10.1161/CIRCULATIONAHA.121.057816

Efficacy and Safety of Appropriate Shocks and Antitachycardia Pacing in Transvenous and Subcutaneous Implantable Defibrillators: An Analysis of All Appropriate Therapy in the PRAETORIAN trial

Running title: *Knops et al.; Appropriate therapy in PRAETORIAN*

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**This work was presented AHA Scientific Sessions 2021, November 13-November 15, 2021.

Abstract

Background The PRAETORIAN trial showed non-inferiority of the subcutaneous implantable cardioverter-defibrillator (S-ICD) compared to the transvenous ICD (TV-ICD) with regard to inappropriate shocks and complications. In contrast to the TV-ICD, the S-ICD cannot provide antitachycardia pacing (ATP) for monomorphic ventricular tachycardia (VT). This pre-specified secondary analysis evaluates appropriate therapy and whether ATP reduces the number of appropriate shocks.

Methods: The PRAETORIAN trial was an international, investigator-initiated randomized trial, which included patients with an indication for ICD therapy. Patients with prior VTs below 170 bpm or refractory recurrent monomorphic VTs were excluded. In 39 centers, 849 patients were randomized to receive an S-ICD (N=426) or TV-ICD (N=423) and were followed for a median of 49.1 months. ICD programming was mandated by protocol. Appropriate ICD therapy was defined as therapy for ventricular arrhythmias. Arrhythmias were classified as discrete episodes and storm episodes (≥3 episodes within 24 hours). Analyses were performed in the modified intention-to-treat population.

Results: In the S-ICD group, 86/426 patients received appropriate therapy, versus 78/423 patients in the TV-ICD group, during a median follow-up of 52 months (48-month Kaplan–Meier estimates 19.4% and 17.5%, P=0.45). In the S-ICD group, 83 patients received at least one shock, versus 57 patients in the TV-ICD group (48-month Kaplan–Meier estimates 19.2% and 11.5%, P=0.02). Patients in the S-ICD group had a total of 254 shocks, compared to 228 shocks in the TV-ICD group (P=0.68). First shock efficacy was 93.8% in the S-ICD group and 91.6% in the TV-ICD group (P=0.40). The first ATP attempt successfully terminated 46% of all monomorphic VTs, but accelerated the arrhythmia in 9.4%. Ten S-ICD patients experienced 13 electrical storms, versus 18 TV-ICD patients with 19 electrical storms. Patients with appropriate therapy had an almost two-fold increased relative risk of electrical storms in the TV-ICD group compared to the S-ICD group (P=0.05).

Conclusions: In this trial, no difference was observed in shock efficacy of the S-ICD compared with the TV-ICD. Although patients in the S-ICD group were more likely to receive an ICD shock, the total number of appropriate shocks was not different between the two groups.

Clinical Trial registration: URL: http://www.clinicaltrials.gov Unique identifier: NCT01296022

Keywords: Implantable cardioverter defibrillator, shock efficacy, antitachycardia pacing

Nonstandard Abbreviations and Acronyms

ICD	Implantable cardioverter-defibrillator
S-ICD	Subcutaneous implantable cardioverter-defibrillator
TV-ICD	Transvenous implantable cardioverter-defibrillator
ATP	Antitachycardia pacing
VT	Ventricular tachycardia
VF	Ventricular fibrillation
IQR	Interquartile range
HR	Hazard ratio
95%CI	95% confidence interval
RR	Relative risk
GEE	Generalized estimation equation

Clinical Perspective

What is new?

- This is the first trial to study the shock efficacy of the S-ICD and the TV-ICD in a randomized population.
- Although efficacy of the first ATP attempt was 46% in monomorphic VTs, the number of shocks was not different between the S-ICD and the TV-ICD.

What are the clinical implications?

- Shock efficacy is not statistically different between the S-ICD and TV-ICD, and the decision for either device should be made in a shared decision-making process between patient and physician.
- Physicians are recommended to observe the efficacy of ATP in the individual patient. When ATP is repeatedly unsuccessful in terminating ventricular arrhythmias, we recommend to limit programming to a single ATP attempt.

Introduction

Implantable cardioverter-defibrillators (ICDs) improve survival in those at risk for ventricular arrhythmias and sudden cardiac death[1-3]. The subcutaneous ICD (S-ICD) is an effective and extravascular alternative to the traditional transvenous ICDs (TV-ICD). The randomized controlled PRAETORIAN trial demonstrated non-inferiority of the S-ICD compared to the TV-ICD with regard to inappropriate shocks and complications in patients with a class I or IIa indication for ICD therapy according to current guidelines[4]. Antitachycardia pacing (ATP) has been developed as a painless method to terminate ventricular tachycardias (VT) and might decrease the number of appropriate shocks[5]. On the other hand, ATP might be given unnecessarily for VTs that would have ended spontaneously and might even accelerate VTs. The reported efficacy ranges from 52-81%, and some studies have observed a higher mortality in patients treated by ATP[6-10]. Due to its extrathoracic design, the S-ICD is incapable of providing pacing therapy including ATP[11,12]. In this pre-specified secondary analysis of the PRAETORIAN trial, we aim to determine the efficacy and safety of ATP and shocks by comparing appropriate therapies in the S-ICD and TV-ICD. Specifically, we investigated whether ATP reduced the number of appropriate ICD shocks.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Design and population of the PRAETORIAN trial

The PRAETORIAN trial was an international, investigator-initiated, multicenter, randomized noninferiority trial that was conducted in the United States and Europe[4]. Enrollment started in March 2011 and ended in January 2017. Patients with a class I or IIa indication for ICD therapy and without the need for bradycardia pacing or cardiac resynchronization therapy

were eligible to participate in this trial. Patients with known VT at a rate below 170 beats per minute and patients with refractory recurrent monomorphic VT that could not be managed with medication or ablation therapy were excluded. Patients were randomly assigned in a 1:1 ratio to receive either an S-ICD or TV-ICD, with stratification according to center. Programming of detection and therapy parameters was standardized and aimed to reduce avoidable appropriate and inappropriate shocks (Table 1). Deviation from the recommended device programming was allowed in order to fit the specific characteristics of the patient. The study protocol was approved by the institutional review committees and all the patients provided written informed consent.

Endpoint definitions

The main endpoints of this secondary analysis include total appropriate therapy and patients with appropriate therapy and first shock efficacy. A post hoc analysis was performed to evaluate the efficacy of ATP and the occurrence of electrical storms. Appropriate ICD therapy was defined as ATP or shock therapy for either VT or ventricular fibrillation (VF). Successful therapy was defined as either a shock or ATP that is able to convert the ventricular arrhythmia to sinus rhythm or atrial fibrillation within 5 seconds. Shock efficacy was defined as the percentage of successful shocks of the total amount of shocks. ATP efficacy was calculated as the proportion of successful ATP attempts of the total ATP delivered on a monomorphic VT. ATP for polymorphic VT and VF were excluded from the calculation of ATP efficacy, since ATP is not expected to be successful for these arrhythmias. The start of a ventricular arrhythmia marked the beginning of an episode and episodes end after conversion of the arrhythmia. Episodes were classified as discrete and storm episodes. An electrical storm was defined as three or more episodes of VT/VF within 24 hours[13]. Cardiac rhythm at time of ICD therapy was adjudicated by an independent Clinical Event Committee, consisting of three experienced electrophysiologists not otherwise involved in the trial. Analyses for all the

endpoints were performed in the modified intention-to-treat population, which included patients according to the group to which they had been randomly assigned, regardless of the device they received, but excluded patients who did not receive any ICD. An as-treated analysis that included patients according to the ICD that they first received, as well as a per protocol analysis that censors patients if they receive a different ICD at any moment in the study, were performed for the occurrence of electrical storms in both groups and are included in the Supplementary Appendix.

Statistical analyses

Descriptive statistics are reported as mean ± SD or median with interquartile range (IQR) for continuous variables and numbers and percentages for categorical variables. Baseline variables were compared using the fisher exact test, $\chi 2$ test, Student's t-test or Mann–Whitney U-test when appropriate. For time to event variables, Kaplan-Meier curves displaying the pattern of events are constructed and 4-year Kaplan-Meier estimates of the event rate are reported for both study groups and compared using log-rank tests. Subjects without events are censored at their last known event-free time point. Hazard ratios (HR) and 95% confidence intervals (95%CI) were calculated by Cox proportional-hazards model. Univariable and multivariable Cox' proportional hazard models were performed to find predictors of appropriate therapy. Relative risks (RR) and 95%CI were estimated using the Wald method. A negative binomial regression analysis was performed to assess the rate ratio of appropriate shocks between the groups. In order to adjust for multiple episodes per patient, shock and ATP efficacy estimations were adjusted using the generalized estimating equation (GEE) method with exchangeable correlation matrix. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using R software version 4.0.3 (RStudio PBC, Boston, Massachussets). Detailed information on the statistical analyses can be found in the Supplementary Appendix.

Results

In the PRAETORIAN trial, a total of 849 patients were included of whom 426 patients were assigned to the S-ICD group and 423 patients to the TV-ICD group. Baseline characteristics of the population are presented in Table S1. Further details and results of the PRAETORIAN trial are published elsewhere[4,14].

In the S-ICD group, 86 patients had a total of 256 episodes with appropriate therapy, versus 78 patients in the TV-ICD group with 348 episodes, during a median follow-up time of 52 months (IQR 41.4 – 68.5 months). There was no statistical difference in the number of patients with appropriate therapy between the two groups (48-month Kaplan–Meier estimated cumulative incidence, 19.4% and 17.5%, respectively; HR 1.12; 95%CI 0.83 – 1.53; P=0.45, Figure 1). Median time from start arrhythmia to first therapy was 17.4 seconds in the S-ICD group (IQR 15.0 – 20.4 seconds) versus 10.4 seconds in the TV-ICD group (IQR 9.2 – 12.6 seconds).

In the S-ICD group, of 2/256 episodes (0.8%) the electrograms of appropriate therapy were not available, versus 106/348 episodes (30.5%) with an unavailable electrogram in the TV-ICD group. Three patients who received appropriate therapy were primarily implanted with a different device than the group they were randomized to (0/86 in the S-ICD group versus 3/78 in the TV-ICD group). Five additional patients crossed over during follow-up (5/86 in the S-ICD group versus 0/78 in the TV-ICD group) and 13 patients received an upgrade to a CRT-D during follow-up (8/86 in the S-ICD group versus 5/78 in the TV-ICD group). A list of the crossovers is presented in Table S2.

The clinical characteristics at baseline of patients with appropriate therapy were similar in the two groups (Table 2). Median age was 63 years (IQR 55 – 68), 17.1% were women, 68.3% had an ischemic cardiomyopathy and 28.1% received their ICD due to a secondary prevention indication. The median ejection fraction was 28% (IQR 20% – 35%). A

multivariable analysis showed that a secondary prevention indication for ICD therapy and a lower left ventricular ejection fraction at baseline were significantly associated with an increased risk for appropriate therapy (P<0.01 and P<0.01, Table S3).

Appropriate shocks

In the S-ICD group, 83 patients were treated with at least one shock, versus 57 patients in the TV-ICD group (48-month Kaplan–Meier estimated cumulative incidence, 19.2% and 11.5%, respectively; HR 1.52, 95%CI 1.08 – 2.12, P=0.02, Figures 2 and 3). A total of 254 shocks occurred in 242 episodes in the S-ICD group and 228 shocks occurred in 193 episodes in the TV-ICD group (0.60 versus 0.54 shock per patient, Rate Ratio=1.11, P=0.68, Table S4). First and final shock efficacy were 93.8% and 97.9% in the S-ICD group versus 91.6% and 98.4% in the TV-ICD group (P=0.40 and P=0.70, Figure S1). The arrhythmias that were not terminated by the ICD all ended spontaneously after the final shock and no deaths were observed due to an inefficient shock. Shock efficacy adjusted per multiple episodes per patient is described in Table S5A. This analysis included 11 S-ICD patients who had 18 shocks on VTs below the programmed therapy zone due to cardiac oversensing. Details of the number of shocks across different arrhythmia rates are provided in Table S6. Median time from start arrhythmia to first shock was shorter in the TV-ICD group (17.8 seconds in the S-ICD group [IQR 15.3 – 20.6 seconds] versus 13.8 seconds in the TV-ICD group [IQR 11.6 – 17.1 seconds]).

Appropriate ATP

As this analysis was performed on the modified intention-to-treat population, which included crossovers, 18 ATP attempts were observed in 5 patients in the S-ICD group. In the TV-ICD group, 328 ATP attempts occurred in 56 patients, of which 259 (79.0%) were first ATP attempts. Three of 86 patients (3.5%) in the S-ICD group and 21/78 patients (26.9%) in the TV-ICD group were treated by ATP only. Of the 259 total first ATP attempts, 234 (90.3%)

were given on monomorphic VTs with an efficacy of 46% (95%CI 39.9% – 52.6%). The first ATP attempt on a monomorphic VT accelerated the tachycardia in 9.4% of all episodes, which affected 15 patients (19.2%, Figure 4). ATP efficacy decreased when multiple attempts were given (Table S5B). In total, 102/182 discrete episodes (56%) in the TV-ICD group were terminated by ATP only. Details of the efficacy of ATP across different arrhythmia rates are provided in Table S7.

Electrical storms

A total of 10/86 patients (11.6%) in the S-ICD group experienced 13 electrical storms, with 89 storm episodes in which 91 shocks were administered by the ICD. In the TV-ICD group, 18/78 patients (23.1%) experienced 19 electrical storms with 166 storm episodes in which 149 shocks and 148 ATP attempts were delivered (Figure 5). Patients with appropriate therapy had an almost two-fold increased relative risk of electrical storms in the TV-ICD group compared to the S-ICD group (RR 1.98, 95%CI 0.98 –4.04, P=0.05). These findings were consistent in the as-treated (relative risk 1.99, 95%CI 1.02 – 4.04, P=0.04) and per protocol analyses (relative risk 1.99, 95%CI 0.98 – 4.04, P=0.05, Table S8).

There were no significant differences in baseline characteristics of patients with an electrical storm compared with patients without an electrical storm (Table S9). In 6/19 electrical storms (32%) in the TV-ICD group, more than one ATP attempt per episode was given and ICDs were programmed with more than the single ATP attempt that was specified in the protocol. The first ATP attempt successfully terminated the monomorphic VT in 54.6% of the discrete episodes, versus 35.9% in storm episodes (P<0.01). In the TV-ICD group, 77/166 electrograms of storm episodes (46%) were overwritten due to limited storage capacity of the device (Figures S2 and S3).

Discussion

In this secondary analysis of the randomized PRAETORIAN trial, we found no statistical difference in number of patients treated with appropriate ICD therapy in the S-ICD group and TV-ICD group. S-ICD patients were more likely to receive an appropriate shock, but the overall number of appropriate shocks was comparable between the two groups, despite the inability of the S-ICD to deliver ATP. We observed no difference in first and final shock efficacy in the two groups. ATP successfully terminated approximately half of the monomorphic VTs and one in four patients could be treated by ATP only. The efficacy of ATP decreased after the first attempt and the first ATP attempt accelerated the arrhythmia in 9.4% of the episodes.

The median time from start arrhythmia to first therapy and shock was shorter in the TV-ICD group compared to the S-ICD group, probably due to a combination of a shorter time to detection, the delivery of ATP and a shorter capacitor charge time of the TV-ICD. It is often postulated that a longer time to shock would result in a lower number of shocks, as it reduces the risk of needless treatment of unsustained ventricular arrhythmias. This was not confirmed by our results, as we showed a comparable number of shocks in the two groups.

ATP is recommended as preferred therapy for most ICD patients and has been considered a safe and painless alternative to defibrillation shocks[8,15]. Our results show that a number of monomorphic VTs in patients in the TV-ICD group could be terminated by ATP only, without affecting the overall number of appropriate shocks compared to patients in the S-ICD group. Simultaneously, there were more treated appropriate episodes in the TV-ICD group than in the S-ICD group, which may be the result of unnecessary treatment with ATP on ventricular arrhythmias that would otherwise have ended spontaneously. Although we observed that the first ATP attempt was successful in 46% of all episodes with a monomorphic VT, subsequent ATP attempts seem to yield little additional efficacy. The

lower success rate, compared to previous studies[6-8], can be explained by the patient selection in the PRAETORIAN trial, which excluded patients with VTs at a rate below 170 beats per minute or recurrent monomorphic VTs prior to implant. It has been indicated that VT acceleration by ATP might lead to electrical storms and a higher mortality [10]. Whereas there was no difference in mortality in the PRAETORIAN trial[4], patients with a TV-ICD had indeed a higher risk of electrical storms compared to patients with an S-ICD, despite the comparable baseline. In this study, ATP had a proarrhythmogenic effect in 9.4% of the episodes. In addition, we observed a significantly lower ATP efficacy in storm episodes, compared to discrete episodes. The higher incidence of electrical storms in the TV-ICD group could be associated with the capability of the TV-ICD to provide ATP, since 32% of the storms were given more than one ATP attempt per episode. Our data suggest that, in the studied population, ATP therapy should be limited to a single attempt to observe the efficacy in the individual patient. After a positive effect of ATP is demonstrated, ATP programming may be extended.

This analysis has several limitations. First, patients with known VT at a rate below 170 beats per minute and patients with refractory recurrent monomorphic VT that could not be managed with medication or ablation therapy were not eligible to participate in the PRAETORIAN trial. It is therefore unclear whether the results of this analysis apply to all ICD patients. Second, the majority of episodes with missing electrograms occurred in the TV-ICD group, as this device often overwrites previously stored episodes to preserve storage capacity. These episodes could not be adjudicated and lead to an underestimation of the amount and nature of appropriate therapy in the TV-ICD group. Finally, the morphology of the electrograms of the TV-ICD does not resemble the surface electrocardiogram as much as the electrograms of the S-ICD. As a result, it is more difficult to discriminate between

ventricular and supraventricular arrhythmias, which could have influenced the classification of appropriate therapy in the TV-ICD group.

Conclusions

The results of this analysis show that the S-ICD is equally effective as the TV-ICD in terminating ventricular arrhythmias. The capability to provide ATP in the TV-ICD group led to fewer patients with appropriate shocks, but the total number of appropriate shocks was not different in the two study groups. ATP is less effective during storm episodes than during discrete episodes and ATP efficacy is mainly a result of the first attempt. In addition, ATP can accelerate arrhythmias and more electrical storms were observed in the TV-ICD group. In patients who are not expected to benefit from ATP, we suggest to limit ATP therapy to a single attempt.

Acknowledgments

We would like thank the members of the Clinical Event Committee, Regitze Videbaek, Alexander H. Maass and Pascal H.F.M. van Dessel for adjudicating all events in the PRAETORIAN trial.

Sources of Funding

The PRAETORIAN trial was funded by Boston Scientific, which had no role in the design of the trial, analysis of the data, or the drafting and submission of the manuscript.

Disclosures

R.E. Knops reports consultancy fees and research grants from Abbott, Boston Scientific, Medtronic and Cairdac and has stock options from AtaCor Medical Inc. S. Mittal reports consultancy fees for Boston Scientific. K. Vernooy reports consultancy fees for Medtronic and Abbott. M.C. Burke is a consultant and receives honoraria as well as research grants from Boston Scientific; has equity and is chief medical officer for AtaCor Medical, Inc. D.J. Wright has consultancy arrangements with Boston Scientific and Medtronic and a research

grant from Boston Scientific. P. Nordbeck reports modest speaker honoraria from Biotronik, Boston Scientific and Medtronic. M.A. Miller reports consultancy fees for Boston Scientific. Z. Whinnett is an advisor for Boston Scientific and on the advisory board for Medtronic and Abbot and reports speaker fees for Medtronic. The other authors report no relevant disclosures.

Supplemental Material

Supplementary Methods Section

Supplemental Tables I - IX

Supplemental Figures I - III

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Table 1. Standardized ICD programming in the PRAETORIAN trial.

	S-ICD		**TV-ICD**		
	Conditional zone	**Unconditional zone**	**Monitor zone**	**Fast VT zone**	**VF zone**
Arrhythmia detection zones (beats/min)	>180	>250	>167	>182	>250
Time to initiate therapy (charge for shock or ATP)	Fixed (18/24: 6 seconds)	Fixed (18/24: 4.3 seconds)	11 seconds	10 seconds	7.2 seconds
Therapy	Shocks at maximum output	Shocks at maximum output	No therapy	(1) 1 burst of ATP* (2) Shocks at maximum output	Shocks at maximum output
Pacing programming	Postshock pacing "On"		VVI 40 beats/min		

*Consists of 8 intervals with a pacing length of 88% of the tachycardia length

Table 2. Patient characteristics of patients with appropriate therapy

	Patients with appropriate therapy (N=164)		**P-value**
	S-ICD	**TV-ICD**	
	N = 86	**N = 78**	
Median age (IQR)	63 (55-68)	63 (54-68)	0.90
Female — no.(%)	11 (12.8)	17 (21.8)	0.13
Diagnosis — no.(%)			0.91
- Ischemic cardiomyopathy	58 (67.4)	54 (69.2)	
- Nonischemic cardiomyopathy	21 (24.4)	18 (23.1)	
- Genetic arrhythmia syndrome	4 (4.7)	4 (5.1)	
- Idiopathic VF	1 (1.2)	2 (2.6)	
- Congenital heart disease	1 (1.2)	0 (0.0)	
- Other	1 (1.2)	0 (0.0)	
Secondary prevention — no.(%)	22 (25.6)	24 (30.8)	0.46
Median ejection fraction (IQR)	28 (20-35)	29 (22-35)	0.55
Mean QRS duration ±SD	107±19	108±19	0.83
NYHA class — no.(%)			0.13
- I	32/86 (37.2)	34/77(44.2)	
- II	38/86 (44.2)	37/77 (48.1)	
- III/IV	16/86 (18.6)	6/77 (7.8)	
Median body mass index (IQR)*	27.2 (24.4-30.1)	27.4 (25.0-30.5)	0.52
Medication at discharge — no.(%)			
- Beta blocker	68 (79.1)	67 (85.9)	0.25
- Amiodarone	6 (7.0)	4 (5.1)	0.87

*The body-mass index is the weight in kilograms divided by the square of the height in meters.

Figure Legends

Figure 1. Kaplan Meier curve of all patients with appropriate therapy in the PRAETORIAN trial

Figure 2. Overview of all patients with appropriate therapy, appropriate episodes and therapies.

Figure 3.

A) Total number of patients with appropriate therapy. B) Total delivered therapy.

Figure 3A: Patients can be represented in both discrete and storm episodes.

Figure 4.

A) Successful conversion to sinus rhythm after ATP. B) Acceleration of VT after ATP, ultimately terminated by a shock (shock not shown).

Figure 5.

Electrical storms in the S-ICD and TV-ICD. A) Number of shocks and ATP per episode per storm. B) Electrical storms with only shocks. Figure 5A**:** Each horizontal row represents one electrical storm. Therapies that accelerated the arrhythmia are shown with a dot above the therapy. Figure 5B: Each horizontal row represents one electrical storm. Only electrical storms with at least one shock are presented in this figure. There were 91 shocks in the S-ICD group and 149 shocks in the TV-ICD group.

Appendix

The PRAETORIAN investigators:

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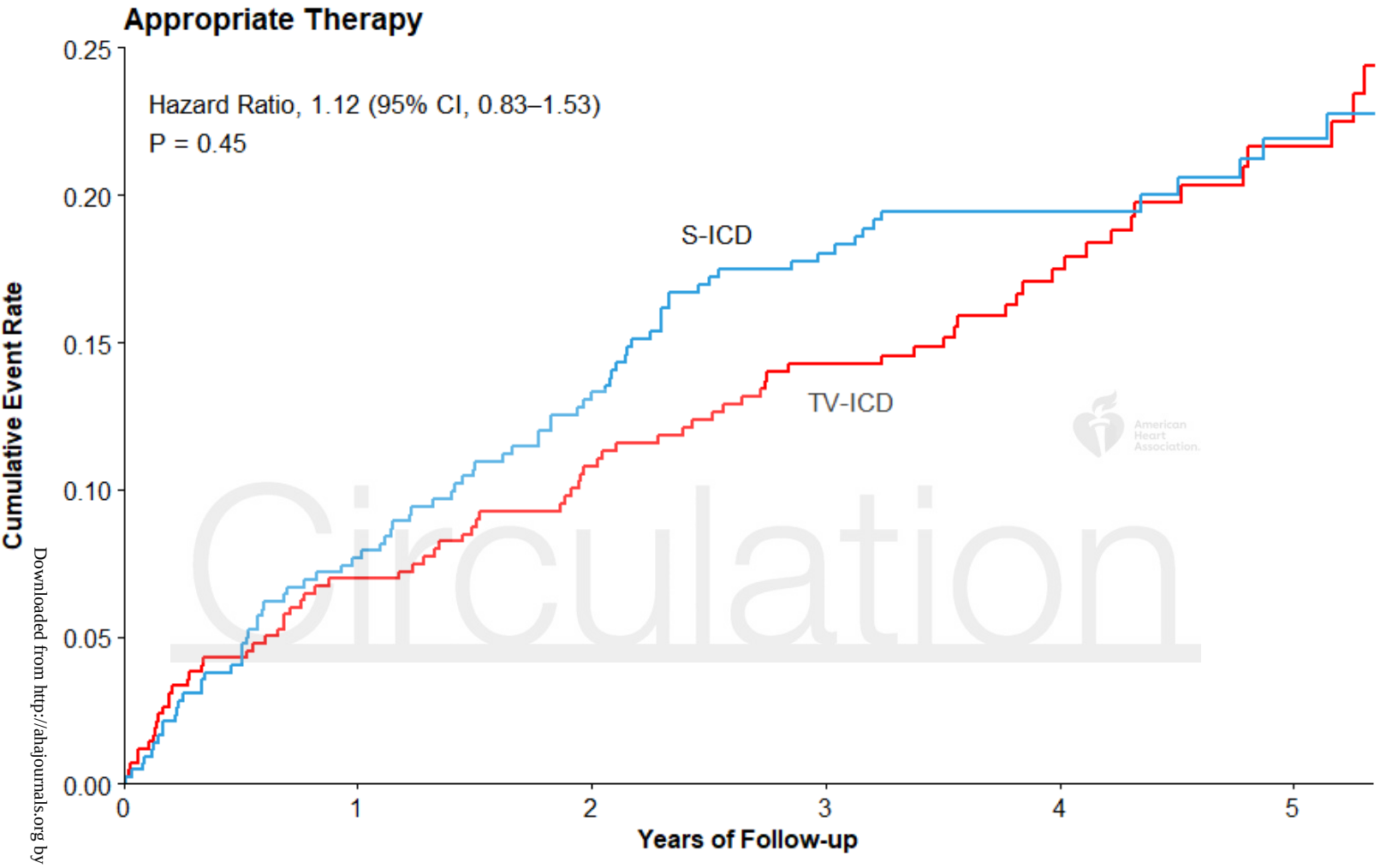

No. at Risk

TV-ICD	423	374	346	313	192	103
S-ICD	426	372	331	301	178	105