Device-related infection in de novo transvenous implantable cardioverter-defibrillator Medicare patients

Mikhael F. El-Chami, MD, FHRS,* Caroline M. Jacobsen, MPhil,† Robert I. Griffiths, MS, ScD, DPhil,† Linda K. Hansen, MPH, PhD,† Nick Wold, MS,† Stacey L. Amorosi, MA,† Timothy M. Stivland, MBA,† Bradley P. Knight, MD, FACC, FHRS,‡ Raul Weiss, MD, FACC,§ George E. Mark, MD, FACC, FHRS,‖ Mauro Biffi, MD,¶ Vincent Probst, MD,# Pier D. Lambiase, PhD, FRCP, FHRS,** Marc A. Miller, MD,†† Larry M. Baddour, MD, FIDSA, FAHA‡‡§§

*From the *School of Medicine, Emory University, Atlanta, Georgia, †Boston Scientific Corporation, St. Paul, Minnesota, ‡Center for Heart Rhythm Disorders Bluhm Cardiovascular Institute, Northwestern Memorial Hospital, Chicago, Illinois, §Cardiology, DHLRI, The Ohio State University Wexner Medical Center, Columbus, Ohio, ‖Department of Cardiology, Cooper University Hospital, Camden, New Jersey, ¶Institute of Cardiology, S. Orsola Malpighi Hospital, Bologna, Italy, #L'Institut du Thorax, CHU de Nantes, Cardiology, Nantes, France, **UCL Institute of Cardiovascular Science, and Barts Heart Center, London, United Kingdom, ††Icahn School of Medicine at Mount Sinai, Mount Sinai Hospital, New York, New York, ‡‡Division of Infectious Diseases, Department of Medicine, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, and §§Department of Cardiovascular Disease, Mayo Clinic College of Medicine and Science, Rochester, Minnesota.*

BACKGROUND Cardiac device infection is a serious complication of implantable cardioverter-defibrillator (ICD) placement and requires complete device removal with accompanying antimicrobial therapy for durable cure. Recent guidelines have highlighted the need to better identify patients at high risk of infection to assist in device selection.

OBJECTIVE To estimate the prevalence of infection in de novo transvenous (TV) ICD implants and assess factors associated with infection risk in a Medicare population.

METHODS A retrospective cohort study was conducted using 100% Medicare administrative and claims data to identify patients who underwent de novo TV-ICD implantation (July 2016–December 2017). Infection within 720 days of implantation was identified using ICD-10 codes. Baseline factors associated with infection were identified by univariable logistic regression analysis of all variables of interest, including conditions in Charlson and Elixhauser comorbidity indices, followed by stepwise selection criteria with a $P \leq .25$ for inclusion in a multivariable model and a backwards, stepwise elimination process with $P \leq .1$ to remain in the model. A time-to-event analysis was also conducted.

RESULTS Among 26,742 patients with *de novo* TV-ICD, 519 (1.9%) developed an infection within 720 days post implant. While more than half (54%) of infections occurred during the first 90 days, 16% of infections occurred after 365 days. Multivariable analysis revealed several significant predictors of infection: age <70 years, renal disease with dialysis, and complicated diabetes mellitus.

CONCLUSION The rate of de novo TV-ICD infection was 1.9%, and identified risk factors associated with infection may be useful in device selection.

KEYWORDS Device; Implantable cardioverter-defibrillator; Infection; Prevalence; Risk factors

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Introduction

Implantable cardioverter-defibrillators (ICD) are an established treatment for individuals considered at risk for sudden cardiac death,[1] and have demonstrated safety and efficacy in both randomized controlled trials[2] and studies of real-world practice.[3,4] However, ICD implantation is associated with a risk of device infection. An analysis of the Nationwide Inpatient Sample from 1993 to 2008 revealed an increasing trend in infection rates over time in the United States.[5] There are also differences in infection rates within the first year across device categories described in prospective and retrospective studies ranging from 0.6% to 1.3% to 2.3% to 3.4%, respectively, as highlighted in a European Heart Rhythm Association consensus document published in 2020.[6]

Previous studies have identified patients at high risk of infection in clinical trials[7] for the broader cardiac implantable electronic device (CIED) category and limited follow-up to 1 year. Some single-center settings[8–10] have also identified variables associated with high risk of infection, although sample sizes were relatively low, and generalizability to other patient populations may be limited. In response, the objective of this study is to estimate the prevalence of device infection in de novo transvenous (TV) ICD implants and assess risk factors associated with device infection in a large, real-world, Medicare population with long-term (>1 year) follow-up. Ultimately, these data could be used to help guide clinical decisions for device type and patient selection.[11]

Methods

Study design and data source

A retrospective cohort study was performed using 100% Medicare administrative and claims data from January 1, 2016 to December 31, 2018. The Medicare files contain insurance claims for 100% of fee-for-service (FFS) beneficiaries and include diagnosis and procedure data for all facility-level encounters (eg, hospital inpatient, hospital outpatient, skilled nursing facility), but do not include physician office visits or pharmacy claims. Institutional review board approval was not required, as preexisting deidentified claims data were analyzed, but methodological guidelines for real-world data were referenced.[12]

Patient selection

International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) procedure codes supplemented with current procedural terminology (CPT) codes (Supplemental Tables 1 and 2), where available, were used to identify patients who underwent TV-ICD implantation between July 1, 2016 and December 31, 2017 (Figure 1), with index implantation being defined as the first observed TV-ICD implant during that interval. The cohort was required to have met the following inclusion criteria: continuous enrollment in Medicare FFS for 6 months prior to index and no enrollment in a health maintenance organization on or after January 1, 2016. Patients were excluded if there was evidence of previous CIED infection in the 6 months prior to index and/or infection present on admission (Supplemental Tables 3–6). These criteria ensured de novo index implantation and that patients had enough claims prior to index implantation with which to identify baseline characteristics. Additionally, these criteria allowed for continuous follow-up to identify device infections without interruptions in their claims history.

Observation period

Patients were followed from index implantation until first device infection or death, up to 720 days. In order to compare with prior published work and based on clinical relevance, prevalence of device infection was captured at 4 time periods: overall study period (0–720 days), early (0–90 days), mid (91–365 days), and late (366–720 days).

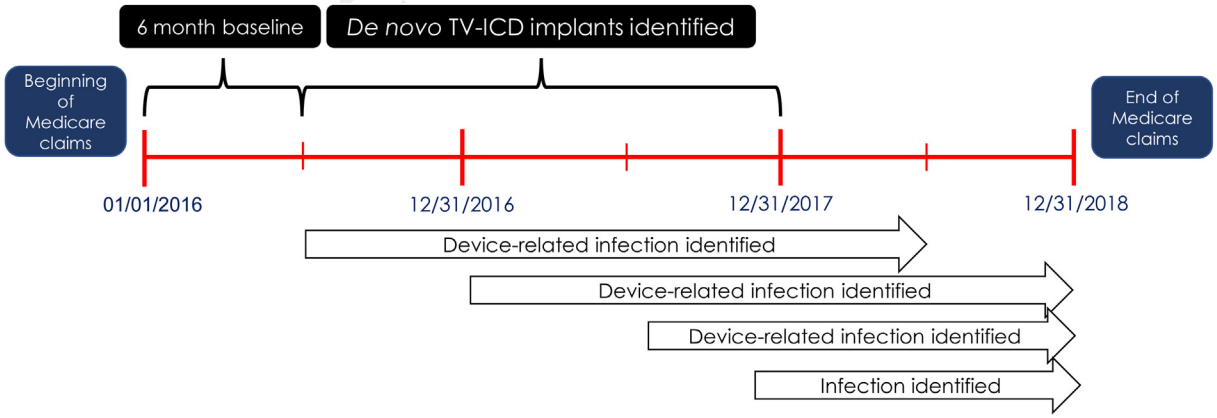

Figure 1 Study design: a retrospective cohort study design using 100% Medicare administrative and claims data to identify patients who underwent de novo transvenous implantable cardioverter-defibrillator (TV-ICD) implantation between July 1, 2016 and December 31, 2017. Comorbidities were identified in the 6-month baseline period prior to implant. Patients were followed for up to 720 days, which was defined as the overall study period, to identify device infection.

Table 1 Patient characteristics for those with and without device infection

Characteristic	Infection (n = 519)		No infection (n = 26,223)		*P* value
Age (years)	n	%	n	%	<.0001
<65	149	3.1	4658	96.9	
65–69	128	2.0	6328	98.0	
70–74	89	1.5	6016	98.5	
75–79	75	1.5	4859	98.5	
80–84	53	1.7	3069	98.3	
≥85	25	1.9	1293	98.1	
Sex					
Female	165	2.2	7262	97.8	.039
Male	354	1.8	18,961	98.2	
Race					
White	383	1.8	20,996	98.2	.001
Black	101	2.7	3606	97.3	
Other	35	2.1	1621	97.9	
HIV/AIDS					
No	516	1.9	26,125	98.1	.452
Yes	3	3.0	98.0	97.0	
Cerebrovascular disease					
No	448	1.9	22,712	98.1	.847
Yes	71	2.0	3511	98.0	
Chronic pulmonary disease					
No	302	1.7	17,510	98.3	<.0001
Yes	217	2.4	8713	97.6	
Heart failure					
No	31	1.4	2155	98.6	.065
Yes	488	2.0	24,068	98.0	
Dementia					
No	498	1.9	25,330	98.1	.426
Yes	21	2.3	893	97.7	
Hemiplegia/paraplegia					
No	511	1.9	25,856	98.1	.785
Yes	8	2.1	367	97.9	
Myocardial infarction					
No	267	1.9	13,539	98.1	.933
Yes	252	1.9	12,684	98.1	
Peptic ulcer					
No	507	1.9	25,747	98.1	.402
Yes	12	2.5	476	97.5	
Peripheral vascular disease					
No	374	1.8	19,998	98.2	.026
Yes	145	2.3	6225	97.7	
Renal disease					
No	294	1.6	17,702	98.4	<.0001
Yes	225	2.6	8521	97.4	
Rheumatic disease					
No	492	1.9	25,318	98.1	.031
Yes	27	2.9	905	97.1	
Cancer					
No	481	1.9	24,411	98.1	.727
Nonmetastatic	37	2.0	1788	98.0	
Metastatic	1	4.0	24	96.0	
Diabetes					
No	380	2.0	18,905	98.0	.675
Without complications	114	1.8	6161	98.2	
With complications	25	2.1	1157	97.9	
Liver disease					
No	493	1.9	25,359	98.1	.004
Mild	22	2.6	815	97.4	
Moderate/severe	4	7.5	49	92.5	

Patient characteristics

Baseline patient characteristics included age at index, sex, and race (white, black, or other). General comorbidities were identified and defined by both Charlson and Elixhauser comorbidity indices.[13,14] Additional study-specific comorbidities were identified based on a recent meta-analysis of prospective and retrospective studies that examined risk factors associated with CIED infections.[15] Using procedural and diagnosis code definitions with claims available prior to implant, the following comorbidities were included: presence of a prosthetic cardiovascular device; end-stage renal disease with chronic dialysis; renal disease without dialysis; diabetes mellitus with and without chronic complications; chronic obstructive pulmonary disease; heart failure; lymphoma, metastatic cancer, and solid tumor without metastasis as proxies for malignancy; atrial fibrillation as a proxy for anticoagulant drug use; and immunosuppression as a proxy for corticosteroid use (Supplemental Table 7). Patients were characterized according to whether they had device infection.

Outcomes

Device infection was identified using ICD-10 diagnosis and procedure codes and supplemented with CPT codes where available within Medicare claims (Supplemental Tables 8–10).[16] To maximize the likelihood that infections were device-related, claims were searched for patient records with at least 1 infection diagnosis that included a device procedure code for removal or revision during the same encounter; then claims were searched for device infection based solely on ICD-10 diagnosis code T82.7XXX.

Statistical analysis

Patient baseline demographics and Charlson Comorbidity Index variables were summarized based on frequency and percentage according to presence of device infection and were compared using Pearson χ^2 test. The rate of device infection was presented using frequency and percentage based on presence of infection within each time period. Kaplan-Meier analysis was conducted to assess the trend of device infection over the study period.

Risk prediction

For estimating the risk of device infection, age, sex, and race were assessed with 3 sets of comorbidity variables: Charlson, Elixhauser, and study-specific. Device infection was treated as a binary outcome variable. A univariable logistic regression analysis was performed for demographic variables and each set of comorbidity variables to assess the relationship between each risk factor and device infection. All variables from the univariable analysis with $P \leq .25$ were included in a multivariable model implementing a stepwise backward elimination process with a $P \leq .1$ to remain in the model.

After a series of univariable and multivariable logistic regression analyses was performed for each set of comorbidities, a hybrid set of predictors was created using the comorbidities that remained significant in the multivariable analyses of the 3 models as a candidate for the fourth. In instances where the same concept was represented in more than 1 of the multivariable models, the concept with the largest coefficient was used in the hybrid model. A final multivariable logistic regression analysis was performed on the hybrid predictors to determine device infection risk in the 4 study time periods: overall study period (0–720 days), early (0–90 days), mid (91–365 days), and late (366–720 days). Using the final multivariable model for the overall study period, the predicted probability of infection represented as a percentage was calculated using a series of hypothetical patients and combinations of patient characteristics. To estimate the mortality impact of infection, multivariable survival analysis was performed with infection as a time-dependent covariate, while adjusting for all the variables from the hybrid model. All statistical analyses were performed in STATA 15.[17]

Results

Patient characteristics

There were 26,742 patients with a de novo TV-ICD implant identified with an overall mean age of 71 years and an average follow-up of 517 days. Of the full patient cohort, 28% of patients were female and 80% were white (Table 1). According to the Charlson Comorbidity Index variables, 92% of all patients had a heart failure diagnosis, 48% had prior myocardial infarction, 33% had renal disease, and 28% had diabetes mellitus (Table 1).

Outcomes

Over the study period, 519 (1.9%) patients developed device-related infection (Table 1). Patients with TV-ICD infections were younger, were more likely female and nonwhite, and had a higher incidence of chronic obstructive pulmonary disease, peripheral vascular disease, renal disease, rheumatic disease, and liver disease. The mean patient age with and without device infection was 68 and 71 years, respectively. Among the patients who developed an infection, 54% (n = 281) were early, 30% (n = 156) were mid, and 16% (n = 82) were late infections (Table 2). Figure 2 depicts the time to first device infection based on the proportion of patients at risk after index through the maximum 720 days. While more than one-half of infections occurred within 90 days post implant, 46% of infections occurred after 90 days.

Table 2 Device infection rate based on duration of follow-up status/post device implantation

	Infection	(%)	All
Time periods	n		n
Overall study period	519	(1.9)	26,742
Early (0–90 days)	281	(1.1)	26,742
Mid (91–365 days)	156	(0.6)	25,286
Late (366–720 days)	82	(0.4)	22,157

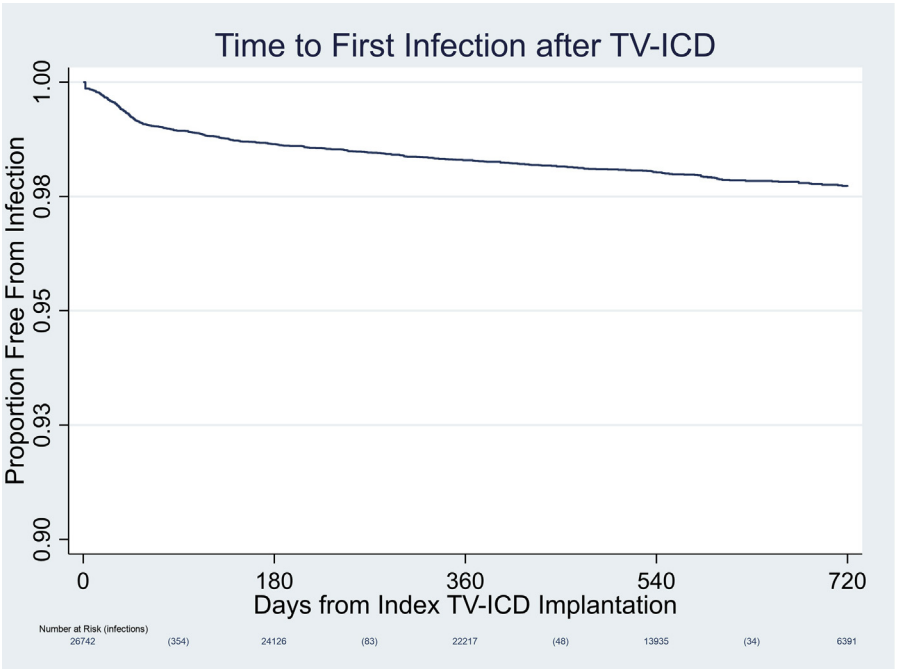

Figure 2 Kaplan-Meier analysis depicts the time in days to first device-related infection after de novo transvenous implantable cardioverter-defibrillator (TV-ICD) implant.

Risk prediction

The final hybrid multivariable regression model included age and the following significant risk factors for device infection from each comorbidity set: diabetes mellitus and chronic pulmonary disease from the Charlson; valvular disease, drug abuse, weight loss, anemias, and depression from the Elixhauser; and renal disease and prosthetic cardiovascular device from the study-specific set. Among these, age <70

Variable	Odds Ratio (95% CI)	P-value
Age (ref 70-74)		
Age <65	1.81 (1.37 - 2.38)	
Age 65-69	1.37 (1.04 - 1.80)	
Age 75-79	1.04 (0.76 - 1.42)	<0.001
Age 80-84	1.19 (0.84 - 1.67)	
Age ≥ 85	1.37 (0.87 - 2.14)	
Renal disease (ref no)		
No dialysis	0.84 (0.54 - 1.31)	0.05
Dialysis	1.25 (1.02 - 1.53)	
Diabetes (ref no)		
Without complications	1.13 (0.90 - 1.41)	0.04
With complications	1.33 (1.07 - 1.66)	
Chronic pulmonary disease	1.23 (1.03 - 1.48)	0.025
Prosthetic cardiovascular device	1.43 (0.98 - 2.08)	0.064
Valvular disease	1.22 (1.02 - 1.47)	0.033
Drug abuse	1.66 (1.13 - 2.42)	0.009
Weight loss	1.35 (0.99 - 1.84)	0.058
Anemia	1.83 (1.44 - 2.33)	<0.001
Depression	1.30 (1.04 - 1.63)	0.024

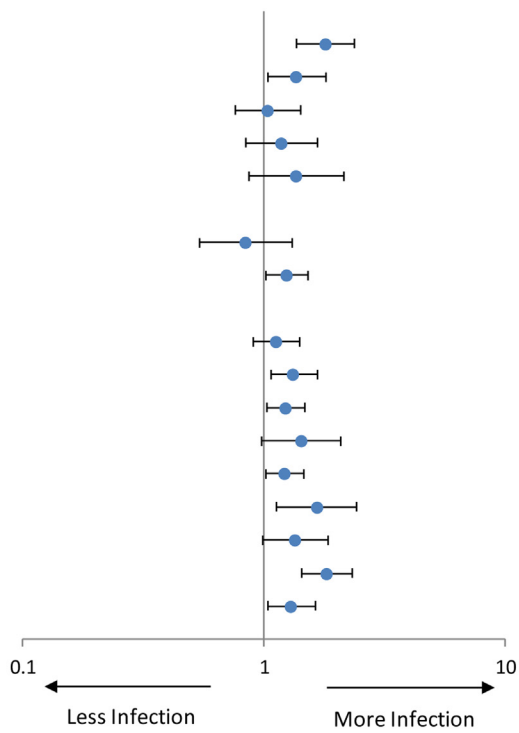

Figure 3 Multivariable analysis of risk factors associated with device infection. Baseline variables associated with an increased risk of device infection over the study period.

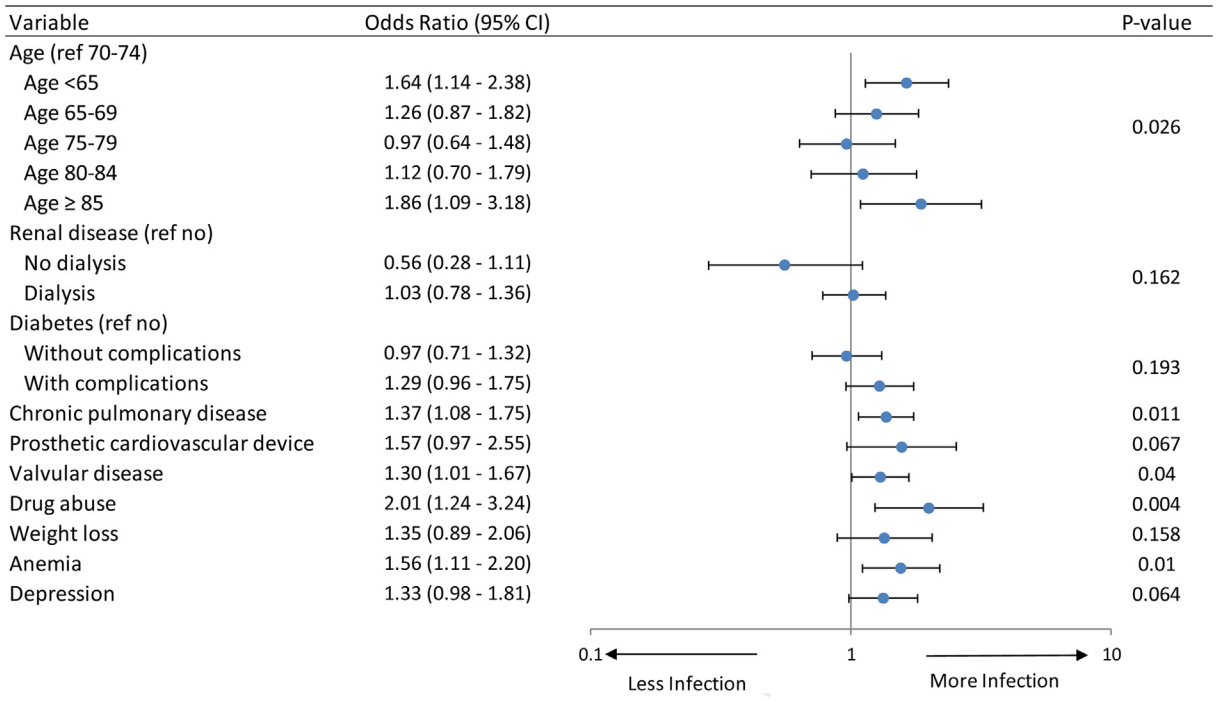

Figure 4 Multivariable analysis of risk factors associated with device infection. Baseline variables associated with an increased risk of early (0–90 days) device infection.

years, end-stage renal disease with dialysis, diabetes mellitus with complications, chronic pulmonary disease, valvular disease, drug abuse, anemia, and depression (Figure 3) had significantly higher risk of device infection in the overall study period. In the early period, patients in the youngest (<65) and oldest (85+) age groups and patients with chronic pulmonary disease, valvular disease, drug abuse, and anemia were at significantly higher risk of device-related infection

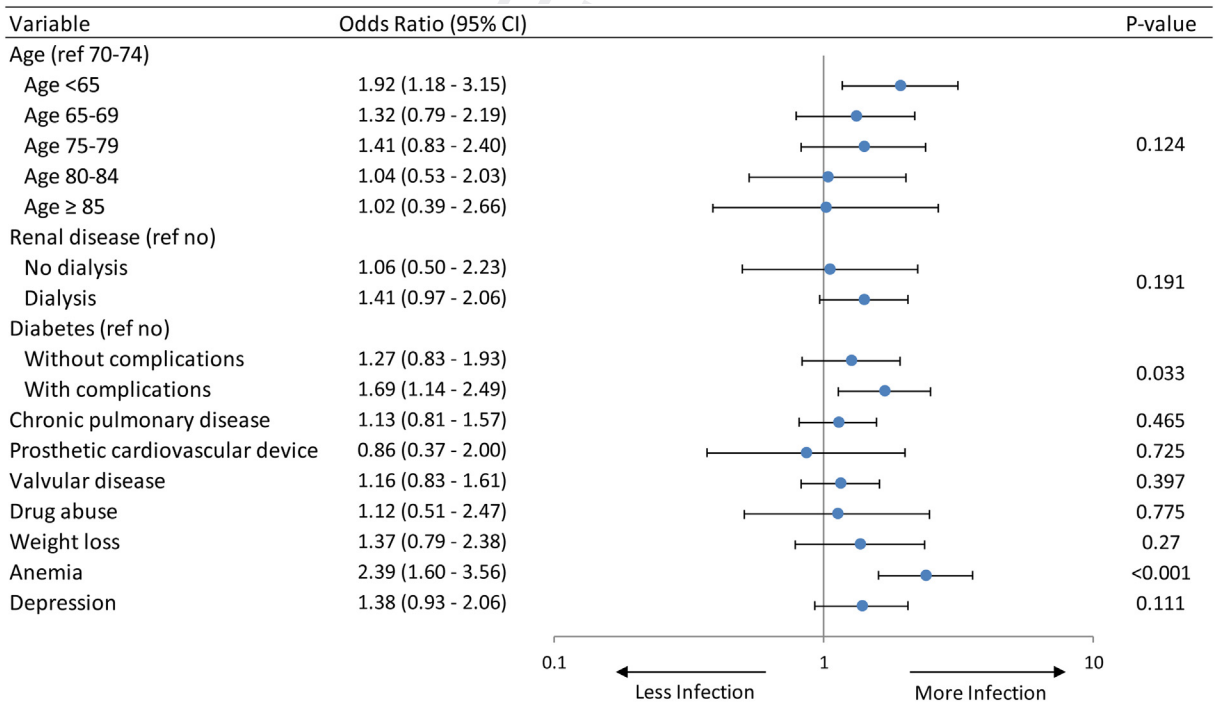

Figure 5 Multivariable analysis of risk factors associated with device infection. Baseline variables associated with an increased risk of mid (91–365 days) device infection.

(Figure 4). In the mid period, factors significantly associated with risk of device infection included youngest age group, diabetes mellitus with complications, and anemia (Figure 5). Factors associated with risk of late device infection were youngest age group, end-stage renal disease with dialysis, and anemia (Figure 6). Results for 5 hypothetical patient scenarios run using the final multivariable model for the overall study period are presented in Supplemental Table 11. Of note, a patient 50 years of age with end-stage renal disease on dialysis, complicated diabetes mellitus, anemia, and depression had a 6.1% probability of device infection. Multivariable survival analysis demonstrated that infection was associated with a 2.33 (hazard ratio)-fold increase in the risk of death, adjusting for other covariables.

Discussion

ICDs are a cornerstone treatment for patients at risk of sudden cardiac death. Device infection can cause significant patient morbidity and mortality, as well as impose a substantial financial burden to patients and healthcare systems.[5,16,18–20] Identifying patients at high risk of infection prior to implant in order to mitigate the risk of device infection and associated complications is important. Practice guidelines recommend the use of a subcutaneous (S) ICD in patients at risk of sudden cardiac death and high risk for infection,[11] though these guidelines do not clearly define patients at high risk for infection. This has prompted a need to better identify the clinical characteristics of patients at high risk of infection to assist in de novo device selection. Although our study is not the first to evaluate risk factors associated with device infection,[7–10,15,19] our investigation has distinct advantages. Our patient population was limited to de novo TV-ICDs to ensure specificity of the CIED designation. Identified risk factors were limited to those that may be available to a clinician prior to implant, thereby having the practical application of mitigating device infection risk. Finally, we analyzed the outcome of device infection beyond the first year post implant, which is longer than that performed in previous studies.[7–10,19] In this study, we assessed the rate of device infection for de novo TV-ICD patients in a Medicare population and identified risk factors associated with infection within and beyond 1 year of device placement. Time-to-event analysis revealed a rapid onset of infections, followed by a persistent post-implantation risk. Overall, the rate of device infection was 1.9%, with 46% of episodes occurring after 90 days and 16% occurring after 1 year. This study identifies several risk factors of infection that were not previously reported in prior studies, including drug abuse, weight loss, anemia, and depression. In the overall study period, younger age, diabetes mellitus with complications, end-stage renal disease with dialysis, chronic pulmonary disease, valvular disease, drug abuse, anemia, and depression were all associated with a significant increase in infection risk in the multivariable model. Interestingly, during the period beyond 1 year post implant, age <70 years, end-stage renal disease with dialysis, and anemia were associated with an increased risk of device infection. In the

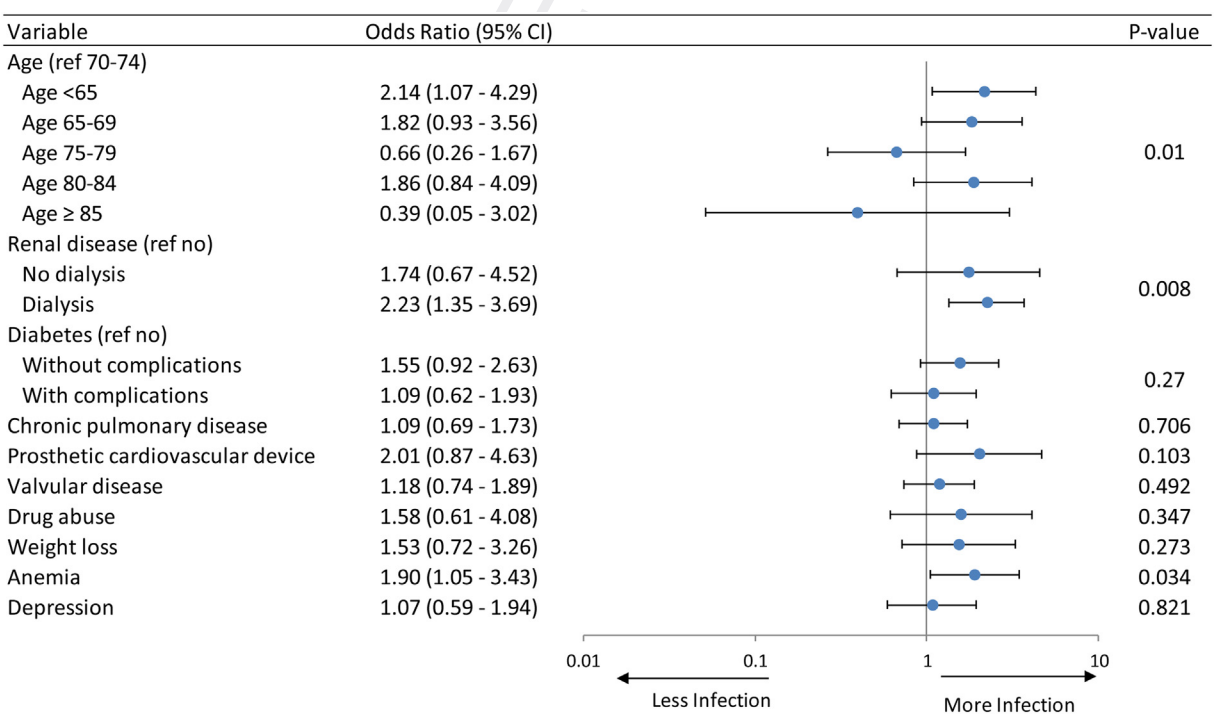

Figure 6 Multivariable analysis of risk factors associated with device infection. Baseline variables associated with an increased risk of late (366–720 days) device infection.

overall study period, end-stage renal disease with dialysis had a 25% increased odds of device infection; when focusing on risk in late infections, the odds increased to almost 125%.

The increased risk associated with renal disease, diabetes mellitus, chronic pulmonary disease, and valvular heart disease is consistent with previous studies.[15] Additionally, younger age as a risk factor associated with infection has been identified in other cohorts.[7,21,22] Of note, patients <65 years old who are enrolled in Medicare FFS are eligible owing to either disability or end-stage renal disease, and are therefore less healthy and are at increased risk of infection; thus these findings may not be generalizable to younger non-Medicare patients.

It is of interest that renal disease with dialysis, which has been identified as a predictor of device infection in previous studies,[15] had an increased effect size beyond the first year in the current analysis. This suggests that mechanisms of infection other than initial surgical site infection complicating the implant procedure may be the mechanism of microbial contamination of the device. Because dialysis utilizes arterial access, the possibility exists that repeated arterial-venous fistula access required with chronic dialysis may introduce blood-borne pathogens that could seed distal devices within the vasculature, including TV-ICDs. Since the S-ICD provides protection from SCD without vascular exposure, distinguishing the risk of surgical site vs vascular pathogen exposure may provide important information to guide device choice. In addition, the use of novel devices that reduce surgical site infection, including antimicrobial pouches,[23] may be better guided by understanding the patients at risk for early surgical site vs later vascular access infection risks. Additional analyses comparing the late infection rate of TV-ICS vs S-ICD infections is warranted to determine the potential risk of bloodstream infections leading to TV device infections.

Assessment of infection risk for individual patients based on real-world data can be a powerful tool for physicians to guide shared clinical decision-making for patients who may benefit from ICDs. While infection-risk scoring systems have been described previously,[7–10] most used limited patient-related parameters and were based on multivariable analyses within the first year or less of implantation. Since 1 in 6 of the total infections occurred more than 1 year after implantation, utilizing risk analysis data over a longer duration is critical for understanding the full risk potential of these patients. Utilization of multivariable models, such as the one presented in this publication, can provide valuable information to tailor the right device(s) for each patient based on their calculated infection risk.

Key surgical interventions to reduce the risk of device infection include use of chlorhexidine wash, antibiotic-coated sutures, recommended antibiotic prophylaxis and its timing of administration, and glycemic control. These practices can result in substantial reductions in infection risk by 54% (1.3% to 0.6% [$P < .03$; confidence interval, 0.25, 1.36]) in 1 investigation, and also resulted in substantial cost savings with avoidance of device removal.[24]

Limitations

Using 100% Medicare administrative and claims data provided a large study population to evaluate for device infection. This could, however, limit generalizability of our results to other distinct populations such as ICD patients under 65 years old without end-stage renal disease or disability, and private payor beneficiaries. Additionally, we limited our patient population to single- and dual-chamber ICDs, which will inherently limit the generalizability to the broader CIED population. The data set did not include medications to identify associated risk factors, such as corticosteroids and anticoagulants. Diagnosis codes for immunosuppression and atrial fibrillation, however, were used as proxies for these agents, though they may not have been specific enough to correlate with an increased infection risk. Owing to the nature of claims analyses, infection was defined based on diagnosis codes or a combination of diagnosis and procedure codes, which did not include microbiologic data and limits the ability to define specific pathogens, as well as the level of infection (local vs systemic). Because the bulk of infections are due to staphylococcal species, the impact of this latter issue should be minimal. Finally, the current model has not been validated in other data sets; such validation should be performed.

Conclusion

The rate of TV-ICD infection of 1.9% was clinically significant in this real-world Medicare population of ICD recipients. Moreover, 1 in 6 infections occurred beyond 1 year of device implantation, and different patient-related factors were predictive of infections >1 year as compared to that for early infections. Understanding factors that contribute to infection risk over a prolonged follow-up period is imperative and could be useful in guiding physicians with device selection prior to implant.

Appendix

Supplementary data

Supplementary data associated with this article can be found Q3 in the online version at https://doi.org/10.1016/j.hrthm.2021.04.014.

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