

EFFECTS OF PHYSIOLOGIC PACING VERSUS VENTRICULAR PACING ON THE RISK OF STROKE AND DEATH DUE TO CARDIOVASCULAR CAUSES

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ABSTRACT

Background Evidence suggests that physiologic pacing (dual-chamber or atrial) may be superior to single-chamber (ventricular) pacing because it is associated with lower risks of atrial fibrillation, stroke, and death. These benefits have not been evaluated in a large, randomized, controlled trial.

Methods At 32 Canadian centers, patients without chronic atrial fibrillation who were scheduled for a first implantation of a pacemaker to treat symptomatic bradycardia were eligible for enrollment. We randomly assigned patients to receive either a ventricular pacemaker or a physiologic pacemaker and followed them for an average of three years. The primary outcome was stroke or death due to cardiovascular causes. Secondary outcomes were death from any cause, atrial fibrillation, and hospitalization for heart failure.

Results A total of 1474 patients were randomly assigned to receive a ventricular pacemaker and 1094 to receive a physiologic pacemaker. The annual rate of stroke or death due to cardiovascular causes was 5.5 percent with ventricular pacing, as compared with 4.9 percent with physiologic pacing (reduction in relative risk, 9.4 percent; 95 percent confidence interval, -10.5 to 25.7 percent [the negative value indicates an increase in risk]; $P=0.33$). The annual rate of atrial fibrillation was significantly lower among the patients in the physiologic-pacing group (5.3 percent) than among those in the ventricular-pacing group (6.6 percent), for a reduction in relative risk of 18.0 percent (95 percent confidence interval, 0.3 to 32.6 percent; $P=0.05$). The effect on the rate of atrial fibrillation was not apparent until two years after implantation. The observed annual rates of death from all causes and of hospitalization for heart failure were lower among the patients with a physiologic pacemaker than among those with a ventricular pacemaker, but not significantly so (annual rates of death, 6.6 percent with ventricular pacing and 6.3 percent with physiologic pacing; annual rates of hospitalization for heart failure, 3.5 percent and 3.1 percent, respectively). There were significantly more perioperative complications with physiologic pacing than with ventricular pacing (9.0 percent vs. 3.8 percent, $P<0.001$).

Conclusions Physiologic pacing provides little benefit over ventricular pacing for the prevention of stroke or death due to cardiovascular causes. (N Engl J Med 2000;342:1385-91.)

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PERMANENT cardiac-pacemaker therapy is widely recognized as beneficial in the treatment of various types of symptomatic bradycardia. Early pacemakers were capable of pacing only one chamber of the heart, usually the right ventricle. More recently, dual-chamber pacemakers have been devised that can sense the activity of, and pace, both the atrium and the ventricle and thus are able to achieve atrioventricular synchrony (so-called physiologic pacing). In patients with complete atrioventricular nodal block, dual-chamber pacing is superior to ventricular pacing in terms of increasing the heart rate during exercise.¹ Now, however, sensors are available that provide a means by which an adequate heart-rate response to exercise can be achieved without atrial sensing.² The results of several nonrandomized, observational studies of patients with pacemakers have suggested that physiologic pacing may reduce the risk of atrial fibrillation, stroke, and death.³⁻⁶ A small, randomized study comparing physiologic (atrial) pacing with ventricular pacing in patients with sinus-node disease demonstrated a reduction in the risk of stroke, and extended follow-up showed a reduction in the rates of death and atrial fibrillation as well.^{7,8} The purpose of this study was to provide a more precise estimate of the benefit of physiologic pacing in patients requiring a pacemaker for symptomatic bradycardia.

METHODS

Patients were eligible for this study if they were scheduled for an initial implantation of a pacemaker to correct symptomatic bradycardia, did not have chronic atrial fibrillation, and were at least 18 years old. Patients were excluded if the indication for pacemaker implantation was related to the presence of atrioventricular nodal ablation or if they were expected to die of a noncardiovascular cause within two years. In order to maintain the usual practice of

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*Centers and investigators participating in the study are listed in the Appendix.

the centers participating in the study and to conduct the study without increasing the budget allocated to pacemaker implantation at any center, the principal investigator at each clinical center chose, in advance, one of the following ratios of ventricular pacing to physiologic pacing for randomization: 67:33, 60:40, 50:50, 40:60, or 33:67. The calculation of the total number of patients required to provide adequate statistical power took into account an expected imbalance in the size of the treatment groups.

After obtaining written informed consent, we randomly assigned eligible patients to one of the two types of pacing within 48 hours before a scheduled pacemaker implantation. Patients assigned to receive a physiologic pacemaker could receive an atrial pacemaker if an optional intraoperative atrial pacing test demonstrated 1:1 atrioventricular conduction up to a rate of 130 beats per minute. The other patients assigned to physiologic pacing received a dual-chamber pacemaker. The patients were required to receive a rate-adaptive pacemaker if there was clinical evidence of chronotropic incompetence (inadequate heart-rate response to exercise) or if they had permanent third-degree atrioventricular nodal block and were randomly assigned to the ventricular-pacing group.

The first follow-up visit occurred between two and eight months after randomization, and there were yearly visits thereafter. At each visit, pacemaker function was assessed and the occurrence of any outcome events was determined. The primary outcome event in the study was the occurrence of either stroke or death due to cardiovascular causes. Death due to cardiovascular causes was defined as any death that did not have a clear noncardiovascular cause, such as trauma, cancer, infection, or respiratory failure. Stroke was defined as a focal neurologic deficit of sudden onset, such as would be expected with occlusion of one of the major cerebral arteries, which did not resolve within 24 hours. If a patient had more than one stroke, only the first was counted. The secondary outcome events were death from any cause, documented atrial fibrillation lasting more than 15 minutes, and admission to the hospital for congestive heart failure (as ascertained by evidence of interstitial or alveolar edema on chest radiography).

All reported primary and secondary outcome events were reviewed by an adjudication committee whose members were unaware of the patients' treatment assignments. If there was disagreement with the clinical center's report, the clinical investigator was asked to address the issue and was given the opportunity to provide further information. This committee made the final decision about the classification of each reported event.

With an enrollment period of 3 years and 2 further years of follow-up, the mean duration of follow-up was expected to be 3.5 years (range, 2 to 5 years). The annual rate of stroke or death due to cardiovascular causes was anticipated to be 5.0 percent in the ventricular-pacing group. For the study to have 90 percent power (with a two-sided type I error of 5 percent) to detect a 30 percent reduction in the relative risk of the primary outcome, we estimated that 2550 patients would need to be enrolled. The risk of the outcome events in the two treatment groups was estimated by the Kaplan-Meier method, and the results were compared with the use of log-rank tests.^{9,10} The effects of base-line variables on the benefit associated with physiologic pacing were evaluated with the use of Cox proportional-hazards modeling.¹¹ Since the proportion of patients randomly assigned to each intervention varied from center to center according to the prespecified ratios, all statistical tests were stratified according to the individual center and all analyses were based on the intention-to-treat principle. The proportional-hazards assumption was tested with the method of Grambsch and Therneau.¹² All P values are two-sided.

An external safety and efficacy monitoring committee reviewed the study data every six months and performed two formal interim analyses of efficacy, one after half of the patients had completed follow-up and the other after three quarters of the patients had completed follow-up. The purpose of these analyses was to determine whether physiologic pacing was superior to ventricular pacing with respect to the primary outcome ($P < 0.001$) and to notify the steering committee if this was the case. The study was approved by the institutional review board or ethics committee of each clinical center.

RESULTS

Screening of Patients

A total of 7734 patients underwent implantation of a first pacemaker at participating clinical centers during the study enrollment period. Of these, 4499 (58 percent) were eligible for the study. Written informed consent was obtained from 2568 eligible patients (57 percent), who were enrolled in the study and randomly assigned to ventricular pacing or physiologic pacing. The other 1931 eligible patients were not enrolled because they declined to participate (16 percent), their physician declined to participate (56 percent), or for technical reasons they were not asked to participate (28 percent). Eligible patients who were not enrolled had a mean age of 71 years, and 49 percent had symptoms of heart failure of New York Heart Association functional class II or higher. Among the patients who were eligible but not enrolled, the indication for pacing was sinoatrial nodal disease in 35 percent and atrioventricular block in 46 percent. Physiologic pacing was used in 41 percent, and the rest received ventricular pacing.

Treatment Assignment

Because of the variable and unequal nature of the randomization ratios, 1474 patients were assigned to ventricular pacing and 1094 patients to physiologic pacing. Most clinical centers used a randomization ratio (ventricular pacing to physiologic pacing) of 67:33 or 60:40; the overall ratio was 57:43. Among the patients assigned to ventricular pacing, 99.1 percent received a ventricular device, 0.7 percent received a physiologic device, and 0.2 percent received no pacemaker. The majority of patients randomly assigned to ventricular pacing (74.6 percent) received a device capable of rate-adaptive pacing. Of the patients randomly assigned to physiologic pacing, 93.5 percent received a physiologic device, 0.9 percent received no pacemaker, and 5.6 percent received a ventricular device (most often because of technical problems with atrial-lead implantation or the occurrence of atrial fibrillation at the time of surgery). An atrial pacemaker was implanted in 5.2 percent of the patients randomly assigned to physiologic pacing after appropriate testing of atrioventricular nodal function.

At the time of hospital discharge after pacemaker implantation, the pacemakers of 99.2 percent of the patients assigned to ventricular pacing were programmed to a ventricular mode and 91.7 percent of the devices of the patients assigned to physiologic pacing were programmed to a physiologic mode. Subsequently, the percentages of patients assigned to ventricular pacing who had their devices programmed to a physiologic mode at one, three, and five years were 2.1 percent, 2.7 percent, and 4.3 percent, respectively. The percentages of patients assigned to physiologic pacing who had their devices programmed to a ventricular mode at one, three, and five years

were 10.8 percent, 12.8 percent, and 17.1 percent, respectively. Thus, throughout the study, there was a substantial difference between the groups in the percentage of patients who actually received the type of pacing to which they had been assigned.

Complications related to pacemaker implantation, which are summarized in Table 1, were more frequent among the patients assigned to physiologic pacing than among those assigned to ventricular pacing, primarily because of the added complexity of implantation, resulting from the insertion of the additional atrial lead.

Base-Line Characteristics

The base-line clinical characteristics of the two groups of patients are shown in Table 2. The two treatment groups were very well balanced with regard to these characteristics. The mean age of the patients was 73 years, and 59 percent were men. The most common indication for pacing was atrioventricular block, which was present in about 60 percent of the patients. Sinoatrial nodal disease was present in just over 40 percent of the patients. One of the following rhythms (which constitute an unequivocal requirement for pacing) was documented in 66.7 percent of patients: sinoatrial-node arrest lasting more than four seconds, sinus bradycardia (heart rate, <40 beats per minute), or third-degree atrioventricular block. Vascular disease (indicated by a history of myocardial infarction, coronary artery disease, stroke, or transient ischemic attacks) was present in 36 percent of the patients. A fifth of the patients had previously had intermittent atrial fibrillation. Roughly 70 percent of the patients had normal left ventricular function.

Outcome Events

The primary outcome event in this study was a first occurrence of either stroke or death due to car-

diovascular causes. The annual rate of the primary outcome event was 5.5 percent among the patients with a ventricular pacemaker and 4.9 percent among those with a physiologic pacemaker (reduction in relative risk, 9.4 percent; 95 percent confidence interval, -10.5 to 25.7 percent [the negative value indicates an increase in risk]; P=0.33). A reduction in risk of the size hypothesized (30 percent) was thus ruled out with reasonable certainty by the upper boundary of the 95 percent confidence interval. Figure 1 shows the cumulative risk of the primary outcome in the two treatment groups. The type of pacemaker had virtually no effect on the annual rate of death from all causes, which was 6.6 percent among the patients with a ventricular pacemaker and 6.3 percent among those with a physiologic pacemaker (reduction in relative risk, 0.9 percent; 95 percent confidence interval, -18.1 to 16.8 percent; P=0.92). The annual

TABLE 1. INCIDENCE OF PERIOPERATIVE COMPLICATIONS.*

COMPLICATION	VENTRICULAR PACING	PHYSIOLOGIC PACING	P VALUE
	(N=1471)	(N=1084)	
	% of patients		
Any	3.8	9.0	<0.001
Pneumothorax	1.4	1.8	0.42
Hemorrhage	0.4	0.2	0.32
Inadequate pacing	0.3	1.3	0.002
Inadequate sensing	0.5	2.2	<0.001
Device malfunction	0.1	0.2	0.40
Lead dislodgment	1.4	4.2	<0.001

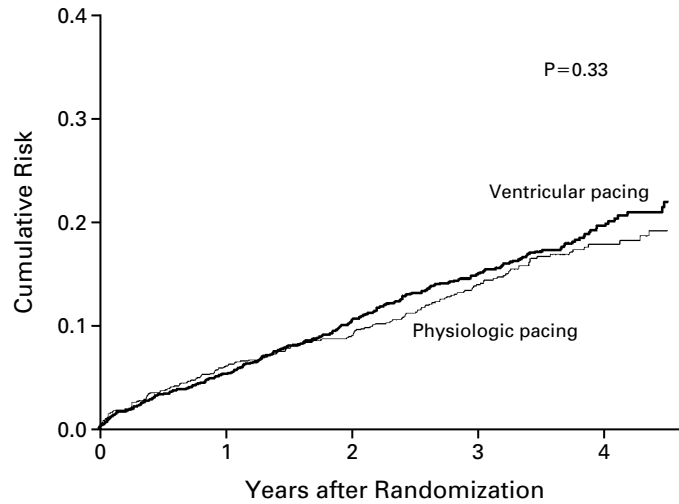
*Only patients who received a pacemaker are included. Some patients had more than one complication.

TABLE 2. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	VENTRICULAR PACING (N=1474)	PHYSIOLOGIC PACING (N=1094)
Mean age (yr)	73±10	73±10
Male sex (%)	60.2	57.0
New York Heart Association functional class ≥II (%)	37.2	41.5
Indication for pacing (%)		
Sinoatrial nodal disease	33.9	33.4
Atrioventricular nodal disease	52.2	50.8
Both sinoatrial and atrioventricular nodal disease	8.1	8.5
Other	3.7	4.8
Unknown	2.1	2.6
Medical history (%)		
Myocardial infarction	24.5	26.0
Documented coronary artery disease	17.5	17.4
Stroke or transient ischemic attack	9.3	9.7
Intermittent atrial fibrillation	20.9	21.4
Diabetes mellitus	15.5	13.8
Systemic hypertension	35.2	35.2
Medications (%)		
Anticoagulant drugs	10.4	11.9
Antiplatelet drugs	34.9	33.7
Antiarrhythmic drugs	11.5	12.6
Left ventricular function (%)†		
Clinical assessment		
Normal	51.4	51.1
Abnormal	11.6	12.2
Objective assessment		
Normal	19.4	17.5
Abnormal	15.5	16.8
Unknown	2.1	2.4
Symptoms of bradycardia (%)		
Ever had syncope	42.8	40.7
Ever had presyncope	61.3	58.0
Fatigue	63.4	59.3

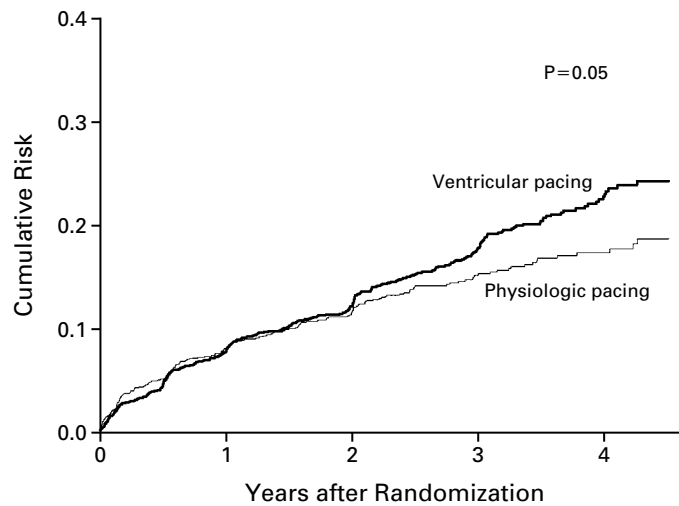
*Plus-minus values are means ±SD.

†Study investigators were asked to give their best assessment of each patient's left ventricular function on the basis of physical examination (clinical assessment) and angiographic or echocardiographic examination (objective assessment); no particular criteria were specified.



No. AT RISK					
Ventricular pacing	1474	1369	1259	847	366
Physiologic pacing	1094	1005	954	637	287

Figure 1. The Cumulative Risk of Stroke or Death Due to Cardiovascular Causes According to Mode of Cardiac Pacing.



No. AT RISK					
Ventricular pacing	1474	1276	1127	731	303
Physiologic pacing	1094	936	857	559	250

Figure 2. The Cumulative Risk of Atrial Fibrillation According to Mode of Cardiac Pacing.

rate of atrial fibrillation was significantly lower among the patients with a physiologic pacemaker (5.3 percent) than among those with a ventricular pacemaker (6.6 percent), for a reduction in relative risk of 18.0 percent (95 percent confidence interval, 0.3 to 32.6 percent; $P=0.05$). Of the 427 patients in whom atrial fibrillation developed during the study, 155 (36 percent) received anticoagulant therapy at the next

follow-up visit. Figure 2 shows the cumulative risk of atrial fibrillation for each group; the curves overlap for two years and then progressively separate. A test of whether there was a constant proportional hazard between ventricular pacing and physiologic pacing for the outcome event of atrial fibrillation ($P=0.002$) indicates that there is truly a delay before the effect of physiologic pacing on atrial fibrillation occurs.

There was no significant difference in the incidence of hospitalization for congestive heart failure between the two groups; the annual rates were 3.5 percent among the patients with a ventricular pacemaker and 3.1 percent among those with a physiologic pacemaker (reduction in relative risk, 7.9 percent; 95 percent confidence interval, -18.5 to 28.3 percent; $P=0.52$). The annual rate of stroke was 1.1 percent in the ventricular-pacing group and 1.0 percent in the physiologic-pacing group.

Subgroup Analysis

We investigated whether the presence or absence of various base-line clinical features had an effect on the effectiveness of physiologic pacing in reducing the risk of stroke or death due to cardiovascular causes (Fig. 3). There was a trend toward an interaction between age and the mode of pacing that suggested that the younger patients (those under 74 years of age) might have derived a benefit from physiologic pacing.

DISCUSSION

The main results of this large, randomized trial were that, during a mean follow-up period of three years, there was no significant effect on the risk of death, stroke, or hospitalization for congestive heart failure associated with the type of pacemaker used and that the annual rate of atrial fibrillation was significantly lower in the physiologic-pacing group (5.3 percent) than in the ventricular-pacing group (6.6 percent). The reduction in the relative risk of atrial fibrillation was moderate (18.0 percent), and the absolute reduction in risk was 3.9 percent over the course of the three-year average follow-up period of this study. Thus, for every 100 patients treated for three years with physiologic rather than ventricular pacing, the occurrence of atrial fibrillation would be prevented in 4 patients. The relatively late emergence of the benefit of physiologic pacing with respect to the incidence of atrial fibrillation (after two years) suggests that a greater benefit could become evident after longer follow-up. The potential benefit of physiologic pacing with respect to stroke was hypothesized to occur through a reduction in the incidence of atrial fibrillation. Several factors could explain the lack of effect of such treatment on stroke. The difference in the rates of atrial fibrillation between the two groups was small, and only a small fraction of patients with atrial fibrillation (5 percent) would be expected to have a stroke each year. In addition, about one third of the patients in whom atrial fibrillation developed received anticoagulant therapy, which reduced the risk of stroke. Therefore, the study did not have the power to detect a difference between the two modes of pacing in their effect on stroke. We hypothesized that the maintenance of atrioventricular synchrony would improve cardiac performance and, in turn, reduce episodes of heart failure. On the basis of our

findings, there is no reason to expect that physiologic pacing reduces the risk of heart failure. There was an increased risk of perioperative complications associated with physiologic pacing, which is not surprising given that the need for a second lead to achieve physiologic pacing in most patients would be expected to result in more procedural complications.

One of the strengths of this study was its large size, which gave it considerable statistical power. We can rule out a reduction in the risk of stroke or death due to cardiovascular causes of 30 percent or more with physiologic pacing with reasonable confidence, since the upper boundary of the 95 percent confidence interval was 25.7 percent. In addition, there was a high rate of compliance with the assigned therapy. Some patients changed from physiologic to ventricular pacing because the mode could be easily reprogrammed. The pacemaker syndrome is the occurrence of palpitations, fatigue, and presyncope, which are thought to be caused by ventricular pacing and potentially improved by physiologic pacing. Very few patients switched from ventricular pacing to physiologic pacing. This suggests that the pacemaker syndrome occurred less frequently in this study than in previous studies.¹³

The main limitation of this study is the relatively short follow-up period. The mean follow-up of three years may not have been adequate to detect a true treatment effect if there is a delay before such an effect becomes evident. Ventricular pacing may induce atrial fibrillation through changes in the atrial structure resulting from asynchronous ventricular contraction. A prolonged period of atrioventricular asynchrony may be required for atrial fibrillation to occur.

The results of this study differ from those of several previous nonrandomized studies, but those studies were probably affected by bias in the choice of pacemakers for different types of patients.³⁻⁶ A randomized trial in Denmark compared physiologic (atrial) pacing with ventricular pacing in 212 patients with sinoatrial nodal disease who were followed for a mean of 3.3 years. The investigators initially failed to demonstrate a significant effect of physiologic pacing on mortality, but a reduction in the incidence of stroke was reported.⁷ After a mean follow-up of 5.5 years, a further analysis of the same patients showed a significant relative reduction in mortality of 44 percent associated with physiologic pacing ($P=0.04$).⁸ Although these results are interesting, the assessment of statistical significance requires adjustment for multiple examinations of the data.

One difference between the Danish study and ours is the fact that only patients with sinoatrial nodal disease were included in the Danish study. This factor does not explain the differences in results, however, since there were more than 800 patients with sinoatrial nodal disease in our study and subgroup analyses show that they received no particular bene-

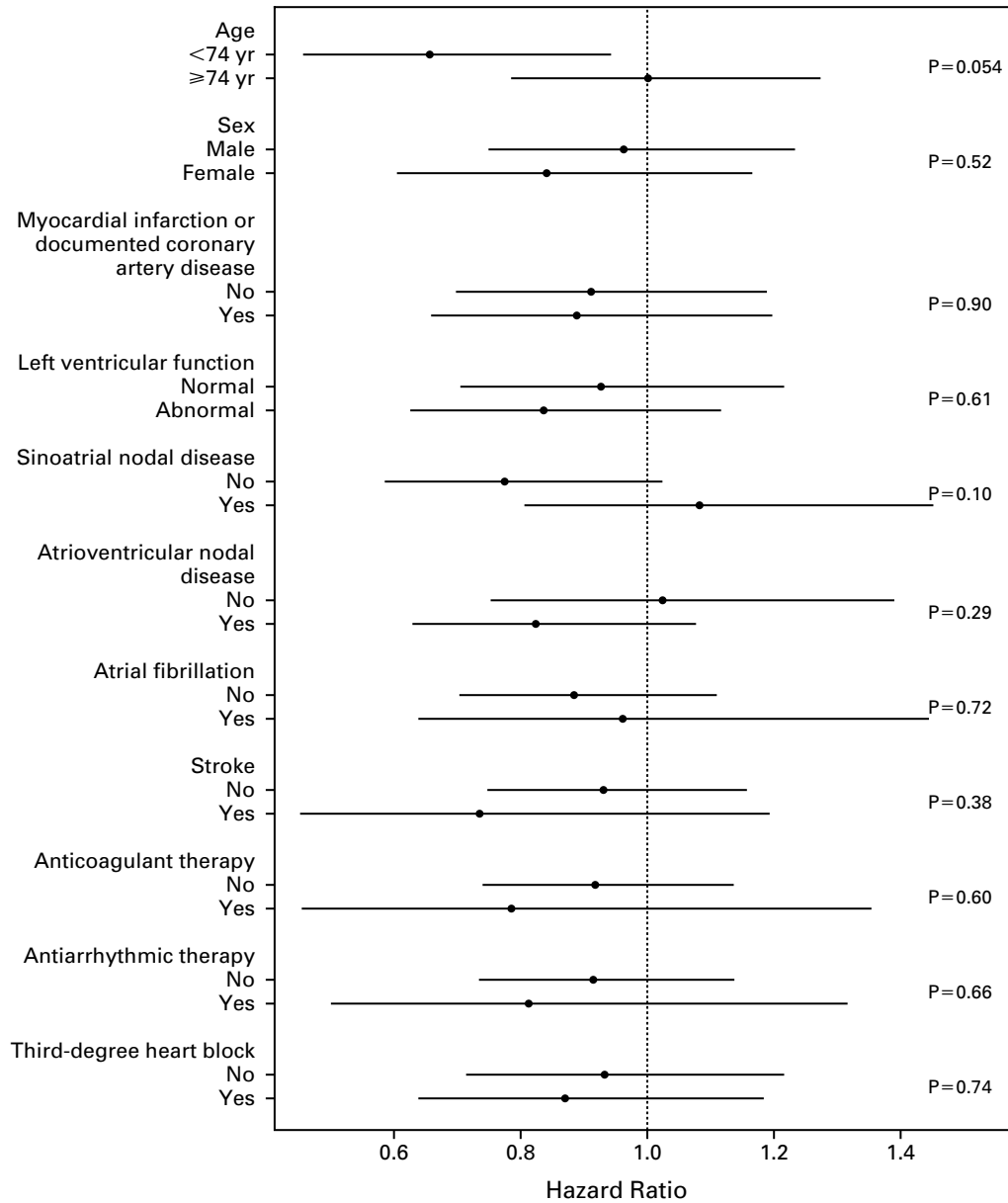


Figure 3. Effect of Treatment on the Risk of Stroke or Death Due to Cardiovascular Causes, According to Subgroup. Each point and bar indicate, for the given subgroup, the hazard ratio of stroke or death due to cardiovascular causes and associated 95 percent confidence interval for physiologic pacing, as compared with ventricular pacing. The associated P value (for heterogeneity) indicates whether there was a significant interaction between the subgroups defined by each base-line characteristic and the type of pacemaker. Points to the left of the dotted vertical line indicate that physiologic pacing was better, and points to the right indicate that ventricular pacing was better.

fit from physiologic pacing. In fact, as shown in Figure 3, there was a trend for the patients with sinoatrial nodal disease to benefit less from physiologic pacing than those without this indication for pacing. It is possible that atrial pacing, by preserving the synchrony of right and left ventricular contractions, confers a benefit that is not present with dual-chamber pacing. It is also possible that the benefit of physiologic

pacing does not become apparent until there have been more than three years of follow-up. If this is the case, longer follow-up of the patients in this study should provide clarification.

The Pacemaker Selection in the Elderly study, in which 407 patients were randomly assigned to physiologic or ventricular pacing, reported no survival benefit associated with physiologic pacing.¹³ In the

Pacemaker Atrial Tachycardia trial, 198 patients with the bradycardia-tachycardia syndrome were randomly assigned to physiologic pacing or ventricular pacing.¹⁴ There was no difference between treatments in the risk of atrial arrhythmia, but there was a significant reduction in mortality associated with physiologic pacing.¹⁴ At present, the most likely explanation for the differences between the results of these trials is that the smaller studies, by the play of chance, may have overestimated the benefit of a physiologic pacemaker.

Our study did demonstrate a significant reduction of 18.0 percent in the relative risk for the secondary outcome of atrial fibrillation. This is an important finding that provides a clinically relevant rationale for the use of physiologic pacing. Patients with ventricular pacemakers or with dual-chamber pacemakers in which the mode can be switched may not be aware of the presence of atrial fibrillation, and there may be a delay before atrial fibrillation comes to the attention of their physicians. This might explain the delay in the onset of the benefit of physiologic pacing with respect to atrial fibrillation. Atrial fibrillation is associated with an increased risk of stroke and death, and it frequently causes symptoms. On the other hand, the absolute reduction in the risk of atrial fibrillation with physiologic pacing was small, and the reduction in the rate of atrial fibrillation did not translate into a beneficial effect with respect to the incidence of stroke or death during the duration of follow-up of this study. Atrial fibrillation was one of several secondary outcomes in this study. Because each outcome was tested for significance, there is a greater possibility that the significant difference in the rate of atrial fibrillation between the two treatment groups occurred by chance. The decision about whether to use a physiologic pacemaker or a ventricular pacemaker should be made on an individual basis. It is reasonable to expect a small reduction in the rate of atrial fibrillation and an increase in the rate of perioperative complications with physiologic pacing, but not a reduction in the risk of death, stroke, or hospitalization for heart failure during the first three years after implantation of the pacemaker.

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APPENDIX

The following persons and institutions (listed in descending order according to the number of patients enrolled) participated in the Canadian Trial of Physiologic Pacing: **Sunnybrook Health Science Centre, Toronto:** C. Lau, A.W. Harrison, B. Goldman, G.M. Froggatt, S. Nishimura, M. MacPherson; **Ottawa Civic Hospital, Ottawa, Ont.:** A.S.L. Tang, W. Goldstein, M. Green, P. Hendry, C. Carey; **St. Michael's Hospital, Toronto:** D. Newman, O. Dorian, J.K.Y. Yao, M. Paquette, L. DeBellis, J. Laslop, D. Darling; **Hamilton General Hospital, Hamilton, Ont.:** S.J. Connolly, C. LeFeuvre, S. Yusuf, B. Doobay, O. Wesley-James, J. Kwasney, M. Menard; **St. Boniface General Hospital, Winnipeg, Man.:** S.N. Sinha, A.R. Friesen, B. Shearer; **Scarborough General Hospital, Toronto:** N. Perera, S. Roth, J. Cherry, V. Rambihar, R. Huhlewych, P. Taylor; **University of Calgary Hospital, Calgary, Alta.:** A. Gillis, J.M. Rothschild, K. Hillier, S. Heal, C. Hale; **Kingston General Hospital, Kingston, Ont.:** J. Pym, H. Abdollah, F.J. Brennan, S. Fair, M. Charrette; **University**

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