Long-Term Clinical Outcomes of Subcutaneous Versus Transvenous Implantable Defibrillator Therapy

Tom F. Brouwer, MD,a Dilek Yilmaz, MD,b Robert Lindeboom, PhD,c Maurits S. Buiten, MD, PhD,b Louise R.A. Olde Nordkamp, MD, PhD,a Martin J. Schalij, MD, PhD,b Arthur A. Wilde, MD, PhD,a Lieselot van Erven, MD, PhD,b Reinoud E. Knops, MDa

ABSTRACT

BACKGROUND Transvenous implantable cardioverter-defibrillators (TV-ICDs) improve survival in patients at risk for sudden cardiac death, but complications remain an important drawback. The subcutaneous ICD (S-ICD) was developed to overcome lead-related complications. Comparison of clinical outcomes of both device types in previous studies was hampered by dissimilar patient characteristics.

OBJECTIVES This retrospective study compares long-term clinical outcomes of S-ICD and TV-ICD therapy in a propensity-matched cohort.

METHODS The authors analyzed 1,160 patients who underwent S-ICD or TV-ICD implantation in 2 high-volume hospitals in the Netherlands. Propensity matching for 16 baseline characteristics, including diagnosis, yielded 140 matched pairs. Clinical outcomes were device-related complications requiring surgical intervention, appropriate and inappropriate ICD therapy, and were reported as 5-year Kaplan-Meier rate estimates.

RESULTS All 16 baseline characteristics were balanced in the matched cohort of 140 patients with S-ICDs and 140 patients with TV-ICDs (median age 41 years [interquartile range: 30 to 52 years] and 40% women). The complication rate was 13.7% in the S-ICD group versus 18.0% in the TV-ICD group (p = 0.80). The infection rate was 4.1% versus 3.6% in the TV-ICD groups (p = 0.36). Lead complications were lower in the S-ICD arm compared with the TV-ICD arm, 0.8% versus 11.5%, respectively (p = 0.03). S-ICD patients had more nonlead-related complications than TV-ICD patients, 9.9% versus 2.2%, respectively (p = 0.047). Appropriate ICD intervention (antitachycardia pacing and shocks) occurred more often in the TV-ICD group (hazard ratio [HR]: 2.42; p = 0.01). The incidence of appropriate (TV-ICD HR: 1.46; p = 0.36) and inappropriate shocks (TV-ICD HR: 0.85; p = 0.64) was similar.

CONCLUSIONS The complication rate in patients implanted with an S-ICD or TV-ICD was similar, but their nature differed. The S-ICD reduced lead-related complications significantly, at the cost of nonlead-related complications. Rates of appropriate and inappropriate shocks were similar between the 2 groups. (J Am Coll Cardiol 2016;68:2047–55) © 2016 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Implantable cardioverter-defibrillators (ICDs) improve survival of patients at increased risk of sudden cardiac death (SCD) (1,2). Advances in ICD programming have reduced the burden of shocks, but device-related complications remain an important drawback of transvenous implantable cardioverter-defibrillator (TV-ICD) therapy, resulting in significant morbidity (3). Transvenous sensing and defibrillation...
leads are associated with both infective and mechanical complications, such as lead endocarditis, pneumothorax, venous occlusion, and cardiac perforation (4,5). Lead failure may cause inappropriate shocks and impede delivery of appropriate therapy for ventricular arrhythmias (6–8).

The subcutaneous implantable cardioverter-defibrillator (S-ICD) was designed to eliminate complications related to transvenous leads, but lacks pacing capabilities and can therefore only be used in patients without a need for pacing (9). Studies of the S-ICD have demonstrated clinical efficacy, but also reported a 13.1% inappropriate shock rate at 3 years follow-up, which was significantly reduced with dual-zone programming (10–12). However, direct comparison of clinical outcomes of the available S-ICD cohorts to TV-ICD cohorts is limited by varying patient characteristics, follow-up durations, and definitions of complications.

The objective of the current retrospective study is to compare long-term clinical outcomes of S-ICD and TV-ICD therapy in a propensity score–balanced cohort.

**METHODS**

**STUDY SETTING.** Patients with ICDs implanted in 2 hospitals in the Netherlands, Academic Medical Center (AMC) and Leiden University Medical Center (LUMC), were included. For this analysis, patients implanted with single- and dual-chamber TV-ICDs between 2005 and 2014 at the LUMC, and patients implanted with S-ICDs between 2009 and 2015 at the AMC were selected. During this period of time, LUMC had not adopted the S-ICD into their clinical practice, and therefore, this variation in practice between AMC and LUMC was used to compare the 2 types of ICD therapy. Patients included in the ongoing PRAETORIAN (Prospective, RANDomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy) trial were excluded from this analysis (13). The need for informed consent was waived in both centers due to the observational nature of the study.

**STUDY POPULATION.** At the LUMC, 1,312 patients received a TV-ICD between 2005 and 2014. In the AMC, 148 patients were implanted with an S-ICD between 2009 and 2015. Because baseline characteristics were significantly different, we used propensity score matching as the primary analysis. The devices used were S-ICDs (Boston Scientific, Marlborough, Massachusetts) and TV-ICDs (Biotronik, Berlin, Germany; Boston Scientific; Medtronic, Dublin, Ireland; and St. Jude Medical, Saint Paul, Minnesota). The majority of both S-ICD and TV-ICD patients were implanted under local anesthesia, according to the prevailing local hospital protocol (14). LUMC is an experienced implantation center for TV-ICDs, as is AMC for S-ICDs and TV-ICDs.

**DATA COLLECTION.** Data collection in both centers was performed at regular intervals by reviewing medical records for baseline characteristics, implantation data, and follow-up data on clinical outcomes, complications, and therapy delivery. The survival status of patients was retrieved from municipal civil registries.

**DEFINITION OF OUTCOMES.** Complications were defined as all device related complications requiring surgical intervention. Lead complications were defined as complications requiring replacement or repositioning of the lead, without elective pulse generator replacement. In addition, lead survival was defined as the time between lead implantation and lead failure, with or without elective pulse generator replacement. Appropriate therapy consisted of anti-tachycardia pacing (ATP) only and shocks (whether preceded by ATP or not) for ventricular tachycardia (VT) or ventricular fibrillation (VF). Inappropriate therapy consisted of ATP and shocks for heart rhythms other than VT or VF. Local electrophysiologists adjudicated all arrhythmia episodes.

**STATISTICAL ANALYSIS.** **Entire cohort.** Categorical variables were presented as numbers and percentages, and were compared for the entire cohort using the Fisher exact test. On the basis of their distributions, continuous variables are presented as mean ± SD or median with interquartile range (IQR) (25th to 75th) and compared using the Student t test or Wilcoxon rank sum test.

**PROPENSITY SCORE MATCHING.** Propensity score matching was performed with patients for whom complete baseline variables were available (total N = 1,154). Analysis of excluded patients due to missing baseline data did not suggest selection bias. We used logistic multivariable regression with device type (S-ICD or TV-ICD) as the dependent variable and 16 baseline variables as independent predictors to calculate the propensity score (Table 1, Online Table 1). The Harrell’s C-statistic for the propensity score logistic regression model was 0.89. Patients were 1-to-1 greedy matched using the nearest-neighbor method. There was sufficient overlap in the propensity scores to individually match each S-ICD case to a TV-ICD control (Online Figure 1).
ANALYSIS OF THE MATCHED COHORT. Baseline variables of the matched cohort were compared with paired tests, McNemar and Wilcoxon signed rank, and standardized mean differences were calculated. We used the Kaplan-Meier method to correct for differences in follow-up and estimate the cumulative incidence of outcomes at 5-year follow-up. p Values and hazard ratios (HRs) were calculated using conditional proportional hazards models with adjustment for ICD programming. Conditional proportional hazards assumptions were visually inspected by plotting Schoenfeld residuals.

SENSITIVITY ANALYSES. A sensitivity analysis was performed excluding patients exposed to transient external factors: patients implanted with advisory leads, that is, Medtronic Sprint Fidelis and St. Jude Medical Riata (n = 20) in the TV-ICD group, and an equal number of patients exposed to the operators’ learning curve in the S-ICD group (15,16). Additionally, a sensitivity analysis for patients with a left ventricular ejection fraction ≤ 35% was performed.

All statistical analyses were conducted in R Studio and R version 3.2.2 and the package MatchIt for propensity matching (17,18). All reported p values were 2-tailed, and p < 0.05 was considered statistically significant.

RESULTS

ENTIRE COHORT. In the entire cohort, before matching, most baseline variables were significantly different between the 2 groups (Table 1, left columns). The characteristics of the TV-ICD group represent a typical ICD cohort, with ischemic cardiomyopathy as the predominant diagnosis (64%), significant cardiovascular comorbidity, and a median left ventricular ejection fraction of 34%. The S-ICD group is younger,
with less comorbidity, higher left ventricular ejection fractions (50%), and genetic arrhythmia syndromes as the main diagnosis (53%).

**PROPENSITY-MATCHED COHORT.** In the propensity-matched cohort, S-ICD cases (n = 140) were similar to their TV-ICD controls (n = 140), with no significant differences in any baseline characteristics (**Table 1**, right columns). Compared with the entire cohort, the matched cohort was younger, with a median age of 41 years (IQR: 30 to 52 years) and had a higher left ventricular ejection fraction. In the TV-ICD group, 124 devices (88.6%) were dual-chamber and 16 (11.4%) were single-chamber. The median follow-up duration was longer in the TV-ICD group than in the S-ICD group: 5 years versus 3 years, respectively (p < 0.001).

**ICD PROGRAMMING.** The conditional zones in S-ICDs and the fast VT zones in TV-ICDs were similar, with a median of 190 beats/min (IQR: 180 to 200 beats/min) and 188 beats/min (IQR: 188 to 200 beats/min), respectively; p = 0.77. The unconditional zone in the S-ICD and VF zone in the TV-ICD differed, with medians of 250 beats/min (IQR: 250 to 250 beats/min) and 231 beats/min (IQR: 230 to 231 beats/min), respectively; p < 0.001. Defibrillation testing was performed in 92% of S-ICD and 97% of TV-ICD patients. There were 13 patients (9.3%) in the TV-ICD group with >5% bradycardia pacing (atrial or ventricular) in the first year. In the S-ICD group, 6 patients (4.3%) had a concomitant transvenous pacemaker.

**CLINICAL OUTCOMES. Complications.** The complication rate at 5 years of follow-up was 13.7% (95% CI: 6.4% to 20.3%) in the S-ICD group versus 18.0% (95% CI: 10.5% to 24.8%) in the TV-ICD group; p = 0.80 (**Central Illustration**). **Table 2** presents the
crude number of patients, the type of complications, and the Kaplan-Meier complication rate, corrected for follow-up duration. Lead complications necessitating surgical intervention that was not performed during elective pulse generator replacement occurred more often in the TV-ICD group (11.5%; 95% CI: 5.3% to 17.2%) compared with the S-ICD group (0.8%; 95% CI: 0.0% to 2.2%), p = 0.03 (Figure 1A). Infections occurred in 4.1% (95% CI: 0.5% to 7.7%) of the S-ICD group and in 3.6% (95% CI: 0.0% to 7.1%) of the TV-ICD group; p = 0.03. Of the 20 TV-ICD patients with bacteremia in the TV-ICD group and 1 in the S-ICD group, who also had a concomitant transvenous pacemaker. S-ICD patients had more nonlead-related complications (pocket erosion, defibrillation threshold testing failure, and device failure) than TV-ICD patients: 9.9% (95% CI: 2.0% to 15.4%) and 2.2% (95% CI: 0.0% to 4.6%), respectively; p = 0.047 (Figure 1C). Lead survival was significantly longer in the S-ICD group: 99.2% (95% CI: 97.8% to 100.0%) compared with the TV-ICD group 85.9% (95% CI: 78.46% to 92.7%); p = 0.02 (Figure 1D).

**APPROPRIATE ICD INTERVENTIONS.** Appropriate ICD intervention rates (shocks and ATP) were lower in the S-ICD group, at 17.0% (95% CI: 6.3% to 26.4%) versus 31.3% (95% CI: 22.6% to 39.7%) (Figure 2A). In the Cox proportional hazards model adjusted for ICD programming, the HR for appropriate intervention for the TV-ICD group was 2.42; p = 0.01. Appropriate shock rates were 17% (95% CI: 6.3% to 26.4%) in the S-ICD group and 21.3% (95% CI: 12.6% to 27.3%) in the TV-ICD group (Figure 2B). In the Cox proportional hazards model with adjustment for ICD programming, this difference was not significant; TV-ICD HR: 1.46, p = 0.36.

**INAPPROPRIATE ICD INTERVENTIONS.** Inappropriate ICD interventions (shocks and ATP) were 20.5% (95% CI: 11.5% to 28.6%) in the S-ICD group versus 29.7% (95% CI: 19.7% to 37.6%) in the TV-ICD group (Figure 2C). The HR for inappropriate therapy, adjusted for ICD programming, in the TV-ICD group was 1.29; p = 0.42. The percentage of patients who experienced inappropriate shocks was 20.5% (95% CI: 11.5% to 28.6%) in the S-ICD group and 19.1% (95% CI: 11.6% to 26.0%) in the TV-ICD group (Figure 2D). This difference was not significantly different after adjustment for programming (HR: 0.85 for TV-ICD group; p = 0.64). In 94%, inappropriate shocks from TV-ICDs were for supraventricular tachycardia (atrial fibrillation, atrial flutter, and sinus tachycardia). Inappropriate shocks in S-ICD patients were for oversensing in 85% and for supraventricular tachycardia in 15%.

**FOLLOW-UP.** Five-year patient survival was 96.0% (95% CI: 90.1% to 100.0%) in the S-ICD arm and 94.8% (95% CI: 90.7% to 99.0%) in the TV-ICD arm; p = 0.42. Pulse generator replacement due to battery depletion did not differ at the 5-year follow-up; p = 0.18. Of S-ICD patients, 1.3% (95% CI: 0.0% to 3.7%) were upgraded to a TV-ICD or cardiac synchronization therapy device versus 4.6% (95% CI: 0.5% to 8.5%) in the TV-ICD group; p = 0.26.

**SENSITIVITY ANALYSES.** The first sensitivity analysis, which excluded 20 patients implanted with advisory leads (Medtronic Sprint Fidelis and St. Jude Medical Riata) and the 20 chronologically first S-ICD implants (to account for the learning curve), did not show a difference in clinical outcomes compared with the primary analysis (Online Table 2 and Online Figures 2 to 11). The complication rate at the 5-year follow-up was 14.0% (95% CI: 5.4% to 21.8%) in the S-ICD group versus 13.8% (95% CI: 6.3% to 20.7%) in the TV-ICD group; p = 0.36. Of the 20 TV-ICD patients implanted with advisory leads, 8 (41%, 95% CI: 14.6% to 59.7%) leads failed at 5 years. In the
chronologically first 20 S-ICD implants, there were 3 (15%, 95% CI: 0.0% to 29.3%) complications at the 5-year follow-up.

The second sensitivity analysis, which included patients with left ventricular ejection fractions ≤35%, yielded 38 S-ICD and 51 TV-ICD patients with median ejection fractions of 25% and 28%, respectively. None of the comparisons for clinical outcomes demonstrated a significant difference between the S-ICD and the TV-ICD patients, and trends were similar except for a nonsignificant trend towards more inappropriate shocks in the S-ICD arm (Online Table 3, Online Figures 12 to 21).

**DISCUSSION**

**MAIN FINDINGS.** The current study provides the first balanced comparison of S-ICD and TV-ICD therapy for clinical outcomes during long-term follow-up.

The main findings of this study are as follows: the complication rate was similar, but the nature of the complications differed significantly. Appropriate and inappropriate shocks were delivered at equal rates in both groups. TV-ICD patients received more appropriate and inappropriate therapy when ATP was also taken into account.

**COMPLICATIONS.** The complication rates in both groups were similar, but the nature of complications differed significantly, as could be expected due to the different designs of the devices. The weakest link of the TV-ICD system is the lead, which remained true after exclusion of advisory leads. In the S-ICD group, inappropriate sensing resulted in explantation of the device in 1 patient and in the need for lead repositioning in another. Improvements of the S-ICD algorithm may avoid sensing issues. The observed complication rate at the 5-year follow-up is similar to that in the SCD-HeFT (Sudden Cardiac Death in Heart
Failure Trial) (9% acute and 5% long-term complications during 3.8 years of follow-up) and previous reports on complications in younger patients (22% during 4.5 years of follow-up) (2,19).

THERAPY. The difference in appropriate therapy may be explained by the ability of TV-ICDs to deliver ATP instantly after VT detection, whereas the S-ICD has a longer charging time, which allows nonsustained VTs to terminate. Although ATP has been demonstrated to successfully terminate approximately 70% of VT episodes, it did not result in fewer appropriate shocks in this cohort (20–23). This may be explained by the fact that patients with ischemic scars represented a minority in this study.

The incidences of inappropriate therapy and inappropriate shocks were high in both groups, but are in line with a previous publication on younger ICD patients (19). The reasons for inappropriate shocks differed between the 2 groups: the majority of inappropriate shocks by TV-ICDs were for supraventricular tachycardia and those by S-ICDs were for cardiac over-sensing.

OTHER ENDPOINTS. This study did not find a difference in patient survival rate, but may be underpowered to detect such a difference. None of the patients died of SCD and all spontaneous ventricular arrhythmias were successfully treated in both groups. The number of patients that required upgrade to a CRT device was low, but similar to what has previously been reported (24). The shorter battery longevity of the S-ICD, as projected by the manufacturer, was not detected in this analysis, but is likely to be demonstrated with longer follow-up.

SENSITIVITY ANALYSES. The first analysis excluded patients that were implanted with advisory leads in the TV-ICD group and during the S-ICD
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which are associated with specific risks (27). The observed rate of dual-chamber ICDs resulted from the implanter’s preference, as opposed to a need for chronic bradycardia pacing, a tendency that was also reported in another large cohort (28). Fourth, there may be hospital bias present. This was explored by comparing dual-chamber ICD complications in both centers, which did not reveal a difference.

CONCLUSIONS

In this matched cohort of S-ICD and mostly dual-chamber TV-ICD patients, complication rates were similar, although their nature differed. The S-ICD effectively reduced lead-related complications at the cost of nonlead-related complications. Both appropriate and inappropriate shock rates were similar.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Tom F. Brouwer, Department of Cardiology, Academic Medical Center, PO Box 22700; 1100 DE Amsterdam, the Netherlands. E-mail: t.f.brouwer@amc.uva.nl.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: S-ICD devices reduce lead-related complications compared with TV-ICDs, but not the overall complication rate, which includes delivery of inappropriate shocks.

TRANSLATIONAL OUTLOOK: Randomized trials that encompass larger, more diverse patient cohorts and longer follow-up are needed to clarify the advantages and disadvantages of these 2 approaches to ICD therapy.

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APPENDIX For supplemental tables and figures, please see the online version of this article.