Clinical Characteristics and Outcome of Infective Endocarditis Involving Implantable Cardiac Devices

Eugene Athan, MD
Vivian H. Chu, MD, MHS
Pierre Tattevin, MD, PhD
Christine Selton-Suty, MD
Phillip Jones, MD
Christoph Naber, MD, PhD
José M. Miró, MD, PhD
Salvador Ninot, MD
Nuria Fernández-Hidalgo, MD
Emanuele Durante-Mangoni, MD
Denis Spelman, MD
Bruno Hoen, MD, PhD
Tatjana Lejko-Zupanc, MD, PhD
Enrico Cecchi, MD
Franck Thuny, MD
Margaret M. Hannan, MD
Paul Pappas, MS
Margaret Henry, PhD, BSc (Hons)
Vance G. Fowler Jr, MD, MHS
Anna Lisa Crowley, MD, MHS
Andrew Wang, MD
for the ICE-PCS Investigators

Context Infection of implantable cardiac devices is an emerging disease with significant morbidity, mortality, and health care costs.

Objectives To describe the clinical characteristics and outcome of cardiac device infective endocarditis (CDIE) with attention to its health care association and to evaluate the association between device removal during index hospitalization and outcome.

Design, Setting, and Patients Prospective cohort study using data from the International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS), conducted June 2000 through August 2006 in 61 centers in 28 countries. Patients were hospitalized adults with definite endocarditis as defined by modified Duke endocarditis criteria.

Main Outcome Measures In-hospital and 1-year mortality.

Results CDIE was diagnosed in 177 (6.4% [95% CI, 5.5%-7.4%]) of a total cohort of 2760 patients with definite infective endocarditis. The clinical profile of CDIE included advanced patient age (median, 71.2 years [interquartile range, 59.8-77.6]); causation by staphylococci (62 [35.0% {95% CI, 28.0%-42.5%}] *Staphylococcus aureus* and 56 [31.6% {95% CI, 24.9%-39.0%}] coagulase-negative staphylococci); and a high prevalence of health care–associated infection (81 [45.8% {95% CI, 38.3%-53.4%}]). There was coexisting valve involvement in 66 (37.3% [95% CI, 30.2%-44.9%]) patients, predominantly tricuspid valve infection (43/177 [24.3%]), with associated higher mortality. In-hospital and 1-year mortality rates were 14.7% (26/177 [95% CI, 9.8%-20.8%]) and 23.2% (41/177 [95% CI, 17.2%-30.1%]), respectively. Proportional hazards regression analysis showed a survival benefit at 1 year for device removal during the initial hospitalization (28/141 patients [19.9%] who underwent device removal during the index hospitalization had died at 1 year, vs 13/34 [38.2%] who did not undergo device removal; hazard ratio, 0.42 [95% CI, 0.22-0.82]).

Conclusions Among patients with CDIE, the rate of concomitant valve infection is high, as is mortality, particularly if there is valve involvement. Early device removal is associated with improved survival at 1 year.

JAMA. 2012;307(16):1727-1735 www.jama.com

CARDIAC ELECTRONIC DEVICES, including permanent pacemakers and implantable cardioverter-defibrillators (ICDs), are increasingly implanted worldwide, with estimates of more than 4.2 million patients with a permanent pacemaker or ICD implanted in the United States between 1993 and 2008.[1,2] Cardiac device infection is a serious, emerging disease with a 210% increase in incidence between 1993 and 2008.[1,3,4] In-hospital charges for this complication are estimated to be at least US $146 000 per case.[1,5,6] Cardiac device infective endocarditis (CDIE) in particular has a substantially higher mortality rate than cardiac device infection without endocarditis.[7]

The pathogenesis of CDIE usually involves skin contamination at the time of implantation or sometimes later from the generator site.[8,9] The majority of car-

Author Affiliations and a List of the ICE-PCS Investigators are at the end of this article.
Corresponding Author: Andrew Wang, MD, DUMC 3428, Duke Hospital, Room 7401, Erwin Rd, Durham, NC 27710 (a.wang@duke.edu).

diac device infections affect the subcutaneous generator pocket, with approximately 10% to 23% resulting in CDIE.[7,10] The incidence of CDIE has been reported as between 0.06% and 0.6% per year,[11,12] or 1.14 per 1000 device-years.[12] Risk factors include host factors, such as malnutrition, malignancy, diabetes mellitus, skin disorders, and use of corticosteroids and anticoagulants,[13] as well as procedural factors, such as type of device, prolonged duration, generator replacement, or catheter-related bloodstream or sternal infection.[3,8,11,12] The management of CDIE is complex and usually requires prolonged antibiotic therapy, percutaneous or surgical removal of the device, and possible device reimplantation.[3,8,14,15]

The objectives of this prospective, observational study were to describe the characteristics and outcome of CDIE with attention to health care–associated infection and to determine prognostic factors associated with in-hospital and 1-year mortality, particularly the association between device removal and outcome.

METHODS

International Collaboration on Endocarditis–Prospective Cohort Study

Data from the International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS) were used for this study. The background and inclusion criteria of this prospective, multicenter, international registry of infective endocarditis have been reported.[16-18]

Between June 2000 and September 2006, 3284 patients from 61 centers in 28 countries were enrolled. The ICE-PCS database is maintained at the Duke Clinical Research Institute, which is the data coordinating center for ICE studies. The ICE-PCS protocol was reviewed by institutional review boards and ethics committees at all sites, including Duke University; written informed consent was obtained from patients unless the requirement was waived by the boards and committees.

Patient Selection and Data Collection

Patients were identified prospectively using site-specific procedures to ensure consecutive enrollment.[17,18] Patients were enrolled in ICE-PCS if they met criteria for possible or definite infective endocarditis based on modified Duke criteria.[17,18] Only patients with definite infective endocarditis were included in the current study. To preserve the assumption of independence of observations, only the first episode of infective endocarditis recorded for an individual patient was used in the analysis.

The method of data collection for ICE-PCS has been previously reported.[16] Briefly, a standard case report form was used at all sites to collect data. The case report form included 275 variables and was developed by ICE according to standard definitions.[18] Data were collected during the index hospitalization and then entered at the coordinating center or by site investigators using an Internet-based data entry system. Clinical characteristics including demographics, comorbid conditions, preexisting valvular conditions, details regarding the current episode of infective endocarditis (including source of acquisition, microbiology and echocardiography findings, complications, management, and outcome) were collected. All sites were queried to obtain 1-year outcome data for survival, with use of national death indices, medical records, or patient contact, as available.

Outcome and Definitions

The outcomes of interest in this study were in-hospital and 1-year mortality. Definitions of the variables included in the ICE-PCS case report form have been reported.[16] Definite CDIE was clinically defined as valvular or lead vegetations detected by echocardiography or as meeting the Duke criteria for infective endocarditis.[19] Pathologic diagnostic criteria for definite infective endocarditis included microorganisms detected by culture or histology in a vegetation or by culture of a cardiac device lead.[7]

Health care–associated CDIE was defined as either nosocomial infection or nonnosocomial health care–associated infection.[20,21] Nosocomial infection was defined as infective endocarditis developing in a patient hospitalized for more than 48 hours prior to the onset of signs or symptoms consistent with infective endocarditis. Nonnosocomial, health care–associated infection was defined if signs or symptoms consistent with infective endocarditis developed before hospitalization in patients with extensive out-of-hospital contact with health care interventions, including (1) receipt of intravenous therapy, wound care, or specialized nursing care at home within the 30 days prior to the onset of CDIE; (2) visiting a hospital or hemodialysis clinic or receiving intravenous chemotherapy within the 30 days before the onset of CDIE; (3) hospitalization in an acute care hospital for 2 or more days in the 90 days before the onset of CDIE; or (4) residing in a nursing home or long-term care facility.[20,21] Community-acquired infective endocarditis was defined as signs or symptoms of infective endocarditis developing before hospitalization in a patient without extensive out-of-hospital contact with health care interventions or systems.[21]

Intravascular access devices were defined as an arterial venous fistula or an indwelling vascular catheter; a long-term indwelling central venous catheter was defined as a tunnelled, cuffed catheter or as a subcutaneous port catheter. An intravascular access device was presumed to be a possible source of infective endocarditis if it was present at the onset of symptoms of infective endocarditis. Persistent bacteremia was defined as previously reported.[19] Intracardiac abscess was defined as a thickened area or mass with a heterogeneous echogenic or echolucent appearance by echocardiography or as the presence of pus by direct visualization at the time of surgery.[22]

Statistical Analysis

Data are presented as medians (interquartile ranges) for continuous variables and as frequencies (percent-

ages) for categorical variables. Simple comparisons were made with the Wilcoxon rank-sum test or the χ^2 test as appropriate.

A generalized estimating equation method was used to determine if device removal is associated with in-hospital mortality among patients with CDIE. The method produces consistent parameter estimates while accounting for the correlation in outcomes of patients from the same hospital. The final parameter estimate is converted to an odds ratio (OR) with a corresponding 95% Wald CI. The relative risk (RR) and corresponding 95% CI were also computed. Removal or nonremoval of the cardiac device was analyzed for the end points, because it was hypothesized to be prognostically significant.

A proportional hazards regression model was used to determine if device removal is associated with survival among patients with CDIE. Survival curves were produced by plotting the estimated survival distribution obtained from the proportional hazards regression model, stratified by device removal. Survival times were censored at 1 year or date of last contact. The potential interaction between concomitant valve infection and cardiac device removal during index hospitalization was evaluated by comparing the survival for each pairwise combination of valve infection and cardiac device removal. Pairwise tests were performed, and results were adjusted for multiple comparisons using the Bonferroni method.

All tests were 2-sided, and statistical significance was determined at the .05 level. All statistical analyses were performed using SAS version 9.2.

RESULTS

Cardiac device infective endocarditis was diagnosed in 177 (6.4% [95% CI, 5.5%-7.4%]) of the total cohort of 2760 patients with definite infective endocarditis, including 152 (85.9% [95% CI, 79.9%-90.7%]) with a permanent pacemaker, 21 (11.9% [95% CI, 7.5%-17.6%]) with an ICD, and 4 (2.3% [95% CI, 0.6%-5.7%]) with device type not specified. The geographic distribution of these cases was North America (n=43 patients), Europe (n=95), South America (n=15), and others, including Australia, Asia, the Middle East, and Africa (n=24).

The clinical characteristics of CDIE are shown in TABLE 1 and FIGURE 1. Patients were predominantly men (74.0% [95% CI, 66.9%-80.3%]), with a median age of 71.2 (interquartile range, 59.8-77.6) years; 27.1% (95% CI, 20.7%-34.3%) had diabetes mellitus. Blood cultures were positive in 149 patients (84.2% [95% CI, 78.0%-89.2%]), and isolates were predominantly staphylococcal (*Staphylococcus aureus*, 35.0% [95% CI, 28.0%-42.5%]; coagulase-negative staphylococci, 31.6% [95% CI, 24.9%-39.0%]). Vegetations were visualized by echocardiography in 159 patients (89.8% [95% CI, 84.4%-93.9%]), of whom 135 (76.3% [95% CI, 69.3%-82.3%]) had vegetation on a cardiac device lead.

Coexisting valve infection was found in 66 patients (37.3% [95% CI, 30.2%-44.9%]), with echocardiographic detection of valvular vegetations in 63. Vegetations involved a native valve in 57 patients (32.2% [95% CI, 25.4%-39.6%]) or a prosthetic valve in 9 (5.1% [95% CI, 2.4%-9.4%]). The distribution of valve involvement included the tricuspid (n=43), mitral (n=17), aortic (n=6), and pulmonic (n=1) valves. Concomitant valve infection with CDIE was associated with in-hospital mortality (OR, 3.31 [95% CI, 1.71-6.39]; *P*=.004; RR, 2.75 [95% CI, 1.30-5.83]).

Device and lead removal was performed during the index hospitalization in 141 of 177 patients (79.7% [95% CI, 73.0%-85.3%]), with a median delay of 12 days (interquartile range, 5-25 days) after admission; data on device removal were not available for 2 patients. Comparisons between patients who did and did not undergo device removal during the index hospitalization are shown in TABLE 2. These patient groups were similar for most characteristics, although patients who underwent device removal had a lower percentage of positive blood cultures and lower rate of heart failure. Thirty of the 66 patients with concomitant valve infection (45.5% [95% CI, 33.1%-58.2%]) underwent valve surgery during the index hospitalization, representing 17.0% (95% CI, 11.7%-23.3%) of the overall CDIE cohort.

Twenty-six of the patients with CDIE (14.7% [95% CI, 9.8%-20.8%]) died during the index hospitalization, including 18 of 141 (12.8%) who underwent device removal and 8 of 34 (23.5%) who did not. Simple logistic regression analysis demonstrated that removal of the cardiac device was not associated with lower in-hospital mortality (OR, 0.47 [95% CI, 0.19-1.21]; *P*=.12; RR, 0.54 [95% CI, 0.26-1.14]).

Between hospital discharge and 1-year follow-up, 15 patients died and 10 were lost to follow-up. Overall, of the 177 patients with CDIE enrolled, 126 (71.2% [95% CI, 63.9%-77.7%]) were alive at 1 year, 41 (23.2% [95% CI, 17.2%-30.1%]) had died, and 10 (5.6% [95% CI, 2.7%-10.1%]) had been lost to follow-up. At 1 year, 28 of 141 (19.9% [95% CI, 13.6%-27.4%]) patients who underwent device removal during the index hospitalization had died, compared with 13 of 34 (38.2% [95% CI, 22.2%-56.4%]) who did not undergo device removal. FIGURE 2A shows survival as a function of device removal during index hospitalization, censored at 1 year or date of last contact. Device removal during the index hospitalization was associated with improved 1-year survival (hazard ratio, 0.42 [95% CI, 0.22-0.82]; *P*=.01; RR, 0.52 [95% CI, 0.30-0.89]). When survival at 1 year was stratified by presence of concomitant valve infection during initial hospitalization, the presence of concomitant valve infection was found to confer worse survival, regardless of device removal (Figure 2B). There was no evidence of significant interaction between concomitant valve infection and device removal.

Health care–associated infection was identified in 81 (45.8% [95% CI, 38.3%-53.4%]) patients with CDIE, includ-

Table 1. Characteristics of Study Patients and Cardiac Device Infective Endocarditis and Their Association With In-Hospital Mortality

Variable	CDIE Total (n = 177)	In-Hospital Survival (n = 151)	In-Hospital Death (n = 26)	Unadjusted OR (95% CI)	*P* Value
Age, median (IQR), y (OR per 10-y intervals)	71.2 (59.8-77.6)	72.2 (56.2-77.2)	71.0 (64.0-78.0)	1.47 (1.07-2.02)	.02
Men	131 (74.0)	112 (74.2)	19 (73.1)	1.05 (0.29-3.82)	.94
Fever >38°C	143 (80.7)	120 (7.4)	23 (88.5)	2.44 (0.62-9.58)	.20
Presentation <1 mo of symptoms	119 (67.2)	97 (64.2)	22 (84.6)	2.72 (0.97-7.61)	.06
Health care–associated infection	81 (45.8)	63 (41.7)	18 (69.2)	3.22 (1.52-6.80)	.002
Transferred from another hospital	77 (43.5)	70 (46.4)	7 (26.9)	0.44 (0.17-1.13)	.09
Device type (n = 173)					<.001
Pacemaker	152 (87.9)	130 (86.1)	22 (84.6)	0.72 (0.22-2.34)	.37
ICD	21 (12.1)	17 (11.2)	4 (15.4)	1.39 (0.43-4.52)	.53
Endocarditis type					
CDIE only	110 (62.1)	101 (67)	9 (34.6)	1 [Reference]	
CDIE + valve infection	66 (37.2)	49 (32.5)	17 (65.4)	3.31 (1.71-6.39)	.004
Native valve	57 (32.2)	42 (27.8)	15 (57.7)		
Prosthetic valve	9 (5.1)	7 (4.6)	2 (7.7)		
Geographic region					
North America	43 (24.3)	36 (23.8)	7 (26.9)	1 [Reference]	
Europe	95 (53.7)	82 (54.3)	13 (50.0)	0.72 (0.16-3.22)	.67
South America	15 (8.5)	13 (8.6)	2 (7.7)	0.73 (0.11-4.84)	.75
Other	24 (13.6)	20 (13.2)	4 (15.4)	0.86 (0.21-3.49)	.83
Diabetes mellitus	48 (27.1)	38 (25.1)	10 (38.5)	1.98 (1.11-3.53)	.02
Cancer	19 (10.7)	12 (7.9)	7 (26.9)	4.92 (1.78-13.62)	.002
Hemodialysis	11 (6.2)	6 (4.0)	5 (19.2)	5.25 (1.48-18.54)	.01
Microbiology					
Positive blood cultures	149 (84.2)	126 (83.4)	23 (88.5)	1.74 (0.69-4.38)	.24
Positive lead or vegetation culture	93 (52.5)	79 (52.3)	14 (53.8)	0.62 (0.03-11.83)	.40
Staphylococcus aureus	62 (35.0)	46 (30.5)	16 (61.5)	3.32 (1.95-5.64)	<.001
MRSA	26 (14.7)	18 (11.9)	8 (30.7)	3.54 (1.52-8.28)	.004
Coagulase-negative staphylococci	56 (31.6)	50 (33.1)	6 (23.1)	0.69 (0.33-1.45)	.33
Enterococcus	9 (5.1)	9 (6.0)	0		
Viridans streptococci	5 (2.8)	4 (2.6)	1 (3.8)	1.11 (0.04-27.92)	.95
Gram negative	8 (4.5)	8 (5.3)	0		
Echocardiography					
Vegetation on device lead	135 (76.3)	115 (76.2)	20 (76.9)	1.20 (0.49-2.92)	.69
Intracardiac abscess	4 (2.2)	2 (1.3)	2 (7.7)	5.34 (0.81-35.07)	.08
Any valvular vegetation	63 (36)	47 (31)	16 (62)	3.54 (1.50-8.38)	.05
Tricuspid valve vegetation	43 (24.3)	33 (2.2)	10 (38.4)	2.22 (1.14-4.32)	.02
New moderate or severe tricuspid regurgitation	24 (13.6)	21 (13.9)	3 (11.5)	0.77 (0.23-2.62)	.68
Complications					
Pulmonary embolism	17 (9.6)	14 (9.3)	3 (11.5)	1.03 (0.26-4.19)	.96
Systemic embolism	25 (14.1)	21 (13.9)	4 (15.4)	0.88 (0.36-2.15)	.78
Heart failure	27 (15.3)	19 (12.6)	8 (30.7)	3.11 (1.42-6.83)	.005
Persistent bacteremia	28 (15.8)	18 (11.9)	10 (38.5)	5.00 (2.12-11.77)	<.001
Treatment					
Device removal surgery during index hospitalization	141 (79.7)	123 (81.5)	18 (69.2)	0.48 (0.19-1.21)	.12
Concomitant valve surgery	30 (16.9)	23 (15.3)	7 (26.9)	1.81 (0.72-4.54)	.21

Abbreviations: CDIE, cardiac device infective endocarditis; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio.

ing 61 (34.5% [95% CI, 27.5%-42.0%]) with nosocomial and 20 (11.3% [95% CI, 7.0%-16.9%]) with nonnosocomial infections. Compared with community-acquired infections, health care–associated infections in patients with CDIE presented earlier, occurred more often in patients referred from other facilities, and were associated with intravascular access and hemodialysis (TABLE 3). Health care–associated CDIE also was more often caused by *S aureus* (49.4% [95% CI, 38.1%-60.7%]), particularly methicillin-resistant *S aureus* (MRSA) (25.9% [95% CI, 16.8%-36.9%]), and associated with persistent bacteremia (19.8% [95% CI, 11.7%-30.1%]) and increased in-hospital mortality (22.2% [95% CI, 13.7%-32.8%]).

Compared with staphylococcal endocarditis of native and prosthetic valves in patients without cardiac devices who were also enrolled in ICE-PCS, patients with CDIE were significantly older, more likely to be men, and more likely to have a delayed presentation (eTable, available at http://www.jama.com). Patients with CDIE also were more likely to have health care–associated infections and in particular to have undergone a recent device-related procedure. However, in-hospital mortality was lower in patients with CDIE (18.6% [95% CI, 12.1%-26.9%]), compared with in-hospital mortality of patients without cardiac devices who had native-valve (22.4% [95% CI, 19.4%-25.6%]) or prosthetic-valve (31.3% [95% CI, 25.2%-38.0%]) staphylococcal infective endocarditis (*P* = .01).

COMMENT

This study describes the clinical characteristics and outcome of CDIE in what is to our knowledge the largest prospective cohort of patients reported to date. Cardiac device infective endocarditis accounted for 6.4% of all cases of definite infective endocarditis. Compared with patients with infective endocarditis but with no cardiac devices in place, patients with CDIE were more likely to be male, older, and diabetic,

as shown in recent discharge data from the National Inpatient Sample.[1] The advanced age of patients with CDIE reflects the population likely to have indications for cardiac devices but also potential host factors, including exposure to other medical care, as predispositions to device-related infection. Along these lines, the etiology of CDIE was characterized by a predominance of staphylococci (coagulase-negative staphylococci and *S aureus*) as recently described by other investigators,[7,11,15,23,24] and health care–associated infection was identified in nearly half of patients with CDIE. The high percentage of patients with health care–associated CDIE reiterates the significant recent epidemiologic trend and prognostic influence on survival previously described in both native- and prosthetic-valve infective endocarditis.[16,25,26]

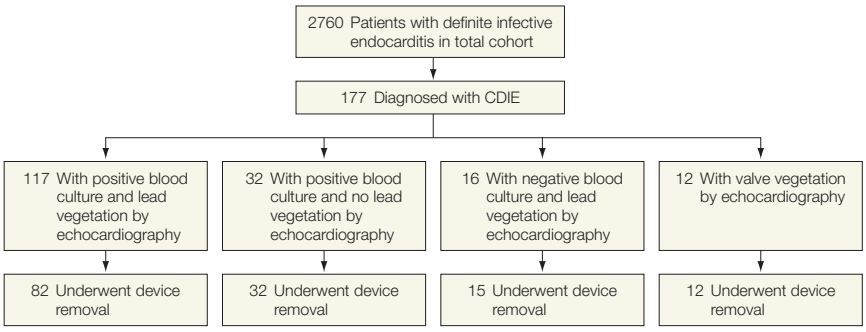
In addition to these host-related characteristics of CDIE, this study illustrates the high prevalence of associated acute and longer-term complications of this condition, including concomitant valve involvement (37.2%), heart failure (15.3%), and persistent bacteremia (15.8%) during the index hospitalization. Several of these complications were found to be associated with in-hospital and 1-year mortality in patients with CDIE. The high rates of mortality emphasize the need for improved preventive measures, including optimal skin decontamination and appropriate antibiotic administration at the time of cardiac device insertion or manipulation,[27] as well as careful attention to any invasive or intravascular procedures performed after device implantation.

A recent retrospective study evaluated risk factors for 6-month mortality in patients with cardiac device infection, including systemic infection in 113 patients.[28] Of note, only 51% of patients had positive blood cultures, and 23% had lead vegetation visualized (compared with 84% and 76%, respectively, in the present study). In the overall cohort of that study, mortality was associated with moderate or severe tricuspid regurgitation, abnormal right ventricular function, systemic embolization, and abnormal renal function.[28] Administrative data from the National Inpatient Sample also demonstrated associations between comorbid conditions (such as respiratory or renal conditions or heart failure) and in-hospital mortality of cardiac device infection.[1] Our study confirms the prognostic influence of concomitant cardiac conditions, specifically valve infection and heart failure, on mortality.

Current American Heart Association recommendations on infections of cardiovascular implantable electronic devices strongly support complete device and lead removal for all patients with definite infection as evidenced by valvular vegetations, lead vegetations, or both.[29] In a retrospective, single-center study of 60 patients with CDIE, 95% underwent device removal, and the overall mortality rate was only 10% at 3 years.[30] However, only 4 patients (7%) had concomitant valve infection.[30]

In the present study of CDIE, device removal was performed in a similarly high percentage of cases, despite the older age of patients and the higher prevalence of comorbid conditions such as diabetes mellitus compared with other forms of staphylococcal infective endocarditis. Device removal was not associated with improved in-hospital survival but was associated with significantly higher 1-year survival. The lack of benefit for in-hospital mortality may be related to the total number of deaths in this study and

Figure 1. Distribution of Patients in Study by Clinical Characteristics and Device Removal Status



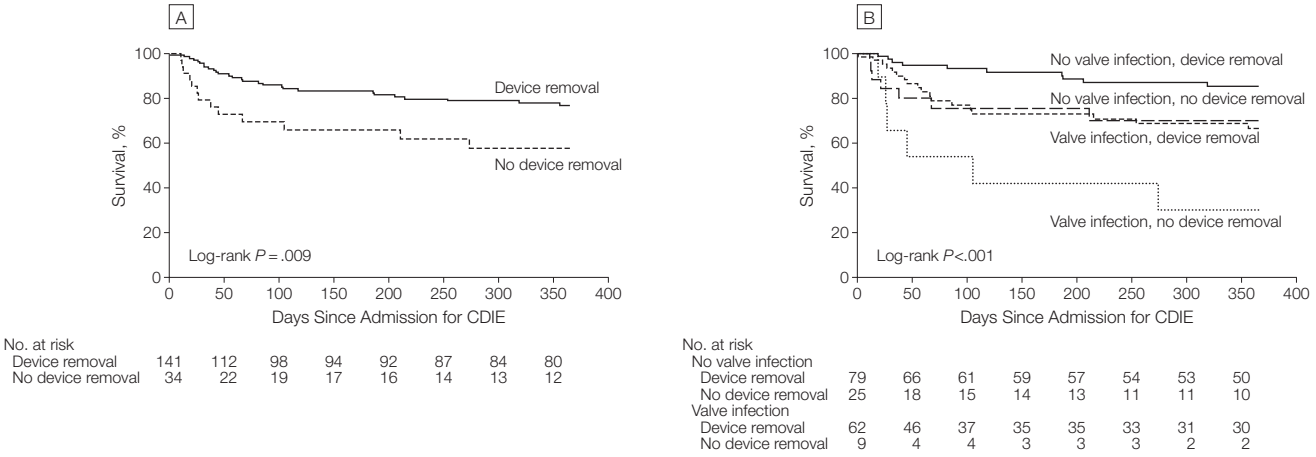
Device removal was performed during the index hospitalization.

Table 2. Characteristics of Patients With Cardiac Device Infective Endocarditis and With or Without Cardiac Device Removal During Hospitalization

Variable	Device Removal (n = 141)	No Device Removal (n = 34)	*P* Value
Age, median (IQR), y	70.1 (59.8-76.3)	70.4 (68.1-78.6)	.13
Diabetes mellitus	39 (27.7)	8 (23.5)	.76
Hemodialysis	9 (6.4)	2 (5.9)	.93
History of cancer	13 (9.2)	6 (17.7)	.14
Transferred from another hospital	61 (43.3)	16 (47.1)	.61
Positive blood cultures	114 (80.9)	34 (100)	.006
Staphylococcus aureus	47 (33.3)	15 (44.1)	.24
Coagulase-negative staphylococci	46 (32.6)	10 (29.4)	.72
Health care–associated infection	62 (44.0)	19 (55.9)	.21
Concomitant valve vegetation	54 (38.3)	9 (26.5)	.20
Heart failure	18 (12.8)	9 (26.5)	.03
Pulmonary embolism	14 (9.9)	2 (5.9)	.46
In-hospital mortality	18 (12.8)	8 (23.5)	.12
1-y mortality	28 (19.9)	13 (38.2)	.02

Abbreviation: IQR, interquartile range.

Figure 2. Outcome of Patients With Cardiac Device Infective Endocarditis (CDIE)



A, One-year survival related to device removal vs no removal during index hospitalization, with survival censored at 1 year or date of last contact. Data on device removal were not available for 2 patients. B, One-year survival stratified by presence of concomitant valve infection and device removal during index hospitalization, with survival censored at 1 year or date of last contact. Data on device removal were not available for 2 patients.

Table 3. Comparison of Patients With Health Care–Associated and Community-Acquired Cardiac Device Infective Endocarditis (CDIE)

Variable	Health Care–Associated CDIE (n = 81)	Community-Acquired CDIE (n = 96)	*P* Value
Age, median (IQR), y	68.2 (64.0-77.2)	72.2 (56.2-77.2)	.46
Men	61 (75.3)	70 (72.9)	.72
Presentation <1 mo of symptoms	65 (80.2)	55 (57.3)	.002
Transferred from another facility	45 (55.6)	32 (33.3)	.004
Diabetes mellitus	24 (29.6)	24 (25.0)	.43
Cancer	11 (13.5)	8 (8.3)	.25
Hemodialysis	8 (9.9)	3 (3.1)	.06
Staphylococcus aureus	40 (49.4)	22 (22.9)	<.001
MRSA[a]	21 (52.5)	5 (22.7)	.02
Coagulase-negative staphylococci	23 (28.4)	33 (34.4)	.39
Device removal surgery	62 (76.5)	79 (82.3)	.21
In-hospital mortality	18 (22.2)	8 (8.3)	.009
1-y mortality	30 (37.0)	19 (19.8)	<.001

Abbreviations: IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*.
[a]Denominators used to calculate percentages are 40 for health care–associated endocarditis and 22 for community-acquired endocarditis.

to insufficient statistical power to detect a significant difference. This delayed benefit of device removal also may be related to the operative risk of device removal in this older patient population. In addition, appropriate antibiotic therapy may mitigate short-term complications of CDIE but not prevent long-term complications or be curative of infection.

The presence of concomitant valve infection was associated with increased mortality at 1 year, regardless of device removal. This finding suggests an important additional risk associated with CDIE and an influence on its outcome. Furthermore, only approximately half of patients with CDIE and concomitant valve infection underwent valve surgery, reflecting the anticipated operative risk in this older patient population with preexisting cardiac disease and potentially increasing the mortality rate associated with this complication. For patients with CDIE with or without concomitant valve infection, a multidisciplinary approach to management involving specialists in cardiology, infectious disease, and cardiac surgery may optimize the use of surgical therapy and improve long-term outcome.

Health care–associated infection has been associated with poorer prognosis in both native- and prosthetic-valve infective endocarditis.[16,25] The results of the present study also confirmed an adverse effect of health care–associated infection in CDIE that was independent of *S aureus* infection. Interestingly, the percentage of infections attributable to coagulase-negative staphylococci was similar between health care–associated and community-acquired cases. The current definition of health care–associated infection has not been applied to cardiac device infections and may lack sensitivity, thus underestimating the prevalence of infections (such as those attributable to coagulase-negative staphylococci) associated with delayed presentations after remote implantation or other medical interventions. Although the ICE-PCS registry did not collect data regarding the time interval between cardiac device implantation and infection, recent (within 90 days) implantation would be included in the current, validated definition of

health care–associated infection, because the Prospective Evaluation of Pacemaker Lead Endocarditis study previously found that cardiac device infections are typically diagnosed within 2 months of device implantation.[10]

Compared with other forms of staphylococcal infective endocarditis, including prosthetic-valve endocarditis, patients with CDIE, as well as the subset with health care–associated CDIE, had a higher prevalence of MRSA infection. Because many experts continue to recommend a first-generation cephalosporin for prophylaxis at the time of device implantation, additional studies are needed to define the role for glycopeptides or other antistaphylococcal antibiotics to reduce the incidence of CDIE, particularly in geographic regions with higher rates of MRSA infection.

Although ICE-PCS was designed as a large, multinational, prospective registry of definite infective endocarditis, this study has certain limitations. This is an observational study involving centers with voluntary participation; thus, population sampling was not obtained, limiting any epidemiologic inferences. Specifically, because this cohort only included patients with CDIE, risk factors for developing CDIE could not be evaluated. Data on presence of device-pocket infection were not collected, so the relationship between pocket infection and CDIE could not be evaluated. The Mayo Clinic Cardiovascular Infections Study Group has reported that pocket-site infection was negatively associated with CDIE.[24] The effect of device removal on outcome may be confounded by selection and survival biases, as well as by the effect of other interventions such as valve surgery. Although device removal was documented, data regarding duration since device implantation, the means of removal (such as percutaneous or surgical), the incidence and timing of device reimplantation, and recurrence of infection after discharge were not collected. Patient enrollment in this registry was completed in 2006, and our cohort included a smaller percentage of patients with ICDs than recently reported.[31] Patients with ICDs have an adverse cardiac risk profile that may affect outcome, yet the results of the present study are comparable with those of other CDIE cohorts with higher percentages of these devices.[31]

In conclusion, CDIE, similar to native- and prosthetic-valve endocarditis, is significantly influenced by health care interventions in its development, microbiology, and outcome. It is associated with a high rate of complications, especially concomitant valve infection, and results in high in-hospital and 1-year mortality rates, particularly if there is valve involvement. Device removal is associated with higher survival at 1 year. Given that numbers of cardiovascular implantable electronic devices placed are increasing rapidly, further studies on the prevention and treatment of this serious complication are needed.

Author Affiliations: Department of Infectious Diseases, Barwon Health, Geelong, Australia (Drs Athan and Henry); Duke Clinical Research Institute (Drs Chu and Fowler and Mr Pappas) and Department of Medicine (Drs Crowley and Wang), Duke University Medical Center, Durham, North Carolina; Infectious Diseases and ICU, Pontchaillou University, Rennes, France (Dr Tattevin); CHU Nancy-Brabois, Nancy, France (Dr Selton-Suty); University of New South Wales, Sydney, Australia (Dr Jones); Department of Cardiology, West German Heart Center, Essen (Dr Naber); Hospital Clinic–IDIBAPS, University of Barcelona, Barcelona, Spain (Drs Miró and Ninot); Hospital Universitari Vall d'Hebron, Barcelona (Dr Fernández-Hidalgo); Second University of Naples, Monaldi Hospital, Naples, Italy (Dr Durante-Mangoni); Alfred Hospital, Melbourne, Australia (Dr Spelman); University Medical Centre of Besancon, Besancon, France (Dr Hoen); Medical Center Ljubljana, Ljubljana, Slovenia (Dr Lejko-Zupanc); Maria Vittoria Hospital, Torino, Italy (Dr Cecchi); Faculté de Medicine de Marseille, Marseille, France (Dr Thuny); and Department of Microbiology, Mater University Hospitals, Dublin, Ireland (Dr Hannan).

Author Contributions: Mr Pappas had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Athan, Tattevin, Fernández-Hidalgo, Spelman, Hannan, Fowler, Wang.
Acquisition of data: Athan, Chu, Tattevin, Selton-Suty, Jones, Naber, Miró, Ninot, Fernández-Hidalgo, Durante-Mangoni, Spelman, Hoen, Lejko-Zupanc, Cecchi, Thuny, Fowler, Crowley.
Analysis and interpretation of data: Athan, Tattevin, Miró, Ninot, Fernández-Hidalgo, Durante-Mangoni, Spelman, Hoen, Cecchi, Hannan, Pappas, Henry, Crowley, Wang.
Drafting of the manuscript: Athan, Spelman, Fowler, Wang.
Critical revision of the manuscript for important intellectual content: Athan, Chu, Tattevin, Selton-Suty, Jones, Naber, Miró, Ninot, Fernández-Hidalgo, Durante-Mangoni, Spelman, Hoen, Lejko-Zupanc, Cecchi, Thuny, Hannan, Pappas, Henry, Crowley, Wang.
Statistical analysis: Miró, Spelman, Hannan, Pappas, Henry.
Obtained funding: Chu, Wang.
Administrative, technical, or material support: Athan, Chu, Hannan, Fowler, Crowley, Wang.
Study supervision: Athan, Miró, Ninot, Cecchi, Wang.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Chu reported receiving a career development award from the American Heart Association. Dr Tattevin reported receiving travel support to attend a meeting from Novartis. Dr Miró reported serving on the advisory boards of Cubist and Novartis; serving as a consultant for Abbott, Bristol-Myers Squibb, Cubist, Gilead Sciences, Merck, Novartis, Pfizer, and Theravance; receiving grants or grants pending from Cubist, Novartis, Fondo de Investigaciones Sanitarias (FIS, Spanish Ministry of Health), the National Institutes of Health, and RIS-III (Spanish Network for AIDS Research); and receiving payment for lectures from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Cubist, GlaxoSmithKline, Gilead Sciences, Janssen-Cilag, MSD, Novartis, Pfizer, Roche, Schering-Plough, Theravance, and ViiV. Dr Durante-Mangoni reported receiving payment for lectures from Novartis. Dr Hannan reported receiving an educational travel grant from Pfizer and receiving travel grants to attend international meetings from Pfizer and MSD. Dr Fowler reported serving as a consultant for Astellas, Cubist, Merck, Johnson & Johnson, Galderma, NovaDigm, The Medicines Company, Biosynexus, MedImmune, Novartis, and Pfizer; receiving grants or grants pending from the National Institutes of Health, Astellas, Cubist, Merck, Theravance, Cerexa, Pfizer, Novartis, Advanced Liquid Logic, and MedImmune; holding a patent (planned, pending, or issued) for a diagnostic approach; receiving royalties from UpToDate; and receiving honoraria for development of educational presentations from Arpida, Astellas, Cubist, Inhibitex, Merck, Pfizer, Targanta, Theravance, Wyeth, Ortho-McNeil, Novartis, Vertex Pharmaceuticals, and MedImmune. Dr Wang reported providing expert testimony for trial defense; receiving grants or grants pending from Gilead Sciences, Edwards Lifesciences, and Abbott Vascular; receiving payment for lectures from American Physician; receiving royalties for serving as an editor from Springer; and receiving payment for development of educational presentations from the American College of Cardiology Foundation. No other authors reported disclosures. None of the investigators received compensation for participation in ICE-PCS.
Funding/Support: This work was supported in part by grants from the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, Madrid, Spain, and the Spanish Network for Research in Infectious Diseases (REIPI RD06/0008). Dr Miró holds an INT10/219 Intensification Research Grant (I3SNS & PRICS programs) from the Instituto de Salud Carlos III, Madrid, Spain, and the Departament de Salut de la Generalitat de Catalunya, Barcelona, Spain.
Role of the Sponsors: The funding sources had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

International Collaboration on Endocarditis–Prospective Cohort Study Investigators and Sites: *Argentina:* Liliana Clara, MD, Marisa Sanchez, MD (Hospital Italiano). Francisco Nacinovich, MD, Pablo Fernandez Oses, MD, Ricardo Ronderos, MD, Adriana Sucari, MD, Jorge Thierer, MD (Instituto Cardiovascular). José Casabé, MD, PhD, Claudia Cortes, MD (Hospital Universitario de la Fundaciòn Favaloro). Javier Altclas, MD, Silvia Kogan, MD (Sanatorio de la Trini-

dad Mitre). *Australia:* Denis Spelman, MD (Alfred Hospital). Eugene Athan, MD, Owen Harris, MBBS (Barwon Health). Karina Kennedy, MBBS, Ren Tan, MBBS (Canberra Hospital). David Gordon, MBBS, PhD, Lito Papanicolas, MBBS (Flinders Medical Centre). Damon Eisen, MBBS, MD, Leeanne Grigg, MBBS, Alan Street, MBBS (Royal Melbourne Hospital). Tony Korman, MD, Despina Kotsanas, BSc (Hons) (Southern Health). Robyn Dever, MD, Phillip Jones, MD, Pam Konecny, MD, Richard Lawrence, MD, David Rees, MD, Suzanne Ryan, MHSc (St George Hospital). Michael P. Feneley, MD, John Harkness, MD, Phillip Jones, MD, Suzanne Ryan, MHSc (St Vincent's Hospital). *Austria:* Phillip Jones, MD, Suzanne Ryan, MHSc (Sutherland). Phillip Jones, MD, Jeffrey Post, MD, Porl Reinbott, Suzanne Ryan, MHSc (The University of New South Wales). Rainer Gattringer, MD, Franz Wiesbauer, MD (Vienna General Hospital). *Brazil:* Adriana Ribas Andrade, Ana Cláudia Passos de Brito, Armenio Costa Guimarães, MD (Ana Neri Hospital). Max Grinberg, MD, PhD, Alfredo José Mansur, MD, PhD, Rinaldo Focaccia Siciliano, MD, Tania Mara Varejao Strabelli, MD, Marcelo Luiz Campos Vieira, MD (Heart Institute [Incor], University of São Paulo Medical School). Regina Aparecida de Medeiros Tranchesi, MD, Marcelo Goulart Paiva, MD (Hospital 9 de Julho). Claudio Querido Fortes, MD (Hospital Universitario Clementino Fraga Filho/UFRJ). Auristela de Oliveira Ramos, MD (Instituto Dante Pazzanese de Cardiologia). Giovanna Ferraiuoli, MD, Wilma Golebiovski, MD, Cristiane Lamas, MD, PhD, Marisa Santos, MD, PhD, Clara Weksler, MD (Instituto Nacional de Cardiologi). *Canada:* James A. Karlowsky, MD, Yoav Keynan, MD, Andrew M. Morris, MD, Ethan Rubinstein, MD, LLB (University of Manitoba). *Chile:* Sandra Braun Jones, MD, Patricia Garcia, MD (Hospital Clínico Pontificia Universidad Católica de Chile). Mauricio Cereceda, MD, Alberto Fica, Rodrigo Montagna Mella, MD (Hospital Clinico Universidad de Chile). *Croatia:* Bruno Barsic, MD, PhD, Suzana Bukovski, MD, PhD, Vladimir Krajinovic, MD, Ana Pangercic, MD, Igor Rudez, MD, Josip Vincelj, MD, PhD (University Hospital for Infectious Diseases). *Czech Republic:* Tomas Freiberger, MD, PhD, Jiri Pol, MD, Barbora Zaloudikova, MSc (Centre for Cardiovascular Surgery and Transplantation). *Egypt:* Zainab Ashour, MD, Amani El Kholy, MD, Marwa Mishaal, MD, Hussien Rizk, MD (Cairo University Medical School). *France:* Neijla Aissa, MD, Corentine Alauzet, MD, Francois Alla, MD, PhD, Catherine Campagnac, RN, Thanh Doco-Lecompte, MD, Christine Selton-Suty, MD (CHU Nancy-Brabois). Jean-Paul Casalta, MD, Pierre-Edouard Fournier, MD, Gilbert Habib, MD, Didier Raoult, MD, PhD, Franck Thuny, MD (Faculté de Médecine de Marseille). Francois Delahaye, MD, PhD, Armelle Delahaye, Francois Vandenesch, MD (Hospital Louis Pradel). Erwan Donal, MD, Pierre Yves Donnio, PhD, Christian Michelet, MD, PhD, Matthieu Revest, MD, Pierre Tattevin, MD, PhD, Jérémie Violette, MD (Pontchaillou University). Florent Chevalier, MD, Antoine Jeu, MD, Dan Rusinaru, MD, Claire Sorel, MD, Christophe Tribouilloy, MD, PhD (South Hospital Amiens). Yvette Bernard, MD, Catherine Chirouze, MD, Bruno Hoen, MD, PhD, Joel Leroy, MD, Patrick Plesiat, MD (University Medical Center of Besançon). *Germany:* Bahram Mazaheri, PhD, Christoph Naber, MD, PhD, Carl Neuerburg (University Essen). *Greece:* Sofia Athanasia, MD, Efthymia Giannitsioti, MD (Attikon University General Hospital). Elena Mylona, MD, Olga Paniara, MD, PhD, Konstantinos Papanicolaou, MD, John Pyros, MD, Athanasios Skoutelis, MD, PhD (Evangelismos General Hospital of Athens). *India:* Gautam Sharma, MD (All India Institute of Medical Sciences). Johnson Francis, MD, DM, Lathi Nair, MD, DM, Vinod Thomas, MD, DM, Krishnan Venugopal, MD, DM (Medical College Calicut). *Ireland:* Margaret Hannan, MB, BCh BAO, MSc, John Hurley, MB, BCh (Mater Hospitals). *Israel:* Dan Gilon, MD, Sarah Israel, MD, Maya Korem, MD, Ethan Rubinstein, MD, LLB, Jacob Strahilevitz, MD (Tel-Aviv University School of Medicine). *Italy:* Roberta Casillo, MD, PhD, Susanna Cuccurullo, MSc, Giovanni Dialetto, MD, Emanuele Durante-Mangoni, MD, PhD, Mattucci Irene, MD, Enrico Ragone, MD, PhD, Marie Françoise Tripodi, MD, Riccardo Utili, MD, PhD (Università di Napoli). Enrico Cecchi, MD, Francesco De Rosa, MD, Davide Forno, MD, Massimo Imazio, MD, Rita Trinchero, MD (Maria Vittoria Hospital). Alessandro Tebini, MD, Paolo Grossi, MD, PhD, Mariangela Lattanzio, MD, Antonio Toniolo, MD (Ospedale di Circolo Varese). Antonio Goglio, MD, Annibale Raglio, MD, DTM&H, Veronica Ravasio, MD, Marco Rizzi, MD, Fredy Suter, MD (Ospedali Riuniti di Bergamo). Giampiero Carosi, MD, Silvia Magri, MD, Liana Signorini, MD (Spedali Civili–Università di Brescia). *Lebanon:* Tania Baban, MD, Zeina Kanafani, MD, MS, Souha S. Kanj, MD, Mohamad Yasmine, MD (American University of Beirut Medical Center). *Malaysia:* Imran Abidin, MD (University of Malaya Medical Center). Syahidah Syed Tamin, MD (National Heart Institute). *Mexico:* Eduardo Rivera Martínez, MD, Gabriel Israel Soto Nieto, MD (Instituto Nacional de Cardiología Ignacio Chávez). *The Netherlands:* Jan T. M. van der Meer, MD, PhD (University of Amsterdam). *New Zealand:* Stephen Chambers, MD, MSc (University of Otago). David Holland, MB, ChB, PhD (Middlemore Hospital). Arthur Morris, MD (Diagnostic Medlab). Nigel Raymond, MB, ChB (Wellington Hospital). Kerry Read, MB, ChB (North Shore Hospital). David R. Murdoch, MD, MSc, DTM&H (University of Otago). *Romania:* Stefan Dragulescu, MD, PhD, Adina Ionac, MD, PhD, Cristian Mornos, MD (Victor Babes University of Medicine and Pharmacy). *Russia:* O. M. Butkevich, PhD (Learning-Scientific Centre of Medical Centre of Russian Presidential Affairs Government Medical Centre of Russia). Natalia Chipigina, PhD, Ozerecky Kirill, MD, Kulichenko Vadim, Tatiana Vinogradova, MD, PhD (Russian Medical State University). *Saudi Arabia:* Jameela Edathodu, MBBS, Magid Halim, MBBS (King Faisal Specialist Hospital & Research Center). *Singapore:* Luh-Nah Lum, BSN, Ru-San Tan, MBBS (National Heart Centre). *Slovenia:* Tatjana Lejko-Zupanc, MD, PhD, Mateja Logar, MD, PhD, Manica Mueller-Premru, MD, PhD (Medical Center Ljublijana). *South Africa:* Patrick Commerford, MD, Anita Commerford, MD, Eduan Deetlefs, MD, Cass Hansa, MD, Mpiko Ntsekhe, MD (University of Cape Town and Groote Schuur Hospital). *Spain:* Manuel Almela, MD, Yolanda Armero, MD, Manuel Azqueta, MD, Ximena Castañeda, MD, Carlos Cervera, MD, Ana del Río, MD, PhD, Carlos Falces, MD, Cristina Garcia-de-la-Maria, PhD, Guillermina Fita, MD, José M. Gatell, MD, PhD, Francesc Marco, MD, PhD, Carlos A. Mestres, MD, PhD, José M. Miró, MD, PhD, Asunción Moreno, MD, PhD, Salvador Ninot, MD, Carlos Paré, MD, PhD, Joan Pericas, MD, José Ramírez, MD, PhD, Irene Rovira, MD, Marta Sitges, MD (Hospital Clínic–IDIBAPS, University of Barcelona, Barcelona). Ignasi Anguera, MD, PhD, Bernat Font, MD, Joan Raimon Guma, MD (Hospital de Sabadell, Barcelona). Javier Bermejo, Emilio Bouza, MD, PhD, Miguel Angel García Fernández, MD, Víctor González-Ramallo, MD, Mercedes Marín, MD, Patricia Muñoz, MD, PhD, Miguel Pedromingo, MD, Jorge Roda, Marta Rodríguez-Créixems, MD, PhD, Jorge Solís, MD (Hospital General Universitario Gregorio Marañón, Madrid). Benito Almirante, MD, Nuria Fernández-Hidalgo, MD, Pilar Tornos, MD (Hospital Universitari Vall d'Hebron, Barcelona). Arístides de Alarcón, Ricardo Parra (Hospital Universitario Virgen del Rocío, Sevilla). *Sweden:* Eric Alestig, MD, Magnus Johansson, MD, PhD, Lars Olaison, MD, PhD, Ulrika Snygg-Martin, MD (Sahlgrenska Universitetssjukhuset/Östra) . *Thailand*: Orathai Pachirat, MD, Pimchitra Pachirat, MD, Burabha Pussadhamma, MD, Vichai Senthong, MD (Khon Kaen University). *United Kingdom:* Anna Casey, MBBS, Tom Elliott, PhD, DSc, Peter Lambert, BSc, PhD, DSc, Richard Watkin, MBBS (Queen Elizabeth Hospital). Christina Eyton, John L. Klein, MD (St Thomas' Hospital). *United States:* Suzanne Bradley, MD, Carol Kauffman, MD (Ann Arbor VA Medical Center). Roger Bedimo, MD, MS (Dallas VA Medical Center). Vivian H. Chu, MD, MHS, G. Ralph Corey, MD, Anna Lisa Crowley, MD, MHS, Pamela Douglas, MD, Laura Drew, RN, BSN, Vance G. Fowler, MD, MHS, Thomas Holland, MD, Tahaniyat Lalani, MBBS, MHS, Daniel Mudrick, MD, Zainab Samad, MD, MHS, Daniel Sexton, MD, Martin Stryjewski, MD, MHS, Andrew Wang, MD, Christopher W. Woods, MD, MPH (Duke University Medical Center). Stamatios Lerakis, MD (Emory University). Robert Cantey, MD, Lisa Steed, PhD, Dannah Wray, MD, MHS (Medical University of South Carolina). Stuart A. Dickerman, MD (New York University Medical Center). Hector Bonilla, MD, Joseph DiPersio, MD, PhD, Sara-Jane Salstrom, RN (Summa Health System). John Baddley, MD, Mukesh Patel, MD (University of Alabama at Birmingham). Gail Peterson, MD, Amy Stancoven, MD (University of Texas–Southwestern Medical Center). Luis Afonso, MD, Theresa Kulman, RN, Donald Levine, MD, Michael Rybak, PharmD, MPH (Wayne State University). Christopher H. Cabell, MD, MHS (Quintiles). **ICE Coordinating Center:** Khaula Baloch, MPH, Vivian H. Chu, MD, MHS, G. Ralph Corey, MD, Christy C. Dixon, Vance G. Fowler Jr, MD, MHS, Tina Harding, RN, BSN, Marian Jones-Richmond, Paul Pappas, MS, Lawrence P. Park, PhD, Thomas Redick, MPH, Judy Stafford, MS. **ICE Publications Committee:** Kevin Anstrom, PhD, Eugene Athan, MD, Arnold S. Bayer, MD, Christopher H. Cabell, MD, MHS, Vivian H. Chu, MD, MHS, G. Ralph Corey, MD, Vance G. Fowler Jr, MD, MHS, Bruno Hoen, MD, PhD, A. W. Karchmer, MD, José M. Miró, MD, PhD, David R. Murdoch, MD, MSc, DTM&H, Daniel J. Sexton MD, Andrew Wang, MD. **ICE Steering Committee:** Arnold S. Bayer, MD, Christopher H. Cabell, MD, MHS, Vivian Chu, MD, MHS, G. Ralph Corey, MD, David T. Durack, MD, DPhil, Susannah Eykyn, MD, Vance G. Fowler Jr, MD, MHS, Bruno Hoen, MD, PhD, José M. Miró, MD, PhD, Philipe Moreillon, MD, PhD, Lars Olaison, MD, PhD, Didier Raoult, MD, PhD, Ethan Rubinstein, MD, LLB, Daniel J. Sexton, MD.

Online-Only Material: The eTable is available at http://www.jama.com.

REFERENCES

1. Greenspon AJ, Patel JD, Lau E, et al. 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States 1993 to 2008. *J Am Coll Cardiol*. 2011;58(10):1001-1006.

2. Jarcho JA. Biventricular pacing. *N Engl J Med*. 2006; 355(3):288-294.

3. Chua JD, Wilkoff BL, Lee I, Juratli N, Longworth DL, Gordon SM. Diagnosis and management of infections involving implantable electrophysiologic cardiac devices. *Ann Intern Med*. 2000;133(8):604-608.

4. Cabell CH, Heidenreich PA, Chu VH, et al. Increasing rates of cardiac device infections among Medicare beneficiaries: 1990-1999. *Am Heart J*. 2004; 147(4):582-586.

5. Darouiche RO. Treatment of infections associated with surgical implants. *N Engl J Med*. 2004; 350(14):1422-1429.

6. Ferguson TB Jr, Ferguson CL, Crites K, Crimmins-Reda P. The additional hospital costs generated in the management of complications of pacemaker and defibrillator implantations. *J Thorac Cardiovasc Surg*. 1996;111(4):742-752.

7. Sohail MR, Uslan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. *J Am Coll Cardiol*. 2007;49(18):1851-1859.

8. Klug D, Lacroix D, Savoye C, et al. Systemic infection related to endocarditis on pacemaker leads: clinical presentation and management. *Circulation*. 1997; 95(8):2098-2107.
9. Da Costa A, Lelièvre H, Kirkorian G, et al. Role of the preaxillary flora in pacemaker infections: a prospective study. *Circulation*. 1998;97(18):1791-1795.
10. Klug D, Balde M, Pavin D, et al; PEOPLE Study Group. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. *Circulation*. 2007;116 (12):1349-1355.
11. Duval X, Selton-Suty C, Alla F, et al; Association pour l'Etude et la Prevention de l'Endocardite Infectieuse. Endocarditis in patients with a permanent pacemaker: a 1-year epidemiological survey on infective endocarditis due to valvular and/or pacemaker infection. *Clin Infect Dis*. 2004;39(1):68-74.
12. Uslan DZ, Sohail MR, St Sauver JL, et al. Permanent pacemaker and implantable cardioverter defibrillator infection: a population-based study. *Arch Intern Med*. 2007;167(7):669-675.
13. Chamis AL, Peterson GE, Cabell CH, et al. *Staphylococcus aureus* bacteremia in patients with permanent pacemakers or implantable cardioverter-defibrillators. *Circulation*. 2001;104(9):1029-1033.
14. Cacoub P, Leprince P, Nataf P, et al. Pacemaker infective endocarditis. *Am J Cardiol*. 1998;82(4): 480-484.
15. Arber N, Pras E, Copperman Y, et al. Pacemaker endocarditis: report of 44 cases and review of the literature. *Medicine (Baltimore)*. 1994;73(6):299-305.
16. Fowler VG Jr, Miró JM, Hoen B, et al; ICE Investigators. *Staphylococcus aureus* endocarditis: a consequence of medical progress. *JAMA*. 2005; 293(24):3012-3021.
17. Cabell CH, Jollis JG, Peterson GE, et al. Changing patient characteristics and the effect on mortality in endocarditis. *Arch Intern Med*. 2002;162(1): 90-94.
18. Cabell CH, Abrutyn E. Progress toward a global understanding of infective endocarditis: early lessons from the International Collaboration on Endocarditis investigation. *Infect Dis Clin North Am*. 2002; 16(2):255-272.
19. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30(4): 633-638.
20. Friedman ND, Kaye KS, Stout JE, et al. Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med*. 2002;137 (10):791-797.
21. Benito N, Miró JM, de Lazzari E, et al; ICE-PCS (International Collaboration on Endocarditis–Prospective Cohort Study) Investigators. Health care–associated native valve endocarditis: importance of non-nosocomial acquisition. *Ann Intern Med*. 2009; 150(9):586-594.
22. Daniel WG, Mügge A, Martin RP, et al. Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography. *N Engl J Med*. 1991;324(12):795-800.
23. Sohail MR, Uslan DZ, Khan AH, et al. Infective endocarditis complicating permanent pacemaker and implantable cardioverter-defibrillator infection. *Mayo Clin Proc*. 2008;83(1):46-53.
24. Le KY, Sohail MR, Friedman PA, et al; Mayo Cardiovascular Infections Study Group. Clinical predictors of cardiovascular implantable electronic device-related infective endocarditis. *Pacing Clin Electrophysiol*. 2011;34(4):450-459.
25. Wang A, Athan E, Pappas PA, et al; International Collaboration on Endocarditis–Prospective Cohort Study Investigators. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA*. 2007;297(12):1354-1361.
26. Murdoch DR, Corey GR, Hoen B, et al; International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS) Investigators. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis–Prospective Cohort Study. *Arch Intern Med*. 2009;169(5):463-473.
27. Da Costa A, Kirkorian G, Cucherat M, et al. Antibiotic prophylaxis for permanent pacemaker implantation: a meta-analysis. *Circulation*. 1998;97(18): 1796-1801.
28. Baman TS, Gupta SK, Valle JA, Yamada E. Risk factors for mortality in patients with cardiac device–related infection. *Circ Arrhythm Electrophysiol*. 2009; 2(2):129-134.
29. Baddour LM, Epstein AE, Erickson CC, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee; Council on Cardiovascular Disease in Young; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Nursing; Council on Clinical Cardiology; Interdisciplinary Council on Quality of Care; American Heart Association. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. *Circulation*. 2010;121(3):458-477.
30. Massoure PL, Reuter S, Lafitte S, et al. Pacemaker endocarditis: clinical features and management of 60 consecutive cases. *Pacing Clin Electrophysiol*. 2007;30(1):12-19.
31. Greenspon AJ, Prutkin JM, Sohail MR, et al. Timing of the most recent device procedure influences the clinical outcome of lead-associated endocarditis: results of the MEDIC (Multicenter Electrophysiologic Device Infection Cohort). *J Am Coll Cardiol*. 2012; 59(7):681-687.