The ICD for Primary Prevention in Patients With Inherited Cardiac Diseases

Indications, Use, and Outcome: A Comparison With Secondary Prevention

Louise R.A. Olde Nordkamp, MD; Arthur A.M. Wilde, MD, PhD; Jan G.P. Tijssen, PhD; Reinoud E. Knops, MD; Pascal F.H.M. van Dessel, MD, PhD; Joris R. de Groot, MD, PhD

Background—Indications for prophylactic implantable cardioverter-defibrillator (ICD) therapy in patients with inherited cardiac diseases stem from observational studies and are uncertain. This study evaluates the efficacy and harm rate of ICD implantations for primary prevention compared with secondary prevention in inherited cardiac diseases.

Methods and Results—Between January 1, 1993, and April 1, 2011, 354 patients with inherited cardiac diseases were treated with ICDs. Incidence rates of appropriate shocks in primary prevention patients with arrhythmogenic right ventricular cardiomyopathy and hypertrophic cardiomyopathy were 4.2 to 6.7/100 patient-years, whereas the risk for appropriate shocks in primary prevention patients with Brugada syndrome, long QT syndrome, or carrying the DPP6 haplotype approached zero. Conversely, in secondary prevention patients there was a considerably higher incidence rate of appropriate shocks. None of the indications for primary prevention were associated with appropriate shock therapy. One hundred twenty-three patients (35%) experienced ICD-related adverse events.

Conclusions—For Brugada syndrome, long QT syndrome, and DPP6 the efficacy of an ICD for primary prevention contrasts with the amount of harm, and factors that formed the indication for ICD implantation do not relate to the occurrence of appropriate shocks. The higher appropriate discharge rates in arrhythmogenic right ventricular cardiomyopathy and hypertrophic cardiomyopathy compared with primary electric diseases might result from a more advanced risk stratification scheme in these inherited cardiomyopathies. (Circ Arrhythm Electrophysiol. 2013;6:91-100.)

Key Words: genetic heart disease ■ implanted cardioverter-defibrillators ■ risk factors ■ tachyarrhythmias

Using implantable cardioverter-defibrillators (ICDs) is effective in preventing sudden cardiac death (SCD) in patients with ischemic and nonischemic heart disease. Most of these patients are in their sixth or seventh decade of life.

Clinical Perspective on p 100

The increasing awareness and diagnosis of patients with a genetic predisposition for SCD has augmented the number of young ICD recipients. In these patients, appropriate selection criteria for ICD implantation is ill-defined because of the lack of randomized trials, and relies on nonrandomized studies and consensus statements. ICD therapy is undisputed in survivors of ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) because of the risk of recurrence. Indications for prophylactic device implantation in patients without spontaneous VT/VF are uncertain, but there might be overuse regardless of risk stratification in certain disease categories. The group of patients with a genetic predisposition to SCD is likely to grow further in the coming years because they are less prone to nonarrhythmic death compared with the general ICD population. These young and active patients are more likely to encounter device complications during the course of many decades of expected use, including inappropriate shocks and lead-related problems, which subsequently might lead to morbidity and reduced quality of life.

We do not know whether the potential adverse effects on morbidity outweigh the efficacy in this population. Therefore, we examined efficacy and harm rate in ICD recipients with different inherited diseases implanted for primary prevention compared with secondary prevention.

Methods

Study Design

This is a single-center retrospective study. Patients in whom the indication for ICD therapy was set in our hospital between January 1, 1993, and April 1, 2011, for Brugada syndrome (BrS), long QT syndrome (LQTS), hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricle cardiomyopathy/dysplasia (ARVC), dilated cardiomyopathy with conduction disease caused by a mutation in the Lamin A/C gene (LMNA), dilated cardiomyopathy caused by a mutation in the Phospholamban gene (PLN), catecholaminergic polymorphic VT, short QT syndrome, short-coupled torsade de pointes (TdP),
familial VF carrying a DPP6 haplotype (DPP6),
12 idiopathic familial VT/VF or for inherited cardiac disease not otherwise specified were included in this study. Forty-eight patients with BrS were previously
reported in the multicenter FINGER (France, Italy, Netherlands, Germany) registry4 and 28 patients with LQTS in a multicenter study.5
The most recent data available before first ICD implants were extracted from medical records. These included demographic data, clinical
information (age at onset, family history of SCD, genetic testing, and medical therapy), genotype (when available), ECG data, 24-hour Holter
monitoring, echocardiography, and electrophysiological studies (EPS; when available). ICD-related data included type of ICD (ie, single-
dual-chamber, or biventricular), type of lead, indication for implant and device interrogation data including nonsustained and sustained ventricu-
lar and supraventricular episodes. The institutional review board of our institution waived the requirement for informed consent.

Definitions
BrS was defined as the presence of ST-segment elevation ≥2 mm direct-
ly followed by a negative T-wave (type 1 ECG) in ≥1 right precordial
lead (V1–V3) in the presence or absence of a sodium channel-blocking
agent.13 LQTS was defined according to the diagnostic criteria de-
scribed by Schwartz et al.14 The QT interval was assessed from lead
II/V5 and corrected for heart rate using Bazett formula. HCM was di-
agnosed when a left ventricular wall thickness ≥15 mm in the absence
of another cardiac or systemic disease that could have accounted for
the hypertrophy.15 Patients with ARVC fulfilled the diagnostic criteria
(either borderline or definite) of the Task Force criteria, last updated in
2010.16 Patients with short-coupled variant of TdP had a typical TdP
with an unusually short coupling interval (always <300 ms) of the first
beat of the TdP or of the isolated ventricular premature beats.17 Patients
with idiopathic familial VF had a presumed risk of SCD based on the
presence of 1 or more family members with a history of sustained VT/
VF and in the absence of any of the other diseases entities. The cat-
egory, inherited cardiac disease not otherwise specified were all other patients with overlap genetic arhythmia syndromes or mutation-spe-
cific diseases that did not fit the criteria of the other disease entities (eg,
including a patient with a combination of LQTS and HCM, and a pa-

tient with a mitochondrial encephalomyopathy). In all patients, in case
of doubt on the diagnosis, clinical characteristics and ECGs were re-

Reports of all device interrogations with ICD therapy were validated
by a cardiologist-electrophysiologist, and systematically analyzed. An
ICD shock was considered appropriate if it resulted from sustained VT/
VF, assessed by device interrogation. Absence of VT/VF when a shock
was delivered was defined as an inappropriate shock. Electric storm
was defined as the occurrence of 3 or more separate episodes of VT/VF
requiring shock therapy within a 24-hour period. In diseases associated
with the occurrence of monomorphic VTs (HCM, ARVC, LMNA, and
PLN) the rate of appropriate therapy by antitachycardia pacing (ATP)
was also calculated. Serious harm was defined as the presence of ei-
ther an inappropriate shock or an ICD-related complication. Secondary
prevention was defined as ICD implant after resuscitated cardiac arrest,
sustained VT/VF or syncope deemed of cardiac origin. The absence of
a secondary prevention indication defined a primary prevention. A
family history of SCD was defined as a sudden death <60 years of ≥1
family members of first or second degree.

Statistics
All data were analyzed with SPSS (18.02 SPSS Inc. Chicago, IL).
Categorical data are displayed as percentage and compared between
groups using a χ2 test. The Shapiro–Wilk test was used to verify
whether continuous data followed a normal distribution. Normally
distributed continuous data were described as mean (SD) and com-
pared between groups using Student t tests. Continuous data not nor-
mally distributed were expressed as median and compared between
groups using the Mann–Whitney U test. Incidence rates of appropri-
ate shocks or ICD harm were calculated as the number of events per
100 patient-years of observation and 95% confidence intervals (CIs)
using the Fisher exact test. For this calculation, observation started
at implantation and ended when patients experienced an event or
were censored. Univariable Cox-regression analyses were performed
to identify factors associated with the outcome of appropriate shock
therapy. P value <0.05 were considered statistically significant.

Results
Patient Characteristics
From January 1, 1993, to April 1, 2011, 354 patients with inher-
ited cardiac diseases had an ICD implanted in our institution. The
underlying inheritable cardiac diseases are shown in Figure 1.

ICD Implantation
Mean age at the time of ICD implantation was 41±16 years
(range, 1 month to 82 years), and 72% of the patients were
<50 years of age at the time of implantation (Appendix I in
the online-only Data Supplement). The notion that 94% of all
first implantations were performed between 2001 and 2011
and 55% between 2006 and 2011 reflects the increase in ICD
use in patients with inherited cardiac disease.

Single-chamber ICDs were initially implanted in 57% of the
patients, whereas dual-chamber ICDs were initially implanted
in 42% of the patients. Three patients (1%) with dilated cardio-
myopathy due to LMNA or PLN mutations received biventricu-
lar ICD systems. ICDs were replaced in 139 patients (39%),
of whom 10 with an initial single-chamber system had an
upgrade to dual-chamber (n=9) or biventricular (n=1) systems.

ICD Efficacy
Patients with catecholaminergic polymorphic VT (n=4), short
QT syndrome (n=2), short-coupled torsade des pointes (n=5),
and inherited cardiac disease not otherwise specified (n=6)
were excluded from the ICD efficacy analysis, because the
groups were too small.

Brugada Syndrome
Seventy-five patients with BrS (88% male; mean age, 46±12
years) received an ICD. ICDs were implanted for primary
prevention in 29 (39%) patients, and for secondary prevention
in 46 (61%). Inducible sustained ventricular arrhythmia with
EPS was the most common indication for primary prevention
(n=23, 79%; Table 1). Most of these patients (17/23, 74%) had
an ICD implantation before 2006.

With a median follow-up of 62 (interquartile range [IQR], 32–
91) months, no primary prevention patient and 7 of 46 secondary
prevention patients received an appropriate ICD shock (P=0.04),
mostly on VF (Appendix II in the online-only Data Supplement).
Thus, for primary prevention inducibility of VT/VF at EPS was not
predictive for appropriate shock therapy (Figure 2A). The incidence
rate of appropriate shocks was 0/100 patient-years for primary and
3.0/100 patient-years (CI, 1.2–6.2) for secondary prevention.

Hypertrophic Cardiomyopathy
Sixty-seven patients with HCM (67% male; mean age, 43±17
years) received an ICD. Thirty-six (54%) were implanted for
primary prevention, of whom 53% had ≥2 risk factors for
SCD. Non-sustained ventricular tachycardia (NSVT) or a
family history of SCD (with or without a malignant mutation)
was the most common indication for primary prevention in
patients with only one risk factor for SCD.
With a median follow-up of 39 (IQR, 20–73) months, 4 of 36 primary prevention patients, of whom 3 had 2 risk factors for SCD, and 7 of 31 secondary prevention patients received appropriate shocks ($P=0.21$). Two or more major risk factors were associated with a 2.6-fold risk (CI, 0.27–25) for appropriate shocks in primary prevention. A reduced left ventricular ejection fraction (LVEF) was more prevalent in patients with appropriate shocks compared with patients without.

### Table 1. Indications for ICD Implantation

<table>
<thead>
<tr>
<th></th>
<th>Brugada Syndrome</th>
<th>Hypertrophic Cardiomyopathy</th>
<th>Long QT Syndrome</th>
<th>ARVC</th>
<th>Familial VF With DPP6 Haplotype</th>
<th>Cardiomyopathy With LMNA Mutation</th>
<th>Cardiomyopathy With PLN Mutation</th>
<th>Idiopathic Familial VF</th>
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<tbody>
<tr>
<td></td>
<td>N=75 (%)</td>
<td>N=67 (%)</td>
<td>N=55 (%)</td>
<td>N=47 (%)</td>
<td>N=32 (%)</td>
<td>N=24 (%)</td>
<td>N=20 (%)</td>
<td>N=13 (%)</td>
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<td><strong>Secondary prevention</strong></td>
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<tr>
<td>Genotype positive</td>
<td>46 (61)</td>
<td>31 (46)</td>
<td>41 (75)</td>
<td>33 (70)</td>
<td>2 (6.3)</td>
<td>1 (4.2)</td>
<td>8 (40)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Sustained VT/VF</td>
<td>14 (30)</td>
<td>17 (55)</td>
<td>24 (59)</td>
<td>24 (73)</td>
<td>2 (100)</td>
<td>1 (100)</td>
<td>6 (80)</td>
<td>4 (80)</td>
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<tr>
<td>Cardiac syncope</td>
<td>32 (70)</td>
<td>14 (45)</td>
<td>17 (41)</td>
<td>9 (27)</td>
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<td><strong>Primary prevention</strong></td>
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<tr>
<td>Genotype positive</td>
<td>29 (39)</td>
<td>36 (52)</td>
<td>14 (25)</td>
<td>14 (30)</td>
<td>30 (94)</td>
<td>23 (96)</td>
<td>12 (60)</td>
<td>8 (62)</td>
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<tr>
<td>NSVT</td>
<td>15 (52)*</td>
<td>26 (74)*</td>
<td>14 (100)*</td>
<td>5 (36)*</td>
<td>30 (100)*</td>
<td>23 (100)*</td>
<td>12 (100)*</td>
<td>0 (0)*</td>
</tr>
<tr>
<td>Inducible EPS</td>
<td>2 (6.9)</td>
<td>22 (61)</td>
<td>1 (7.1)</td>
<td>12 (86)</td>
<td>1 (3.3)</td>
<td>5 (22)</td>
<td>4 (33)</td>
<td>5 (63)</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>13 (45)</td>
<td>23 (64)</td>
<td>12 (86)</td>
<td>30 (100)</td>
<td>9 (39)</td>
<td>9 (75)</td>
<td>8 (100)</td>
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<td>Mutation</td>
<td>5 (14)</td>
<td>9 (64)</td>
<td>30 (100)</td>
<td></td>
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<tr>
<td>Presyncope</td>
<td>6 (21)</td>
<td>5 (14)</td>
<td>1 (7.1)</td>
<td>4 (29)</td>
<td>1 (4.3)</td>
<td></td>
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<tr>
<td>LVEF &lt;35%</td>
<td>2 (5.6)</td>
<td>6 (26)</td>
<td>7 (58)</td>
<td></td>
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<td>Palpitations</td>
<td>1 (4.3)</td>
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<tr>
<td>Conduction abnormalities</td>
<td>2 (6.9)</td>
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<tr>
<td>BP drop or septum&gt;30 mm</td>
<td>13 (36)</td>
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</table>

ARVC indicates arrhythmogenic right ventricle cardiomyopathy; BP, blood pressure; EPS, electrophysiological studies; ICD, implantable cardioverter-defibrillators; LMNA, Lamin A/C gene; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; PLN, Phospholamban; SCD, sudden cardiac death; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*No statistical difference between the number of genotype positive patients in primary and secondary prevention.
The incidence rate of appropriate shocks was 4.2/100 patient-years (CI, 1.2–10.8) for primary and 4.4/100 patient-years (CI, 1.8–9.1) for secondary prevention.

### Long QT Syndrome

Fifty-five patients with LQTS (31% male; mean age, 36±19 years; LQT1, 13%; LQT2, 38%; LQT3, 29%) had an ICD implanted. ICDs were implanted in 14 (25%) primary and 41 (75%) secondary prevention. The incidence rate of appropriate shocks was 4.2/100 patient-years (CI, 1.2–10.8) for primary and 4.4/100 patient-years (CI, 1.8–9.1) for secondary prevention.

### Brugada syndrome

History of sustained VT/VF

Hypertrophic cardiomyopathy

Reduced LVEF<60%

Long QT syndrome

Family history of SCD

ARVC

Age at implantation

History of sustained VT/VF

Male gender

Nonsustained ventricular tachycardia

Atrial fibrillation documented

Recurrent ventricular fibrillation

Complex ventricular arrhythmias

Sustained VT

Hazard Ratio (95% CI)

### Figure 2

Comparison of patients with and without appropriate shocks.

A. Predictors of appropriate shocks.

B. Univariable hazard ratios for significant predictors of appropriate shocks. ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CI, confidence interval; EPS, electrophysiological studies; HCM, hypertrophic cardiomyopathy; LMNA, Lamin A/C gene; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; VF, ventricular fibrillation; and VT, ventricular tachycardia.
prevention and 41 (75%) secondary prevention patients. A positive family history for SCD, with or without a malignant mutation (10/12 LQT3), was the main primary prevention indication (Table 1). Most of these patients had type 3 LQTS (10/12; 83%). Thirty-one percent primary prevention patients received β-blockers, and median QTc interval was 480 (range, 400–560) ms.

With a median follow-up of 54 (IQR, 30–88) months, 1 of 14 primary prevention and 15 of 41 secondary prevention patients received appropriate shocks (P=0.05). One primary prevention LQT1 male experienced 4 appropriate shocks. He was implanted at the age of 72 because of short-coupled NSVT during exercise testing performed after an episode of angina pectoris and inducible VT during EPS (in the absence of coronary artery disease or any cardiomyopathy). All tachycardias were initiated with a short-coupled ventricular extrasystole (average cycle length 345 ms) and had a cycle length of ≈200 ms, suggesting VF rather than TdP. Thirty-two patients (58%), including all patients with LQT3, were paced at a lower rate of 55 beats per minute and a median pacing percentage of 12%. The incidence rate of appropriate shocks was 1.8/100 patient-years (CI, 0.05–9.9) in primary prevention and 0/100 patient-years in secondary prevention.

Arrhythmogenic Right Ventricle Cardiomyopathy
Forty-seven patients with ARVC (62% male; mean age, 43±13 years) received an ICD. ICDS were implanted in 14 (30%) primary prevention and 33 (70%) secondary prevention patients. The most common primary prevention indication was the presence of NSVT at Holter monitoring in combination with a family history of SCD (Table 1).

With a median follow-up of 62 (IQR, 32–84) months, 3 of 14 primary prevention and 18 of 33 secondary prevention patients received appropriate shocks (P=0.04). NSVT at Holter monitoring in combination with a family history of SCD was not associated with more appropriate shocks (hazard ratio [HR], 1.2; CI, 0.1–13.2). Also, sotalol use was not associated with the prevention of appropriate shocks (P=0.10); 6 of 9 patients on sotalol (median dose 160 mg) experienced appropriate shocks. Male sex was associated with appropriate shocks (46% versus 81%; HR, 4.9; CI, 1.6–14.9; Figure 2B). The incidence rate of appropriate shocks was 6.7/100 patient-years (CI, 1.4–19.7) for primary and 18.3/100 patient-years (CI, 10.9–29.0) for secondary prevention.

Dilated Cardiomyopathy Caused by Mutations in the LMNA Gene
Twenty-four patients with a LMNA mutation (50% male; mean age, 48±13 years) received an ICD. ICDS were implanted in 23 (96%) primary and 1 (4.2%) secondary prevention patient. Conduction abnormalities, with or without a LVEF <35%, was the most common primary prevention indication.

With a median follow-up of 29 (IQR, 9–48) months, 1 of 23 primary prevention and none of the secondary prevention patients received appropriate shocks (P=1.00). During follow-up, 3 patients died because of progressive heart failure (n=2) and pneumonia (n=1). The incidence rate of appropriate shocks was 1.8/100 patient-years (CI, 0.05–9.9) in primary and 0/100 patient-years in secondary prevention.

Dilated Cardiomyopathy Caused by Mutations in the Phospholamban Gene
Twenty patients with a PLN mutation (45% male, mean age 42±15 years) received an ICD, in 12 (60%) for primary prevention. The main primary prevention indication was a LVEF <35% with or without NSVT.

With a median follow-up of 45 (IQR, 27–70) months, 6 of 12 PLN primary prevention and 6 of 8 secondary prevention patients received appropriate shocks (P=0.37). The main primary prevention indication was not predictive for appropriate shocks (HR, 1.9; CI, 0.34–11.4). During follow-up, 4 patients died because of progressive heart failure (n=2) and incessant VT (n=2). The incidence rate of appropriate shocks was 24.1/100 patient-years (CI, 8.8–52.4) for primary and 36.9/100 patient-years (CI, 13.5–80.3) for secondary prevention.

Familial VF Carrying a DPP6 Haplotype
Thirty-six patients with familial VF due to the DPP6 haplotype (61% male; mean age, 32±10 years) received an ICD. Four patients were implanted because of family history initially but appeared not to be carrying the DPP6 haplotype during follow-up. They were excluded from this analysis, and their ICD was removed. Family history of SCD (Figure 3A) was the primary prevention indication in 30 patients; 2 patients had a secondary prevention indication.

With a median follow-up of 35 (IQR, 29–38) months, 0 of 30 primary prevention and 4 of 33 secondary prevention patients received appropriate shocks. Thus, the most common indication for primary prevention was not predictive for ICD therapy. The incidence rate of appropriate shocks was 0/100 patient-years for primary and 240/100 patient-years (CI, 29.1–867) for secondary prevention.

Idiopathic Familial VF
Thirteen patients (53% male; mean age, 33±19 years) received an ICD because of idiopathic familial VF (Figure 3B). ICDS were implanted for primary prevention in 8 (62%) and for secondary prevention in 5 (38%) patients.

With a median follow-up of 57 (IQR, 21–85) months, 1 of 8 primary prevention and 1 of 5 secondary prevention patients received appropriate shocks (P=0.01). The incidence rate of appropriate shocks was 4.8/100 patient-years (CI, 0.12–26.9) for primary and 2.5/100 patient-years (CI, 0.06–13.7) for secondary prevention.

Role of ATP in Diseases Associated with Monomorphic VT
In addition to shock therapy, ATP was delivered in 3 HCM, 6 ARVC, 1 LMNA, and 1 PLN patients. When counted as appropriate therapy, this increased the rate of appropriate therapy in primary prevention from, respectively, 4.2, 6.7, 1.8, and 24.1/100 patient-years to 6.3, 10.6, 1.8, and 28.7/100 patient-years. Similarly, it would increase the rate of appropriate therapy for secondary prevention from 4.4, 18.3, 0, and 36.9/100 patient-years to 5.1, 34.9, 25.5, and 36.9/100 patient-years.

Serious Harm (Inappropriate Shocks and Complications)
In the entire cohort (n=354), inappropriate shocks occurred in 50 patients (14%) during a follow-up of 46 (IQR, 27–82)
months; 15 patients experienced both appropriate and inappropriate shocks. Nine patients experienced >1 episode of inappropriate shocks. The most common reason for inappropriate shocks was supraventricular tachycardia (Table 2). In 12 of 50 patients (24%), ICD revision (lead replacement or reposition: n=11; ICD replacement: n=1) was performed after an inappropriate ICD therapy. Age, underlying disease, and single-chamber devices were not associated with inappropriate shocks. Atrial fibrillation increased the risk of inappropriate shocks (HR, 2.7; CI, 1.5–4.8).

Ninety-four patients (27%) experienced device-related complications. One hundred thirty-one complications occurred (38 [29%] within 1 month after implantation, 93 [71%] during long-term follow-up), all requiring medical or surgical intervention for correction or more frequent ICD surveillance. Among all events, lead failures and/or fractures were the most common complications, accounting for 23% (Table 2). The trend was that patients implanted with dual-chamber devices were more likely to encounter complications than patients with a single-chamber device (HR, 1.4; CI, 0.9–2.1). The complication rate increased concordantly with the number of device replacements (Figure 4).

In total, 123 patients (35%) had an adverse event caused by ICD therapy (either inappropriate shocks or ICD-related complications).

**Psychological Burden**
Seventy-nine patients (22%) were referred to a psychologist/psychiatrist or were taking psychotropic medication. Appropriate or inappropriate shocks were not associated with psychological problems (P=0.14 and P=0.27, respectively).

**Relation Between Efficacy and Harm**
The incidence rate of appropriate shocks was higher in patients implanted for secondary prevention. In HCM, ARVC, and PLN patients who received ICDs for primary prevention the incidence rate of appropriate shocks was, respectively, 4.0, 6.7, and 24.1/100 patient-years. For LQTS and LMNA patients, this risk was considerably lower and none of the BrS and DPP6 patients with an ICD implanted for primary prevention received appropriate shocks. The incidence rate to be seriously harmed is higher than the risk of appropriate shocks in BrS, LQTS, LMNA, and DPP6 patients (Figure 5).

**Discussion**

**Main Findings**
ICDs proved reliable in terminating life-threatening VT/VF in inherited cardiac diseases. Among various arrhythmia syndromes, indications for primary prevention were not predictive for appropriate shock therapy. The risk of appropriate shocks in BrS, LQTS, and DPP6 patients implanted for primary prevention was considerably lower compared to patients with secondary prevention. The incidence rate to be seriously harmed is higher than the risk of appropriate shocks in BrS, LQTS, LMNA, and DPP6 patients (Figure 5).

**Figure 3.** Representative pedigrees of a DPP6 and an idiopathic ventricular fibrillation (IVF) family. A, Displays a family with idiopathic VF based on the DPP6 haplotype. Dashed symbols indicate carriers of the DPP6 haplotype. Two patients received an implantable cardioverter-defibrillators (ICD) but seemed not to be carrying the DPP6 haplotype; the ICDs were removed during follow-up (see text for further details). B, Displays a family with idiopathic familial VF, in whom ICD implantation for both secondary (closed symbols) and primary prevention (open symbols) was deemed necessary because of the presumed risk based on the family history. The twin never showed up for clinical investigation. Patients who received an ICD are indicated with an arrow. SCD indicates sudden cardiac death.
prevention is even close to zero (cumulative: 1 appropriate shock in 259 patient-years). Therefore, because 35% of our young study population had ICD-related morbidity, the risk to be seriously harmed might outweigh the risk of appropriate shocks in patients with BrS, LQTS, and DPP6 implanted for primary prevention. This, however, does not imply that SCD is similar to an ICD-related complication because the severity of an arrhythmia requiring appropriate ICD therapy may still justify ICD implantation in this group.

Secondary Prevention

Previous studies have uniformly demonstrated the efficacy of ICDs in patients with inherited cardiac diseases who survived sustained VT/VF because of their high incidence of arrhythmia recurrences.\textsuperscript{3,4,17,18} In this study, patients with a cardiac syncope were presumed to have experienced a sustained VT, and therefore considered secondary prevention. This study confirms that ICDs are efficacious in patients with a history of sustained VT/VF.

Primary Prevention

In patients without a history of life-threatening cardiac events, there remains doubt in whom the risk may be (or may not be) sufficiently high to justify ICD therapy. Earlier studies demonstrated various appropriate shock rates in primary prevention, depending on the underlying inherited cardiac disease. In HCM and ARVC appropriate shock incidence rates between 2.3 and 10/100 patient-years have been reported,\textsuperscript{19,20} which are similar to our findings. The higher appropriate discharge rates in HCM and ARVC than in primary electric diseases might represent an advanced risk stratification scheme in these cardiomyopathies.\textsuperscript{18,20} Also dilated cardiomyopathy caused by LMNA is known to be arrhythmogenic; the incidence rate of appropriate ICD therapies (ATP and shocks) may be as high as 13/100 patient-years.\textsuperscript{21} However, we found an incidence rate of appropriate shocks in LMNA patients of 1.8/100 patient-years, also when adjusted for ATP. Only limited data on ICD therapy in PLN patients are available, but this study suggests a high incidence rate of appropriate shocks (≈24/100 patient-years). In both LMNA and PLN, patients with appropriate shocks had a LVEF <35%. To compare, in the prophylactic SCD-HeFT trial the incidence rate of appropriate shocks was 5.1/100 patient-years.\textsuperscript{1}

Appropriate shock incidence rates around 2.5% in primary prevention BrS and LQTS patients (excluding cardiac syncope) have been reported.\textsuperscript{3,22} Sarkozy et al\textsuperscript{23} even found an incidence rate of 3.8/100 patient-years in primary prevention BrS patients. The discharge rates in BrS and LQTS in our study were lower than in other prophylactic ICD trials. None of the primary prevention BrS and only 1 LQTS patient received appropriate shocks. The latter patient might have received appropriate therapy because of ischemic episodes, despite the absence of significant coronary artery disease. Most primary prevention LQTS patients had type 3 because of the presumed higher mortality risk than in LQT1 and 2. However,
no appropriate therapy occurred in LQT3 patients, although pacing therapy might have prevented bradycardia-associated VT/VF. It remains unclear whether β-blockers, used in 1/3 of patients with LQT3, reduced the risk for VT/VF.

None of the primary prevention DPP6 patients experienced appropriate shocks. However, the median follow-up in our DPP6 population was shorter (35 months versus 48 and 46 months in BrS and LQTS, respectively) and the presumed long-term risk is considerable because 50% of the patients with this haplotype died before the age of 58.12 Alternatively, nonidentified factors add to the risk of SCD in this DPP6 population.

Currently, our prophylactic ICD indications in inherited cardiac diseases are more conservative. For example, in LQTS, only patients with type 3 and a QTc >530 ms and patients with Jervel and Lange–Nielsen syndrome with a QTc >550 ms are considered for prophylactic ICD therapy. Patients with HCM are only considered for prophylactic ICD therapy. Patients with BrS are considered for prophylactic ICD therapy. Patients with ARVC are considered for prophylactic ICD therapy. Patients with familial VF are only considered for prophylactic ICD implantation if they have ≥2 risk factors.15 Asymptomatic patients with BrS and inducible VT/VF with EPS and LQTS patients with only a family history of SCD are not considered for ICD implantation anymore.24 The absence of prospective randomized studies makes it difficult to identify patients at risk, and risk factors for SCD and ICD indications have been derived from the abovementioned observational studies. However, we demonstrate a discrepancy between the indications and predictors for appropriate shocks in primary prevention.

**Serious Harm**

Inappropriate shocks and lead and device complications remain a problem in 14% and 27% of the patients, respectively. The incidence rate of inappropriate shocks of 3.5/100 patient-years found in this study is similar to other studies (range, 2.4%–6.9%).13,17,18,21,22,25,26 Dual-chamber devices were not associated with less inappropriate shocks,27 but this study showed a trend toward more ICD-related complications in dual-chamber devices. Patients with atrial fibrillation were at increased risk for inappropriate shocks.

The incidence rate of complications of 7.1/100 patient-years is similar to that found in other studies (range, 3.3–9.3)13,17,18,22 and the number of complications increased with the number of ICD implantations. Considering that young ICD recipients have a higher life-expectancy than those with ischemic and dilated cardiomyopathy, this might result in multiple lead and device replacements. These young ICD patients are, therefore, likely to face a substantial burden of future complications.

Additionally, the cost of frequent shocks in terms of pain and fear is substantial, although 1 inappropriate shock is not as devastating as multiple inappropriate shocks and may be considered as an acceptable, minor complication of ICD therapy in the context of prevention of SCD.

**Limitations**

The low event rates in a relatively small and heterogeneous study population particularly in primary prevention, makes drawing definite conclusions regarding predictors of future events difficult. Additionally, retrospective data collection restricts the selection of predictor variables to those that were routinely collected during first implant.

Successful ATP was not considered as a primary efficacy end point. The rate of ATP therapy for VTs was not well documented because ICD-electrograms were not stored systematically in the device in case of multiple NSVT or ATP events. The available data show that the rate of appropriate therapy in diseases associated with monomorphic VTs increased only modestly. The majority of patients with appropriate ATP therapy also experienced appropriate shocks and were, therefore, correctly scored as appropriate ICD discharges.

The reported appropriate ICD discharge rates are not necessarily representative of a truly general population with inherited cardiac arrhythmias. In the absence of a control population without an ICD, there is no validation of the performance of ICD therapy, and this therefore precludes the quantification of survival benefits. Prospective randomized trials would be preferable, but hold ethical concerns.
Lastly, the available data does not allow assessing how many of the treated arrhythmias would terminate spontaneously, which might lead to a surplus of appropriate, but unnecessary ICD shocks. However, this could be prevented by programming the detection interval.

Conclusions
Guidelines on ICD implantation in patients with inherited cardiac diseases have been derived from observational trials. We demonstrated that for some inherited diseases the efficacy of ICDs contrasts with the amount of harm, and that the factors that formed the indication for ICD implantation do not relate to the occurrence of appropriate shocks. This does not imply that ICDs should not be implanted in those patients because the severity of SCD might outweigh the burden of ICD-related complications. The absolute risk of ICD-related complications outweighs the mere chance of any appropriate shock in BrS, LQTS, and so far, in DPPE. In patients with ICDs implanted for secondary prevention, there was no such discrepancy.

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Disclosures
None.

References
The use of implantable cardioverter-defibrillators (ICDs) is an established therapy for the prevention of death from ventricular arrhythmia in patients with inherited cardiac diseases who survived an episode of ventricular fibrillation or sustained ventricular tachycardia. However, indications for prophylactic ICD therapy in patients with inherited cardiac diseases have been derived from observational studies and consensus statements and are uncertain. We report the efficacy and adverse events for ICD implantations for primary prevention compared with secondary prevention in >350 patients with different inherited cardiac diseases. This study demonstrates that for primary prevention appropriate shock rates are high in some disorders, whereas they are close to zero in others. In addition, this study reports for the first time that none of the factors that informed indications for primary prevention ICD implantation were associated with the outcome of appropriate shock therapy. A large number of patients, however, experienced ICD-related adverse events, defined as inappropriate shock therapy and ICD-related complications. With the increasing awareness and diagnosis of patients with a genetic predisposition for sudden cardiac death and subsequent ICD implantations, this knowledge is very important to prevent device overuse in the future.
The ICD for Primary Prevention in Patients With Inherited Cardiac Diseases: Indications, Use, and Outcome: A Comparison With Secondary Prevention


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Supplemental material

Appendix I: Age at first ICD implant

![Chart showing age at first ICD implant]
## Appendix I: Appropriate shock characteristics (in patients with appropriate shock therapy)

<table>
<thead>
<tr>
<th></th>
<th>Brugada syndrome</th>
<th>Hypertrophic cardiomyopathy</th>
<th>Long QT syndrome</th>
<th>ARVC</th>
<th>Familial VF with DPP6 haplotype</th>
<th>Cardiomyopathy with LMNA mutation</th>
<th>Cardiomyopathy with PLN mutation</th>
<th>Idiopathic familial VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>appropriate shocks</td>
<td>7</td>
<td>11</td>
<td>16</td>
<td>21</td>
<td>2</td>
<td>1</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Number of patients with</td>
<td>NA</td>
<td>4</td>
<td>NA</td>
<td>22</td>
<td>NA</td>
<td>2</td>
<td>7</td>
<td>NA</td>
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<tr>
<td>ATP therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of shock episodes</td>
<td>3.6±5.9</td>
<td>2.5±1.8</td>
<td>3.8±4.5</td>
<td>2.4±1.7</td>
<td>11.0±2.8</td>
<td>1.0</td>
<td>5.1±4.5</td>
<td>1.5±0.7</td>
</tr>
<tr>
<td>Number of ATP episodes</td>
<td>-</td>
<td>2.3±2.5</td>
<td>-</td>
<td>7.0±14.7</td>
<td>-</td>
<td>5.5±0.7</td>
<td>3.9±3.0</td>
<td>-</td>
</tr>
<tr>
<td>Number of shocks per</td>
<td>3.6±5.9</td>
<td>5.0±3.7</td>
<td>5.7±6.5</td>
<td>4.5±4.5</td>
<td>40±37.5</td>
<td>1.0</td>
<td>6.8±6.1</td>
<td>1.5±0.7</td>
</tr>
<tr>
<td>episode</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Electrical storms</td>
<td>1 (14%)</td>
<td>5 (45%)</td>
<td>4 (27%)</td>
<td>6 (29%)</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
<td>4 (33%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Median time to first</td>
<td>17</td>
<td>21</td>
<td>9</td>
<td>11</td>
<td>5</td>
<td>38</td>
<td>11</td>
<td>33</td>
</tr>
<tr>
<td>shock or ATP (months)</td>
<td>(IQR 13-42)</td>
<td>(IQR 11-75)</td>
<td>(IQR 4-36)</td>
<td>(IQR 4-27)</td>
<td>(IQR 4-6)</td>
<td>(IQR 29-47)</td>
<td>(IQR 3-37)</td>
<td>(IQR 15-50)</td>
</tr>
<tr>
<td>Underlying rhythm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- VF</td>
<td>21 (88%)</td>
<td>7 (26%)</td>
<td>37 (41%)</td>
<td>4 (7.8%)</td>
<td>22 (100%)</td>
<td>1 (100%)</td>
<td>15 (26%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>- VT</td>
<td>2 (8.3%)</td>
<td>9 (33%)</td>
<td>20 (11%)</td>
<td>42 (82%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>41 (67%)</td>
<td>2 (67%)</td>
</tr>
</tbody>
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