

Assessment of primary prevention patients receiving an ICD – Systematic evaluation of ATP: APPRAISE ATP



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BACKGROUND The value of antitachycardia pacing (ATP) in the overall cohort of primary prevention patients who receive implantable cardioverter-defibrillators (ICDs) remains uncertain. ATP success reported in prior trials potentially included a large number of patients receiving unnecessary ATP for arrhythmias that may have self-terminated owing to the prematurity of the intervention. Although some patients derive benefit from initial ATP in terminating rapid ventricular arrhythmias and thereby preventing shocks, there are limited data allowing us to identify those patients *a priori*.

OBJECTIVE The purpose of APPRAISE ATP is to understand the role of ATP in primary prevention patients currently indicated for ICD therapy in a large prospective randomized controlled trial with modern programming parameters.

METHODS The study is a global, prospective, randomized, multicenter clinical trial conducted at up to 150 sites globally, enrolling approximately 2600 subjects. The primary endpoint of the trial is *time to first all-cause shock* in a 2-arm study with an equivalent study design in which the incidence of all-cause shocks will be

compared between primary prevention subjects programmed with shocks only vs subjects programmed to standard therapy (ATP and shock).

RESULTS An Electrogram and Device Interrogation Core Laboratory will review interrogation data to determine primary endpoints that occur in APPRAISE ATP. Their decisions are based on independent physician review of the data from device interrogation.

CONCLUSION The ultimate purpose of the study is to aid clinicians in the selection of ICD technologies based on hard endpoint evidence across the spectrum of indications for primary prevention implantation.

KEYWORDS ICD; Primary prevention; VT

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Background

Multiple randomized controlled clinical trials, registries, and observational studies have indicated that patients at risk for sudden cardiac death (SCD) with reduced left ventricular ejection fraction (LVEF) and heart failure enjoy a survival benefit from implantable cardioverter-defibrillators (ICD) as a primary prevention strategy. An ICD is capable of terminating potentially lethal ventricular arrhythmias by shock, antitachycardia pacing (ATP), or both. The frequency, timing, and

mode of termination of these ventricular arrhythmias have a direct impact on the quality of life of ICD recipients. ICD programming is aimed at minimizing device shocks by preventing inappropriate therapies, avoiding unnecessary interventions in self-terminating ventricular arrhythmias (by delaying interventions and choosing appropriate rate cutoffs), and maximizing the utility and efficiency of ATP. The advent of the subcutaneous ICD, which avoids some of the potential complications of endovascular devices but currently lacks ATP capabilities, highlights the need to identify appropriate subgroups of primary prevention cohorts that will be better served by subcutaneous or endovascular devices, or in a not-so-distant future by the addition of ATP modules to subcutaneous devices.

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KEY FINDINGS

- The purpose of APPRAISE ATP (Assessment of Primary Prevention Patients Receiving an ICD – Systematic Evaluation of ATP) is to understand the role of antitachycardia pacing (ATP) in primary prevention patients currently indicated for implantable cardioverter-defibrillator (ICD) therapy in a large prospective randomized controlled trial with modern programming parameters.
- The primary endpoint of the trial is *time to first all-cause shock* in a 2-arm study with an equivalent study design in which the incidence of all-cause shocks will be compared between primary prevention subjects programmed with shocks only vs subjects programmed to standard therapy (ATP and shock).
- APPRAISE ATP is a global, prospective, randomized, multicenter clinical trial. The study will be conducted at up to 150 sites globally, enrolling approximately 2600 subjects followed for a minimum of 18 months.
- The conclusions of the trial would then inform clinical decision-making regarding the selection of ICD technologies and ATP availability and programming based on hard endpoint evidence across the spectrum of indications for primary prevention.

Termination by ATP of fast ventricular tachycardia in secondary prevention patients

ATP was originally developed to terminate macroreentrant ventricular arrhythmias by interfering with the propagation and/or refractoriness of some portion of the tachycardia circuit. Pace termination success is limited by the conduction time to the circuit, the size of the excitable gap, and the ventricular refractoriness of intervening tissue and circuit alike. Given these factors, it was originally believed that termination by pacing was increasingly difficult as the tachycardia cycle length (CL) shortened, and its use was most effective with secondary prevention ICD recipients with relatively slow tachycardias.¹ Success in terminating slow ventricular tachycardia (VT) was achieved in approximately 90% of patients. In 2%–4% of patients, however, ATP accelerated VT into ventricular fibrillation (VF) zones, requiring a shock for arrhythmia termination.

The PainFREE Rx trial was an observational study to evaluate the use of empiric ATP in fast VT (FVT) in a secondary prevention population.² They analyzed 1100 episodes in 65 patients, of which 446 (40%) were classified as FVT (>240 and <320 ms CL) and 57% had slower VTs and 3% VF. They observed FVT termination after 1 ATP sequence in 85% of cases. A sequence of 8 beats at 88% CL was the initial sequence, followed by a second burst at 88% CL minus 10 ms, which raised the success rate to 89%. The median duration of FVT episodes terminated by ATP was <6 seconds, while those requiring shocks for failed ATP sustained for a median of 21 seconds before receiving a

shock. Interestingly, there was a statistically significant difference in the history of nonsustained VT among those patients in which ATP was successful to terminate FVT. The authors acknowledged in the discussion that the high efficacy of ATP in terminating FVT might have been in part owing to the possibility that they were treating self-terminating VTs, which led to the design of a subsequent randomized trial.

PainFREE Rx II³ was a multicenter, randomized study comparing the use of ATP vs shock as first treatment for FVT as defined in the prior study. Patients were randomized to receive 1 ATP sequence followed by shock or shocks only, with both arms programmed to detection of 18 of 24 fast intervals at a rate cutoff of 188 beats per minute (bpm). This study enrolled patients from January 2001 to March 2002 and included patients with secondary indications. ATP was found to have successfully terminated 229 of 284 episodes of FVT (81% unadjusted, 72% after adjusting for multiple events). In the ATP arm 57 episodes were treated by shocks, compared to 99 episodes treated by shocks in the shock-only arm. The number of patients receiving shocks in each arm was not reported. Only 43% of episodes were adjudicated for analysis, given the memory limitation of device storage. All-cause mortality was 10% in the ATP arm and 7% in the shock-only arm. Over one-third of episodes in the shock arm self-terminated during a median 3.3-second capacitor charge time, leading to the possibility that longer detection times could further reduce the rate of ATP and/or shocks for VT. Although it is likely that ATP therapy reduced the number of shocks in a secondary prevention population, the short detection times and the committed nature of shocks used in both PainFREE RX trials did not eliminate the confounding effects of self-terminating episodes that would otherwise require no therapy, and potentially increased the number of shocks in the shock-only arm as compared to the ATP arm. Despite these caveats, the PainFREE trials demonstrated the utility of ATP in terminating FVT in secondary prevention cohorts.

Primary prevention indications trials with secondary prevention programming

The MADIT,⁴ MADIT II,⁵ and SCD-HeFT⁶ trials expanded indications for use of ICDs beyond those patients with a history of VT/VF to those at risk of developing a ventricular tachyarrhythmia. MADIT II allowed physicians to program devices according to investigator discretion. In SCD-HeFT, devices were programmed to deliver shocks alone and the use of ATP was not permitted. These studies did not provide medical evidence to help guide the use of ATP, rate cutoffs, or therapy delays in primary prevention populations. Thus, appropriate programming in primary prevention cohorts remained undefined when primary prevention indications were approved. Thus, legacy secondary prevention programming guidelines were used in primary prevention cohorts, which resulted in high frequency of inappropriate or unnecessary therapies relative to appropriate device use.^{7–9} It became clear that intelligent, specific programming was needed for primary prevention patients.

Primary prevention programming trials

The PREPARE¹⁰ study was a 1-armed observational study that evaluated the effect of prolonged detection intervals in primary prevention patients compared to historical controls. Patients were programmed to a detection interval of 30 of 40 fast beats with a rate cutoff of 182 bpm. The authors reported a significant reduction in the morbidity index (a composite of all-cause shocks, syncope of arrhythmic origin, and untreated sustained symptomatic VT/VF events), from 0.26 events/year in the PREPARE cohort, as compared to 0.69 events/year in the historical cohort ($P = .003$).

The ADVANCE III¹¹ study tested the hypothesis that further prolongation of the delay prior to initiating therapy may reduce ICD therapies, consisting of both shock and ATP delivery. Patients were enrolled from March 2008 to December 2010 and included both secondary and primary prevention patients (25% and 75%, respectively). Patients were randomized to ATP delivery with standard detection (18/24 intervals) vs ATP delivery with long detection (30/40 intervals) with a rate cutoff of 188 bpm in both arms. Assuming a ventricular tachyarrhythmia with a 300 ms CL, this analysis compared a 5.4-second to a 9.0-second delay. After an average follow-up interval of 12 months, the authors reported a 37% reduction in the incidence of a composite of shock and ATP therapies ($P < .001$) that was driven predominantly by a 42% reduction in the incidence of ATP alone ($P < .001$). In the treatment arm, 3% of patients received appropriate ATP and no shocks. The reduction in the incidence of shocks approached but did not achieve statistical significance (23%, $P = .06$). No stratification between primary and secondary prevention patients was reported. The authors concluded that a strategy of prolonged device detection significantly reduced the rate of ICD therapies.

MADIT-RIT was the first randomized programming trial in a homogeneous primary prevention population and compared conventional programming with either high-rate cutoff therapy (>200 bpm) or delayed therapy (60 seconds between 170 and 200 bpm and 12 seconds between 200 and 250 bpm).¹² Both strategies were very successful in reducing the risk of inappropriate ICD therapy (ATP or shock), with high-rate therapy associated with a 79% reduction ($P < .001$) and delayed therapy associated with a 76% reduction ($P < .001$) in inappropriate therapies.

Interestingly, examination of *appropriate* ATP delivered in MADIT-RIT revealed 446 therapy events in the conventional programming arm, compared to 113 events in the high-rate therapy arm and 143 events in the delayed therapy arm. The authors noted that this finding suggested that much of the ATP delivered in the conventional programming arm was prematurely delivered for nonsustained ventricular tachyarrhythmias and was therefore clinically unnecessary. Syncopal events were equally distributed among all therapy arms. Moreover, the conventional therapy arm was associated with a statistically significant increase in all-cause mortality when compared to each of the novel programming arms. An analysis of mortality in MADIT-RIT revealed a statistically significant

association between ATP (mostly inappropriate delivered ATP) and all-cause mortality (hazard ratio = 3.25, 95% confidence interval 1.33–7.94, $P = .01$) while no association was found between appropriate ATP and all-cause mortality (hazard ratio = 1.02, 95% confidence interval 0.36–2.88, $P = .977$).¹³ The association does not necessarily imply causality but suggested that further investigation into ATP in primary prevention populations is warranted.

A recently published sub-study of MADIT-RIT aimed to evaluate the therapy distribution for adjudicated VA ≥ 200 bpm among the 3 arms of the study.¹⁴ The only difference between programming arms in the 200–250 bpm zone was therapy delay (1, 2.5, and 12 seconds, respectively, after confirmed detection). In all arms, therapy started with a sequence of ATP followed by shock. Above 250 bpm all patients received shocks with no preceding ATP, as shown in Figure 1. This study revealed a statistically significant reduction of ATP interventions for VA ≥ 200 bpm with therapy delays up to 12 seconds, suggesting that most VT events were self-terminating. Initial therapy was ATP in 10.5% in the conventional arm compared to 4.2% and 2.5% in high-rate and delayed programming arms (Figure 1). Most strikingly, despite this difference in initial ATP therapy, final shock therapy rate was similar in all arms, suggesting that the value of ATP in terminating rapid ventricular arrhythmias may have been overestimated in past trials owing to the prematurity of the intervention in otherwise self-terminating arrhythmias.

APPRAISE ATP study

We conclude from these data that the value of ATP in the overall cohort of primary prevention patients who receive ICDs remains uncertain. ATP success reported in prior trials potentially included a large number of patients receiving unnecessary ATP for arrhythmias that may have self-terminated owing to the prematurity of the intervention. Although some patients derive benefit from initial ATP in terminating rapid ventricular arrhythmias and thereby preventing shocks, there are limited data allowing us to identify those patients *a priori*.

The purpose of APPRAISE ATP is to understand the role of ATP in primary prevention patients currently indicated for ICD therapy in a large prospective randomized controlled trial with modern programming parameters. This knowledge would then inform clinical decision-making regarding the selection of ICD technologies based on hard endpoint evidence across the spectrum of indications for primary prevention.

The primary endpoint of the trial is *time to first all-cause shock* in a 2-arm study with an equivalent study design in which the incidence of all-cause shocks will be compared between primary prevention subjects programmed with shocks only vs subjects programmed to standard therapy (ATP and shock).

Study design

Assessment of Primary Prevention Patients Receiving an ICD-Systemic Evaluation of ATP (APPRAISE ATP; [ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT02923726) is a global,

VENTRICULAR ARRHYTHMIAS

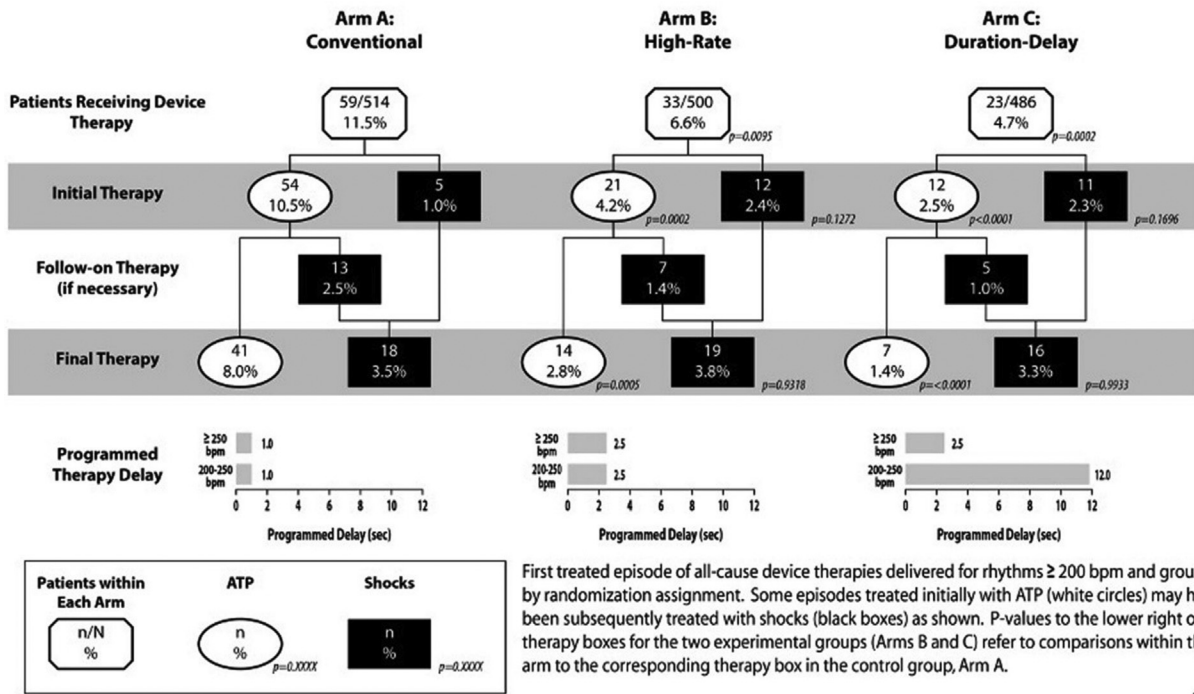


Figure 1 MADIT-RIT ventricular arrhythmias occurring above 200 beats per minute (bpm). ATP = antitachycardia pacing.

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prospective, randomized, multicenter clinical trial. The study will be conducted at up to 150 sites globally, enrolling approximately 2600 subjects. Institutional review board approval at each participating institution will be obtained in compliance with ethical guidelines, prior to patient enrollment. Subjects will be consented for follow-up visits through 60 months. Their length of participation will differ depending on when they entered the study.

The study will conclude after the earliest of 1 of following occurrences: (1) 1 arm is determined to be superior at 1 of the 3 interim analyses, or (2) a number of adjudicated shock episodes have occurred to sufficiently power the primary endpoint. Under current assumptions, it is expected that the last enrolled patient will be followed for approximately 18 months and the first enrolled patient will be followed for approximately 60 months. The study flow, data collection, and patient follow-up are illustrated in Figure 2.

Endpoints

The primary endpoint collected postrandomization is time to first all-cause shock.

The secondary endpoints are:

- Time to first all-cause shock or death from any cause
- Time to death from any cause
- Time to first appropriate shock
- Time to first inappropriate shock

The tertiary objective is a multivariate analysis to determine covariates associated with the use of ATP, bradycardia

pacing, and the need for future cardiac resynchronization therapy pacing therapy.

Study population

The study population for the APPRAISE ATP trial consists of patients who meet the guidelines¹⁵ for ICD therapy for primary prevention patients.

Patients may be included with a prior myocardial infarction and LVEF ≤ 30%, or LVEF ≤ 35% and NYHA class II or III (ischemic or nonischemic cardiomyopathy). Key exclusion criteria are history of spontaneous sustained VT (≥160 bpm at ≥30 seconds in duration) or VF not due to a reversible cause, NYHA class IV documented in medical records 90 days prior to enrollment, scheduled cardiac resynchronization therapy implant, previous subcutaneous ICD, existing transvenous ICD device implanted for greater than 60 days, coronary artery bypass graft or percutaneous coronary intervention 90 days prior to enrollment, documented myocardial infarction within 90 days prior to enrollment, on the active heart transplant list, current or scheduled to receive ventricular assist device, life expectancy shorter than 18 months owing to any medical condition, currently requiring hemodialysis, and known to be pregnant or plans to become pregnant over the course of the trial.

Programming

Each arm will be programmed to 3 tachycardia detection zones. Zones 1 (monitor) and 3 (VF) are the same in each arm, while zone 2 (VT) is programmed to ATP and shock

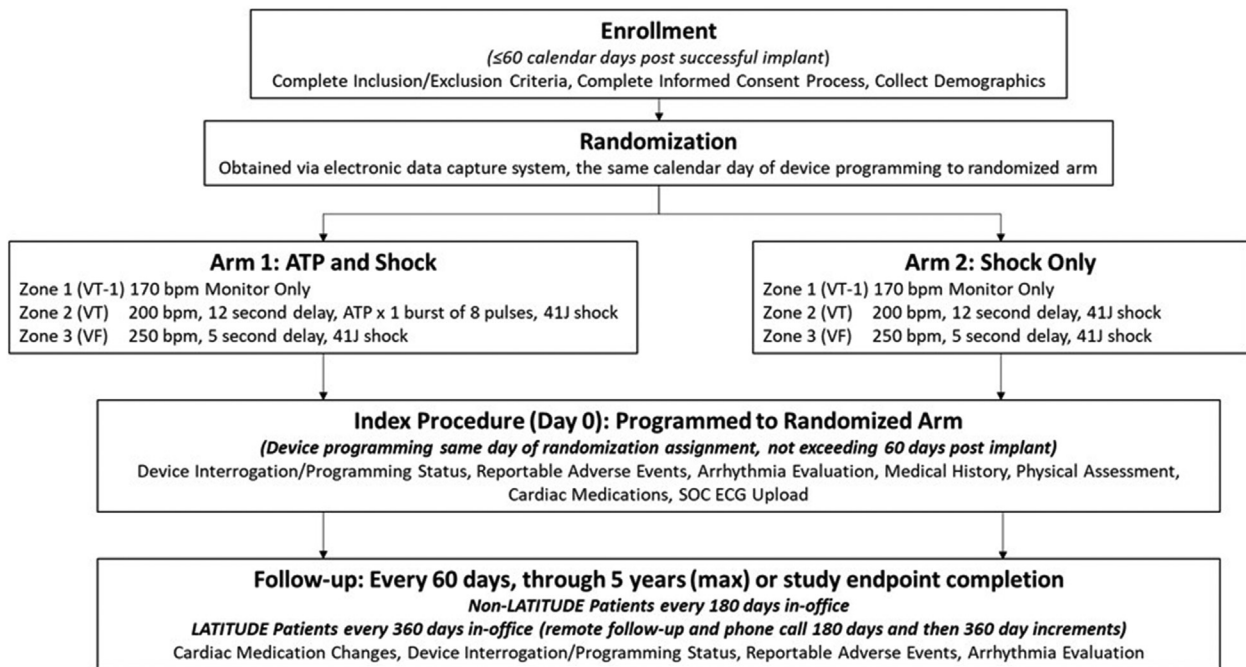


Figure 2 APPRAISE ATP study design. ATP = antitachycardia pacing; bpm = beats per minute; SOC ECG = standard-of-care electrocardiogram; VF = ventricular fibrillation; VT = ventricular tachycardia.

or shock only (Table 1 and Figure 3). Programming is aligned with the current 2015 HRS Consensus guidelines – Manufacturer Specific Translation of the HRS Consensus^{16,17}:

VT Zone: ≥200 bpm, 12-second delay, ATP × 1 burst of 8 pulses at 84% CL followed by 41 joule shock if necessary, vs no ATP and 41 joule shock.

VF Zone: ≥250 bpm, 5-second delay, 41 joule shock.

Statistical methods and sample size calculation

The study was designed to show that the absence of ATP therapy in a primary prevention ICD cohort is not only non-inferior but equivalent to devices delivering ATP by measuring the incidence of all-cause shock. Noninferiority and equivalence appear to be used interchangeably in the medical literature but have specific meanings:

- **Noninferiority** indicates that the new treatment is no worse than the reference treatment by some margin that represents a difference that is clinically meaningful; may be used for a treatment that is cheaper or easier to administer.

Table 1 Programming by randomized arm

	Arm 1: ATP and shock	Arm 2: shock only
Zone 1 (VT-1)	≥170 bpm monitor only	
Zone 2 (VT)	≥200 bpm, 12-second delay ATP (1 burst of 8 pulses, 84% CL) 41 J shock	≥200 bpm, 12-second delay 41 J shock
Zone 3 (VF)	≥250 bpm, 5-second delay, 41 J shock	

ATP = antitachycardia pacing; bpm = beats per minute; CL = cycle length; VF = ventricular fibrillation; VT = ventricular tachycardia.

- **Equivalence** indicates that the new treatment is no better and no worse than the reference treatment by some margin (\pm delta) that represents a difference that is clinically meaningful.

The hazard ratio of all-cause shocks will be used to evaluate the equivalence of shock-only programming vs standard (ATP and shock) therapy. A relative equivalence margin (delta) of 35% in each direction will be employed, resulting in an equivalence region ranging from 0.65 to 1.54 (1/0.65). The APPRAISE ATP steering committee selected this equivalence region because it represented a clinical margin of indifference that could be studied with a reasonable number of subjects and duration of follow-up. The following hypotheses will be used to test the primary endpoint:

H_0 : hazard ratio \leq 0.65 or hazard ratio \geq (1/0.65)

H_A : $0.65 <$ hazard ratio $<$ (1/0.65)

A total of at least 2600 randomized subjects—1300 per group—will be required to sufficiently power the primary endpoint. The sample size of 2600 subjects will provide the 284 subjects with a shock therapy episode necessary to power the primary endpoint. The following assumptions were used to determine the required number of primary endpoint shock therapy events: shock rate of 6%–7% at 18 months; attrition rate owing to death, withdrawal, or loss to follow-up of 10% at 18 months; 5% type I error/alpha and 90% power.

All randomized subjects will contribute to the analysis of the primary endpoint. Cox proportional hazards modeling will be performed with time to first shock therapy episode used as the outcome and programming scheme used as the covariate in the model. Traditional therapy (ATP and shock) will be considered the reference group in the analysis. Each

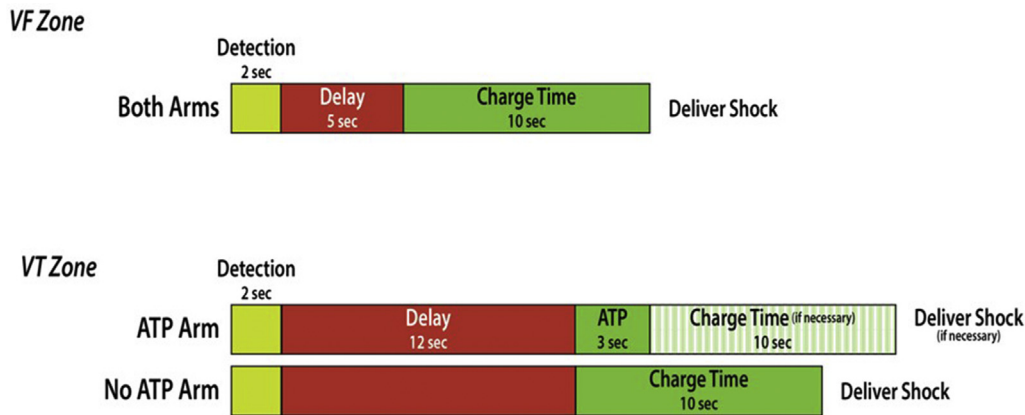


Figure 3 Programming of zones 2 and 3 of the trial, with estimated times to therapy. ATP = antitachycardia pacing; VF = ventricular fibrillation; VT = ventricular tachycardia.

subject’s first shock therapy episode will contribute to the analysis. Subjects without a shock therapy episode will be censored at their date of death, withdrawal, or study exit, or on the date of the data snapshot, whichever occurs first. If the confidence interval for the hazard ratio is fully contained within the equivalence region—between 0.65 and 1.54—equivalence of shocks only and standard programming will be concluded.

If equivalency cannot be established, further testing for superiority will be performed without need for a multiplicity adjustment to the significance level of the test beyond the adjustment necessary to accommodate the interim superiority tests. This additional testing is possible because the equivalence test is composed of 2 separate 1-sided noninferiority tests. If noninferiority is established for only 1 of the 2 1-sided noninferiority tests, superiority can further be tested, per gating methodology (Figure 4).

Planned interim analyses

Despite the overall hypothesis of equivalency for the study, interim superiority analyses were designed to identify the scenario in which the shock rates significantly differed between the 2 groups. Four analyses (3 interim analyses and 1 final) will be performed, occurring after approximately 71, 142, 213, and 284 primary endpoint events have been observed. The overall study type I error/alpha will be maintained at 5% through use of an O’Brien-Fleming-type error spending function.

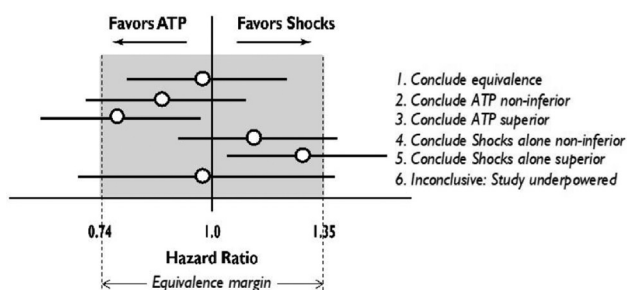


Figure 4 Possible outcomes of the APPRAISE ATP study: equivalence, noninferior, superior, inconclusive. ATP = antitachycardia pacing.

Subgroup analyses

Analyses will be performed to assess whether significant interactions exist between randomization group and various baseline characteristics. Analyses will evaluate, but are not limited to, baseline characteristics subgroups by gender, ischemic status, diabetes, and age ≥ 65 or < 65 .

Regardless of the results of the interaction test for each characteristic, analyses of each subgroup will be performed. Analyses will be conducted for the primary endpoint and all secondary endpoints.

Core lab and event adjudication

An Electrogram and Device Interrogation Core Laboratory will review interrogation data to determine primary endpoints that occur in APPRAISE ATP. Their decisions are based on independent physician review of the data from device interrogation. The Duke Clinical Research Institute Arrhythmia Core Lab (ACL) is responsible for study event adjudications. The ACL reviewers will be composed of a panel of physicians who have expertise in cardiovascular medicine and clinical cardiac electrophysiology. No sponsor representative will serve as an ACL reviewer.

The ACL Committee will review and adjudicate arrhythmia events for the following:

- All-cause ICD therapies
- Appropriate ICD therapies
- Inappropriate ICD therapies
- Sustained arrhythmias without therapy

Every event that meets these criteria will be adjudicated until the primary endpoint is met.

Discussion

The retrospective analysis of the MADIT-RIT cohort for appropriate therapies at or above 200 bpm demonstrated that increasing therapy delays resulted in marked reductions in the utilization of ATP therapies as the time to therapy was increased from 3.4 seconds (arm A) to 4.9 seconds (arm B) to 14.4 seconds (arm C).¹⁴ Furthermore, analysis of the 2 types of ICD therapies (ATP or shock) revealed that the incidence

of appropriate shocks delivered for ventricular arrhythmias ≥ 200 bpm was similar across all 3 arms, with no significant differences. These findings altogether suggested a limited value of ATP for treating fast ventricular arrhythmias ≥ 200 bpm once modern programming with longer detection delays was applied in primary prevention ICD populations as opposed to ATP great efficacy in secondary prevention populations with documented VT.

The only plausible explanation for the above observations is that as therapy delay is increased, many of the ventricular arrhythmias self-terminate; hence the value of ATP effectiveness in a primary prevention population could be overestimated. Moreover, MADIT RIT and ADVANCE III study results demonstrated that relatively long therapy delays are well tolerated, without an increase in cardiovascular morbidity, while enormously reducing the frequency of unnecessary interventions, mainly ATP.

We surmise from the data that the value of ATP in primary prevention ICD patients may have been overestimated in earlier studies owing to the prematurity of the intervention. Considering these findings, a substantially larger prospective randomized controlled trial is necessary to reassess the value of ATP in primary prevention cohorts. Given that inappropriately delivered ATP has been associated with increased mortality and that the value of ATP maybe limited to a specific subset of patients, APPRAISE ATP has been designed to identify such cohorts and ascertain in a large clinical trial with modern programming parameters if ATP should be available to all patients. The result of this trial will aid clinical practice as to appropriate selection of the right device platform for different subsets and establish when ATP is likely to be of value or potentially detrimental.

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Disclosures

Claudio D. Schuger reports honoraria for advisory board, event committees from Boston Scientific, Medtronic; James P. Daubert reports honoraria for advisory boards, events committees, lectures from Medtronic, Boston Scientific, Abbott, Microport, Biotronik, Biosense Webster, Farrapulse and VytronUS; ZOLL. The other authors have no conflicts to disclose.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent

All subjects will complete an informed consent process.

Ethics Statement

Institutional review board approval at each participating institution will be obtained in compliance with ethical guidelines.

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