ORIGINAL ARTICLE

Single-Chamber versus Dual-Chamber Pacing for High-Grade Atrioventricular Block

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ABSTRACT

BACKGROUND

In the treatment of atrioventricular block, dual-chamber cardiac pacing is thought to confer a clinical benefit as compared with single-chamber ventricular pacing, but the supporting evidence is mainly from retrospective studies. Uncertainty persists regarding the true benefits of dual-chamber pacing, particularly in the elderly, in whom it is used less often than in younger patients.

METHODS

In a multicenter, randomized, parallel-group trial, 2021 patients 70 years of age or older who were undergoing their first pacemaker implant for high-grade atrioventricular block were randomly assigned to receive a single-chamber ventricular pacemaker (1009 patients) or a dual-chamber pacemaker (1012 patients). In the single-chamber group, patients were randomly assigned to receive either fixed-rate pacing (504 patients) or rate-adaptive pacing (505 patients). The primary outcome was death from all causes. Secondary outcomes included atrial fibrillation, heart failure, and a composite of stroke, transient ischemic attack, or other thromboembolism.

RESULTS

The median follow-up period was 4.6 years for mortality and 3 years for other cardiovascular events. The mean annual mortality rate was 7.2 percent in the single-chamber group and 7.4 percent in the dual-chamber group (hazard ratio, 0.96; 95 percent confidence interval, 0.83 to 1.11). We found no significant differences between the group with single-chamber pacing and that with dual-chamber pacing in the rates of atrial fibrillation, heart failure, or a composite of stroke, transient ischemic attack, or other thromboembolism.

CONCLUSIONS

In elderly patients with high-grade atrioventricular block, the pacing mode does not influence the rate of death from all causes during the first five years or the incidence of cardiovascular events during the first three years after implantation of a pacemaker.

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*Other participating investigators are listed in the Appendix.

CARDIAC PACING IS THE ESTABLISHED treatment for high-grade atrioventricular block, but the appropriate pacing mode remains the subject of debate.[1] Single-chamber ventricular pacing prevents bradycardia and death from ventricular standstill, but dual-chamber pacing better emulates normal cardiac physiology by restoring atrioventricular synchrony and matching the ventricular pacing rate to the sinus rate. As a result, dual-chamber pacing, as compared with single-chamber ventricular pacing, improves hemodynamic function,[2-4] but the clinical benefit is uncertain.

Nonrandomized studies suggest that dual-chamber pacing is associated with a lower incidence of atrial fibrillation, stroke, and heart failure than is single-chamber pacing.[5] There is also evidence of improved survival, but the data are confounded by selection bias, because of the preferential use of dual-chamber pacing in younger patients with fewer coexisting illnesses.[6] Some current guidelines recommend dual-chamber pacing unless atrial fibrillation is present,[7] but the limitations of the supporting data have led to questions about the guidelines[8] and the apparent underuse of dual-chamber pacing, particularly in the elderly.[9,10]

The United Kingdom Pacing and Cardiovascular Events (UKPACE) trial compared the clinical benefits of single-chamber ventricular pacing and dual-chamber pacing in elderly patients with atrioventricular block.[10]

METHODS

The UKPACE trial was a randomized, parallel-group trial conducted in 46 centers in the United Kingdom, representing a wide range of experience among centers and operators. The trial was approved by the North West Multi-Centre Research Ethics Committee and the local research ethics committee for each center. All patients provided written informed consent.

PATIENT SELECTION

Patients were recruited from August 22, 1995, to September 24, 1999. All new pacemaker implantations were registered, and trial eligibility was recorded. Eligible patients were 70 years of age or older and scheduled for their first pacemaker implantations for high-grade (i.e., second-degree or complete) atrioventricular block. Exclusion criteria included chronic established atrial fibrillation,

New York Heart Association (NYHA) class IV heart failure, advanced cognitive dysfunction, total immobility, and advanced cancer (life expectancy of less than one year). Patients with persistent atrial fibrillation of less than three months' duration were eligible if they had undergone cardioversion and had normal sinus rhythm at enrollment.

DATA COLLECTION, RANDOMIZATION, IMPLANTATION, AND PROGRAMMING

Baseline demographic and clinical characteristics of the patients were recorded by physicians, nurses, or cardiac technicians. Patients were randomly assigned, up to 24 hours before the scheduled implantation, to receive either a fixed-rate or rate-adaptive single-chamber ventricular pacing system or a dual-chamber system (with or without sensor-modulated rate adaptation). Within the single-chamber group, assignment to fixed-rate or rate-adaptive pacing was randomly determined. Randomization was performed with the use of a 24-hour automated telephone-based system, linked to a computer at the data center, with a dynamic balancing algorithm that stratified patients by center and age (<80 years or ≥80 years). Implantation was performed according to the operator's usual practice.

The use of sensor-based rate adaptation in the dual-chamber group and the programming of variables other than mode were determined by the investigator. Suggested settings for dual-chamber pacemakers were an atrioventricular delay of 150 msec, rate-adaptive atrioventricular shortening to 75 msec, and lower and upper rate limits of 60 beats per minute and 125 beats per minute, respectively. For rate-adaptive single-chamber pacemakers, the suggested lower and upper rate limits were 70 beats per minute and 125 beats per minute, respectively. For fixed-rate single-chamber pacemakers, a rate of 70 beats per minute was suggested. The operators and patients were not blinded to the type of pacing system used or the programming of the system.

END POINT AND OUTCOMES

The primary end point was death from all causes. Prespecified cardiovascular events included atrial fibrillation (defined as an episode, with or without symptoms, lasting 15 minutes or more and verified by electrocardiography), new or significantly worsening heart failure, a composite of stroke, transient ischemic attack, or other thromboembolism, revision of the pacing system, new-onset angina

or newly diagnosed ischemic heart disease, and myocardial infarction. Crossover, in the event of suspected intolerance of the pacing mode, was at the discretion of the investigator.

Patients were followed for a minimum of 3 years, with scheduled visits at 1, 4, 10, 16, and 36 months, at which the pacemaker function was assessed and outcome events were recorded. Patients were given a diary in which the details of any medical contacts between their follow-up visits were to be recorded. The identity of enrolled patients was given to the U.K. Office for National Statistics, which provided automatic notification of registered deaths. Mortality data were censored on September 24, 2002. Data for other cardiovascular events were censored at the actual or intended date of the 36-month visit. If the visit was missed, outcome data were sought through a review of clinical records or through contact with the patient's family doctor. Deaths and specified cardiovascular events were adjudicated and classified by an independent committee on end points and events, with members unaware of the pacing modes. Deaths were classified as due to cardiovascular or noncardiovascular causes and treated as the result of cardiovascular causes if attributed to old age or if the cause was unclear. Safety was monitored by an independent data-monitoring committee.

STATISTICAL ANALYSIS

The database was maintained and analyzed by an independent data-management group (Nottingham Clinical Research Group, Nottingham, United Kingdom). The trial was designed to have a power of at least 90 percent to detect a 25 percent reduction in the primary end point, with a target recruitment of 2000 patients. This assumed an annual mortality rate of 8 percent in the single-chamber group, with allowance for a 6 percent crossover from single-chamber to dual-chamber pacing. More deaths were reported than anticipated, giving the study 95 percent power to detect a 25 percent reduction in mortality.

Differences in the proportion of ventricular beats that were paced were compared with the use of the Wilcoxon rank-sum test. Cumulative-event rates were calculated according to the Kaplan–Meier method,[11] and differences between the groups were assessed with the use of the Cox proportional-hazards model,[12] with adjustment for the baseline covariates of age (≤80 years vs. >80 years), sex, and NYHA class (I or II vs. III or IV). Relative risk was calculated after adjustment for age, sex, and NYHA class at baseline and expressed as hazard ratios with 95 percent confidence intervals. The primary analysis was the comparison of single-chamber and dual-chamber pacing. A prespecified secondary analysis involved the separate comparisons of fixed-rate and rate-adaptive single-chamber pacing with dual-chamber pacing. The impact of baseline covariates on the hazard ratio for the primary end point was assessed with the use of the log-rank test.[13] The incidence of procedural and predischarge complications in the two groups was compared with the use of the chi-square test. All statistical tests were two-tailed. Analysis was performed on the basis of the intention-to-treat principle.

The study was designed by Drs. Toff, Skehan, and Camm and David de Bono in collaboration with the trial steering committee and other participating investigators (see the Appendix) and funded by the Medical Research Council of the United Kingdom. Pacemakers were purchased according to normal practice, but in centers that had previously implanted less than 50 percent dual-chamber pacing systems, additional hardware costs were met by a subsidy from pacemaker manufacturers and suppliers under the terms of an agreement with the International Association of Prosthesis Manufacturers. No pacemaker manufacturer or supplier had any involvement in the study design, data collection, analysis of results, or writing of the manuscript. The manuscript was written by the principal investigators and the first draft reviewed by the trial steering committee and other participating investigators.

RESULTS

SCREENING

During the recruitment period, 16,375 patients received a first pacemaker implantation at the participating centers. Of these, 5308 (32.4 percent) had high-grade atrioventricular block and were 70 years of age or more. Exclusion criteria were documented in 945 patients, leaving 4363 eligible for the study, of whom 1972 (45.2 percent) were enrolled. The remaining patients were excluded because the patient declined to participate (13.2 percent), because the physician declined (15.0 percent), or for other or unstated reasons (26.6 percent). Forty-nine patients who were enrolled were not included in the registry either because they did not receive a pacemaker or because registry data were missing for the relevant period.

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*			
Characteristic	Single-Chamber Fixed-Rate Pacing Group (N=504)	Single-Chamber Rate-Adaptive Pacing Group (N=505)	Dual-Chamber Pacing Group (N=1012)
Age (yr)	79.8±6.0	80.1±6.1	79.9±6.1
Male sex (%)	56.0	57.4	57.2
White race (%)†	95.2	95.2	96.5
New York Heart Association functional class (%)			
I	26.4	27.5	30.1
II	43.4	45.0	42.1
III	25.6	23.0	24.0
IV	1.0	2.2	0.9
Unknown	3.6	2.4	2.9
Cardiothoracic ratio on chest radiograph (%)	55.7±9.8	55.9±10.6	55.6±11.8
Primary electrocardiographic indication for implantation (%)			
Second-degree atrioventricular block	26.2	25.1	26.6
Complete atrioventricular block	73.2	74.3	72.9
Other or unknown	0.6	0.6	0.5
Presenting bradycardia (%)			
Intermittent	38.7	38.2	38.0
Constant	60.7	61.2	61.6
Unknown	0.6	0.6	0.4
Symptoms of bradycardia (%)			
Symptomatic	79.2	81.4	84.7
Asymptomatic	20.2	18.0	15.0
Unknown	0.6	0.6	0.3
Medical history (%)			
Hypertension	30.8	32.1	35.7
Diabetes	9.9	11.5	13.5
Angina	20.8	22.0	22.7
Prior myocardial infarction	15.5	15.4	12.8
Prior heart failure	15.1	16.0	16.0
Cardiac surgery	3.2	4.0	5.3
Percutaneous coronary angioplasty	0.6	0.8	0.5
Paroxysmal atrial fibrillation	3.6	3.8	4.6
Other arrhythmia	10.9	10.7	11.5
Stroke	6.3	5.9	5.4
Prior transient ischemic attack	4.6	7.5	3.9

TREATMENT ASSIGNMENT

Of 2021 patients enrolled, 1009 were randomly assigned to receive single-chamber pacing and 1012 to receive dual-chamber pacing. In the single-chamber group, 504 were assigned to fixed-rate pacing and 505 to rate-adaptive pacing. Of those assigned to single-chamber pacing, 99.4 percent received a single-chamber system, 0.2 percent received a dual-chamber system, and 0.4 percent received no pacemaker. Of those assigned to dual-chamber pacing, 95.8 percent received a dual-chamber system, 3.6 percent received a single-chamber system, and 0.6 percent received no pacemaker.

At hospital discharge, the programmed mode

Table 1. (Continued.)

Characteristic	Single-Chamber Fixed-Rate Pacing Group (N=504)	Single-Chamber Rate-Adaptive Pacing Group (N=505)	Dual-Chamber Pacing Group (N=1012)
Medication at randomization (%)			
Aspirin	38.7	39.4	42.2
Warfarin or other anticoagulant	5.6	5.9	5.6
Angiotensin-converting–enzyme inhibitor	18.7	18.4	17.8
Diuretic	44.6	47.7	49.1
Nitrate or other vasodilator	17.7	18.2	18.8
Beta-blocker	8.5	5.5	6.9
Calcium-channel blocker	13.1	14.5	17.2
Digoxin	1.4	1.4	1.9
Other antiarrhythmic agent	2.4	2.0	2.0
Lipid-lowering agent	2.6	3.8	2.9
Oral hypoglycemic agent	4.0	6.3	6.7
Insulin	2.0	2.2	2.3
Nonsteroidal antiinflammatory drug	9.1	6.5	7.0
Antidepressant	3.2	4.4	4.4

* Plus–minus values are means ±SD. Because of rounding, not all percentages total 100.
† Race was determined by the investigators.

of pacing was documented for 99 percent of the patients enrolled. At least 98.9 percent of those assigned to single-chamber pacing were being paced in a single-chamber mode, and at least 95.2 percent of those assigned to dual-chamber pacing were being paced in a dual-chamber mode. At the final follow-up or at the study end point, at least 96.9 percent of the patients assigned to single-chamber pacing were receiving this type of pacing, and at least 91.7 percent of those assigned to dual-chamber pacing were being paced in a dual-chamber mode. At the conclusion of the study, 3.1 percent of patients had crossed over from single-chamber to dual-chamber pacing, primarily because of suspected intolerance of the pacing mode.

The extent of ventricular pacing, as assessed from the pacemaker's memory at one month, was recorded for 65 percent of all patients. The median percentage of ventricular beats that were paced was 94 percent in the fixed-rate single-chamber group, 93 percent in the rate-adaptive single-chamber group, and 99 percent in the dual-chamber group. The difference in ventricular paced beats between the 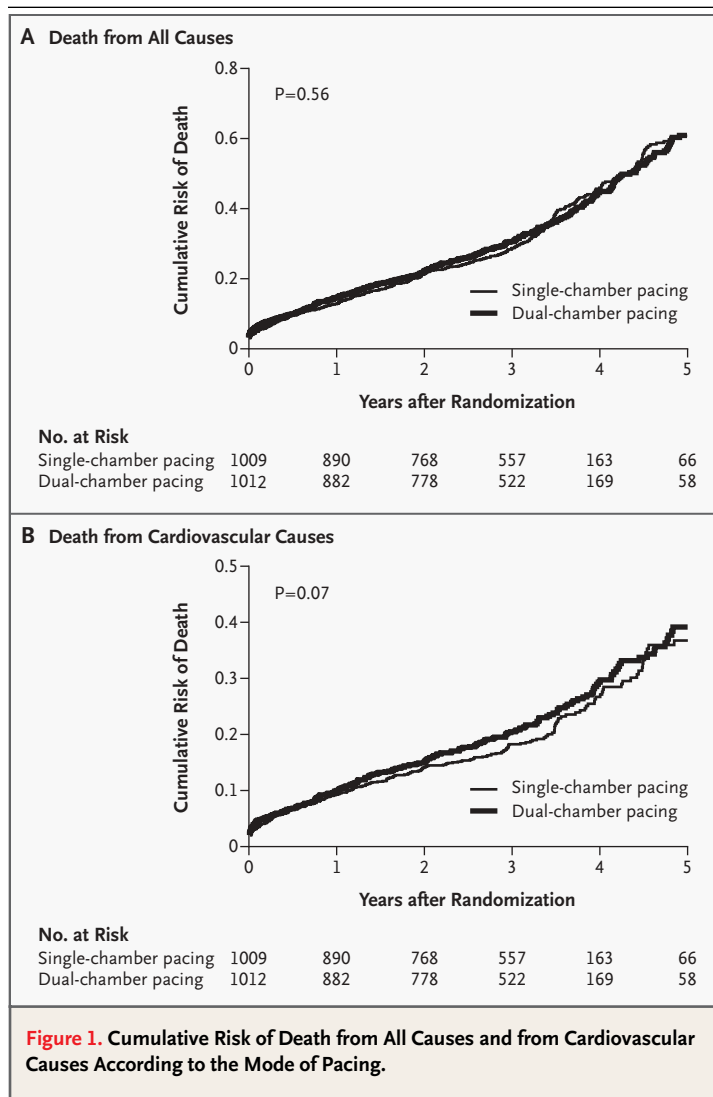single-chamber group and the dual-chamber group was statistically significant (P<0.001), but the difference between fixed-rate and rate-adaptive single-chamber pacing was not (P=0.85).

BASELINE CHARACTERISTICS

The treatment groups were well balanced with regard to baseline demographic and clinical characteristics (Table 1). The mean age of the patients was 79.9 years; 57 percent were male. The indication for pacing was second-degree atrioventricular block in 26.1 percent of patients and complete atrioventricular block in 73.3 percent. Bradycardia was judged as constant in 61.3 percent of patients and intermittent in 38.2 percent. Eighty-three percent of patients were symptomatic.

OUTCOME EVENTS

The median follow-up period was 4.6 years for death and 3 years for other cardiovascular events. No patients were lost to follow-up with respect to the primary end point. Figure 1 shows Kaplan–Meier estimates of the cumulative risk of death from all causes and from cardiovascular causes in the two treatment groups, and Figure 2 shows es-

A Death from All Causes

P=0.56

Cumulative Risk of Death

— Single-chamber pacing
— Dual-chamber pacing

Years after Randomization

No. at Risk

Single-chamber pacing	1009	890	768	557	163	66
Dual-chamber pacing	1012	882	778	522	169	58

B Death from Cardiovascular Causes

P=0.07

Cumulative Risk of Death

— Single-chamber pacing
— Dual-chamber pacing

Years after Randomization

No. at Risk

Single-chamber pacing	1009	890	768	557	163	66
Dual-chamber pacing	1012	882	778	522	169	58

Figure 1. Cumulative Risk of Death from All Causes and from Cardiovascular Causes According to the Mode of Pacing.

timates for the risk of the specified cardiovascular events. Table 2 shows event rates and hazard ratios for death from all causes, death from cardiovascular causes, and specified cardiovascular events for the primary comparison of single-chamber pacing with dual-chamber pacing; also shown are the event rates and hazard ratios for the separate comparison of fixed-rate and rate-adaptive single-chamber pacing with dual-chamber pacing.

Mortality
The mean annual rate of death from all causes during the first five years after pacemaker implantation was 7.2 percent in the single-chamber group and 7.4 percent in the dual-chamber group (P=0.56). The mean annual rate of death due to cardiovascular causes was 3.9 percent in the single-chamber group and 4.5 percent in the dual-chamber group (P=0.07).

Atrial Fibrillation
There was a higher incidence of atrial fibrillation in the dual-chamber group during the first 18 months after pacemaker implantation but no significant difference in the mean annual event rates at 3 years, which were 3.0 percent in the single-chamber group and 2.8 percent in the dual-chamber group (P=0.74).

*Stroke, Transient Ischemic Attack,
or Thromboembolism*
For the combined outcome of stroke, transient ischemic attack, or thromboembolism, the mean annual event rate was 2.1 percent in the single-chamber group and 1.7 percent in the dual-chamber group (P=0.20). There was a significantly higher event rate with fixed-rate single-chamber pacing (2.5 percent per year) than with dual-chamber pacing (P=0.04), but the event rate in the rate-adaptive single-chamber group (1.7 percent per year) was the same as that in the dual-chamber group (P=0.93).

Heart Failure, Angina, and Myocardial Infarction
There was no significant difference in the mean annual event rate for heart failure, which was 3.2 percent in the single-chamber group and 3.3 percent in the dual-chamber group (P=0.80). Similarly, there was no significant difference between the single-chamber and dual-chamber groups in event rates for new-onset angina or ischemic heart disease or for myocardial infarction.

SUBGROUP ANALYSIS
The subgroup analysis showed that the presence or absence of selected baseline characteristics did not affect the influence of the pacing mode on the primary end point (Fig. 3).

COMPLICATIONS
Procedural complications were more common in the dual-chamber group than in the single-chamber group (7.8 percent vs. 3.5 percent, P<0.001), as were other complications before discharge (10.4 percent vs. 6.1 percent, P<0.001). The need for therapeutic intervention was also more frequent in the dual-chamber group (8.8 percent vs. 5.6 percent, P=0.005), as were complications requiring

repeated operation before discharge (4.2 percent vs. 2.5 percent, P=0.04). The differences in complication rates were principally due to problems with the placement or stability of atrial leads.
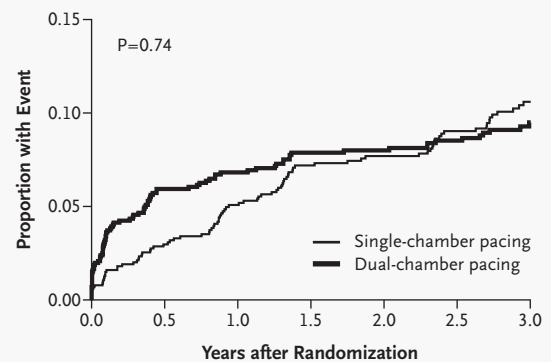
DISCUSSION

The key finding from this randomized trial was that in elderly patients with high-grade atrioventricular block, dual-chamber pacing provided no survival advantage over single-chamber pacing. This result contrasts with the findings of nonrandomized studies that suggested there was improved survival with dual-chamber pacing, which probably reflected selection bias.[6,14]

Our trial focused on atrioventricular block in the elderly, but the absence of a survival advantage for dual-chamber pacing is consistent with the results of other trials that included younger patients and those with sinus-node disease. In the Pacemaker Selection in the Elderly (PASE) study, 407 patients 65 years of age or older with sinus-node disease or atrioventricular block were randomly assigned to receive single-chamber ventricular pacing or dual-chamber pacing.[15] The study was not powered to assess mortality, but there was no significant difference in survival or clinical outcomes during the mean follow-up period of 18 months, although the crossover rate from ventricular to dual-chamber pacing was high (26 percent).

In the Canadian Trial of Physiologic Pacing (CTOPP), 2568 patients 18 years of age or older who had sinus-node disease or atrioventricular block were randomly assigned to physiologic (atrial or dual-chamber) pacing or single-chamber ventricular pacing.[16] During the mean follow-up period of three years, there was no significant difference in the rate of death from all causes or in the primary end point of cardiovascular death or stroke. There was an 18 percent reduction in the relative risk of atrial fibrillation with dual-chamber pacing but no significant difference in the rate of hospitalization for heart failure or in the occurrence of stroke. Follow-up extended to a mean of 6.4 years showed a further reduction in the relative risk of atrial fibrillation (20.1 percent) but no other benefit from physiological pacing.[17]

The absence of a reduction in atrial fibrillation with dual-chamber pacing in the UKPACE trial contrasts with the findings of the CTOPP trial. This difference may reflect the older age of our patients, in whom any propensity toward atrial fibrillation
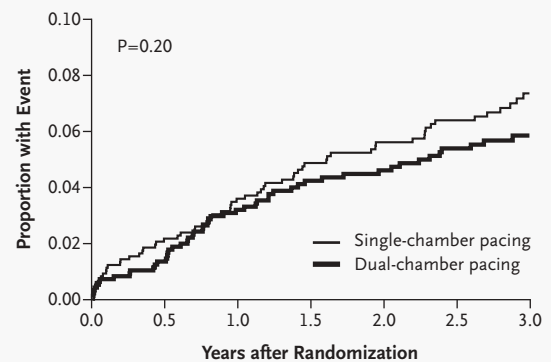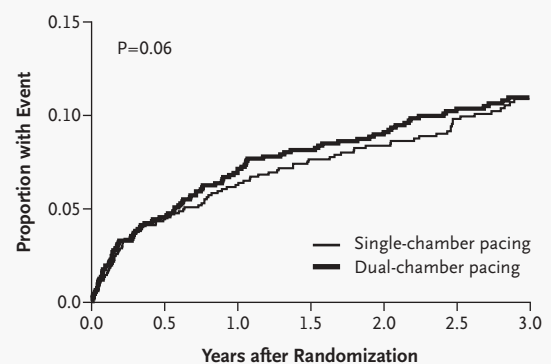

Figure 2. Cumulative Risk of Cardiovascular Events According to the Mode of Pacing.

TIA denotes transient ischemic attack.

Table 2. Event Rates and Hazard Ratios for Death from All Causes, Death from Cardiovascular Causes, and Specified Cardiovascular Outcomes in the Pacing Groups.*

	Single-Chamber Fixed-Rate Pacing Group (N=504)	Single-Chamber Rate-Adaptive Pacing Group (N=505)	Dual-Chamber Pacing Group (N=1012)	Fixed-Rate or Rate-Adaptive Single-Chamber vs. Dual-Chamber System		Fixed-Rate Single-Chamber vs. Dual-Chamber System		Rate-Adaptive Single-Chamber vs. Dual-Chamber System	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Death from all causes									
Events at 3 yr — no. (%)	125 (24.8)	128 (25.3)	277 (27.4)						
3-yr event-free survival — %	73.6	73.5	71.5						
Events at 5 yr — no. (%)	188 (37.3)	177 (35.0)	376 (37.2)	0.96 (0.83–1.11)	0.56	1.03 (0.86–1.23)	0.74	0.89 (0.75–1.07)	0.22
5-yr event-free survival — %	33.5	46.0	40.0						
Death from cardiovascular causes									
Events at 3 yr — no. (%)	73 (14.5)	82 (16.2)	179 (17.7)						
3-yr event-free survival — %	83.8	82.4	80.8						
Events at 5 yr — no. (%)	94 (18.7)	105 (20.8)	228 (22.5)	0.84 (0.69–1.01)	0.07	0.81 (0.64–1.04)	0.10	0.86 (0.68–1.08)	0.19
5-yr event-free survival — %	62.7	64.4	61.2						
Atrial fibrillation									
Events at 3 yr — no. (%)	47 (9.3)	43 (8.5)	86 (8.5)	1.05 (0.78–1.41)	0.74	1.07 (0.75–1.53)	0.72	1.03 (0.73–1.47)	0.85
3-yr event-free survival — %	88.7	90.1	90.5						
Stroke, transient ischemic attack, or other thromboembolism									
Events at 3 yr — no. (%)	38 (7.5)	25 (5.0)	51 (5.0)	1.28 (0.88–1.86)	0.20	1.58 (1.03–2.42)	0.04†	0.98 (0.60–1.60)	0.93
3-yr event-free survival — %	91.1	94.2	94.2						
Heart failure									
Events at 3 yr — no. (%)	41 (8.1)	55 (10.9)	99 (9.8)	0.96 (0.73–1.28)	0.80	0.86 (0.60–1.23)	0.41	1.07 (0.77–1.49)	0.69
3-yr event-free survival — %	90.7	87.6	89.0						
New-onset angina or ischemic heart disease									
Events at 3 yr — no. (%)	5 (1.0)	5 (1.0)	9 (0.9)	0.89 (0.38–2.10)	0.79	0.91 (0.31–2.61)	0.86	0.88 (0.31–2.53)	0.81
3-yr event-free survival — %	98.9	98.9	99.0						
Myocardial infarction									
Events at 3 yr — no. (%)	12 (2.4)	11 (2.2)	32 (3.2)	0.72 (0.42–1.22)	0.22	0.70 (0.35–1.39)	0.31	0.73 (0.38–1.42)	0.35
3-yr event-free survival — %	97.3	97.5	96.4						
Revision of pacing system									
Events at 3 yr — no. (%)	28 (5.6)	35 (6.9)	59 (5.8)	1.12 (0.54–2.35)	0.76	1.30 (0.56–3.01)	0.54	0.95 (0.37–2.39)	0.91
3-yr event-free survival — %	93.5	92.0	93.1						

* Event-free survival rates were estimated with the use of the Kaplan–Meier method.
† The result was significant at the 5 percent level.

	Hazard Ratio (95% CI)	P Value	Single-Chamber Group		Dual-Chamber Group	
			No. of Patients	Deaths	No. of Patients	Deaths
Age ≤75 yr	0.85 (0.61–1.20)	0.36	263	59	282	78
Age >75 yr	0.99 (0.85–1.15)	0.86	746	328	730	315
Male	0.95 (0.80–1.14)	0.59	572	246	579	248
Female	1.02 (0.81–1.29)	0.86	436	141	432	145
NYHA class I	1.03 (0.77–1.39)	0.84	272	85	305	91
NYHA class II–IV	0.94 (0.79–1.10)	0.43	707	281	678	287
Second-degree heart block	1.04 (0.77–1.40)	0.80	259	86	289	86
Complete heart block	0.96 (0.82–1.13)	0.64	744	299	738	304
History of chronic heart failure	0.89 (0.66–1.20)	0.45	157	83	162	90
No history of chronic heart failure	1.01 (0.86–1.18)	0.93	848	300	842	298
Known ischemic heart disease	0.95 (0.75–1.21)	0.68	293	131	291	134
No known ischemic heart disease	0.99 (0.83–1.18)	0.91	713	253	714	254
Hypertension	1.01 (0.77–1.31)	0.97	317	105	361	121
No hypertension	0.95 (0.81–1.13)	0.59	688	278	644	267
Diabetes	0.97 (0.67–1.40)	0.87	108	49	137	71
No diabetes	0.99 (0.85–1.16)	0.93	898	335	868	317
Aspirin use	0.97 (0.77–1.21)	0.76	396	149	429	165
No aspirin use	0.98 (0.82–1.18)	0.82	609	234	576	223
ACE-inhibitor therapy	0.86 (0.62–1.17)	0.33	187	78	181	79
No ACE-inhibitor therapy	1.00 (0.85–1.17)	0.98	814	302	824	309
Diuretic therapy	1.13 (0.93–1.37)	0.22	468	211	499	204
No diuretic therapy	0.85 (0.69–1.04)	0.12	536	171	506	184
Overall	0.96 (0.83–1.11)	0.56	1009	387	1012	393

0.5 1.0 1.5

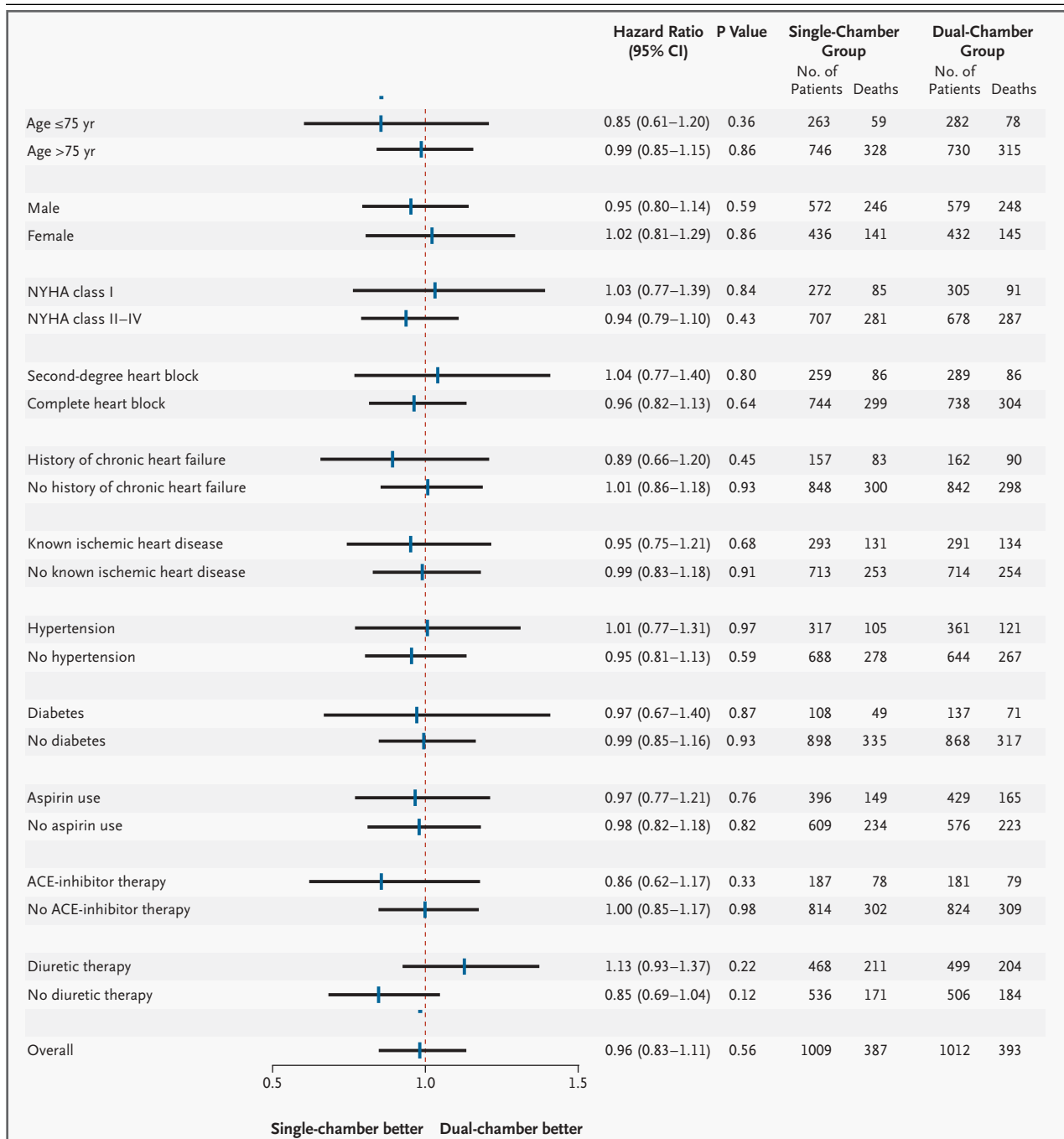Single-chamber better   Dual-chamber better

Figure 3. Effect of Pacing Mode on Deaths from All Causes, According to Subgroups.

Blue vertical lines and bars indicate, for each specified subgroup, the hazard ratio for death from all causes and the associated 95 percent confidence intervals (CIs) for single-chamber pacing as compared with dual-chamber pacing. NYHA denotes New York Heart Association, and ACE angiotensin-converting enzyme.

might be less readily influenced by pacing mode. Although the CTOPP trial included patients with sinus-node disease, the reduction in atrial fibrillation with physiologic pacing was also seen in the subgroup with atrioventricular block.[18] In the CTOPP trial, the difference in the incidence of atrial fibrillation emerged only at two years. It is possible that with longer follow-up of our patients, a difference might also emerge among them.

An interesting feature in our study was the increased early incidence of atrial fibrillation in the dual-chamber group. It is possible that the atrial lead may be arrhythmogenic in the early months after implantation. Alternatively, the capacity of dual-chamber pacemakers to detect high-rate atrial episodes might have led to an earlier recognition of atrial fibrillation. This capability might also increase the overall likelihood that atrial fibrillation will be detected with these systems, potentially masking a benefit of dual-chamber pacing; however, the diagnostic requirement of an electrocardiographically verified episode lasting 15 minutes or longer would be expected to attenuate the effect of such a bias.

The finding that there was a higher rate of stroke, transient ischemic attack, or thromboembolism with fixed-rate ventricular pacing is intriguing. Conceivably, the lower heart rates associated with fixed-rate pacing might promote atrial stasis, but the finding could be due to the play of chance amid multiple comparisons and should be interpreted with caution. The observation may, however, favor the use of a rate-adaptive system if a single-chamber ventricular pacemaker is used.

Our results, supported by the PASE and CTOPP trials, suggest that the clinical benefits associated with dual-chamber pacing for atrioventricular block have been overestimated. It is perhaps counterintuitive that the hemodynamic advantages of atrioventricular synchrony do not result in greater clinical benefit. One explanation for this may be that intraventricular and interventricular dyssynchrony resulting from stimulation at the right ventricular apex might counteract the benefit of atrioventricular synchrony.[19,20] This effect might be accentuated by the higher proportion of paced ventricular beats in the dual-chamber group. It is possible that alternative strategies, such as biventricular or septal pacing, might improve hemodynamic function and clinical outcomes. This hypothesis requires testing in clinical trials.

The low crossover rate (3.1 percent) from single-chamber to dual-chamber pacing in our study was similar to that in the CTOPP trial (2.7 percent), suggesting that single-chamber pacing is well tolerated. The higher crossover rate in the PASE study (26 percent), in which randomization to mode of pacing was made by software programming rather than by assignment of hardware, may reflect variation in the incidence of pacemaker syndrome but also highlights the subjective element in the diagnosis of this syndrome.

The choice of pacing mode for elderly patients with high-grade atrioventricular block should be made on an individual basis. Over three years, dual-chamber pacing is unlikely to influence mortality or the incidence of cardiovascular events, and single-chamber ventricular pacing should be regarded as an acceptable mode. The occasional need to upgrade to dual-chamber systems because of pacing-mode intolerance must be weighed against the increased risk of complications with dual-chamber implants. In elderly patients, factors other than the mode of pacing are more likely to determine the clinical outcome.

In elderly patients with high-grade atrioventricular block, the mode of pacing has no significant influence on the rate of death from all causes in the first five years after pacemaker implantation. Fixed-rate single-chamber ventricular pacing is associated with an increased risk of stroke, transient ischemic attack, or thromboembolism, but the pacing mode does not otherwise influence the incidence of cardiovascular events in the first three years after pacemaker implantation.

APPENDIX

The following institutions and investigators participated in the UKPACE trial (total numbers of patients recruited are indicated in parentheses): *Glenfield Hospital, Leicester* (343) — J.D. Skehan, W.D. Toff, J. Villanueva, J. Kovac, K. Percy, and G.H. Broomes; *Freeman Hospital, Newcastle* (170) — R.S. Bexton, S. Henderson, and J. Cronin; *St George's Hospital, London* (154) — A.J. Camm, E. Rowland, D.E. Ward, and S. Jones; *Cardiothoracic Centre, Liverpool* (139) — R.G. Charles, J. Morland-Duff, and S. Hughes; *Queen Elizabeth Hospital, Birmingham* (120) — M.D. Gammage, D. Jones, A. Barber, and Z. Harris; *Derbyshire Royal Infirmary, Derby* (79) — A. McCance and J.E. Penrice; *Northern General Hospital, Sheffield* (72) — R.J. Bowes and R. Ecob; *Blackpool Victoria Hospital, Blackpool* (71) — G.K. Goode and A. Delaney; *Hull Royal Infirmary, Hull* (68) — G.C. Kaye and T. Houghton; *Treliske Hospital, Truro* (64) — A.K.B. Slade and F. Westwood; *University Hospital of Wales, Cardiff* (60) — M.B. Buchalter and C. McCormack; *John Radcliffe Hospital, Oxford* (52) — O.J.M. Ormerod, K. Johnston, and Y. Bashir; *UCH/Middlesex Hospitals, London* (50) — D. Holdright, R.H. Swanton, and M. Squirrell; *Queen's Medical Centre, Nottingham* (49) — R.G. Wilcox and S. Jones; *Royal Devon and Exeter Hospital, Exeter* (45) — J.W. Dean and S. Crowsley; *Ninewells Hospital, Dundee* (39) — T.H. Pringle and D. Jamieson; *Wessex Cardiothoracic Centre, Southampton* (39) — J.M. Morgan and R. Williams; *Solihull Hospital, Solihull* (39) — K. Priestley and P. Brennan; *Wordsley Hospital, Stourbridge* (35) — E.J. Flint, P. Forsey, and A. Drewnicki; *Good Hope Hospital, Sutton Coldfield* (30) — R.E.A. Smith and J. Tipping; *Derriford Hospital, Plymouth* (29) — C.J. Burrell and I. Lines; *Southern General Hospital, Glasgow* (26) — D. Murdoch and C. Vaughan; *Ipswich Hospital, Ipswich* (24) — R.M. Oliver and C.J. Woollard; *St. Bartholomew's Hospital, London* (24) — A.W. Nathan and J. Sibley; *Papworth Hospital, Cambridge* (23) — M.C. Petch and S. Newell; *Western Infirmary, Glasgow* (22) — J.D. McArthur and S. Starkey; *Nottingham City Hospital, Nottingham* (20) — A.J. Ahsan and J. Riley; *County Hospital, Hereford* (16) — J. Glancy and D. Thomas; *Stobhill Hospital, Glasgow* (14) — K.J. Hogg and Y. Brown; *Stafford General Hospital, Stafford* (12) — P.A. Woodmansey and M. Batthew; *Royal Sussex County Hospital, Brighton* (12) — S. O'Nunain and L. Bennett; *Manor Hospital, Walsall* (11) — A. Cunnington and C. Boden; *New Cross Hospital, Wolverhampton* (10) — J.W. Pidgeon and K. Nicholas; *Glasgow Royal Infirmary, Glasgow* (9) — S.M. Cobbe and C. Armour; *Hairmyres Hospital, East Kilbride* (7) — K. Oldroyd, B. Vallance, and J. Young; *Glan Clwyd Hospital, Bodelwyddan* (6) — G.J. Green and N. Waterfield; *Maelor Hospital, Wrexham* (6) — R.P.W. Cowell and M.E. Antony; *The General Infirmary, Leeds* (5) — G.W. Reynolds and A. Nicholls; *Royal Free Hospital, London* (5) — J.G. Coghlan and W. Smith; *St Mary's Hospital, London* (4) — N.S. Peters and J. Varghese; *Sandwell Hospital, West Bromwich* (4) — P.J. Cadigan and A. Ridney; *Wansbeck General Hospital, Ashington* (4) — B. Thwaites and J. Cronin; *Beaumont Hospital, Dublin* (3) — T. Gumbrielle and J. Bedford; *City Hospital, Birmingham* (3) — T. Millane; *Doncaster Royal Infirmary, Doncaster* (3) — G.E. Payne and V. Hayward; *Heartlands Hospital, Birmingham* (1) — P. Ludman, J.M. Beattie, and S. Ramzan: *Trial Steering Committee* — S.M. Cobbe (chair), S.G. Ball, J.M. Bland, M.J. Buxton, and R. Sutton; *Data Monitoring Committee* — P. Sleight (chair), R.J.C. Hall, S.J. Pocock, and P.A. Poole-Wilson; *End Points and Events Committee* — M.C. Petch (chair), M.B. Buchalter, C.J. Burrell, J.C. Cowan, M.D. Gammage, R.T. Johnston, A.N. Sulke, and G.S. Venables; *Data Management Center (Nottingham Clinical Research Group)* — A.M. Skene (director), L. Brown, A. Charlesworth, M. Goulder, J. Sprague, and S. Stead.

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