formed in the emergency department.[12] Diagnostic testing is performed inconsistently,[5,13] and 60% of admitted patients receive no specific therapies during their admission.[13] Hospitalization appears to have minimal effect on 1-year mortality in high-risk patients, including those with known or suspected coronary artery disease, congestive heart failure, or abnormal electrocardiograms.[14]

Professional societies' guidelines provide recommendations for hospitalizing patients who present with syncope.[3,15,16] Furthermore, clinical prediction rules may identify patients at low risk for developing syncope-related adverse outcomes.[17–20] The adoption of similar rules in clinical practice may safely reduce syncope-related admissions and health care costs. Our findings provide important baseline data for evaluating the cost effectiveness of such efforts in the future.

1. Blanc JJ, L'Her C, Touiza A, Garo B, L'Her E, Mansourati J. Prospective evaluation and outcome of patients admitted for syncope over a 1 year period. *Eur Heart J* 2002;23:815–820.
2. Day SC, Cook EF, Funkenstein H, Goldman L. Evaluation and outcome of emergency room patients with transient loss of consciousness. *Am J Med* 1982; 73:15–23.
3. American College of Emergency Physicians. Clinical policy: critical issues in the evaluation and management of patients presenting with syncope. *Ann Emerg Med* 2001;37:771–776.
4. Gallagher EJ. Hospitalization for fainting: high stakes, low yield. *Ann Emerg Med* 1997;29:540–542.
5. Kapoor WN, Karpf M, Maher Y, Miller RA, Levey GS. Syncope of unknown origin. The need for a more cost-effective approach to its diagnosis evaluation. *JAMA* 1982;247:2687–2691.

6. Agency for Healthcare Research and Quality. HCUP Nationwide Inpatient Sample—Design of the HCUP Nationwide Inpatient Sample. Rockville, Maryland: Agency for Healthcare Research and Quality; 2000.
7. National Center for Health Statistics. 1997 reason for visit classification. Available at: *http://www.cdc.gov/nchs/data/ahcd/rvc97.pdf*. Accessed August 9, 2004.
8. Agency for Healthcare Research and Quality. HCUP Quality Control Procedures. Rockville, Maryland: Agency for Healthcare Research and Quality; 2002.
9. Smith DH, Malone DC, Lawson KA, Okamoto LJ, Battista C, Saunders WB. A national estimate of the economic costs of asthma. *Am J Respir Crit Care Med* 1997;156:787–793.
10. Bozzette SA, Berry SH, Duan N, Frankel MR, Leibowitz AA, Lefkowitz D, Emmons CA, Senterfitt JW, Berk ML, Morton SC, et al. The care of HIV-infected adults in the United States. HIV Cost and Services Utilization Study Consortium. *N Engl J Med* 1998;339:1897–1904.
11. Ward MM, Javitz HS, Smith WM, Bakst A. Direct medical cost of chronic obstructive pulmonary disease in the U.S.A. *Respir Med* 2000;94:1123–1129.
12. Mozes B, Confino-Cohen R, Halkin H. Cost-effectiveness of in-hospital evaluation of patients with syncope. *Isr J Med Sci* 1988;24:302–306.
13. Getchell WS, Larsen GC, Morris CD, McAnulty JH. Epidemiology of syncope in hospitalized patients. *J Gen Intern Med* 1999;14:677–687.
14. Crane SD. Risk stratification of patients with syncope in an accident and emergency department. *Emerg Med J* 2002;19:23–27.
15. Brignole M, Alboni P, Benditt D, Bergfeldt L, Blanc JJ, Bloch Thomsen PE, van Dijk JG, Fitzpatrick A, Hohnloser S, Janousek J, et al. Guidelines on management (diagnosis and treatment) of syncope. *Eur Heart J* 2001;22:1256–1306.
16. Linzer M, Yang EH, Estes NA III, Wang P, Vorperian VR, Kapoor WN. Diagnosing syncope. Part 1: value of history, physical examination, and electrocardiography. Clinical Efficacy Assessment Project of the American College of Physicians. *Ann Intern Med* 1997;126:989–996.
17. Quinn JV, Stiell IG, McDermott DA, Sellers KL, Kohn MA, Wells GA. Derivation of the San Francisco Syncope Rule to predict patients with short-term serious outcomes. *Ann Emerg Med* 2004;43:224–232.
18. Martin TP, Hanusa BH, Kapoor WN. Risk stratification of patients with syncope. *Ann Emerg Med* 1997;29:459–466.
19. Sarasin FP, Hanusa BH, Perneger T, Louis-Simonet M, Rajeswaran A, Kapoor WN. A risk score to predict arrhythmias in patients with unexplained syncope. *Acad Emerg Med* 2003;10:1312–1317.
20. Colivicchi F, Ammirati F, Melina D, Guido V, Imperoli G, Santini M. Development and prospective validation of a risk stratification system for patients with syncope in the emergency department: the OESIL risk score. *Eur Heart J* 2003;24:811–819.

Permanent Pacing Is a Risk Factor for the Development of Heart Failure

Ronald S. Freudenberger, MD, Alan C. Wilson, PhD, Janet Lawrence-Nelson, PhD, Joshua M. Hare, MD, and John B. Kostis, MD, for the Myocardial Infarction Data Acquisition System Study Group (MIDAS 9)

No previous study has examined the importance of right ventricular pacing as a risk factor for the development of heart failure (HF) in subjects without a history of HF. A cohort study of patients who underwent initial pacemaker implantation (n = 11,426) was conducted to test the hypothesis that patients with ventricular dyssynchrony created by permanent pacing would develop HF, as shown by new HF hospitalizations or HF-related deaths, at a higher rate than matched controls. ©2005 by Excerpta Medica Inc.

(Am J Cardiol 2005;95:671–674)

From the Department of Medicine, Robert Wood Johnson Medical School, New Brunswick, New Jersey; and the Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland. Dr. Freudenberger has received research support from and is on the speakers' bureau of Medtronic, Inc., Minneapolis, Minnesota. Dr. Freudenberger's address is: Robert Wood Johnson Medical School, 125 Paterson Street, Suite 6100, New Brunswick, New Jersey 08903. E-mail: freuders@umdnj.edu. Manuscript received August 10, 2004; revised manuscript received and accepted October 18, 2004.

The Myocardial Infarction Data Acquisition System is a statewide surveillance system that combines hospital (Uniform Billing 92) discharge data and death certificate registration data to track cardiac patients who have been discharged from the 85 acute care hospitals in New Jersey.[1] Institutional review board approval for the Myocardial Infarction Data Acquisition System study was obtained from the state and the medical school.

• • •

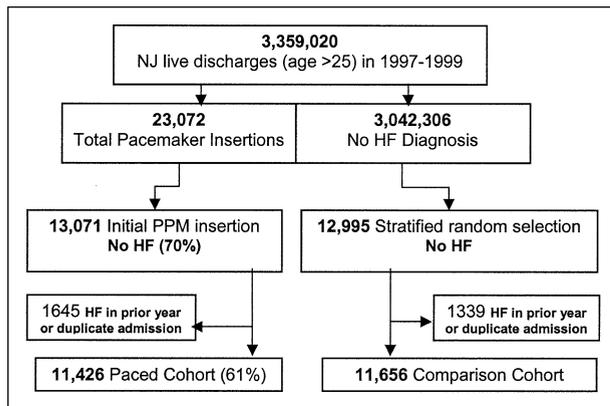The study cohort construction scheme is illustrated in Figure 1. Of the patients implanted with pacemak-

FIGURE 1. Study cohort construction scheme. Each year (1997,1998, and 1999) was processed separately to identify the index admissions for patients who received pacemakers and the matched comparison cases. The inclusion criteria were New Jersey (NJ) residency, age >25 years, unique insurance identifier, discharged alive, and initial pacemaker implantation or match by stratified random sampling within age groups. The exclusion criteria were nonunique identifiers, nonindex admission, and evidence of HF in admission during the previous year (minimum).

TABLE 1 Baseline Characteristics

Characteristic	Paced Cohort (n = 11,426)	Comparison Cohort (n = 11,656)
Age (yrs) (mean ± SD)	75.6 ± 10.7	75.3 ± 10.8
26–64	12.7%	13.3%
65–79	48.4%	48.7%
≥80	38.9%	38.0%
Black men	6.2%	7.7%
Black women	6.8%	7.5%
White men	45.9%	44.2%
White women	41.1%	40.6%
Hypertension	52.4%	51.6%
Myocardial infarction	2.9%	2.7%
Diabetes mellitus	17.9%	18.4%
Sinus node dysfunction	59.1%	0.5%
Atrioventricular block	39.7%	2.3%
Atrial fibrillation	38.5%	9.3%
Dizziness or syncope	12.9%	3.7%
Carotid hypersensitivity	2.6%	0.01%
Pacemaker ICD-9 code		
Single chamber, code 37.81	10%	—
Single chamber, code 37.82	17%	—
Dual chamber, code 37.83	73%	—
Renal disease	11.8%	19.3%
Cancer	5.0%	17.0%

ICD-9 = *International Classification of Diseases,* Ninth Revision.

ers for the first time, 13,071 (70%) met the inclusion criteria for this study, of whom 1,645 (13%) were excluded because of previous heart failure (HF) hospitalizations, leaving 11,426 (61%) as the cohort of interest (Figure 1). A randomly selected, matched cohort of patients without pacemakers or diagnoses of HF (n = 11,656) was used as a control group. The comparison cohort subjects (not paced, without HF) were selected by stratified random sampling (5-year age group strata reflecting the age distribution of the index subjects) with matching on variables associated with HF development (gender and diagnosis codes indicating myocardial infarction, hypertension, or diabetes mellitus [*International Classification of Diseases*-9th Revision, clinical modification codes 410, 401 to 405, or 250]). The initial random selection generated a cohort of 12,995 patients, of whom 1,339 (10%) were excluded for HF hospitalization in the previous year to yield the comparison cohort.

The 2 cohorts were followed by record linkage through 2001 to determine the rates of occurrence of HF hospitalization or death. The median length of follow-up was 32.6 months and ranged from ≥2 years (for discharges in 1999) to 5 years (for discharges in 1997). Record linkage was performed with the Automatch-Generalized Record Linkage System, version 3.0 (Match Ware Technologies, Inc., Silver Springs, Maryland). The method is described elsewhere.[2]

The stratified random selection procedure and the comparison of the event rates of the primary outcome (new HF hospitalization) and secondary outcome (HF hospitalization or mortality) were performed using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina). Kaplan-Meier survival curves (product-limit method) for time to first event were constructed for the paced cohort and the comparison, nonpaced group. The log-rank test was used to compare the 2 groups. All hazard ratios (HRs) associated with pacing

or pacemaker type were adjusted to control for possible confounding factors with multivariable Cox regression, including age, gender, myocardial infarction, hypertension, diabetes, and atrial fibrillation in the models.

By design, the cohorts were similar to each other with respect to the matching variables (age, gender, and race) and for history of hypertension, previous or acute myocardial infarction, and diabetes (Table 1). The predominant differences between the cohorts were indications for pacemaker implantation, including sinus node dysfunction, atrioventricular block, and atrial fibrillation. Seventy-three percent of the permanent pacemakers implanted were dual-chamber devices.

Over a median follow-up of 33 months for the 2 groups from 1997 to 2001, 20% of the paced group (2,314 patients) experienced new HF hospitalization events (Table 2) compared with 12.5% in the control group (1,459 patients; Cox adjusted HR 1.55, 95% confidence interval [CI] 1.44 to 1.66). For the combined end point of HF hospitalization or all-cause mortality over the same time period, 35% of the paced group (4,019 patients) experienced events compared with 33% of the control group (3,845 patients; HR 0.96, 95% CI 0.91 to 1.00).

Deaths attributed to HF were also more frequent in the pacemaker cohort (81 vs 53, p = 0.035). Kaplan-Meier survival analysis of time to first HF hospitalization or fatal HF demonstrated a statistically significant increase in the incidence of this composite end point in the paced group (log-rank p <0.0001, Cox adjusted HR 1.44, 95% CI 1.34 to 1.54) beginning early after implantation, which persisted throughout the period of analysis (Table 2). When these analyses

TABLE 2 Hospitalization for HF and Fatal Events by Pacemaker Status and Type

| Variable | No. of Events | | p Value | HR (adjusted*) | 95% CI |
	Paced (n = 11,426)	Control (n = 11,656)			
Nonfatal events					
HF hospitalization	2,314	1,459	<0.0001	1.55	1.44–1.66
Deaths					
Total deaths	2,439	2,907	<0.0001	0.74	0.70–0.79
Cardiovascular					
Stroke	127	125	NS		
Sudden	6	14	—		
Myocardial infarction	232	242	NS		
Left ventricular failure	81	53	0.035	1.44	1.34–1.54
Atherosclerotic heart disease	387	381	NS		
Noncardiovascular					
Infections	83	109	NS		
Cancer	447	796	<0.0001	0.57	0.51–0.64
Diabetes/endocrine	120	125	NS		
Mental	51	105	<0.0001	0.49	0.35–0.69
Respiratory	171	254	<0.0001	0.69	0.57–0.83
Renal	94	96	NS		
Combined events					
HF hospitalization or HF death	2,355	1,490	<0.0001	1.44	1.34–1.54
HF hospitalization or all-cause mortality	4,019	3,845	0.075	0.96	0.91–1.00
Single chamber					
HF hospitalization or HF death	805	1,490	<0.0001	1.59	1.43–1.77
HF hospitalization or all-cause mortality	1,461	3,845	<0.0001	1.19	1.11–1.28
Dual chamber					
HF hospitalization or HF death	1,550	1,490	<0.0001	1.36	1.26–1.44
HF hospitalization or all-cause mortality	2,558	3,845	<0.0001	0.87	0.83–0.92

*Cox model included paced status, diabetes, hypertension, myocardial infarction, atrial fibrillation, age, gender, and race (white = 1).
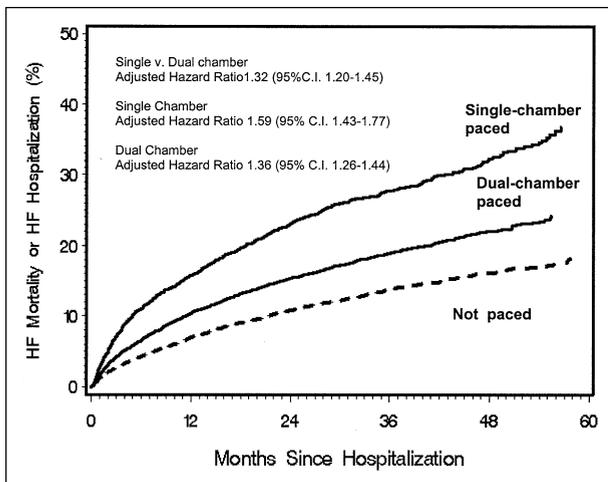

FIGURE 2. Kaplan-Meier plots of hospitalization for HF or HF death in 3,093 New Jersey residents who underwent initial single-chamber permanent pacemaker insertion *(top line)* and 8,333 New Jersey residents who underwent initial dual-chamber permanent pacemaker insertion *(middle line)* in 1997, 1998, and 1999 compared with a matched comparison cohort of 11,656 nonpaced patients *(broken line)*. All were followed through 2001.

were repeated (Figure 2 and Table 2), taking into consideration the type of pacemaker implanted (i.e., single or dual chamber), it was found that the implantation of a single-chamber pacemaker was more strongly associated with HF hospitalization or fatal HF compared with the control group (HR 1.59, 95% CI 1.43 to 1.77) than was the implantation of a dual-chamber pacemaker (HR 1.36, 95% CI 1.26 to 1.44). There was a 32% increase in the adjusted risk for fatal or nonfatal HF comparing the risk associated with the implantation of a single-chamber pacemaker with that of a double-chamber device (HR 1.32, 95% CI 1.20 to 1.45).

Unadjusted survival analysis of the composite end point of HF hospitalization and all-cause mortality also revealed a significant increase in risk in the paced group (Table 3) beginning after 6 months, which persisted throughout the course of the follow-up (log-rank p = 0.0006, adjusted HR 0.96, 95% CI 0.91 to 1.00). Analysis by device type revealed that the implantation of single-chamber devices was associated with a 19% greater risk for death or HF hospitalization (HR 1.19, 95% CI 1.11 to 1.28). Dual-chamber insertion was not associated with increased adjusted risk for HF hospitalization and all-cause mortality (HR 0.87, 95% CI 0.83 to 0.92).

• • •

In this large, statewide analysis, we found that permanent pacing in patients who did not have HF diagnoses for ≥1 year before pacemaker implantation significantly increased their risk of being hospitalized for HF or experiencing HF-related deaths compared with a matched control group. This finding was true in unadjusted analysis and after adjusting for confounding variables, including atrial fibrillation, sick sinus syndrome, atrioventricular block, history of myocardial infarction, gender, African-American race, age,

TABLE 3 HF Death and Hospitalization for HF by Pacemaker Status, Showing Univariate and Adjusted Cox HRs for Demographic and Clinical Factors

Variable	Univariate HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Pacemaker	1.64 (1.54–1.75)	<0.0001	1.44 (1.30–1.60)	<0.0001
Age (10 yrs)	1.50 (1.45–1.56)	<0.0001	1.52 (1.47–1.57)	<0.0001
Race (white)	1.02 (0.93–1.21)	0.627	0.93 (0.85–1.03)	0.149
Sex (male)	0.93 (0.87–0.99)	0.015	1.03 (0.96–1.10)	0.425
Myocardial infarction	1.68 (1.43–1.97)	<0.0001	1.59 (1.36–1.87)	<0.0001
Hypertension	1.20 (1.12–1.28)	<0.0001	1.08 (1.01–1.15)	0.025
Diabetes mellitus	1.66 (1.55–1.79)	<0.0001	1.78 (1.65–1.91)	<0.0001
Atrial fibrillation	1.75 (1.64–1.87)	<0.0001	1.52 (1.41–1.64)	<0.0001
Atrioventricular block	1.34 (1.25–1.44)	<0.0001	1.09 (0.99–1.20)	0.066
Sinus node dysfunction	1.40 (1.32–1.50)	<0.0001	0.94 (0.85–1.03)	0.164

The Cox proportional-hazards regression model contained all 10 factors.

diabetes, and hypertension. These findings support the concept that right ventricular pacing represents a risk factor for developing HF and implicates ventricular dyssynchrony or a lack of appropriate atrioventricular sequence as a potential cause of adverse outcomes in patients without HF.

We observed a significant increase in HF-related events, including HF hospitalization or HF death, that was seen as early as 6 months after pacemaker implantation and that persisted throughout follow-up. Interestingly, total mortality was less in the paced group, as was renal disease, cancer, neurologic dysfunction, and death from respiratory disease, implying a significant selection bias regarding the patients in whom physicians choose to implant permanent pacemakers, particularly expensive dual-chamber devices. Patients with diagnoses indicating renal dysfunction, cancer, or neurologic dysfunction were less likely to receive pacemakers.

The present study is the first population-based study to describe an increased risk for adverse events with single- or dual-chamber pacemakers in patients without clinical diagnoses of HF. This result is consistent with previous studies that have examined the impact of ventricular pacing in patients with left ventricular dysfunction. In the Dual Chamber and VVI Implantable Defibrillator Trial, permanent pacing increased the combined end point of death or hospitalization for HF compared with backup bradycardia pacing.[3] Our study is also consistent with a post hoc analysis of the Mode Selection Trial, [4] a trial of pacemaker therapy for sick sinus syndrome that demonstrated that the cumulative percentage of right ventricular apical pacing, calculated from stored pacemaker data, was a strong predictor of HF hospitalization.

There are several potential limitations to this study. First, because this was a cohort study based on administrative data, the ability to control for the severity of co-morbidities and concomitant medical therapy was lacking, and it is difficult to determine whether any associations derived from it imply causality. It is possible that those patients who required permanent pacemakers were also patients already at risk for death or the development of HF requiring hospitalization. However, we matched the 2 cohorts for possible risk factors that may identify a patient for greater risk for

cardiac dysfunction. In addition, the differences persisted after adjustment for the available risk factors for HF development by Cox regression analysis. Second, we do not know the cumulative percentage of time of ventricular pacing in those patients who received pacemakers. However, if the patients were not paced a significant amount of the time, we would expect to see a lower rate of end points. If anything, this would dilute the effect and result in an underestimate of the relative risk. Third, we were unable to determine the percentage of patients with pacemakers who received only atrial pacing. However, according to industry sources, <1% of pacemakers implanted during the period under study, from 1997 to 1999, were atrial pacemakers. Fourth, we assumed that our group of interest either had no HF, subclinical HF, or mild HF that did not require hospitalization. A baseline assessment of cardiac function was not available in this population study. A recent report estimated that patients with advanced HF have a hospitalization rate of 24% to 31% per year.[5] Therefore, our assumptions are likely to be valid, because patients with advanced HF would probably have had HF hospitalizations or diagnoses of HF either at the time of permanent pacemaker implantation or during the 1-year period preceding permanent pacemaker implantation.[6] Last, errors or omissions in coding exist, but a similar rate of errors and omissions could occur in the 2 cohorts.

1. Kostis JB, Wilson AC, Lacy CR, Cosgrove NM, Ranjan R, Lawrence-Nelson J. Time trends in the occurrence and outcome of acute myocardial infarction and coronary heart disease death between 1986 and 1996 (a New Jersey statewide study). *Am J Cardiol* 2001;88:837–841.
2. Gregory PM, Rhoads GG, Wilson AC, O'Dowd KJ, Kostis JB. Impact of availability of hospital-based invasive cardiac services on racial differences in the use of these services. *Am Heart J* 1999;138:507–517.
3. The DAVID Trial Investigators. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002;288:3115–3123.
4. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, Lamas GA, Mode Selection Trial Investigators. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 2003;107:2932–2937.
5. Bobbio M, Ferrua S, Opasich C, Porcu M, Lucci D, Scherillo Tavazzi L, Maggioni APM. Survival and hospitalization in heart failure patients with or without diabetes treated with beta-blockers. *J Card Fail* 2003;9:192–202.
6. Benatar D, Bondmass M, Ghitelman J, Avitall B. Outcomes of chronic heart failure. *Arch Intern Med* 2003;163:347–352.