Inappropriate Implantable Cardioverter-Defibrillator Shocks
Incidence, Predictors, and Impact on Mortality

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Objectives The purpose of this study was to assess the incidence, predictors, and outcome of inappropriate shocks in implantable cardioverter-defibrillator (ICD) patients.

Background Despite the benefits of ICD therapy, inappropriate defibrillator shocks continue to be a significant drawback. The prognostic importance of inappropriate shocks outside the setting of a clinical trial remains unclear.

Methods From 1996 to 2006, all recipients of defibrillator devices equipped with intracardiac electrogram storage were included in the current analysis and clinically assessed at implantation. During follow-up, the occurrence of inappropriate ICD shocks and all-cause mortality was noted.

Results A total of 1,544 ICD patients (79% male, age 61 ± 13 years) were included in the analysis. During the follow-up period of 41 ± 18 months, 13% experienced ≥1 inappropriate shocks. The cumulative incidence steadily increased to 18% at 5-year follow-up. Independent predictors of the occurrence of inappropriate shocks included a history of atrial fibrillation (hazard ratio [HR]: 2.0, p < 0.01) and age younger than 70 years (HR: 1.8, p < 0.01). Experiencing a single inappropriate shock resulted in an increased risk of all-cause mortality (HR: 1.6, p < 0.01). Mortality risk increased with every subsequent shock, up to an HR of 3.7 after 5 inappropriate shocks.

Conclusions In a large cohort of ICD patients, inappropriate shocks were common. The most important finding is the association between inappropriate shocks and mortality, independent of interim appropriate shocks. (J Am Coll Cardiol 2011;57:556–62) © 2011 by the American College of Cardiology Foundation

Ventricular tachycardia (VT), deteriorating to ventricular fibrillation (VF) is responsible for an estimated one third of all cardiovascular mortality worldwide (1–3). Several important clinical trials have shown that the implantable cardioverter-defibrillator (ICD) provides a substantial and significant reduction in mortality in survivors of sudden cardiac arrest and high-risk patients with cardiovascular disease (4–9). Despite proven survival benefits, ICD treatment still has drawbacks, one of the most important being shocks delivered for causes other than potentially life-threatening VT or VF. These inappropriate shocks are painful, psychologically disturbing, and potentially arrhythmogenic (10–13). Recently, a subgroup analysis of 2 major ICD clinical trials reported on the prognosis of ICD shocks and raised concern by establishing an association between inappropriate shocks and increased mortality (14,15). However, extrapolating these results to ICD recipients into everyday or routine clinical practice is difficult because these clinical trials comprised a selected population. Therefore, we analyzed a large population of ICD patients with long-term follow-up outside the setting of a clinical trial to evaluate the occurrence of inappropriate ICD shocks, to identify potential predictive parameters for inappropriate shocks, and to assess the impact of inappropriate shocks on long-term outcome.

Methods

Patient population. Since 1996, all patients who received an ICD at the Leiden University Medical Center were recorded in the departmental Cardiology Information System (EPD-vision, Leiden University Medical Center). For the current analysis, all ICDs implanted up to 2006 were...
included to ensure a minimum in follow-up duration. Eligibility for ICD treatment was determined in accordance with the international guidelines and included patients with sustained VT and patients with a severely depressed left ventricular ejection fraction, regardless of previous ventricular arrhythmia (16–18). As a result of advancing guidelines, the eligibility has changed over time.

To retrieve accurate information about the origin and classification (i.e., appropriate vs. inappropriate) of ICD shocks, only recipients of ICDs equipped with intracardiac electrogram storage were included in the current analysis. Baseline characteristics were collected to identify potential predictors of inappropriate shocks. In addition, the effect of inappropriate shocks on mortality was assessed.

**Device implantation and programming.** All defibrillator systems were implanted in the pectoral region. During the implant procedure, testing of sensing and pacing threshold and defibrillation threshold was performed. The systems used were manufactured by Biotronik (Berlin, Germany), Medtronic (Minneapolis, Minnesota), Boston Scientific (Natick, Massachusetts), and St. Jude Medical (St. Paul, Minnesota).

Defibrillators were programmed as follows: ventricular arrhythmia faster than 150 beats/min was monitored by the device without consequent defibrillator therapy (zone 1). Ventricular arrhythmias faster than 188 beats/min were initially attempted to be terminated with 2 bursts of anti-tachycardia pacing and, after continuation of the arrhythmia, with defibrillator shocks (zone 2). In the case of a ventricular arrhythmia faster than 210 beats/min, device shocks were the initial therapy (zone 3). Furthermore, atrial arrhythmia detection was set to >170 beats/min with supraventricular tachycardia discriminators enabled. In all devices, stability and sudden onset algorithms were activated to reduce the occurrence of inappropriate shocks (19). Moreover, additional discriminators were activated in dual-chamber ICDs and cardiac resynchronization therapy defibrillators (20,21). Settings were adapted only when clinically indicated (i.e., hemodynamic well-tolerated VT at high rate, VT in the monitor zone).

**Follow-up.** In the Dutch health care system, the implanting center is responsible for the device follow-up, which is performed every 3 to 6 months after implantation. At every follow-up, device storage was checked for delivered therapy (appropriate/inappropriate). Adjudication of the delivered therapy was performed by a trained electrophysiologist.

An inappropriate shock was defined as an episode, starting with a shock not delivered for VT or VF and ending if sinus rhythm was redetected by the ICD. Consequently, it was possible that multiple inappropriate shocks occur within 1 episode. If a subsequent episode started within 5 min after the previous episode ended, it was not considered as a new episode. Furthermore, the cause of an inappropriate shock was categorized into supraventricular tachycardia (including atrial fibrillation [AF]), sinus tachycardia, or abnormal sensing.

Patients with missing data for more than 6 months were considered lost to follow-up.

**Statistical analysis.** Continuous variables were presented as mean ± SD and categorical variables as number and percentage. Cumulative event rates were calculated by using the Kaplan-Meier method and log-rank test, in which patient death and device replacement were considered censoring events. Causes of inappropriate shocks for the different device types were compared using the chi-square test. Predictors of inappropriate shocks were determined by the method of Cox proportional hazards regression. First, univariate analysis was performed, containing all baseline variables and interim appropriate shocks. Subsequently, all variables with a p value <0.10 were included in the multivariate analysis. A p value <0.25 was considered as statistically significant for the multivariate regression. To examine differences in the occurrence of inappropriate shocks per time span of ICD implantations, patients were divided into 2 groups by the median calendar year of ICD implantations. A log-rank test was used to compare the cumulative event rates between both groups.

The relationship between inappropriate shocks and all-cause mortality was assessed using a Cox proportional hazard model with first inappropriate shock or multiple inappropriate shocks (≥5 shocks) as a time-dependent covariate, adjusting for commonly used predictors of all-cause mortality (history of AF, age older than 70 years [22], New York Heart Association (NYHA) functional class higher than II, renal clearance <90 ml/min [determined with the Cockroft-Gault formula] [23], QRS duration >120 ms, use of β-blockers [22], and interim appropriate shocks [15]).

Interim appropriate shocks were defined as appropriate ICD shocks before an inappropriate ICD shock and considered time-dependent covariates in analyses for prediction of inappropriate shocks as well as for prediction of all-cause mortality. The calculated relationship was presented as a hazard ratio (HR) with a 95% confidence interval (CI).

The statistical software program SPSS version 16.0 (SPSS, Inc., Chicago, Illinois) was used for statistical analysis. A p value <0.05 was considered significant, with the exception of multivariate analyses.

**Results**

**Patient population.** From 1996 to 2006, 1,658 patients received an ICD system with intracardiac electrogram technology according to the international guidelines (16–18). One hundred fourteen patients (7%) were lost to follow-up. The remaining 1,544 patients (93%) constituted the patient population. Of these patients (79% men, average age 61 ± 13 years), 56% received an ICD for primary prevention and
64% had ischemic heart disease. Baseline patient characteristics are summarized in Table 1.

### Incidence of inappropriate shocks.

During the follow-up period of 41 ± 18 months, 204 of 1,544 patients (13%) experienced a total of 665 inappropriate ICD shocks. The average time from implantation to first inappropriate shock was 17 ± 16 months. The cumulative event rate for first inappropriate shocks was 7% (95% CI: 5% to 9%) at 1 year, 10% (95% CI: 7% to 12%) at 2 years, and 11% (95% CI: 9% to 14%) at 3 years (Fig. 1). A second inappropriate shock was experienced by 73 of 204 patients (36%) with an average time from first to second shock of 11 ± 11 months. The cumulative event rate for a second inappropriate shock was 8% (95% CI: 6% to 10%) at 1 year, 12% (95% CI: 9% to 14%) at 2 years, and 14% (95% CI: 11% to 16%) at 3 years (Fig. 3).

### Predictors of inappropriate shocks.

To determine specific clinical parameters predicting the occurrence of inappropriate ICD shocks, the univariate Cox model disclosed that age younger than 70 years (HR: 1.7, 95% CI: 1.1 to 2.3; p < 0.01), history of AF (HR: 2.0, 95% CI: 1.5 to 2.7; p < 0.01), nonischemic heart disease (HR: 1.3, 95% CI: 1.0 to 1.8; p = 0.04), nonuse of statins (HR: 1.4, 95% CI: 1.0 to 1.8; p = 0.03), and interim appropriate shocks (HR: 1.6, 95% CI: 1.0 to 2.7; p = 0.04) were independent predictors of inappropriate shocks (Table 2). By multivariate analysis,
In multivariate risk analysis, adjusted for baseline and interim variables (history of AF, age younger than 70 years, no statin use, and interim appropriate shocks), patients who received an ICD after May 2004, compared with before May 2004, tended to experience more inappropriate shocks (HR: 1.3, 95% CI: 1.0 to 1.8; \(p_{\text{H0.05}}\)).

**Causes and differences between device types.** The main cause of inappropriate shocks was misdiagnosis of supraventricular tachycardia, occurring in 155 of the 204 patients (76%). The mean ventricular cycle length at the time of a patient’s first inappropriate shock for supraventricular tachycardia was 299 ± 39 ms and occurred predominantly in ICD program zone 2 (60%).

As can be seen in Table 3, comparison per device type did not show significant differences in the occurrence of inappropriate shocks. However, the cause of inappropriate shocks did differ between device types. Patients with a single-chamber ICD received significantly more shocks resulting from misdiagnosis of sinus tachycardia than patients with a dual-chamber ICD (24% vs. 8%, \(p = 0.02\)). Furthermore, patients with cardiac resynchronization therapy with a defibrillator tended to experience more inappropriate discharges due to abnormal sensing than ICD recipients with a single-chamber ICD (15% vs. 8%, \(p = 0.28\)).

**Effect of inappropriate shocks on survival.** A total of 298 patients (19%) died during the study follow-up. Compared with patients without inappropriate shocks, the occurrence of the first inappropriate shock tended to increase the risk of all-cause mortality (HR: 1.4, 95% CI: 1.0 to 2.0; \(p = 0.07\)). Adjustment for potential confounders (history of AF, age older than 70 years, NYHA functional class higher than II, renal clearance <90 ml/min, QRS duration >120 ms, beta-blocker use, and interim appropriate shocks) demonstrated that the occurrence of an initial inappropriate shock was related to a 60% increase in risk of mortality (HR: 1.6, 95% CI: 1.1 to 2.3; \(p = 0.01\)). Moreover, adjusted time-dependent mortality risk of subsequent inappropriate shocks had an HR of 1.4 (95% CI: 1.2 to 1.7, \(p = 0.01\)) per additional shock, up to an HR of 3.7 after experiencing 5 inappropriate shocks (Table 4).

**Discussion**

The main findings of the current study on the incidence, predictors, and outcome of inappropriate shocks can be summarized as follows: 1) the cumulative incidence of inappropriate shocks was 7% at 1-year follow-up, 13% at 3-year follow-up, and 18% at 5-year follow-up; 2) misdiagnosis of supraventricular tachycardia was the leading cause (76%) of inappropriate shocks; 3) age younger than 70 years, history of AF, no statin use, and interim appropriate shocks were predictors of inappropriate shocks; and 4) inappropriate shocks were associated with a higher risk of all-cause mortality.

**Incidence.** In major randomized clinical trials, the occurrence of inappropriate ICD therapy (i.e., anti-tachycardia pacing and shocks) is well assessed, ranging from 10% to 24% over 20 to 45 months of follow-up (24). However, lower incidences were
reported when assessing inappropriate shocks only, such as 9% in the AVID (Antiarrhythmics versus Implantable Defibrillators) trial (15) and 11.5% in the MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) (25), both reported during 2-year follow-up. The current analysis demonstrated a comparable cumulative event rate of 10% at 2-year follow-up and showed that this incidence steadily increased to 18% at 5-year follow-up. In addition, more than one-half of the patients who received a single inappropriate shock experienced another one within the 5-year follow-up.

**Predictors.** Because more than one-half of all inappropriate shocks are due to misdiagnosis of AF, several studies found a history of AF was the most significant baseline clinical predictor of inappropriate shocks (15,26–31). Then again, these studies showed less consistency in identifying other predictors. For instance, Hreybe et al. (27) demonstrated patients with severe symptomatic heart failure (NYHA functional classes III and IV) to be at increased risk of inappropriate shocks, whereas Nanthakumar et al. (28) demonstrated NYHA functional class I as an independent predictor of inappropriate shocks. Furthermore, other predictors included the absence of coronary artery disease, use of β-blockers, ICD device type, history of smoking, no statin use, younger age, and increased diastolic blood pressure (15,26,27,29,31).

In the current study, multivariate analysis demonstrated that ICD recipients with a history of AF have a significantly higher risk of inappropriate shocks (HR: 2.0, p < 0.01). Additionally, the present study showed that age younger than 70 years independently predicted the occurrence of inappropriate shocks (HR: 1.8, p < 0.01). Most likely, this is due to the fact that 23% of all inappropriate shocks were caused by abnormal sensing and sinus tachycardia, both associated with younger age (32).

The large cohort and long follow-up assessed in the current analysis might provide more accurate identification of predictors of inappropriate shocks than that proposed in previous studies.

**Prevention of inappropriate shock over time.** Ever since the first implantation, ICDs are under constant development to improve treatment of tachyarrhythmias and decrease adverse events. Advanced algorithms, multiple sensing leads, and improved device programming should reduce the occurrence of inappropriate shock (19–21). Interestingly, the current study did not confirm this theory. Patients who received their ICD system after May 2004, compared with before May 2004, did...
not experience fewer inappropriate shocks (Fig. 3). In addition, multivariate analysis, adjusted for baseline and interim variables, even showed that these patients were at increased risk of experiencing inappropriate shocks. The most plausible explanation for this paradox is found within the evolving guidelines, which intermittently change ICD patient population from mostly secondary prevention patients to mostly primary prevention patients. In general, primary prevention patients are in poor cardiac condition (33), which could result in higher risk and prevalence of AF—the strongest predictor of the occurrence of inappropriate shocks. Hence, the increasing number of primary prevention patients could downgrade the effect of advanced ICD technology in reducing the occurrence of inappropriate shock.

**Single-chamber ICDs versus dual-chamber ICDs versus cardiac resynchronization therapy defibrillators.** With supraventricular arrhythmias as the principal cause of inappropriate shocks, one might hypothesize that additional sensing information would improve discrimination between supraventricular tachyarrhythmias and ventricular tachyarrhythmias to prevent inappropriate therapy. Therefore, in theory, dual-chamber ICDs should perform better than single-chamber ICDs. However, in the literature, there are doubts regarding the performance of devices with extra sensing/pacing leads compared with single-chamber ICDs. Theuns et al. (34) performed a prospective, randomized study to evaluate the performance of tachyarrhythmia detection algorithms in single- and dual-chamber ICDs, but did not find a significant reduction in the number of inappropriate arrhythmia classifications. Other studies found similar results (20,35,36). In contrast, a randomized trial conducted by Friedman et al. (37) demonstrated a small but significant reduction of inappropriate supraventricular tachyarrhythmias detection (8.6%) when using optimized programmed dual-chamber ICDs compared with single-chamber ICDs. These findings were supported by Soundarraj et al. (29).

In the present study, no significant differences were observed in the incidence of inappropriate shocks when comparing the 3 different device types.

**Long-term outcome.** Recent subgroup analysis of the MADIT II and the SCD-HeFT (Sudden Cardiac Death In Heart Failure Trial) found an association between increased mortality risk and ICD shocks, irrespective of appropriateness (14,15). For appropriate shocks, this association is explicable because patients who receive appropriate shocks also have VT or VF due to progressively deteriorating cardiac condition. In contrast, it was unforeseen that this association also applied to inappropriate shocks.

The present study confirmed this finding in routine clinical practice, outside the setting of a clinical trial, by demonstrating a significant correlation between inappropriate shocks and death. Moreover, the risk of all-cause mortality increased per delivered inappropriate shock; up to an HR of 3.7 after experiencing 5 inappropriate shocks.

One might postulate different explanations for the increased risk of death, including: 1) myocardial injury resulting in deterioration of left ventricular ejection fraction; 2) increased anxiety and depression associated with increased mortality; and 3) the indirect result of AF, being the leading mechanism for inappropriate shocks and also associated with an increased risk of mortality (38-40). From the current study, it is difficult to favor one explanation over another. However, various studies have supported the first explanation because they found increased markers for myocardial damage after uncomplicated ICD testing at implantation, implying cardiac tissue damage due to these high-voltage electrical discharges (38,41,42).

When comparing the results of the subgroup analysis of the MADIT II and SCD-HeFT with the current study, a notable difference was seen in the risk of all-cause mortality after experiencing an inappropriate shock (HR: 2.2 vs. HR: 2.0 vs. HR: 1.6, respectively). This difference could be explained if one assumed that (inappropriate) ICD shocks indeed cause myocardial tissue injury. In addition, ICD patients with poor cardiac condition and left ventricular function have less reserve to withstand extra cardiac damage. Therefore, inappropriate shocks will have more adverse consequences in a population with reduced cardiac function, as assessed in the MADIT II and SCD-HeFT (5,14).

Overall, it remains difficult to state that the higher risk of death was indeed caused by inappropriate ICD shocks, but so far, 3 large independent studies demonstrated an adverse relationship between ICD shocks and patient survival.

**Study limitations.** The current study used prospectively collected data from a single-center ICD registry. Because ICDs were implanted over a 10-year period, evolving and expanding guidelines for the implantation of ICDs, device programming, and pharmacological treatment of arrhythmias could have created a heterogeneous population. Furthermore, we attempted to control for potential confounders using multivariate statistical with time-dependent covariate analysis. However, the influence of potentially included unknown confounders could not be ruled out.

**Conclusions**

The current study demonstrates that in an ICD patient cohort, outside the setting of a clinical trial, inappropriate shocks occur in 13% of ICD recipients, mainly due to misdiagnosis of supraventricular tachycardia. Clinical predictors of inappropriate shocks were younger age, history of AF, no statin use, and interim appropriate shocks. Finally, inappropriate shocks were associated with a higher risk of all-cause mortality, which increased per delivered inappropriate shock and was independent of interim appropriate shocks.

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