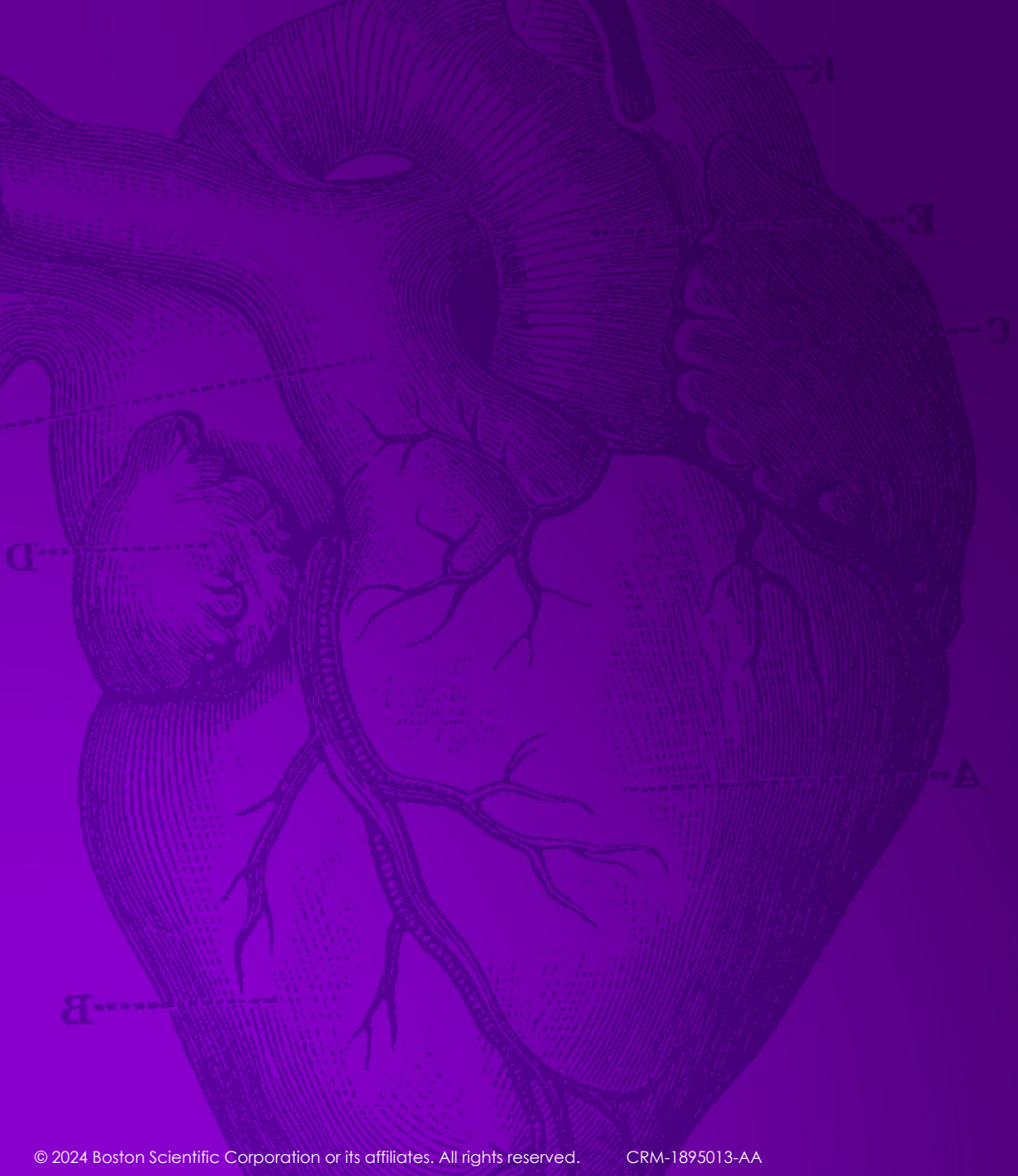

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Assessment of primary prevention patients receiving an ICD – Systematic evaluation of ATP: **APPRAISE ATP**

HRS Late Breaking Clinical Trials: LB-469803-02, 2024

 CRM-1895013-AA

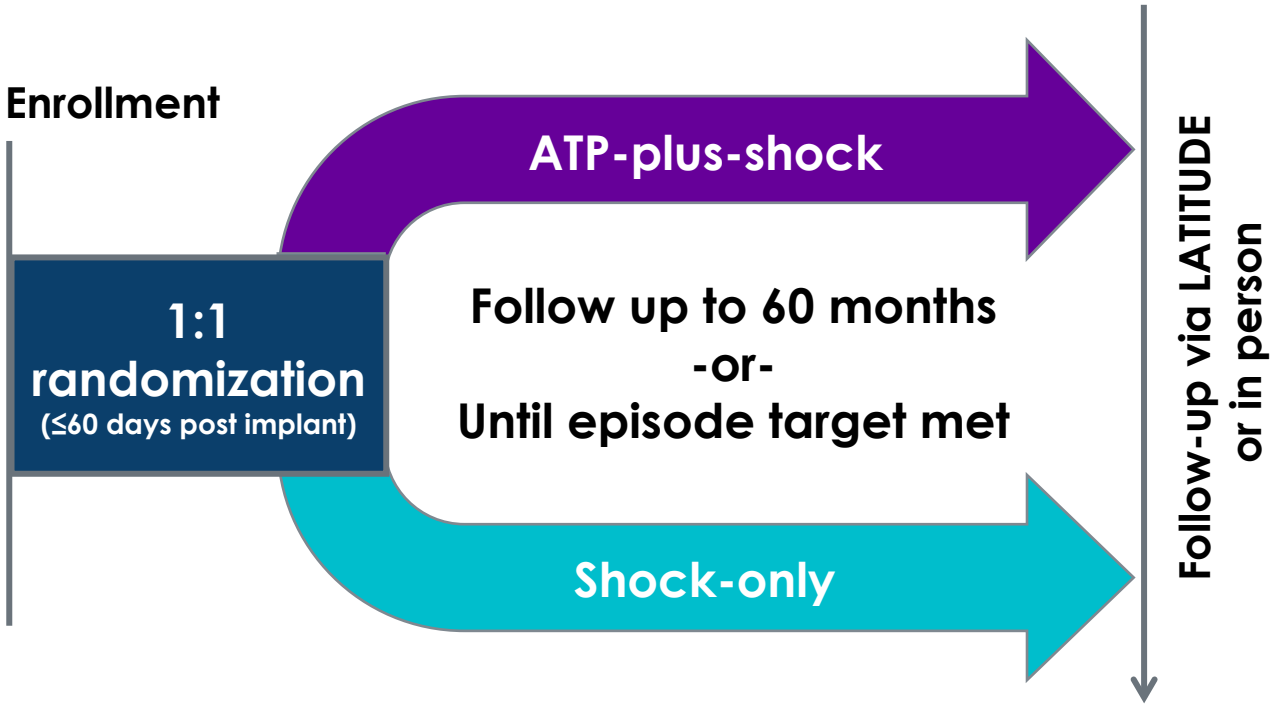
Background on ATP[1-7]

- Current Primary Prevention (PP) ICD programming guidelines come from large randomized clinical trials (MADIT-RIT, ADVANCE III, PROVIDE).
  - Safety and efficacy of increasing therapy rate cutoffs and/or prolonging the time from detection to therapy were tested in these large trials
  - Intention to reduce inappropriate and unnecessary therapy .
- These trial results are the foundation of the 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement about optimal ICD programming.
- PainFREE and PainFREE Rx II Trials
  - ATP as first line therapy to painlessly terminate ventricular arrhythmias was tested.
  - PainFREE Rx II published in 2004 remains the only prospective, randomized evaluation of ATP.
    - However, the patients studied were both primary and secondary prevention patients.
    - Devices programmed with a short delay before therapy and a therapy zone of 188-250 bpm .
- Multiple retrospective registries and nonrandomized observational studies support ATP in PP ICD patients who receive modern programming however, they lack uniform detection and therapy.

Clinical justification for evaluating ATP in Primary Prevention (PP) patients

- PainFREE RX II, the only prospective randomized trial of ATP in PP cohorts, likely overestimated the success of ATP by treating arrhythmias prematurely compared to current recommendations.[8]
- No prospective trial evaluating ATP as first line of therapy has been done with current guideline directed ICD programming (longer delay before therapy).[8]
- The emergence of the S-ICD that does not offer ATP at present, and the Substernal ICD where ATP has been associated with pain and discomfort[9,10], require the reevaluation of ATP for shared decision making in PP cohorts.[8]

Largest Prospective Randomized Trial of ATP and TV-ICD in Primary Prevention Patients[8,11]



- Prospective, multicenter, randomized trial
- Powered for 2600 primary prevention patients enrolled at up to 150 sites worldwide
- Equivalence trial with sequential superiority analysis of each arm

Primary Endpoint: Time to first all-cause shock

Secondary Endpoints: Time to first appropriate shock, time to first inappropriate shock, time to death from any cause, and time to first all-cause shock or death from any cause

Enrollment and Randomization[8,11]

PP ICD indicated patients received a Boston Scientific de novo single or dual chamber TV-ICD

Randomized 1:1 (n=2,595)

Arm 1: ATP ON or ATP-plus-Shock (n=1302)

Arm 1 Programming

- **Zone 1:** 170 bpm, monitor only
- **Zone 2:** 200 bpm, 12 sec delay, ATP x1 burst of 8 pulses, 41 J shock
- **Zone 3:** 250 bpm, 5 sec delay, 41 J shock

Arm 2: ATP OFF or Shock Only (n=1293)

Arm 2 Programming

- **Zone 1:** 170 bpm, monitor only
- **Zone 2:** 200 bpm, 12 sec delay, 41 J shock
- **Zone 3:** 250 bpm, 5 sec delay, 41 J shock

Required contemporary programming[8,†]

Zone1: VT-1 Zone (170-199 bpm)

Both Arms — ***Monitor Only***

Zone 2: VT Zone (200-249 bpm)

ATP = one burst of 8 beats at 88% CL

Detection 2 sec

ATP-plus-shock Arm
~3 second longer delay*

	Delay 12 sec	**ATP** 3 sec	**Charge Time (if necessary)** 10 sec

Deliver Shock (if necessary)

Shock-only Arm

	Delay 12 sec	**Charge Time** 10 sec

Deliver Shock

Zone 3: VF Zone (≥250 bpm)

Detection 2 sec

Both Arms

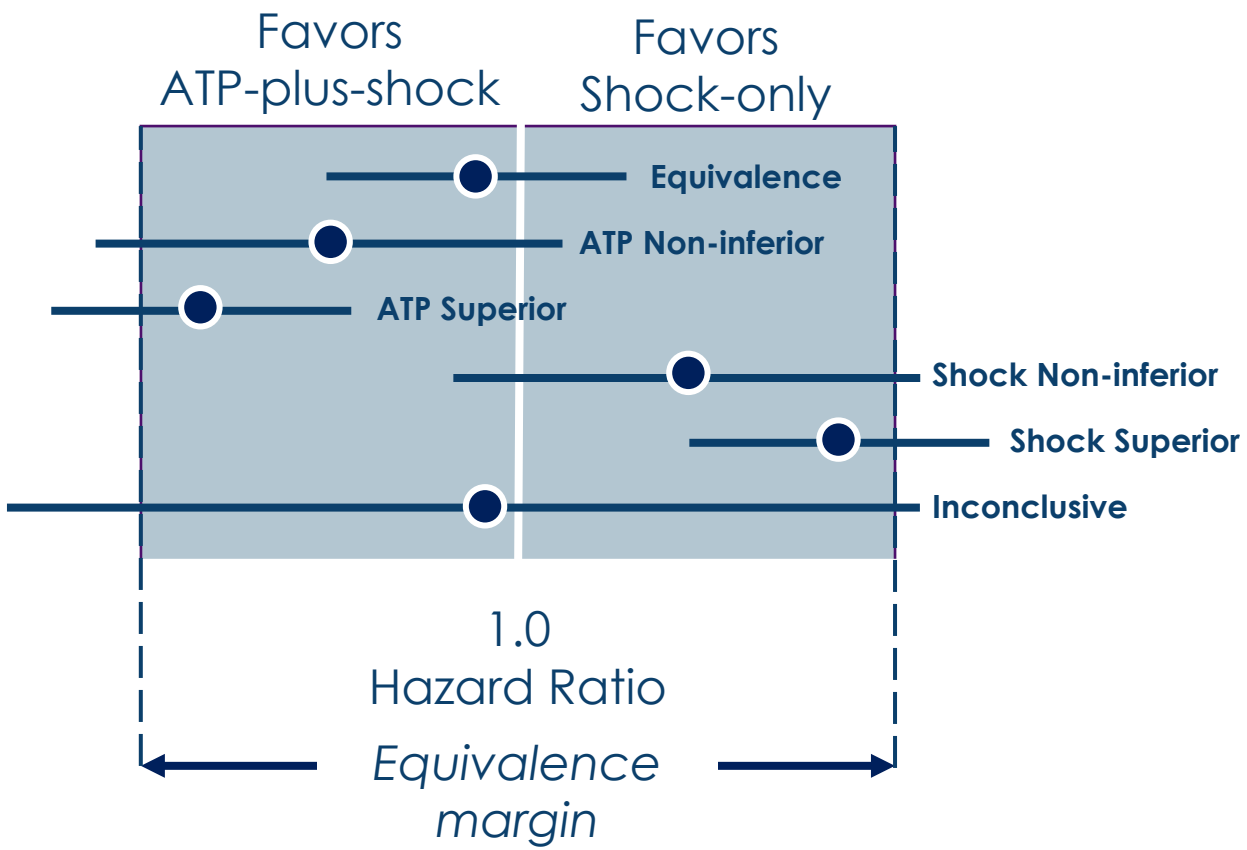
	Delay 5 sec	**Charge Time** 10 sec

Deliver Shock

† Per protocol, device programming could be changed at the investigator's discretion following a patient's first shock (appropriate or inappropriate).
* Unknown at this time if this additional delay impacted primary endpoint. The APPRAISE ATP chose this programming option vs shortening delay in shock-only arm to avoid concern that the programming was biased in favor of the Shock-only arm.

How was the primary endpoint evaluated?[8]

- Powered for equivalence between arms with interim superiority analysis when pre-specified numbers of shock episodes occurred.
- 284 subjects with a shock therapy episode needed to power the primary endpoint of time to first all-cause shock.
- All arrhythmia events were adjudicated by an independent committee.



Inclusion and Exclusion Criteria[8]

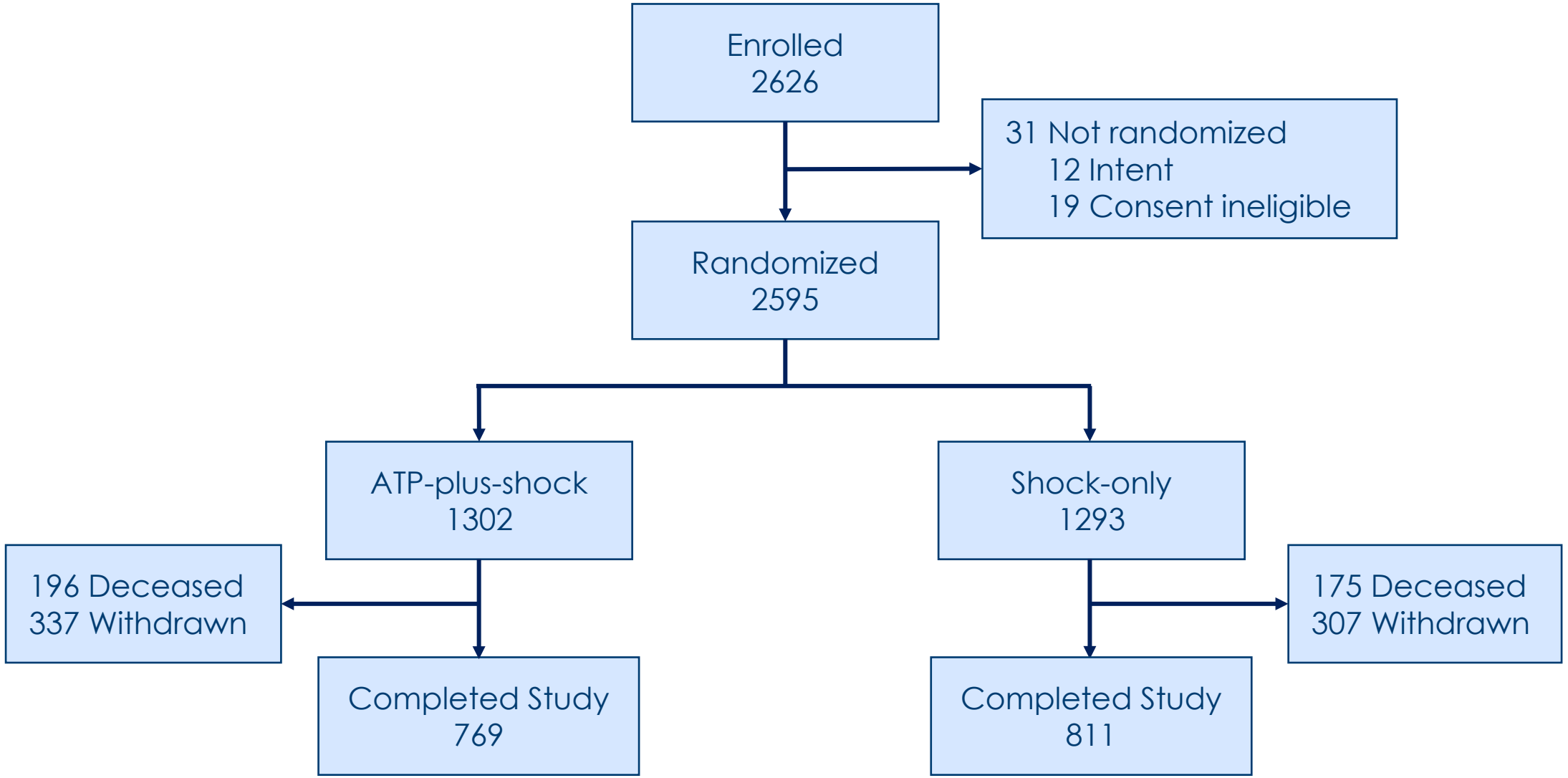
Inclusion:

- Transvenous ICD implanted within 60 days of enrollment due to:
  - Prior MI with LVEF ≤ 30% OR ischemic or non-ischemic cardiomyopathy and LVEF ≤ 35% and NYHA class II or III
  - ≥ 21 years of age

Exclusion:

- History of spontaneous sustained VT (≥ 160 bpm at ≥ 30 seconds in duration) or VF not due to a reversible cause
- NYHA Class IV within 90 days prior to enrollment
- Scheduled for cardiac resynchronization implant
- On active heart transplant list
- Previous subcutaneous ICD (S-ICD) or existing TV-ICD device implanted for greater than 60 days
- Coronary artery bypass graft surgery or percutaneous coronary intervention within 90 days prior to enrollment
- Documented MI within 90 days prior to enrollment
- Has a VAD or is to receive VAD
- Life expectancy shorter than 18 months due to any medical condition (e.g., cancer, uremia, liver failure, etc.)
- Hemodialysis

Patient Flowchart[11]

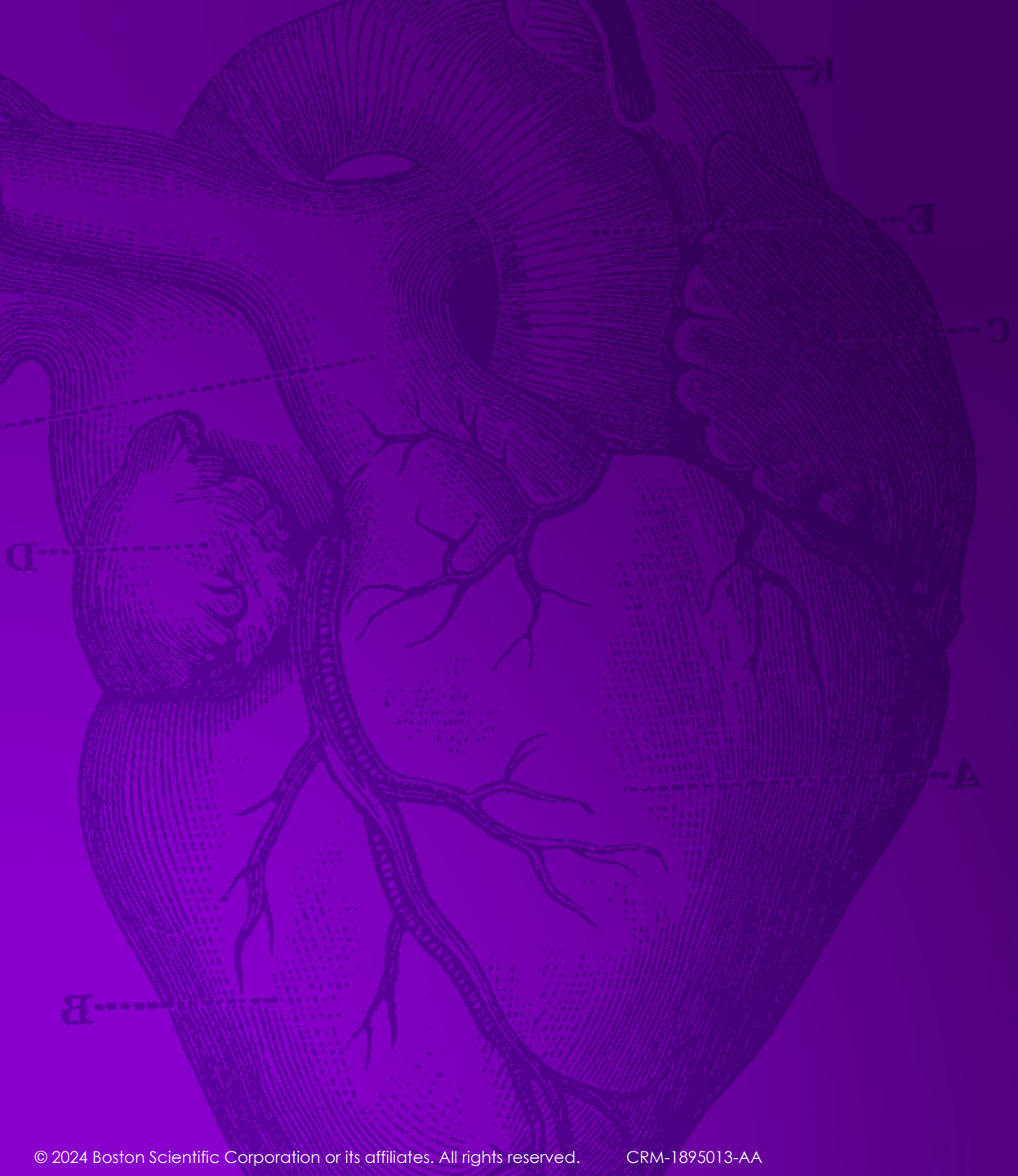


Typical Primary Prevention Patients[11]

The APPRAISE ATP Trial included a **typical Primary Prevention population** with a **mean age of 64** and a **high percent had ischemic cardiomyopathy and a mean EF of 27%**[11]

Characteristic	ATP-shock (N=1302)	Shock-only (N=1293)
Mean age ± SD — years	64.0 ± 11.5	63.8 ± 11.1
Female sex — no. (%)	277 (21.3)	304 (23.5)
Ischemic etiology — no. (%)	757 (58.1)	753 (58.2)
Mean follow-up duration ± SD — months	37.4 ± 16.9	38.6 ± 16.5
Race or ethnic group* — no. (%)		
American Indian or Alaska Native	5 (0.4)	8 (0.6)
Asian	209 (16.3)	206 (16.2)
Black or African heritage	169 (13.2)	178 (14.0)
Caucasian	860 (67.2)	849 (66.8)
Hispanic or Latino	39 (3.0)	37 (2.9)
Native Hawaiian or other Pacific Islander	2 (0.2)	3 (0.2)
Other race	3 (0.2)	1 (0.1)
Not disclosed	22 (1.7)	22 (1.7)
Device type		
Single chamber ICD — no. (%)	678 (52.2)	646 (50.0)
Dual chamber ICD — (%)	622 (47.8)	646 (50.0)

Characteristic	ATP-shock (N=1302)	Shock-only (N=1293)
Mean LV ejection fraction ± SD — %	27.4 ± 6.2	27.1 ± 6.0
Mean QRS duration ± SD — msec	107 ± 21	108 ± 21
NYHA class — no. (%)		
I or II	913 (70.3)	932 (72.2)
III or IV	385 (29.7)	359 (27.8)
Mean body mass index (BMI) ± SD — kg/m^2	29.3 ± 7.1	29.2 ± 6.8
Hypertension	928 (71.7)	914 (71.1)
Current or previous smoking — no./total no. (%)	753/1298 (58.0)	771/1291 (59.8)
Diabetes — no. (%)	525 (40.3)	520 (40.2)
Previous coronary artery bypass graft — no. (%)	271 (20.9)	289 (22.4)
History of atrial fibrillation — no. (%)	341 (26.2)	356 (27.5)
QRS morphology — no./total no. (%)		
Normal	633/973 (65.1)	631/960 (65.7)
Right bundle branch block (RBBB)	72/973 (7.4)	63/960 (6.6)
Left bundle branch block (LBBB)	42/973 (4.3)	46/960 (4.8)
Other	226/973 (23.2)	220/960 (22.9)
LATITUDE remote monitoring usage — no. (%)	983 (75.5)	968 (74.9)



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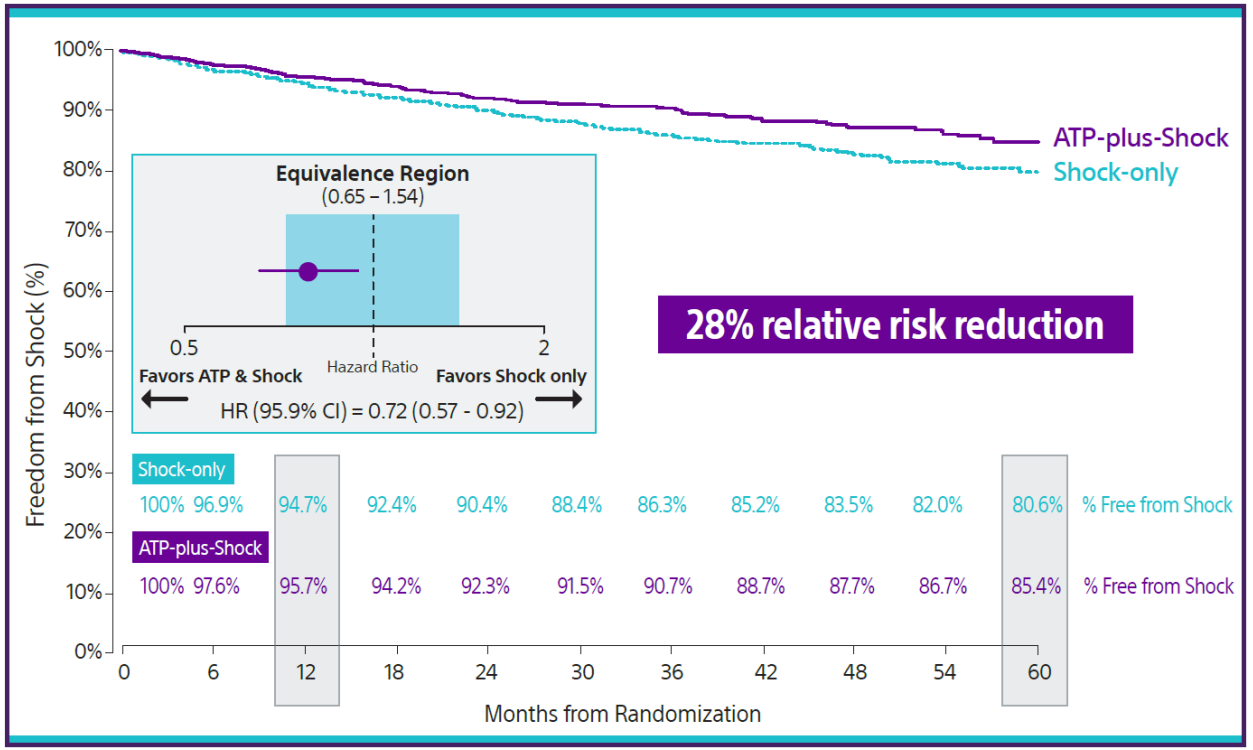
Results from the APPRAISE ATP Trial

 CRM-1895013-AA

Primary Endpoint: Time to First All-Cause Shock[11]

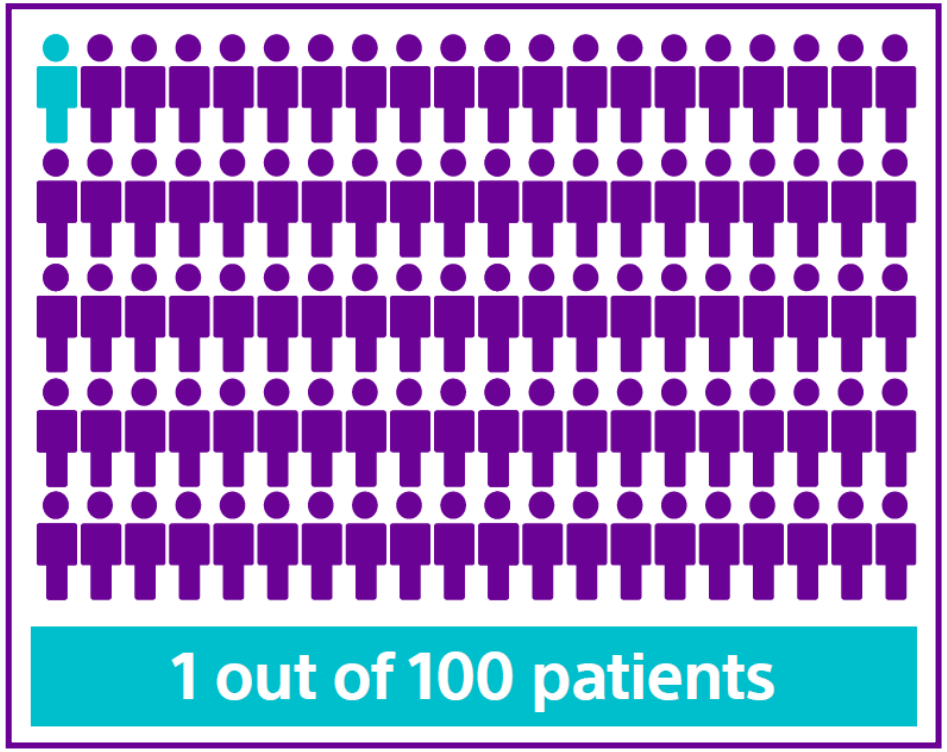
Relative Risk

The APPRAISE ATP trial demonstrated superiority with a **28% relative risk reduction** in time to first all-cause shock for the ATP ON arm compared to the ATP OFF arm (Log-rank P-value=0.005).[11]

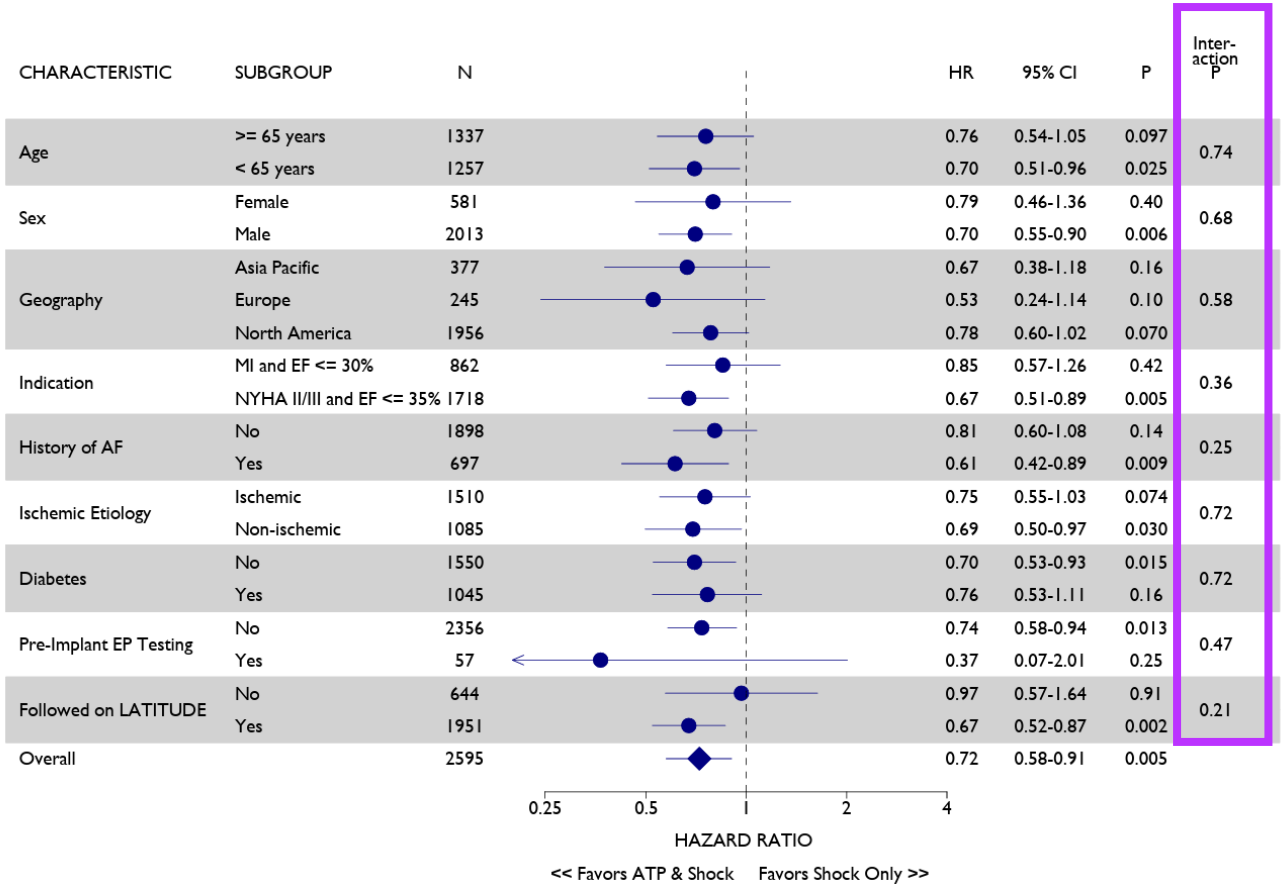


Absolute Risk

This represents an absolute all-cause shock reduction in **1% of primary prevention ICD indicated patients/year**.[11]



The benefit of ATP-plus-shock therapy in TV-ICDs was similar across all subgroups including patients with ischemic cardiomyopathy (ICM)[11]

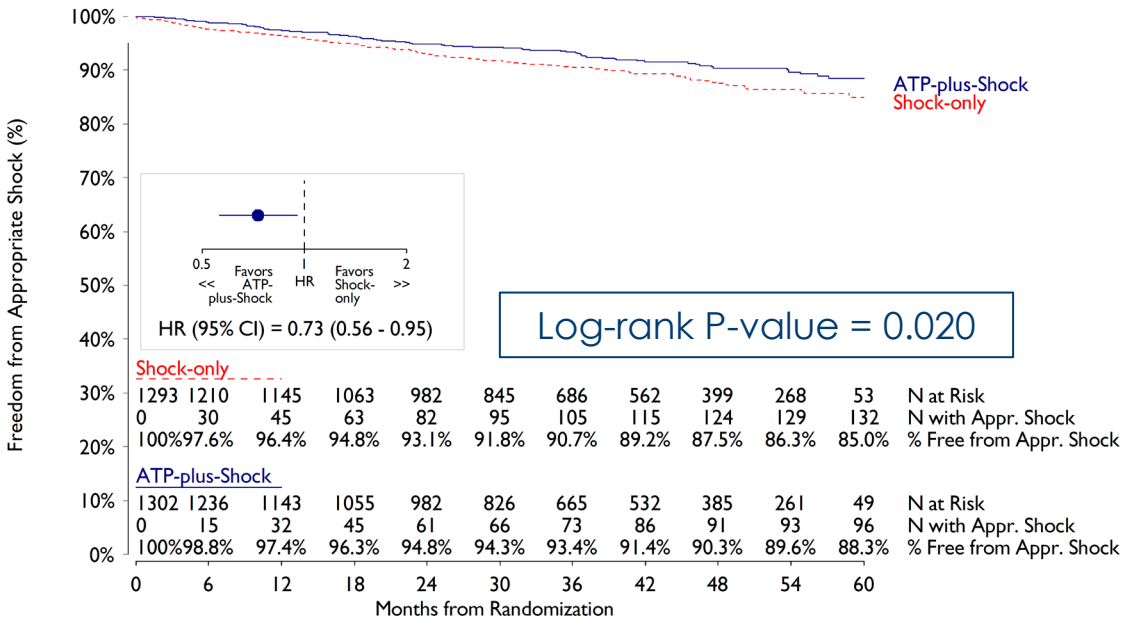


No significant interactions between randomization group and baseline characteristics[11]

- 58% of patients had ICM.[11]
  - ICM patients were not any more likely to benefit from ATP than patients with non-ischemic cardiomyopathy (NICM).[11]
- Only 1% (1 out of 100) of ICD-indicated PP patients with ICM will avoid a shock each year after TV-ICD implant.[11]

While rates of Appropriate Shocks were significantly different throughout follow-up (p=0.020), <1% per year avoided an appropriate shock in the ATP ON arm[11]

Time to First Appropriate Shock



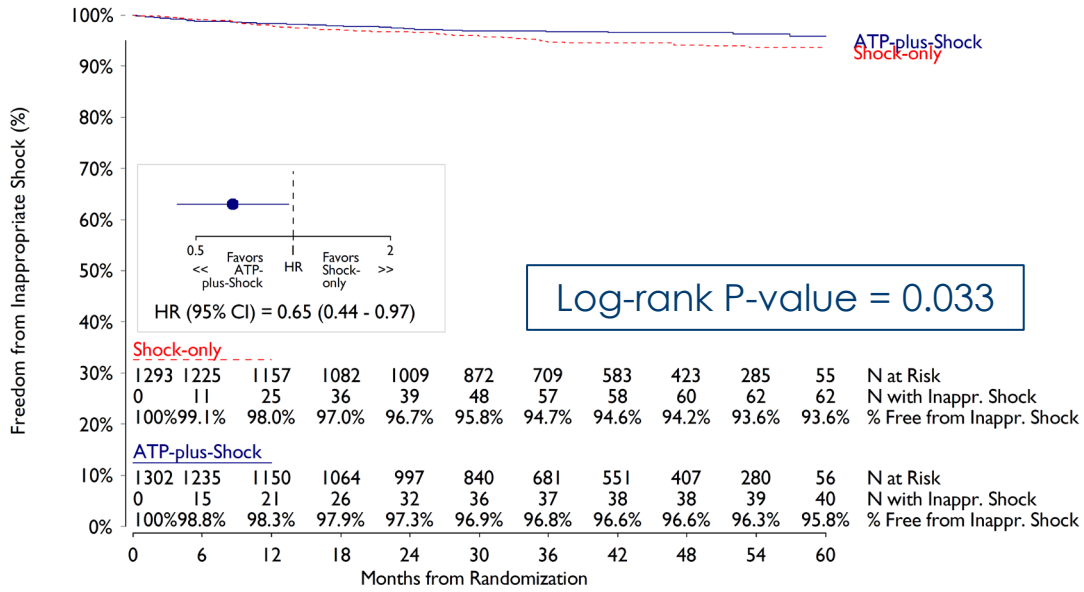
27% lower risk of an appropriate shock in ATP-plus-shock group[11]

- Percent of patients free from appropriate shocks[11]:
  - **At 1 year:** 97.4% for the ATP-plus shock arm vs 96.4% for the shock-only arm.
  - **At 5 years:** 88.3% for the ATP-plus-shock arm vs 85.0% for the shock-only arm.
- The absolute differences at 1 year and 5 years were 1% and 3.3% of patients, respectively.[11]

While rates of Inappropriate Shocks were significantly different throughout follow-up (p=0.033), ~0.5% of patients per year avoided an inappropriate shock in the ATP ON arm[11]

- Percent of patients free from inappropriate shocks[11]:
  - **At 1 year:** 98.3% for the ATP-plus-shock arm vs 98.0% for the shock-only arm.
  - **At 5 years:** 95.8% for the ATP-plus-shock arm vs 93.6% for the shock-only arm.
- IAS rates in both arms were low due to the use of guideline recommended programming.[11]
- The absolute differences at 1 year and 5 years were 0.3% and 2.2% of patients, respectively.[11]

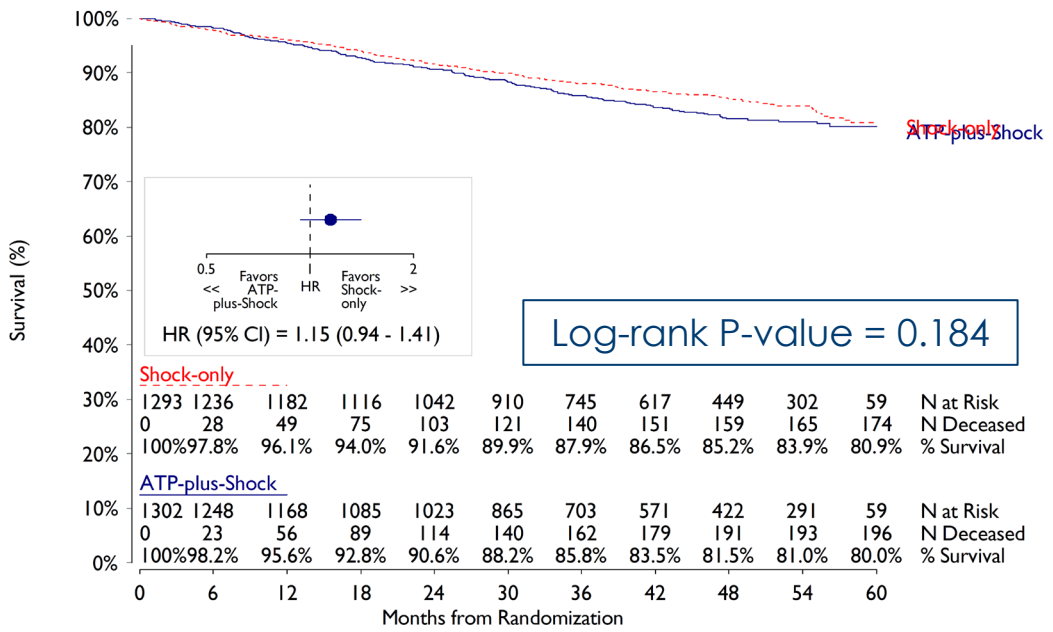
Time to First Inappropriate Shock



35% lower risk of an inappropriate shock in ATP-plus-shock group[11]

Deaths from any cause were numerically higher in the ATP-plus-shock arm, however, there was no significant difference in deaths between the TV-ICD programming arms (HR: 1.15, p=0.184)[11]

All-Cause Mortality

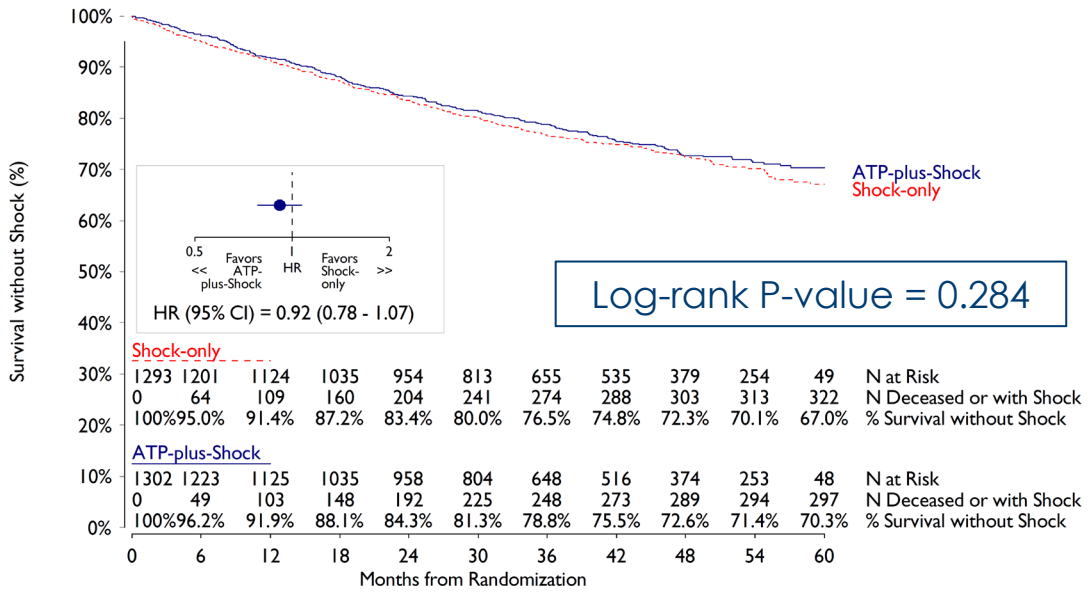


No significant difference between groups[11]

This finding demonstrates there was no signal that shock-only increased mortality or that ATP decreased mortality.[11]

There was no significant difference in the combined endpoint of time to first all-cause shock or death between the ATP-plus-shock arm and shock-only arm (HR: 0.92, p=0.284)[11]

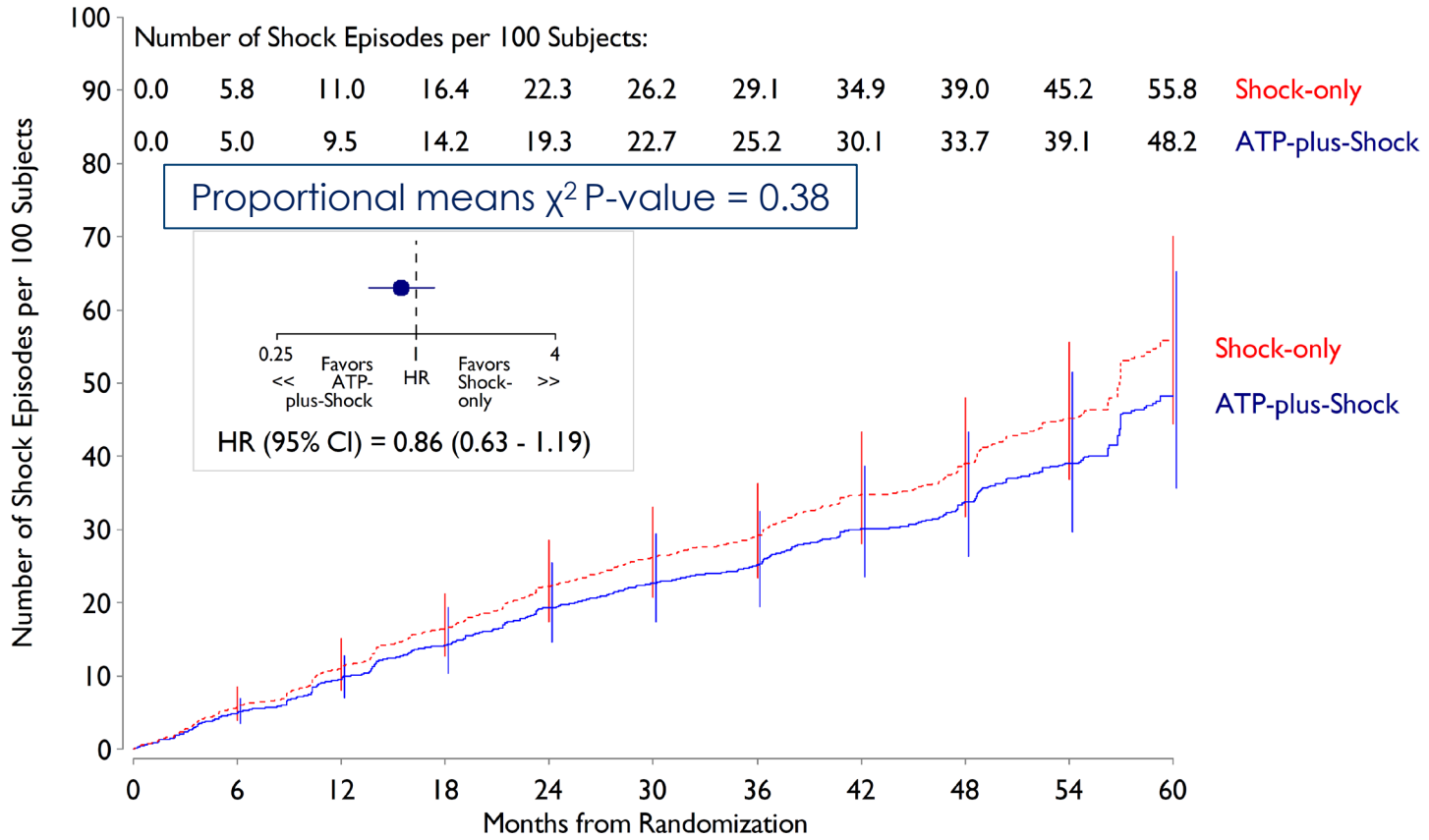
Time to First All-Cause Shock or Death



No significant difference between groups[11]

The numerically higher deaths in the ATP-plus-shock arm was enough to cancel the benefit of ATP for the composite endpoint of time to first all cause shock or death.[11]

No significant difference in total all-cause shock burden (p=0.38)[11]

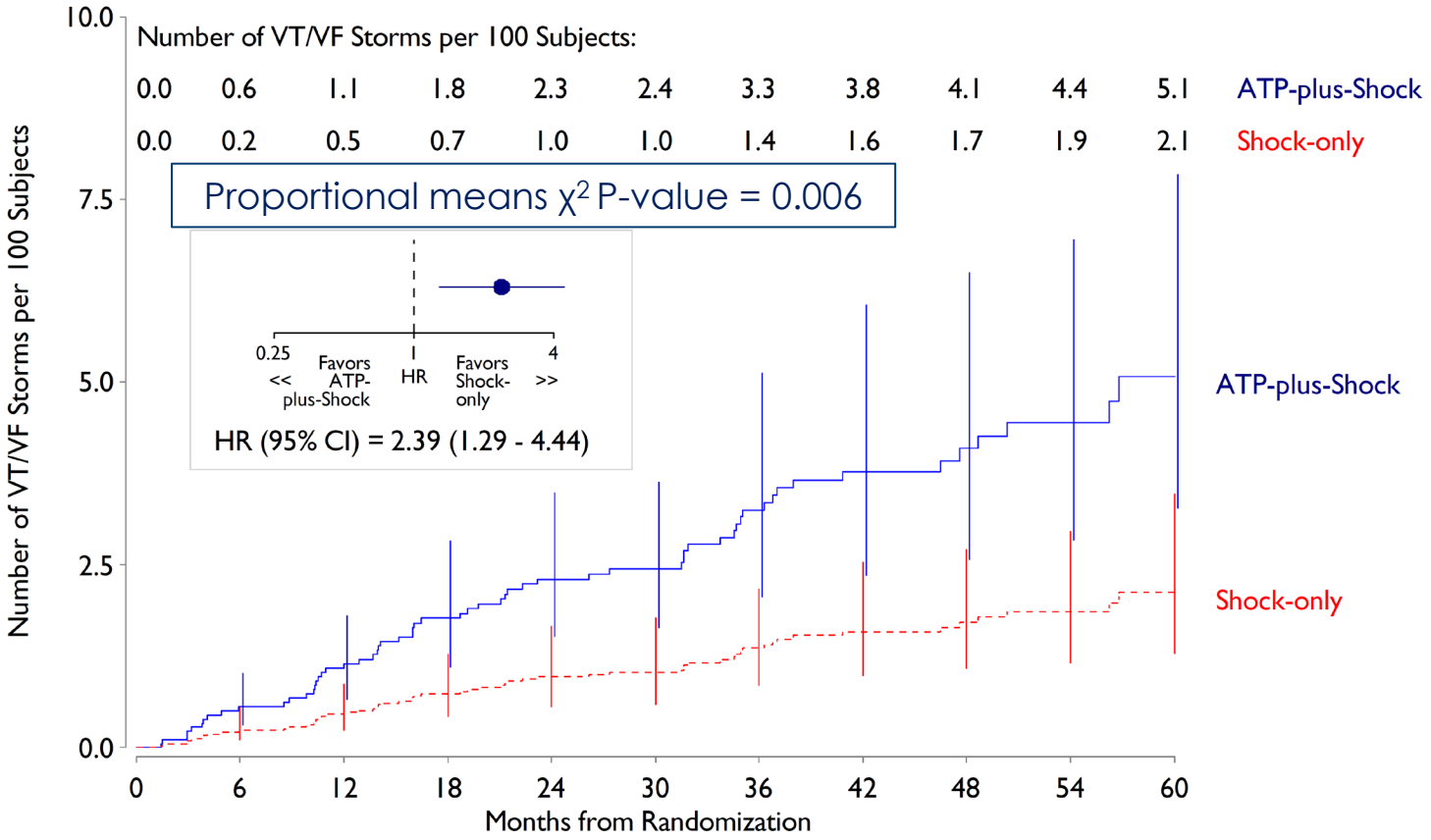


Finding driven primarily by patients with multiple interventions[11]

This finding suggests that even though programming with ATP prolonged time to first shock for patients in the ATP-plus-shock arm, the total amount of shocks over the duration of follow-up in the two groups was not significantly different.[11]

The ATP-plus-shock arm was more than twice as likely to experience VT/VF storms than the shock-only arm[11]

- During the follow-up period, there was a significant increased risk of all VT/VF storm events for the ATP-plus-shock arm (p=0.006).[11]
- VT/VF storm events possibly occurred because reprogramming was allowed after the patient experienced a shock.[11]
- **Important to note[11]:** This does not prove ATP causes more VT/VF storm events, but the association is interesting and will be evaluated further in future publications.



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Importance of Shared Decision Making

- Primary prevention patients eligible for an S-ICD should know the lifetime risks as well as the benefits of the transvenous ICD.[11,12-15]
- The benefit of ATP should also be compared to the lifetime risk of having a lead in the heart with a TV-ICD.[12-15]

Conclusions and Summary[11]

- A single burst of ATP prior to shock in the VT zone (200-249 bpm) resulted in a relative risk reduction in time to first all-cause shock by 28% (HR 0.72, CI 0.57-0.92, p=0.005), representing an absolute reduction of 1% per year for the study population.
- No significant interactions between any prespecified patient subgroup and the primary endpoint were found, implying that all PP patients responded similarly to their assigned study arm.
- The total shock burden per 100 subjects was not statistically different (HR 0.86, CI 0.63-1.19, p=0.38).
- The risk of VT/VF storm events was significantly greater in the ATP-plus-shock arm (HR 2.39, CI 1.29-4.44, p=0.006).
- Although not statistically significant, there were numerically more deaths in the ATP-plus-shock arm and the composite endpoint of all-cause shocks and death was non-significant.
- These results should be carefully considered in the shared decision-making of selecting ICD technologies in PP populations.

Summary: Across five years of follow up, data demonstrated a statistically significant, but small absolute first all-cause shock reduction in only 1% of patients per year. Shock burden, or the number of shocks experienced by a patient, was not significantly different between the two arms, and the majority of patients did not require ATP therapy.[18]

mCRM™ System* – designed for the future of personalized patient care

- Upon the EMPOWER™ Leadless Pacemaker* and mCRM system receiving FDA approval, EMPOWER will be the first and only LP designed to be a standalone VVIR pacemaker** that is compatible with all existing EMBLEM™ S-ICD devices as part of the mCRM system.[16]
- Will provide an upgrade pathway to patients with an EMBLEM S-ICD who develop a need for ATP or VVIR pacing.[16]
- Designed to deliver painless intracardiac ATP and/or brady pacing.[16,17]
- Designed to provide upgrade pathways regardless if the EMBLEM S-ICD or EMPOWER LP is implanted first.[16]

* Caution: Investigational Device. Limited by US law to investigational use only. Not available for sale.
** Rate-response results will be reported in a future publication.

Practical implications of MODULAR & APPRAISE ATP Trials[18]

"Together, data from the MODULAR ATP and APPRAISE ATP trials reinforce the promise of the groundbreaking mCRM System, illustrating a clear path forward for physicians to offer therapies that prevent sudden cardiac death and deliver ATP for the small number of patients who benefit from it."

"Instead of subjecting all patients to the risks of more invasive approaches, such as placing leads in the heart or tunneling them under the sternum to provide therapies they might not require, these data indicate physicians may have the opportunity to tailor therapy to the patient's individual needs and health."

- Ken Stein MD, Global Chief Medical Officer BSC

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