PLACE

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IL CUORE SENZA…..

S-ICD vs ICD: dall'equivalenza alla superiorità?

L'APPROCCIO SOTTOCUTANEO EVITA I RISCHI NON NECESSARI

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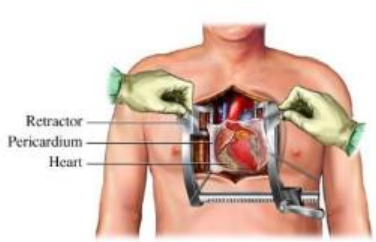
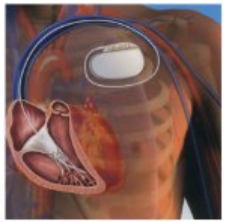
ICD & leads history





1956
Paul Zoll 1st human external defibrillation

1980
1st human implant of AICD

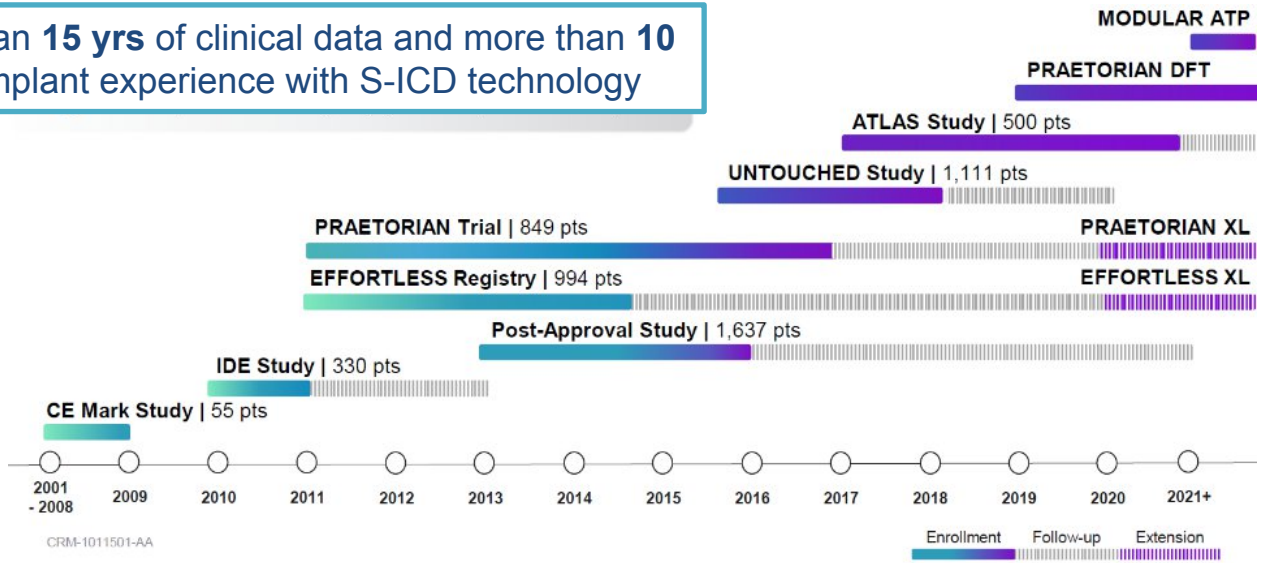
1988
1st human implant of endocardial shocking lead
Eliminated need for thoracotomy

1999
First CRT-D in Europe

2008
S-ICD

THE S-ICD JOURNEY TO FIRST LINE THERAPY

More than **15 yrs** of clinical data and more than **10 yrs** of implant experience with S-ICD technology



TV-ICD COMPLICATIONS

TV-ICD complications, both acute and chronic, are more prevalent than generally acknowledged[1]

Infection

Lead failure

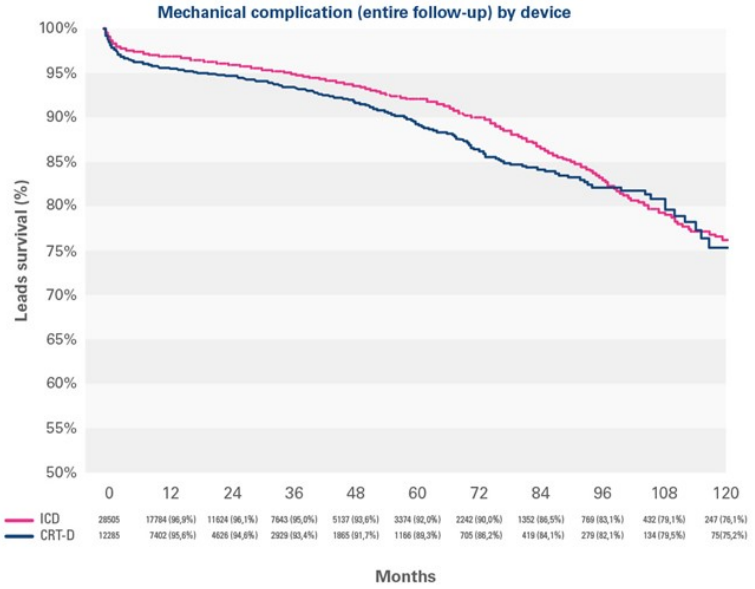
Risk of complication* at 6 years:[2-4]

15.5%

* Complication either: implant related, system/ lead related or infection (Infection, Device malfunction, Lead malfunction, Lead dislodgment, Pericardial effusion, Thrombotic event, Reintervention for pocket complication, Hematoma, Pneumothorax. Based on 4890 patients)

TV-ICD LEAD COMPLICATIONS

OPTUM database shows lead failure rate of ~25% at 10 years[7]



OPTUM database showed that,

1 IN 4 TV-ICD PATIENTS

experienced a lead complication within 10 years.[1]

ICD INFECTIONS

Cardiac device infections (rates up to 3%)[11,12,13]

ENDOVASCULAR INFECTIONS
(lead-related)

POCKET INFECTIONS
(device-related)

> "THE INCIDENCE OF CIED INFECTION IS INCREASING OUT OF PROPORTION TO CIED IMPLANTATION"[14]

Infection can manifest at any time post-procedure, from early (up to 1 month post procedure) to late (>1 year)[12]

PREDICTORS OF CIED INFECTION

MORE THAN 70%
OF ICD INDICATED PATIENTS **OVER 60 YRS**
HAVE AT LEAST **ONE PREDICTOR OF DEVICE INFECTION.**[1,2]

Predictors of device infection include[15]**:**

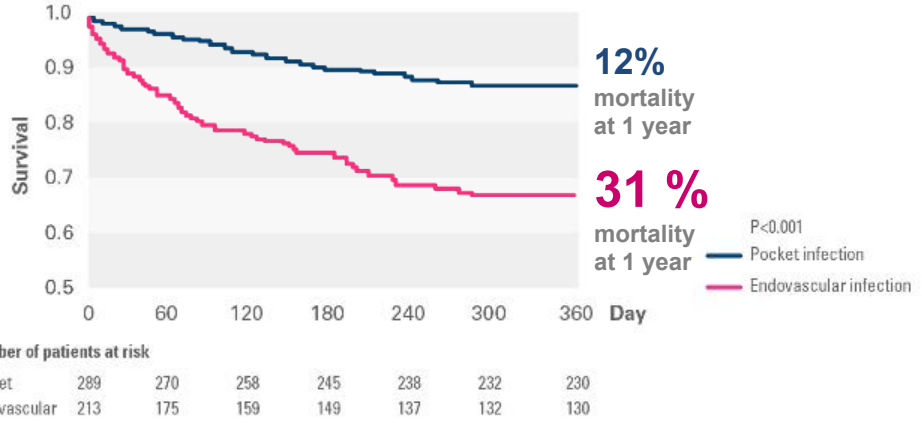
- Diabetes
- Heart failure
- Kidney disease
- Previous device infection

Diabetes increases cardiac device infection risk by up to **3x**[1,2]

Renal dysfunction* increases cardiac device infection risk by up to **4x**

PATIENT OUTCOMES FOLLOWING ICD INFECTION

1 year survival among TV-ICD patients with pocket infection or endovascular infection following TV-ICD system removal[13]



Endovascular infections were associated with 3x higher risk of death when compared to a pocket infection[13,20]

PATIENT OUTCOMES FOLLOWING ICD INFECTION

Large vegetation on an extracted right ventricular ICD lead[21]

In the ELECTRa registry,*

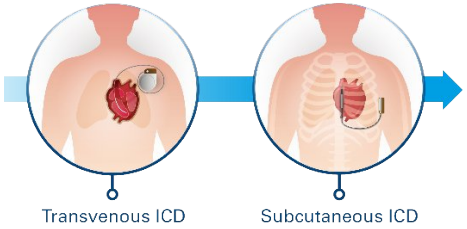
1 IN 6 patients died

after systemic infection resulting in transvenous lead extraction[22]

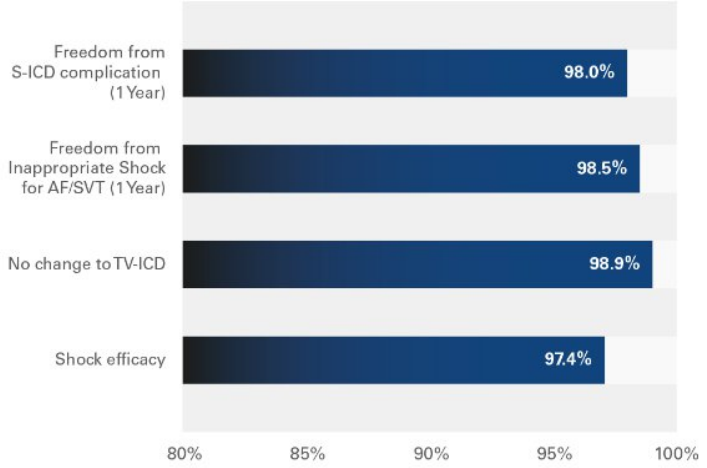
Low incidence of mortality linked to procedure, but significant post-procedural mortality, with a strong correlation between mortality and lead extraction for infection[22]

* European Lead Extraction ConTrolled Registry (ELECTRa). This study only included TV ICD, mortality linked directly to procedure was 0.5%.[22]

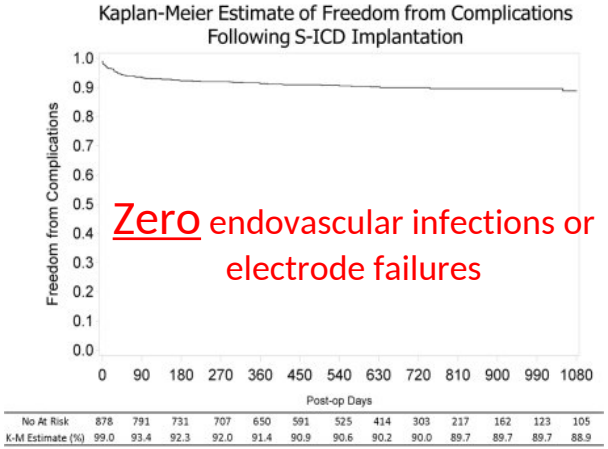
S-ICD: EFFECTIVE DEFIBRILLATION WITHOUT TRANSVENOUS LEADS



Outcomes after S-ICD implantation in the EFFORTLESS mid-term follow-up: 1 year[25]



S-ICD Pooled Results Complications



Zero endovascular infections or electrode failures

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[1,2]

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

S-ICD LEAVES THE HEART UNTOUCHED

In the EFFORTLESS registry of almost

1000 PATIENTS OVER **3** YEARS,

Zero ENDOVASCULAR INFECTIONS[1]

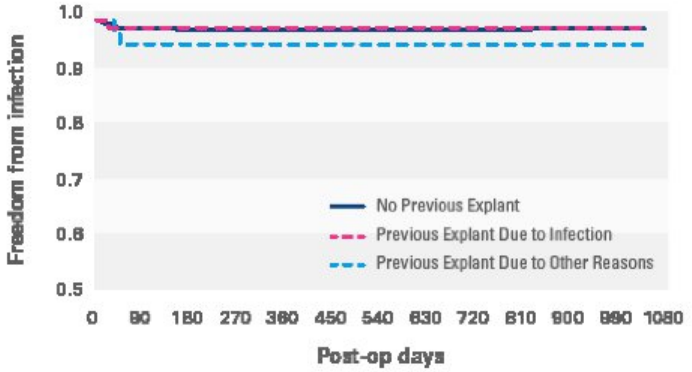
Zero SYSTEMIC INFECTIONS[1]

Zero ELECTRODE FAILURES[1]

Dutch study
S-ICD IMPLANTATION AFTER TV-ICD EXTRACTION

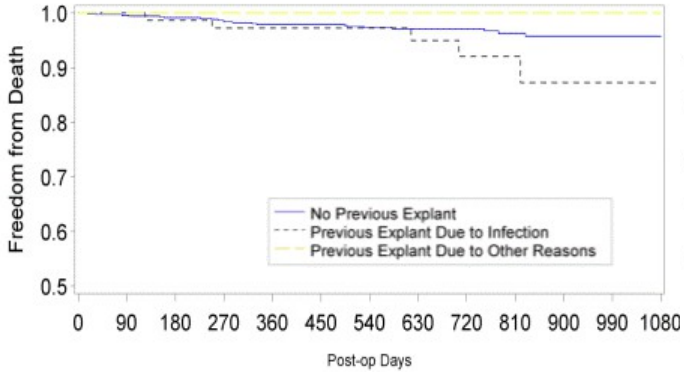
Patients re-implanted with an S-ICD after explantation of a TV-ICD experienced low rates of major complications and mortality compared with published data for transvenous devices. Suggesting that the S-ICD is a suitable alternative for TV-ICD replacement.[25]

S-ICD implant following TV-ICD extraction did not result in higher risk of re-infection [27]



Infection and mortality after implantation of the subcutaneous ICD following transvenous ICD extraction

Low mortality rates in patients re-implanted with an S-ICD following explant of a TV-ICD



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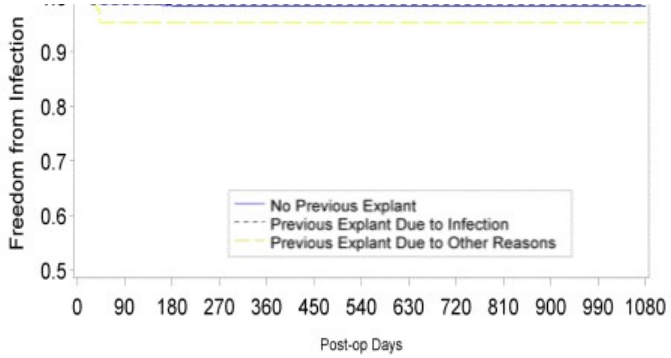


Re-implantation with S-ICD following explant of a TV-ICD results in low rates of major complications and mortality compared to published data for TV-devices[2], suggesting that the S-ICD is a suitable alternative for TV-ICD replacement.

L Boersma et al. Heart Rhythm 2015. Sept 1 – in press
2. . Maytin M et al. Circ Arrhythm Electrophysiol. 2012; Tarakji et al; Europace, 2014;16:1490-1495

S-ICD SHOCKS WERE NOT ASSOCIATED WITH MYOCARDIAL DAMAGE

An Italian experience

Clinical data shows that markers of myocardial damage are increased following TV-ICD shock[29]

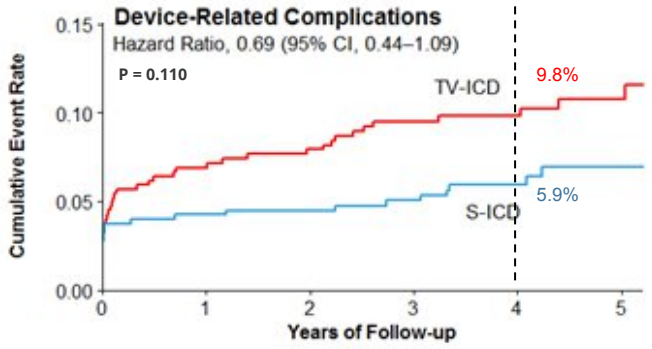
Markers of cardiac injury and haemodynamic stress neither increased after S-ICD implantation, nor at 6 or 24 hours post-shock, suggesting that S-ICD shock does not cause cardiac injury[30]

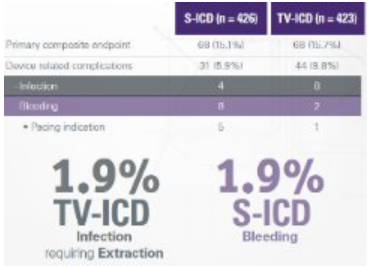
PRAETORIAN STUDY

Device-related complications

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

	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





PRAETORIAN STUDY

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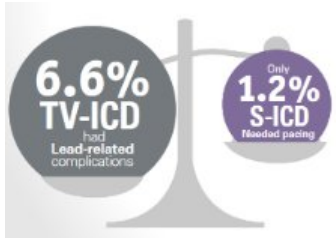
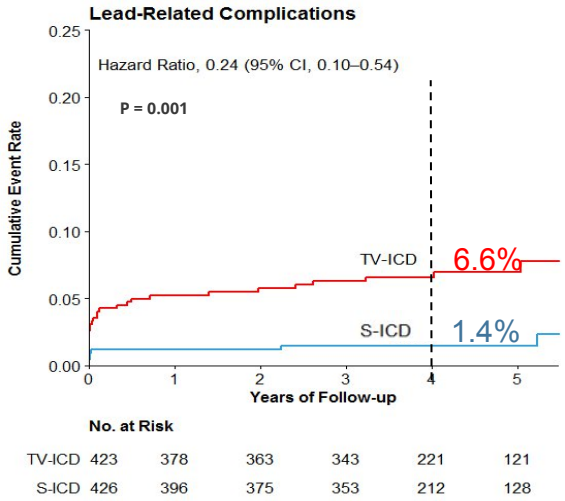




Significantly fewer lead-related complications

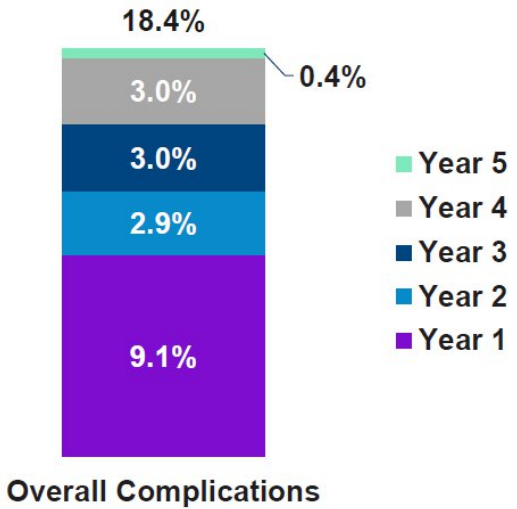
EFFORTLESS 5ys follow-up

Complications primarily occurred in the first year but **remained low at an average annualized rate of 2.3% for years 2-5.**[5]

Complications in year 1 did not predict later complications.

Most Prevalent Complications:

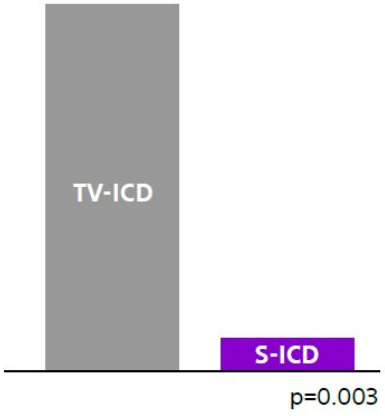
Infection requiring device removal (3.3%), erosion (2.4%), and IAS for cardiac oversensing (2.6%).



ATLAS randomized study

Primary Outcome
S-ICD is **Superior** to TV-ICD
Lead-related complications

SERIOUS LEAD RELATED COMPLICATIONS*

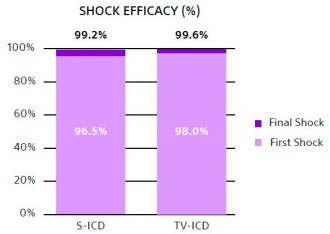


92% fewer
serious lead-related complications* for S-ICD patients

Spontaneous Conversion Efficacy for VT/VF[1]

Over 99%
conversion efficacy

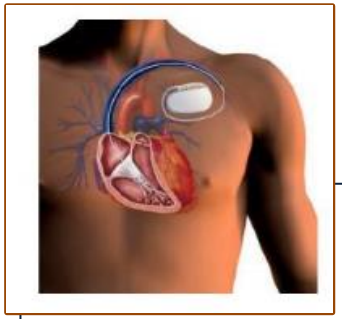
High conversion efficacy, low arrhythmic death rates for both study arms.



S-ICD IS RECOMMENDED IN BOTH US AND EU GUIDELINES

Guidance	2017 AHA/ACC/HRS Guidelines[19]	2015 ESC Guidelines[34]	For ICD patients…
Class I	✓		With high risk of infection, including Diabetic patients **(up to 35% of the ICD population)**[19]
Class IIa	✓	✓	Without need for pacing (CRT, bradycardia, ATP)

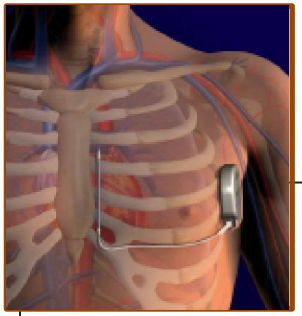
TV vs S-ICD comparison



Pros:
- Different therapies availability: shock, ATP, pacing
- Supported by several randomized clinical trials

Cons:
- High rate of acute and long-term complications:
  - **25%** lead failure: 1out of 4 in 10 years [1]
  - **16%** mortality risk for extraction in infected pts [2]
  - **6%** systemic infection and endocarditis [3]
  - **1-2%** tamponade and pneumothorax [4]

vs



Pros:
No life-threatening risks reported in major clinical trials:
- **0%** lead failure[5]
- **0%** mortality risk extraction procedure[6]
- **0%** systemic infection and endocarditis[7]
- **0%** tamponade and pneumothorax[8]

Better performances:
- Lower Inappropriate Shock rate[9]
- better patient acceptance with similar QOL[10,11]
- S-ICD shocks were not associated with myocardial damage[12]
- Subcutaneous approach is preferred in athletes[13]

Cons:
- Therapies availability: shock and post shock-pacing

Conclusion

- ✓ S-ICD is a safe, effective, without vascular access therapy
- ✓ No endovascular and systemic infection are reported in the S-ICD recipients from the studies
- ✓ Studies showed that S-ICD is superior vs TV-ICD in reducing lead-related complications

Thank you

REFERENCES

1. Kirkfeldt, R.E. et al. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. European Heart Journal (2014) 35, 1186–1194.
2. L.R.A. Olde Nordkamp et al. Implantable Cardioverter-Defibrillator Harm in Young Patients with Inherited Arrhythmia Syndromes: A Systematic Review and Meta-Analysis of Inappropriate Shocks and Complications. Heart Rhythm 2015.
3. Ranasinghe, I. et al. Long-Term Device-Related Adverse Events After Implantable Cardioverter-Defibrillator Therapy. AHA 2014 Abstract 20158.
4. Ascoeta, M. S. et al. Impact of Early Complications on Outcomes in Patients with Implantable Cardioverter-Defibrillator for Primary Prevention. Heart Rhythm, 2016; 13:1045–1051.
5. Olde-Nordkamp, L.R.A. et al. Implantable Cardioverter-Defibrillator Harm in Young Patients with Inherited Arrhythmia Syndromes: A Systematic Review and Meta-Analysis of Inappropriate Shocks and Complications. Heart Rhythm 2015.
6. Honarbakhsh S, Providencia R, Srinivasan N, Ahsan S, Lowe M, Rowland E, et al. A propensity matched case-control study comparing efficacy, safety and costs of the subcutaneous vs. transvenous implantable cardioverter defibrillator. Int J Cardiol 2017; 228:280-5.
7. Koneru JN. Multiple Procedures Increase the Risk of Infection but Not Mechanical Complications in Patients with Implantable Cardiac Defibrillators. Heart Rhythm Society; 2017; Chicago.
8. Borleffs, C.J.W. et al. Risk of Failure of Transvenous Implantable Cardioverter-Defibrillator Leads. CLINICAL PERSPECTIVE. Circ Arrhythmia Electrophysiol. 2009; 2:411-416.
9. Kleeman, T. et al. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 Years Circulation 2007; 115:2474-2480.
10. Saxon, L.A. et al. Long-Term Outcome After ICD and CRT Implantation and Influence of Remote Device Follow-Up: The ALTITUDE Survival Study, Circulation. 2010; 122: 2359-2367.
11. Greenspon, A.J. et al., 16-Year Trends in the Infection Burden for Pacemakers and Implantable Cardioverter-Defibrillators in the United States. JACC, 2011; 58, 10.
12. Lekkerkerker, J.C. et al. Risk factors and time delay associated with cardiac device infections: Leiden device registry. Heart; 2009; 95.
13. Tarakji, K.G. et al. Cardiac Implantable Electronic Device Infection in Patients at Risk. Arrhythmia & Electrophysiology Review, 2016; 5(1).
14. Chamis, A.L. et al., Staphylococcus aureus Bacteremia in Patients With Permanent Pacemakers or Implantable Cardioverter-Defibrillators. Circ . 2001.
15. Polyzos, KA, et al. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. Europace, 2015. 17(5): p. 767-777.
16. 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. 1(8): p. 900-911.
17. Nery, P.B. Device-Related Infection Among Patients With Pacemakers and Implantable Defibrillators: Incidence, Risk Factors, and Consequences. J Cardiovasc Electrophysiol, 2010; 21.
18. Steiner, H. et al. Characteristics and outcomes of diabetic patients with an implantable cardioverter defibrillator in a ral world setting: results form the Israeli ICD registry. Cardiovasc Diabetol. 2016; 15:160.
19. Al-Khatib, SM, et al., 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. Heart Rhythm, 2017.

REFERENCES

20. Maytin, M. et al., Long-Term Mortality After Transvenous Lead Extraction. Circ. Arrhyth. Electrophysiol. 2012; 5: 252-257.
21. https://consultqd.clevelandclinic.org/2014/08/leading-from-experience-in-transvenous-lead-extraction/
22. Bongiorni, M.G. et al. Results from the ELECTRaMulticenter Lead Extraction Study. May 5th, 2016, HRS.
23. Burke, M. et al. Safety and Efficacy of the Totally Subcutaneous Implantable Defibrillator: 2-year Results from a Pooled Analysis of the IDE Study and EFFORTLESS Registry. JACC 2015; 65: 16.
24. Boston Scientific CRM Product Performance Report published February 13th, 2017.
25. Boersma, L. et al. Implant and mid-term outcomes of the complete EFFORTLESS subcutaneous implantable-defibrillator cohort. JACC, 2017; 70,7.
26. Basu-Ray, I. et al. Subcutaneous Versus Transvenous Implantable Defibrillator Therapy. A Meta-Analysis of Case-Control Studies. JACC 2017.
27. Boersma, L. et al. Infection and Mortality After Implantation of the Subcutaneous ICD Following Transvenous ICD Extraction Heart Rhythm 2015.
28. Proietti, R. et al. A Systematic Review and Meta-analysis of the Association Between Implantable Cardioverter-Defibrillator Shocks and Long-term Mortality. Canadian Journal of Cardiology , 2015; 31, 270-277.
29. Semmler. V. et al. ICD Shock, Not Ventricular Fibrillation, Causes Elevation of High Sensitive Troponin T after Defibrillation Threshold Testing – The Prospective, Randomized, Multicentre TropShock-Trial. PLoS ONE , 2015; 10(7).
30. D'Onofrio A, et al. Effects of defibrillation shock in patients implanted with a subcutaneous defibrillator: a biomarker study. Europace 2017; Epub 2017/11/03.
31. Pedersen SS et al. A Comparison of the Quality of Life of Patients With an Entirely Subcutaneous Implantable Defibrillator System Versus a Transvenous System (from the EFFORTLESS S-ICD Quality of Life Substudy). Am J Cardiol. 2016 Aug 15;118(4):520-6.
32. Weiss, et al. The safety and efficacy of a totally subcutaneous implantable defibrillator. Circulation 2013; 128:944-953.
33. Gold, M.R. The subcutaneous ICD Post-Market Approval Study: Clinical Characteristic and perioperative Results, Heart Rhythm (2017), doi: 10.1016/j.hrthm.2017.05.016.
34. Priori, SG. et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2015; Nov 1;36(41):2793-867.
35. Botto GL, et al. The Italian subcutaneous implantable cardioverter-defibrillator survey: S-ICD, why not? Europace 2016; Epub 2016/12/25.
36. Moss, A.J. et al. Reduction in Inappropriate Therapy and Mortality through ICD Programming. NEJM, 2012; 367: 24.
37. de Bie MK, et al. Suitability for subcutaneous defibrillator implantation: results based on data from routine clinical practice. Heart 2013;99:1018–1023.
38. Groh CA, et al. Use of an electrocardiographic screening tool to determine candidacy for a subcutaneous implantable cardioverter-defibrillator. Heart Rhythm. 2014 Aug;11(8):1361-6.
39. Ziacchi M, et al. Electrocardiographic Eligibility for Subcutaneous Implantable Cardioverter Defibrillator: Evaluation during Bicycle Exercise. Heart Lung Circ. 2016 May;25(5):476-83.
40. Poole, J. & Gold, M. The Subcutaneous Implantable Cardioverter Defibrillator (ICD) Should Be Considered in all ICD Patients Who Do Not Require Pacing. Circulation: Arrhythmia and Electrophysiology. 2013;6:1236-1245.
41. Boersma, L. ICD from real life to the future: ICD innovations. ESC 2014.
42. Kutyifa. et al. The Need for Pacing in patients who qualify for and ICD: Clinical Implications. ESC abstract 2014.
43. Boriani, G. et al. Battery drain in daily practice and medium-term projections on longevity of cardioverter-defibrillators: an analysis from a remote monitoring database. Europace, http://dx.doi.org/10.1093/europace/euv436.

REFERENCES

44. Kalantarian S, et al. Predictors of Right Ventricular Pacing (RVP) in ICD Recipients Without Baseline Pacing Needs: A report from the NCDR Registry. Presented at American Heart Association in Los Angeles 2017. Poster: M3118.
45. Deftereos, S. et al. Relation of ventricular tachycardia/fibrillation to beta-blocker dose maximization guided by pacing mode analysis in nonpacemaker-dependent patients with implantable cardioverter defiibrillator. Am J Cardiol, 2011.
46. Quast ABE, et al. Six year follow-up of the initial dutch subcutaneous implantable cardioverter defibrillator cohort: Long term complications and battery longevity. EP Europace 2017; 19:iii128-iii9.
47. Sponder M, et al. Specific indications and clinical outcome in patients with subcutaneous ICD - A nationwide multicentre registry. European journal of internal medicine 2017; Epub 2017/10/06.
48. Bardy G, et al. and Sudden Cardiac Death in Heart Failure Trial : Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure.NEngl J Med 2005;352:225–237.
49. Poole, J. et al. Who Should Receive the Subcutaneous Implanted Defibrillator? The Subcutaneous Implantable Cardioverter Defibrillator (ICD) Should Be Considered in all ICD Patients Who Do Not Require Pacing. Circulation: Arrhythmia and Electrophysciology 2013; 6: 1236-1245
50. Atalleh, J. et al. Multi-Institutional Study of Implantable Defibrillator Lead Performance in Children and Young Adults Results of the Pediatric Lead Extractability and Survival Evaluation (PLEASE) Study. Circulation. 2013; 127:2393-2402.
51. Schukro C, et al. Impact of accelerated ventricular tachyarrhythmias on mortality in patients with implantable cardioverter-defibrillator therapy. Int J. Cardiol 2013;167:3006-10.
52. Clementy, N. et al. Very-high-rate programming in primary prevention patients with reduced ejection fraction implanted with a defibrillator: Results from a large multicenter controlled study. Heart Rhythm 2017; 14: 2, 211 – 217.
53. Auricchio, A. et al. Low inappropriate shock rates in patients with single- and dual/triple-chamber implantable cardioverter-defibrillators using a novel suite of detection algorithms: PainFree SST trial primary results. Heart Rhythm 2015; 12: 926–936.
54. Gasparini, M. et al., Long Detection Programming in Single-Chamber Defibrillators Reduces Unnecessary Therapies and Mortality: The ADVANCE III Trial. JACC: Clinical Electrophysiology, 2017; 3: 11.
55. Sweeney MO, et al. Appropriate and inappropriate ventricular therapies, quality of life, and mortality among primary and secondary prevention implantable cardioverter defibrillator patients: results from the Pacing Fast VT REduces Shock ThErapies (PainFREE Rx II) trial. Circulation. 2005;111:2898–2905.
56. Wathen MS, et al. PainFREE Investigators. Shock reduction using antitachycardia pacing for spontaneous rapid ventricular tachycardia in patients with coronary artery disease. Circulation. 2001;104:796–801.
57. Young JB, et al. Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA. 2003;289:2685–2694.
58. Moss, A. et al. Long-Term Benefit of Primary Prevention With an Implantable Cardioverter-Defibrillator An Extended 8-Year Follow-Up Study of the Multicenter Automatic Defibrillator Implantation Trial, Circulation. 2010;122:1265-1271.
59. Betz, J., et al. Outcomes Among Older Patients Receiving Implantable Cardioverter-Defibrillators for Secondary Prevention From the NCDR ICD Registry. JACC, 2017; 69, 3.

REFERENCES

60. Kusumoto, FM, et al., 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. Heart Rhythm, 2017.
61. 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia. Richard L. Page et al. Circulation. 2015;10.1161/CIR.0000000000000311.
62. Gold, M. R., et al. (2011). Head-to-Head Comparison of Arrhythmia Discrimination Performance of Subcutaneous and Transvenous ICD Arrhythmia Detection Algorithms: The START Study. J Cardiovasc Electrophysiol. In press Epub, doi: 10.1111/j.1540-8167.2011.02199
63. Moss, A. et al. Long-Term Benefit of Primary Prevention With an Implantable Cardioverter-Defibrillator An Extended 8-Year Follow-Up Study of the Multicenter Automatic Defibrillator Implantation Trial, Circulation. 2010;122:1265-1271.
64. Ferretto, S. et al. Implantable cardioverter-defibrillator in the elderly: Predictors of appropriate interventions andmortality at 12-month follow-up. Pacing Clin Electrophysiol. 2017;1–6.
65. Bardy, G. H., et al. (2010). “An entirely subcutaneous implantable cardioverter-defibrillator.” N Engl J Med 363(1): 36-44.
66. Olde Nordkamp, L.R. et al. Rationale and design of the PRAETORIAN trial: a Prospective, randomized comparison of subcutaneous and transvenous implantablle cardioverter-defibrillator therapy. Am. Heart.J. 2012 May;163(5):753-760.e2. doi: 10.1016/j.ahj.2012.02.012.
67. Kutyifa, V. et al., Multicenter Automatic Defibrillator Implantation Trial–Subcutaneous Implantable Cardioverter Defibrillator (MADIT S-ICD): Design and clinical Protocol. Am. Heart J., 189:2017
68. Gold M.R. et al. The Subcutaneous ICD Post-Market Approval Study: Clinical Characteristics and Perioperative Results. Heart Rhythm Journal 2017.
69. Heart Rhythm - May 2012; Vol 9:5(S1-33) AB07-2.
70. Lambiase, et al. A worldwide experience with a totally subcutaneous ICD; Preliminary results of the EFFORTLESS S-ICD Registry. European Heart Journal Mar2014.
71. M.C. Burke et al. Safety and Efficacy of the Totally Subcutaneous Implantable Defibrillator: 2-year Results from a Pooled Analysis of the IDE Study and EFFORTLESS Registry. JACC 2015.
72. S-ICD® System Post Approval Study: https://clinicaltrials.gov/ct2/show/NCT01736618.
73. Understanding Outcomes With the EMBLEM™ S-ICD in Primary Prevention Patients With Low Ejection Fraction (UNTOUCHED): https://clinicaltrials.gov/ct2/show/NCT02433379.
74. EMBLEM S-ICD, EMBLEM MRI S-ICD User’s Manual, 359481-019 EN Europe 2016-11.
75. BSC Data on File 2017.
76. PubMed.gov [Internet]. National Center for Biotechnology Information, US National Library of Medicine. [Cited 2017 March 7]. Available from https://www.ncbi.nlm.nih.gov/pubmed.
77. Estimation from completed and ongoing clinical trials. BSC 2018.
78. Boston Scientific. Rhythm Management Performance Report, Q1 2018, Published Jan 2018.
79. Data on File. Based on analysis of >2900 Emblem patients followed on LATITUDE™. June 2017.
80. Moss, A. et al. Long-Term Benefit of Primary Prevention With an Implantable Cardioverter-Defibrillator An Extended 8-Year Follow-Up Study of the Multicenter Automatic Defibrillator Implantation Trial, Circulation. 2010;122:1265-1271.
81. EMBLEM MRI S-ICD A219: MRI Technical manual 359475-001 EN US 2015-11.
82. Theuns, D.A.M.J. et al. Evaluation of a High Pass Filter Designed to Reduce Over sensing in the S-ICD, HRS 2016; AB05-01.
83. Wilkoff B, et al. Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients: results from the PREPARE (Primary Prevention Parameters Evaluation) study. JACC 2008; 52:541-550.

REFERENCES

84. Data on file at Boston Scientific, validation report DN-23333 .
85. Brisben, A.J., et al. A new algorithm to reduce inappropriate therapy in the S-ICD system. J. Cardiovasc. Electrophysiol. Pp 1 – 7.
86. Gold, M. R., et al. (2011). "Head-to-Head Comparison of Arrhythmia Discrimination Performance of Subcutaneous and Transvenous ICD Arrhythmia Detection Algorithms: The START Study." J Cardiovasc Electrophysiol. In press Epub, doi: 10.1111/j.1540-8167.2011.02199.
87. Biton Y. et al. Relationship between age and inappropriate implantable cardioverter-defibrillator therapy in MADIT-RIT. Heart Rhythm. 2015 Dec 19.
88. System Algorithm Validation Test Report For Project: S-ICD Automated Screening Tool (AS) Product: EMBLEM™ S-ICD System. Rev. A, Page 15 & 20.
89. Data on file at Boston Scientific, System Algorithm Validation Report 1132474.
90. Winter, J. et al. Submuscular is Superior to Subcutaneous Implantation for Subcutaneous Implantable Cardioverter Defibrillator. Circulation. 2013;128:A14688.
91. Ferrari, P. et al. Intermuscular pocket for subcutaneous implantable cardioverter defibrillator: single-centre experience. Journal of Arrhythmia. 2016; 32, 223–226.
92. Winter, J. et al. Intermuscular technique for implantation of the subcutaneous implantable cardioverter defibrillator: long-term performance and complications. Europace. 2016; doi:10.1093/europace/euw297.
93. Droghetti, A. et al. Totally submuscular implantation of subcutaneous implantable cardioverter defibrillator: a safe and effective solution for obese or oversized patients. Clinical Case Reports. 2016; doi: 10.1002/ccr3.652.
94. Brouwer, T.F. et al. Implantation of the subcutaneous implantable cardioverter-defibrillator: an evaluation of 4 implantation techniques. Circ Arrhythm Electrophysiol. 2017; 10.1161/CIRCEP.116.004663.
95. Kondo, Y. et al. Successful intermuscular implantation of subcutaneous implantable cardioverter defibrillator in a Japanese patient with pectus excavatum. Journal of Arrhythmia. 2016; http://dx.doi.org/10.1016/j.joa.2016.04.005.
96. Migliore, F. et al. Intermuscular Two-Incision Technique for Subcutaneous Implantable Cardioverter Defibrillator Implantation: Results from a Multicenter Registry. Pace. 2016; doi: 10.1111/pace.12987.
97. EMBLEM™ S-ICD Electrode Delivery System Manual: 360210-001 EN Europe 2017-01.
98. Knops RE, et al. Two-incision technique for implantation of the subcutaneous implantable cardio-verter-defibrillator. Heart Rhythm. 2013; 10:1240-1243. doi: 10.1016/j.hrthm.2013.05.016.
99. EMBLEM S-ICD Subcutaneous Electrode Manual User's Manual, 360213 EN EU 2016-09
100. Knops, R.E. et al. The learning curve associated with the introduction of the subcutaneous implantable defibrillator. Europace (2016) 18, 1010–1015.
101. Boston Scientific CRM Product Performance Report published February 13th, 2017.
102. Essandoh, M.K. Monitored Anesthesia Care for Subcutaneous Implantable Cardioverter Defibrillator Implantation: A Single Center Experience. Journal of Cardiothoracic and Vascular Anesthesia, 2016.
103. Ueshima, H. et al. Correspondence: Successful cases of S-ICD implantation performed under the serratus plane block. J Clin Anesth 2016; 33:1478.
104. Ueshima H. and Hiroshi O. A successful case of subcutaneous implantable cardioverter-defibrillator implantation performed under the transversus thoracic muscle plane. J Clin Anesth 2016; 32:253-4.
105. Boveda S, et al. Implantation of subcutaneous implantable cardioverter defibrillators in Europe: results of the European Heart Rhythm Association survey. Europace 2016; 9,1:1434–1439.

INFECTIONS

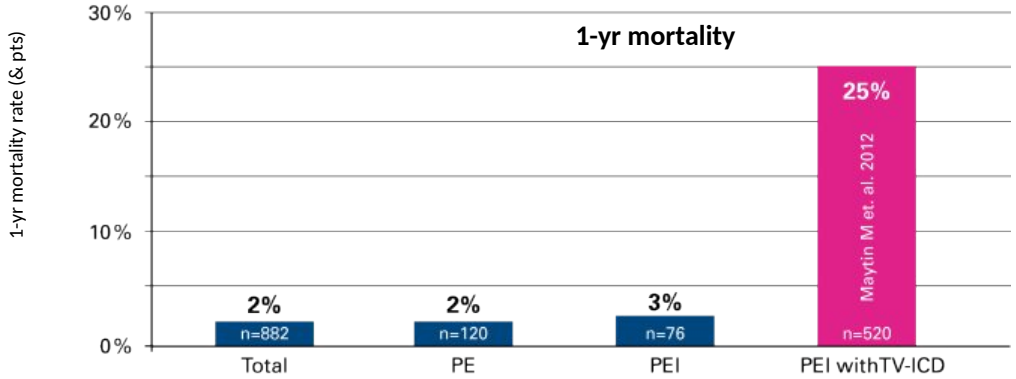
- *When talking about infections it is important to clarify which kind of infections is taken into account*
- The Subcutaneous approach avoids, by-design, **major complication** related to TV-ICD, such as systemic infections, endocarditis and lead-extraction complications. Endovascular infections are associated with double mortality risk compared to pocket infections
- There were ZERO endovascular infections in the S-ICD POOLED Data Analysis[1].
- In the POOLED Data Analysis, advances in operator experience, preparation and implant technique further reduced infections and implant complications for S-ICD patients[1].
- Rate of explants due to (pocket) infections IDE & Effortless is low (1,3-1,6%) and most infections were managed non-invasively[2]

1. MC Burke, MR Gold, et al. JACC 2015;65:1605-15
2. Weiss, et al. The safety and efficacy or a totally subcutaneous implantable defibrillator. Circulation 2013; 128:944-953.

Infections – Proof Points

Total Pooled S-ICD cohort n = 889 → **Post TV-ICD extraction D (PE) n = 120** → **Post TV-ICD infection (PEI) n = 76**

- Mean follow-up time was 676 ± 317 days (range 98-1505 days)



rsma, et al. Safety of the S-ICD in patients after Transvenous ICD infection: long-term follow-up in the IDE and EFFORTLESS trial. *HRS* 2014.
ytin M et al. Circ Arrhythm Electrophysiol. 2012.

Infections

Advances in operator experience, preparation and implant technique further reduced 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

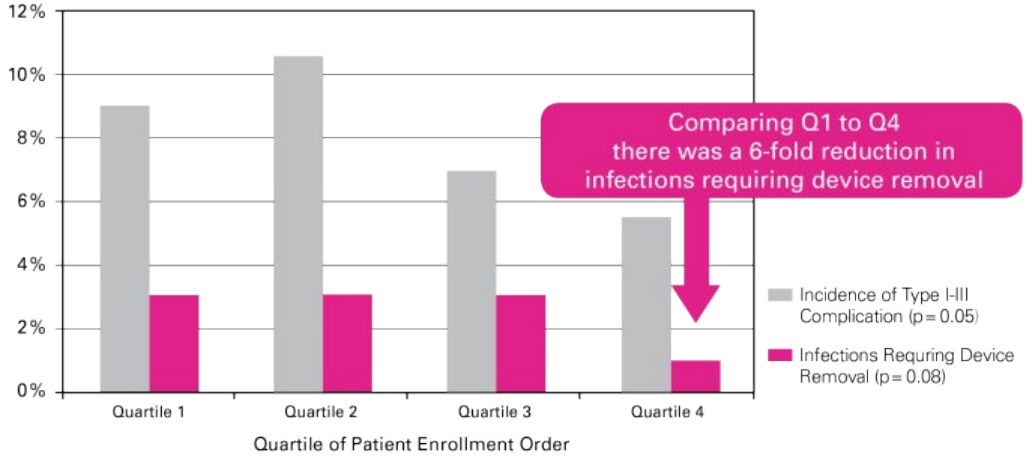
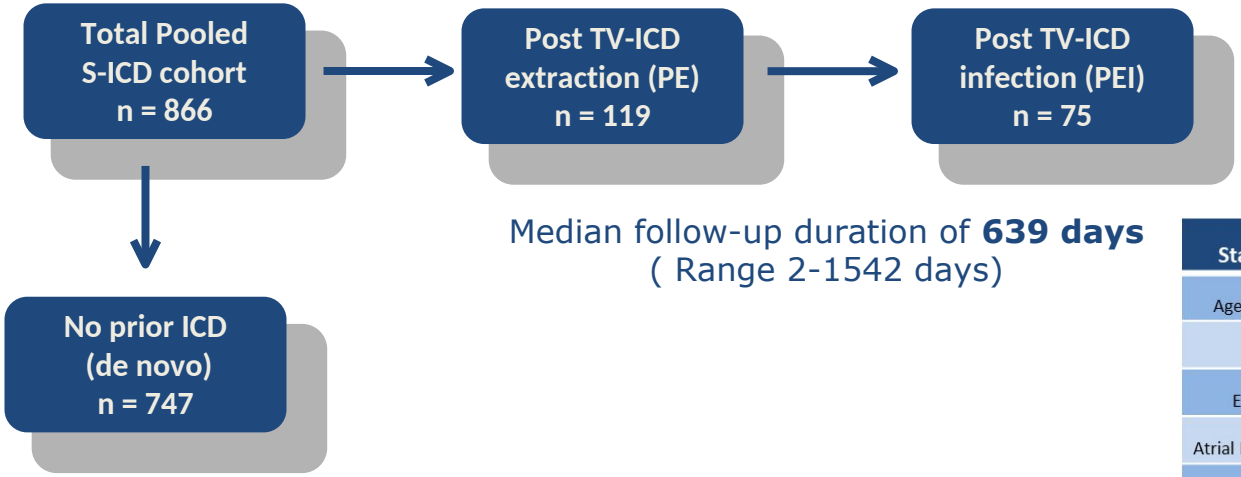


Figure 4B: Six Month Incidence of Appropriate Shocks, and Initial Programming by Enrollment Date

Burke, MR Gold, et al. JACC 2015;65:1605-15 *(POOLED Data Analyisis)*

Infection and mortality after implantation of the subcutaneous ICD following transvenous ICD extraction



Median follow-up duration of **639 days**
(Range 2-1542 days)

Statistic	PEI	PE	De Novo	P-Value
Age (years)	**55.5 ± 14.6**	47.8 ± 14.3	49.9 ± 17.3	0.0146
PP	43 (57.3)	27 (62.8)	**554 (74.4)**	<.0001
EF (%)	41.8 ± 17.0	46.3 ± 19.3	**38.7 ± 17.5**	0.0314
Atrial Fibrillation	**19 (25.3)**	5 (11.4)	119 (15.9)	0.0720
Diabetes	**22 (29.3)**	2 (4.5)	130 (17.4)	0.0023
Hypertension	**37 (49.3)**	7 (15.9)	284 (38.1)	0.0014
MI	**39 (52.0)**	10 (22.7)	252 (33.8)	0.0015

L Boersma et al. Heart Rhythm 2015. Sept 1

S-ICD is a viable option after TV extraction for infection

- 75 patients in IDE and EFFORTLESS[1] received S-ICD following TV-ICD extracted for infection (651 day follow up; low all cause mortality: 3.2%)[1]
- S-ICD was successfully implanted and complication rate in patients with previous infections was no higher than those with *de novo* implants
- 1 patient (1.3%) experienced subsequent re-infection that required intervention
- *De novo* cohort infection rate:1.6%

  - Brouwer *et al.* (2015) concluded that "in most patients with a complication, S-ICD therapy could be continued after intervention, avoiding the need to convert to a transvenous system"

- In this study, 5 S-ICD patients had an infection which required extraction of the device – 4 patients were re-implanted with S-ICD (after antibiotic treatment and bridging therapy)

1. Boersma, L. *et al.* (2015). **Infection and mortality after implantation of the subcutaneous ICD following transvenous ICD extraction.** Heart Rhythm, http://dx.doi.org/10.1016/j.hrthm.2015.08.039.
2. Brouwer, T. F. *et al.* (2015). Surgical Management of Implantation-Related Complications of the Subcutaneous Implantable Cardioverter-Defibrillator. *Jacc: Clinical Electrophysiology*.