Journal of the American Heart Association

ORIGINAL RESEARCH

Outcomes of Patients Hospitalized With Cardiovascular Implantable Electronic Device–Related Infective Endocarditis, Prosthetic Valve Endocarditis, and Native Valve Endocarditis: A Nationwide Study, 2003 to 2017

Pegah Khaloo, MD, MPH;* Uwajachukwumma A. Uzomah, MD, MPH;* Ayman Shaqdan, MBBS; Pablo A. Ledesma, MD; Jennifer Galvin, PA; Leon M. Ptaszek, MD, PhD; Jeremy N. Ruskin, MD

BACKGROUND: Most published reports describing outcomes of patients with cardiovascular implantable electronic device–related infective endocarditis (CIED-IE) are single-center studies with small patient sample sizes. The goal of this study was to utilize population-based data to assess trends in CIED-IE hospitalization and to compare outcomes between patients hospitalized with CIED-IE, prosthetic valve endocarditis (PVE), and native valve endocarditis (NVE).

METHODS AND RESULTS: A query of the National (Nationwide) Inpatient Sample (NIS) database between 2003 and 2017 identified 646 325 patients hospitalized with infective endocarditis in the United States of whom 585 974 (90%) had NVE, 27 257 (4.2%) had CIED-IE, and 26 111 (4%) had PVE.

There was a 509% increase in CIED-IE hospitalizations in the United States from 2003 to 2017 (*P* trend<0.001). In-hospital mortality and length of stay associated with CIED-IE decreased during the study period from 15% and 20 days in 2003 to 9.7% and 19 days in 2017 (*P* trend=0.032 and 0.018, respectively). The in-hospital mortality rate was lower in patients hospitalized with CIED-IE (9.2%) than in patients with PVE (12%) and NVE (12%). Length of stay was longest in the CIED-IE group (17 compared with 14 days for both NVE and PVE). Hospital costs were highest for the CIED-IE group ($56 000 compared with $37 000 in NVE and $45 000 in PVE).

CONCLUSIONS: Despite the fact that the number of comorbidities per patient with CIED-IE increased during the study period, mortality rate and hospital length of stay decreased. The mortality rate was significantly lower for patients with CIED-IE than for patients with NVE and PVE. Patients with CIED-IE had the longest lengths of stay and highest hospital costs.

Key Words: electronic cardiac device ■ infective endocarditis ■ mortality ■ prosthetic valve endocarditis ■ trends

The implantation rate of cardiovascular implantable electronic devices (CIEDs) in the United States has increased steadily over the past 3 decades.[1–6] This trend has been associated with a disproportionate increase in CIED infection rates, largely attributable to the aging of the general population and the

Correspondence to: Jeremy N. Ruskin, MD, Cardiac Arrhythmia Service, Massachusetts General Hospital, 55 Fruit Street, GRB 849, Boston, MA 02114. Email: jruskin@mgh.harvard.edu

* P. Khaloo and U. A. Uzomah contributed equally.

For Disclosures and Sources of Funding, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This retrospective study of the National (Nationwide) Inpatient Sample demonstrated a reduction in mortality rate and hospital length of stay for patients hospitalized with cardiovascular implantable electronic device–related infective endocarditis (CIED-IE) from 2003 to 2017.
- Patients hospitalized with CIED-IE had a lower risk of in-hospital mortality than patients admitted with either prosthetic valve endocarditis or native valve endocarditis, but hospital length of stay and hospitalization costs were higher for CIED-IE than for the prosthetic valve endocarditis or native valve endocarditis.

What Are the Clinical Implications?

- The progressive increase in the number of CIED-IE–related hospitalizations and disproportionate increases in hospital length of stay and costs for CIED-IE (as compared with prosthetic valve endocarditis and native valve endocarditis) emphasize the need for more efficient strategies for the prevention and management of CIED-IE.

Nonstandard Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
CIED-IE	cardiovascular implantable electronic device–related infective endocarditis
HCUP	Healthcare Cost and Utilization Project
ICE-PC	International Collaboration on Endocarditis––Prospective Cohort Study
IE	infective endocarditis
NIS	National (Nationwide) Inpatient Sample
NVE	native valve endocarditis
PVE	prosthetic valve endocarditis

expansion in clinical indications for use of CIEDs.[1, 3, 7–10] The infection rate for CIEDs is estimated to be 2% to 2.5% per annum, with CIED-related infective endocarditis (CIED-IE) accounting for 10% to 40% of all CIED infections.[11–14] CIED-IE is a serious complication associated with significantly higher morbidity and mortality rates compared with other CIED-related infections and usually requires extraction of the device and prolonged antibiotic therapy.[15, 16] Published reports show that CIED infection is associated with up to 10% of all endocarditis cases.[15, 16] As a result of the unique problems associated with the population of patients with CIED-IE compared with patients with noncardiac device–related native and prosthetic valve endocarditis (PVE), a better understanding of CIED-IE is important to inform prompt diagnosis and treatment.[17] However, most published studies are single-center studies with smaller sample sizes and less diverse populations, limiting the generalizability of their results and conclusions.

The goal of this study was to utilize population-based data to compare demographics and outcomes of patients hospitalized with CIED-IE with those of patients hospitalized with PVE and native valve endocarditis (NVE). This study also included an analysis of the predictors of mortality for patients hospitalized with CIED-IE, PVE, and NVE.

METHODS

Data Source

A query of the National (Nationwide) Inpatient Sample (NIS) was performed to obtain data on infective endocarditis (IE)–related hospitalizations in the United States between 2003 and 2017. The NIS is sponsored by the Agency for Healthcare Research and Quality (AHRQ) and is one of a group of databases developed by the Healthcare Cost and Utilization Project (HCUP). It is currently the largest publicly available database of all-payer data on inpatient hospitalizations in the United States and represents ≈20% of all inpatient discharges from US hospitals. In 2012, the NIS expanded to include discharges from all hospitals participating in the HCUP.[18] Data in the NIS are grouped based on hospital size, teaching status, location (urban versus nonurban), and geographic region. All entries in the NIS database are deidentified and contain patient information for each hospital stay regardless of payer. All of the NIS data used in this study are deidentified. Therefore, this study was exempt from institutional review by the Human Research Committee. All data utilized in this study are publicly available and can be accessed through the NIS database (https://www.hcup-us.ahrq.gov/).

Study Design

This study included data from the NIS database corresponding to hospitalizations in the United States from 2003 to 2017. The query of the NIS database was performed with diagnosis and procedure codes as defined in the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) for entries before October 1, 2015, and the *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) for entries after September 30, 2015. Each data entry represented a unique

hospitalization record and was associated with a principal discharge diagnosis, up to 29 possible secondary diagnoses, and up to 25 procedure entries.[19]

All patients aged ≥18 years hospitalized with a principal or secondary discharge diagnosis of IE in the United States between 2003 and 2017 were identified using the *ICD-9-CM* (421, 4210, 4211, 4219, 03642, 09884, 11 281, 11 504, 11 514, 11 594, and 07422) and *ICD-10-CM* (I33, I330, I339, A3282, A3951, B3321, B376, and 088.81) codes. Patients with syphilitic endocarditis, acute rheumatic endocarditis, and nonspecific cardiac infections were excluded. Using *International Classification of Diseases* (*ICD*) codes to identify IE has been previously validated, and specificity, sensitivity, and positive predictive values of 99%, 94%, and 94%, respectively, were reported.[20] Additional patient-level data retrieved from the NIS database included comorbidities, demographics, and outcomes, including mortality and hospital length of stay. Additional hospital-level data retrieved included location, size (number of beds), region (urban versus nonurban), teaching status, and health economic data. The Elixhauser comorbidity index (designed to predict the risk of readmission and in-hospital mortality) was calculated for each patient.[21, 22]

In this study, cases of CIED-IE were characterized as: (1) patients hospitalized with a diagnosis of IE in the setting of a CIED infection (an *ICD-CM* code for cardiac device–, graft-, or implant-related infection (996.61, T827, T827XXA, T827XXD, T827XXS) along with any *ICD-CM* diagnosis code indicating presence of CIED in patients), or (2) patients who were diagnosed with IE and assigned a CIED removal *ICD-CM* procedure code. Cases of PVE were characterized as patients hospitalized with IE who were also diagnosed with a prosthetic valve infection (an *ICD-CM* code for cardiac device–, graft-, or implant-related infection (996.61, T82.6, T826XXA, T826XXD, T826XXS) along with any *ICD-CM* diagnosis code indicating presence of prosthetic valve in patients). The remaining patients with IE were characterized as having NVE.

Study Outcomes

The primary study outcome was in-hospital mortality for patients hospitalized with IE. Predictors of in-hospital mortality were analyzed. These included patient age, stroke, central nervous system (CNS) abscess, cardiac valve replacement, pulmonary embolism, and acute renal failure. Exploratory outcomes included mean length of hospital stay and cost of hospital stay.

Statistical Analysis

All analyses for temporal trends were performed by applying the nonparametric test for trends by Cuzick.[23] All patients aged <18 years were excluded from the study and age was formatted as a categorical variable with the following categories: 18 to 44, 45 to 64, 65 to 74, 75 to 84, and ≥85 years. Patients with both CIED-IE and PVE were excluded from the comparison analyses. For univariable analyses, ANOVA was used for continuous variables and chi-square test was used for categorical variables. A 2-level mixed-effects multivariable logistic regression model with random hospital-level intercept was constructed to identify predictors of in-hospital mortality. This regression model adjusted for race, calendar year, median household income, primary payer, hospital bed size, teaching status, location, and region. For each identified predictor of mortality, interactions among the 3 categories of endocarditis were tested with a multivariable logistic regression model. In this model, in-hospital mortality was treated as the dependent variable and confounders were treated as independent variables.

Survey estimation was utilized in all analyses to account for the complex survey design of the NIS database. According to the instructions provided by the NIS database, the discharge weight (DISCWT) was used as sampling weight (pweight) for years 2012 and after. The HCUP NIS was redesigned beginning with 2012 data to improve national estimates. To facilitate the analysis of trends using multiple years of NIS data, AHRQ developed new discharge trend weights for the 1993 to 2011 NIS (TRENDWT). Therefore, trend weight files provided by AHRQ were used as sampling weights for years before 2012.[18] For all analyses, a P value <0.05 was considered significant. All analyses were performed using the Stata/SE software package, version 12.1 (StataCorp LLC).

RESULTS

IE-Related Hospitalization

Query of the NIS database from 2003 to 2017 revealed 646 325 patients who were hospitalized with IE in the United States (Figure 1). Of these patients, 27 257 (4.2%) were hospitalized with CIED-IE. PVE was identified in 26 111 patients (4%) and NVE was identified in 585 974 (90%).

Baseline Characteristics of Patients With CIED-IE

Baseline characteristics of all patients admitted with CIED-IE in the United States between 2003 and 2017 as identified in the NIS database are summarized in Table 1. There was a 509% increase in CIED-IE hospitalizations in the United States, from 568 in 2003 to 2845 in 2017 (P trend<0.001). The proportion of CIED-IE cases among all patients with IE also increased from 1.7% in 2003 to 4.8% in 2017 (P Trend<0.001). The median age of patients was 67 years (interquartile range, 56–77 years) and the median age decreased from 70

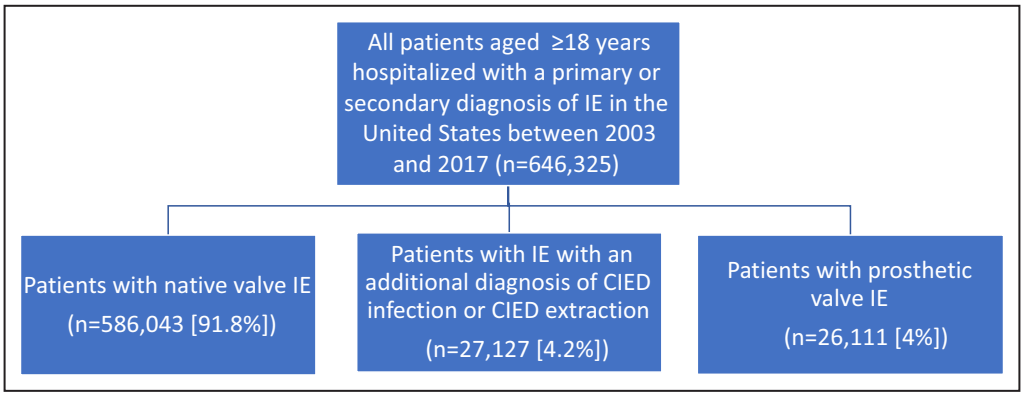

Figure 1. Description of the patient populations included in this study.
The total number of patients with infective endocarditis (IE) included in this study were separated into 3 different groups, represented in the flow chart. Outcomes were analyzed for each group separately. CIED indicates cardiovascular implantable electronic device.

to 66 years over the study period (*P* trend=0.004). The majority of patients hospitalized with CIED-IE were aged <74 years (70%), 69% of the patients were men, and 72% were of White race. There was no significant trend in sex distribution of patients over the duration of the study. Medicare was the primary payer in a majority (67%) of the cases.

The most prevalent comorbidities among patients with CIED-IE were hypertension (53%), chronic kidney disease (CKD; 38%), diabetes (34%), congestive heart failure (CHF; 30%), chronic pulmonary disease (24%), valvular disease (17%), peripheral vascular disease (14%), and drug abuse (5.4%). The most common causative organisms associated with CIED-IE were *Staphylococcus aureus* (43%), other *Staphylococcus* species (18%), *Streptococcus* species (14%), and *Enterococcus* species (10%).

Longitudinal Trends in CIED-Related Hospitalization

During the study period, there was a 509% increase in CIED-IE hospitalizations in the United States (from 568 in 2003 to 2845 in 2017, *P* trend<0.001). The proportion of CIED-IE cases among all patients hospitalized with IE also increased during this period from 1.7% in 2003 to 4.8% in 2017 (*P* trend <0.001).

The prevalence of several comorbidities increased during the study period. Greater than 5-fold increases in prevalence were observed for CHF (12% to 68%, *P* trend=0.001) and liver disease (1.5% to 7.6%, *P* trend=0.004). Greater than 3-fold increases were observed for drug abuse (2.6% to 7.8%, *P* trend=0.003) and valvular disease (8.1% to 29%, *P* trend=0.002). The increases in prevalence observed for peripheral vascular disease (6.7% to 15.4%, *P* trend<0.001) and CKD (20% to 42%, *P* trend=0.001) were >2-fold and significant increases in diabetes (23% to 44%, *P* trend=0.001) and chronic pulmonary disease (16% to 25%, *P* trend=0.024) were also observed.

Most patients in this study (76%) had Elixhauser comorbidity scores >3. The proportion of patients with an Elixhauser score >3 increased during the study period from 52% in 2003 to 91% in 2017 (*P* trend <0.001).

Longitudinal Trends in Complications Associated With CIED-IE

Acute complications associated with CIED-IE were commonly observed during the study period (Table 2, Figure 2). For many types of complications, the observed frequency increased during the study period. The percentage of patients with acute renal failure increased from 20% in 2003 to 49% in 2017 (*P* trend=0.001). This corresponded to an average of 38% of patients who developed acute renal failure over the course of the study period. Increases were also observed for CNS abscess from 0% in 2003 to 1.4% in 2017 (*P* trend=0.031) and pulmonary embolism from 3.2% in 2003 to 17% in 2017 (*P* trend<0.001). The average frequency of pulmonary embolism during the study period was 10%. Stroke occurred in 4.5% of patients with CIED-IE. There was no significant change in the frequency of stroke during the study period.

Cardiac valve replacement was required in a total of 9.3% of all patients with CIED-IE during the study period, and the total CIED extraction rate was 75%. There was no statistically significant trend in the frequency of either cardiac valve replacement or CIED extraction during the study period.

Hospital Length of Stay and Cost of Hospitalization for Patients With CIED-IE

The average length of stay for patients with CIED-IE was 17 days. A decrease in the length of stay was observed during the study period from 20 days in 2003 to

Table 1. Baseline Characteristics of Patients Hospitalized With CIED-IE Between 2003 and 2017

Baseline characteristics	Total	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	*P* (Trend)
CIED-IE Weighted (N)	27257	567	517	665	778	1091	1438	2218	1965	2294	2225	2330	2610	2935	2730	2890	<0.001
Total CIED-IE (%)	4.3	1.7	1.5	1.9	2.1	3.1	3.8	5.6	5.0	5.4	5.1	5.1	5.6	5.9	5.0	4.8	0.007
Median age, Y (IQR)	67 (56–77)	70 (60–78)	71 (56–77)	72 (55–80)	69 (57–79)	66 (56–76)	67 (57–77)	68 (57–78)	68 (57–77)	67 (59–77)	68 (57–77)	66 (54–75)	68 (55–77)	66 (54–76)	66 (54–74)	66 (55–75)	0.004
Age group, y, %																	
18–44	11	10	12	18	13	11	7.1	7.9	9.3	7.7	8.5	12	11	12	13	13	0.625
45–64	33	21	25	18	26	38	36	34	35	34	34	34	31	33	34	33	0.339
65–74	27	30	30	21	25	24	26	24	25	29	27	29	26	25	30	29	0.654
75–84	23	27	28	34	25	21	24	26	23	23	23	17	24	22	18	20	0.004
≥85	7	11	5	9	10	7	6	8	7	7	8	9	8	7	5	6	0.179
Sex, %																	
Female	32	37	40	34	30	30	32	34	31	33	32	31	29	27	31	34	0.106
Race or ethnicity, %																	
White	72	79	75	73	72	69	70	73	72	72	75	72	75	72	73	68	0.219
Black	15	13	13	4.1	14	14	16	15	18	16	15	15	14	15	15	19	0.009
Hispanic	7.3	3.1	10	17	8.3	9.8	4.9	8.8	6.0	4.8	5.8	7.5	5.6	7.4	7.6	8.9	0.621
Asian/Pacific Islander	1.7	*	0.0	2.6	2.1	2.0	3.9	*	1.1	2.4	1.0	1.2	1.3	2.9	1.4	1.7	0.815
Native American	0.6	0.0	0.0	0.0	*	2.0	0.0	0.6	*	0.7	0.5	0.5	0.6	0.7	0.6	0.9	0.060
Other	2.8	3.2	2.2	2.6	3.1	3.3	5.3	3.0	1.9	3.4	2.9	3.5	2.9	2.4	2.5	1.5	0.267
Comorbidities, %																	
Hypertension	53	43	42	42	49	48	49	58	59	68	68	66	64	56	35	29	0.521
CHF	30	12	13	17	19	13	16	16	17	18	19	20	24	31	67	68	0.001
PVD	14	6.7	*	7.2	7.1	9.0	9.6	11	14	15	13	15	15	16	20	15	<0.001
Valvular disease	17	8.1	9.1	8.3	8.0	8.5	8.9	11	7.7	13	14	15	16	21	31	29	0.002
Diabetes	37	23	26	18	22	32	28	35	38	39	37	39	39	37	44	44	0.001
CKD	38	20	16	23	25	37	34	35	39	42	41	40	40	39	42	42	0.001
CPD	24	16	19	22	26	23	17	21	24	24	22	27	26	24	24	25	0.024
Liver disease	5.0	*	*	3.7	*	4.7	3.6	2.3	5.9	5.2	5.2	4.5	3.3	7.7	6.8	7.6	0.004
HIV	0.3	0.0	*	0.0	0.0	0.0	0.0	0.0	*	*	0.9	*	0.6	0.5	*	*	0.069
Drug abuse	5.4	2.6	*	1.6	4.2	5.1	3.8	1.5	3.1	3.1	4.7	6.7	7.1	9.4	7.0	7.8	0.003
Elixhauser score ≥3	76	52	52	65	59	68	68	68	74	77	74	76	78	79	90	91	<0.001
Income percentile, %																	
0–25	30	23	23	26	28	25	28	26	30	28	30	29	27	29	36	35	0.003

(*Continued*)

Table 1. (Continued)

Baseline characteristics	Total	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	*P* (Trend)
26–50	26	27	27	19	25	20	27	24	28	24	22	24	30	28	26	24	0.639
51–75	23	25	24	27	24	28	20	23	20	28	23	23	22	23	20	24	0.197
76–100	22	24	27	28	23	28	25	27	22	20	25	23	21	20	18	17	0.005

The category "other" was provided by the database and no further information is available. CHF indicates congestive heart failure; CIED-IE, cardiac implantable electronic device-related infectious endocarditis; CKD, chronic kidney disease; CPD, chronic pulmonary disease; and PVD, peripheral vascular disease.
*N<11: small cell size data suppressed in compliance with HCUP Nationwide Data Use Agreement (DUA).

19 days in 2017 (*P* trend=0.018). The average in-hospital mortality rate during the study period was 9.2%. In-hospital mortality decreased during the study period from 15% in 2003 to 9.7% in 2017 (*P* trend=0.032). The average cost of hospitalization for patients admitted with CIED-IE in the United States was $56 000. The highest average cost was observed in 2017 ($70 000, Table 2).

Patients With Both CIED-IE and PVE

PVE coexisted in 3224 patients (0.5% of the total study population). The median age of this subset of patients was 70 years (interquartile range, 58–79 years), and 67% were men. The mortality rate was 9.2%, and the mean length of stay was 15 days. The incidence rates of other complications including stroke, acute renal failure, pulmonary embolism, CNS abscess, and valve replacement were 6.7%, 37%, 4.5%, 0.7%, and 9.3%, respectively. This small group of patients was excluded from the comparison analysis.

Comparison of Outcomes of Patients Hospitalized With CIED-IE, NVE, and PVE

Baseline characteristics of patients with NVE, PVE, and CIED-IE are displayed in Table 3. Patients with NVE were younger (median age, 60 years) than patients with PVE (median age, 66 years) or CIED-IE (median age, 67 years), while male predominance was greater with PVE (67%) and CIED-IE (69%) compared with those with NVE (58%). The proportion of patients with Elixhauser scores >3 (reflective of overall comorbidity burden) was highest in patients with PVE (78%). However, compared with patients with NVE and PVE, a larger proportion of patients with CIED-IE had a history of hypertension (53%), CHF (30%), CKD (38%), and chronic pulmonary disease (24%). *S aureus* was the most prevalent causative organism in patients hospitalized with CIED-IE (43%) and NVE (40%), while the most prevalent cause of PVE was *Streptococcus* species (24%, Table 4).

Outcomes of patients with NVE, PVE, and CIED-IE are summarized in Table 5 and Figure 3. Comparison of these groups revealed that patients with CIED-IE had the highest incidence of acute renal failure (38%) and the lowest incidence of stroke (4.5%) and CNS abscess (0.7%). Patients with NVE had the highest incidence of CNS abscess (2.3%) and pulmonary embolism (10%). Cardiac valve replacement surgery was required in 9.3% of patients with CIED-IE, which was comparable to that in patients with NVE (10%) but lower than that in patients with PVE (18%). The average in-hospital mortality rate for patients with IE during the study period was 12%. Comparative mortality rates for patients with CIED-IE, NVE, and PVE are shown in Table 5. This comparison revealed a significantly lower mortality

Table 2. Outcomes of Patients Hospitalized With CIED-IE in the United States From 2003 to 2017

Outcome	Total	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	*P* (Trend)
Mortality (%)	9.2	15	13	10	12	10	10	7.5	9.2	8.9	8.3	5.8	10	10	8.1	9.7	0.032
Cardiac valve replacement, %	9.3	14	8.5	13	8.0	8.0	7.5	8.2	8.8	6.0	8.5	8.4	10	8.9	10	14	0.395
Device extraction, %	74	75	61	69	65	76	79	77	77	72	70	73	68	70	82	83	0.150
Stroke, %	4.5	*	1.9	4.2	6.6	2.6	2.4	5.7	4.6	3.7	5.6	4.9	6.7	3.2	4.6	4.0	0.149
CNS abscess, %	0.7	0.0	0.0	2.3	0.0	*	0.7	*	*	*	*	1.1	0.8	0.7	0.9	1.4	0.031
Pulmonary embolism, %	9.9	3.2	3.8	3.7	4.3	5.6	7.6	8.1	9.1	10	11	13	14	15	15	17	<0.001
Acute renal failure, %	38	20	20	24	19	32	34	36	34	34	36	36	46	44	43	49	0.001
Mean hospitalization cost, $	56K	49K	56K	59K	50K	59K	66K	55K	52K	54K	48K	53K	49K	54K	59K	70K	0.748
Length of stay, d	17	20	21	21	19	19	20	17	17	16	15	18	15	16	17	19	0.018

CIED-IE indicates cardiac implantable electronic device-related infective endocarditis; and CNS, central nervous system.
*N<11: small cell size data suppressed in compliance with HCUP Nationwide Data Use Agreement (DUA).

rate for patients hospitalized with CIED-IE (9.2%) than for patients with PVE (12%) and NVE (12%, $P < 0.001$). Longitudinal analysis revealed a reduction in the mortality rate associated with CIED-IE and NVE during the study period (P trend=0.032 and <0.001, respectively). There was no significant trend in the mortality rate associated with PVE (P trend=0.229).

Predictors of in-Hospital Mortality in Patients With CIED-IE, PVE, and NVE

The results of the multivariable logistic regression analyses performed to determine predictors of in-hospital mortality in patients hospitalized with IE are shown in Table 6. For patients with CIED-IE, the strongest predictors of in-hospital mortality were acute kidney injury (odds ratio [OR], 2.5; 95% CI, 2.0–3.1 [$P < 0.001$]) and incident stroke (OR, 2.3; 95% CI, 1.5–3.6 [$P < 0.001$]). Additional independent predictors of in-hospital mortality included age (OR per year, 1.02; CI, 1.01–1.02 [$P < 0.001$]), CHF (OR, 1.7; 95% CI, 1.3–2.2 [$P < 0.001$]), coagulopathy (OR, 2.1; 95% CI, 1.6–2.7 [$P < 0.001$]), CKD (OR, 1.3; 95% CI, 1.1–1.7 [P=0.011]), and abnormal weight loss (OR, 1.4; 95% CI, 1.1–1.9 [P=0.009]). Patients with Elixhauser scores ≥3 had higher odds of in-hospital mortality than patients with scores <3 (OR, 2.0; 95% CI, 1.2–2.7 [P=0.003]). Compared with other patients hospitalized with CIED-IE from other causative organisms, infection with *S aureus* was associated with higher odds of in-hospital mortality (OR, 1.4; 95% CI, 1.2–1.7 [P=0.001]). Sex was not a predictor of mortality in patients with CIED-IE. Interaction analysis revealed that the risk of mortality associated with age ≥75 years, Elixhauser score ≥3, and CKD was significantly different among patients with CIED-IE, NVE, and PVE. The association of age ≥75 years, Elixhauser score ≥3, and CKD with mortality was stronger in CIED-IE and NVE than PVE (Table 6).

Length of Hospital Stay, Cost of Hospitalization, and Disposition at Discharge

For patients hospitalized with IE, the average hospital stay was longer for patients with CIED-IE (17 days) than for patients with NVE (14 days) and PVE (14 days, $P < 0.001$; Table 5). Increased length of hospitalization for patients with CIED-IE was associated with increased cost of hospitalization. The mean cost of hospitalization for patients with CIED-IE was $56 000, which was 1.3- and 1.5-fold higher than the hospitalization costs for patients with PVE and NVE, respectively (Table 5). For patients who survived hospitalization, the most common discharge disposition was transfer to other skilled-nursing or intermediate-care facilities: 37% of patients with NVE, 35% of patients with PVE, and 40% of patients with CIED-IE (Table 7). Among

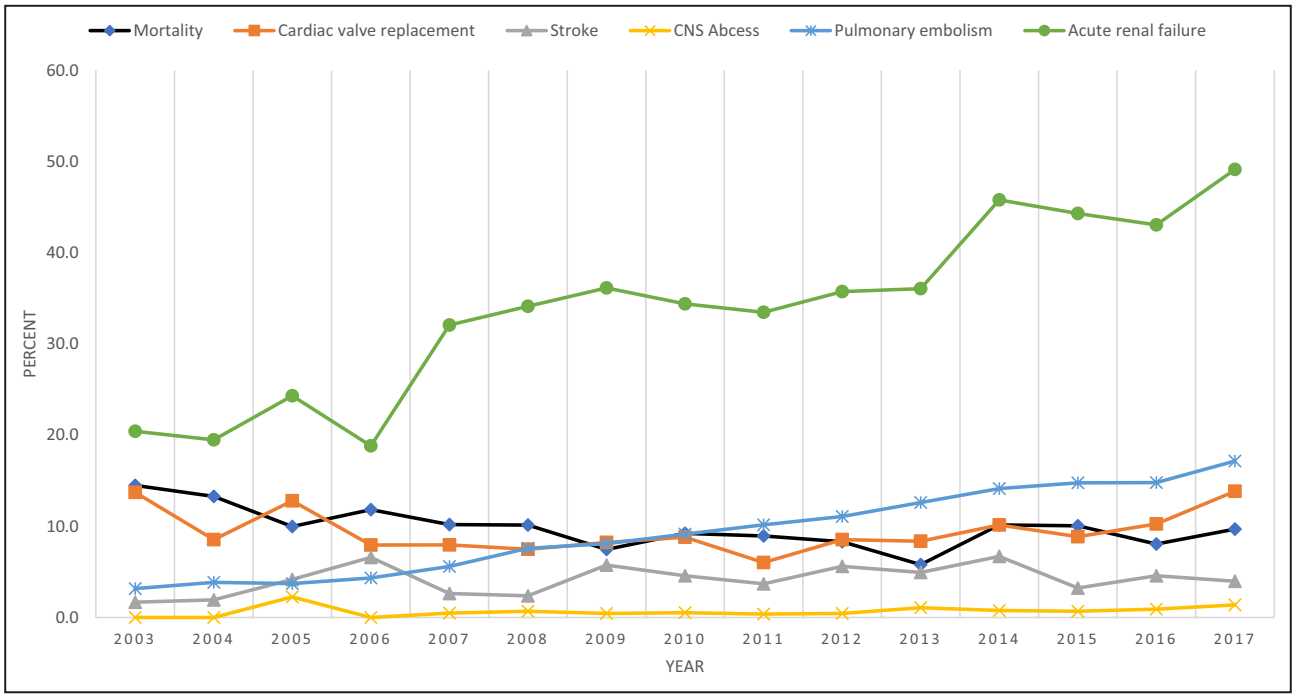

Figure 2. Trends in outcomes of patients hospitalized with cardiovascular implantable electronic device–related infective endocarditis (CIED-IE) in the United States, 2003 to 2017.
Line graph representing the percentage of patients with CIED-IE in whom the included outcomes were observed during the study period. CNS indicates central nervous system.

patients with CIED-IE, 19% were discharged routinely, compared with 25% of patients with NVE and 21% of patients with PVE.

DISCUSSION

This study, which analyzes outcomes of patients with CIED-IE over a 15-year period, is the first nationwide study of IE that compares patients hospitalized with CIED-IE, PVE, and NVE. Most previously published studies of CIED-IE reported single-center experiences with small numbers of patients.[24–26] Although some nationwide studies have reported on the incidence and outcomes of CIED infections in general,[5, 27] none specifically addressed trends in incidence and outcomes of CIED-IE, the most dangerous type of CIED-related infection.

Our analysis of the NIS database revealed a 5-fold increase in hospitalizations for CIED-IE from 2003 to 2017. The proportion of CIED-IE cases among all patients hospitalized with IE also increased during this period. In this study, CIED-IE accounted for 4.3% of all cases of IE, which is comparable to rates reported in prior studies.[20, 24] The proportion of patients with CIED-IE increased from 1.7% in 2003 to 4.8% in 2017. The increase in CIED infections has been attributed to the combined impact of higher rates of CIED implants and the aging of the general population.[9] The prevalence of most comorbidities increased during the study period, as did the incidence of in-hospital complications including renal failure, pulmonary embolism, and CNS abscess.

In-hospital mortality was lower for patients with CIED-IE than for patients with PVE and NVE. The rate of other complications, such as in-hospital CNS infection and stroke, were also less common in patients with CIED-IE than in patients with PVE and NVE. However, patients with CIED-IE had longer lengths of stay and higher hospitalization costs than patients with PVE and NVE.

In-hospital mortality for patients with CIED-IE decreased during the study period, despite increases in the number of comorbidities and the rate of in-hospital complications. Our study does not reveal a specific reason for the observed decline in mortality, but analysis of trends revealed some possibilities. One potential explanation for decreased mortality during the study period is patient age: the median patient age was significantly lower at the end of the study period than at the start. It is also possible that device extraction, which has been shown to improve outcomes in CIED-IE, played a role. In this study, the total number of device extractions performed per annum increased during the study period, but this change was not statistically significant. Although the guidelines for CIED-IE management were updated during the study period, there

Table 3. Baseline Characteristics of Patients Hospitalized With NVE, PVE, and CIED-IE From 2003 to 2017

General characteristics	NVE	PVE	CIED-IE	*P* value
Weighted, no.	585 974	26 111	27 257	
Median age (IQR), y	60 (45–74)	66 (49–76)	67 (56–77)	
Age group, y, %				<0.001
18–44	24	21	11	
45–64	35	29	33	
65–74	18	23	27	
75–84	16	21	23	
≥85	7	7	7	
Sex, %				<0.001
Women	42	33	32	
Race or ethnicity, %				<0.001
White	71	80	72	
Black	16	9.4	15	
Hispanic	8.2	7	7.3	
Asian/Pacific Islander	2	1.6	1.7	
Native American	0.7	0.5	0.6	
Other	2.6	2.1	2.8	
Comorbidities, %				
Hypertension	45	42	53	<0.001
CHF	20	27	30	<0.001
PVD	13	17	14	<0.001
Valvular disease	20	42	17	<0.001
Diabetes	27	22	22	<0.001
CKD	28	24	38	<0.001
CPD	19	16	24	<0.001
Liver disease	9.2	6.8	5	<0.001
HIV	0.6	0.2	0.3	0.002
Drug abuse	17	16	5.4	<0.001
Elixhauser score				<0.001
≥3	72	78	76	
Payer, %				<0.001
Medicare	51	56	67	
Medicaid	18	17	11	
Private	21	21	18	
Self-pay	6.3	3.3	1.4	
No charge	0.7	0.4	0.4	
Others	2.8	2.5	2.1	
Income percentile, %				<0.001
0–25	31	26	30	
26–50	25	25	26	
51–75	23	23	23	
76–100	21	25	22	
Hospital type, %				<0.001
Rural	7.4	4.7	2.7	
Urban nonteaching	35	27	19	
Urban teaching	58	68	78	
Hospital region, %				<0.001
Northeast	23	28	25	
Midwest	21	21	24	
South	36	30	35	
West	20	22	16	

The category "other" was provided by the database and no further information is available. CHF indicates congestive heart failure; CIED-IE, cardiovascular implantable electronic device–related infective endocarditis; CKD, chronic kidney disease; CPD, chronic pulmonary disease; IQR, interquartile range; NVE, native valve endocarditis; PVD, peripheral valvular disease; and PVE, prosthetic valve endocarditis.

Table 4. Organisms Responsible for Patients Hospitalized With IE in the United States From 2003 to 2017

Organism	NVE, %	PVE, %	CIED-IE, %
Staphylococcus aureus	40	20	43
Other *Staphylococcus*	12	19	18
Streptococcus	24	24	14
Enterococcus	9.6	17	10
Gram negatives	7.2	5.8	6.9
Anaerobic bacteria	0.4	0.8	0.4
Other bacterial infection	5.5	12	5.4
Fungal	1.9	2.7	2.2

CIED-IE indicates cardiovascular implantable electronic device–related infective endocarditis; IE, infective endocarditis; NVE, native valve endocarditis; and PVE, prosthetic valve endocarditis.

were no significant changes in the trends of CIED-IE outcomes (eg, hospitalization rate and mortality rate) after publication of these updates.

Previously published studies of CIED-related infections in general reported an increased mortality rate and stable hospital length of stay during an overlapping time interval (1993 to 2011).[5, 27] These studies do not specifically address trends in outcomes of CIED-IE. No single factor definitively explains the discrepancy in mortality trends between our study and prior reports. It is possible that differences in the target population and patient demographics contributed to this. The current study analyzed only the subset of patients with endocarditis, as opposed to prior reports, which included patients with pocket infection and any other signs of systemic infection such as fever, bacteremia, or sepsis.

Prior studies identified the outcomes and predictors of mortality in IE but did not address differences among the 3 different categories of IE. The only cohort that describes clinical characteristics of patients within different categories of IE is the ICE-PC (International Collaboration on Endocarditis––Prospective Cohort Study). In the ICE-PC, patients were enrolled from 28 countries between 2000 and 2006 (both the location and the time frame were different from our study of the NIS database). Moreover, ICE-PC did not include a population-based cohort. In addition, the number of patients with CIED-IE in the ICE-PC (177) was far smaller than the number included in our study (27 257).

Table 5. Outcomes of Patients Hospitalized With NVE, PVE, and CIED-IE in the United States From 2003 to 2017

Outcome	NVE	PVE	CIED-IE	*P* value
Mortality, %	12	12	9.2	<0.001
Cardiac valve replacement, %	10	18	9.3	<0.001
Stroke, %	12	12	4.5	<0.001
CNS abscess, %	2.3	1.2	0.7	<0.001
Pulmonary embolism, %	10	4.5	10	<0.001
Acute renal failure, %	28	36	38	<0.001
Mean cost/patient, $	37K	45K	56K	<0.001
Length of stay, d	14	14	17	<0.001

CIED-IE indicates cardiovascular implantable electronic device–related infective endocarditis; CNS, central nervous system; NVE, native valve endocarditis; and PVE, prosthetic valve endocarditis.

Categorization of patients in our study with respect to the type of IE present (CIED-ED, PVE, NVE) also facilitated analysis of the differential impact of individual in-hospital complications (eg, neurologic events) on patient outcomes.[28] In our study, the stroke rate was significantly lower in patients with CIED-IE (4.5%) than in patients with PVE (12%) and NVE (12%). We also observed lower rates of CNS infection in CIED-IE (0.7%) compared with PVE (1.2%) and NVE (2.3%). Data regarding strokes in patients with CIED infection are scarce and sourced primarily from studies of patients who underwent lead extraction.[29]

Most embolic events in patients with CIED-IE are observed in the pulmonary circulation as a result of the predominance of right-sided heart involvement of IE.[29, 30] A smaller proportion of patients with CIED-IE present with systemic events, attributable to either a right-to-left shunt or direct involvement of structures in the left heart. This difference could explain the observed lower rate of neurological complications in patients with CIED-IE compared with PVE and NVE.

Pulmonary embolism is the dominant type of embolic event in right-sided IE.[31] In our study, pulmonary embolism occurred in 9.5% of patients with CIED-IE. Comparable rates were observed in other studies.[24, 32] In our study, pulmonary embolism was observed in 9.9% of patients with NVE, which was twice the rate observed in patients with PVE. In the NVE group, the higher prevalence of reported drug use, known to be a risk factor for right-sided IE,[31, 33] could partially explain the higher incidence of pulmonary embolism in NVE compared with PVE.

More than one third of patients with CIED-IE and patients with PVE developed acute renal failure during time of hospitalization, while the incidence of acute renal failure was lower in patients with NVE. Increased age and history of hypertension were reported as risk factors for acute renal failure in patients with IE.[34] Therefore, increased age and a higher rate of hypertension among patients with CIED-IE and PVE may explain this observation.

IE is historically a disease associated with high morbidity that requires intensive inpatient management. Hospital length of stay was longest for the CIED-IE group in our study (17 days), likely driven by the frequent requirement for CIED extraction and reimplant.[35, 36] Hospital costs were also highest in patients with CIED-IE: mean cost per hospitalization was $56 000 for CIED-IE, which was 1.3 and 1.5 times greater than that in PVE and NVE, respectively. In addition, the disposition plan for a majority of CIED-IE patients involved

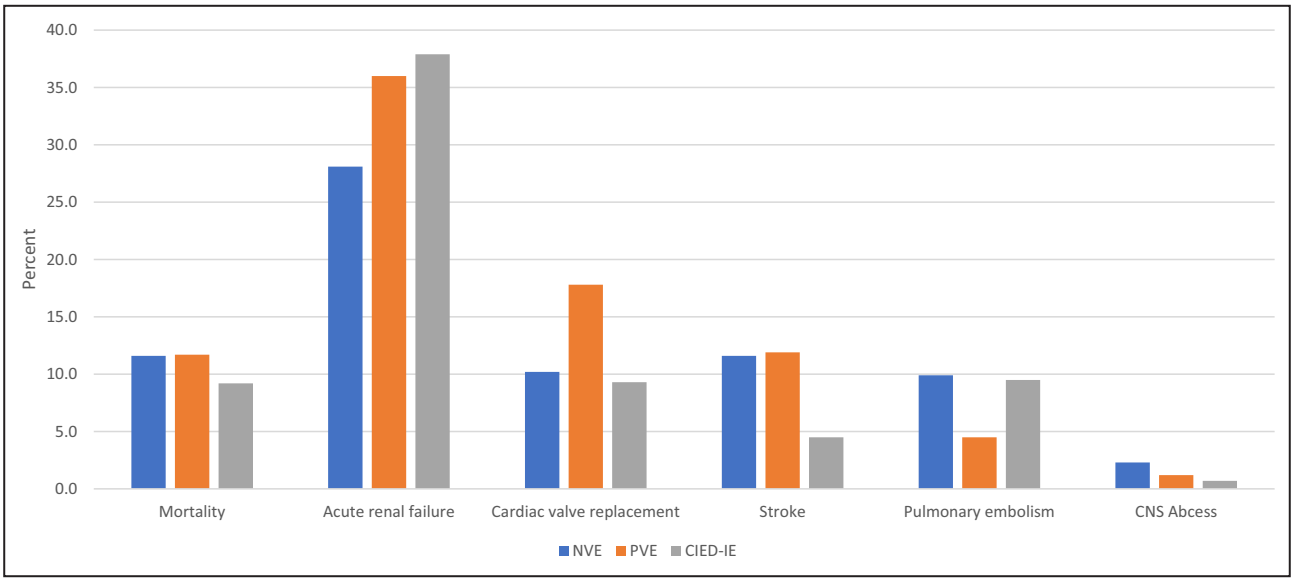

Figure 3. Outcomes of patients hospitalized with native valve endocarditis (NVE), prosthetic valve endocarditis (PVE), and cardiovascular implantable electronic device–related infective endocarditis (CIED-IE) in the United States, 2003 to 2017.
Bar graph in which key patient outcomes are displayed for each type of infective endocarditis included in this study. CNS indicates central nervous system.

transfer from the inpatient facility to other health care facilities. Despite more hospital care needs, older age, and higher rates of comorbidities, in-hospital mortality was lower in patients with CIED-IE, compared to NVE and PVE. The lower stroke rate in CIED-IE, being one of the most important predictors of mortality in patients with IE, may have contributed to the lower mortality rate in this population.

Comparable differences in patient characteristics and outcomes among 3 categories of IE were reported

Table 6. Predictors of In-Hospital Mortality in Patients With CIED-IE, PVE, and NVE in the United States From 2003 to 2017

	CIED-IE			PVE			NVE		
Predictors of mortality	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Age groups, y									
18–44 (reference)									
45–64	1.5	0.9–2.5	0.085	1.3	0.8–2.0	0.385	1.6	1.5–1.7	<0.001
65–74	2.0	1.2–3.5	0.009	1.4	0.8–2.5	0.167	1.9	1.7–2.0	<0.001
75–84	2.6	1.7-4.2	<0.001	1.2	0.8–1.8	0.261	2.2	2.0–2.4	<0.001
≥85	2.3	1.3-3.9	0.003	1.6	1.06–2.5	0.026	2.2	2.0–2.5	<0.001
Sex	1.2	0.9–1.5	0.212	1.2	1.0–1.5	0.042	1.1	1.0–1.1	<0.001
Elixhauser score ≥3	2.0	1.2–2.7	0.003	1.6	1.1–2.4	0.019	1.9	1.8–2.0	<0.001
CHF	1.7	1.3–2.2	<0.001	1.2	1.0–1.4	0.134	1.4	1.4–1.5	<0.001
Coagulopathy	2.1	1.6–2.7	<0.001	1.7	1.4–2.0	<0.001	2.0	1.9–2.1	<0.001
CKD	1.3	1.1–1.7	0.011	0.9	0.8–1.2	0.612	1.2	1.2–1.3	<0.001
Abnormal weight loss	1.4	1.1–1.9	0.009	1.3	1.0–1.7	0.037	1.2	1.2–1.3	<0.001
Staphylococcus aureus infection	1.4	1.2–1.7	0.001	1.4	1.1–1.8	0.003	1.2	1.2–1.3	<0.001
Incident acute kidney injury	2.5	2.0–3.1	<0.001	2.6	2.1–3.1	<0.001	2.6	2.5–2.8	<0.001
Incident stroke	2.3	1.5–3.6	<0.001	1.9	1.5–2.5	<0.001	2.4	2.3–2.5	<0.001

Interaction terms were statistically significant (association of mortality with age ≥75 years, Elixhauser score ≥3, and chronic kidney disease [CKD] was stronger in cardiovascular implantable electronic device–related infective endocarditis [CIED-IE] and native valve endocarditis [NVE] than in prosthetic valve endocarditis [PVE]). CHF indicates congestive heart failure; and OR, odds ratio (models were adjusted for race, calendar year, median household income, primary payer, hospital bed size, teaching status, location, and region).

Table 7. Disposition of Patients Hospitalized With NVE, PVE, and CIED-IE in the United States From 2003 to 2017

Disposition, %	NVE	PVE	CIED-IE
Routine	25	21	19
Transfer to a short-term hospital	12	14	12
Transfer other: including skilled nursing facility, intermediate care facility	37	35	39
Home health care	22	28	29
Against medical advice	3.5	2.2	0.8
Discharge alive, destination unknown	0.1	0.1	0.04

CIED-IE indicates cardiovascular implantable electronic device–related infective endocarditis; NVE, native valve endocarditis; and PVE, prosthetic valve endocarditis.

in the ICE-PC studies. However, the adverse event rates observed in our study were lower than in ICE-PC, which can be explained by differences in the study design. As recognized by the investigators, ICE-PC is not a population-based study and referral bias was likely because the contributors to the study were well-known, locally and internationally, for expertise in management of IE.[16]

The reported mortality rates in patients with CIED-IE vary widely among studies, ranging from 7% to 17%.[24, 26, 32, 37, 38] Prior studies of IE identified predictors of mortality but did not identify which predictors were significantly different among the categories of IE (CIED-IE, PVE, or NVE).[39–41] In the current study, *S aureus* was associated with a 40% increase in mortality risk for patients with CIED-IE. Other comorbidities were also found to be associated with increased mortality risk in patients with CIED-IE, including CHF (70% increase), CKD (30% increase), coagulopathy (2-fold increase), and abnormal weight loss (40% increase). In-hospital mortality was >2-fold higher in patients with CIED who presented with acute renal failure or stroke.

This study included an interaction analysis, which revealed that age ≥75 years, Elixhauser score ≥3, and CKD are stronger predictors of mortality in CIED-IE and NVE than in PVE. Given the observed increase in the incidence of acute renal failure among patients with CIED-IE during the study period, it is possible that careful monitoring and management of renal function in these patients (especially in those with CKD) could improve outcomes.

LIMITATIONS

NIS is an administrative database that uses *ICD* codes, which are subject to coding inaccuracies. The NIS database does not include the time of events, so it is difficult to ascertain the timing of clinical events and interventions/procedures relative to one another. Because the NIS database is a discharge-level database, it does not provide information regarding any postdischarge complications. The change from *ICD-9-CM* to *ICD-10-CM* codes in 2015 may have affected the trend analyses. Although medical treatment could have impacted the outcomes observed in this study, the absence of information regarding medication use in the NIS database made correlation between medical treatment and outcomes impossible.

CONCLUSIONS

This study reports outcomes of patients hospitalized with CIED-IE, NVE, and PVE during a 15-year period. A steady increase in the proportion of patients hospitalized with CIED-IE from 2003 to 2017 was observed. The rates of mortality for patients hospitalized with NVE and PVE were 1.3-fold higher than patients hospitalized with CIED-IE. In addition, rates of neurologic complications in patients with CIED-IE were less than half of the rates observed in patients with PVE or NVE. However, patients with CIED-IE had the longest lengths of stay and highest hospital costs on average. A decline in CIED-IE–related mortality was observed during the study period despite the increased prevalence of CIED-IE and of medical comorbidities. This study does not pinpoint a specific reason for the reduced mortality rate over time, put potential explanations include decreased patient age and an increase in the rate of device extraction.

ARTICLE INFORMATION

Received January 31, 2022; accepted June 1, 2022.

Affiliation

Cardiac Arrhythmia Service, MGH Heart Center, Massachusetts General Hospital, Boston, MA

Sources of Funding

This study was not supported by any dedicated funding sources.

Disclosures

P. Khaloo, A. Shaqdan, P.A. Ledesma, U.A. Uzomah, J. Galvin: no relationships to disclose. L.M. Ptaszek: consultant for Abbott, Aquaheart, Broadview Ventures, Bristol Myers Squibb, Moderna, Neutrace, Pfizer, and World Care Clinical. J.N. Ruskin: consultant for Acesion Pharma, Advanced Medical Education, InCarda and Janssen; and equity in Celero Systems, Element Science, Infobionic, LuxCath, and NewPace.

REFERENCES

1. Voigt A, Shalaby A, Saba S. Continued rise in rates of cardiovascular implantable electronic device infections in the United States: temporal trends and causative insights. *Pacing Clin Electrophysiol*. 2010;33:414–419. doi: 10.1111/j.1540-8159.2009.02569.x
2. Cabell CH, Heidenreich PA, Chu VH, Moore CM, Stryjewski ME, Corey GR, Fowler VG. Increasing rates of cardiac device infections among Medicare beneficiaries: 1990-1999. *Am Heart J*. 2004;147:582–586. doi: 10.1016/j.ahj.2003.06.005
3. Voigt A, Shalaby A, Saba S. Rising rates of cardiac rhythm management device infections in the United States: 1996 through 2003. *J Am Coll Cardiol*. 2006;48:590–591. doi: 10.1016/j.jacc.2006.05.016
4. Dai M, Cai C, Vaibhav V, Sohail MR, Hayes DL, Hodge DO, Tian Y, Asirvatham R, Cochuyt JJ, Huang C, et al. Trends of cardiovascular implantable electronic device infection in 3 decades: a population-based study. *JACC Clin Electrophysiol*. 2019;5:1071–1080. doi: 10.1016/j.jacep.2019.06.016
5. Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, Ho RT, Pavri BB, Kurtz SM. 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;58:1001–1006. doi: 10.1016/j.jacc.2011.04.033
6. Mond HG, Irwin M, Ector H, Proclemer A. The world survey of cardiac pacing and cardioverter-defibrillators: calendar year 2005 - an international cardiac pacing and electrophysiology society (ICPES) project. *Pacing Clin Electrophysiol*. 2008;31:1202–1212. doi: 10.1111/j.1540-8159.2008.01164.x
7. Mateos Gaitán R, Boix-Palop L, Muñoz García P, Mestres CA, Marín Arriaza M, Pedraz Prieto Á, de Alarcón GA, Gutiérrez Carretero E, Hernández Meneses M, Goenaga Sánchez MÁ, et al. infective endocarditis in patients with cardiac implantable electronic devices: a nationwide study. *Europace*. 2020;22:1062–1070. doi: 10.1093/europace/euaa076
8. Klug D, Balde M, Pavin D, Hidden-Lucet F, Clementy J, Sadoul N, Rey JL, Lande G, Lazarus A, Victor J, et al. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: Results of a large prospective study. *Circulation*. 2007;116:1349–1355. doi: 10.1161/CIRCULATIONAHA.106.678664
9. Kurtz SM, Ochoa JA, Lau E, Shkolnikov Y, Pavri BB, Frisch D, Greenspon AJ. Implantation trends and patient profiles for pacemakers and implantable cardioverter defibrillators in the United States: 1993-2006. *Pacing Clin Electrophysiol*. 2010;33:705–711. doi: 10.1111/j.1540-8159.2009.02670.x
10. Birnie D, Williams K, Guo A, Mielniczuk L, Davis D, Lemery R, Green M, Gollob M, Tang A. Reasons for escalating Pacemaker implants. *Am J Cardiol*. 2006;98:93–97. doi: 10.1016/j.amjcard.2006.01.069
11. Armiñanzas C, Fariñas-Alvarez C, Zarauza J, Muñoz P, González Ramallo V, Martínez Sellés M, Miró Meda JM, Pericás JM, Goenaga MÁ, Ojeda Burgos G, et al. Role of age and comorbidities in mortality of patients with infective endocarditis. *Eur J Intern Med*. 2019;64:63–71. doi: 10.1016/j.ejim.2019.03.006
12. Golzio PG, Fanelli AL, Vinci M, Pelissero E, Morello M, Grosso Marra W, Gaita F. Lead vegetations in patients with local and systemic cardiac device infections: prevalence, risk factors, and therapeutic effects. *Europace*. 2013;15:89–100. doi: 10.1093/europace/eus240
13. Baddour LM, Epstein AE, Erickson CC, Knight BP, Levison ME, Lockhart PB, Masoudi FA, Okum EJ, Wilson WR, Beerman LB, et al. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the american heart association. *Circulation*. 2010;121:458–477. doi: 10.1161/CIRCULATIONAHA.109.192665
14. Arber N. Pacemaker endocarditis. Report of 44 cases and review of the literature. *Medicine*. 1994;73:299–305. doi: 10.1097/00005792-199411000-00003
15. Sandoe JAT, Barlow G, Chambers JB, Gammage M, Guleri A, Howard P, Olson E, Perry JD, Prendergast BD, Spry MJ, et al. Guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection. Report of a joint working party project on behalf of the british society for antimicrobial chemotherapy. *J Antimicrob Chemother*. 2015;70:325–359. doi: 10.1093/jac/dku383
16. Murdoch DR, Corey RG, Hoen B, Miró M, Fowler VG, Bayer AS, Karchmer AW, Olaison L, Pappas PA, Moreillon P, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century the international collaboration on endocarditis-prospective cohort study. *Arch Intern Med*. 2009;169:463–473. doi: 10.1001/archinternmed.2008.603
17. Baddour LM, Wilson WR, Bayer AS, Fowler VG, Tleyjeh IM, Rybak MJ, Barsic B, Lockhart PB, Gewitz MH, Levison ME, et al. Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132:1435–1486. doi: 10.1161/CIR.0000000000000296
18. Houchens RL, Ross DN, Elixhauser A, Jiang J. Nationwide Inpatient Sample Redesign Final Report. HCUP NIS Related Reports Online, Apr 4, 2014. U.S. Agency for Healthcare Research and Quality. Available at: http://www.hcup-us.ahrq.gov/db/nation/nis/nisrelatedreports.jsp. Accessed May 2022
19. Healthcare Cost and Utilization Project — HCUP. Introduction to the HCUP National Inpatient Sample (NIS) 2019. Available: https://www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2019.jsp. Accessed May 2022
20. Toyoda N, Chikwe J, Itagaki S, Gelijns AC, Adams DH, Egorova NN. Trends in infective endocarditis in California and New York state, 1998-2013. *J Am Med Assoc*. 2017;317:1652–1660. doi: 10.1001/jama.2017.4287
21. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care*. 1998;36:8–27. doi: 10.1097/00005650-199801000-00004
22. De Giorgi A, Fabbian F. Identifying increased risk of readmission and in-hospital mortality using hospital administrative data. *Med Care*. 2017;55:905. doi: 10.1097/MLR.0000000000000793
23. Cuzick J. A wilcoxon-type test for trend. *Stat Med*. 1985;4:87–90. doi: 10.1002/sim.4780040112
24. Athan E, Chu VH, Tattevin P, Selton-Suty C, Jones P, Naber C, Miró JM, Ninot S, Fernández-Hidalgo N, Durante-Mangoni E, et al. Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices. *J Am Med Assoc*. 2012;307:1727–1735. doi: 10.1001/jama.2012.497
25. Jędrzejczyk-Patej E, Mazurek M, Kowalski O, Sokal A, Kozieł M, Adamczyk K, Przybylska-Siedlecka K, Morawski S, Liberska A, Szulik M, et al. Device-related infective endocarditis in cardiac resynchronization therapy recipients — single center registry with over 2500 person-years follow up. *Int J Cardiol*. 2017;227:18–24. doi: 10.1016/j.ijcard.2016.11.029
26. Nesterovics N, Nesterovics G, Stradins P, Kalejs M, Ansabergs J, Blumbergs M, Maca A, Kamzola G, Lejnieks A, Kalejs O, et al. Lead-related infective endocarditis in Latvia: a single Centre experience. *Medicine*. 2019;55:1–9.
27. Sridhar ARM, Lavu M, Yarlagadda V, Reddy M, Gunda S, Afzal R, Atkins D, Gopinathanair R, Dawn B, Lakkireddy DR. Cardiac implantable electronic device-related infection and extraction trends in the U.S. *Pacing Clin Electrophysiol*. 2017;40:286–293. doi: 10.1111/pace.13009
28. Pigretti S, Zurrú MC, Arias A, Parcerisa F, Luzzi A, Belziti C. Neurologic complications of infective endocarditis: do they have an impact on prognosis? *Medicina (B Aires)*. 2017;77:89–94.
29. Lee JZ, Agasthi P, Pasha AK, Tarin C, Tseng AS, Diehl NN, Hodge DO, DeSimone CV, Killu AM, Brady PA, et al. Stroke in patients with cardiovascular implantable electronic device infection undergoing transvenous lead removal. *Heart Rhythm*. 2018;15:1593–1600. doi: 10.1016/j.hrthm.2018.08.008
30. Athan E. The characteristics and outcome of infective endocarditis involving implantable cardiac devices. *Curr Infect Dis Rep*. 2014;16:446. doi: 10.1007/s11908-014-0446-5
31. Chahoud J, Sharif Yakan A, Saad H, Kanj SS. Right-sided infective endocarditis and pulmonary infiltrates: an update. *Cardiol Rev*. 2016;24:230–237. doi: 10.1097/CRD.0000000000000095
32. Sohail MR, Uslan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR, Steckelberg JM, Jenkins SM, Baddour LM. Infective endocarditis complicating permanent pacemaker and implantable cardioverter-defibrillator infection. *Mayo Clin Proc*. 2008;83:46–53. doi: 10.4065/83.1.46
33. Moreillon P, Que Y-A. Infective endocarditis. *Lancet*. 2004;363:139–149. doi: 10.1016/S0140-6736(03)15266-X
34. Conlon PJ, Jefferies F, Krigman HR, Corey GR, Sexton DJ, Abramson MA. Predictors of prognosis and risk of acute renal failure in bacterial endocarditis. *Clin Nephrol*. 1998;49:96–101.
35. Holland TL, Baddour LM, Bayer AS, Hoen B, Miro JM, Fowler VG. Infective endocarditis HHS public access. *Nat Rev Dis Prim*. 2017;2:1–49.

36. Kusumoto FM, Schoenfeld MH, Wilkoff BL, Berul CI, Birgersdotter-Green UM, Carrillo R, Cha Y-M, Clancy J, Deharo J-C, Ellenbogen KA, et al. 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. *Heart Rhythm*. 2017;14:e503–e551. doi: 10.1016/j.hrthm.2017.09.001
37. Greenspon AJ, Prutkin JM, Sohail MR, Vikram HR, Baddour LM, Danik SB, Peacock J, Falces C, Miro JM, Blank E, 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;59:681–687. doi: 10.1016/j.jacc.2011.11.011
38. Massoure PL, Reuter S, Lafitte S, Laborderie J, Bordachard P, Clementy J, Roudaut R. Pacemaker endocarditis: clinical features and management of 60 consecutive cases. *Pacing Clin Electrophysiol*. 2007;30:12–19. doi: 10.1111/j.1540-8159.2007.00574.x
39. Habib A, Le KY, Baddour LM, Friedman PA, Hayes DL, Lohse CM, Wilson WR, Steckelberg JM, Sohail MR. Predictors of mortality in patients with cardiovascular implantable electronic device infections. *Am J Cardiol*. 2013;111:874–879. doi: 10.1016/j.amjcard.2012.11.052
40. Mistiaen WP. What are the main predictors of in-hospital mortality in patients with infective endocarditis: a review. *Scand Cardiovasc J*. 2018;52:58–68. doi: 10.1080/14017431.2018.1433318
41. Baman TS, Gupta SK, Valle JA, Yamada E. Risk factors for mortality in patients with cardiac device-related infection. *Circ Arrhythm Electrophysiol*. 2009;2:129–134. doi: 10.1161/CIRCEP.108.816868