Academic Medical Center

University of Amsterdam

Selecting the Best ICD for your Patient-SICD v. TV

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CorVita Science Foundation

&

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COI DISCLOSURES

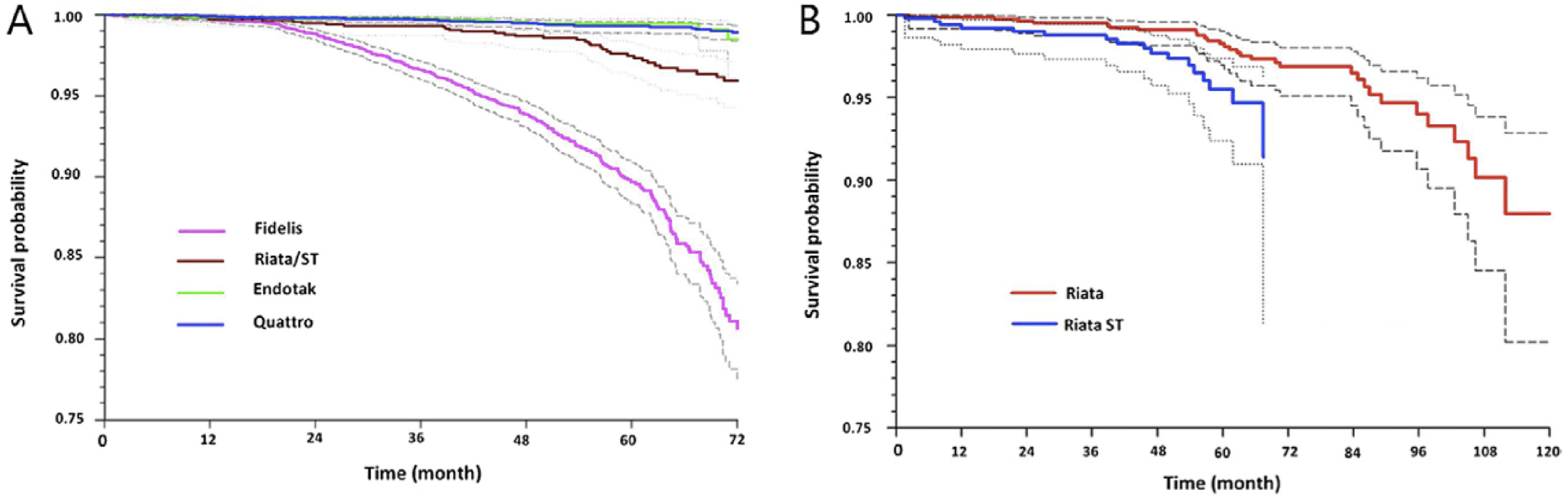
I have received lecture and proctoring honoraria from Spectranetics.

I have been funded by and NIH/SBIR grant to AJ Medical Devices, Inc. (AJMD) and research grants from Boston Scientific, Medtronic, St. Jude Medical, Guidant, Inc. and Cameron Health, Inc.

I am or have been a consultant to AJMD, Boston Scientific and Cameron Health.

I have an equity stake in AtaCor Medical, Inc.

VA Study



Units at Risk:

Fidelis	5073	4671	4135	3478	2265	965	179
Riata/ST	1403	1355	1285	1171	989	703	411
Endotak	2401	2100	1623	1222	798	501	143
Quattro	6091	4764	3479	2337	1760	1455	1156

Units at Risk:

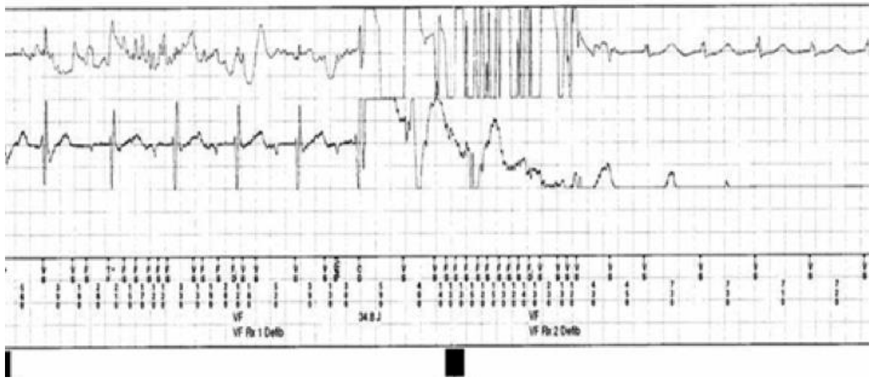
Riata	877	852	822	765	667	554	409	247	135	70	3
Riata ST	526	503	463	406	322	149	2				

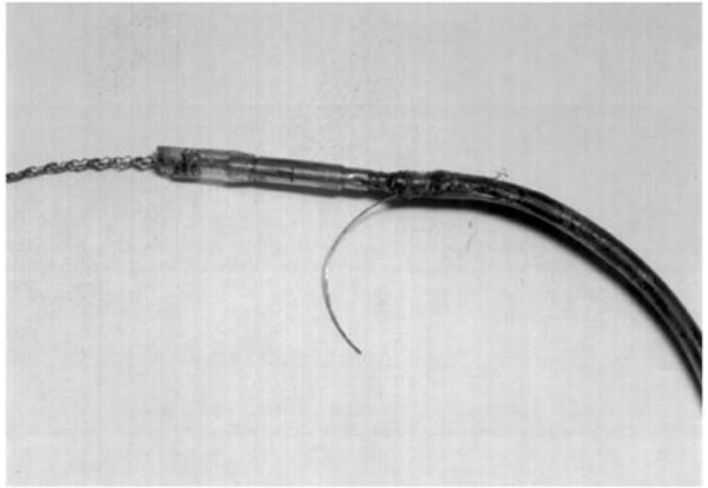
Figure 1 High-voltage lead survival. **A:** Kaplan-Meier survival plot of 4 lead families: Fidelis, Riata/ST (Riata and Riata ST non-Optim), Quattro, and Endotak. **B:** Kaplan-Meier survival plot of Riata vs Riata ST non-Optim lead series.

Sung RK, Massie BM, Varosy PD. Heart Rhythm 2012;9:1954-1961

Consequences of Failure

- Failure to Deliver therapy
- Inappropriate Shocks
- Pro-arrhythmia
- Loss of Capture
- Perforation/Laceration

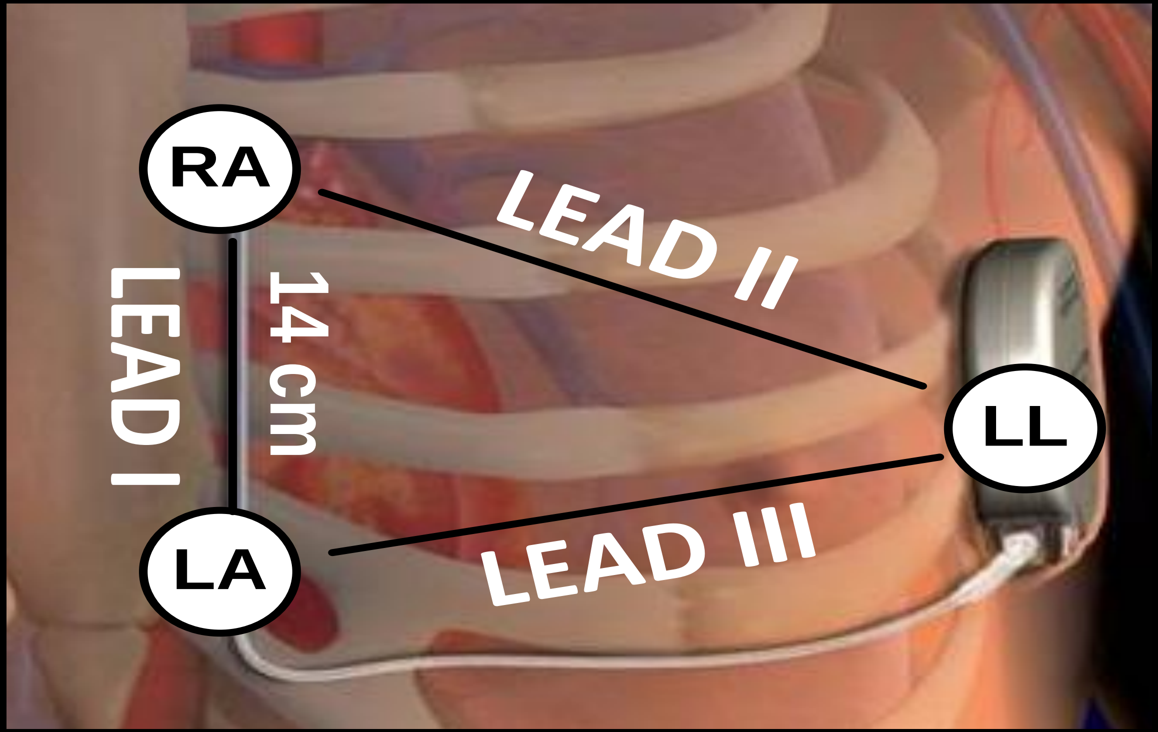




GOROG D A , LEFROY D C Heart 2000;83:563-563

An Entirely Subcutaneous ICD

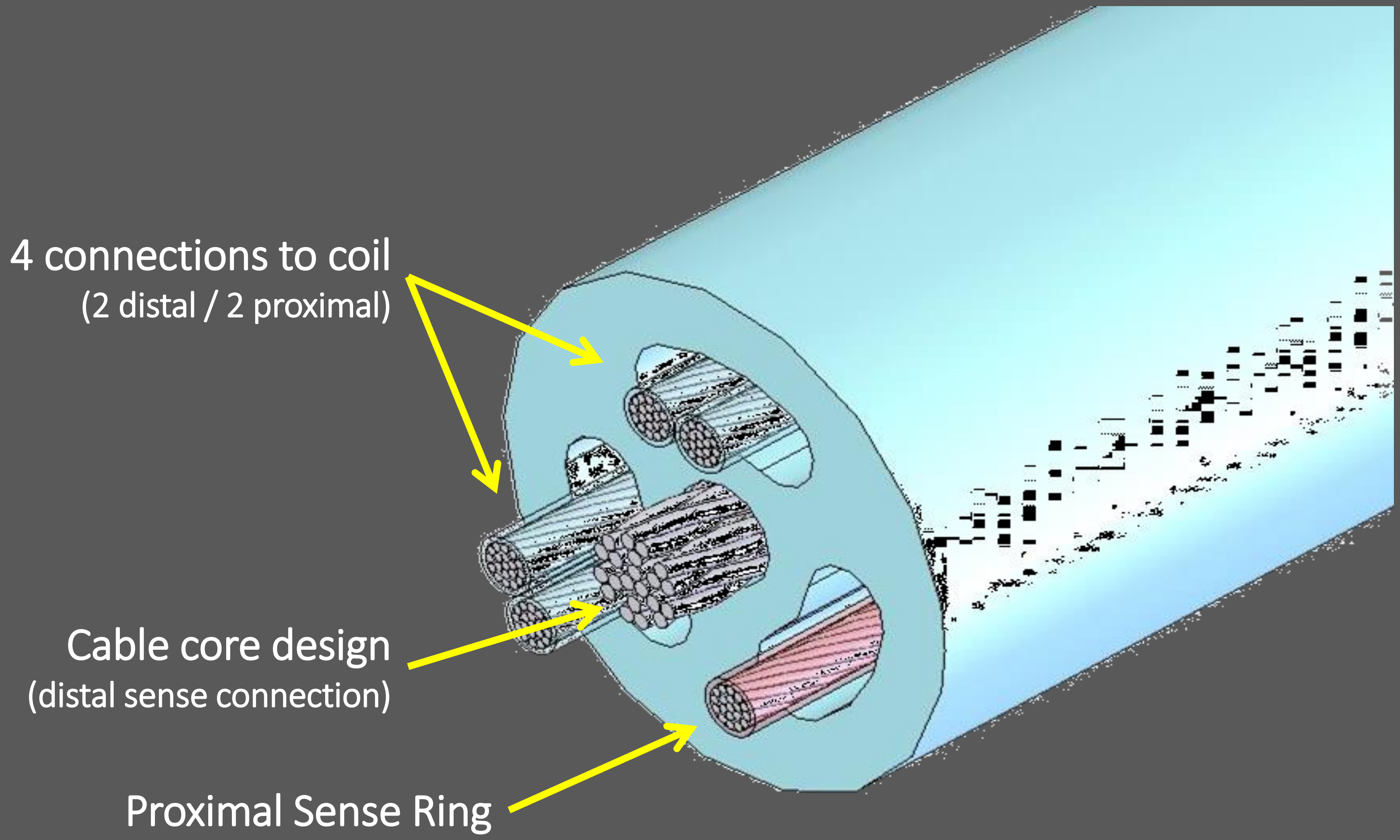
SIMULTANEOUS 3-LEAD ECG



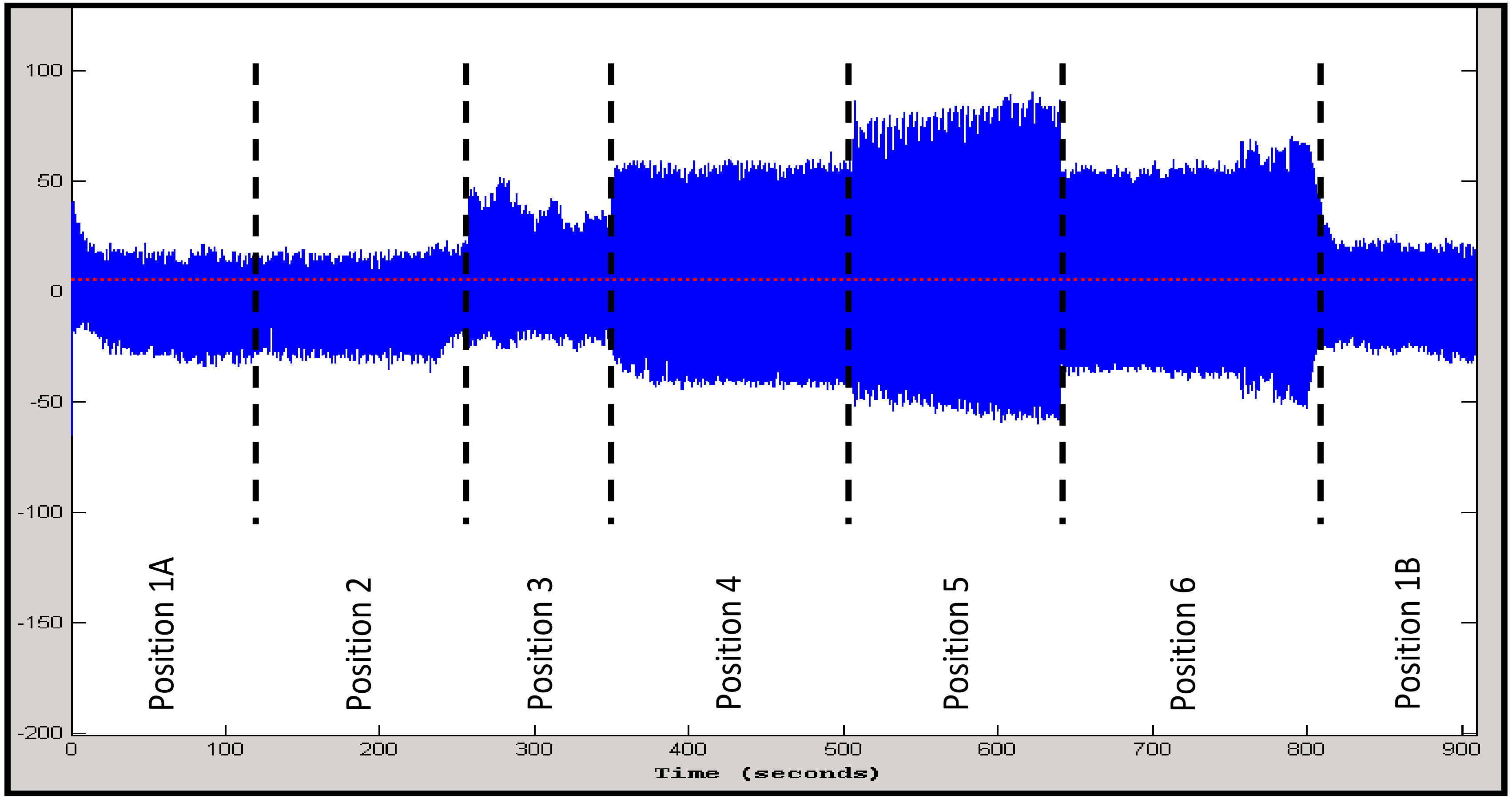
1. **RECORD**: Supine+Standing

25 mm/s, 5-20 mm/mV

S-ICD System Components: Q-TRAK™ Electrode

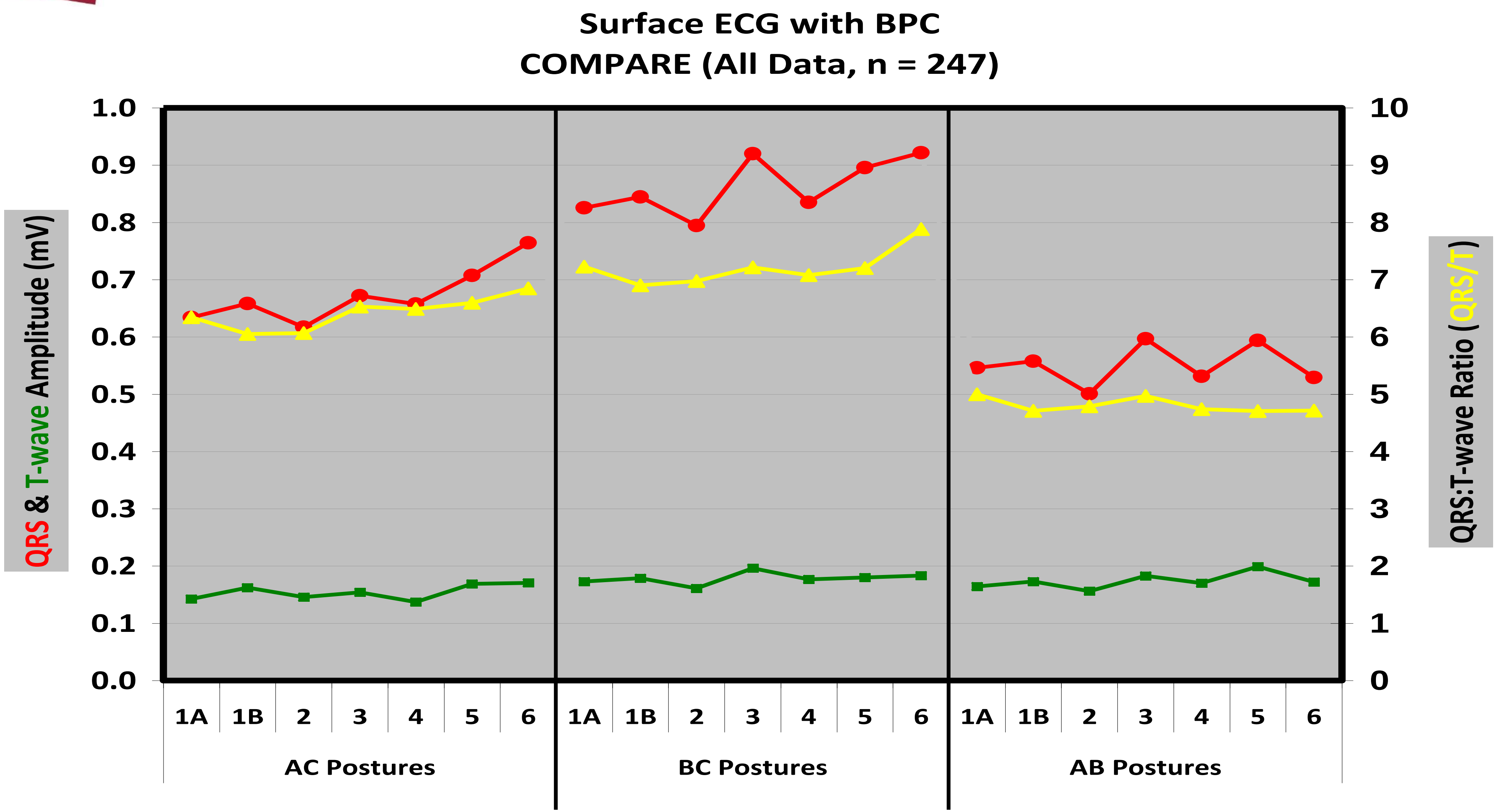


COMPARE TRIAL



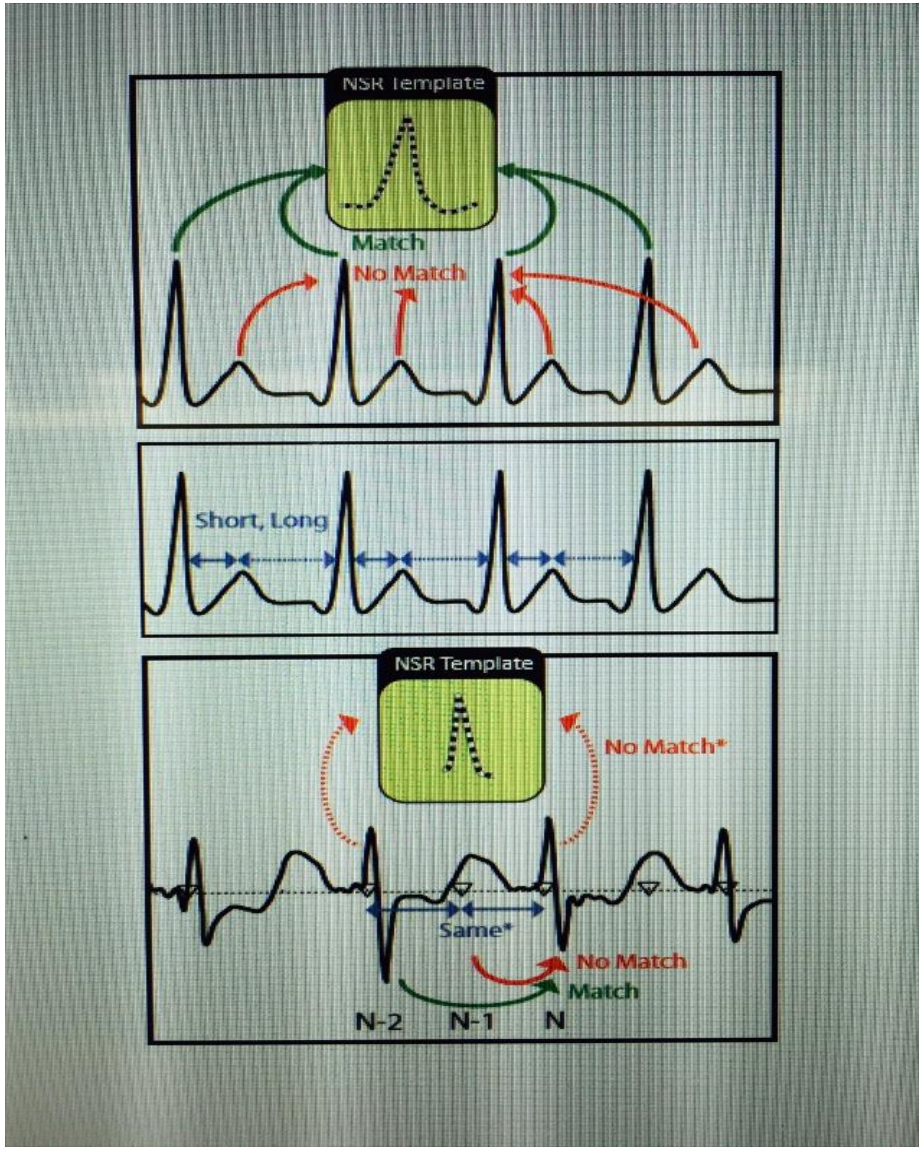
Burke et al . HRJ 2009 (abstr)

COMPARE TRIAL



Burke et al. HRJ 2009 (abstr)

TWOS Algorithm



-Essentially treats repetitive TWOS as bigeminy

-The Algorithm is functional in all zones not just the conditional zone.

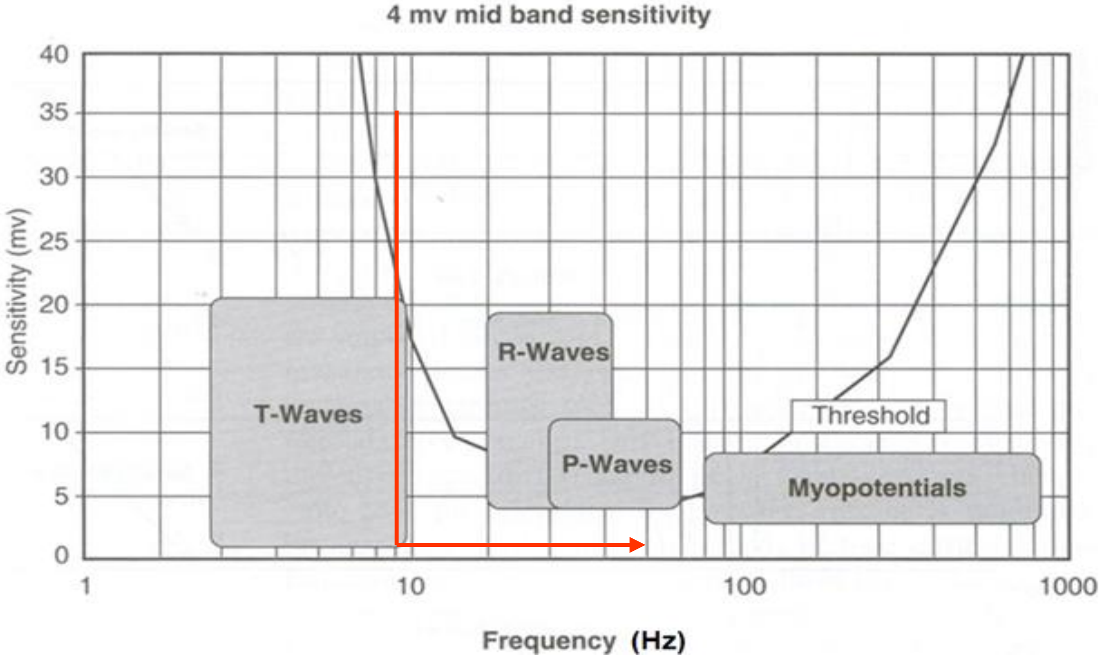
-It has a significant benefit in decreasing TWOS in ambulatory human event library

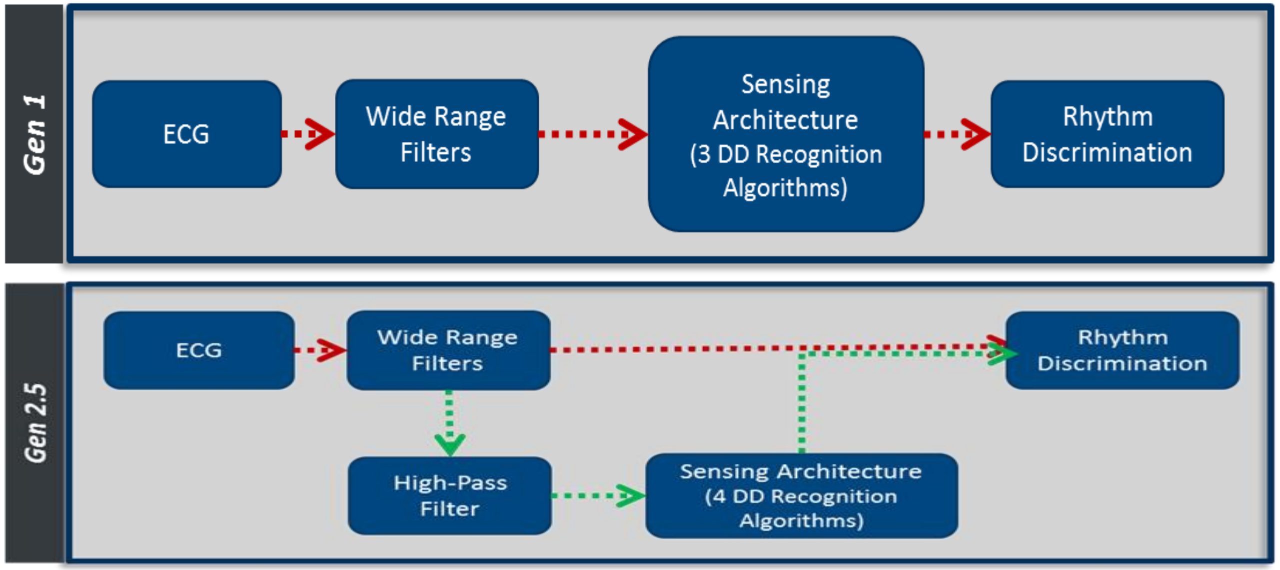
-The algorithm does not inhibit TTT or affect sensitivity for ventricular arrhythmias

Brisben, Burke et al. JCE 2015

SMART Pass algorithm

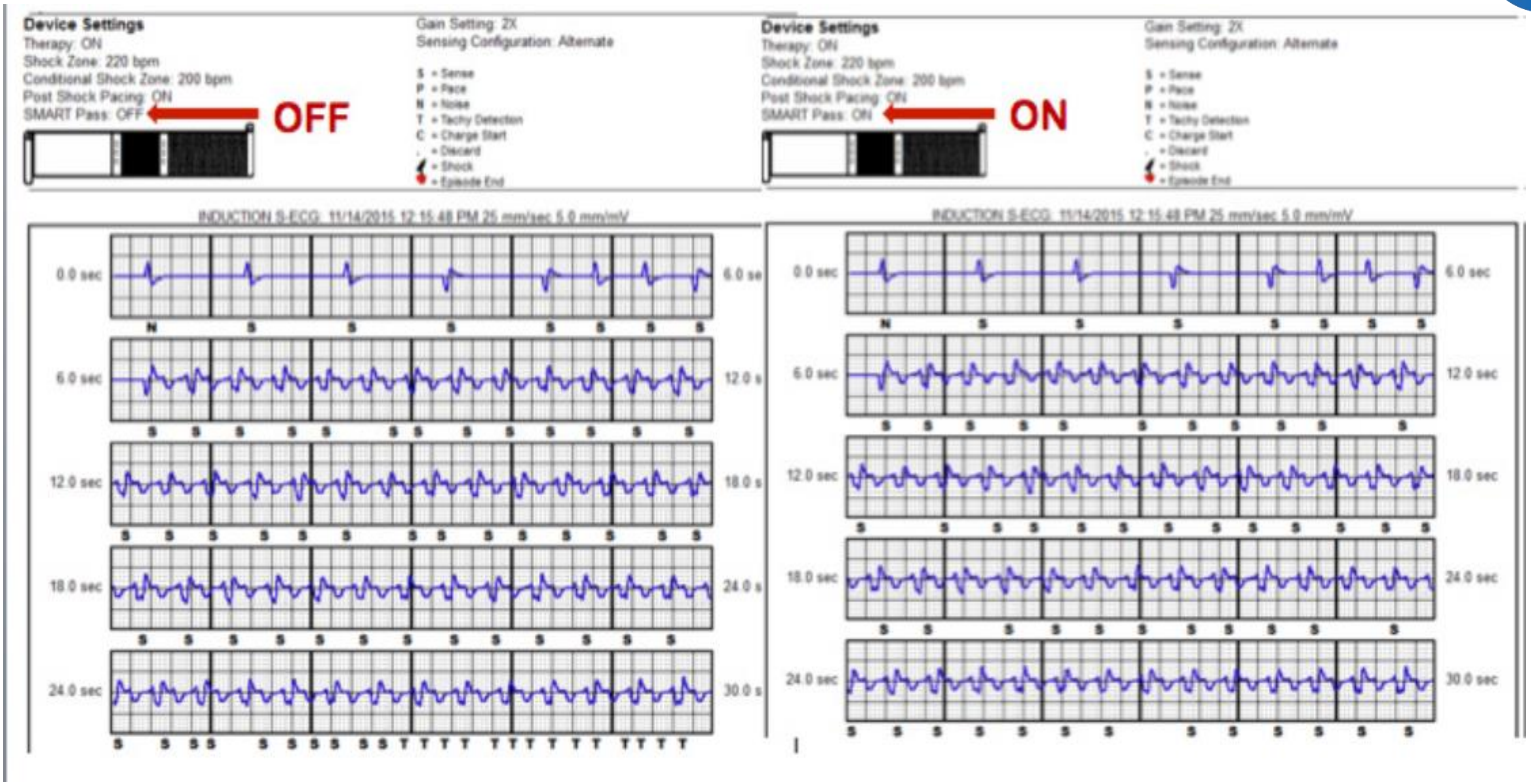
- Enables a high-pass filter (9 Hz) for sensing and heart rate estimate.
- ECG for rhythm discrimination remains unchanged and continues to use the wide-band filtered ECG similar to previous generations.
- Enabled with manual/automatic setup during a session.
- Automatically disabled for low amplitudes and slower rates.





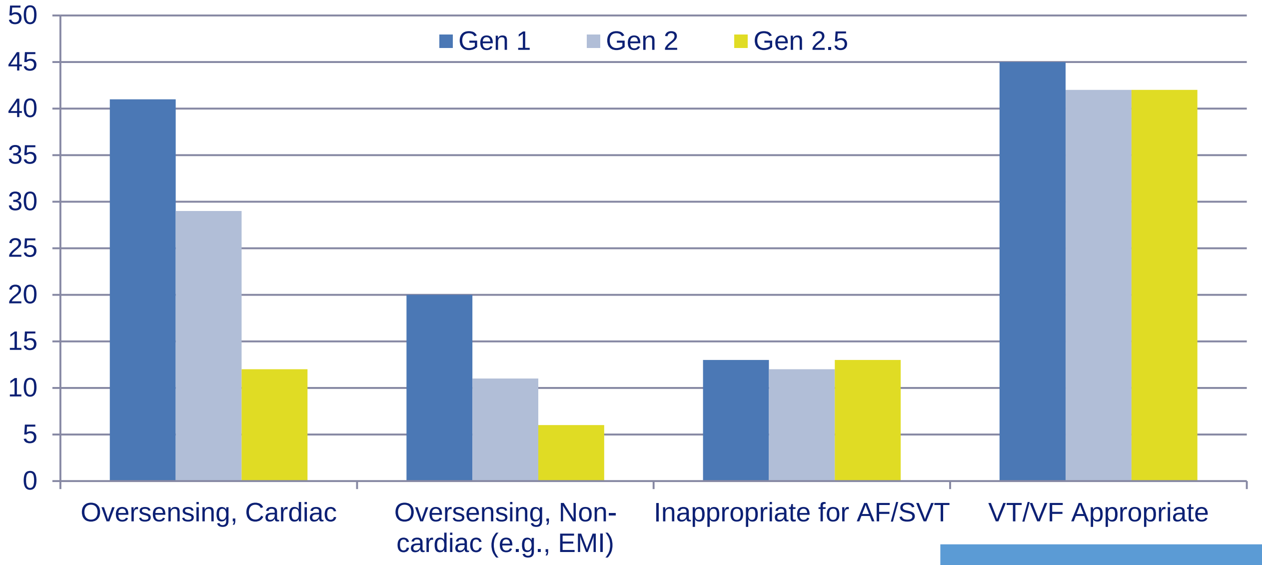
Theuns, Burke et al. HRJ 2016 Abstr.

9 Hz Filter OFF/ON

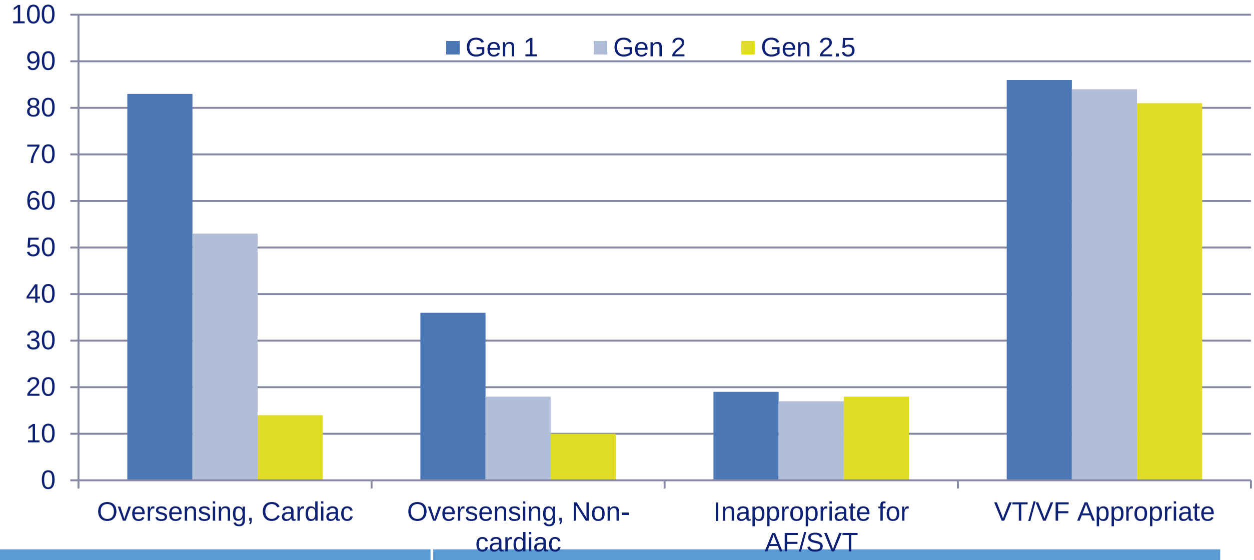


Results – *EFFORTLESS*

Patients



Episodes



	Patients (Pct Reduction)		Episodes (Pct Reduction)	
	Gen 2 vs Gen 1	Gen 2 .5 vs Gen 1	Gen 2 vs Gen 1	Gen 2 .5 vs Gen 1
Oversensing, Cardiac	29.3%	70.7%	36.1%	83.1%
Oversensing, Non-cardiac (e.g., EMI)	45.0%	70.0%	50.0%	72.2%
Inappropriate AF/SVT	7.7%	0.0%	10.5%	5.3%
Total Inappropriate	**28.6%**	**57.1%**	**36.0%**	**69.8%**
VT/VF Appropriate	6.7%	6.7%	2.3%	5.8%

Theuns, Burke et al. HRJ 2016 Abstr.

S-ICD Pooled Results
S-ICD and TV-ICD Spontaneous Conversion Efficacy

When evaluating TV-ICD studies[1-4], S-ICD was as effective as TV-ICD in treating spontaneous arrhythmias

	Spontaneous Shock Efficacy	
	First Shock	Final Shock in episode
S-ICD Pooled Data*	90.1%	98.2%
ALTITUDE First Shock Study[1]	90.3%	99.8%
SCD-HeFT[2]	83%	
PainFree Rx II[2]	87%	
MADIT-CRT[3]	89.8%	
LESS Study[4]		97.3%

* Excluded VT/VT Storm events

S-ICD Pooled Data 100% Clinical conversion to normal sinus rhythm	Of two "unconverted" episodes • One spontaneously terminated after the 5th shock • In the other episode, the device prematurely declared the episode ended. A new episode was immediately reinitiated and the VF was successfully terminated with one shock

1 Cha YM et al. *Heart Rhythm* 2013;10:702–708. 2 Swerdlow CD et al. *PACE* 2007; 30:675–700. 3 Kutyifa V, et al. *J Cardiovasc Electrophysiol* 2013;24:1246-52.
4 Gold MR et al. *Circulation* 2002;105:2043-2048.

S-ICD Pooled Results
Mortality Compared to TV-ICD Studies

S-ICD had a 2 year mortality rate that compared favorably with mortality rates in studies with TV-ICDs

Study	Mortality (At 2 years)	Average Age	1^0 Prevention	Ischemic	NYHA	LVEF
S-ICD Pooled*	3.2%	50	70%	38%	37.5% class II-IV	39%
MADIT RIT[1]	5-7% High rate and Delayed Therapy Arms	63	100%	53%	98% class II or III	26%
SIMPLE[2]	11%	64	70%		63% class II or III	32%

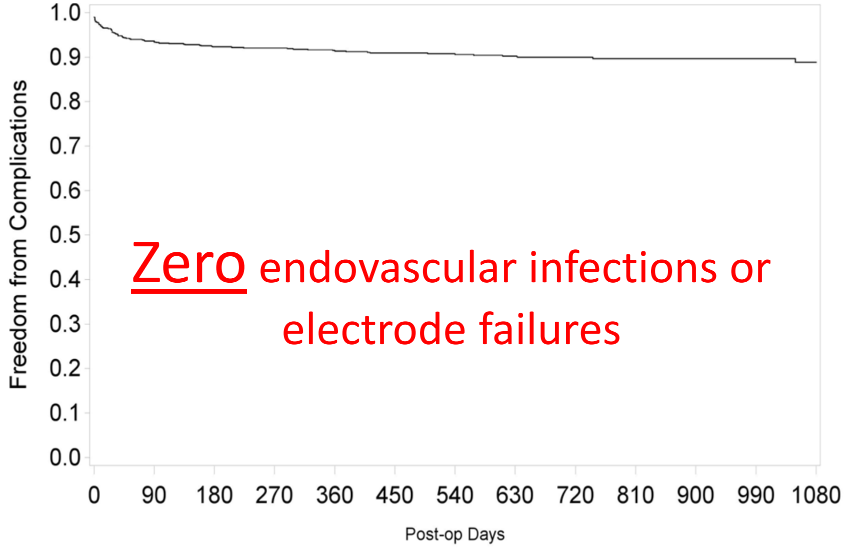
*The **1.6% annual mortality rate** with the S-ICD was deemed **"provocative"** by the authors as it is lower than observed in TV-ICD studies.*

*This analysis was not designed or powered to assess mortality and care should be taken as the population in this analysis may differ from the patient population in TV-ICD studies.

1 Burke MC et al. Pooled Analysis of the EFFORTLESS and IDE Registry. *JACC* April 20th 2015 2 Moss AJ et al. MADIT RIT Study *NEJM* 2012;367;2275-2283. 3 Healy JS et al. SIMPLE Study *Heart Rhythm* 2014;LBCT01;LB01-01.

S-ICD Pooled Results
Complications

Kaplan-Meier Estimate of Freedom from Complications Following S-ICD Implantation



No At Risk	878	791	731	707	650	591	525	414	303	217	162	123	105
K-M Estimate (%)	99.0	93.4	92.3	92.0	91.4	90.9	90.6	90.2	90.0	89.7	89.7	89.7	88.9

There were **zero** endovascular infections or electrode failures which could be a factor in the observed low mortality rate[3]

The acute major complication rate was lower when compared to studies with TV-ICD, likely because S-ICD doesn't require vascular access

Acute Major Complications (% of patients)	S-ICD Pooled Data	TV-ICD NCDR Analysis (Peterson et al, JAMA 2013[1] Meta-analysis (van Rees et. al. JACC 2011)[2]
	2 %	3 - 5 %
	(Hematoma, Lead or Device Mal-position or Displacement, Pneumothorax)	

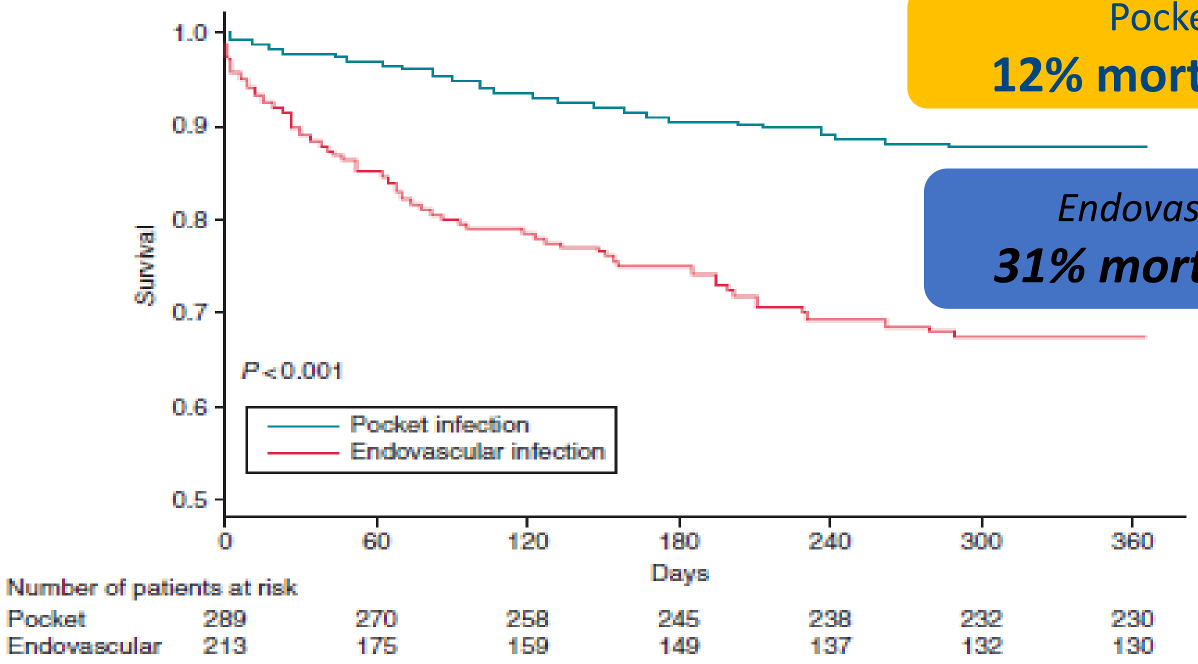
1. Peterson PN et al. *JAMA. 2013;309(19):2025-2034*.
2. Van Rees JB et al. *JACC* 2011;58:995-1000
3. Tarakji KG, Wazni OM, Wilkoff BL et al. Europace 2014; 16:490-495

Transvenous ICD

Mortality After Extraction due to Infection

Cleveland Clinic researchers evaluated 1 year mortality for all patients who developed a CIED infection and found a 3-fold higher risk of death in those who had an endovascular infection compared to a pocket infection.
Tarakji KG, Wazni OM, Wilkoff BL et al. Europace 2014; 16:490-495

1494 K.G. Tarakji et al.



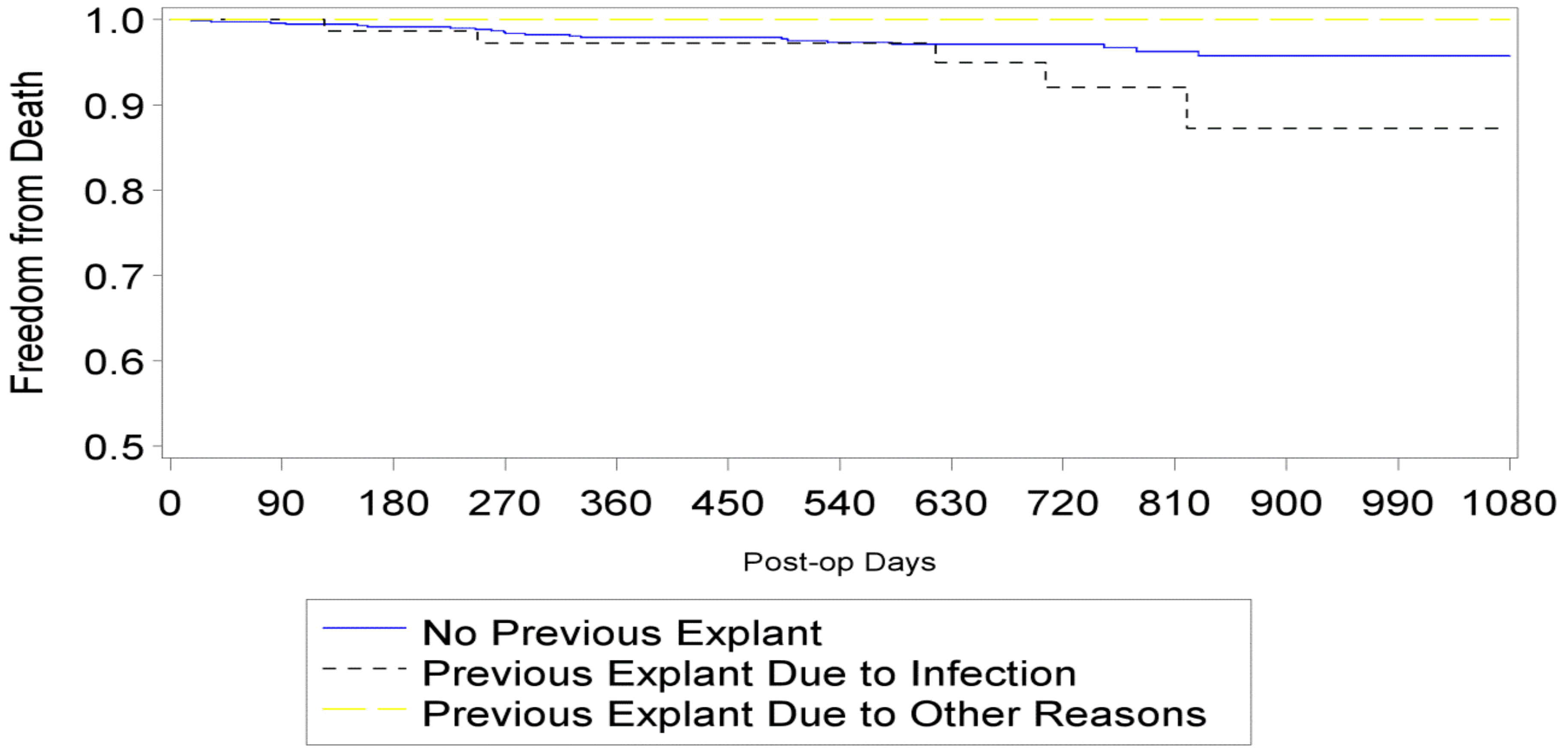
Pocket Infection
12% mortality at 1 year

Endovascular Infection
31% mortality at 1 year

Figure 1 Kaplan–Meier survival curves over 1 year among patients with pocket infection (blue line) and endovascular infection (EVI) (red line) following CIED removal.

In a recent S-ICD publication, there were **zero** endovascular infections
MC Burke, MR Gold, BP Knight, CS, Barr, D Theuns;, et. al., On line JACC xxxxx 2015

Mortality following Extraction and Re-implant with S-ICD



No Previous Explant	100	99.6	99.6	99.6	97.9	97.9	97.3	97.1	97.1	96.3	96.3	95.8	95.8
Prior TV Explant-Infection	100	100	100	100	97.2	97.2	97.2	95.0	92.1	92.1	92.1	87.2	87.2
Prior TV Explant-other reasons	100	100	100	100	100	100	100	100	100	100	100	100	100

Boersma, Burke et al. 2015, Heart Rhythm Journal

Boersma, et al HRS late breaking 2016

Performance and outcomes in patients with the Subcutaneous Implantable Cardiac Defibrillator through Mid Term Follow-Up: The EFFORTLESS Study

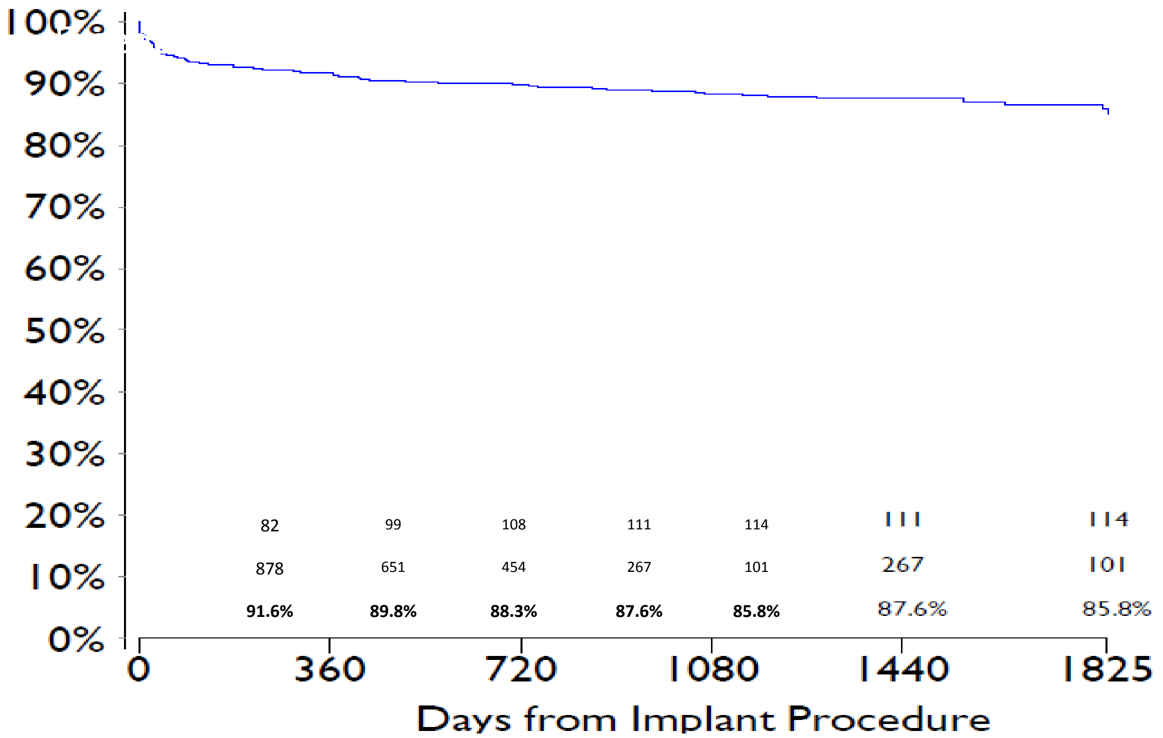
<u>Primary Endpoint:</u>

Freedom from complications caused by the S-ICD at 30&360 day[1]

- At 30 days   99.7% (lower CI 99.4%)
- At 360 days 98.0% (lower CI 96.9%)

- IDE - FDA pre-specified performance goal at 180 days was 79% based on historical TV-ICD data[2]

- IDE endpoint at 180 days was 99.0% (lower CI 97.9%)[2]



- Most common was infection/removal
- Less complications in later enrollments

(Trend test p = 0.12, Q1 vs Q2-Q4: p = 0.06)

Clinical Experience of Subcutaneous and Transvenous Implantable Cardioverter Defibrillators in Children and Teenagers

STEPHEN J. PETTIT, PH.D.,* ANDREW MCLEAN, M.D.,† IAN COLQUHOUN, M.D.,‡ DEREK CONNELLY, M.D.,* and KAREN MCLEOD, M.D.§

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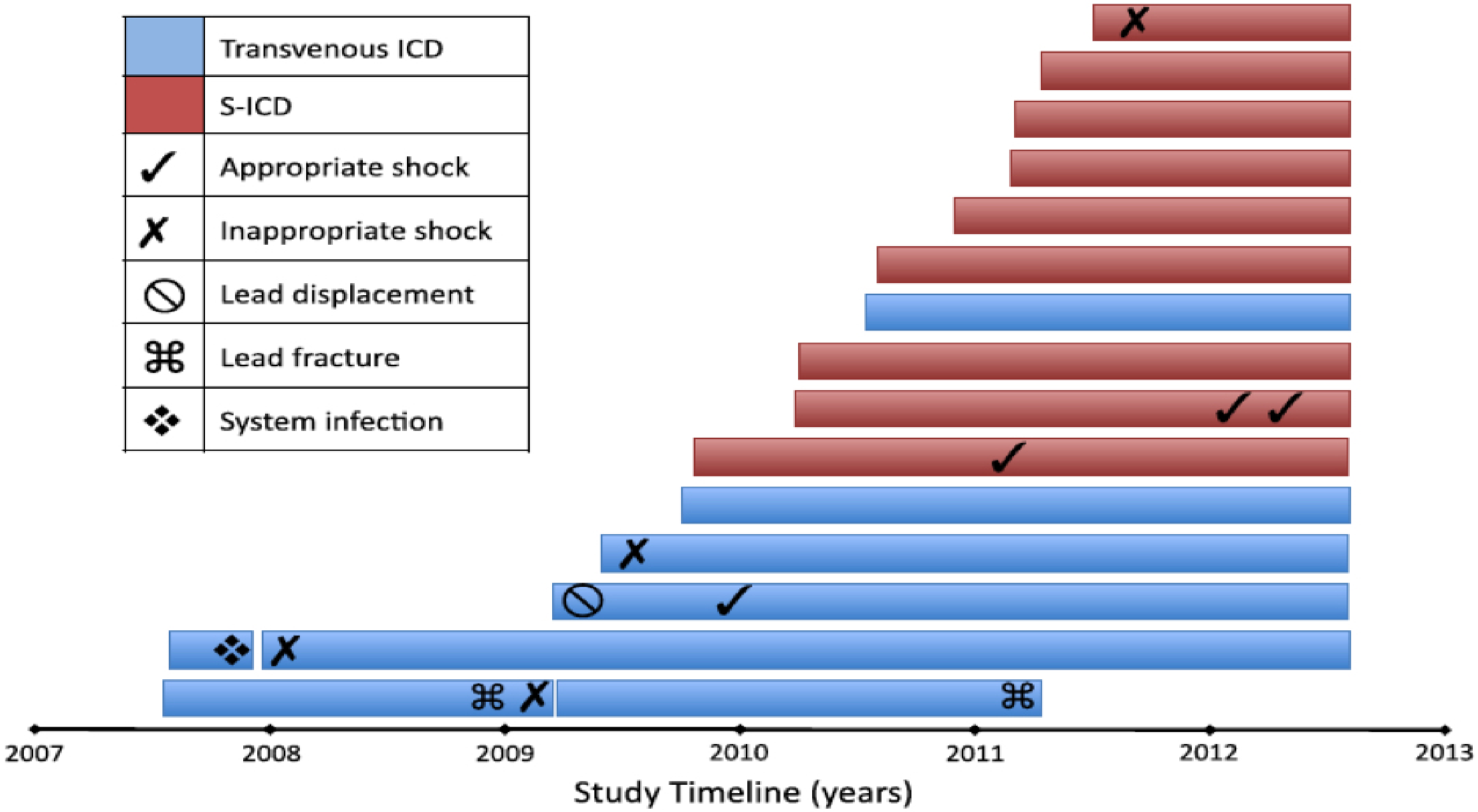
(PACE 2013; 36:1532–1538)

Baseline Characteristics at Time of Implant and Follow-Up Duration

	Transvenous ICD n = 8	S-ICD n = 9	P Value for Difference
Male sex, n (%)	6 (75%)	5 (56%)	NS
Age: median (range), years	11 (5–17)	15 (10–18)	NS
Weight: median (range), kg	54 (17–90)	54 (34–102)	NS
Pathology, n (%)			
HCM	3 (38%)	4 (50%)	NS
ARVC	1 (13%)	0 (0%)	NS
LQTS	0 (0%)	1 (11%)	NS
Brugada	2 (25%)	1 (11%)	NS
CPVT	2 (25%)	1 (11%)	NS
Idiopathic VF	0 (0%)	2 (22%)	NS
Primary prevention, n (%)	1 (13%)	5 (56%)	NS
Redo procedure, n (%)	2 (25%)	0 (0%)	NS
Follow-up: median (range), months	36 (24–55)	20 (12–32)	$P = 0.0263$



(PACE 2013; 36:1532–1538)

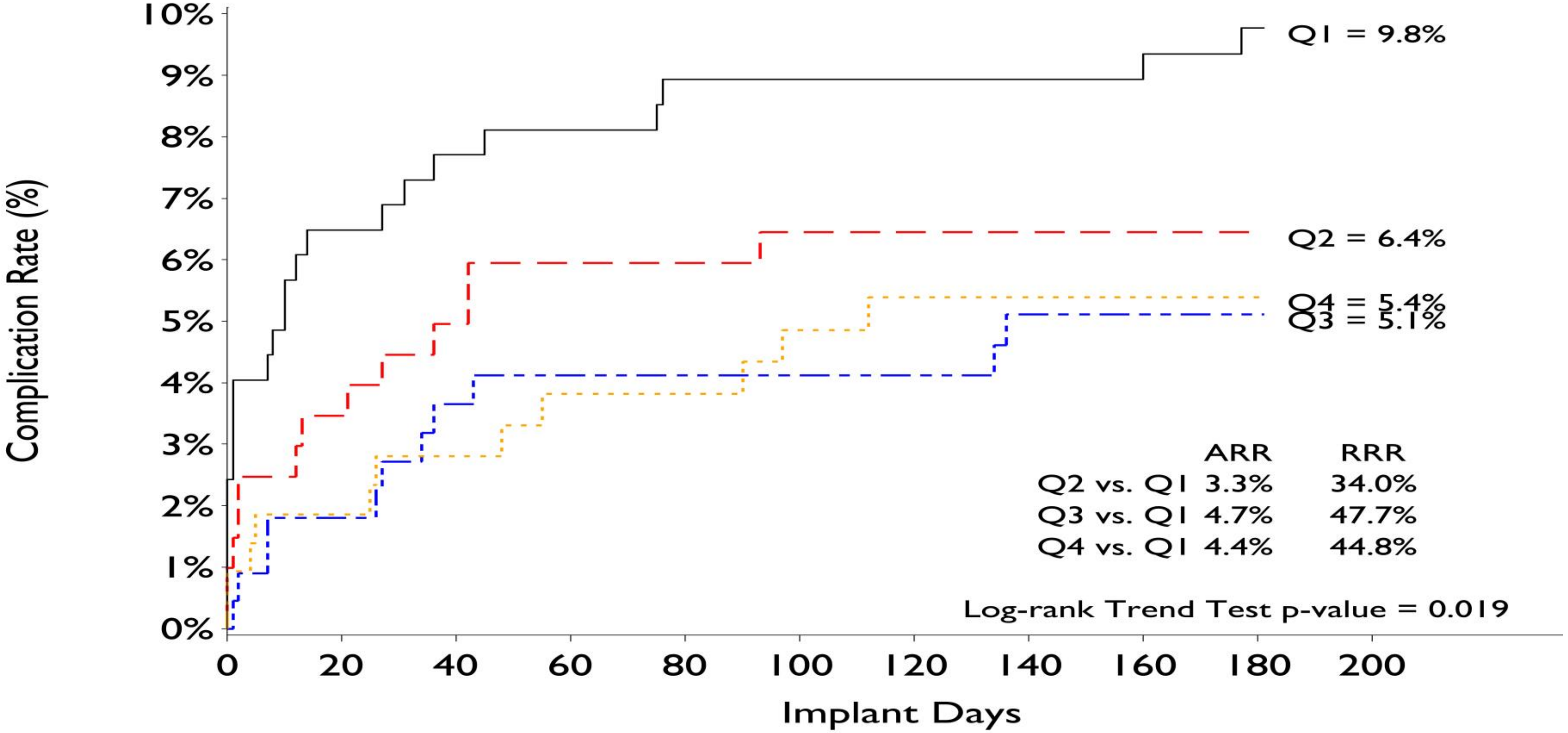
Components of Secondary Outcome Measure

	Transvenous ICD n = 8	S-ICD n = 9	P Value for Difference
Death (%)	0 (0%)	0 (0%)	NS
Inappropriate shocks (%)	3 (38%)	1 (11%)	NS
Reoperation (%)	4 (50%)	0 (0%)	$P = 0.0294$

(PACE 2013; 36:1532–1538)

Learning Curve with Implant

Figure 1: Kaplan-Meier of experience quartiles and complications at 180 days.



Q1: experience quartile 1 (implants 1-4), Q2: experience quartile 2 (implants 5-12), Q3: experience quartile 3 (implants 13-28), Q4: experience quartile 4 (implants >28), ARR: absolute risk reduction, RRR: relative risk reduction. P-value is Kaplan Meier trend test.

Brouwer… Burke, Knops et al. Europace 2015

S-ICD Pooled Results

Complications and Infection with Device Removal by Enrollment Order

Advances in operator experience, prep and implant technique further reduced infections and implant complications for S-ICD patients

Figure 4: Results by Patient Enrollment Order

Figure 4A: Six Month Incidence of Complications and Infections Requiring Device Removal by Enrollment Date

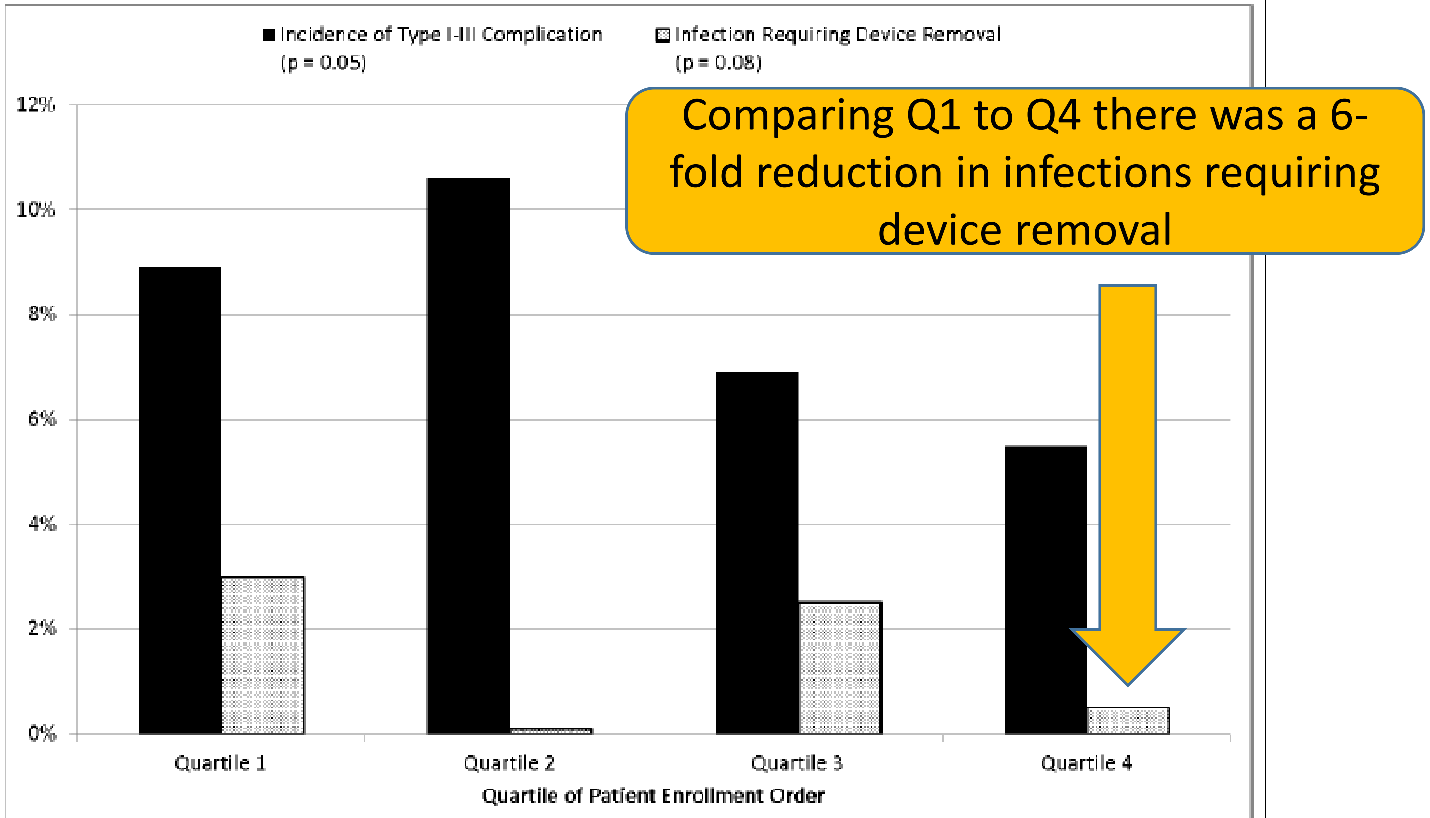
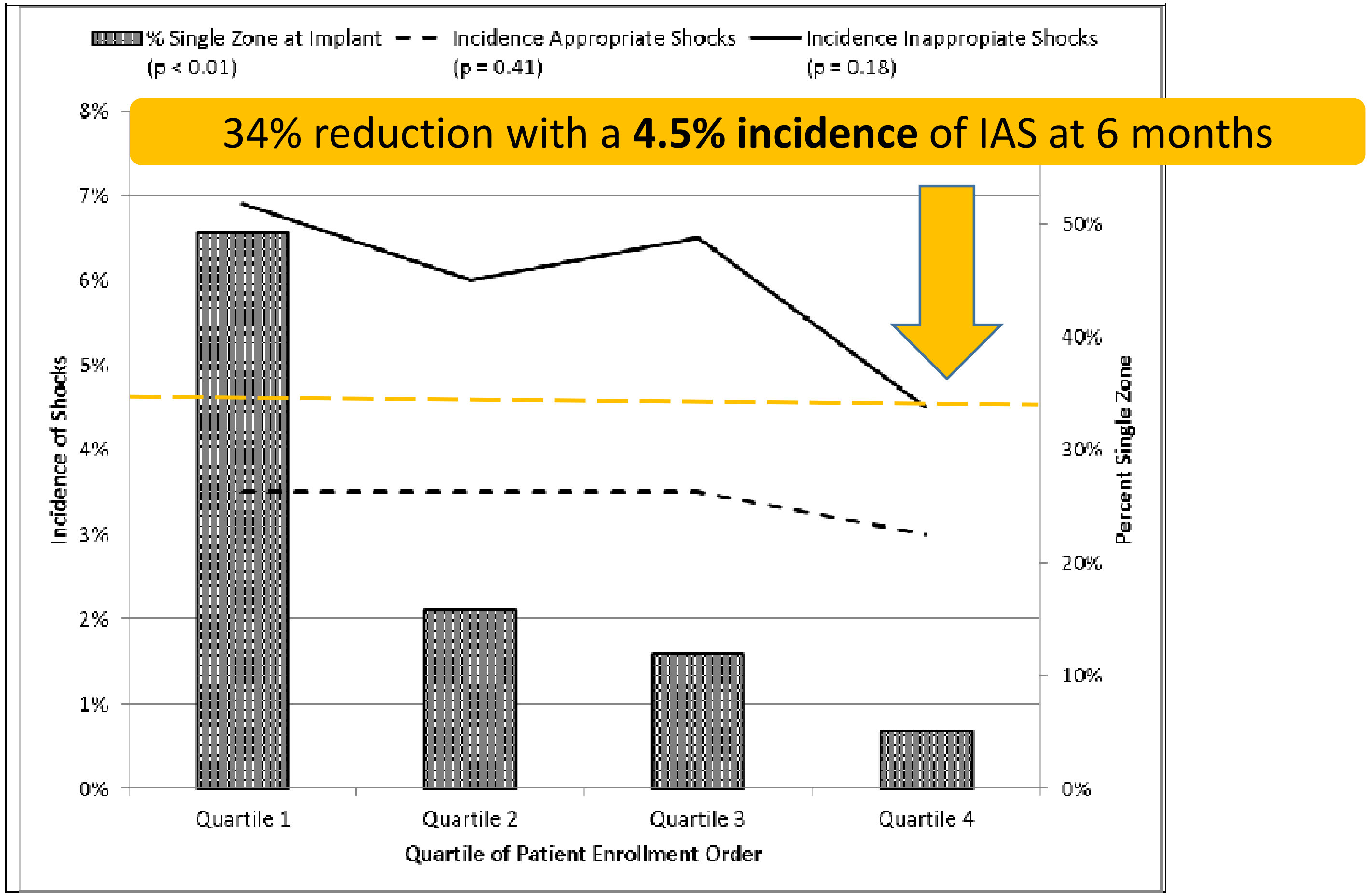


Figure 4B: Six Month Incidence of Appropriate, Inappropriate Shocks, and Initial Programming by Enrollment Date

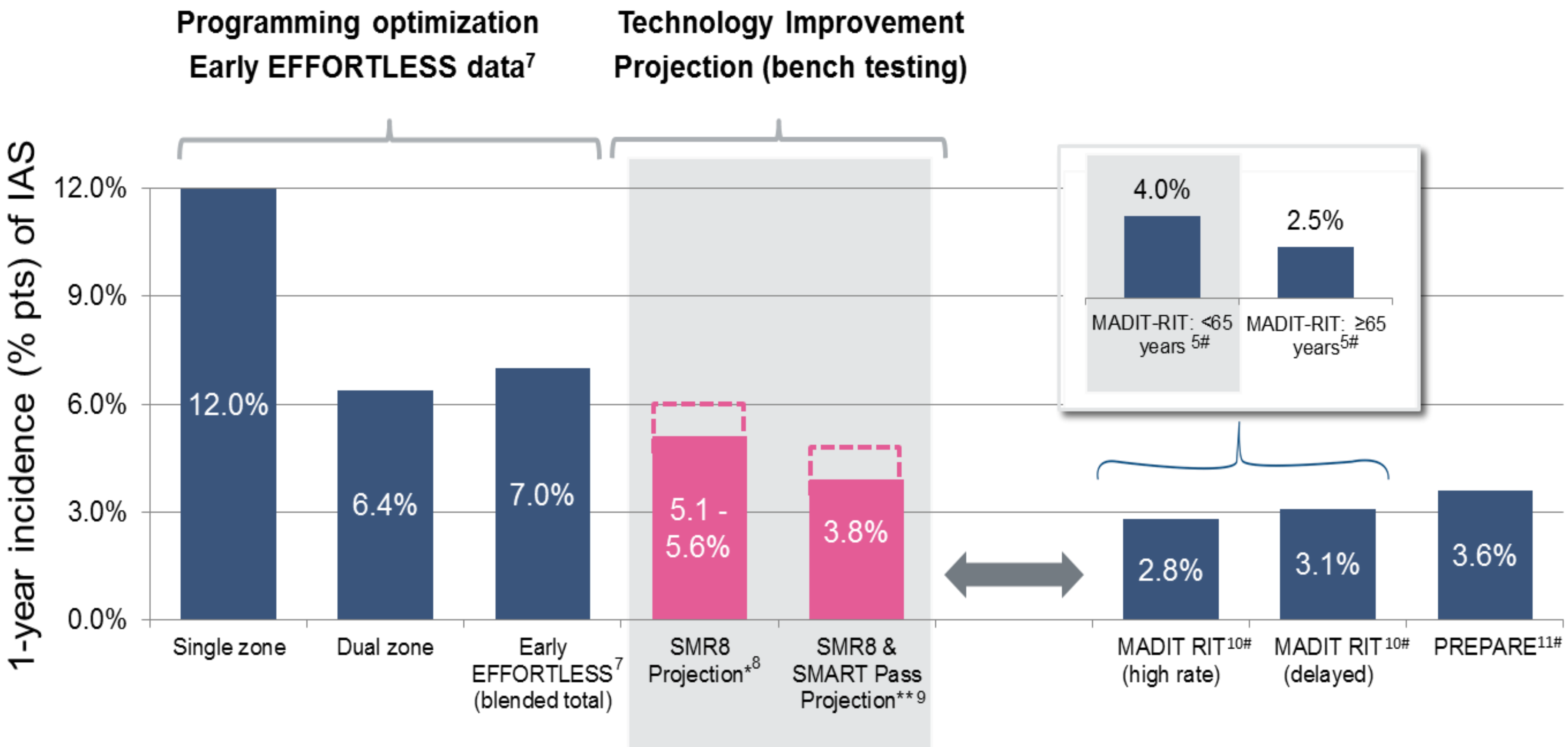
S-ICD Pooled Results

Programming and Therapy by Enrollment Order

Improvements in S-ICD screening and adoption of dual-zone programming were associated with a lower rate of inappropriate shocks



Burke et al. JACC 2015



SMART Pass technology **reduced T-wave over-sensing** (TWOS) by **82%** compared to the Gen 1 S-ICD and **71%** compared to the EMBLEM S-ICD.
– *Theuns, et al*[9]

* Estimated number based on bench testing showing 30-40% reduction of T-wave oversensing with the addition of the Alternating Morphology Algorithm in the heart rate certification phase of the EMBLEM S-ICD INSIGHT™ Technology# (Data on file at Boston Scientific, validation report DN-23333)
** Estimated number on bench testing showing up to 71% reduction in inappropriate therapy from Gen 2 to Gen 2.5[9]
Note: SMART Pass will be automatically disabled when measured ECG amplitudes are <0.5mV
These studies involved transvenous ICDs only

Why did the authors conclude that S-ICD should be considered in all eligible patients?

- Low complication rate and high rates of successful DFT with S-ICD despite use in high risk patients[1]
- A propensity matched analysis showed that in hospital complication rates were similar among patients with S-ICD and TV-ICD[1]

Key Points

Question What are the trends and in-hospital outcomes associated with early adoption of the subcutaneous implantable cardioverter defibrillator (S-ICD) in the United States?

Findings In this analysis of 3717 S-ICD implants, infrequent complications and high rates of successful defibrillation threshold testing were documented despite use in high-risk patients. A propensity-matched analysis showed that in-hospital complication rates were similar among patients with S-ICDs and transvenous-ICDs.

Meaning The S-ICD is associated with infrequent periprocedural complications and high rates of acute conversion of ventricular fibrillation, suggesting it should be considered for all eligible patients.

1 Friedman, D.J., et al., *Trends and In-Hospital Outcomes Associated With Adoption of the Subcutaneous Implantable Cardioverter Defibrillator in the United States.* JAMA Cardiol, 2016. **Published online September 07, 2016. doi:10.1001/jamacardio.2016.2877**.

S-ICD patients had fewer lead complications and a shorter LOS compared to patients implanted with a dual chamber ICD[1]

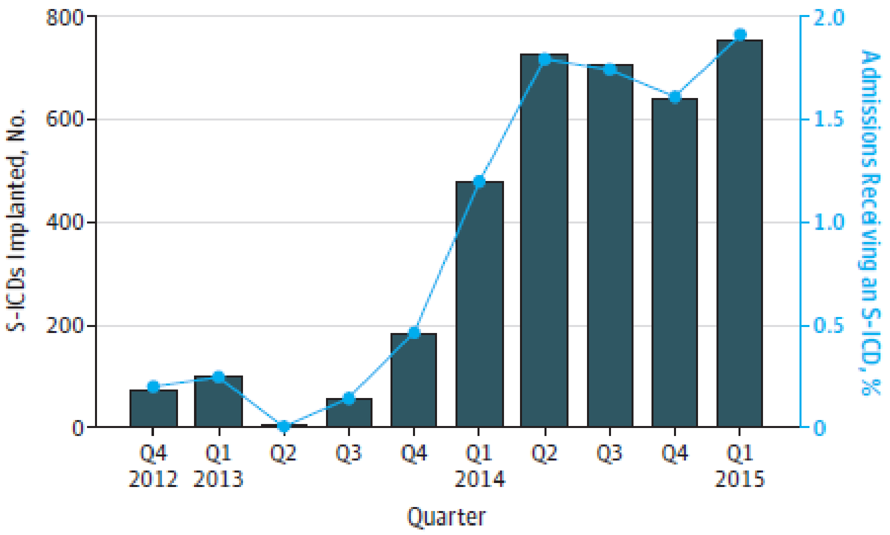
Matched Patient Outcomes	S-ICD	VR TV-ICD	DR TV-ICD
Mean Age (years)	54.0	53.7	54.1
Any Complication (%)	0.9	0.6	1.5
Death	0.2	0.1	0.05
Cardiac Perforation	0	0	0.05
Hemothorax	0.05	0	0.05
Infection	0.05	0	0.1
Pericardial Tamponade	0	0	0.3
Pneumothorax	0	0.2	0.3
Lead Dislodgement	0.1	0.2	0.6
Length of Stay	1.1	1.01	1.17

Early use of S-ICD associated with a low rate of complications including hematoma, lead dislodgement, pneumothorax, tamponade, cardiac perforation and death

1 Friedman, D.J., et al., *Trends and In-Hospital Outcomes Associated With Adoption of the Subcutaneous Implantable Cardioverter Defibrillator in the United States.* JAMA Cardiol, 2016. **Published online September 07, 2016. doi:10.1001/jamacardio.2016.2877**.

Majority of 1st time ICD recipients were candidates for an S-ICD based on lack of bradycardia of CRT indications

Figure. Absolute Number of Subcutaneous Implantable Cardioverter Defibrillators (S-ICDs) Implanted per Quarter (Q) and Percentage of all ICD Admissions in Which an S-ICD Was Implanted



A supply chain disruption occurred during early 2013, corresponding to the observed drop in S-ICD implantation during 2013, Q2.

Close to 55% of 1st time ICD recipients were eligible for an S-ICD based on their lack of bradycardia or CRT indications (n=123,763)

1 Friedman, D.J., et al., *Trends and In-Hospital Outcomes Associated With Adoption of the Subcutaneous Implantable Cardioverter Defibrillator in the United States.* JAMA Cardiol, 2016. **Published online September 07, 2016. doi:10.1001/jamacardio.2016.2877**.

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Long-Term Clinical Outcomes of Subcutaneous Versus Transvenous Implantable Defibrillator Therapy

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Up to 5 years of complication data were evaluated for 140 pairs of patients implanted with an S-ICD or TV-ICD and matched on 16 baseline characteristics

Brouwer et al. JACC Online Nov 8th 2016

Brouwer, T.F., et al., Long-Term Clinical Outcomes of Subcutaneous Versus Transvenous Implantable Defibrillator Therapy. J Am Coll Cardiol, 2016. 68(19): p. 2047-2055.

No differences in the baseline characteristics allowed matching of the 140 patient pairs from the Netherlands

Patient Characteristics	S-ICD*	TV-ICD
Mean Age (years)	41	42
Women(%)	56	53
Mean EF (%)	50	49
Primary Prevention	66	61
% Ischemic Heart Disease	19	29
% Non-ischemic Cardiomyopathy	20	21
% Genetic Arrhythmia Disease	54	39
% Congenital Heart Disease	4	9
% Diabetes	6	4
% Good Renal Function (GFR > 60ml/min)	91	92
NY Heart Class I	74	73
NY Heart Class II	21	22
NY Heart Class III	5	5

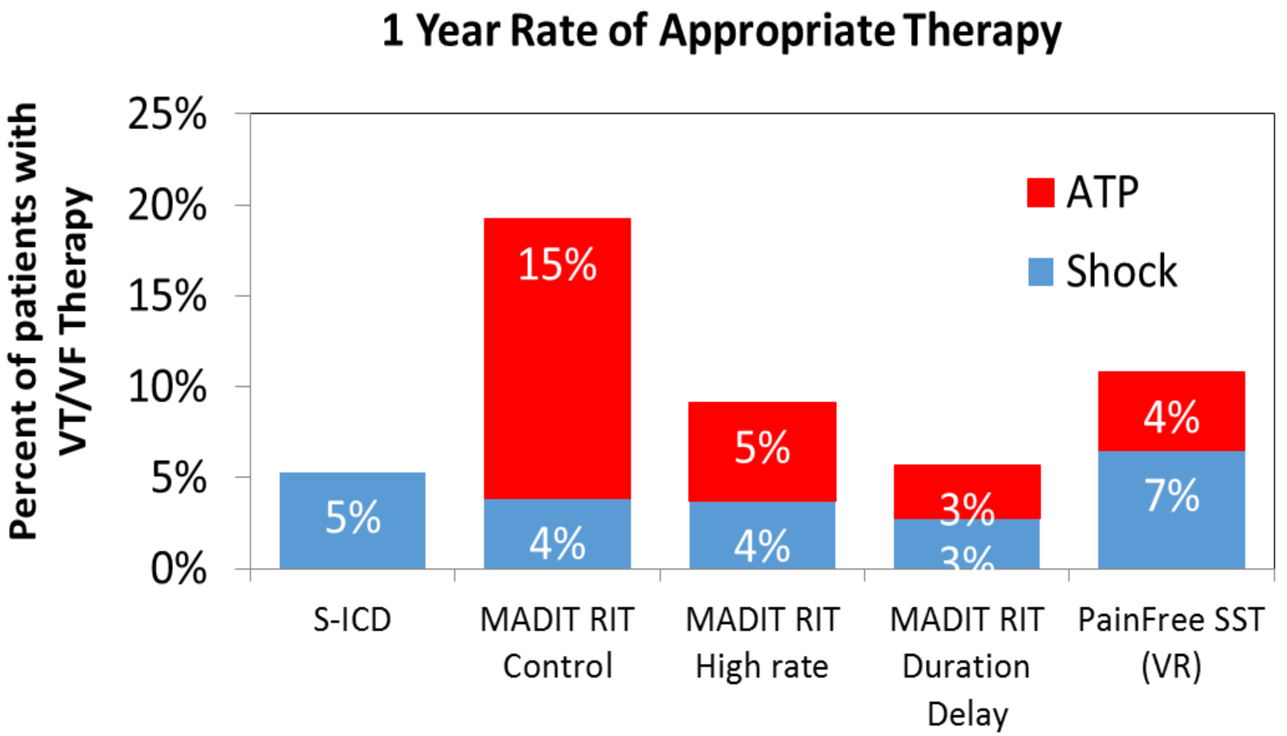
S-ICD patients were from Amsterdam Medical Center & TV-ICD patients were from Leiden University 30 miles away

*Excludes all patients enrolled in Praetorian

Brouwer, T.F., et al., Long-Term Clinical Outcomes of Subcutaneous Versus Transvenous Implantable Defibrillator Therapy. J Am Coll Cardiol, 2016. 68(19): p. 2047-2055.

If ATP prevents unnecessary shocks, why are appropriate shock rates the same?

- Appropriate shock rates similar with or without ATP
- MADIT-RIT found no difference in rate of appropriate shocks despite large differences in ATP delivery.
- Similar rate of VT/VF shocks in S-ICD, MADIT-RIT, PainFREE SST



1 year Kaplan Meier incidence shown for S-ICD and PainFREE SST
1 year rate for MADIT-RIT annualized at an average follow-up of 1.4 years

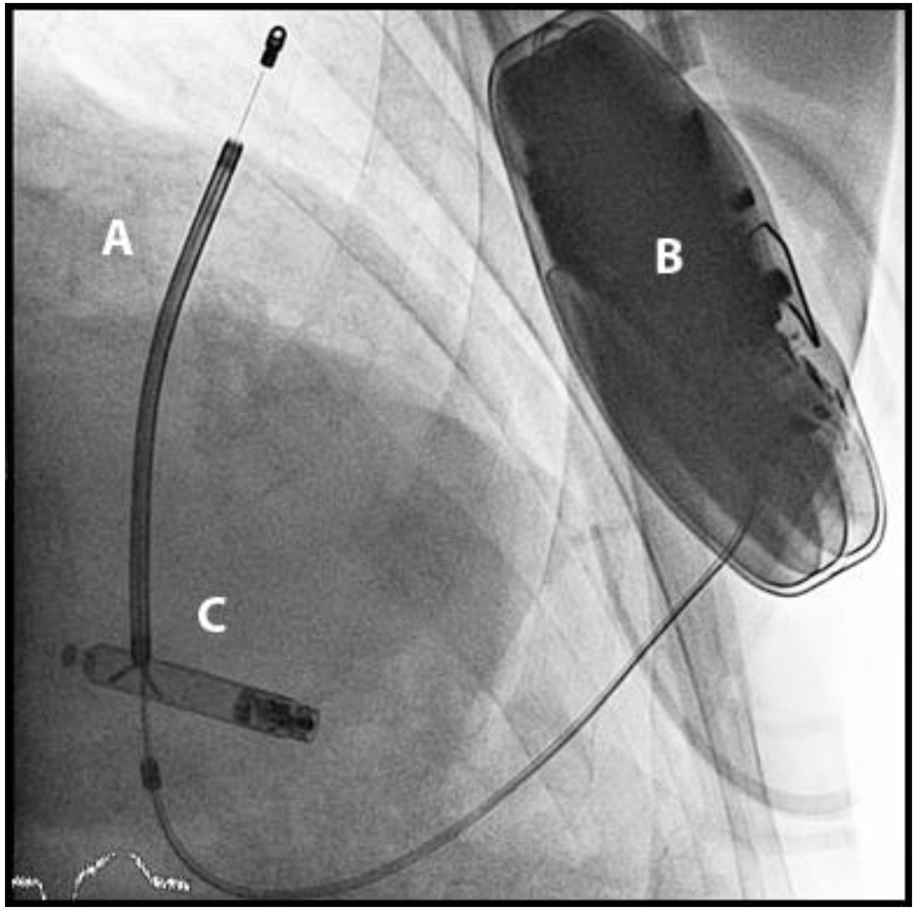
- MADIT-RIT* and PainFREE SST* saw a 4% incidence of appropriate ATP by programming a longer delay
- In MADIT-RIT, 80% reduction in ATP Therapy vs in Duration/Delay Arm vs Control
- Unknown how many ATP therapies were successful in avoiding shocks

*MADIT-RIT and PainFREE SST did not include S-ICD devices.

Moss, A, et al. *NEJM* 2012; 367:2275-2283
Auricchio A, et al. *Heart Rhythm*, online before print http://dx.doi.org/10.1016/j.hrthm.2015.01.017

Application of S-ICD is limited due to lack of pacing capability

Bradypacing:
Limited evidence of S-ICD with LCP & TV-Pacers



Tjong et al. Europace 2016

Anti-tachy pacing: <u>No solution</u>
Substantial ICD subgroup benefits from ATP therapy

Prospective registry data from single center in Germany

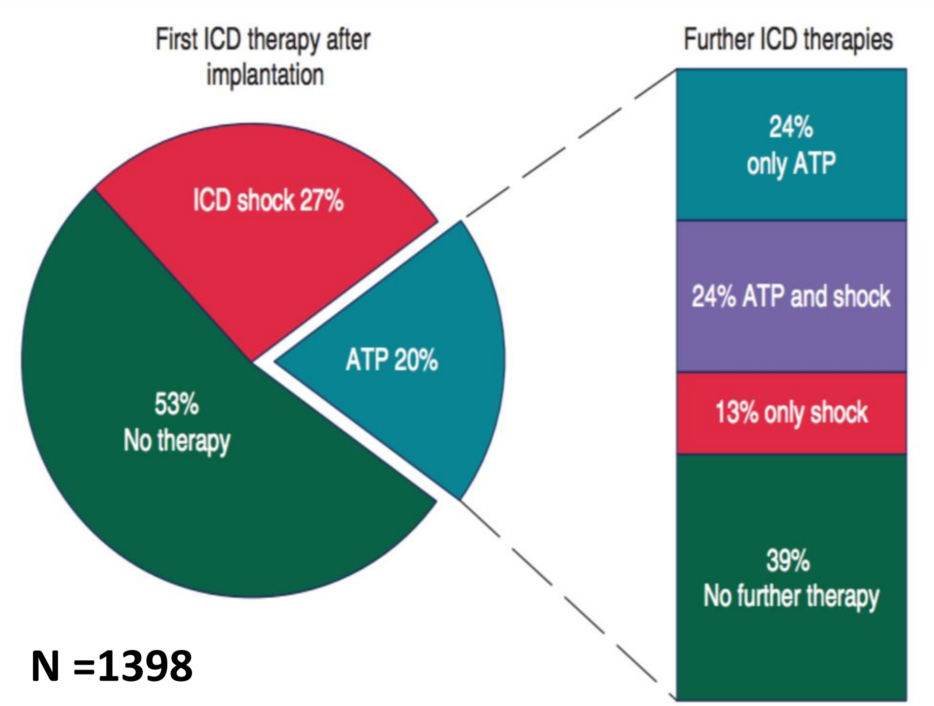
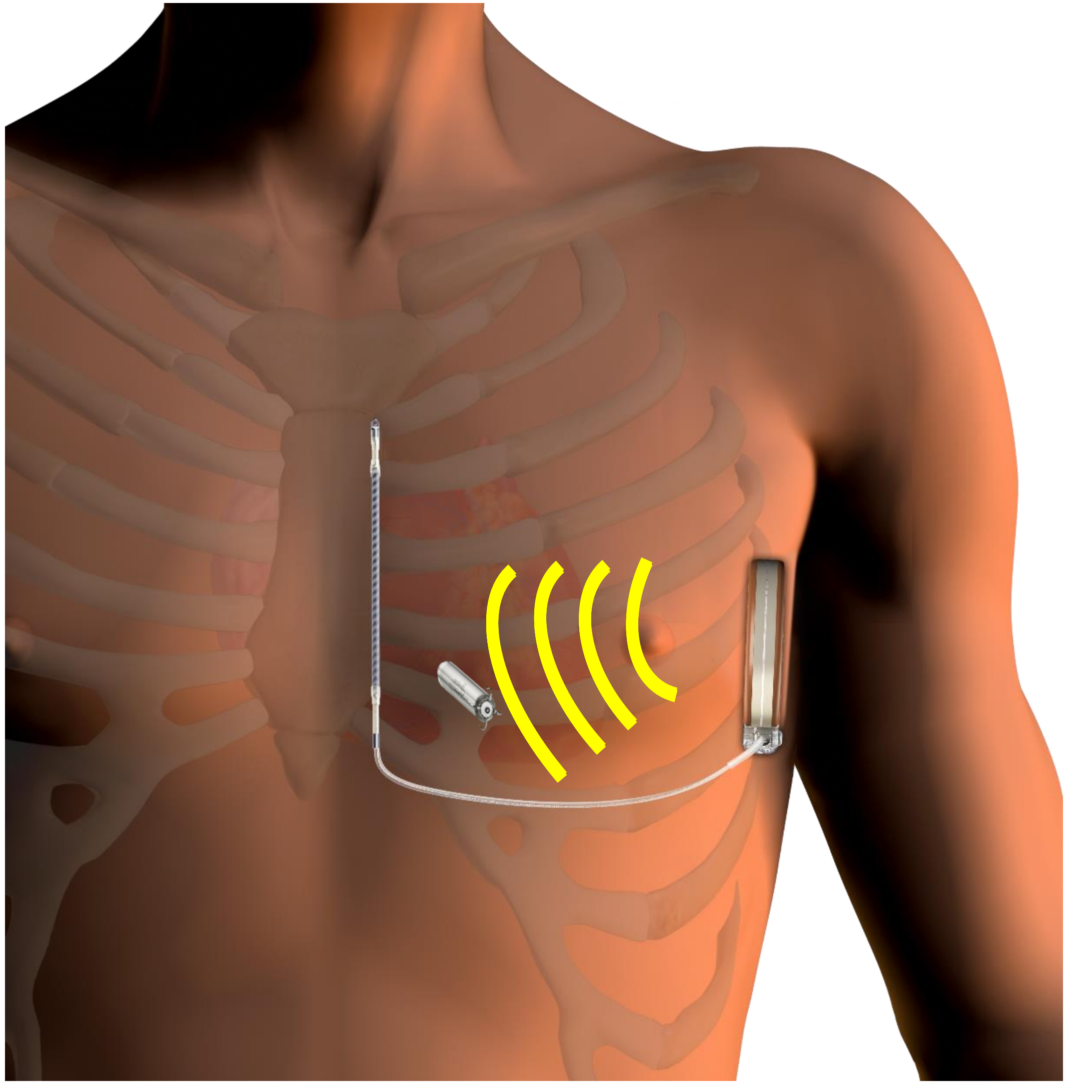


Figure 1 Type of ICD therapies following first ATP therapy.

Kleemann et al. Europace 2015

Combined implant of Communicating ATP-enabled Leadless Pacemaker and S-ICD



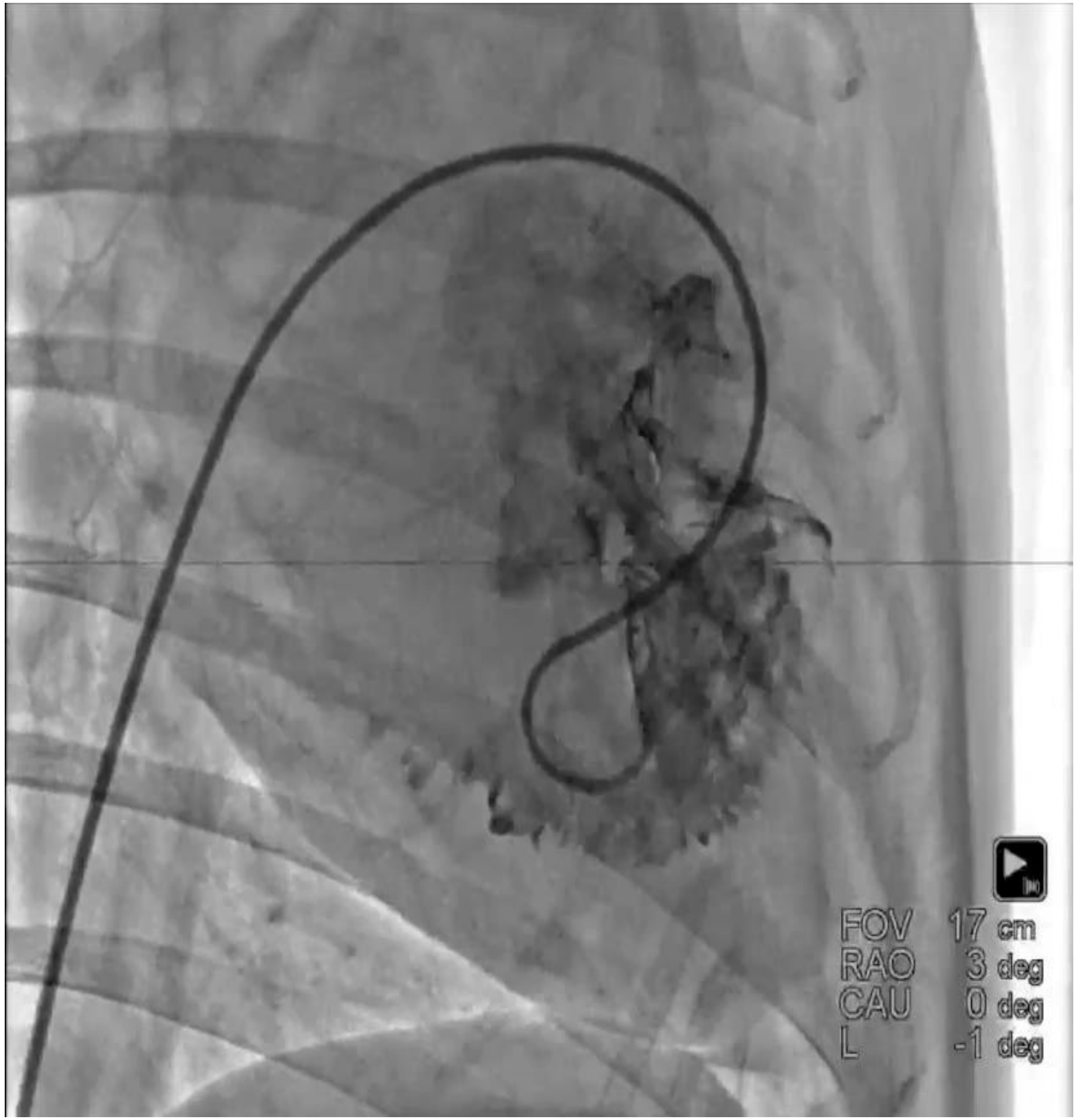
Burke, Tjong, Knops et al.
Europace HRC 2016

Results

1 **LCP implant** 2 Device-device communication 3 Therapy

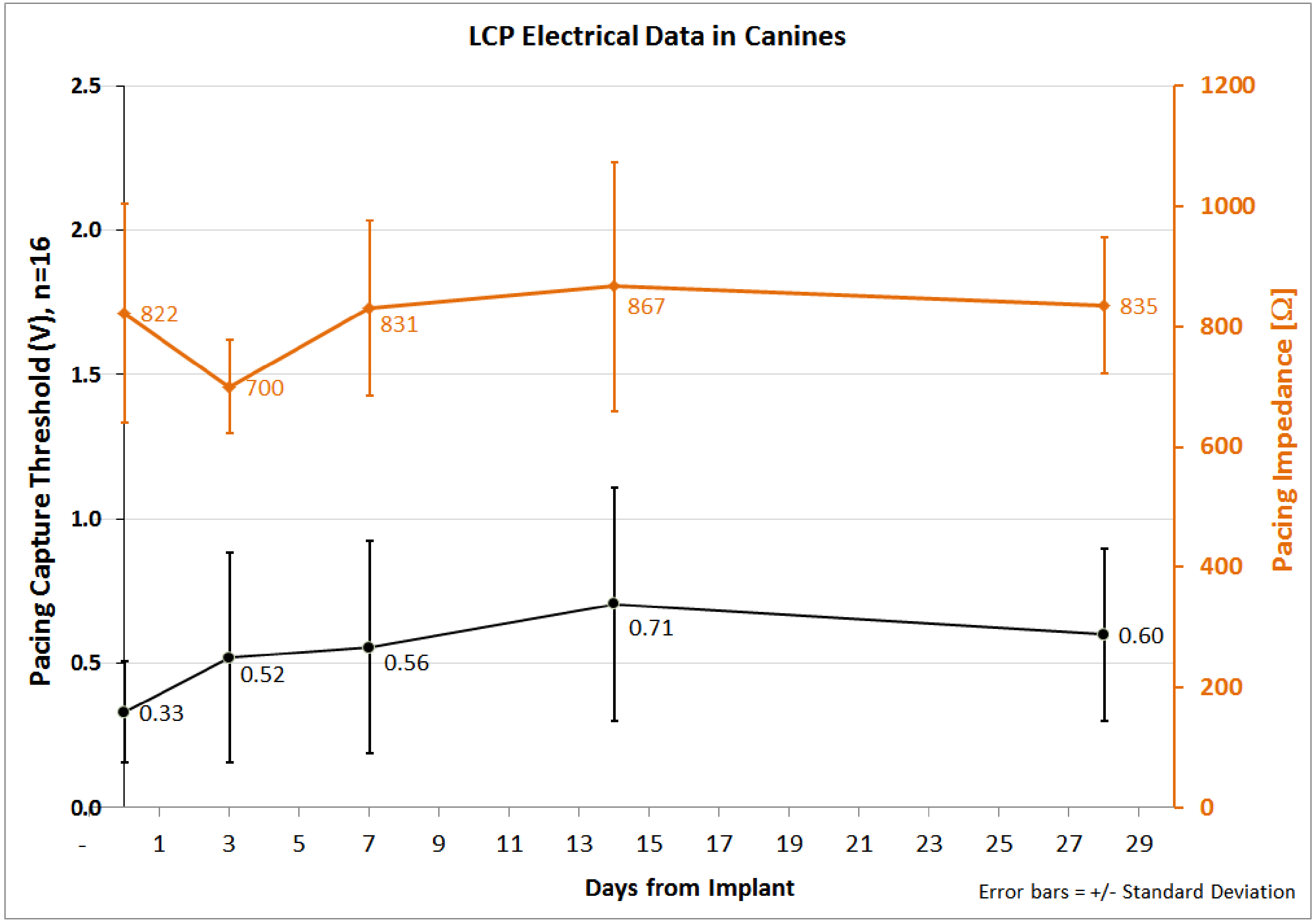
LCP implant steps:

1) RV angio
2) 21F introducer
3) Delivery catheter + LCP
   - Telescope
4) Deployment
5) Tug test
6) Release



Results ① LCP implant ② Device-device communication ③ Therapy

LCP showed adequate electrical performance at 30 days (N=16)

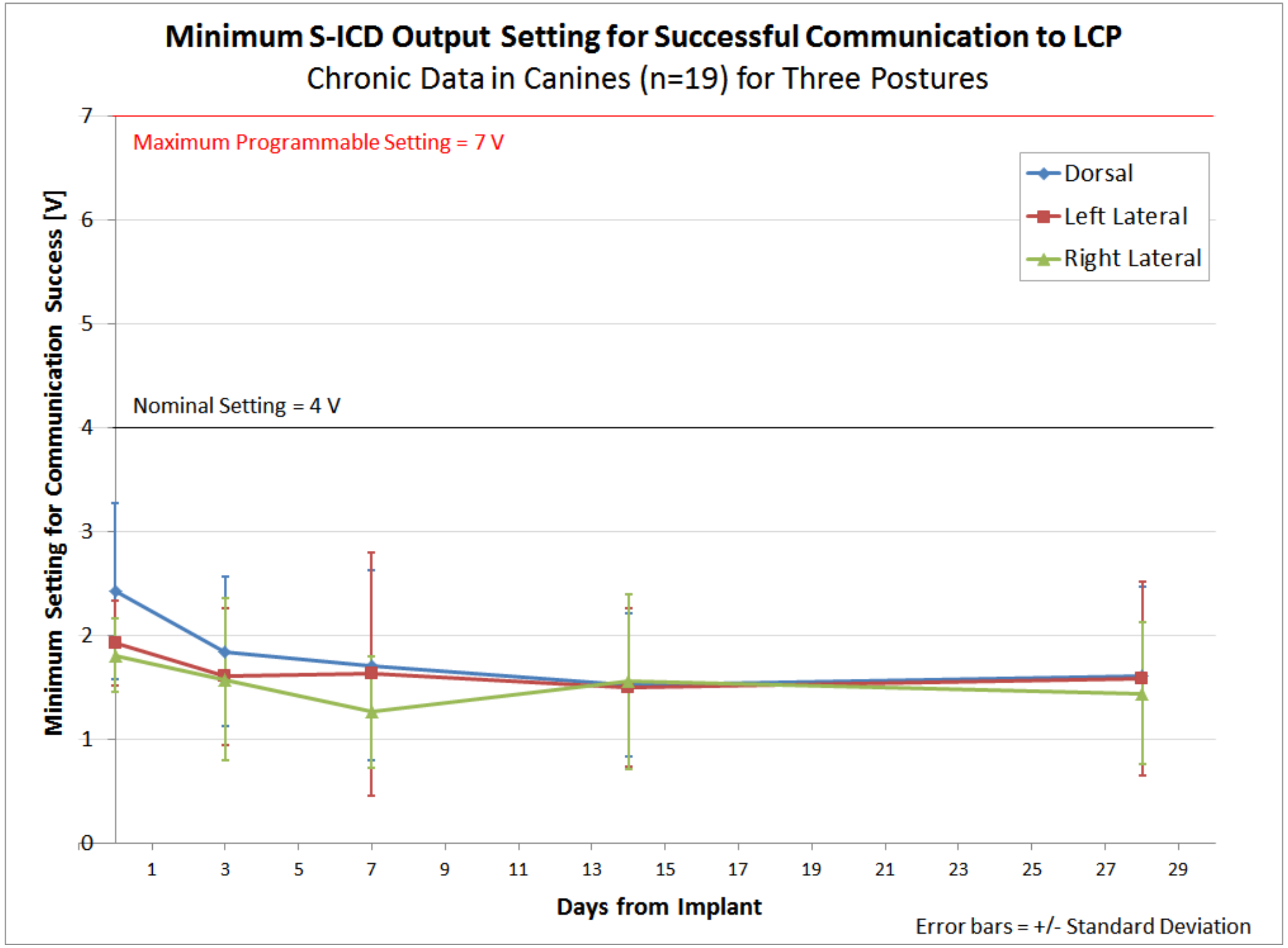


Burke, Tjong, Knops et al. Europace HRC 2016

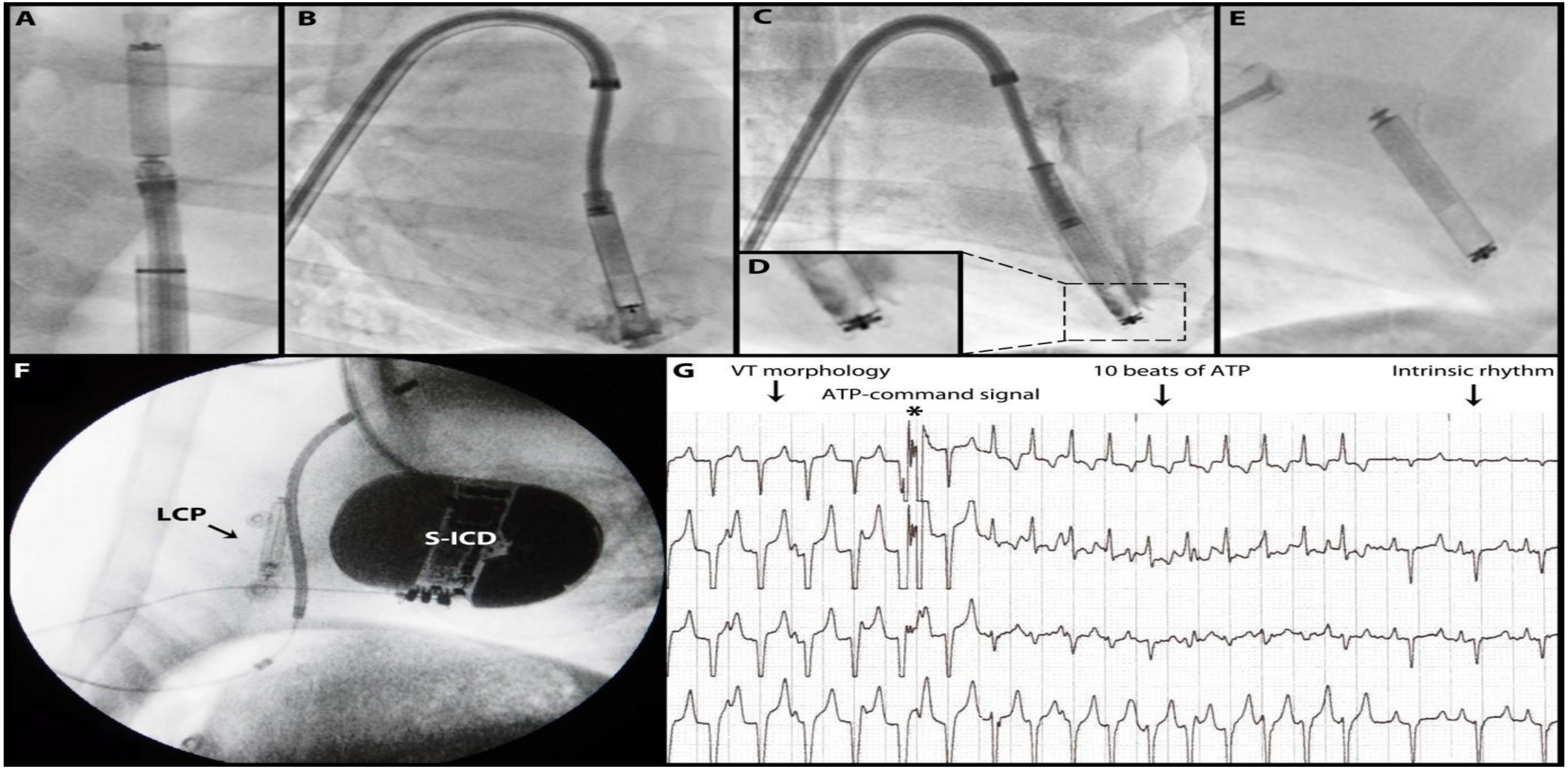
Results

1 LCP implant 2 **Device-device communication** 3 Therapy

LCP showed successful communication in three postures (N=19)



Modular Devices/Medical Body Network



Tjong, Burke et al. JACC 2016

Conclusion

1 LCP implantation

Adequate VVI functionality

- High implant success rate (39/39)

2 Device-device communication

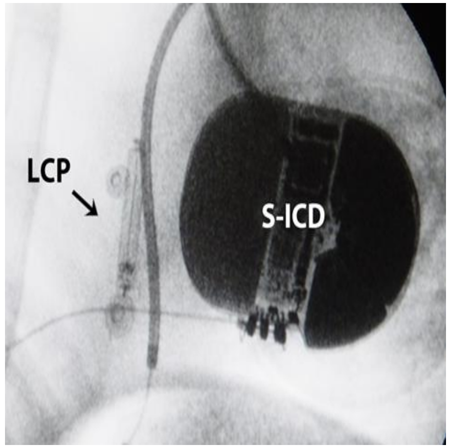
99% device communication success

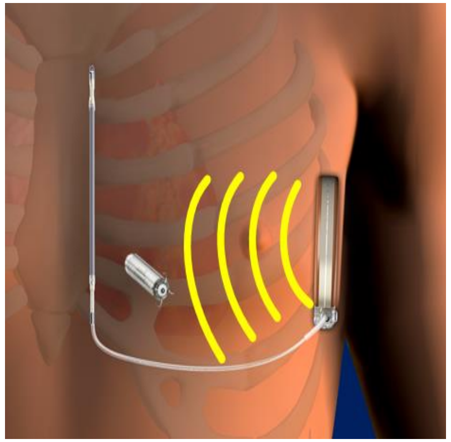
- Orientation S-ICD / LCP important

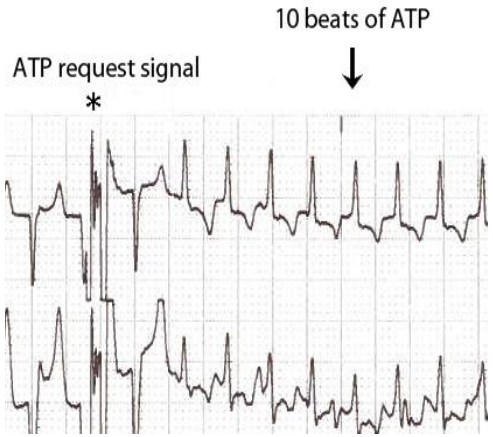
3 Therapy

99% Total ATP delivery success

- Adequate sensing during LCP pacing
- Adequate Post-shock LCP performance
- No dislocations







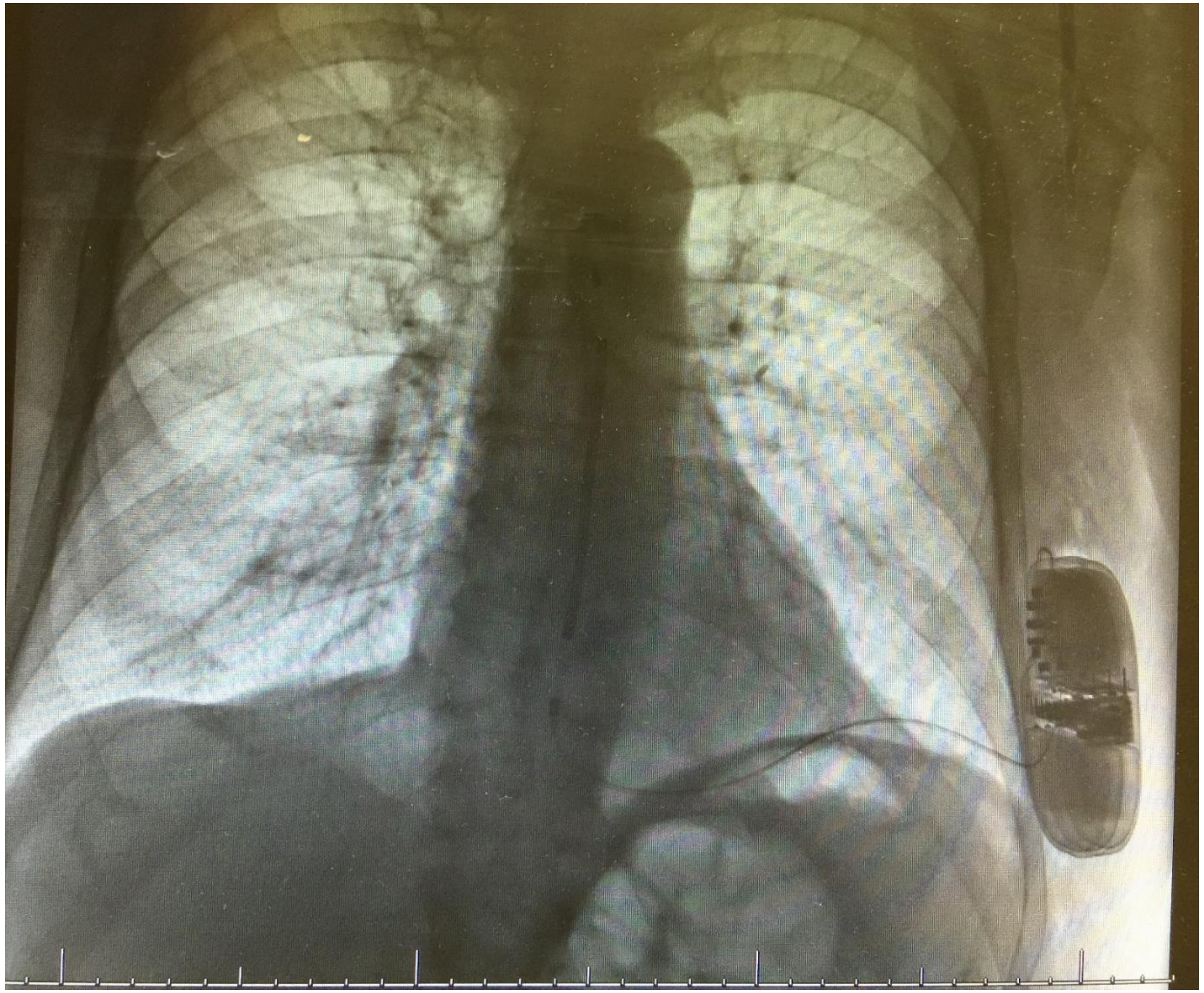
EMBLEM™ MRI S-ICD System (ImageReady™)

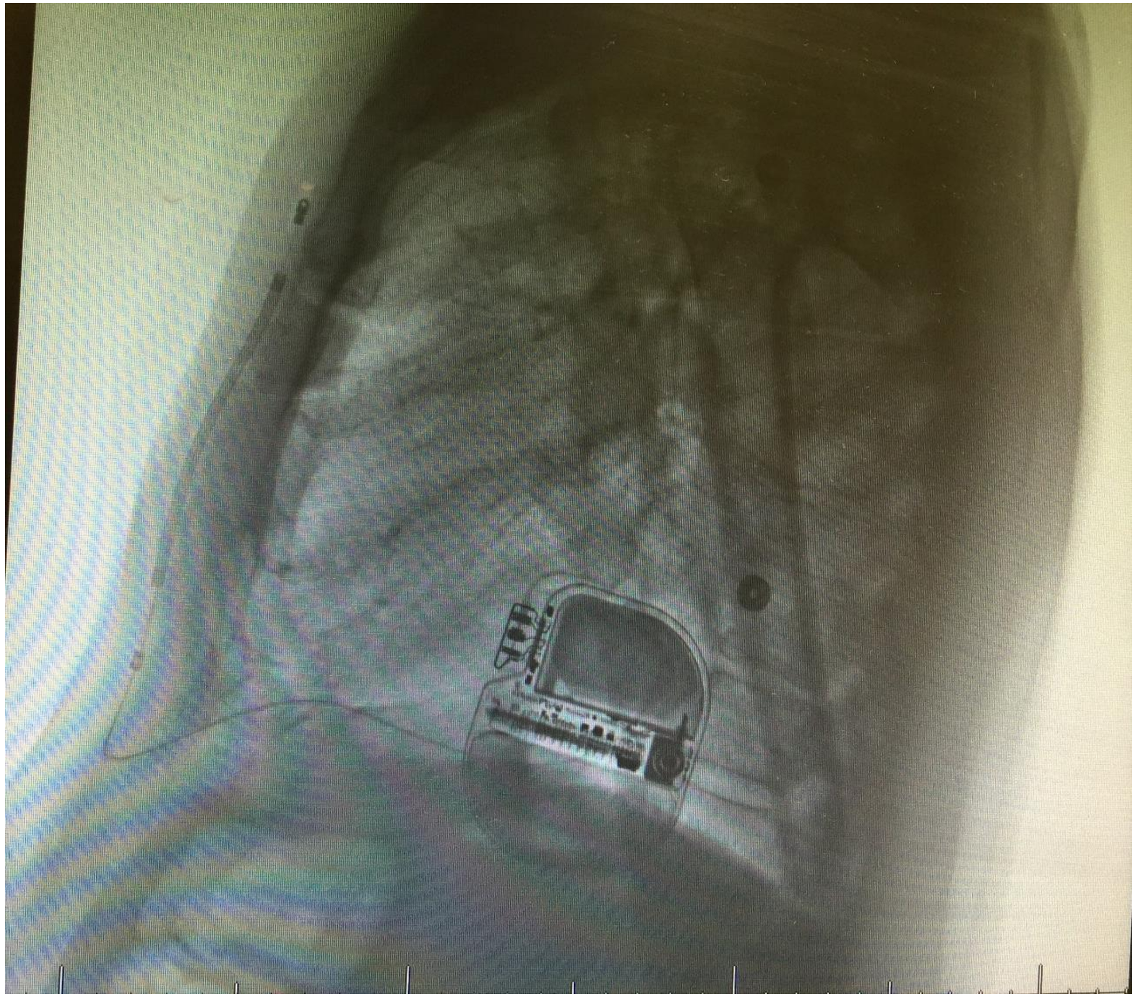
EMBLEM MRI S-ICD System provides full-body MR-conditional scan capabilities for a 1.5T environment*[21,22]

*When conditions of use are met

✓1.5T MR-Conditional
✓Automatic MRI Timeout Mode
✓No exclusions zone
✓No time limitations during MRI scan[21,22]
✓No patient restrictions
✓Simple programmer interface
✓Dedicated MRI report for clinic documentation
✓MRI mode viewable on LATITUDE™
✓Updated MR-conditional label for EMBLEM S-ICD System with any S-ICD electrode

Nice





Summary

- **The Risk/Benefit is clearly in favor of the S-ICD especially in younger patients without a pacing indication regardless of substrate.**
- The acute major complication rate was lower when compared to studies with TV-ICD, likely because S-ICD doesn't require vascular access.
- **There were zero endovascular infections or electrode failures which could be a factor in the observed low mortality rate.**
- Patient selection, exclusion criteria and episode analysis suggests a limited benefit to ATP therapy in these patients.
- **Benefits become significantly improved as the implant experience increases.**
- The power of the S-ICD to coordinate a medical body network and expand clinical artificial intelligence is real.