, and 13.7% at 3 years.

Subgroups

Figure 2 illustrates the hazard ratios and the 95% CIs for all-cause mortality in different subgroups of patients. None of the tests of interaction between the various baseline patient characteristics and treatment was significant. Thus, no identifiable subgroup benefited significantly more or less from the ICD.

TABLE 4.   Cumulative Risks Over Time

Outcome	1 Year	2 Years	3 Years
Total mortality			
ICD	9.46%	14.75%	23.32%
Amiodarone	11.18%	20.97%	27.03%
ARR	1.72%	6.22%	3.71%
RRR	15.4%	29.7%	13.7%
Arrhythmic mortality			
ICD	4.37%	6.68%	9.77%
Amiodarone	6.23%	9.74%	11.88%
ARR	1.86%	3.06%	2.11%
RRR	29.9%	31.4%	17.8%

ARR indicates absolute risk reduction.

Adverse Experiences

Adverse experiences potentially related to ICD or amiodarone therapy are shown in Table 5. The risk of pulmonary infiltrate in amiodarone patients was 1.9% per year. In ICD patients, device malfunction was rare, and pocket infection occurred at a rate of 1.4% per year.

Discussion

This randomized trial compared ICD therapy with amiodarone therapy in patients who had VF, sustained VT, or unmonitored syncope likely due to VT. The study was designed to detect reliably a relative reduction in risk of death of 33% from an expected 3-year mortality rate of 30% on amiodarone. The observed mortality rate in the amiodarone group was, as anticipated, almost 30%, but the observed RRR in all-cause mortality resulting from the use of the ICD was only 19.7%, which is not conventionally significant. However, the analysis of cause-specific mortality in this study supports the presumed mechanism of action of ICD therapy, which is to prevent deaths caused by ventricular arrhythmia. Fifteen fewer deaths occurred in patients randomized to the ICD than in those randomized to amiodarone; this difference was accounted for by 13 fewer arrhythmic deaths and by 2 fewer nonarrhythmic deaths. Thus, almost all of the observed benefit in mortality risk was due to a reduction in arrhythmic death, as would be expected from an antiarrhythmic intervention. This increases confidence that the observed mortality reduction may not be due to chance but to a real benefit of the ICD.

The observed risk reduction in this trial (CIDS) is smaller than that observed in the AVID trial, which had a very similar design.[4] The patients and treatments studied in AVID were almost identical to those in CIDS. Although the design of AVID included the possibility of patients in the medical arm receiving sotalol, virtually all of the medically treated patients actually received amiodarone. At 3 years, mortality was reduced by the ICD by 31% (95 CI, −10% to 52%) in the AVID trial and by 20% (95% CI, −8% to 40%) in CIDS. Although the observed RRR associated with the ICD is less in
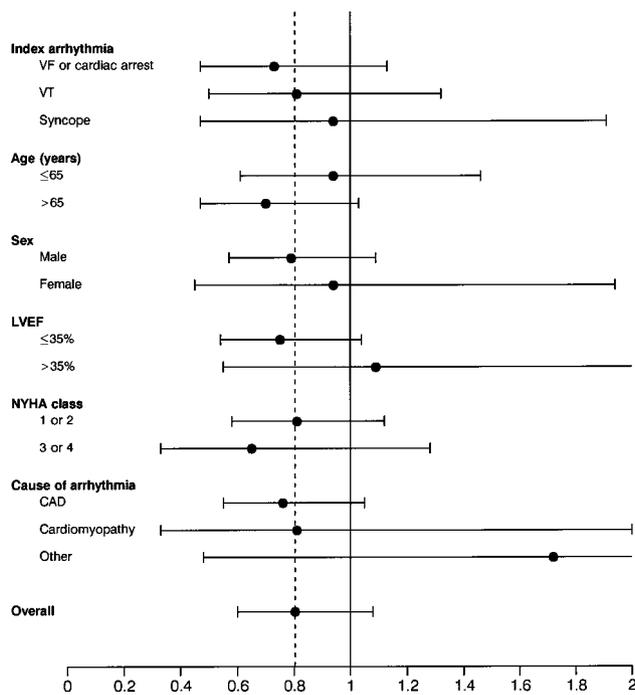
Figure 2. Point estimate (and 95% CIs) of hazard ratios associated with ICD compared with amiodarone therapy for outcome of death from any cause. This figure subdivides total population in various ways according to baseline characteristics. ICD had no significantly greater benefit for any of subgroups shown (*P* value for heterogeneity not significant). LVEF indicates left ventricular ejection fraction; NYHA, New York Heart Association; and CAD, coronary artery disease.

CIDS than in the AVID study, the 95% CIs of the 2 estimates overlap substantially, indicating that the 2 results are not inconsistent with each other. The proportion of medically treated patients actually receiving amiodarone was similar between the studies, as was the mean amiodarone dose. A higher proportion of patients received concomitant β-blocker or sotalol therapy in the amiodarone group in CIDS (23.7%)

TABLE 5.   Adverse Experiences

Adverse Experiences Ever Reported	Amiodarone (n=331)		ICD (n=328)	
	n	%	n	%
Pulmonary infiltrate	18	5.7		
Visual symptoms (blurred, halo, or decreased)	48	14.5		
Bradycardia	10	3.0		
Skin discoloration	21	6.3		
Photosensitivity	34	10.3		
Ataxia	97	17.2		
Tremor	91	15.4		
Insomnia	64	19.3		
Peripheral neuropathy	1	0.3		
ICD product discomfort			25	7.6
ICD malfunction			2	0.6
ICD pocket infection			15	4.6
ICD lead dislodgement/fracture			8	2.4

than in AVID (16.8%) at 1 year. This could have enhanced the effectiveness of amiodarone in CIDS, because a positive interaction between amiodarone and β-blockers has been reported.[9,10]

At 3 years, the rate of concomitant use of amiodarone in ICD patients was 33.7% in AVID and 21.7% in CIDS, and the use of the ICD in amiodarone patients was 24.3% in AVID and 18.6% in CIDS. These higher rates of treatment crossover in AVID would be expected to reduce the observed treatment effect rather than to increase it. The AVID trial was stopped early due to a greater than expected benefit of the ICD over medical therapy. Trials stopped early for this reason have a general tendency to overestimate the benefit of treatment; this may explain, in part, the greater RRR observed in AVID. As shown in Table 4, the RRR in CIDS decreased to 13.7% at year 3. It is possible that the smaller ICD benefit observed in CIDS is due to its longer duration of follow-up compared with the AVID study.

The statistical power of a clinical trial is more directly dependent on the total number of events than on the number of patients. The AVID study enrolled more patients than CIDS, but it followed them for a shorter amount of time; thus, the total number of fatal events in the 2 studies was similar (202 for AVID, 181 for CIDS). We conclude that the overall similarity in design and execution of CIDS and AVID and the overlapping CIs indicate that the difference in observed risk reduction is most likely due to chance. It is probable that the true benefit of the ICD over amiodarone lies between the estimates of AVID and CIDS.

The significantly higher use of β-blockers and digoxin among ICD patients compared with amiodarone patients in this study was anticipated because it is common to use these drugs in patients with an ICD. β-blockers are an effective treatment in patients after a myocardial infarction; they produce a 20% reduction in total death and a 30% reduction in arrhythmic death.[11] Furthermore, evidence exists that the effectiveness of amiodarone may be potentiated by β-blockers.[9,10] It is, therefore, possible that the imbalance in β-blocker therapy accounts for some of the observed treatment benefit of the ICD in both CIDS and AVID. The degree to which this occurred is uncertain because the cointervention was not random, and there are no valid means of correcting for it.

In summary, CIDS observed a relative reduction in all-cause mortality of 19.7% with the ICD compared with amiodarone (which is not statistically significant), with a 33% relative reduction in arrhythmic death. In light of the results of the AVID study, CIDS provides further support for the superiority of the ICD over amiodarone in the treatment of patients with symptomatic sustained VT or resuscitated cardiac arrest.

Appendix

CIDS Participants

The number of patients enrolled by each center is given in parentheses.

Canada
St. Michael's Hospital, Toronto, Ontario (123): P. Dorian, D. Newman, J. Mitchell, and M. Greene; Hamilton Health Sciences Corporation, Hamilton, Ontario (98): S. Connolly, C. LeFeuvre, J. Kwasney, and S. Morino; Institute de Cardiologie de Montreal, Montréal, Quebec (96): D. Roy, M. Dubuc, M. Talajic, and B. Thibault; Calgary General Hospital, Calgary, Alberta (79): R. Sheldon and M. Koshman; Ottawa Civic Hospital, Ottawa, Ontario (44): M. Green, A. Tang, and M. Luce; Foothills Hospital, Calgary, Alberta (41): B. Mitchell, D. Wyse, H.J. Duff, A. Gillis, and P. Cassidy; University Hospital, London, Ontario (31): G. Klein, R. Yee, and C. Norris; Royal Victoria Hospital, Montreal, Quebec (21): M. Sami and D. Liebling; Toronto General Hospital, Toronto, Ontario (21): D. Cameron, E. Downar, L. Harris, M. Waxman, and B. Weller; Hopital du Sacre-Coeur, Montreal, Quebec (17): T. Kus, F. Molin, P. Pagé, and G. Gaudette; Queen Elizabeth, Health Sciences Center, Halifax, Nova Scotia (15): M.J. Gardner, L. Sterns, and G. Blackmore; University of Alberta Hospital, Edmonton, Alberta (10): S. Gulamhusein, K. Kavanagh, S. Kimber, K. Paradon, and R. Tabler; Currans Health Center, Thunder Bay, Ontario (10): C. Lai and K. Kwiatkowski; Montreal General Hospital, Montreal, Quebec (9): M. Rosengarten; Quebec Heart Institute, Saint-Foy, Quebec (7): G. O'Hara, M. Gilbert, F. Philippon, and L. Charbonneau; Royal University Hospital, Saskatoon, Saskatchewan (4): B. Cujec and S. Summach; University Hospital, Vancouver, British Columbia (3): J. Yeung, C. Kerr, C. McIlroy, and M. Hawes; St. Paul's Hospital, Vancouver, British Columbia (2): J. Boone and S. Flavelle; Victoria Clinic, Victoria, British Columbia (1): J. Bonet and K. Ilott.

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External Safety and Efficacy and Monitoring Committee
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Acknowledgments

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