The implantable cardioverter defibrillator (ICD) reduces the risk of sudden cardiac death in patients at high risk of malignant arrhythmias. An estimated 250,000 to 300,000 people die suddenly each year of ventricular tachycardia (VT), which has tremendous implications for the healthcare system. Despite major improvements in device technology to optimize therapy, sudden cardiac death remains the leading cause of death worldwide. Even though the sensitivity of modern ICD

**Efficacy of Long Detection Interval Implantable Cardioverter-Defibrillator Settings in Secondary Prevention Population**

**Data From the Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients III (ADVANCE III) Trial**

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**Background**—Three trials demonstrated recently that a long detection window reduces implantable cardioverter-defibrillator (ICD) therapy in primary prevention patients. Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients III (ADVANCE III) was the only trial that enrolled both primary and secondary prevention patients.

**Methods and Results**—Of the 1902 patients enrolled in the ADVANCE III trial, 477 received a defibrillator for secondary prevention; 248 patients were randomly assigned to a long detection setting (30 of 40 intervals) and 229 to the nominal setting (18 of 24 intervals) for ventricular arrhythmias with cycle length ≤320 ms. Eight-five percent of patients were men, with a mean age of 65±12 years, a previous history of ventricular fibrillation in 37% of the cases, and a mean ejection fraction of 38±13%. The ICD device mix was 37% single chamber, 47% dual chamber, and 16% triple chamber. Over a median period of 12 months, the long detection period was associated with a 25% reduction in the number of overall therapies (115.6 versus 86.8 per 100 patient-years; incidence rate ratio, 0.75; 95% confidence interval, 0.61–0.93; P=0.008) and a 34% reduction in the number of shocks (rate per 100 patient-years, 51.2 versus 38.1; incidence rate ratio, 0.66; 95% confidence interval, 0.48–0.89; P=0.007). Appropriate therapies (89.7 versus 67.7; incidence rate ratio, 0.77; 95% confidence interval, 0.60–0.97; P=0.029) and appropriate shocks (37.1 versus 28.1; incidence rate ratio, 0.64; 95% confidence interval, 0.45–0.93; P=0.018) were also reduced.

**Conclusions**—ADVANCE III is the first randomized trial to assess a long detection window setting in ICDs in both primary and secondary prevention populations and demonstrates a reduction of overall therapies and shocks in the subgroup of secondary prevention patients. These data suggest that even the secondary prevention population may benefit from programming that combines a long detection period with antitachycardia pacing during charging.

**Clinical Trial Registration**—URL:http://www.clinicaltrials.gov. Unique identifier: NCT00617175.

(Circulation. 2014;130:308-314.)

**Key Words:** arrhythmia ■ implantable cardioverter-defibrillators ■ secondary prevention ■ stimulators, electrical, cardiac, shock
devices is very high in detecting life-threatening arrhythmias, the incidence of unnecessary or inappropriate shocks remains as high as 30%.6,7

Clinical Perspective on p 314

Despite the recent shift from a predominantly secondary to primary implantation indication, physicians still face the challenge of ICD programming. Three different trials demonstrated recently that a long detection window and a high rate cutoff reduce ICD therapies in primary prevention (PP) patients8–10; however, few data are available for the secondary prevention (SP) population.

Methods

Study Overview and Patient Selection

The design and the primary results of the Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients III (ADVANCE III) trial have been published previously.8,11 Briefly, the ADVANCE III trial was a randomized, single-blind, parallel, multicenter trial that enrolled and analyzed 1902 patients undergoing their first implantation of a single- or dual-chamber ICD or a biventricular ICD (cardiac resynchronization therapy defibrillator [CRTD]) with a PP or SP indication from 94 centers in Europe, the Middle East, Russia, and Africa. Participants provided written informed consent, were randomly assigned to be programmed with a long-detection setting or with the standard-interval programming, and were followed up for 1 year. To preserve balancing in prespecified subgroups, the randomization was stratified according to ICD indication (primary versus secondary), type of device (single-chamber, dual-chamber, or CRTD), and presence or absence of atrial fibrillation. Each center obtained the approval of its medical ethics committee or institutional review board before study initiation. Other details on inclusion and exclusion criteria are available in the main study publications.8

Interventions

Commercially available ICD and CRTD devices with the ability to deliver antitachycardia pacing (ATP) during the capacitor’s charge were used in this trial. To summarize, ICDs were programmed with a ventricular fibrillation (VF) zone to detect arrhythmias with a cycle length (CL) ≤320 ms, with a single attempt of ATP during the capacitor charge for fast arrhythmias with CL up to 200 ms and shock only for VF with CL <200 ms. In the long-detection arm, prolonged detection was programmed (30 of 40 intervals), whereas in the standard-interval arm, the programming used in the PainFREE II12 trial (Pacing Reduces Shocks for Fast Ventricular Tachycardia II) was used (18 of 24 intervals). In case of documented slow VT with CL >320 ms, a VT zone was allowed, with the specific programming left to the discretion of each physician and tailored on the basis of the recorded VT. Further details on programming considerations of the study have been published previously.8

Study Objectives

The present analysis applied, in SP patients only, the same primary objective of the main study. Therefore, we compared the rate of ventricular ICD therapies delivered to terminate spontaneous episodes with a CL ≤320 ms between the long-detection and standard-detection arms.

All sustained VT/VF and monitored VT with stored electrograms were reviewed by at least 2 members of a blinded episode review committee to assess appropriateness of device classification. Appropriate therapy was defined as therapy delivered for monomorphic or polymorphic VT and for VF. All ICD therapies delivered for supraventricular episodes or for nonarrhythmic events (such as noise, oversensing, etc) were classified as inappropriate therapies. Arrhythmias that were recorded in the monitor-only zone were adjudicated by an independent blinded committee, and true VTs were included. Syncopal events and deaths were classified by a second independent committee to assess potential correlation with arrhythmic events.

Statistical Analysis

Details of the sample size calculation, randomization process, and data collection have been reported previously.11 Continuous data were described as means and SDs, whereas categorical data were expressed as counts and percentages. Follow-up duration was reported as median and 25th to 75th percentiles. The rate of therapies was computed per 100 person-years and reported with 95% confidence intervals (CIs). The incidence rate ratio (IRR) and the relative 95% CI were used to report the comparison in the therapy rate between treatment arms. To adjust for multiple episodes per patient, rates were calculated and compared with a mixed Poisson model, adjusted to take into account intercenter heterogeneity. Results were presented for all delivered therapies and separately for appropriate and inappropriate episodes. Hazard ratios and their 95% CIs were estimated by means of a Cox proportional hazards method to test differences in time to first therapy. Time to first ICD therapy was described by use of Kaplan-Meier curves and compared between groups by means of the log-rank test. Syncope and death rates were computed for 100 patient-years and compared by means of Poisson regression (IRR reported) and the Cox model (hazard ratio reported), respectively. All analyses were performed according to the intention-to-treat approach and were repeatedly considering the on-treatment population (by excluding patients in the primary analysis who deviated from the protocol or until evidence of programming of the wrong number of intervals to detect [NID] ventricular fibrillation). All tests were 2-sided, and a 2-tailed P value <0.05 was considered to indicate statistical significance. Analyses were performed with Stata 12.1 (Stata Corp, College Station, TX).

Results

Of the total 1902 randomized patients, 477 (25%) received a defibrillator for SP (patients with a previous history of hemodynamically significant VT or survival from cardiac arrest; 229 in the long-detection group and 248 in the standard-interval group) and were followed up for a median of 12 months (25th to 75th percentile, 11–13 months). Baseline characteristics are shown in Table 1. Treatment arms were balanced except for a difference in the proportion of men (80% in the long-detection arm and 89% in the standard-interval arm, P=0.008). SP patients had a mean age of 65 years, a short QRS duration (117 ms), a mean ejection fraction of 38%, and left bundle-branch block in 19% of the cases. In 37% of the cases, patients had experienced a previous episode of VF. The implanted device was a CRTD in 15.9% of patients, a dual-chamber device in 47.4%, and a single-chamber device in 36.7%. Device memory (save to disk) was available and used for the analysis in 212 of 229 patients (92.6%) in the long-detection arm and in 226 of 248 patients (91.1%) in the standard-interval arm.

Total Delivered ICD Therapies

A total of 226 episodes were recorded and classified by the devices as ventricular arrhythmias (VAs). An electrogram was available in 222 episodes (98%), which enabled us to classify the appropriateness of the episodes. The devices delivered a total of 419 therapies to treat the 226 episodes (Figure I in the online-only Data Supplement), with a significantly lower
incidence of overall (ATP+shock) therapies in the long-detection arm than in the standard-detection arm (116 therapies per 100 person-years in the control arm versus 87 therapies per 100 person-years in the long-detection arm; IRR, 0.75; 95% CI, 0.52–0.80; \( P<0.001 \)). The data on total and appropriate shocks were also strengthened after on-treatment analysis (\( P=0.004 \) and \( P=0.007 \), respectively).

### On-Treatment Analysis

Adherence to the required programming was extremely high, with only 2 patients in the long-detection group programmed with an 18/24 NID. Nevertheless, on-treatment analysis reinforced the data on the reduction of overall therapies (115 per 100 patient-years in the control group versus 80 per 100 patient-years in the long-detection group; IRR, 0.65; 95% CI, 0.52–0.80; \( P<0.001 \)) and of appropriate therapies (90 per 100 patient-years in the control group versus 60 per 100 patient-years in the long-detection group; IRR, 0.61; 95% CI, 0.48–0.79; \( P<0.001 \)). The data on total and appropriate shocks were also strengthened after on-treatment analysis (\( P=0.004 \) and \( P=0.007 \), respectively).

### Safety

Syncope episodes related to arrhythmic events were rare and did not differ between study arms. During the present study, 11 episodes of syncope in 9 patients were adjudicated to have a direct rhythm-symptom correlation with a ventricular episode with CL <320 ms (4 syncope episodes in the long-detection arm and 7 in the standard-interval arm; 2.0 and 3.2 per 100 person-years, respectively, \( P=0.6 \); Table 4). In all cases, adherence to the device programming as per randomization was confirmed. Twelve patients in the long-detection arm and 16 in the standard-interval arm died, with a rate of 5.5 and 6.9 deaths per 100 person-years, respectively. No difference was found between treatment arms (hazard ratio, 0.80; 95% CI, 0.38–1.69; \( P=0.6 \); Table 4).

### Slow VTs Below Cutoff Rate

Among patients with available save-to-disk memory, a VT zone was enabled in 62.0% of the cases. The mean cutoff rate for the VT zone was 374±27 ms, and ATP was the first therapy in all patients. A total of 110 VTs (with a mean CL of 417±60 ms) in 28 patients were detected by the device in the monitor-only zones and adjudicated by the episode review committee as true VAs, which resulted in a rate of 26.7 (95% CI, 22.1–32.1) per 100 patient-years. Only 6 hospitalizations in 6
patients were reported as being associated with the monitored arrhythmic events; 3 hospitalizations were related to electric storms and the remaining 3 to heart failure.

Discussion

The present ADVANCE III ancillary analysis showed that in patients with a previous history of VAs implanted with any kind of ICD, a programming strategy that combined a long NID detection window and ATP during charging reduced overall therapies and markedly reduced the rate of shocks without increasing the risk of syncope. Although the adverse prognostic value of ICD therapies (shocks and ATP) in PP has been well proven,7,13 and the new programming approach focused on minimizing ICD therapies in that population has a solid clinical evidence base,8–10 a significant proportion of patients still receive ICDs for SP indications, and the effect of delayed-detection programming on this population has not yet been investigated. The SP population presents unique characteristics that must be addressed carefully when focused programming is designed.

The baseline characteristics of the SP population clearly represent a more arrhythmic rather than a heart failure profile. Therefore, it is not surprising that the population described in the present analysis is different from the PP population enrolled in ADVANCE III, MADIT RIT (Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy), and PROVIDE (Programming Implantable Cardioverter-Defibrillators in Patients With Primary Prevention Indication to Prolong Time to First Shock).8–10 In fact, the subset of SP patients included in the ADVANCE III trial had a mean ejection fraction of 38% compared with the 27% reported for the ADVANCE III subgroup of PP patients8 or the 26% and 27% reported in the MADIT-RIT9 and PROVIDE 10 trials, respectively. Interestingly, the SP population appears to have maintained a stable clinical/echocardiographic profile throughout the years, with the ADVANCE III SP population having an ejection fraction similar to what was reported in the AVID (Antiarrhythmics Versus Implantable Defibrillators) trial.5 The data on shorter QRS duration, lower proportion of patients with New York Heart Association functional class III to IV, and low incidence of left bundle-branch block are in accordance with a less compromised condition in terms of heart failure. As a consequence of the above characteristics, only 19% of the patients received a CRTD device versus 49% of the PP subgroup. In addition, although only 9% of PP patients had a previous episode of syncope, roughly half of the SP population had a history of loss of consciousness.

Table 2. Results of Delivered ICD Therapies According to Intention-to-Treat Analysis

<table>
<thead>
<tr>
<th>Therapies</th>
<th>Detection Window NID</th>
<th>No. of Therapies (No. of Treated Episodes)</th>
<th>Therapy Rate per 100 Patient-Years</th>
<th>IRR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>18/24</td>
<td>246 (134)</td>
<td>115.6 (101.6–130.9)</td>
<td>1</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>30/40</td>
<td>173 (92)</td>
<td>86.8 (74.3–100.7)</td>
<td>0.75 (0.61–0.93)</td>
<td>0.24</td>
</tr>
<tr>
<td>ATP</td>
<td>18/24</td>
<td>137 (124)</td>
<td>55.0 (54.0–76.1)</td>
<td>1</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>30/40</td>
<td>97 (83)</td>
<td>48.7 (39.5–59.4)</td>
<td>0.85 (0.64–1.12)</td>
<td>0.66 (0.48–0.89)</td>
</tr>
<tr>
<td>Shock</td>
<td>18/24</td>
<td>109 (68)</td>
<td>51.2 (42.0–61.8)</td>
<td>1</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>30/40</td>
<td>76 (58)</td>
<td>38.1 (30.0–47.7)</td>
<td>0.66 (0.48–0.89)</td>
<td>0.66 (0.48–0.89)</td>
</tr>
</tbody>
</table>

Episodes considered in Table 2 are not mutually exclusive. Of the total 226 episodes recorded, 100 episodes received only ATP, 19 received only shock, and 107 received both ATP and shock. ATP indicates antitachycardia pacing; CI, confidence interval; ICD, implantable cardioverter-defibrillator; IRR, incidence rate ratio; and NID, number of intervals to detect ventricular fibrillation.

Figure. Time to first therapy. NID indicates number of intervals to detect ventricular fibrillation.
Overall Therapies
The present study demonstrated a significantly lower overall incidence of therapies (ATP+shocks) in the long-detection arm than in the standard one. Interestingly, the significant reduction of overall therapies was mostly driven by the reduction of shocks (−34%), which led to a consequent reduction in the delivered energy, which has been associated previously with possible myocardial damage.14 Considering the debated association between ICD shocks and negative outcome, as well as the known detrimental effect of painful therapies on a patient's quality of life and acceptance of the device, the reduction in overall shock burden found in the long-detection arm could have a favorable impact on SP patients in whom an ICD is implanted.

Appropriate Therapies
The number of appropriate therapies in the present analysis was significantly lower in the long-detection arm, with a marked reduction in appropriate shocks (−36%). In light of the general concern regarding programming a delayed therapy in patients with a previous history of VA, these data provided ground-breaking information. Moreover, on-treatment analysis not only confirmed these findings but even emphasized the reduction in overall and appropriate shocks. The present findings suggest that many VAs are self-terminating in the detection window between 19 and 30 beats. These data are in line with the percentage of self-terminating VA episodes observed in a MIRACLE (Multicenter InSync Randomized Clinical Evaluation) ICD trial subanalysis,6 as well as those observed in the PainFREE RX II trial.12 Together, these data confirm that these arrhythmias were probably treated too quickly in the group of patients with standard detection intervals. The present data differ from the data presented in the RELEVANT trial (Role of Long Detection Window Programming in Patients With Left Ventricular Dysfunction, Non-ischemic Etiology in Primary Prevention Treated With a Biventricular ICD),15 in which shock reduction was mainly related to the decrease in inappropriate shocks (5 versus 30 shocks, \( P < 0.001 \)), given that appropriate shock reduction was of only borderline significance (17 versus 29 shocks, \( P = 0.057 \)). This might be explained by the fact that in the RELEVANT trial, only PP patients with nonischemic cardiomyopathy who had received a CRTD were included.

Inappropriate Therapies
The overall rate of inappropriate therapies was low in both groups, with only 4% of the SP patients experiencing inappropriate therapies. Because of the low numbers of events, only the

<table>
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<tr>
<th>Table 3. Appropriate and Inappropriate Delivered Therapies as Separate End Points According to Intention-to-Treat Analysis</th>
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<tbody>
<tr>
<td><strong>End Point</strong></td>
</tr>
<tr>
<td>Appropriate delivered therapy</td>
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<tr>
<td>Overall</td>
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<td>ATP</td>
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<td>Shock</td>
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ATP indicates antitachycardia pacing; CI, confidence interval; ICD, implantable cardioverter-defibrillator; IRR, incidence rate ratio; and NID, number of intervals to detect ventricular fibrillation.

<table>
<thead>
<tr>
<th>Table 4. Safety End Points: Arrhythmic Syncope and All-Cause Death</th>
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</thead>
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<tr>
<td><strong>Detection Window NID</strong></td>
</tr>
<tr>
<td>Arrhythmic syncope</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Death</td>
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CI indicates confidence interval; IRR, incidence rate ratio; and NID, number of intervals to detect ventricular fibrillation.
reduction in overall inappropriate therapies (ATP+shocks) and inappropriate ATP therapies in the long-detection arm reached significance, whereas despite being clinically interesting, the 36% reduction in inappropriate shocks did not (6 patients with 18 shocks versus 8 patients with 29 shocks, respectively). By prolonging the time of detection to longer settings, it is not surprising that fewer inappropriate therapies were delivered; previous studies have shown that most inappropriate therapies are determined by high-rate conducted atrial arrhythmias or lead noises, both of which are influenced favorably by a longer NID.7–16 Nevertheless, in terms of the recent hypothesis of a possible association between unnecessary ATPs and increased risk of adverse events in PP, the present data provide a clear indication for a programming strategy that can safely reduce inappropriate therapies in SP patients as well.

Safety
Interestingly, despite the general concerns about a potential increase in the rate of syncopal events and mortality, particularly in patients who previously had sustained VA, the investigators of ADVANCE III maintained compliance with the required programming as high as 97.2%. Even though the effect of prolonging NID could not be forecast precisely, almost all investigators performed the programming of the device according to the study protocol and did not differ from that during follow-up. There were only 3 patients with 4 syncopal events in the long-detection group versus 6 patients with 7 syncopal events in the standard-interval group; because of the low number of syncopal events observed, no definitive conclusions can be drawn. This is in line with the data presented by the PREPARE trial (Primary Prevention Parameters Evaluation),17 which also used an NID of 30/40 and showed that a long NID significantly decreased the risk of shocks without increasing the incidence of arrhythmic syncopal events.

Similar to syncopal events, even the reported mortality rate was low and not significantly different between the 2 arms (12 deaths in the long-detection arm versus 16 in the control group). Even in this case, the number of these occurrences was too low to speculate on a possible association between therapy occurrence and mortality.

VTs Below Cutoff Rate
Historically, the arrhythmogenic profile of SP patients has presented a challenge for physicians. Specifically, cardiac electrophysiologists were required to choose to maintain a conservative detection setting or a delayed approach to allow for self-terminations. The present study demonstrated that a low rate of true VTs occurred in the monitor-only zone with the vast majority of them self-terminating without leading to substantial adverse events. In particular, 6 hospitalizations were reported to be associated with untreated VTs. This finding provides new insight into the possible worsening of heart failure because of long undetected ventricular events, at least in SP patients.

Study Limitations
The present trial was not designed specifically for the SP population only, and consequently, these analyses are based on a confined number of patients with a lower power than in the main trial results. However, randomization was stratified on the PP or SP indication, which led to equivalent baseline characteristics in the 2 arms and to significant results that deserve credit.

To be consistent with the analyses reported in the ADVANCE III trial main paper,6 the tests presented in the present study were not performed with adjustment for multiplicity for the P values, and some of the P values may not meet the overall significance level at 5% after correction for multiple comparisons. Nevertheless, all comparisons were reported, and P values were relatively lower than the 0.05 level, except for the comparison on ATP in inappropriate events.

Conclusions
ADVANCE III is the first randomized trial that assessed an ICD long-detection window setting in both PP and SP, demonstrating a reduction both in overall therapies and in shocks in the subgroup of SP patients, significantly driven by a reduction in the number of appropriate interventions. These data suggest that in SP, a relevant number of true VTs may be self-terminating within 30 beats, and thus, even patients with a previous history of VA may benefit from a programming strategy that combines a long detection interval with ATP during charging.

Acknowledgments
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Disclosures
Dr Kloppe reported consulting fees from Medtronic, Inc and St Jude Medical, as well as lecture fees from Medtronic Inc, Boston Scientific, and St. Jude Medical. Dr Proclemer reported consulting fees from Medtronic, Inc. Dr Arenal reported consulting fees from Medtronic Inc and Biotronik. E. Santi, L. Manotta, and L. Mangoni are employees of Medtronic, Inc. Dr Gasparini reported consulting fees from Medtronic, Inc and Boston Scientific Corp.

References


CLINICAL PERSPECTIVE

In the past few decades, the expanded indications for implantable cardioverter-defibrillators (ICDs) have led to an increased adoption of ICDs, both in the United States and in Europe, and in addition, the technology and the complexity of the devices have increased significantly. Hence, the challenge of defining the best programming for each patient is in the spotlight of the cardiac electrophysiology literature. The Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients III (ADVANCE III) trial showed that a strategic programming strategy that combined a delay in arrhythmia detection and a first attempt of painless therapy was effective in reducing unnecessary therapies not only in primary prevention patients but also in secondary prevention patients. Secondary prevention patients present unique clinical characteristics with a high arrhythmic profile, which challenges the physician to find the perfect balance between a conservative programming strategy to safely treat all arrhythmia episodes and the need to avoid the well-known adverse effects of unnecessary therapies. The present analysis demonstrated for the first time in the secondary prevention subgroup a reduction in both overall therapies and shocks, significantly driven by a reduction in appropriate interventions. Interestingly, despite the general concerns that this result would likely come at the price of a higher rate of syncopal episodes, a low number of events occurred with no difference between the 2 arms of the trial. These data suggest that in secondary prevention patients as well as primary prevention patients, a relevant proportion of true ventricular arrhythmias may be self-terminating within 16 to 30 beats, and therefore, a programming strategy that combines a long detection interval with ATP during charging should be considered as the first choice for these patients.

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Efficacy of Long Detection Interval Implantable Cardioverter-Defibrillator Settings in Secondary Prevention Population: Data From the Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients III (ADVANCE III) Trial
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Supplemental Material
Supplemental Figure 1: Number of ATPs and Shocks delivered in the long detection group versus the control group

Figure 1

N. of Delivered ICD therapies
Comparison of Incidence Rate p = 0.008