Cardiovascular Outcomes With Atrial-Based Pacing Compared With Ventricular Pacing
Meta-Analysis of Randomized Trials, Using Individual Patient Data

Jeffrey S. Healey, MD, MSc; William D. Toff, MD; Gervasio A. Lamas, MD; Henning R. Andersen, MD; Kevin E. Thorpe, MMath; Kenneth A. Ellenbogen, MD; Kerry L. Lee, PhD; Allan M. Skene, PhD; Eleanor B. Schron, MS; J. Douglas Skehan, MBBS; Lee Goldman, MD, MPH; Robin S. Roberts, MTech; A. John Camm, MD; Salim Yusuf, MD, DPhil; Stuart J. Connolly, MD

Background—Several randomized trials have compared atrial-based (dual-chamber or atrial) pacing with ventricular pacing in patients with bradycardia. No trial has shown a mortality reduction, and only 1 small trial suggested a reduction in stroke. The goal of this review was to determine whether atrial-based pacing prevents major cardiovascular events.

Methods and Results—A systematic review was performed of publications since 1980. For inclusion, trials had to compare an atrial-based with a ventricular-based pacing mode; use a randomized, controlled, parallel design; and have data on mortality, stroke, heart failure, or atrial fibrillation. Individual patient data were obtained from 5 of the 8 identified studies, representing 95% of patients in the 8 trials, and a total of 35 000 patient-years of follow-up. There was no significant heterogeneity among the results of the individual trials. There was no significant reduction in mortality (hazard ratio [HR], 0.95; 95% confidence interval [CI], 0.87 to 1.03; \( P = 0.19 \)) or heart failure (HR, 0.89; 95% CI, 0.77 to 1.03; \( P = 0.15 \)) with atrial-based pacing. There was a significant reduction in atrial fibrillation (HR, 0.80; 95% CI, 0.72 to 0.89; \( P = 0.00003 \)) and a reduction in stroke that was of borderline significance (HR, 0.81; 95% CI, 0.67 to 0.99; \( P = 0.035 \)). There was no convincing evidence that any patient subgroup received special benefit from atrial-based pacing.

Conclusions—Compared with ventricular pacing, the use of atrial-based pacing does not improve survival or reduce heart failure or cardiovascular death. However, atrial-based pacing reduces the incidence of atrial fibrillation and may modestly reduce stroke. (Circulation. 2006;114:11-17.)

Key Words: atrial fibrillation • heart failure • mortality • pacemakers • stroke

Since its development in the 1950s, refinements in pacemaker technology have enabled a closer approximation of normal physiology. The use of atrial or dual-chamber pacing modes allows the maintenance of atrioventricular synchrony, the preservation of sinus node control over heart rate, and the potential for normal ventricular activation over the His-Purkinje system. Nonrandomized comparisons of atrial or dual-chamber pacing with ventricular-based pacing suggested a large clinical advantage of these “physiological” modes.\(^2\) Given the greater cost,\(^3\) increased complications,\(^4\) and reduced longevity\(^5\) of dual-chamber pacing systems, several prospective, randomized trials were performed.

Editorial p 3
Clinical Perspective p 17

During the past 10 years, 8 randomized trials have compared ventricular with atrial or dual-chamber pacing.\(^4,6-13\) The studies evaluated several pacing modes in different patient populations. None of the 3 largest studies (the Canadian Trial Of Physiologic Pacing [CTOPP],\(^4\) the Mode Selection Trial [MOST],\(^8\) and the United Kingdom Pacing and Cardiovascular Events [UKPACE] trial\(^12\)) found a significant reduction in their primary outcome with atrial-based pacing. However, both CTOPP and MOST demonstrated a significant reduction in atrial fibrillation,\(^8,14\) and MOST
found a reduction in heart failure hospitalizations. The only study to show a reduction in stroke or cardiovascular mortality was the small trial of Andersen et al. which used atrial rather than dual-chamber pacing. The very small, unpublished, Pacemaker Atrial Tachycardia Trial (PAC-A-TACH) also suggested a modest mortality benefit.

The suggestion that there might be small reductions in major clinical events, such as stroke and death, that previous trials were underpowered to detect led to the planning and execution of the present meta-analysis. The use of patient-level data for this analysis was preferred, as this would permit a detailed examination of patient subgroups to determine whether any derived a benefit from atrial-based pacing.

Methods

The principal investigators of the major trials of pacemaker mode selection began meeting regularly in 1999 to plan this meta-analysis based on individual patient data. To ensure that no relevant trials were overlooked, a formal systematic review was independently conducted by 2 investigators using standardized database search techniques, analysis of review articles, manual searches of conference proceedings, and personal contact with investigators and industry representatives. For inclusion into the meta-analysis, trials had to compare an atrial or dual-chamber pacing mode with a ventricular-based mode; use a randomized, controlled, parallel design; and have data on clinical events, including mortality, stroke, heart failure, and atrial fibrillation. Studies were excluded if they primarily enrolled patients after cardiac surgery or atrioventricular node ablation, if they used multisite atrial or ventricular pacing, or if they had an average follow-up of <6 months. Identified studies were assessed for quality according to predetermined criteria, and their relevance to the meta-analysis was determined by concordant agreement of 2 reviewers.

The protocol for this study, outcomes, and subgroups of interest were all specified before the start of data collection. All-cause mortality was chosen as the primary outcome of the meta-analysis. Participating authors were asked to convert their databases into a common format with the use of specific operational definitions for clinical variables. To facilitate complete data collection from all studies, some continuous variables (such as heart rate and ejection fraction) were summarized with categorical values, because only the categorical values had been collected by the parent trials. Data were then sent to the coordinating center at McMaster University where analyses were performed on individual data sets to replicate the results of each trial. The results were then returned to each group for resolution of any discrepancies.

All analyses were performed with S-Plus (version 7, Insightful Corp, Seattle, Wash). Heterogeneity between individual trials with respect to clinical outcomes was assessed with the \( \chi^2 \) test. Because patient-level data permit the determination of both outcome and the time to event, the effect of treatment was expressed by a hazard ratio (HR). After the patient-level data were assembled from each of the parent trials into a master database, a pooled HR was calculated for each outcome within a stratified Cox model. Conventional weighting of the treatment effect of individual trials was performed solely for the purposes of graphical display of the data. To determine whether atrial-based pacing offered an advantage to any patient subgroups, Cox proportional-hazards modeling was performed, stratified by the study of origin, to evaluate the interaction between pacing mode and patient characteristics. Tests of significance were not adjusted for the 5 separate clinical outcomes evaluated. The possible relation between the outcomes of atrial fibrillation and stroke was explored with a Cox model, which included atrial fibrillation as a time-dependent variable.

A sensitivity analysis was performed to determine whether using all available summary data for all-cause mortality yielded results that were different from the analysis using available individual-patient data. When no such difference exists and if only a small amount of additional summary data are available, it is acceptable to meta-analyze existing, patient-level data, because this approach is unlikely to bias the results significantly and permits detailed subgroup analyses.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

A total of 8 randomized trials met the prespecified inclusion criteria (Table 1). Patient-level data were obtained for 5 of these trials, which included 95% of the patients in all 8 trials and nearly 35 000 patient-years of follow-up. Two of the remaining trials, 1 published and 1 unpublished, could not supply patient-level data and did not present their results in sufficient detail to allow the construction of 2×2 tables for most outcomes of interest. A third trial (also unpublished) had not completed its final data collection. Together, these trials had a total of 758 patients and an average follow-up of 2 years (Table 1). Sensitivity analysis showed essentially identical results whether available summary data from all studies or...
individual-patient data from the 5 included studies were considered.

The 5 included trials all had appropriate study methodology. All were truly randomized trials, which took steps to conceal treatment allocation and followed the intention-to-treat principle. The 4 largest were multicenter trials, with centralized randomization and blinded adjudication of outcomes.4,8,9,12 The Danish study was a single-center study without blinded outcome adjudication.6,7 All included trials reported baseline patient characteristics, as well as the frequency and reasons for crossovers between treatment groups. The quality of the 2 excluded studies10,11 was lower because they did not report that outcomes were assessed in a blinded fashion and did not clearly report their methods for allocation concealment, and one study10 did not report treatment crossovers.

There was no significant heterogeneity among the trials with respect to any of the outcomes that were evaluated. Compared with ventricular pacing, there was no significant reduction in mortality with atrial-based pacing (HR, 0.95; 95% confidence interval [CI], 0.87 to 1.03; \( P = 0.19 \); Figure 1), nor any difference in the composite outcome of stroke or cardiovascular mortality (HR, 0.94; 95% CI, 0.85 to 1.03; \( P = 0.18 \); Figure 2), nor in heart failure hospitalizations (HR, 0.89; 95% CI, 0.77 to 1.03; \( P = 0.12 \)). Both atrial fibrillation (HR, 0.80; 95% CI, 0.72 to 0.89; \( P = 0.0003 \)) and stroke (HR, 0.81; 95% CI, 0.67 to 0.99; \( P = 0.035 \)) were reduced with atrial-based pacing (Figures 3 and 4). In a time-dependent analysis, there was no evidence of a relation between the reduction in atrial fibrillation and subsequent stroke.
In prespecified subgroup analyses, there was a reduction in the composite of stroke or cardiovascular death with atrial-based pacing in patients with sinus node dysfunction (HR, 0.83; 95% CI, 0.72 to 0.97; \( P = 0.04 \)) but not in those without it (HR, 1.02; 95% CI, 0.90 to 1.15; \( P = 0.98 \); Table 2). The reduction in atrial fibrillation also appeared greater in patients with sinus node dysfunction (HR, 0.76; 95% CI, 0.67 to 0.86; \( P = 0.00016 \)) than in those without it (HR, 0.90; 95% CI, 0.74 to 1.09; \( P = 0.27 \)); Table 2). However, because 3 of the trials limited enrollment to patients with either sinus node dysfunction or atrioventricular block, it was not possible to assess the statistical significance of the possible interaction between pacing mode and the indication for pacing. The effect of pacing mode on all clinical outcomes was not influenced by patient characteristics, such as age, sex, history of hypertension, left ventricular ejection fraction <50%, intrinsic heart rate \( \leq 60/\text{min} \), history of atrial fibrillation, and history of heart failure (Table 3).

In analyses that excluded the MOST and PASE trials, in which all patients received dual-chamber devices and were then randomized to pacing mode, implant complication rates were nearly twice as high with atrial-based pacing (6.2% versus 3.2%) primarily owing to a significant increase in the rate of lead dislodgement and infection (Table 4).

**Discussion**

This meta-analysis reaffirms the results of the major trials: Compared with ventricular pacing, atrial-based pacing does not reduce all-cause mortality nor the combined outcome of
cardiovascular mortality and stroke, but it does reduce the incidence of atrial fibrillation.\textsuperscript{4,7,8}

None of the large randomized trials individually found a reduction in stroke\textsuperscript{4,8,12}; however, given the observed individual and aggregate reduction in atrial fibrillation,\textsuperscript{4,8} a reduction in stroke would seem plausible and should be detectable given a sufficient sample size with adequate follow-up. Although this meta-analysis appears to suggest a moderate reduction in stroke with atrial-based pacing, these data must be interpreted cautiously. The reduction in stroke was of borderline statistical significance, amid several secondary outcomes, with no adjustment for multiple testing. Furthermore, the lack of a relation between the reduction in atrial fibrillation and the reduction in stroke raises questions about its biological plausibility.

Because the overall advantage of atrial-based pacing appeared modest, it was desirable to determine whether any patient groups derived particular benefit. A meta-analysis that uses patient-level data is well suited for such subgroup analyses.\textsuperscript{17} Nonetheless, results should be interpreted conservatively and used primarily for hypothesis generation.\textsuperscript{18} Several patient groups, such as those with left ventricular dysfunction, hypertension, heart failure, or a low unpaced heart rate,\textsuperscript{19} are generally thought to derive added benefit from dual-chamber pacing; however, the pooled data did not demonstrate any such effect. There was a suggestion of greater benefit with atrial-based pacing among patients with sinus node dysfunction, but this, too, must be interpreted cautiously. In these patients, atrial-based pacing significantly reduced both atrial fibrillation and the composite outcome of stroke or cardiovascular death, benefits not seen in patients without sinus node dysfunction. However, the CIs for these 2 subgroups overlapped, and because 3 studies limited enrollment to patients with either sinus node dysfunction\textsuperscript{6,8} alone or

### Table 2. Effect of Pacing Mode on Outcomes, Based on Indication for Pacing

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall, HR (95% CI)</th>
<th>Sinus Node Dysfunction, HR (95% CI)</th>
<th>No Sinus Node Dysfunction, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.95 (0.87-1.03)</td>
<td>0.92 (0.81-1.05)</td>
<td>0.97 (0.87-1.08)</td>
</tr>
<tr>
<td>Stroke or cardiovascular death</td>
<td>0.94 (0.85-1.04)</td>
<td>0.83* (0.72-0.97)</td>
<td>1.02 (0.90-1.15)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.81* (0.67-0.99)</td>
<td>0.84 (0.64-1.11)</td>
<td>0.78 (0.59-1.03)</td>
</tr>
<tr>
<td>Heart failure Hospitalization</td>
<td>0.89 (0.77-1.03)</td>
<td>0.92 (0.75-1.13)</td>
<td>0.86 (0.70-1.06)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.80* (0.72-0.89)</td>
<td>0.76* (0.67-0.86)</td>
<td>0.90 (0.74-1.09)</td>
</tr>
</tbody>
</table>

*P<0.05.

#### Table 3. Effect of Pacing Mode on Outcomes, Based on Patient Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Death, HR (95% CI)</th>
<th>Stroke or Cardiovascular Death, HR (95% CI)</th>
<th>Stroke, HR (95% CI)</th>
<th>Atrial Fibrillation, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;76</td>
<td>1.0 (0.9-1.2)</td>
<td>1.0 (0.8-1.1)</td>
<td>0.8 (0.6-1.1)</td>
<td>0.8 (0.7-0.9)</td>
</tr>
<tr>
<td>≥76</td>
<td>0.9 (0.8-1.0)</td>
<td>0.9 (0.8-1.0)</td>
<td>0.8 (0.6-1.1)</td>
<td>0.8 (0.7-0.9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.0 (0.9-1.1)</td>
<td>1.0 (0.9-1.1)</td>
<td>0.8 (0.6-1.1)</td>
<td>0.8 (0.7-0.9)</td>
</tr>
<tr>
<td>Female</td>
<td>0.9 (0.8-1.0)</td>
<td>0.9 (0.7-1.0)</td>
<td>0.8 (0.6-1.0)</td>
<td>0.8 (0.7-0.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.0 (0.9-1.1)</td>
<td>1.0 (0.9-1.2)</td>
<td>0.9 (0.7-1.2)</td>
<td>0.8 (0.7-1.0)</td>
</tr>
<tr>
<td>No</td>
<td>0.9 (0.8-1.0)</td>
<td>0.9 (0.8-1.0)</td>
<td>0.8 (0.6-1.0)</td>
<td>0.8 (0.7-0.9)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>0.9 (0.6-1.2)</td>
<td>0.9 (0.6-1.4)</td>
<td>0.8 (0.4-2.0)</td>
<td>0.8 (0.5-1.2)</td>
</tr>
<tr>
<td>≥50%</td>
<td>0.9 (0.6-1.2)</td>
<td>0.8 (0.5-1.2)</td>
<td>0.9 (0.5-1.5)</td>
<td>0.7 (0.6-1.0)</td>
</tr>
<tr>
<td>Unpaced heart rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60</td>
<td>1.0 (0.9-1.2)</td>
<td>1.0 (0.9-1.3)</td>
<td>0.9 (0.6-1.3)</td>
<td>0.8 (0.7-1.0)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>1.0 (0.8-1.2)</td>
<td>1.0 (0.8-1.3)</td>
<td>0.7 (0.4-1.0)</td>
<td>0.8 (0.7-1.0)</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.0 (0.9-1.1)</td>
<td>1.0 (0.9-1.1)</td>
<td>0.8 (0.6-1.0)</td>
<td>0.7 (0.6-0.9)</td>
</tr>
<tr>
<td>No</td>
<td>0.8 (0.7-1.0)</td>
<td>0.8 (0.7-1.1)</td>
<td>0.9 (0.6-1.2)</td>
<td>0.8 (0.7-1.0)</td>
</tr>
<tr>
<td>History of heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.9 (0.8-1.1)</td>
<td>1.0 (0.8-1.1)</td>
<td>0.8 (0.7-1.2)</td>
<td>0.8 (0.7-0.9)</td>
</tr>
<tr>
<td>No</td>
<td>1.0 (0.9-1.2)</td>
<td>1.0 (0.8-1.2)</td>
<td>0.8 (0.5-1.1)</td>
<td>0.9 (0.7-1.1)</td>
</tr>
</tbody>
</table>

*Interaction P values were nonsignificant for all outcomes and subgroups evaluated.
atrophicventricular block alone, the proper statistical testing for subgroup interaction could not be performed. Despite its large size, this meta-analysis may have underestimated the clinical benefit of atrial-based pacing in patients with sinus node dysfunction. In the MOST trial, which contributed the majority of patients with sinus node dysfunction, >30% of patients randomized to ventricular pacing were crossed over to dual-chamber pacing, thus reducing the trial’s statistical power to detect an effect of pacing mode. Furthermore, the potential benefit of preserved atrophicventricular synchrony with dual-chamber pacing may have been offset by the harmful effects of unnecessary right ventricular pacing. An important substudy of MOST demonstrated, in patients with sinus node dysfunction and a baseline QRS width <120 ms, that the frequency of ventricular pacing was higher in patients randomized to dual-chamber pacing (90% versus 50%) and that increased ventricular pacing was associated with an elevated risk of atrial fibrillation and heart failure. This greater risk is thought to be the result of inducing dysynchronous activation of the ventricles, analogous to that seen with left bundle branch block, as a result of unnecessary right ventricular pacing. This hypothesis is further supported by the results of the Dual-Chamber or Ventricular Backup Pacing in Patients With An Implantable Defibrillator (DAVID) trial, which randomized patients with implantable defibrillators, impaired systolic function, and no standard indication for antiarrhythmia therapy to be programmed to ventricular pacing at 40/min or dual-chamber pacing at 70/min. As in MOST, dual-chamber pacing resulted in a higher frequency of right ventricular pacing (60% versus 3%) and was associated with an increased risk of death or heart failure hospitalization (26.7% versus 16.1%).

New modes of dual-chamber pacing have been developed to minimize right ventricular pacing and ongoing research will determine whether they improve clinical outcomes in patients with sinus node dysfunction. Another option to avoid unnecessary ventricular pacing in patients with normal atrophicventricular conduction is to use single-chamber atrial pacing. It is notable that, of the trials included in this meta-analysis, the Danish study, which used single-chamber atrial pacing, appeared to show a greater advantage over ventricular pacing than did other trials that used dual-chamber pacing, although the differences between the Danish and the other trials were not statistically significant. Atrial and dual-chamber pacing modes are currently being compared in a large randomized trial, and pilot data from Denmark suggest that single-chamber atrial pacing may be superior.

In addition to the impact of pacing mode on major cardiovascular events, factors such as cost, complication rates (Table 4), and quality of life must be considered when choosing between atrial-based and ventricular pacing. Dual-chamber devices cost more, do not last as long, and have a higher rate of minor complications. However, there is evidence that they modestly improve quality of life. Additionally, some studies demonstrate that dual-chamber pacing may also reduce pacemaker syndrome (occurring in 3% to 30% of patients receiving ventricular pacing and the associated cost of pacemaker upgrade.

### Conclusions

Compared with ventricular pacing, the use of atrial-based pacing does not improve survival or reduce heart failure or cardiovascular death. However, atrial-based pacing reduces the incidence of atrial fibrillation and may modestly reduce stroke.

### Sources of Funding

Dr Healey was the recipient of a research fellowship from the Heart and Stroke Foundation of Canada/Astra-Zeneca Canada, Ltd. Some administrative costs for this research were offset by an unrestricted educational grant from Guidant Canada Ltd. Guidant Canada did not participate in any of the analyses, did not help in the preparation of the manuscript, and had no access to the data.

### Disclosures

None.

### References

Eight randomized trials compared ventricular pacing with atrial-based pacing (mainly dual-chamber). This meta-analysis of individual patient data from >7000 patients with a mean follow-up of ≈5 years provides a definitive summary of the randomized trials of pacemaker mode selection. As in the individual trials, the only benefit seen with atrial-based pacing was a 20% reduction in atrial fibrillation. There was a suggestion of a reduction in stroke; however, this was of borderline statistical significance. Atrial-based pacing did not reduce cardiovascular death or heart failure, and no patient subgroups derived a special benefit from atrial-based pacing. Atrial-based pacing is currently the dominant pacing mode used in North America. Many clinicians believe that the reduction in atrial fibrillation is sufficient to recommend routine use of this mode. Others cite the somewhat conflicting evidence suggesting an improvement in quality of life and a reduction in pacemaker syndrome with atrial-based pacing. This meta-analysis confirms that ventricular pacing remains a legitimate pacing mode for individual patients. However, advances in atrial-based pacing that limit unnecessary ventricular pacing and diagnostic enhancements that permit the accurate detection of asymptomatic atrial arrhythmias may offer new benefits with atrial-based pacing but await prospective evaluation.
Cardiovascular Outcomes With Atrial-Based Pacing Compared With Ventricular Pacing: 
Meta-Analysis of Randomized Trials, Using Individual Patient Data
Jeffrey S. Healey, William D. Toff, Gervasio A. Lamas, Henning R. Andersen, Kevin E. 
Thorpe, Kenneth A. Ellenbogen, Kerry L. Lee, Allan M. Skene, Eleanor B. Schron, J. Douglas 
Skehan, Lee Goldman, Robin S. Roberts, A. John Camm, Salim Yusuf and Stuart J. Connolly

_Circulation_. 2006;114:11-17; originally published online June 26, 2006; 
doi: 10.1161/CIRCULATIONAHA.105.610303
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/114/1/11

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/