Effect of Long-Detection Interval vs Standard-Detection Interval for Implantable Cardioverter-Defibrillators on Antitachycardia Pacing and Shock Delivery

The ADVANCE III Randomized Clinical Trial

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Importance Using more intervals to detect ventricular tachyarrhythmias has been associated with reducing unnecessary implantable cardioverter-defibrillator (ICD) therapies.

Objective To determine whether using 30 of 40 intervals to detect ventricular arrhythmias (VT) (long detection) during spontaneous fast VT episodes reduces antitachycardia pacing (ATP) and shock delivery more than 18 of 24 intervals (standard detection).

Design, Setting, and Participants Randomized, single-blind, parallel-group trial that enrolled 1902 primary and secondary prevention patients (mean [SD] age, 65 [11] years; 84% men; 75% primary prevention ICD) with ischemic and nonischemic etiology undergoing first ICD implant at 1 of 94 international centers (March 2008-December 2010).

Interventions Patients were randomized 1:1 to programming with long- (n=948) or standard-detection (n=954) intervals.

Main Outcomes and Measures Total number of ATPs and shocks delivered for all episodes (primary outcomes) and inappropriate shocks, mortality, and syncopal rate (secondary outcomes).

Results During a median follow-up of 12 months (interquartile range, 11-13), long-detection group had 346 delivered therapies (42 therapies per 100 person-years, 95% CI, 38-47) vs 557 in the standard-detection group (67 therapies per 100 person-years [95% CI, 62-73]; incident rate ratio [IRR], 0.63 [95% CI, 0.51-0.78]; $P<.001$). The long- vs the standard-detection group experienced 23 ATPs per 100 person-years (95% CI, 20-27) vs 37 ATPs per 100 person-years (95% CI, 33-41; IRR, 0.58 [95% CI, 0.47-0.72]; $P<.001$); 19 shocks per 100 person-years (95% CI, 16-22) vs 30 shocks per 100 person-years (95% CI, 26-34; IRR, 0.77 [95% CI, 0.59-1.01]; $P=.06$), with a significant difference in the probability of therapy occurrence ($P<.001$); and a reduction in first occurrence of inappropriate shock (5.1 per 100 patient-years [95% CI, 3.7-6.9] vs 11.6 [95% CI, 9.4-14.1]; IRR, 0.55 [95% CI, 0.36-0.85]; $P=.008$). Mortality (5.5 [95% CI, 4.0-7.2] vs 6.3 [95% CI, 4.8-8.2] per 100 patient-years; HR, 0.87; $P=.50$) and arrhythmic syncope rates (3.1 [95% CI, 2.6-4.6] vs 1.9 [95% CI, 1.1-3.1] per 100 patient-years; IRR, 1.60 [95% CI, 0.76-3.41]; $P=.22$) did not differ significantly between groups.

Conclusions and Relevance Among patients receiving an ICD , the use of a long- vs standard-detection interval resulted in a lower rate of ATP and shocks, and inappropriate shocks. This programming strategy may be an appropriate alternative.

Trial Registration clinicaltrials.gov Identifier: NCT00617175

JAMA. 2013;309(18):1903-1911 www.jama.com

THERAPY WITH IMPLANTABLE CARdioverter-defibrillators (ICDs) is now the standard of care in primary[1,2] and secondary prevention.[3] As indications for implants have expanded, concern about possible adverse effects of ICD therapies on prognosis and quality of life has arisen. Several authors have reported that ICD therapies, both appropriate and inappropriate, are associated with an increased risk of death and worsening of heart failure.[4,5] To reduce these unfavorable outcomes, several studies have focused on identifying the best device programming strategies, either by targeting the antitachycardia pacing (ATP) algorithms for interrupting fast ventricular tachyarrhythmias or by investigating the use of prolonged arrhythmia detection intervals.[6-9] Increasing the number of intervals to detect arrhythmias has been shown to safely permit fast ventricular tachyarrhythmia self-

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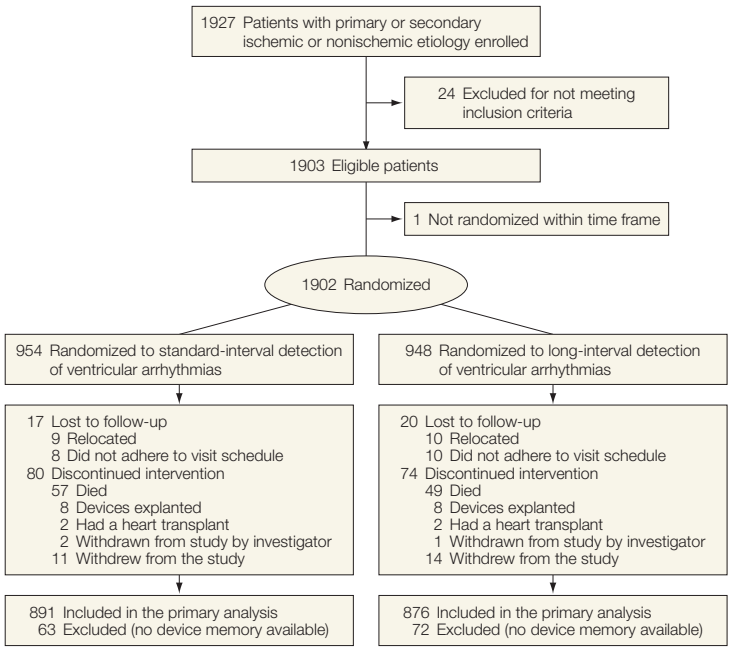
Figure 1. Study Flow of the ADVANCE III Randomized Clinical Trial



termination before therapy delivery.[7,10,11] Recently, the Multicenter Automatic Defibrillator Implantation Trial to Reduce Inappropriate Therapy (MADIT-RIT)[12] demonstrated, in primary prevention patients, that prolonging the detection interval or setting a high cut-off rate reduced inappropriate therapies.

We designed a randomized controlled clinical trial, the ADVANCE III (Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients III) trial, to assess whether increasing the number of detection intervals is an effective strategy in any type of ICD with the capability of delivering ATP during capacitor charge (single-chamber, dual-chamber, and cardiac resynchronization therapy defibrillator devices), among patients with both primary and secondary indications for an ICD implant.

METHODS

Trial Design

The study design has been previously published.[13] ADVANCE III was a randomized, controlled, single-blind (patients were blinded), 1:1 parallel-group, multicenter trial comparing 2 strategies of detection interval device programming in newly implanted ICDs. Enrollment started in March 2008 and stopped in December 2010 at 94 centers in Europe, the Middle East, Russia, and Africa.

Participants

Each center obtained the approval of its medical ethics committee or institutional review board prior to study initiation. All patients were at least 18 years old, provided written informed consent, and underwent their first ICD or cardiac resynchronization therapy defibrillator implant according to current guidelines. Patients were excluded if they had previously undergone ICD implant; had been diagnosed with Brugada syndrome, long QT, hypertrophic cardiomyopathy, ventricular tachyarrhythmia associated with reversible cause; or met other conventional exclusion criteria, as previously published in the trial design.[13] Patients were free to withdraw from the study at any time without compromising their quality of care by the treating cardiologist (FIGURE 1).

Interventions

Implantable cardioverter-defibrillators were programmed to detect arrhythmias with cycle length of 320 ms or less. Therapy settings provided a single attempt at ATP during the capacitor charge for fast arrhythmias with cycle lengths up to 200 ms and shock only for ventricular fibrillation with cycle lengths of less than 200 ms. A "monitor only" ventricular tachycardia detection interval was mandatory for all patients without previous documented ventricular tachycardia. In all patients with a previous history of documented ventricular tachycardia with a cycle length greater than 320 ms, programming was left to each physician and tailored on the recorded ventricular tachycardia. Further details on study programming have been published[13] (eTable 1 available at http://www.jama.com). All other device programming settings were not prespecified and were left to the physicians' discretion.

In the intervention group, prolonged detection was programmed (30 of 40 intervals), which allowed a delay in arrhythmia detection. This delay was applied to allow nonsustained events to self-terminate, thus avoiding unnecessary therapies. Long detection, combined with the ATP-during-charge feature, delays arrhythmia detection, although without excessively delaying therapy, if still needed. Furthermore, in the worst case scenario of ATP failure, the shock is expected to be delivered within 17 to 21 seconds of arrhythmia detection, which is a similar time to that observed in the PainFREE II programming (19-21 seconds).[7] In the standard-interval detection group, conventional detection programming of 18 of 24 intervals was implemented; this had already proved effective in the PainFREE II trial.[7]

End Points

The primary end point hypothesis was that prolonged detection programming of 30 of 40 intervals (long detection) would lead to a 20% reduction in

ICD therapies (ATP or shocks) delivered to terminate spontaneous episodes with a cycle length of 320 ms or less in patients in whom any type of ICD with ATP-during-charge capability had been implanted, in comparison with the number-of-intervals-to-detect programming of 18 of 24 intervals (control group). The rate of ventricular therapies delivered (number of therapies per 100 person-years) was compared between the long-detection and the standard-detection groups over a 12-month follow-up period. *Electrical storm* was defined as the occurrence of 3 or more separate episodes of ventricular tachycardia or ventricular fibrillation within a 24-hour period.[14] Records of the therapies delivered were retrieved either from episodes with electrogram or, if the device had overwritten all the electrograms of the electrical storm, from the episode log. In the case of electrical storm only, the therapies delivered for the first episode were considered for the analysis, as already reported.[11] The principal efficacy secondary end point concerned the evaluation of the percent reduction in the number of shocks delivered per participant to treat appropriate and inappropriate spontaneous episodes with a fast cycle length (cycle length ≤320 ms). Hospitalizations were assessed together with the effects of an ICD therapy on quality of life. Secondary end points regarding safety focused on the rates of death and arrhythmic syncope in the 2 treatment groups.

Sample Size

The study was designed as a superiority trial. The null hypothesis was that the rate of ventricular therapies delivered in number of intervals to detect consisting of 30 of 40 intervals would not differ significantly from the rate of ventricular therapies delivered in number of intervals to detect consisting of 18 of 24 intervals, calculated from a Poisson model. In order to detect an incidence rate ratio (IRR) of 0.80, with a 2-sided type I error of 0.05, the initial sample size of 650 patients per group was computed on the basis of the following assumptions: an incidence rate of ICD therapies of 0.777 per person-year in the standard-interval detection group, an IRR of 0.80 favoring the long-detection group, a Poisson model, a 2-sided α of .05, a power of 92%, and an attrition of 20%.

In 2009, an interim assessment of the rate of events in the control group yielded a lower than expected value of 0.419 per person-year. Thus, the sample size was recalculated under the same null hypothesis, leading to a target size of at least 1800 patients (900 per group) to achieve a 90% power to detect such a difference (with α=5%). The calculations were made using PASS (NCSS LLC) under the assumption of a Poisson distribution of the dependent variable and with adjustment of the sample size for an overdispersion parameter of 1.5. Under this new assumption, we planned to stop enrollment on December 31, 2010. If the minimum number of 1800 patients had not been reached by that date, enrollment would have continued for at most 3 months.

Randomization

Patients were randomized to programming with a long 30 of 40 number of intervals to detect (long-detection group) or the currently used 18 of 24 number of intervals to detect (standard-interval detection group). The randomization list was created by an independent statistician and was centralized and blocked. It was based on randomly permuted blocks. Randomization was strategically stratified to balance baseline characteristics associated with an increased rate of inappropriate shocks, such as device type, atrial fibrillation (AF) and ICD indication.[15,16]

Data Collection

The study required the collection of device data at the baseline and at 3-, 6-, 9- and 12-month follow-up visits. The clinical data collected included quality of life evaluations (EQ-5D) at the baseline and 6- and 12-month visits, and information regarding health care utilization was collected at every visit. The EQ-5D index was reported, whereas 0 refers to the worse and 1 to the best quality of life status. Unscheduled office visits, syncope, adverse events, and data retrieved from the device memory were recorded on case-report forms.

The analysis population included patients for whom device memory data were available at least at one follow-up visit. All sustained ventricular tachycardia or ventricular fibrillation and monitored ventricular tachycardia with stored electrograms were reviewed by at least 2 members of a blind episode review committee to assess appropriateness of device classification and therapy efficacy. In the case of disagreement between the 2 reviewers, the process required a third independent review. If no match was found between the reviews, the episode was adjudicated during a plenary meeting of the episode review committee.

A therapy was deemed successful if the ventricular arrhythmia terminated within 6 beats after therapy delivery. All adverse events were first classified and documented by the study investigators on the case-report forms; they were then reviewed in terms of severity and their relationship with the device and the procedure by a separate independent adverse event committee. The relationship between syncope and arrhythmia episodes was evaluated by means of data from the device memory and case-report form. If no device data were available, the adverse events committee relied on the investigators' classification.

Statistical Methods

Continuous data were summarized for each randomization group as mean (SD) or median (interquartile range [IQR]), and categorical data as counts and percentage. The rate of events (number of therapies, number of hospitalizations, or number of syncopes over time) was computed per 100 person-years and reported separately for each group, together with their 95% confidence intervals.

Rates were compared by means of either a mixed Poisson model or a nega-

tive binomial regression model (if overdispersion was present). A likelihood ratio test was used to evaluate the need for a panel rather than a pooled estimator of the Poisson model (need for random effect) and a negative binomial model rather than a panel Poisson model (need for overdispersion). A random effect was included to take into account intercenter heterogeneity.

Incident rate ratios (IRRs) and 95% confidence intervals were used to measure treatment efficacy of the intervention in comparison with the standard-interval detection group. An IRR of less than 1 would indicate a higher efficacy of the intervention group. The analyses of time-to-the-first event were described by means of Kaplan-Meier curves and compared between the groups by means of the log-rank test. Cox models were fitted and hazard ratios (HRs) with 95% confidence intervals were computed. The proportional hazard assumptions were tested by means of Schoenfeld residuals.

The EQ-5D scores were compared between groups by means of a Wilcoxon signed-rank test. All analyses were performed according to the intention-to-treat principle in the analysis population (as described above) and missing data were not imputed. A sensitivity analysis of the primary end point was performed according to the on-treatment population on those patients included in the primary analysis who did not deviate from the protocol or until there was evidence that the programming did not correctly follow the assigned detection interval as per randomization.

All tests were 2-sided and a 2-tailed P value $<.05$ was considered statistically significant. Stata 12.1 (Stata Corp) was used for computation.

Table 1. Baseline Patient Characteristics

	No. (%) of Patients	
	Standard-Interval Detection (n = 954)	Long-Detection (n = 948)
Patient demographics		
Age, mean (SD), y	65 (11)	65 (11)
Men	803 (84.2)	795 (83.9)
Medical history		
Secondary prevention	248 (26.0)	229 (24.2)
Ventricular fibrillation/ventricular flutter	92 (9.6)	82 (8.7)
Sustained ventricular tachycardia history	160 (16.8)	146 (15.4)
Permanent atrial fibrillation	99 (10.8)	113 (12.3)
New York Heart Association class III or IV	447 (47.5)	460 (49.2)
Angina	126 (13.3)	106 (11.3)
Coronary artery disease	566 (59.3)	567 (59.8)
Previous revascularization	395 (41.5)	396 (41.8)
Previous cardiovascular hospitalizations	467 (49.0)	466 (49.2)
QRS, mean (SD), ms	127 (35)	128 (35)
Left bundle-branch block	303 (31.8)	328 (34.6)
Hypercholesterolemia	494 (52.0)	499 (53.0)
Diabetes	279 (29.3)	275 (29.0)
Chronic kidney disease	105 (11.1)	130 (13.8)
EQ-5D quality of life index[a]	0.72 (0.23)	0.70 (0.23)
Baseline echocardiographic measures		
Moderate or severe mitral regurgitation	113 (13.9)	107 (13.2)
Left ventricular ejection fraction, mean (SD), %	30 (10)	30 (10)
Left ventricular diastolic diameter, mean (SD), mm	64 (9)	64 (9)
Baseline medical therapy		
ACE inhibitors or ARBII	763 (80.0)	768 (81.0)
Antiarrhythmic	204 (21.4)	174 (18.4)
β-Blockers	775 (81.2)	768 (81.0)
Diuretics	767 (80.4)	724 (76.4)
Antiplatelet	556 (58.3)	533 (56.2)
Anticoagulant	307 (32.2)	289 (30.5)
Cardiac glycosides	133 (13.9)	135 (14.2)
Hypolipidemic	541 (56.7)	531 (56.0)
Nitrates	147 (15.4)	130 (13.7)
Other cardiac medications	102 (10.7)	79 (8.3)
Implanted device, chamber		
Triple	387 (40.6)	388 (40.9)
Dual	289 (30.3)	293 (30.9)
Single	278 (29.1)	267 (28.2)

Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitor; ARBII, angiotensin II receptor blockers.
[a]EQ-5D index was reported as 0 indicating the worst and 1 the best quality of life status.

RESULTS

Recruitment and Description of Population

From March 2008 to December 2010, the ADVANCE III trial randomized 1902 patients (948 in the long-interval detection group; 954 in the standard-interval detection group). The median follow-up duration was 12 months (IQR, 11-13 months). Patient disposition is shown in Figure 1. Patient characteristics on randomization were well balanced between treatment groups (TABLE 1). The mean age was 65 years, 84% were men, about 25% were in secondary prevention, 50% were had New York Heart Association class III or IV, and 60% had an ischemic etiology. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers, β-blockers, and diuretics were the most frequent medications and were used in 80% of patients.

Implanted devices included cardiac resynchronization therapy defibrillator in 40.7%, a dual-chamber device in 30.6%; and a single-chamber device in 28.7% of patients. Device memory was

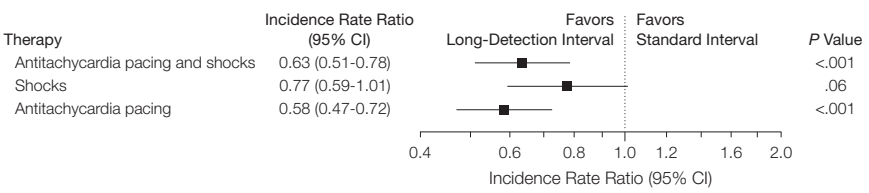
Table 2. Primary End Point Results of Delivered ICD Therapies According to Intention-to-Treat and On-Treatment Analyses

	Exposure, per Patient-Year[a]	No. of Detected Arrhythmias	No. of Therapies Delivered	No. of Patients	Therapy Rate per 100 Patient-Year (95% CI)[b]	IRR (95% CI)[c]	*P* Value
Intention to Treat—Therapies (ATP+Shock)							
Standard-interval detection	830	321	557 Therapies	149	67 (62-73)	1 [Reference]	<.001
Long detection	826	209	346 Therapies	97	42 (38-47)	0.63 (0.51-0.78)	
Intention to Treat—ATP Only							
Standard-interval detection	830	321	308 ATP	192	37 (33-41)	1 [Reference]	<.001
Long detection	826	209	142 ATP	85	23 (20-26)	0.58 (0.47-0.72)	
Intention to Treat—Shock Only							
Standard-interval detection	830	321	249 Shocks	95	30 (26-34)	1 [Reference]	.06
Long detection	826	209	154 Shocks	75	19 (16-22)	0.77 (0.59-1.01)	
On-Treatment—Therapies (ATP+Shock)							
Standard-interval detection	822	313	542 Therapies	147	66 (61-72)	1 [Reference]	<.001
Long Detection	817	181	310 Therapies	91	38 (33-42)	0.60 (0.49-0.74)	

Abbreviations: ATP, antitachycardia pacing; IQR, interquartile range.
[a] Exposure time is measured as the number of patients per year.
[b] Therapy rate is expressed as the number of events per 100 patient-years.
[c] The incident rate ratios (IRRs) and 95% CIs are reported as a measure of efficacy (IRR=rate long-detection group/rate standard-interval detection group) and were tested by means of a negative binomial regression model.

available and used for the analysis in 876 of 948 patients (92.4%) in the long-detection group and in 891 of 954 patients (93.4%) in the standard-interval detection group. A total of 826 patient-years were accumulated in the long-detection group and 830 in the standard-interval detection group.

Figure 2. Treatment Effect Regarding the Primary End Point and Its Components



Primary End Point: ICD Therapies Delivered (ATP+Shocks)

Overall, 530 episodes were recorded and classified by the devices as ventricular arrhythmias. As shown in TABLE 2, a significantly lower combined incidence of ATP and shocks was found in the long-detection group compared with the standard-interval detection group (IRR, 0.63 [95% CI, 0.51-0.78]; $P<.001$; FIGURE 2). The on-treatment analysis gave comparable results (IRR, 0.60 [95% CI, 0.49-0.74] $P<.001$). Considering the 2 components of the primary end point, lower incidences of ATPs and shocks were recorded in the long-detection group, as shown in Figure 2, although statistical significance was reached for ATP only (23 ATP per 100 person-years [95% CI, 20-27] vs 37 ATP per 100 person-years [95% CI, 33-41]; IRR, 0.58 [95% CI, 0.47-0.72]; $P<.001$); 19 shocks per 100 person-years [95% CI, 16-22] vs 30 shocks per 100 person-years [95% CI, 26-34]; IRR, 0.77 [95% CI, 0.59-1.01]; $P=.06$; Figure 2 and Table 2). Of note, Kaplan-Meier estimates of the time to the first ICD therapy (ATP or shock) show a significantly lower probability of receiving a therapy in the long-detection group (log-rank regression test, $P<.001$; FIGURE 3A).

Secondary Efficacy End Points

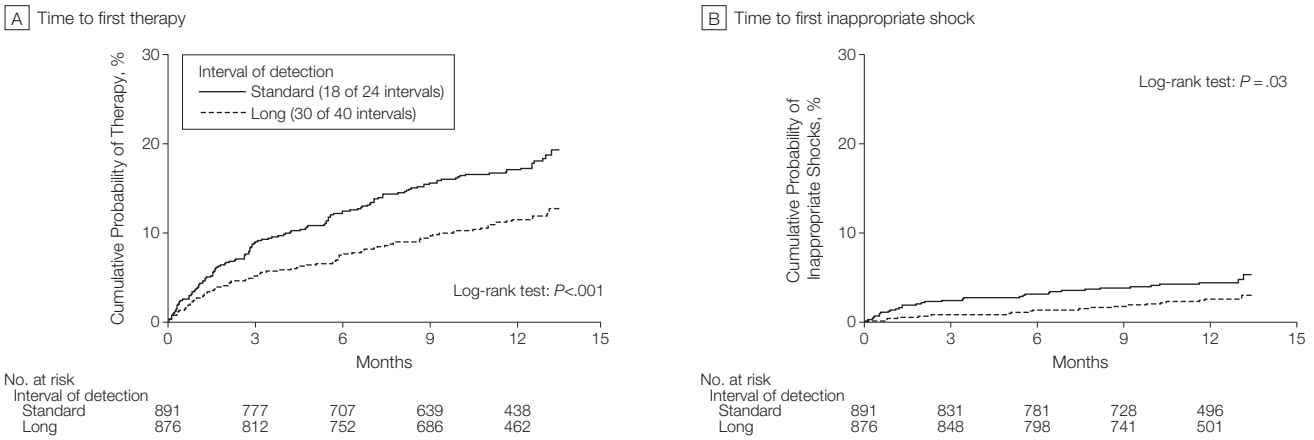
Appropriate and Inappropriate Shocks. The frequency of appropriate shocks was similar between the groups (IRR, 0.95 [95% CI, 0.67-1.37]; $P=.79$), while the long-detection group was associated with a significantly lower incidence of inappropriate shocks (IRR, 0.55 [95% CI, 0.36-0.85]; $P=.008$; TABLE 3). Kaplan-Meier estimates of time to the first inappropriate shock are shown in Figure 3B, confirming the beneficial association with long-interval detection (log-rank test, $P=.03$).

Quality of Life and Hospitalizations. The mean (SD) EQ-5D scores increased from time of implant to the 12-month follow-up examination in both groups (from 0.70 [0.23] to 0.80 [0.22] in the long-detection group and from 0.72 [0.23] to 0.81 [0.22] in the standard-interval detection group, both $P<.001$). The absolute quality-of-life score difference was similar in both groups, with an absolute Δ score of 0.09 (95% CI, 0.00 to 0.23) for the long-detection and 0.05 (95% CI, −0.02 to 0.22) for the standard-interval detection group ($P=.23$).

A lower hospitalization rate was observed in the long-detection group, with a rate of 42.1 per 100 person-years (95% CI, 38.1-46.4) vs 51.7 (95% CI,47.2-56.4; IRR, 0.81 [95% CI, 0.68-0.98]; $P=.03$; eTable 2 available at http://www.jama.com).

Syncope and Death. During the study, 34 patients experienced a total of 40 syncopal episodes related to ar-

Figure 3. Kaplan-Meier Estimates of Time to the First Implantable Cardioverter-Defibrillator Therapy and to the First Inappropriate Shock in Each Group



The analysis population included patients for whom device memory data were available for at least 1 follow-up visit.

rhythmic events (24 events in 20 patients in the long-detection and 16 events in 14 patients in the standard-interval detection group). In all cases, adherence to device programming, according to randomization, was confirmed. The incidence of syncopal episodes was not significantly different in the 2 groups (1.20 and 1.15 syncopes/patient). The rate of syncope in the intervention group (3.1 per 100 person-years; 95% CI, 2.0-4.6) was not significantly different from that of the standard-interval detection group (1.9 per 100 person-years; 95% CI, 1.1-3.1; IRR, 1.60 [95% CI, 0.76-3.41]; $P=.22$).

Forty-nine patients in the long-detection group and 57 in the standard-interval detection group died; this corresponds to a mortality rate of 5.5 per 100 person-years (95% CI, 4.0-7.2) and 6.3 per 100 person-years (95% CI, 4.8-8.2). No significant difference between the groups was seen (HR, 0.87 [0.57-1.32], $P=.50$; eFigure 1).

DISCUSSION

ADVANCE III demonstrated that the use of a long detection setting, in ICDs with the capability of delivering ATP during capacitor charge, significantly reduced the rate of ventricular therapies delivered and inappropriate shocks compared with the standard detection setting. A lower incidence of hospitalizations was also observed in the long-detection group.

Our results confirmed and reinforced, in a larger population, the main results recently presented by the MADIT-RIT trial.[12]

Implantable cardioverter device interventions, especially shocks, have been associated with an increase in mortality and with a worse prognosis in patients with heart failure.[4,17] It is still unclear, however, whether the negative outcome is an adverse effect of shocks or a part of the natural history of extremely compromised patients. Nevertheless, there is general agreement that unnecessary or inappropriate device interventions should be avoided. Previous studies[6-9] have shown that ATP is effective in reducing the number of shocks for fast ventricular tachyarrhythmias. The Primary Prevention Parameters Evaluation (PREPARE)[10] and Role of Long Detection Window Programming in Patients With Left Ventricular dysfunction, Non-ischemic Etiology in Primary Prevention Treated With a Biventricular ICD (RELEVANT)[11] studies demonstrated that, in primary prevention patients, a prolonged detection duration associated with ATP could safely reduce the number of patients receiving shocks. However, both PREPARE and RELEVANT were nonrandomized and included only primary prevention patients. The recently published MADIT RIT trial also enrolled only primary prevention patients; moreover, it excluded patients with single-chamber ICD and those with a history of atrial fibrillation.

Unlike previous studies, ADVANCE III included both primary and secondary prevention patients, with or without atrial fibrillation, in whom single-, dual- and triple-chamber ICD had been implanted; this enabled the strategy of long-detection interval to be extended to a much more comprehensive cohort of ICD recipients. The delayed arrhythmia detection strategy in the ADVANCE III trial resulted in a reduction in the combined end point of all ICD therapies (ATPs and Shocks). Furthermore, additional analysis of the 2 components revealed a significant reduction in ATP ($P<.001$), but no statistically significant difference in the incidence of shocks ($P=.06$). This lack of significance may be related to fact that, in accordance with the trial protocol, ATP was the first therapy in all patients in the event of fast ventricular tachyarrhythmias with a cycle length between 200 and 320 ms, whereas shock therapy was first-line therapy only for extremely fast ventricular arrhythmias (cycle length, <200 ms).

Table 3. Secondary End Point Appropriate and Inappropriate Shocks Results According to Intention-to-Treat Analyses[a]

	Exposure, per Patient-Year)	No. of Ventricular Arrhythmias	No. of Therapies Delivered[b]	No. of Patients	Shock Rate per 100 Patient-Year (95% CI)	IRR (95% CI)[c]	*P* Value
Intention to Treat – Appropriate Shocks							
Standard-interval detection	830	230	147	58	18 (15-20)	1	.80
Long detection	826	163	110	55	13 (11-16)	0.95 (0.67-1.37)	
Intention to Treat – Inappropriate Shocks							
Standard-interval detection	830	85 Inappropriate detections	96	39	11 (9-14)	1	.008
Long detection	826	40 Inappropriate detections	42	22	5 (4-7)	0.55 (0.36-0.85)	

Abbreviation: IQR, interquartile range.
[a] Exposure time is measured as the number of patients per year.
[b] Therapy rate is expressed as the number of events per 100 patient-years.
[c] The incidence rate ratios (IRRs) and 95% CIs are reported as a measure of efficacy (IRR rate long-detection group/rate standard-interval detection group) and were tested by means of a negative binomial regression model.

However, overall therapy-free survival ($P < .001$) as well as inappropriate shock-free survival estimate ($P = .03$) were improved in the long-detection group. At present, the "out of the box" settings used by some ICD manufacturers may be too conservative, with nominal treatment delays as short as 1 to 3 seconds.[18,19] On the basis of the previous evidence[11-13] and the current findings, it seems reasonable that a long-detection interval may be preferable in the majority of patients, especially when using an ICD with ATP-during-charge capability.

The lower incidence of therapies in the long-detection group was not reflected in improved health-related quality of life. ADVANCE III results for quality of life confirm findings previously reported by Mark et al.[20] Shocks seem to be associated with a transitory deleterious effect, which may disappear if quality of life assessments are scheduled weeks or months away from the shock. In our study, quality-of-life questionnaires were required every 6 months; this interval may have been unsuited to recording the temporary effect.[20]

A significant reduction in all-cause hospitalizations was observed in the long-detection group ($P = .03$). Although this aspect was not explored in the MADIT RIT trial, similar findings had previously been reported in the RELEVANT trial,[11] which found a significant reduction in heart failure hospitalizations in primary prevention patients treated with cardiac resynchronization therapy defibrillator devices.

Syncopal events associated with arrhythmic episodes are a major concern. Delayed-detection intervals, if associated with a poorly hemodynamically tolerated arrhythmic event, could lead to complete loss of consciousness and major injuries. In our study, the incidence of syncope was low in both groups, although an excess of 1.2 episodes per 100 person-years was observed in the long-detection group. This could be largely due to individual variability, as also shown by the confidence intervals for the difference in incidence rates, which ranged from −1.4 episodes per 100 person-years (favoring long detection) to 2.3 episodes per 100 person-years (favoring the standard-interval detection group). In addition, syncopal episodes were not associated with serious injuries. Nevertheless, when choosing a delayed detection interval protocol, physicians should be aware of the small potential additional risk associated with long-detection intervals.

The mortality rate reported in the study was low and comparable between the 2 groups (eFigure available at http://www.jama.com). The association between ICD therapies and mortality has been extensively addressed.[4,5,21] Overall survival in our study was comparable with that reported in several similar ICD populations[1,8-10] and to that seen in both the standard-interval detection and the delayed group of MADIT RIT.[12]

To better contextualize the ADVANCE III results, comparison with the recently published MADIT RIT may be useful (eTable 3). Both trials demonstrated that a new device-programming modality that permitted self-termination of nonsustained episodes was associated with a significant reduction in inappropriate therapies and a low incidence of syncope.

However, important differences in both the designs and the results should be discussed.

The MADIT RIT trial enrolled a selected population consisting only of primary prevention patients with sinus rhythm in whom dual-chamber or cardiac resynchronization therapy ICD had been implanted. Conversely, the ADVANCE III strategy may be considered adequate in any patient (primary and secondary prevention, sinus rhythm or atrial fibrillation) with any kind of ICD.

MADIT RIT recorded a reduced mortality rate in the high-rate group, although it is difficult to understand the exact correlation between reduced ATP therapies and reduced mortality. By contrast, ADVANCE III did not observe any difference in mortality between the long-detection and standard-interval detection groups, a finding that is comparable with those previously reported in similar studies.[8-10]

A major concern during our study was that not treating nonsustained arrhythmias, even if not immediately lethal, might lead to a worsening of cardiac condition. Therefore, the ADVANCE III study design also in-

cluded analyses of hospitalizations and quality of life associated with prolonged detection, to provide some understanding of patient outcome.

One of the most important differences between ADVANCE III and MADIT RIT involves the standard-interval detection group. ADVANCE III compared the new detection strategy with the well-accepted 18 of 24 number-of-intervals-to-detect strategy from PainFREE II trial.[7] By contrast, the comparison group in MADIT RIT used the 1- to 2.5-second detection interval presented by the manufacturer as out of the box. Monsour and Khairy[19] pointed out that such a short detection duration might be too aggressive. Moreover, in the ADVANCE III trial, ventricular tachycardia therapies were consistently programmed off in both groups, whereas MADIT RIT used a ventricular tachycardia zone with therapies on in the standard-interval detection group and off in the high-rate group. It is possible that this choice might have inflated the number of events in the standard-interval detection group in MADIT RIT.

Some limitations of the ADVANCE III trial deserve further consideration. All patients enrolled in the trial received devices produced by a single manufacturer. Thus, our results might only apply to patients with ICD from this manufacturer. However, the general idea of the advantages of long detection can be transposed to recent ICD devices, ie, those equipped with an ATP-during-charging capability and a programmable number-of-intervals-to-detect window. Furthermore, in the event of electrical storm, some arrhythmic episodes could have been lost to the final analysis of the primary end point because of the intrinsic limitation of device memory (overwriting previous data). In our study, however, any such loss of follow-up data proved to be limited. In addition, given the randomized nature of the study, no imbalance between the groups, in terms of lost data, should be expected. Although we cannot exclude the possibility that missing information could have biased the results, the percentage of patients exiting the study, both overall and for each reason specified, was sufficiently low and balanced between the study groups; thus, it is unlikely that different conclusions would have been reached with regard to the primary end point.

CONCLUSIONS

The ADVANCE III trial enrolled patients with heart disease of any etiology, in the setting of both primary and secondary prevention, who were treated with single-, dual- or triple-chamber ICDs. In this study, programming a long-detection interval (30 of 40 number of intervals to detect) and ATP during charging compared with a standard-detection interval was effective in reducing the rate of the primary combined end point of total ICD therapies (ATP and shocks) and of inappropriate shocks and hospitalizations. This programming strategy may be a useful approach for ICD recipients.

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Author Contributions: Dr Gasparini had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Gasparini reports serving on the advisory board for Medtronic and Boston SCI. Dr Proclemer reports serving on the advisory board for Medtronic. Dr Klersy reports serving as a statistical consultant for Medtronic. Dr Kloppe reports serving as speaker for Medtronic. Dr Martínez Ferrer reports serving as lecturer and consultant for Medtronic. Dr Lunati reports serving as a consultant for Medtronic, Sorin, Boston SCI, and St Jude Medical. Dr Hersi reports serving as a lecturer for Boehringer-Ingelheim. Dr Gulaj reports serving as a consultant for Biotronik, Medtronic, and Boston SCI, and as a lecturer for Medtronic. Dr Wijffels reports serving as proctor and lecturer for Medtronic. Dr Arenal reports serving as a consultant for Boston SCI and receiving a grant from Biosense-Webster.
Funding/Support: The ADVANCE III study was supported financially by Medtronic Inc.
Role of the Sponsor: Medtronic participated in the design, conduct, and management of the study but had no role in the collection of data; Medtronic participated in review and approval of the manuscript but had no role in the analysis, interpretation of data, or editing of the manuscript.
Independent Statistical Analysis: The statistical analysis of the ADVANCE III data was performed by C. Klersy, MD, MSc, an independent statistician (and author) who had access to the full data set
Online-Only Material: The 3 eTables, eFigure, and eAcknowledgments are available at http://www.jama.com.
Additional Contributions: We dedicate this article to the late Professor Andrzej Okreglicki, MD. The ADVANCE III team is grateful for having had the chance to work with a scientist of such expertise and professionalism. His contributions to the work of the steering committee were an example to the whole team. We thank Joerg O. Schwab, MD, FESC, Bernd Kaup, Giuseppe Ligorio, João de Sousa, MD, and Bernd Lemke, MD, for their input.

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