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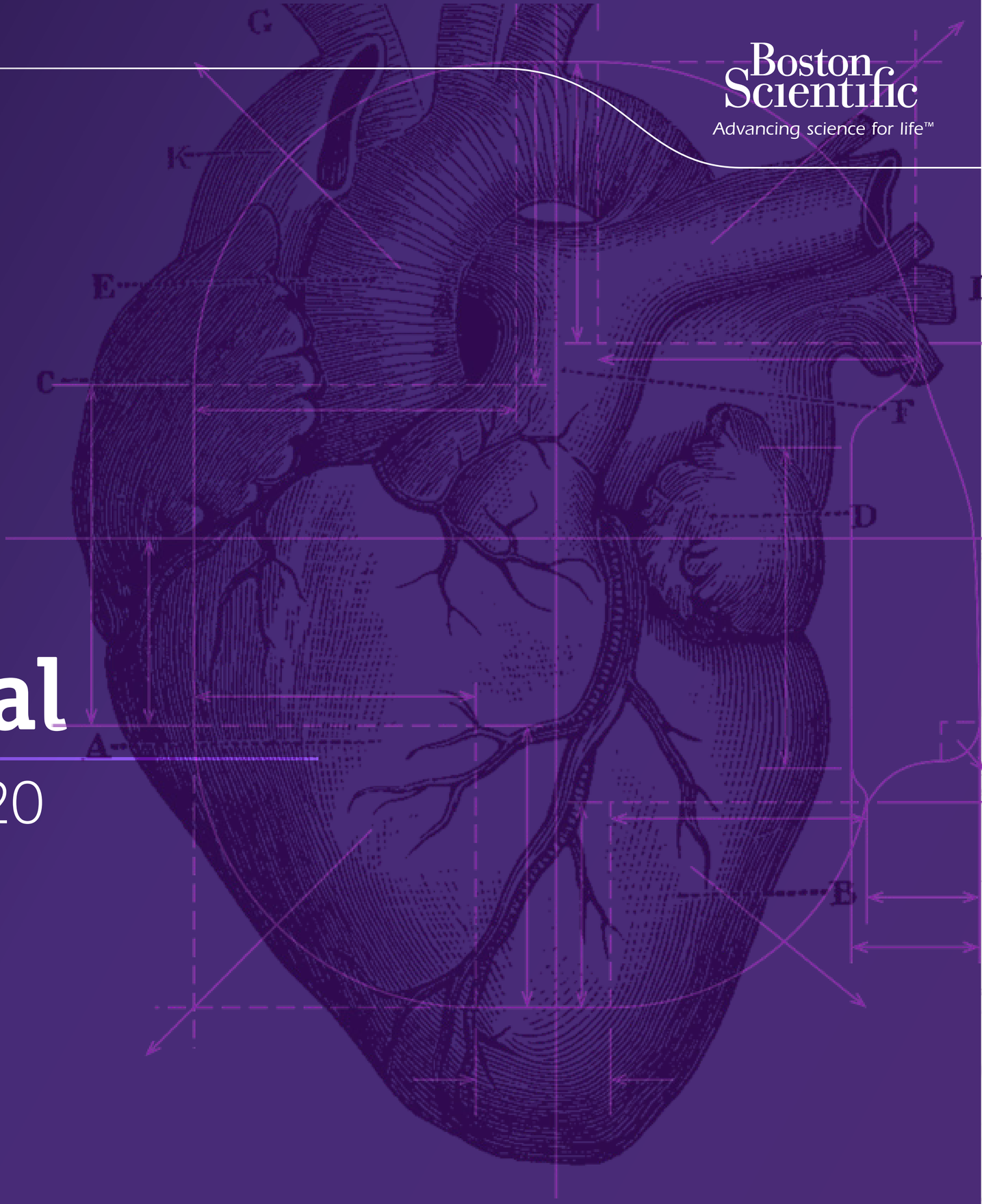

PRAETORIAN Trial

Results from HRS LBCT 2020

PRAETORIAN (2011-2020)

A PRospective, rAndomizEd Comparison of subcuTaneOous and tRansvenous ImplANtable Cardioverter Defibrillator Therapy[1]

Investigator Sponsored Research

HYPOTHESIS

S-ICD is non-inferior to the TV-ICD with respect to major ICD-related adverse events

- Inappropriate shocks
- ICD-related complications that require intervention
  - Lead-related complications

KEY POINTS

- First prospective, randomized head-to-head clinical trial of S-ICD vs TV-ICD
- 849 patients S-ICD (n=426) or TV-ICD (n=423)
  - TV-ICD from all manufacturers allowed
  - Indication for ICD
  - Eligible for S-ICD
- 39 Sites in 6 Countries (EU and US)

Rationale and design of the PRAETORIAN trial: A Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy

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Background Implantable cardioverter-defibrillators (ICDs) are widely used to prevent fatal outcomes associated with life-threatening arrhythmic episodes in a variety of cardiac diseases. These ICDs rely on transvenous leads for cardiac sensing and defibrillation. A new entirely subcutaneous ICD overcomes problems associated with transvenous leads. However, the role of the subcutaneous ICD as an adjunctive or primary therapy in patients at risk for sudden cardiac death is unclear.

Study Design The PRAETORIAN trial is an investigator-initiated, randomized, controlled, multicenter, prospective 2-arm trial that outlines the advantages and disadvantages of the subcutaneous ICD. Patients with a class I or IIa indication for ICD therapy without an indication for bradypacing or tachypacing are included. A total of 700 patients are randomized to either the subcutaneous or transvenous ICD (1:1). The study is powered to claim noninferiority of the subcutaneous ICD with respect to the composite primary endpoint of inappropriate shocks and ICD-related complications. After noninferiority is established, statistical analysis is done for potential superiority. Secondary endpoint comparisons of shock efficacy and patient mortality are also made.

Conclusion The PRAETORIAN trial is a randomized trial that aims to gain scientific evidence for the use of the subcutaneous ICD compared with the transvenous ICD in a population of patients with conventional ICD with respect to major ICD-related adverse events. This trial is registered at ClinicalTrials.gov with trial ID NCT01296022. (Am Heart J 2012;163:753-760.e2.)

PRAETORIAN Trial Study Design

CLASS I & IIA INDICATION NO NEED FOR PACING

n=849

S-ICD

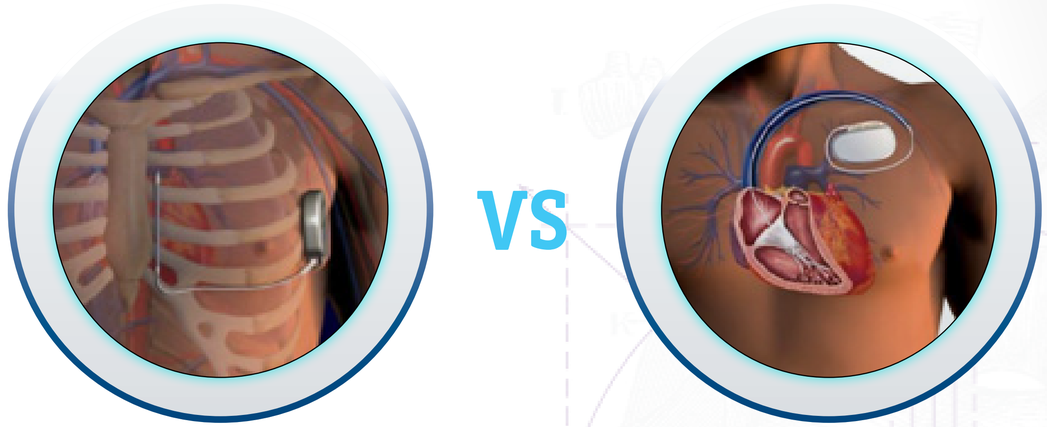
TV-ICD

MEDIAN FOLLOW UP 48 MONTHS

PRIMARY ENDPOINT: NON-INFERIORITY COMPLICATIONS + INAPPROPRIATE SHOCKS

RESULTS HRS 2020

Prospective Randomized Head-Head



- ✓ **“Typical” ICD population**
- ✓ **Composite endpoint (Complications + IAS)**
- ✓ **Standardized programming**
- ✓ **Secondary endpoints:**
  - Device related complications
  - Lead-related complications
  - Inappropriate shocks
  - Cause of inappropriate shocks
  - Mortality (all-cause, arrhythmic, cardiac)

Demographics

The PRAETORIAN Trial[1]

	S-ICD (n = 426)	TV-ICD (n = 423)
Median age (IQR) – yr	63 (54 – 69)	64 (56 – 70)
Female sex – no. (%)	89 (20.9)	78 (18.4)
Diagnosis – no. (%)		
- Ischemic cardiomyopathy	289 (67.8)	298 (70.4)
- Nonischemic cardiomyopathy	99 (23.2)	98 (23.1)
- Other	38 (9.0)	27 (6.5)
Secondary prevention – no. (%)	80 (18.8)	84 (19.9)
Median ejection fraction (IQR) – %	30 (25 – 35)	30 (25 – 30)
Median BMI (IQR) – kg/m^2	27.0 (24.5 – 30.5)	27.9 (25.2 – 31.7)
NYHA class – no. (%)		
- Class I	144/423 (34.0)	136/421 (31.8)
- Class II	205/423 (48.5)	223/421 (53.0)
- Class III/IV	74/423 (17.5)	64/421 (15.2)

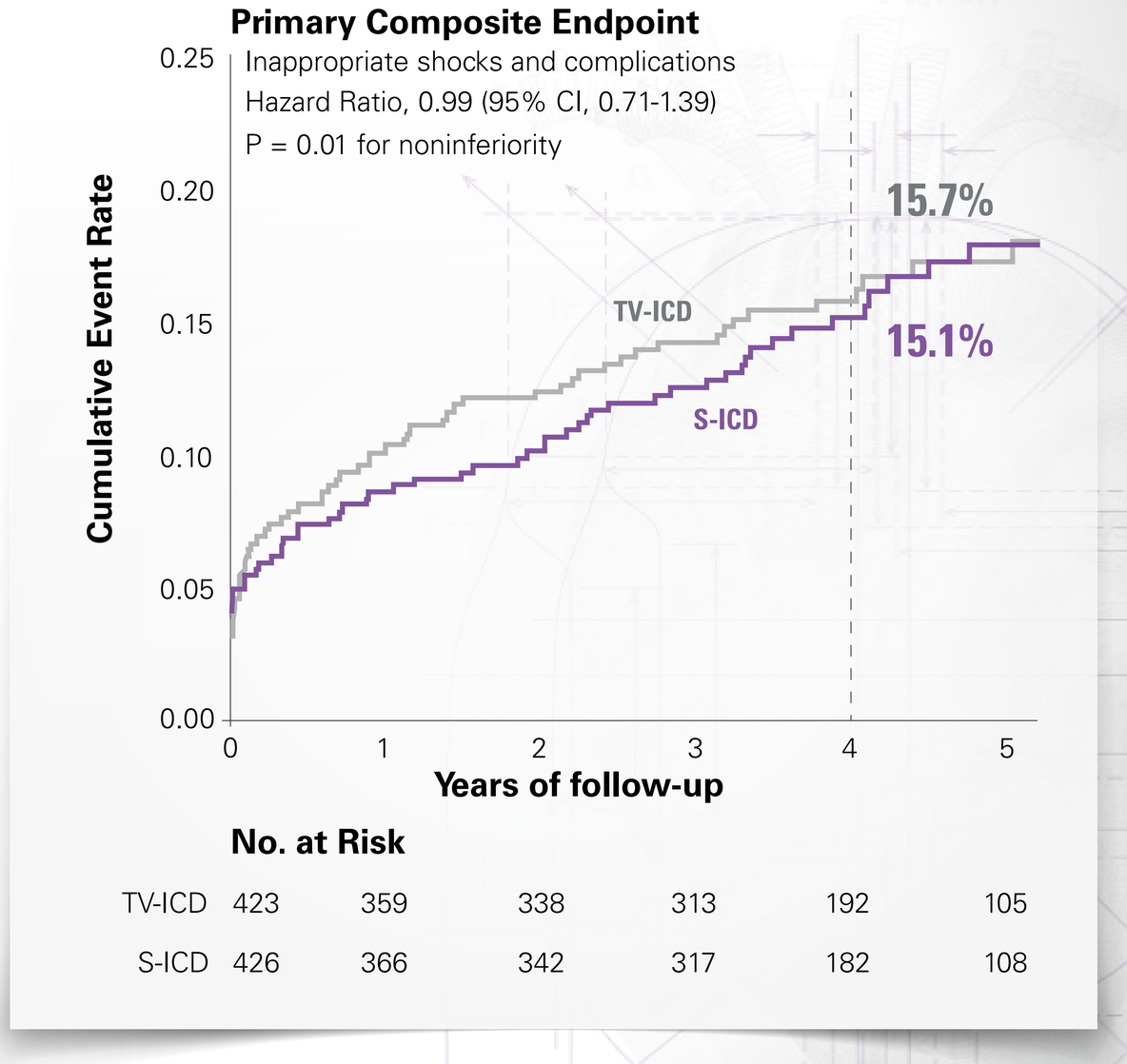
Primary Outcome: Non-inferiority Demonstrated

The PRAETORIAN Trial[1]

S-ICD had comparable performance to TV-ICD yet avoided serious complications including:

- ✓ Infections that required lead extraction
- ✓ Lead complications

Confirms S-ICD can be the preferred choice for most ICD indicated patients w/o need for pacing



Mortality

The PRAETORIAN Trial[1]

Mortality rate low for both S-ICD & TV-ICD

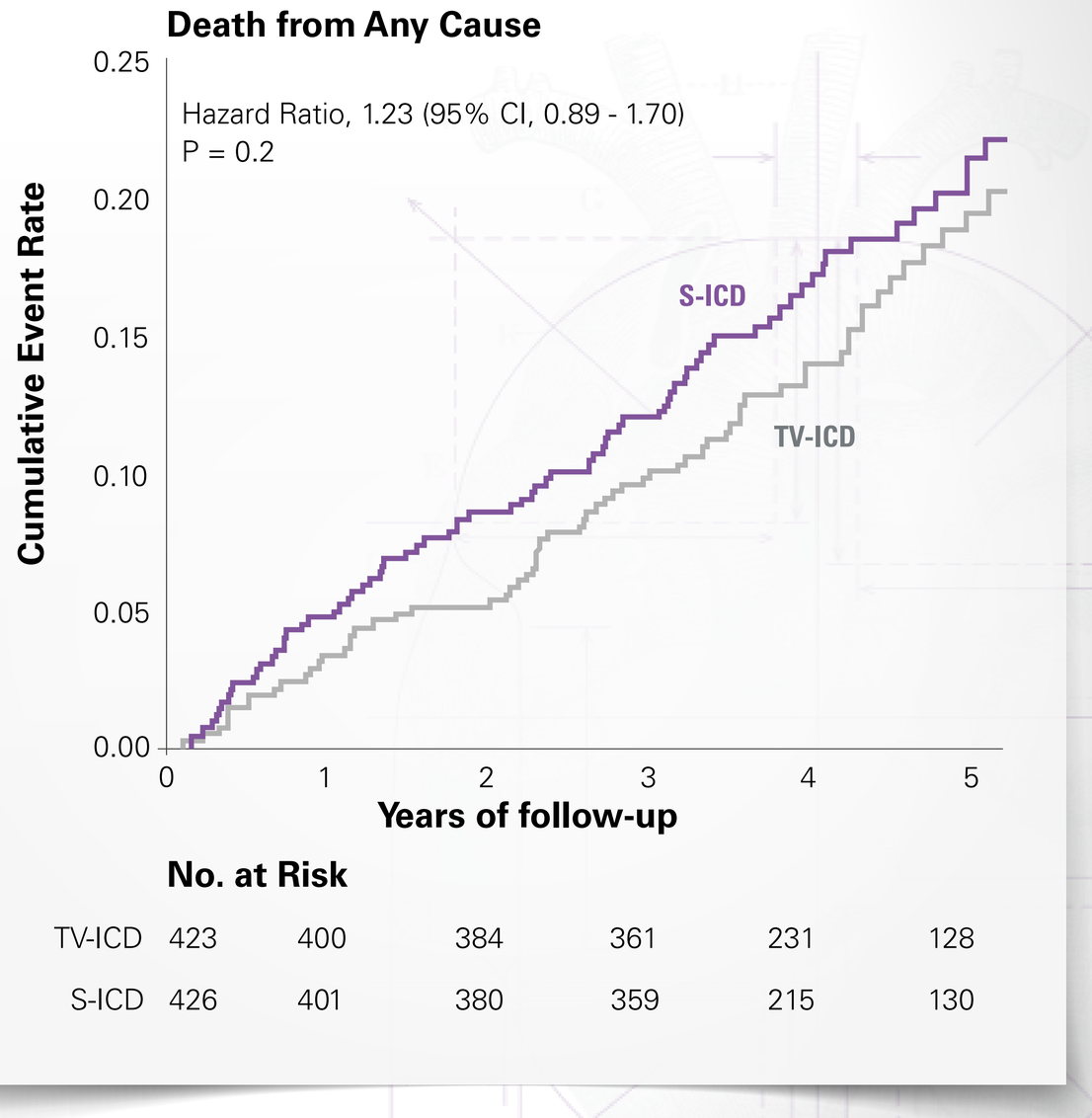
✓ Sudden cardiac deaths were identical for S-ICD and TV-ICD despite enrolling a sicker population than prior S-ICD studies

✓ **Mortality rate was low in both groups despite 90% of patients having ischemic or non-ischemic heart failure.**

- Median EF 30%
- Median age 63 years

✓ **More deaths for S-ICD due to non-cardiac causes**

	S-ICD (n = 426)	TV-ICD (n = 423)
Death from any cause	83 (16.4%)	68 (13.1%)
–Sudden cardiac death	18	18
–Other cardiovascular death	34	28
–Noncardiovascular death	31	22

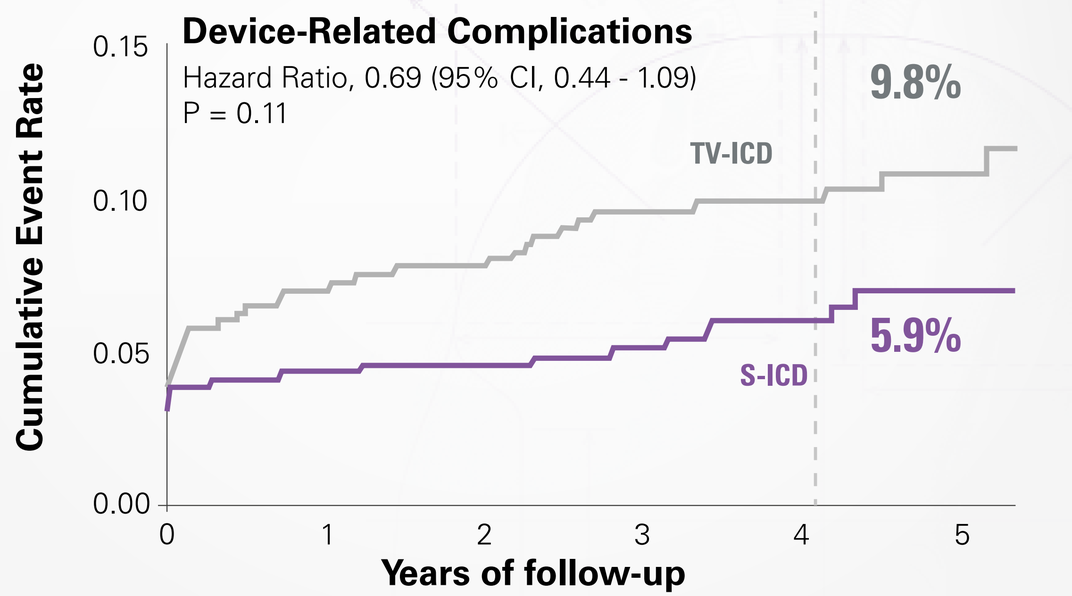


All Complications

The PRAETORIAN Trial[1]

Trend for fewer S-ICD complications expected to increase by 8 years in PRAETORIAN XL*

✓ ***PRAETORIAN XL Long Term Follow Up Study (median 8 years)**



Lead-related Complications

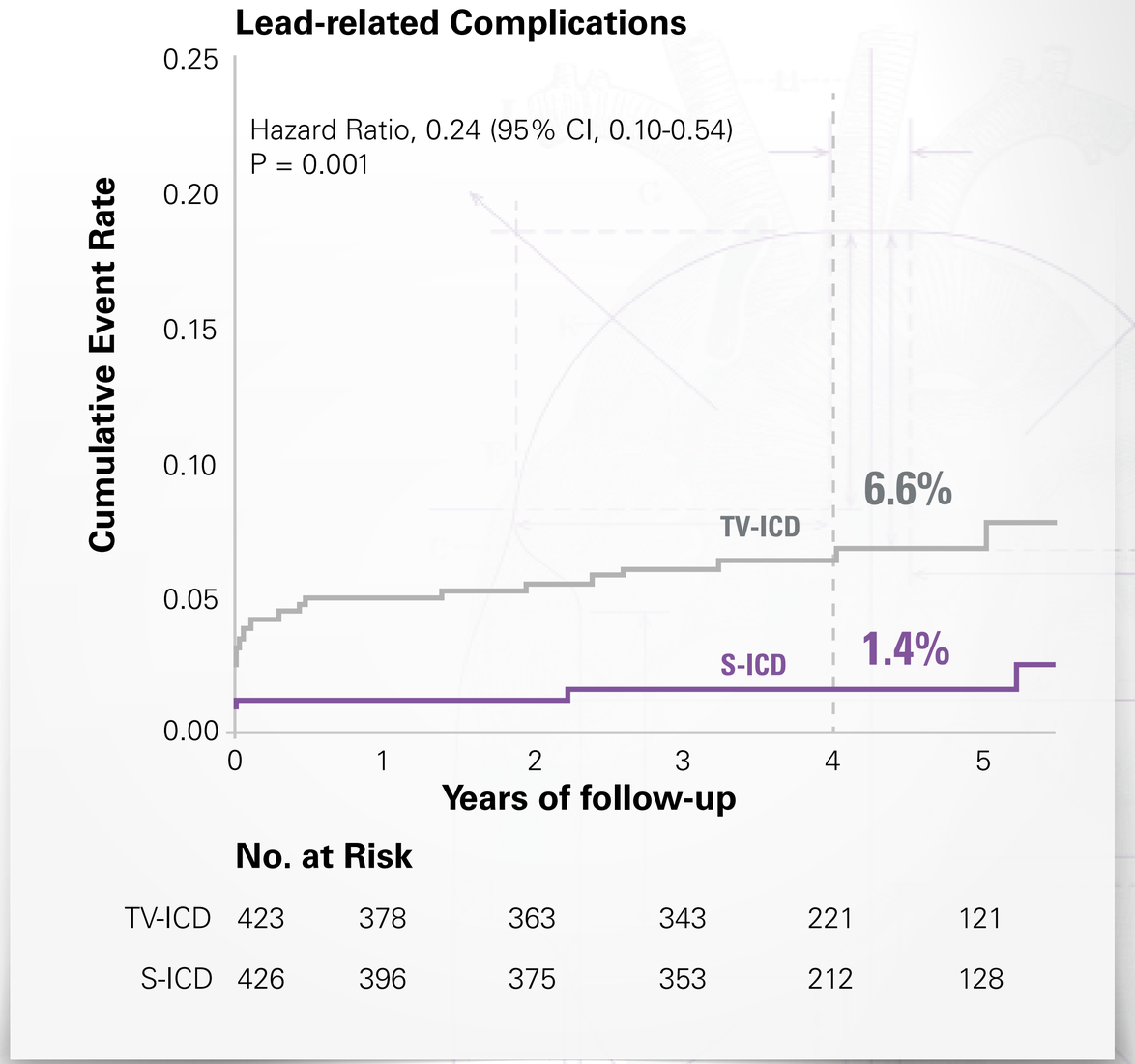
The PRAETORIAN Trial[1]

Significantly fewer lead-related complications

- ✓ 6.6% (n=24) in the TV-ICD arm vs
- ✓ 1.4% (n=5) in the S-ICD arm (P =0.001)

Details

- More than 4 times as many patients experienced a lead complication in the TV-ICD arm
- Eliminating device leads within the vasculature is particularly important for many ICD-indicated patients with comorbidities, such as diabetes, and renal disease who often are at an increased risk of infection and vascular access issues.[3]

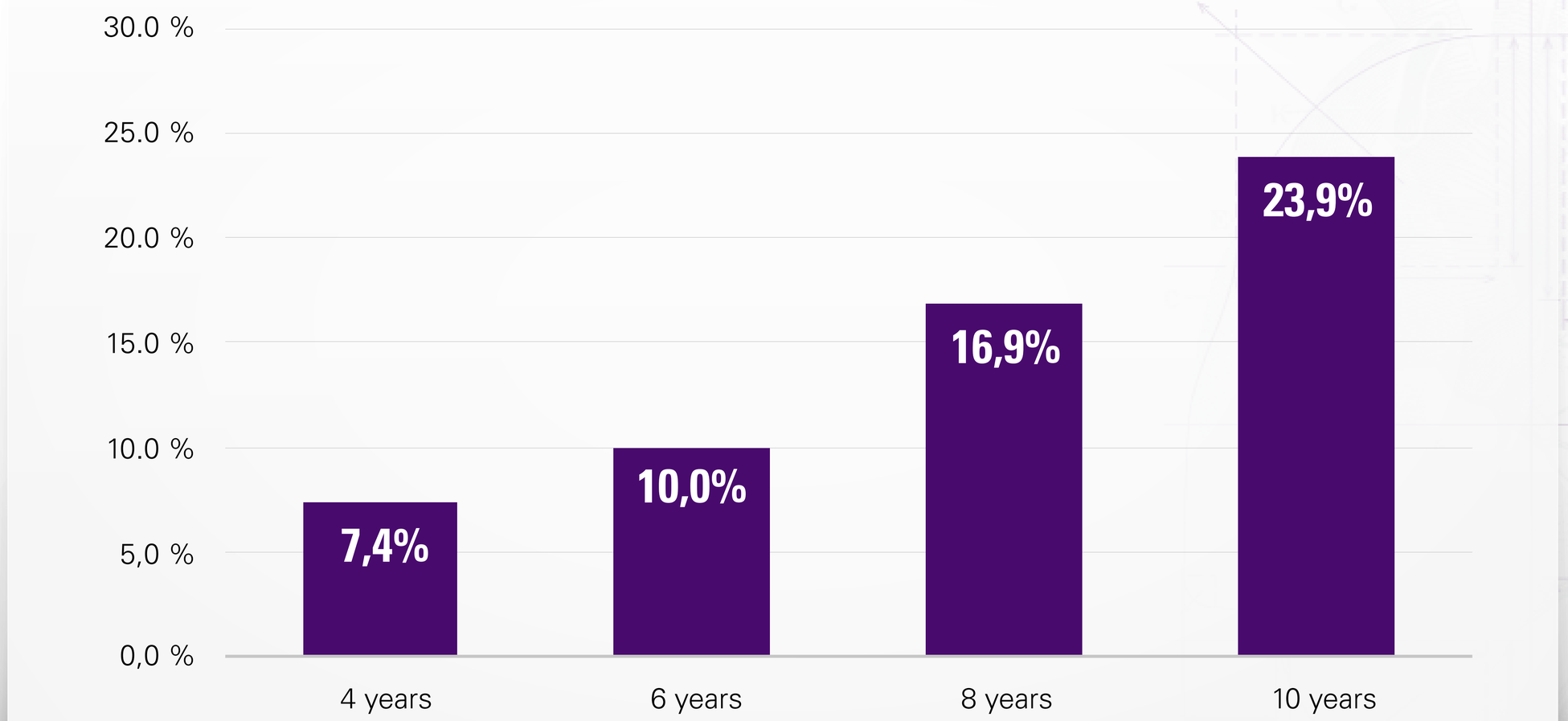


Optum Study Data

Transvenous Lead Complications Over Time

Optum Data[2]

% Patients w/ Mechanical Transvenous Lead Complications Over Time



PRAETORIAN Trial CRM 807201-AA

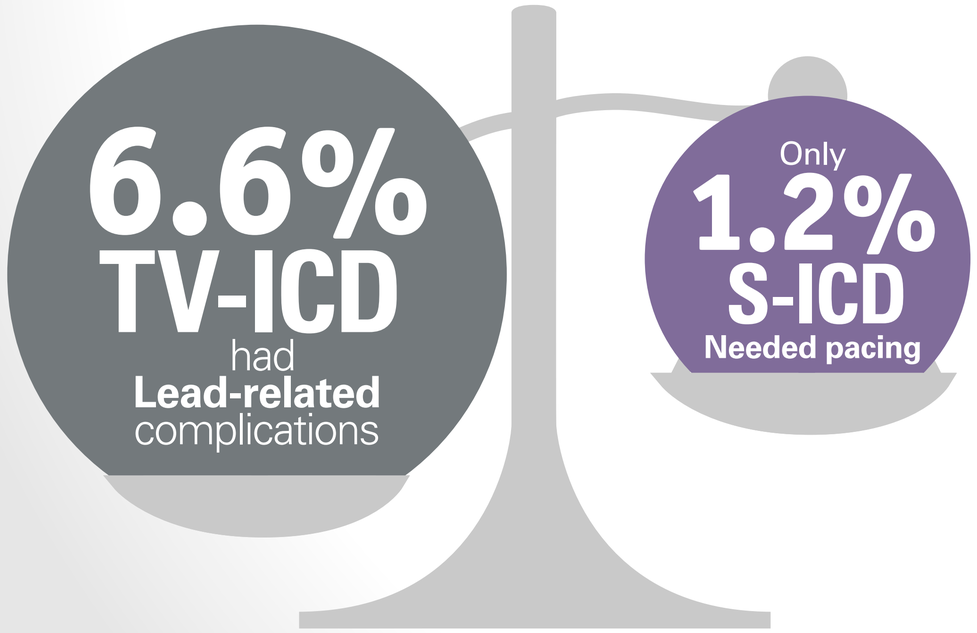
Lead-related Complications

The PRAETORIAN Trial[1]

Significantly fewer lead-related complications

- ✓ 6.6% (n=24) in the TV-ICD arm vs
- ✓ 1.4% (n=5) in the S-ICD arm (P =0.001)

Lead complications requiring intervention more common than developing a need for pacing or ATP



	S-ICD (n = 426)	TV-ICD (n = 423)
Primary composite endpoint	68 (15.1%)	68 (15.7%)
Device related complications	31 (5.9%)	44 (9.8%)
–Infection	4	8
–Bleeding	8	2
–Thrombotic event	1	2
–Pneumothorax	0	4
–Lead perforation	0	4
–Lead repositioning	2	7
–Other	19	20
• Lead replacement	3	9
• Device or sensing malfunction	8	6
• Pacing indication	5	1
• Implantation or DFT failure	3	3
• Pain or discomfort	2	3

Infections requiring extraction

The PRAETORIAN Trial[1]

Higher infection rate requiring extraction for patients with a TV-ICD

- ✓ 8 pts (1.9%) with a TV-ICD
- ✓ 4 pt (0.9%) with an S-ICD

- **Data in >91,000 transvenous lead extractions demonstrated that those extracted for infection had a complication rate of 9.2% vs 7.8% and a hospital mortality rate of 3.6% vs 1.2% compared to those without infection.[4]**

✓ In this study, the median costs of transvenous lead extraction was $39,308 for infected devices versus $14,916 for non-infected leads.

	S-ICD (n = 426)	TV-ICD (n = 423)
Primary composite endpoint	68 (15.1%)	68 (15.7%)
Device related complications	31 (5.9%)	44 (9.8%)
–Infection	4	8
–Bleeding	8	2
• Pacing indication	5	1

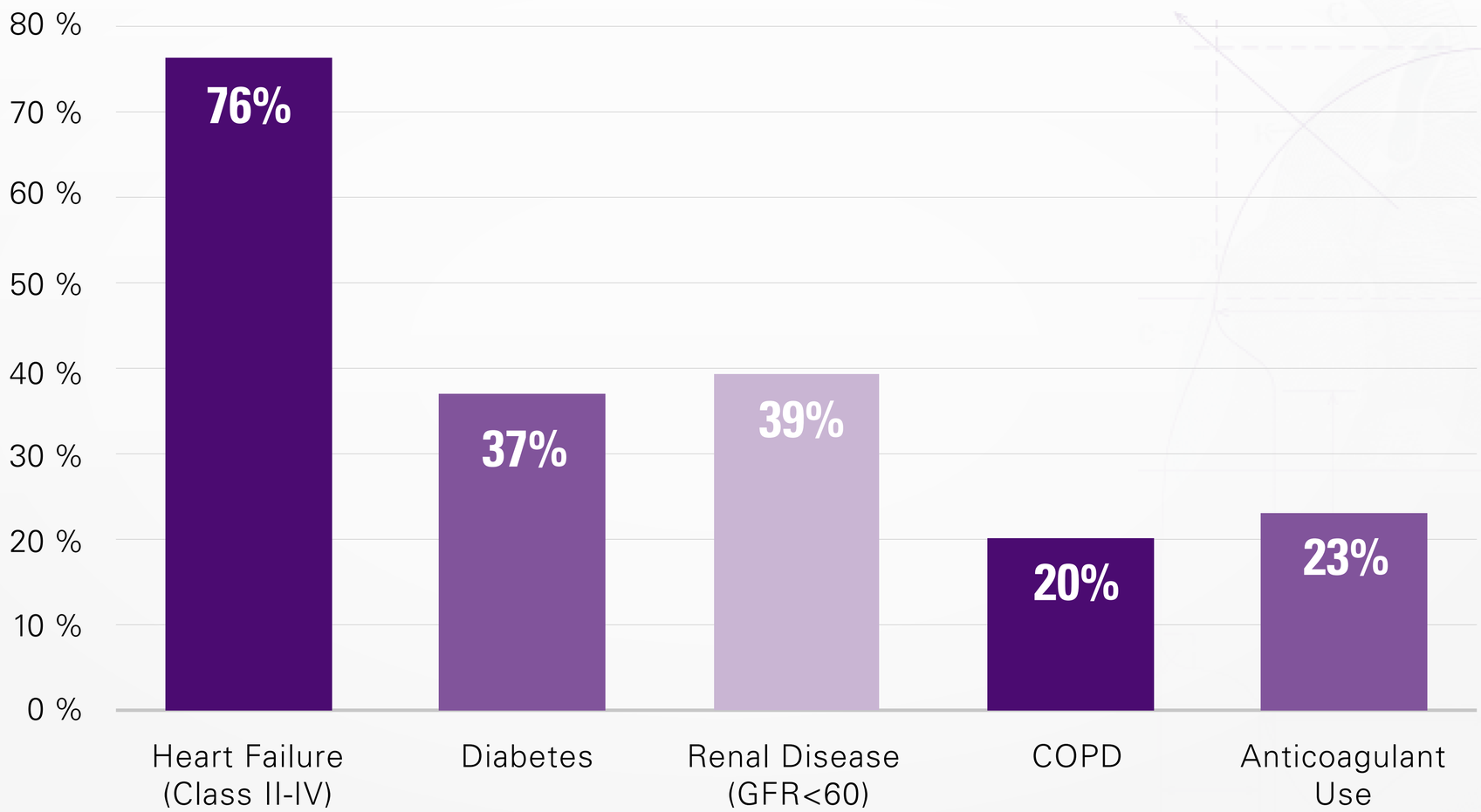
1.9%
TV-ICD
Infection
requiring **Extraction**

1.9%
S-ICD
Bleeding

Guidelines recommend S-ICD in patients at high risk for infection[5]

The PRAETORIAN Trial[1]

% of ICD Patients in the U.S. With Below Comorbidities[6]



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Evidence shows patients with these comorbidities have a 2-8 fold higher risk for TV-ICD infection.[3]

Factor	OR	95% CI	P-value
End stage renal disease/hemodialysis	8.73	3.42 – 22.31	0.00001
History of device infection	7.84	1.94 – 31.60	0.004
Fever prior to implant	4.27	1.13 – 16.12	0.03
Corticosteroid use	3.44	1.62 – 7.32	0.001
Renal insufficiency	3.02	1.38 – 6.64	0.006
COPD	2.95	1.78 – 4.90	0.00003
NYHA Class ≥2	2.47	1.24 – 4.91	0.01
Chronic skin disorders	2.46	1.04 – 5.80	0.04
Malignancy	2.23	1.26 – 3.96	0.006
Diabetes mellitus	2.08	1.62 - 2.67	<0.000001
Heparin bridging	1.87	1.03 – 3.41	0.04
Congestive heart failure	1.65	1.14 – 2.39	0.008
Oral anticoagulation	1.59	1.01 - 2.48	0.04

PRAETORIAN Trial CRM 807201-AA

In this study from the Cleveland Clinic, patients with transvenous device infections had a 12-31% mortality rate 1 year following lead extraction[7]

Europace (2014) **16**, 1490–1495
doi:10.1093/europace/euu147

CLINICAL RESEARCH
Leads and lead extraction

Risk factors for 1-year mortality among patients with cardiac implantable electronic device infection undergoing transvenous lead extraction: the impact of the infection type and the presence of vegetation on survival

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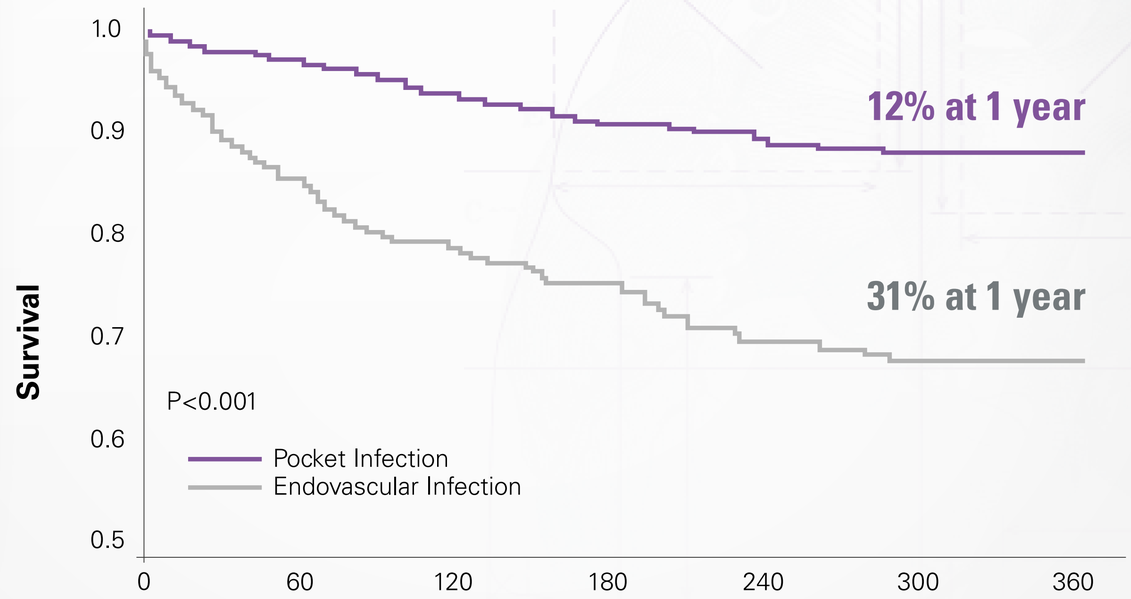
Received 2 April 2014; accepted after revision 9 May 2014; online publish-ahead-of-print 2 August 2014



Number of patient at risk

Pocket	289	270	258	245	238	232	230
Endovascular	213	175	159	149	137	132	130

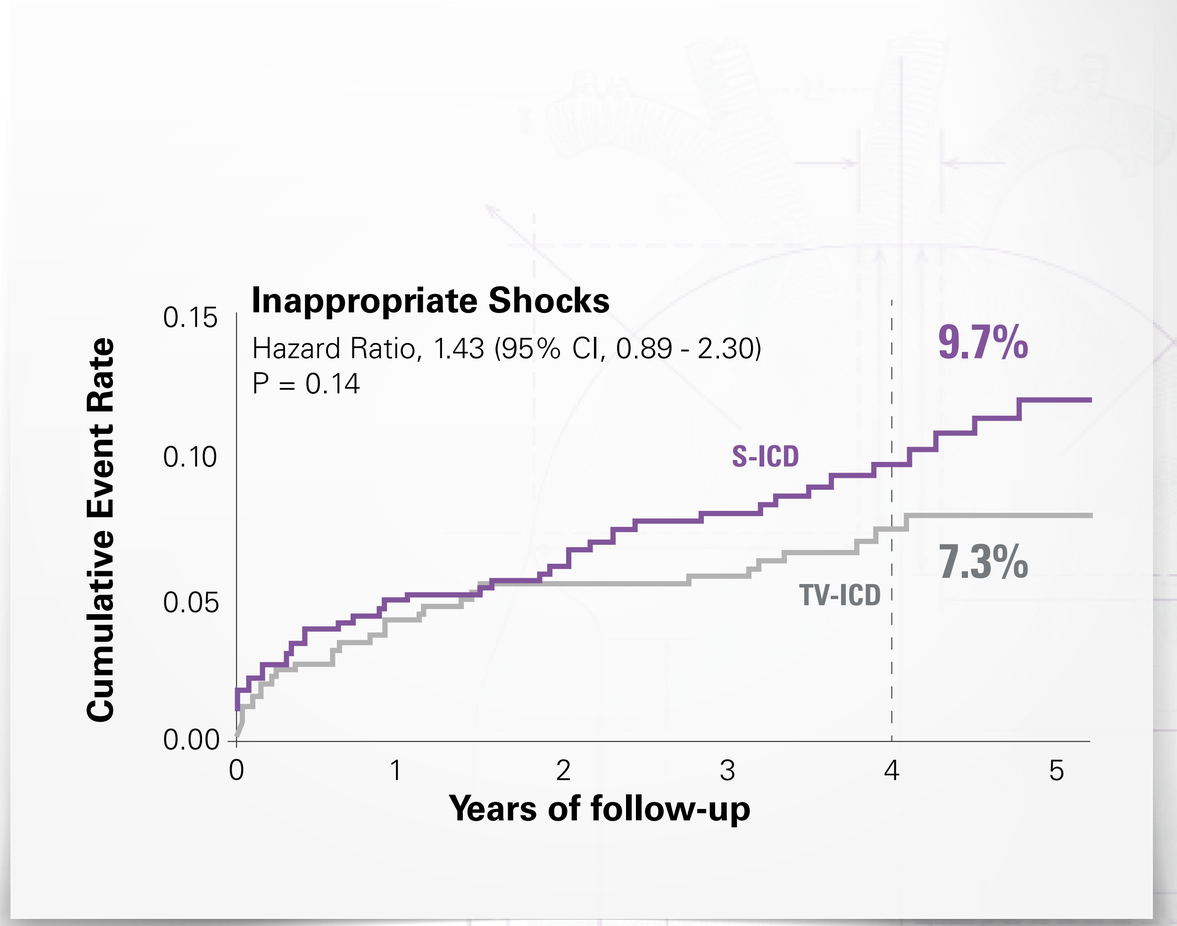
PRAETORIAN Trial CRM 807201-AA

Inappropriate shocks (IAS)

The PRAETORIAN Trial[1]

No significant difference in rate of IAS, which were low for both the S-ICD & TV-ICD groups

- ✓ 4.1% at 1 year in the TV-ICD arm vs
- ✓ 4.8% in the S-ICD arm



Details

- Rate of IAS at 1 years was similar & comparable to rates seen in other TV-ICD studies.[9-11]
- The IAS rate is nearly identical for the first 2 years which includes data from the EMBLEM S-ICD devices. The early implant with Gen 1 1010 S-ICD's are likely driving the curves to separate after 2 years.
- The SMART Pass™ sensing filter, which has been shown to reduce IAS by 68%[8] was either not available or enabled in 78% of S-ICD patients who had an inappropriate shock.

Inappropriate shocks (IAS)

The PRAETORIAN Trial[1]

While no difference in rate of IAS, the reason for IAS differed

- ✓ Afib/SVT most common cause of IAS for TV-ICD
- ✓ Oversensing most common cause of IAS for S-ICD

At 4 years (median)	S-ICD (n = 426)	TV-ICD (n = 423)
Primary composite endpoint	68 (15.1%)	68 (15.7%)
Inappropriate shock	41 (9.7%)	29 (7.3%)
–AF/SVT	15	27
–Cardiac oversensing	20	2
–Noncardiac oversensing	8	0

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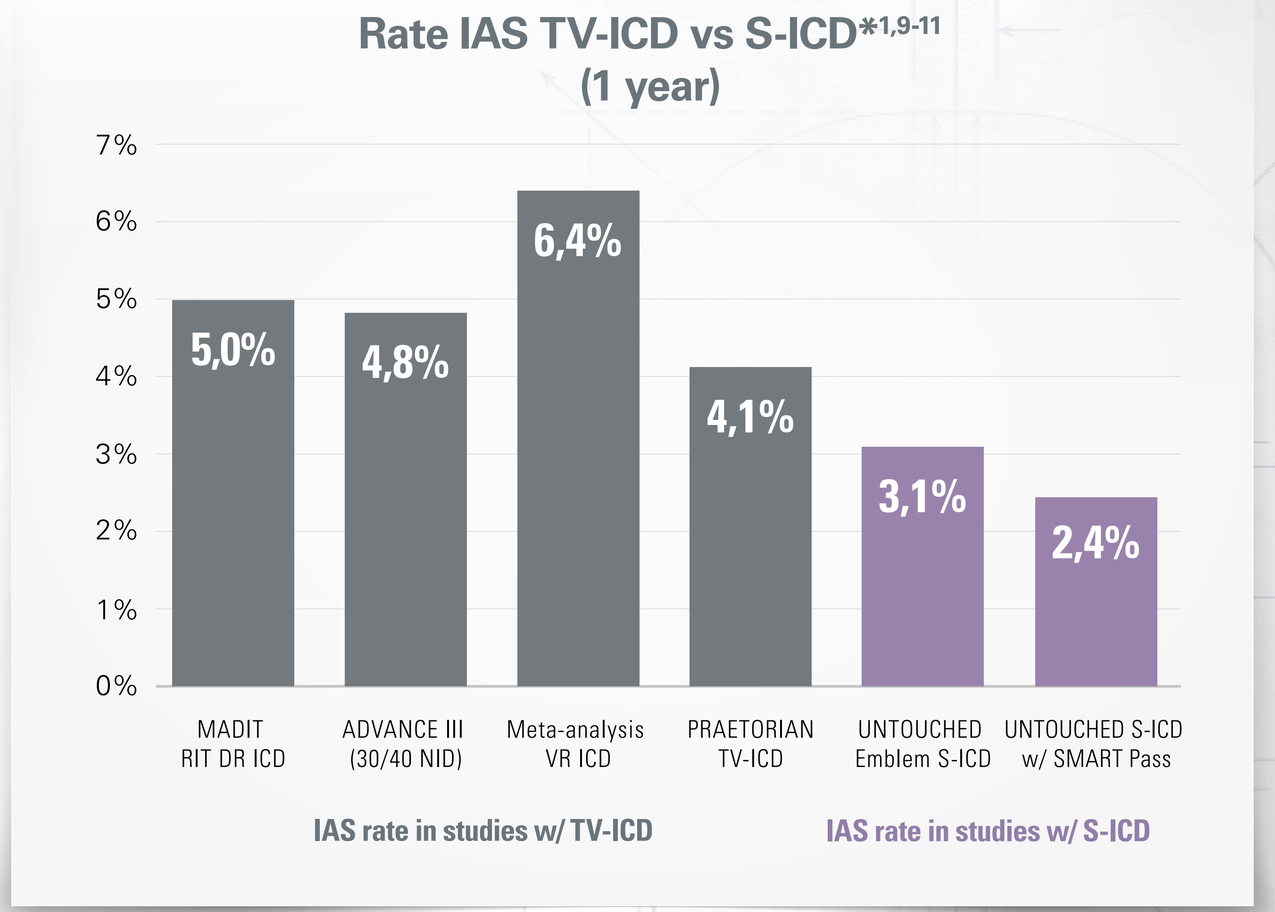
Inappropriate shocks (IAS)

The UNTOUCHED Study of the EMBLEM™ & EMBLEM™ MRI S-ICD System

Low rate of IAS in Primary Prevention low EF

- ✓ 3.1% overall rate of IAS at 1 year[12]
- ✓ 2.4% at 1 year in patients who received an EMBLEM MRI w/ SMART Pass™ Filter[12]

The **IAS rate in UNTOUCHED was comparable to, or lower than**, the rate of IAS observed in other contemporary studies with TV-ICDs including the PRAETORIAN trial[1,9-11]

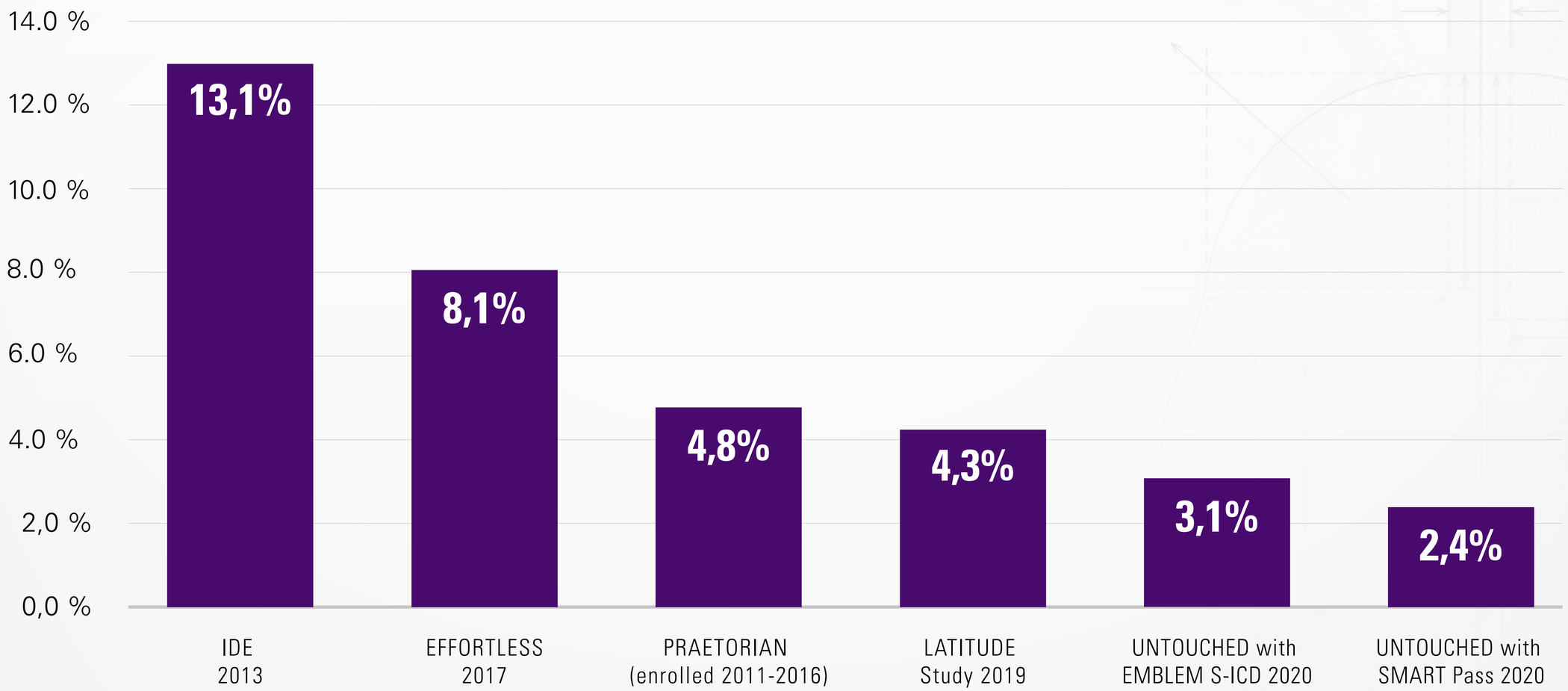


*Results from different clinical investigations are not directly comparable. Information provided for educational purposes only.

PRAETORIAN Trial CRM 807201-AA

Rate of IAS for S-ICD continues to decline

1-year Rate for IAS 2013-2020[1,8,12-14]



PRAETORIAN Trial CRM 807201-AA

Conclusion

The PRAETORIAN Trial[1]

PRAETORIAN[1] demonstrated S-ICD had comparable performance to TV-ICD, despite primarily including older S-ICD devices and implant techniques.

- ✓ S-ICD had significantly **fewer lead-related complications** (P =0.001)
- ✓ **Fewer serious infections** requiring extraction (8 TV-ICD vs 4 S-ICD)
- ✓ Trend in fewer overall complications (P=0.11); likely to be significantly lower at 8 years in PRAETORIAN XL

UNTOUCHED[12] demonstrated patients w/ EMBLEM™ MRI with SMART Pass™ had a 2.4% rate of inappropriate shocks at 1 year which is as low or lower than TV-ICD devices.[1,9-11]

These 2 studies confirm the S-ICD should be strongly considered in all ICD indicated patients without a pacing need.

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EMBLEM™ MRI S-ICD

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INDICATIONS FOR USE
The S-ICD System is intended to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia pacing.

CONTRAINDICATIONS
Unipolar stimulation and impedance-based features are contraindicated for use with the S-ICD System.

WARNINGS
Concomitant use of the S-ICD System and implanted electromechanical devices (for example implantable neuromodulation/neurostimulation systems, ventricular assist device (VAD), or implantable insulin pump or drug pump) can result in interactions that could compromise the function of the S-ICD, the co-implanted device, or both. The S-ICD is intended as lifesaving therapy and should be seen as priority in the decision and evaluation of concomitant system implants over non-lifesaving applications. Electromagnetic (EMI) or therapy delivery from the co-implanted device can interfere with S-ICD sensing and/or rate assessment, resulting in inappropriate therapy or failure to deliver therapy when needed. In addition, a shock from the S-ICD pulse generator could damage the co-implanted device and/or compromise its functionality. Verify sensing configuration, operation modes, surgical considerations and existing placement of all involved devices prior to any co-implant. To help prevent undesirable interactions, test the S-ICD system when used in combination with the co-implanted device, and consider the potential effect of a shock on the co-implanted device. Induction testing is recommended to ensure appropriate detection and time to therapy for the S-ICD and appropriate post-shock operation of the co-implanted device. Failure to ensure appropriate detection and time to therapy delivery of the S-ICD system could result in patient injury or death. Following completion of the interaction testing, thorough follow-up evaluation of all co-implanted devices should be performed to ensure that device functions have not been compromised. If operational settings of the co-implanted devices change or if patient conditions changes which may affect S-ICD sensing and therapy performance, re-evaluation of the co-implanted devices may be required. Do not expose a patient with an implanted S-ICD System to diathermy. EMBLEM S-ICD devices are considered MR Conditional. Unless all MRI Conditions of Use are met, MRI scanning of the patient does not meet MR Conditional requirements for the implanted system. The Programmer is MR Unsafe and must remain outside the MRI site Zone III. During MRI Protection Mode the Tachycardia therapy is suspended. MRI scanning after ERI status has been reach may lead to premature batter depletion, a shortened device replacement window, or sudden loss of therapy. The Beeper may no longer be usable following an MRI scan.

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PRECAUTIONS
For specific information on precautions, refer to the following sections of the product labeling: clinical considerations, sterilization and storage, implantation, device programming, environmental and medical therapy hazards, hospital and medical environments, home and occupational environments, follow up testing, explant and disposal, supplemental precautionary information.

POTENTIAL ADVERSE EVENTS
Potential adverse events related to implantation of the S-ICD System may include, but are not limited to, the following: Acceleration/induction of atrial or ventricular arrhythmia, adverse reaction to induction testing, allergic/adverse reaction to system or medication, bleeding, conductor fracture, cyst formation, death, delayed therapy delivery, discomfort or prolonged healing of incision, electrode deformation and/or breakage, electrode insulation failure, erosion/extrusion, failure to deliver therapy, fever, hematoma/seroma, hemothorax, improper electrode connection to the device, inability to communicate with the device, inability to defibrillate or pace, inappropriate post shock pacing, inappropriate shock delivery, infection, injury to or pain in upper extremity, including clavicle, shoulder and arm, keloid formation, migration or dislodgement, muscle/nerve stimulation, nerve damage, pneumothorax, post-shock/post-pace discomfort, premature battery depletion, random component failures, stroke, subcutaneous emphysema, surgical revision or replacement of the system, syncope, tissue redness, irritation, numbness or necrosis.

Patients who receive an S-ICD System may develop psychological disorders that include, but are not limited to, the following: depression/anxiety, fear of device malfunction, fear of shocks, phantom shocks.

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician. Rx only. Prior to use, please see the complete "Directions for Use" for more information on Indications, Contraindications, Warnings, Precautions, Adverse Events, and Operator's Instructions

92436235 (Rev A)

PRAETORIAN Trial CRM 807201-AA