Preventing cardiac arrest in high risk patients without indication for ICD

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CorVita Science Foundation

COI DISCLOSURES

Funded by and NIH/SBIR grant to AJ Medical Devices, Inc. and research grants from Medtronic, Boston Scientific, Inc., St. Jude Medical, Johnson and Johnson and Cameron Health, Inc.

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

I have an equity stake in AJMD.

Zoll is sponsoring this grand rounds lecture.

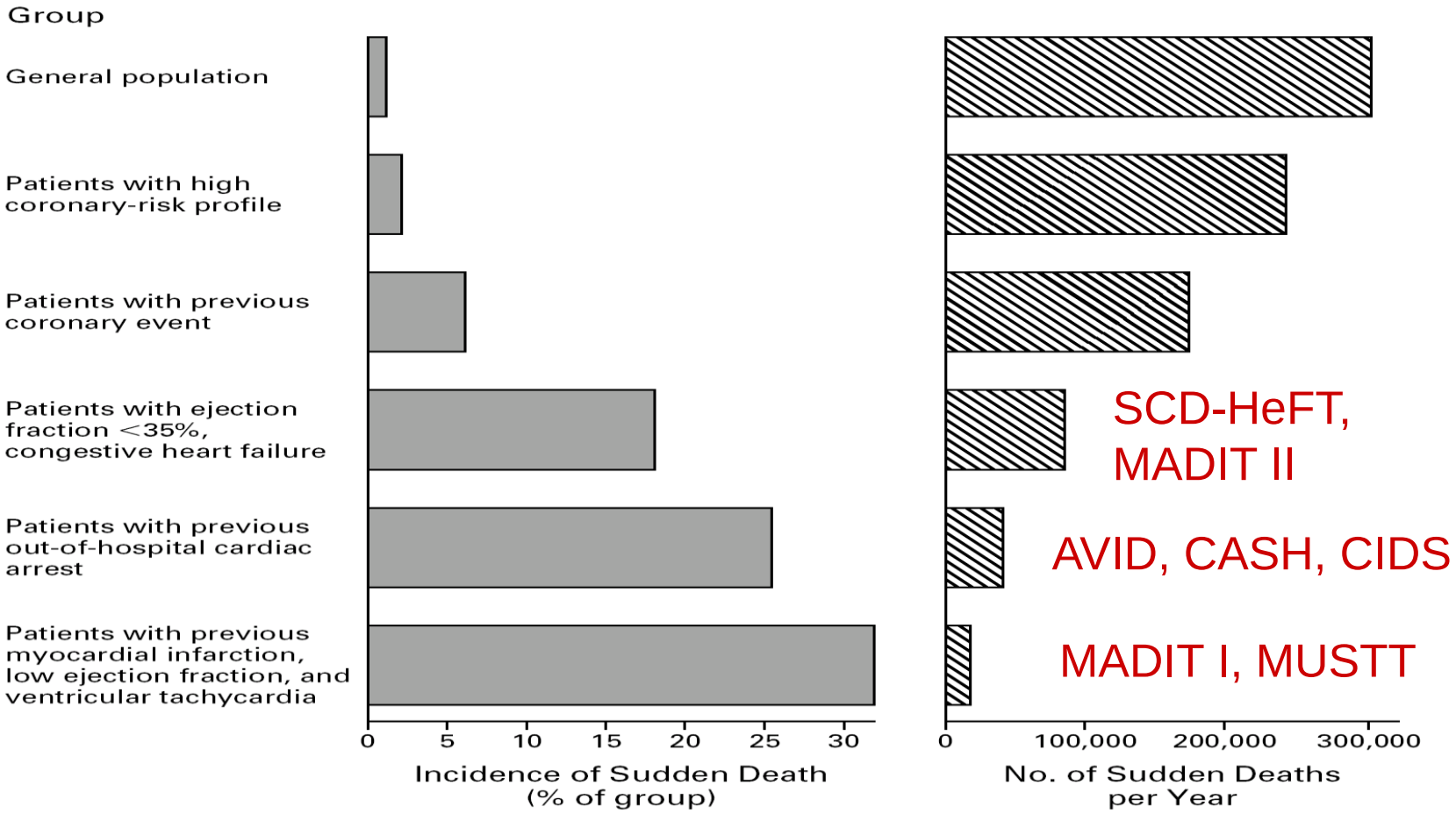
Clinical Case

- **40 year old AA M with ischemic CM (EF on CMR 25%, + extensive late gadolinium enhancement, minimal-to-no viability) presents to EP clinic to discuss ICD implantation.**
  - Suffered a STEMI 10 days prior- PCI of LAD artery; extensive moderate-coronary lesions in multivessel distribution on angiography
  - Statin, BB, ACEI, Aldosterone, DAPT therapy initiated
  - NYHA I
  - No angina or recurrent ischemic presentation
  - No palpitations, syncope, or documented ventricular arrhythmias

Patient is Leary

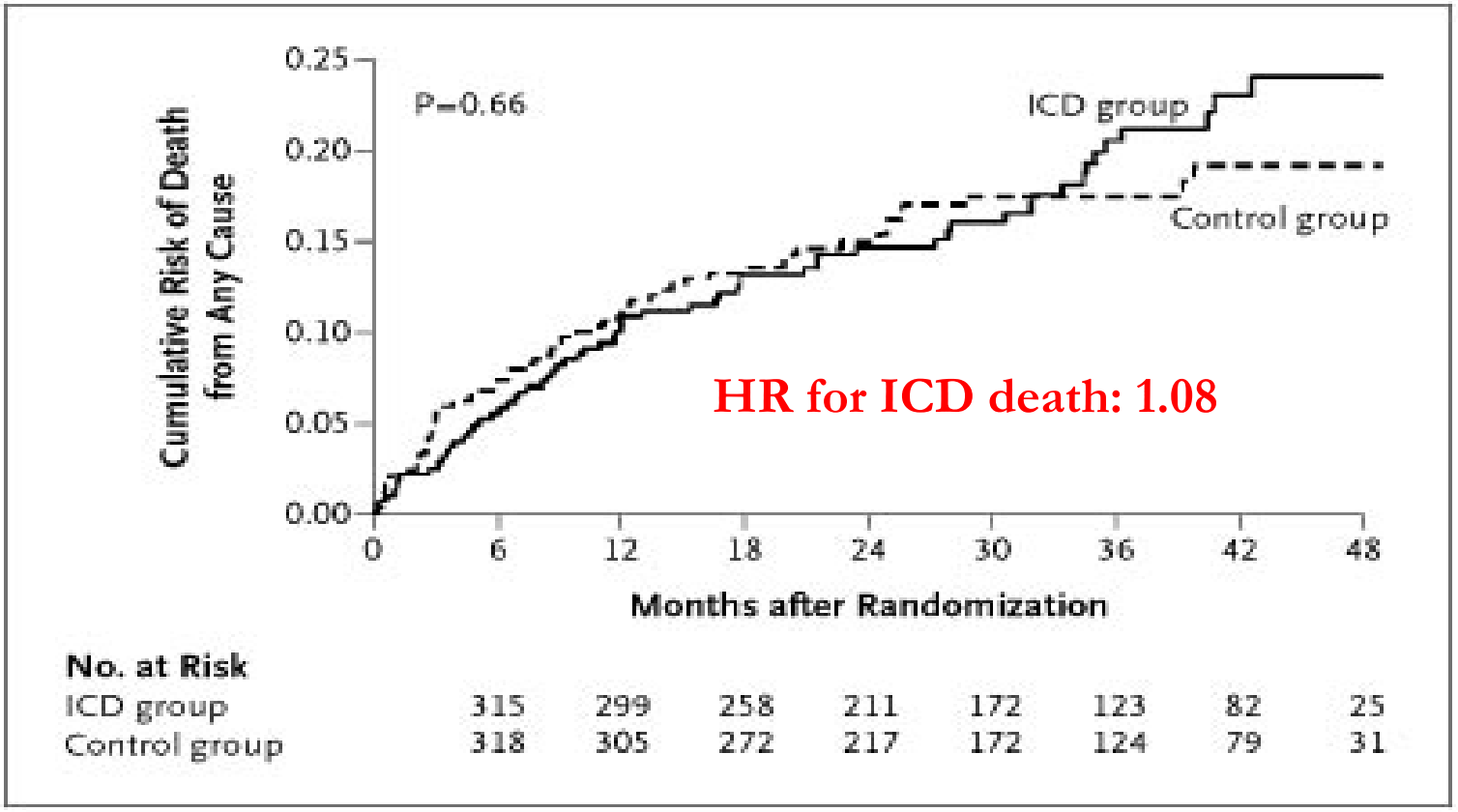
- He is reluctant to get an ICD since he hears that ICDs rarely deliver appropriate shocks in most patients.
- He wants to know if he can wait until he “really needs it”.
- What do you explain to him about his individual risk of SCD in this post-MI period? What are his future risks?
- What clinical characteristics or additional testing might better risk stratify his risk?
- What is the time course of ICD effectiveness post-MI/revasc?

Heart Failure and Left Ventricular Dysfunction are indicators of SCA risk



Myerburg RJ, et al. *Circulation*. 1998. 97:1514-1521.

DINAMIT



Hohnloser SH et al. NEJM 2004; 351:2481-8

DINAMIT

Table 2. Mortality Rates.*

Cause of Death	ICD Group		Control Group		Hazard Ratio (95% CI)†	P Value‡
	No. of Deaths	Rate %/yr	No. of Deaths	Rate %/yr		
Any cause	62	7.5	58	6.9	1.08 (0.76–1.55)	0.66
Arrhythmia	12	1.5	29	3.5	0.42 (0.22–0.83)	0.009
Nonarrhythmic causes	50	6.1	29	3.5	1.75 (1.11–2.76)	0.02
Cardiac, nonarrhythmic	34	4.1	20	2.4	1.72 (0.99–2.99)	0.05
Vascular, noncardiac	5	0.6	3	0.4	1.69 (0.40–7.06)	0.47
Nonvascular	11	1.3	6	0.7	1.85 (0.68–5.01)	0.22

* The data were analyzed with use of the Cox model. ICD denotes implantable cardioverter–defibrillator, and CI confidence interval.
† Hazard ratios are for the ICD group as compared with the control group.
‡ P values are two-sided.

- Device-related complications occurred in 25 pts
- No deaths from device implantation

Hohnloser SH et al. NEJM 2004; 351:2481-8

Immediate Risk-Stratification Improves Survival (IRIS) study

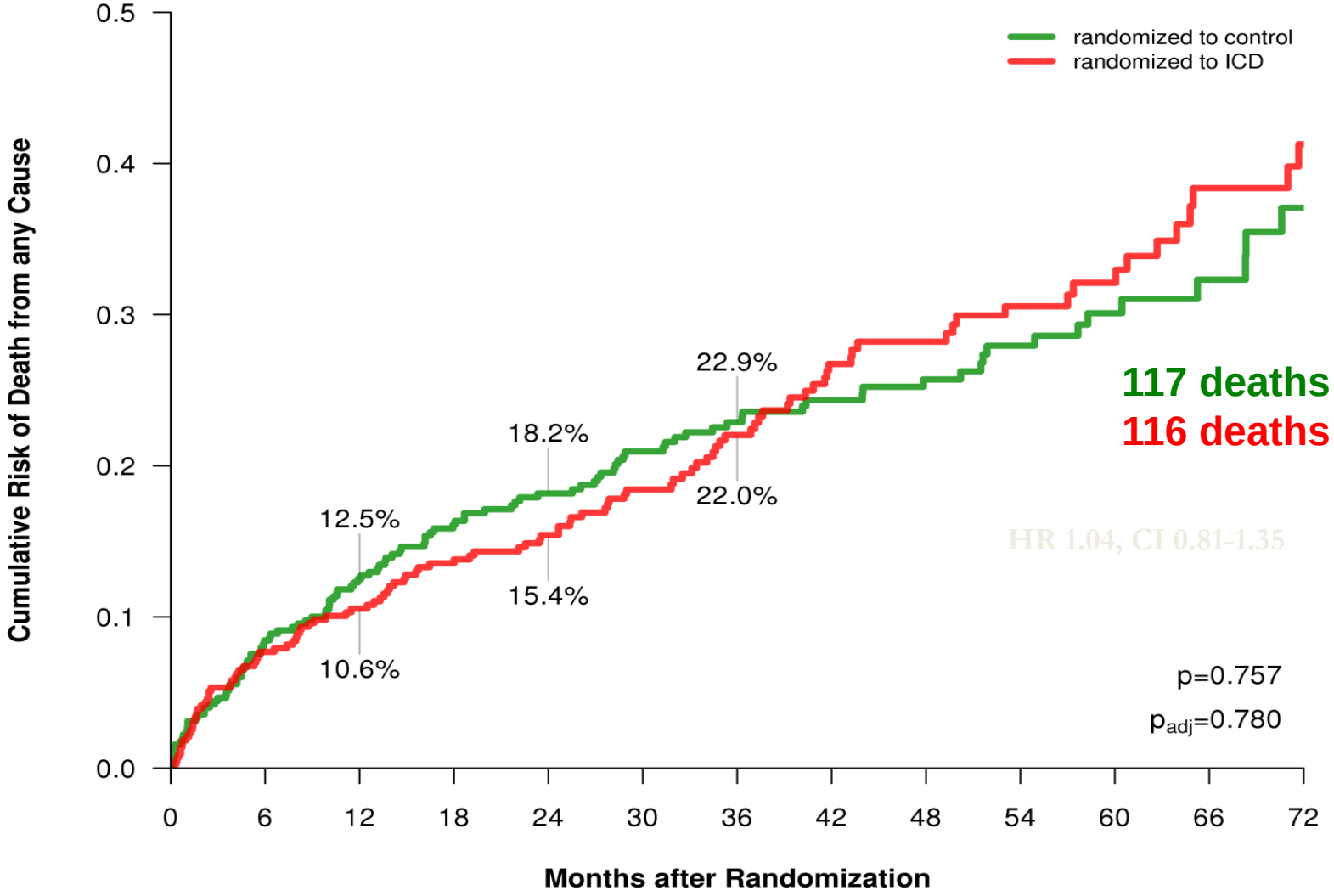
Baseline Characteristics

Characteristic		ICD Group (N=445)		Control Group (N=453)	
		no.	%	no.	%
Left ventricular ejection fraction	Mean ± SD	34.6	±9.3	34.5	±9.4
Criterion I only		32.2	±6.3	31.9	±6.7
Criterion II only		45.9	±10.8	44.8	±11.0
Criteria I+II		29.6	±7.0	31.4	±6.7
Acute medical therapy on admission					
Antiplatelets		438	(98.9%)	442	(97.8%)
Beta-Blockers		394	(89.1%)	388	(85.7%)
ACE-inhibitors		361	(81.5%)	373	(82.3%)
Reperfusion					
PTCA		279	(62.8)	290	(64.0)
Thrombolytic therapy †		55	(12.4)	50	(11.0)
None		110	(24.8)	113	(24.9)

PTCA Percutaneous transluminal coronary angioplasty
† without or with subsequent PTCA

Steinbeck G et al.NEJM 2009;361-1427

IRIS: All Cause Mortality



No. at Risk

Control group	453	410	380	336	307	267	230	187	151	118	79	49	36
ICD group	445	390	366	338	303	253	207	163	137	106	78	48	40

CABG-Patch

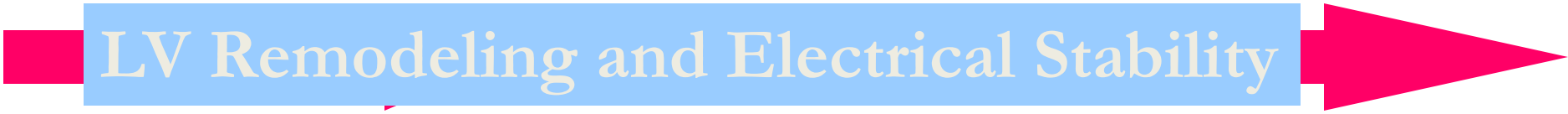
- Bigger JT NEJM 1997: 337:1569-1575

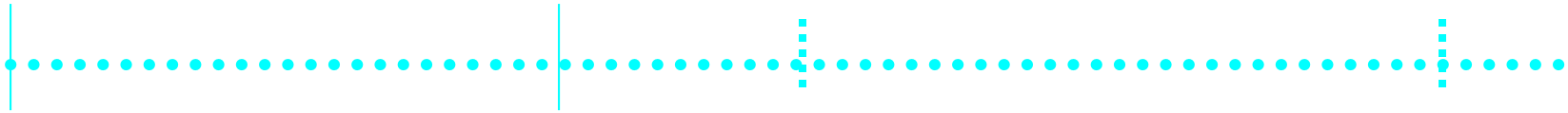
- The CABG patch trial investigators also reported that ICD reduced the rate of death from arrhythmias by 45% but did not reduce overall mortality, because the majority of deaths were non-arrhythmic in nature (71%)

Time Dependency of SCD post-MI: ICD effectiveness

NOT EFFECTIVE

EFFECTIVE, SUPPORTED BY GUIDELINES





***EVENT**
DAY 0

40 days –
18 MOs?

YEAR 2

YEAR 15
And Beyond

Time from index MI

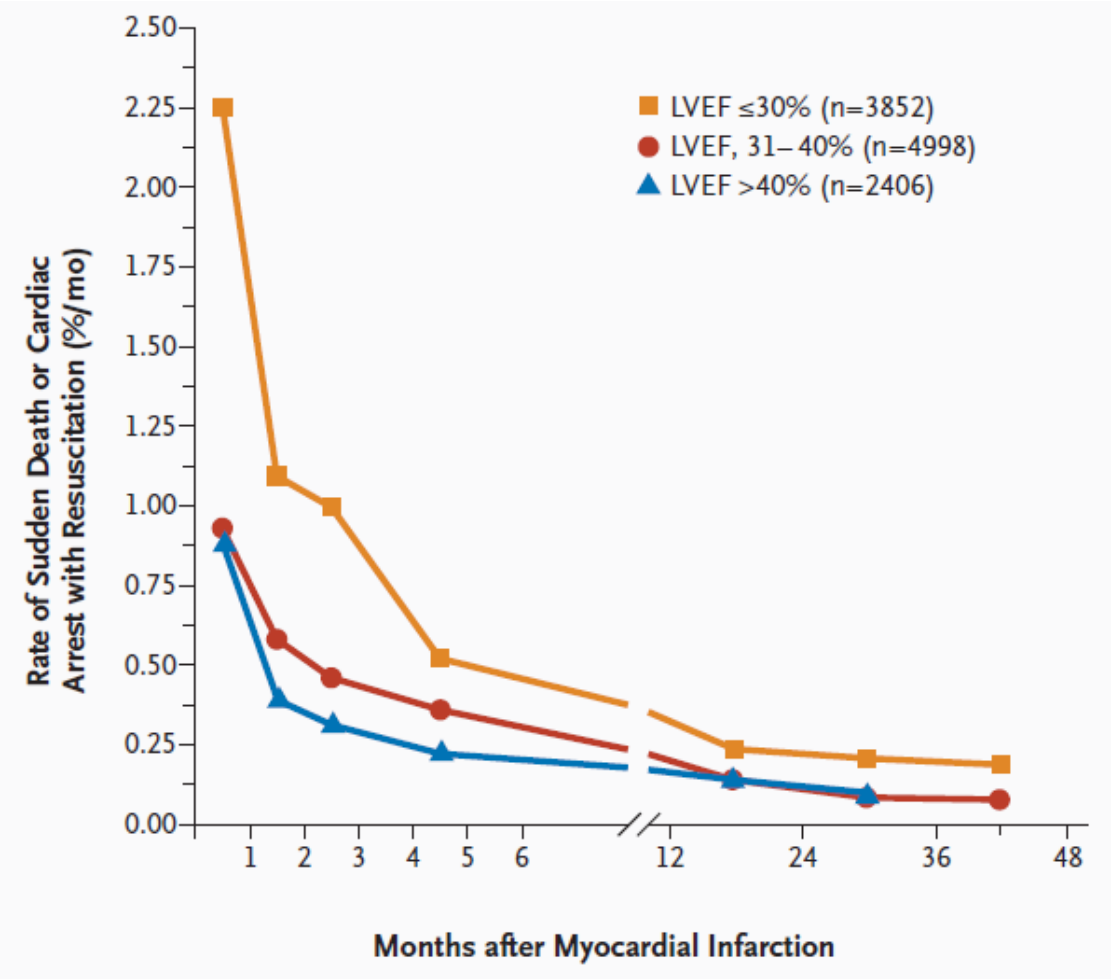
Post MI/Revasc SCD Paradox

- **Risk of sudden cardiac death (SCD) is highest in the first few weeks after MI even in the modern era with aggressive revascularization.**
- **Ventricular arrhythmias account for 20-50% deaths in this group; Anti-arrhythmic medications (with the exception of BB) do not reduce this risk.**
- **Hypothetically, the ICD should have a profound benefit in improving mortality early after MI because ventricular arrhythmias are common in this time period.**
- **Failure of RCTs to show survival benefit for ICDs implanted early post-MI in high risk individuals has led to the "Acute MI-Sudden Cardiac Death Paradox"**

1 Adabag AS, et al. Sudden Death After Myocardial Infarction. JAMA 2008; 300: 2022-2029.
2 Solomon SD, et al. Sudden Death in Patients with Myocardial Infarction and Left Ventricular Dysfunction, Heart Failure, or Both. NEJM 2005; 352: 2581-2588.
3 Exner DV. Non-invasive Risk Stratification Early After a Myocardial Infarction–The Risk Estimation Following Infarction Non-invasive Evaluation (REFINE) Study. J Am Coll Cardiol. 2007; 50: 2275-2284.

VALIANT Trial

High Early Risk of SCA



Post-MI patients with heart failure are at 4-6 times greater risk of SCA in the first 30 days post-MI[1]

- **83% of SCA occurred after hospital discharge.**
- **74% of those resuscitated in the first 30 days were alive at 1 year**

[1] Solomon SD, et al. Sudden Death in Patients with Myocardial Infarction and Left Ventricular Dysfunction, Heart Failure, or Both. NEJM 2005; 352: 2581-2588.

Patients with Low EF Scheduled for PTCA

SCA Risk While Awaiting Procedure

- **Low EF patients scheduled for PTCA are at risk of SCA while awaiting revascularization procedures.**
  - 10% of preoperative PCI patients experience VT/VF.[1]
  - The treatment path for multi-vessel disease often involves treatment of the primary vessel (infarct-related artery) and a second procedure for treatment of the second vessel (non-infarct related artery) 4-6 weeks later.
    - Over 60% of patients have multi-vessel disease.[2]
  - Utilize LifeVest to protect these high risk patients from SCA while awaiting their scheduled procedures and for staged PCI.

[1] Toda, K et al. Revascularization in Sever Ventricular Dysfunction (15% ≤LVEF≤30%): A Comparison of Bypass Grafting and Percutaneous Intervention. Annals of Thoracic Surgery 2002;74:2082-2087.

[2] Ochala, A et al. One Stage versus Two-Stage Treatment in Patients with ST Elevated myocardial infarction: Final Results of the Prospective, Randomized, Multicentre Trial for Primary Angioplasty in Patients with Multi-vessel Disease in Acute Myocardial Infarction (PRIMA II). ESC Congress 2007. www.spo.escardio.org.

Patients with Low EF Following PTCA

SCA Risk During Recovery

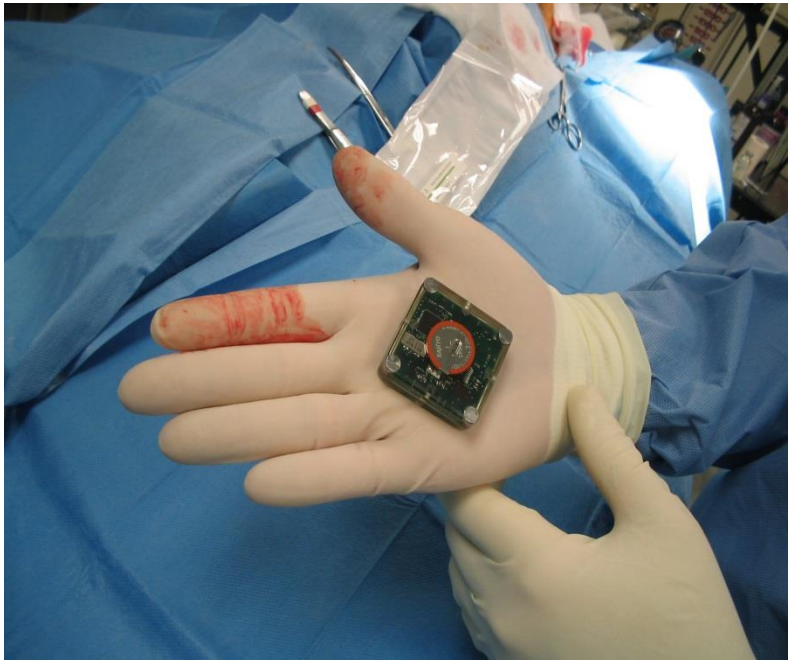
- **Low EF, post-PTCA patients are at risk of SCA during recovery from revascularization.**
  - 6% of patients experience VT/VF within 30 days after a PTCA procedure.[1]
  - Baseline LVEF is the most powerful determinant (predictor) of long-term mortality.[2]
    - In the high risk group (~20% of patients), most mortality occurred in the first 90 days post-PCI (mortality was 7% at 1 month, 11% at 3 months, and 13% at 1 year), with about 60% of this mortality due to SCD.[3]
  - Post-PCI LVEF is an independent predictor of all-cause mortality.[4]
    - 18.5% of patients have an LVEF≤35% post-PCI.

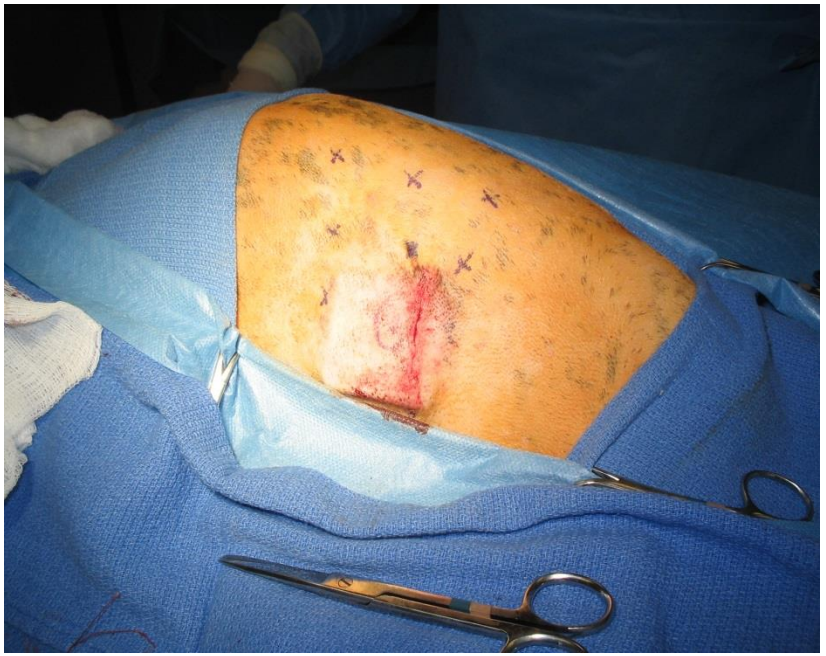
[1] Toda, K et al. Revascularization in Sever Ventricular Dysfunction (15% ≤LVEF≤30%): A Comparison of Bypass Grafting and Percutaneous Intervention. Annals of Thoracic Surgery 2002;74:2082-2087.
[2] Halkin, A et al. Prediction of Mortality After Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction: CADILLAC Risk Score. JACC 2005;45:1397-1405.
[3] Stone, G et al. Prevention of Sudden Cardiac Arrest Post PTCA in High-Risk Patients. http://www.theheart.org/article/1202823.do (April 2011).
[4] Ortolani, P et al. Predictive value of high sensitivity C-reactive protein in patients with ST-elevation myocardial infarction treated with percutaneous coronary intervention. European Heart Journal 2007; 29:1241-1249.

Mechanisms of Electrical Changes

- Alterations in ion channels of both infarcted and non-infarcted tissue = changes in excitability, conduction times, and repolarization, promoting re-entry
- Cellular hypertrophy in non-infarcted myocardium can lead to prolongation of the action potential duration/heterogeneity of repolarization
- Regional changes in neurohormonal agents, fibrosis, neuronal remodeling and abnormal automaticity

Chronic Ambulatory Subcutaneous Sensor Implanted in a Dog

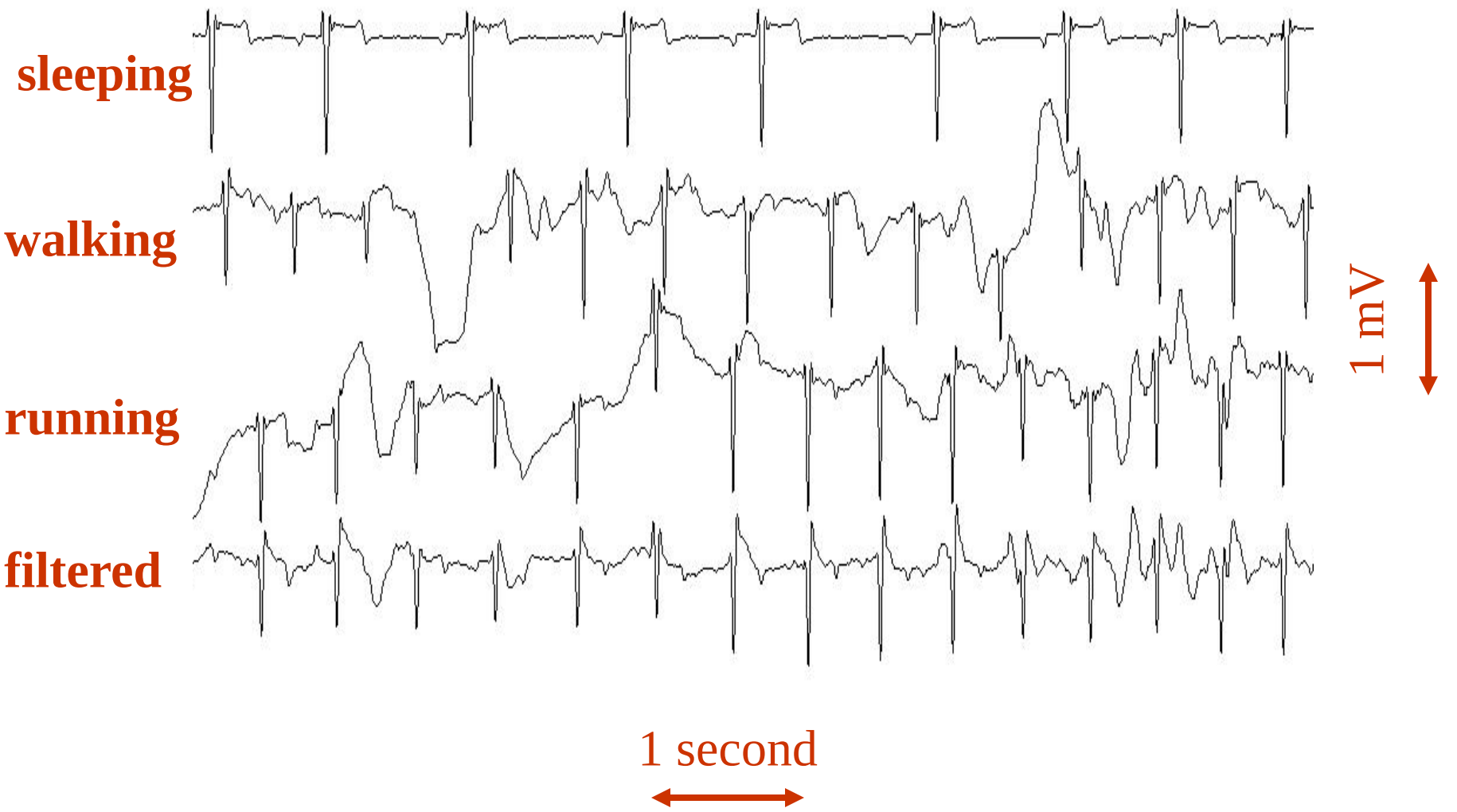




Sensor contains two ECG amplifiers, microprocessor, memory, transceiver, battery. It transmits the event and ECG to an external receiver.

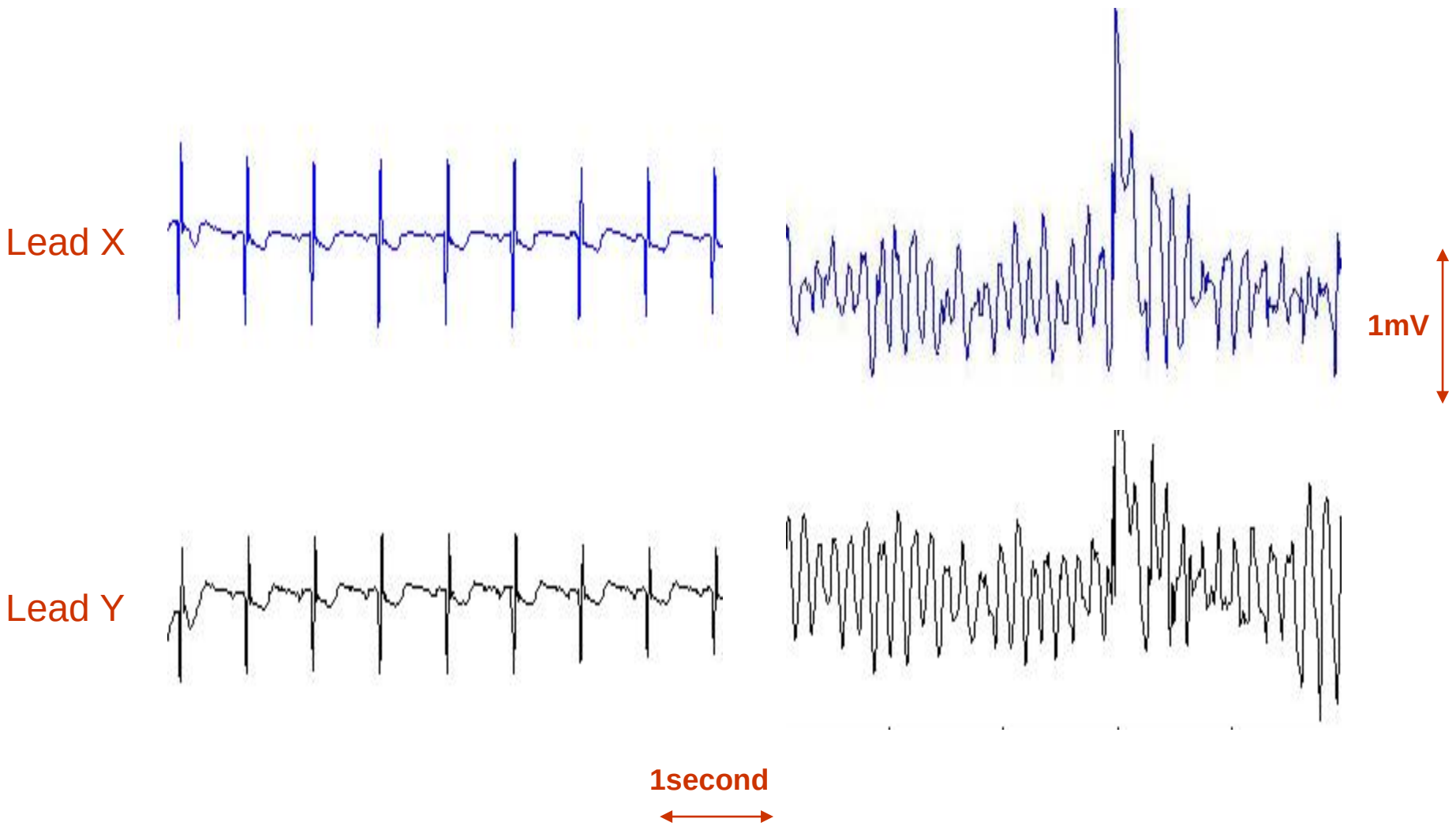
Burke et al Circ 2006

ECGs Transmitted from Chronic SQ Sensor Implant



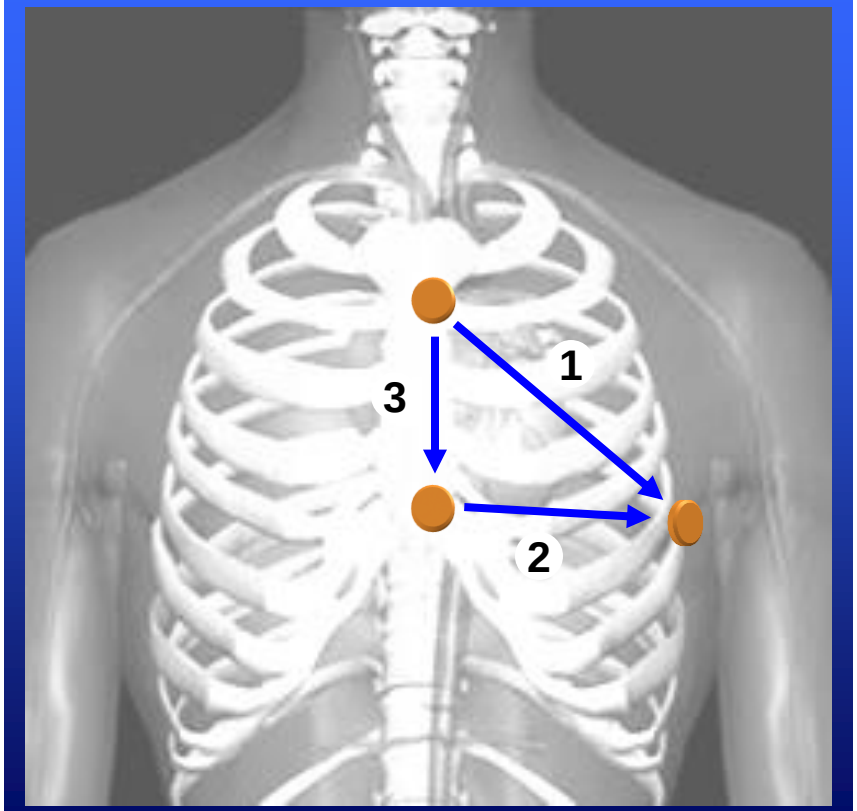
Dog 4 Day 49

Sinus rhythm **Ventricular fibrillation**

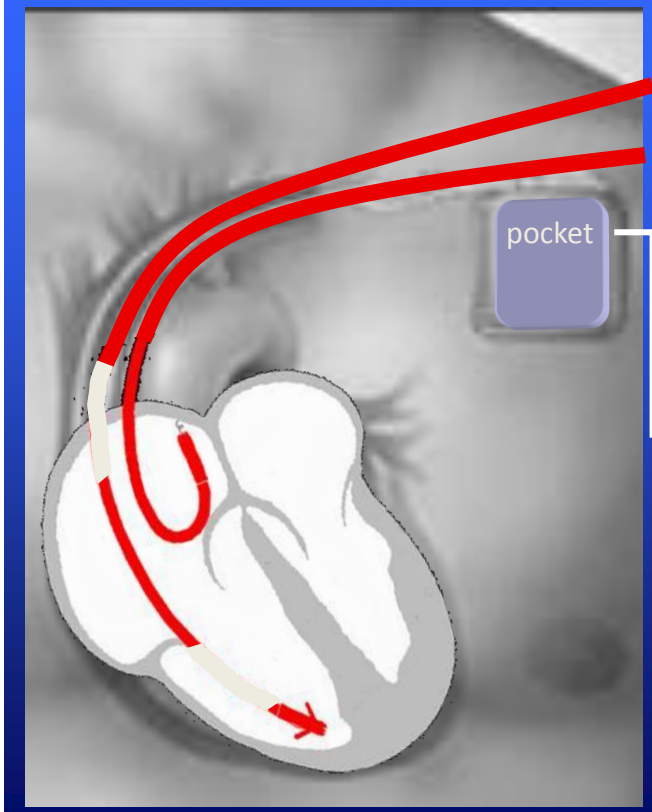


Cutaneous Arrhythmia Library

Subcutaneous equivalent cutaneous connections



Transvenous pocket and lead connections



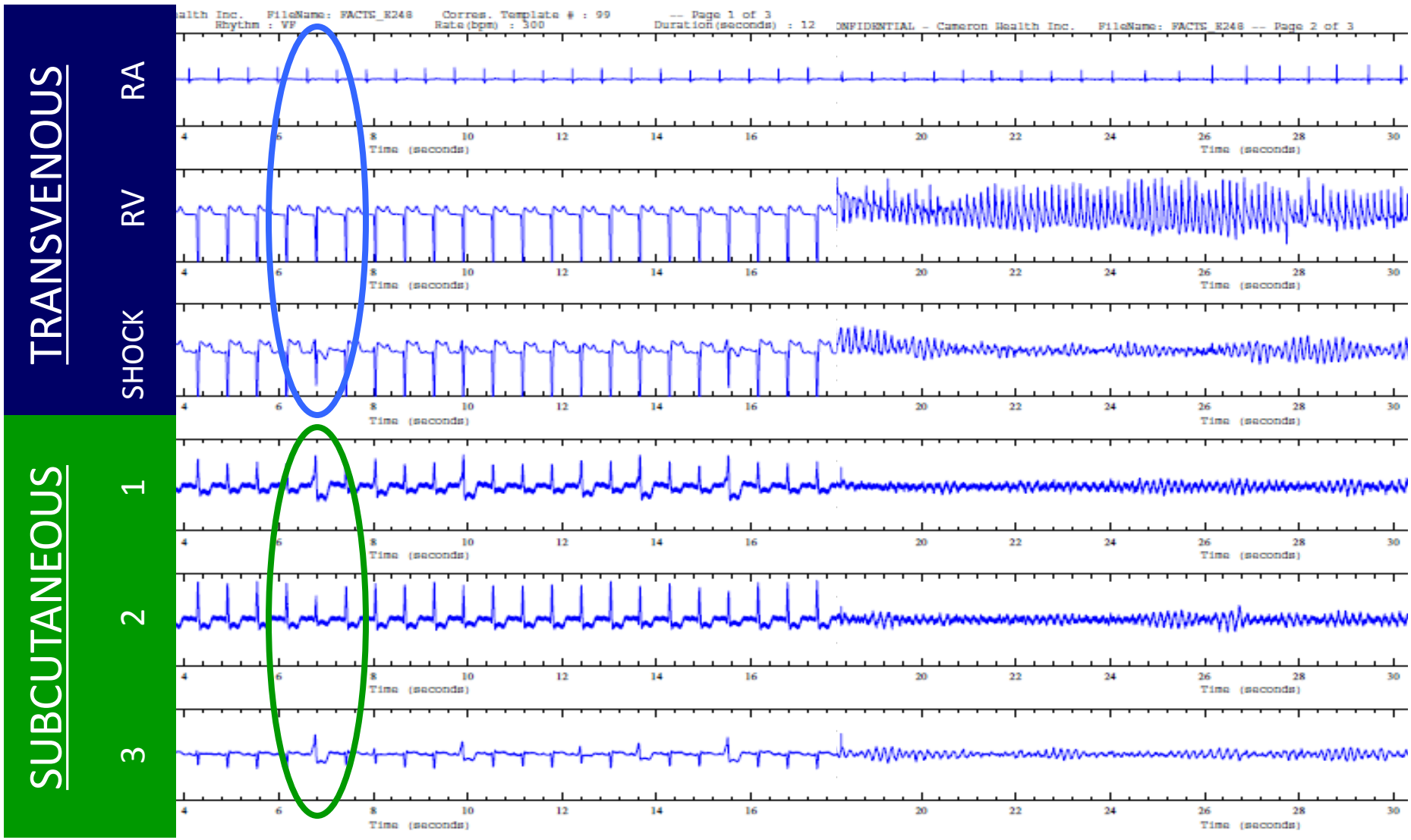
VENTRICULAR
- IS-1 ring
- IS-1 tip
- DF-1 distal
- DF-1 prox

ATRIAL
- IS-1 ring
- IS-1 tip

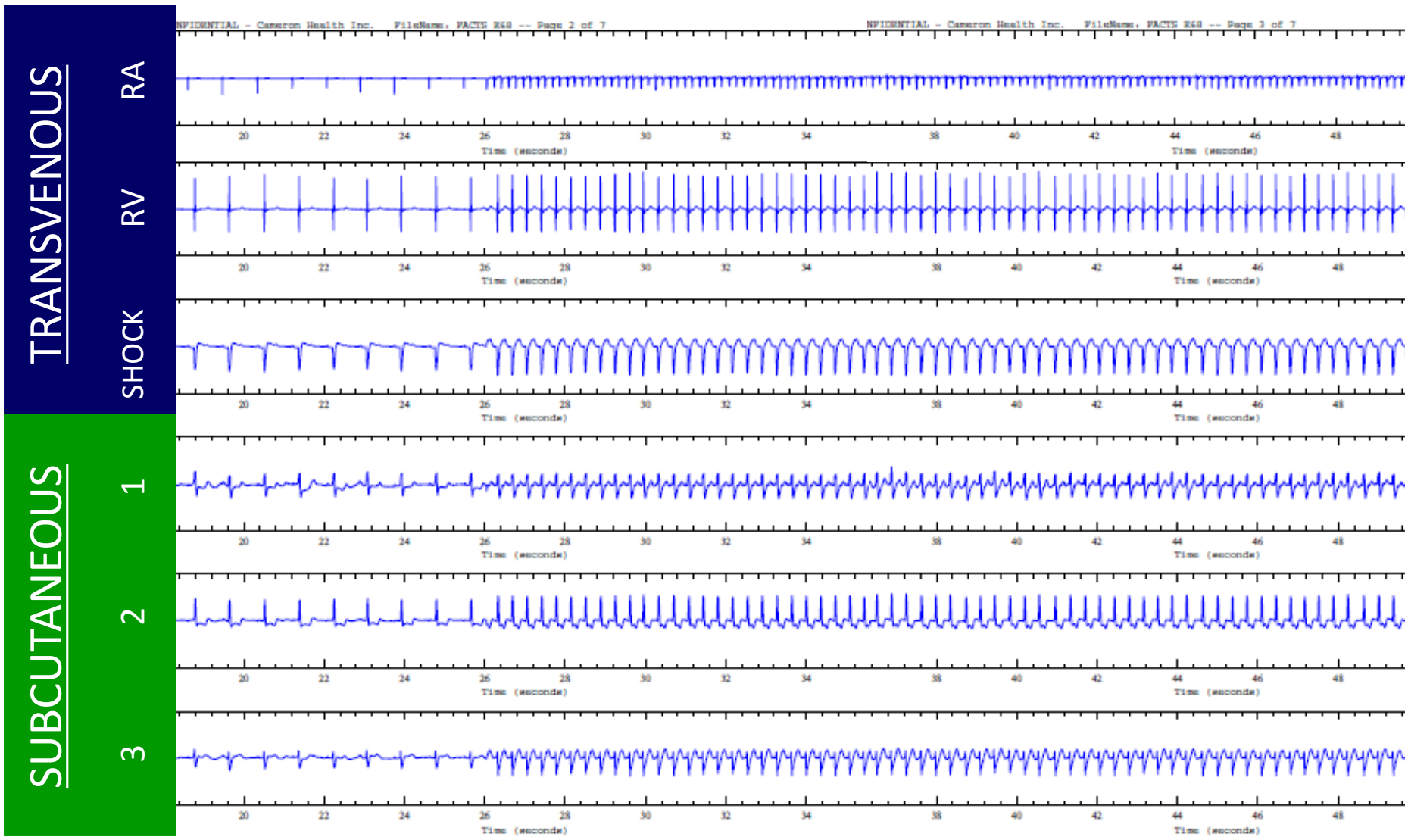
POCKET
- CAN

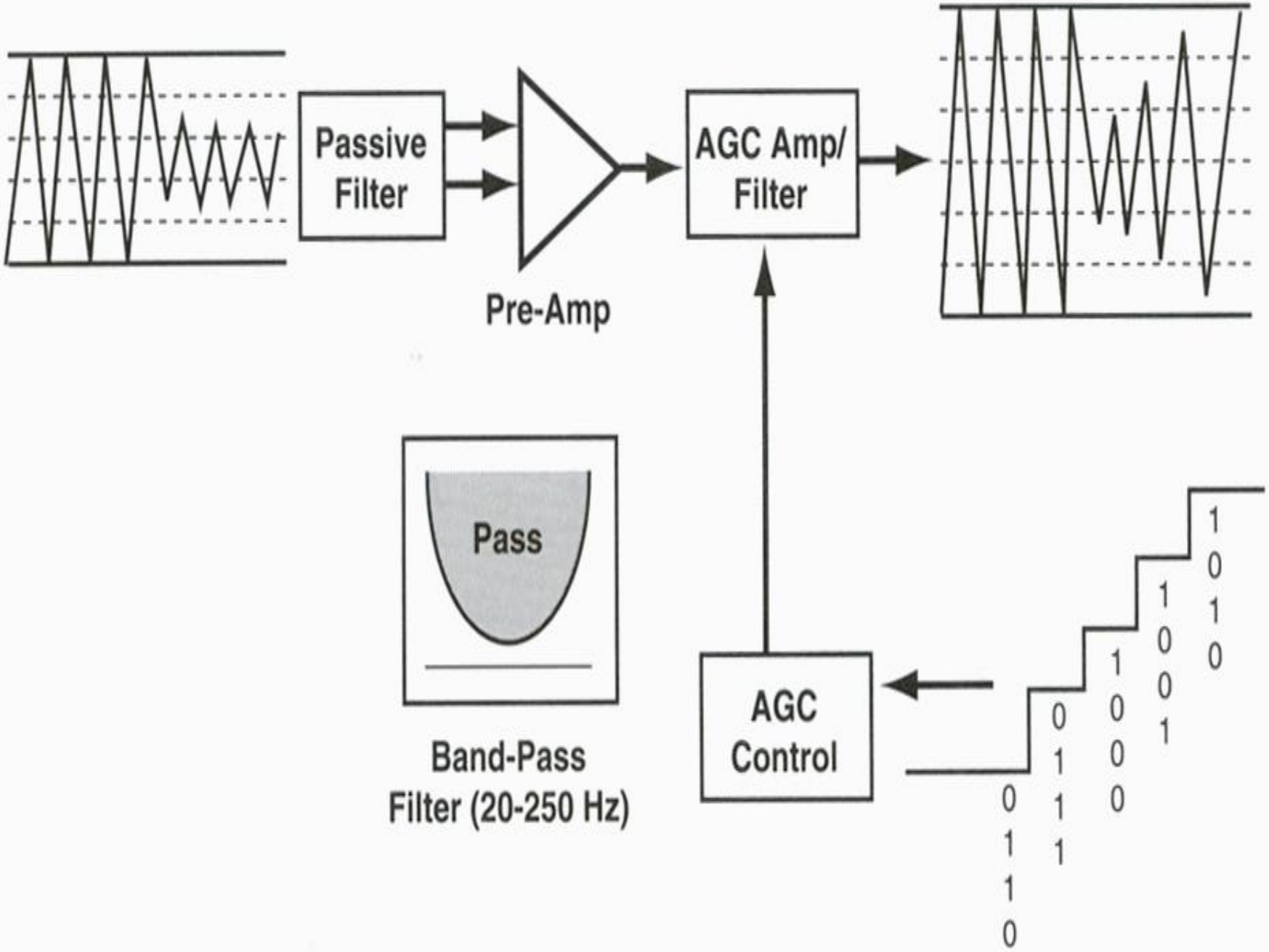
Gold et al JCE 2012

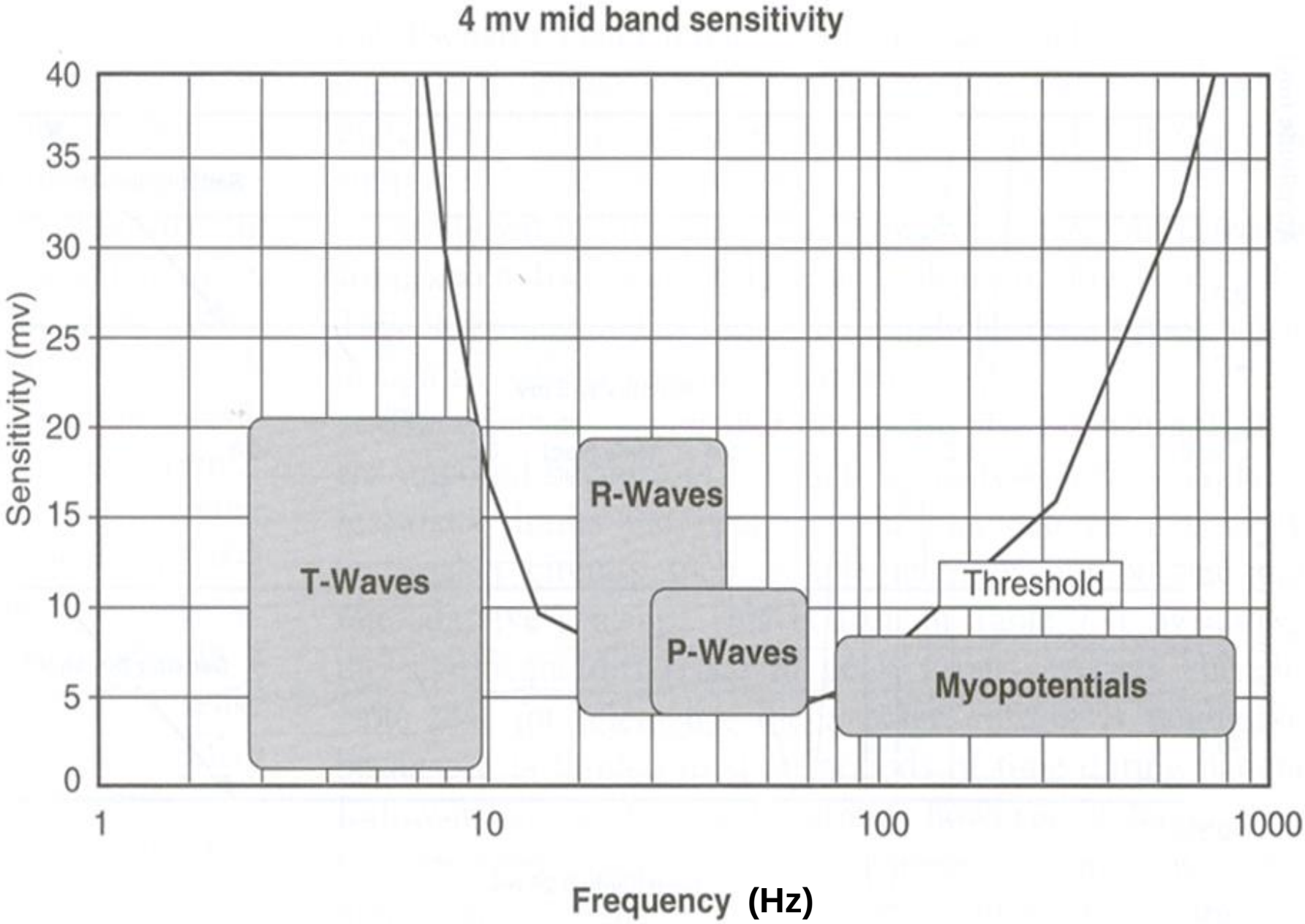
Sample Shockable Arrhythmia



Sample Non-Shockable Arrhythmia




Passive Filter
Pre-Amp
AGC Amp/ Filter
Pass
Band-Pass Filter (20-250 Hz)
AGC Control
0 1 1 0
0 1 1 1
1 0 0 0
1 0 0 1
1 0 1 0


4 mv mid band sensitivity
Sensitivity (mv)
40
35
30
25
20
15
10
5
0
1
10
100
1000
Frequency (Hz)
T-Waves
R-Waves
P-Waves
Myopotentials
Threshold

Initial Vector Testing

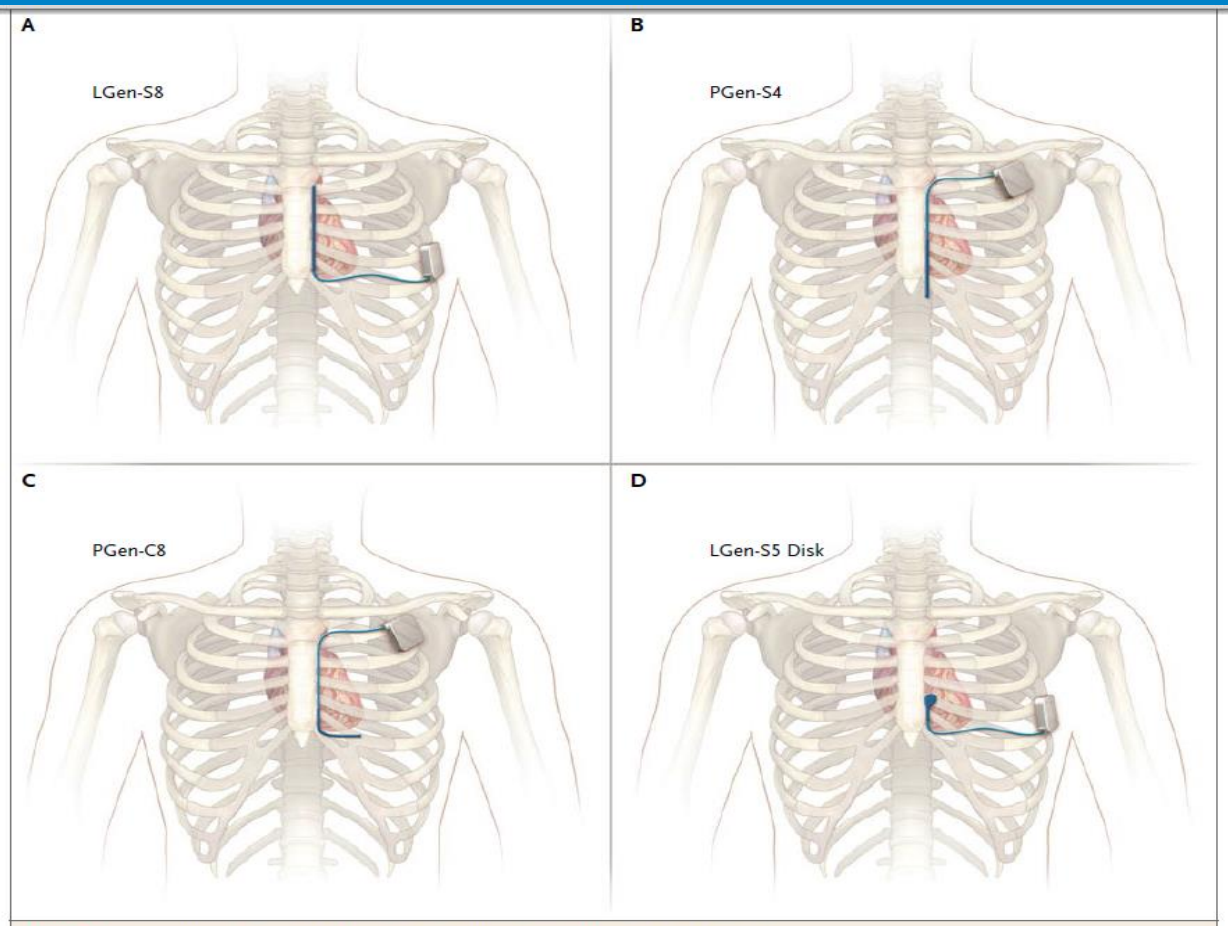
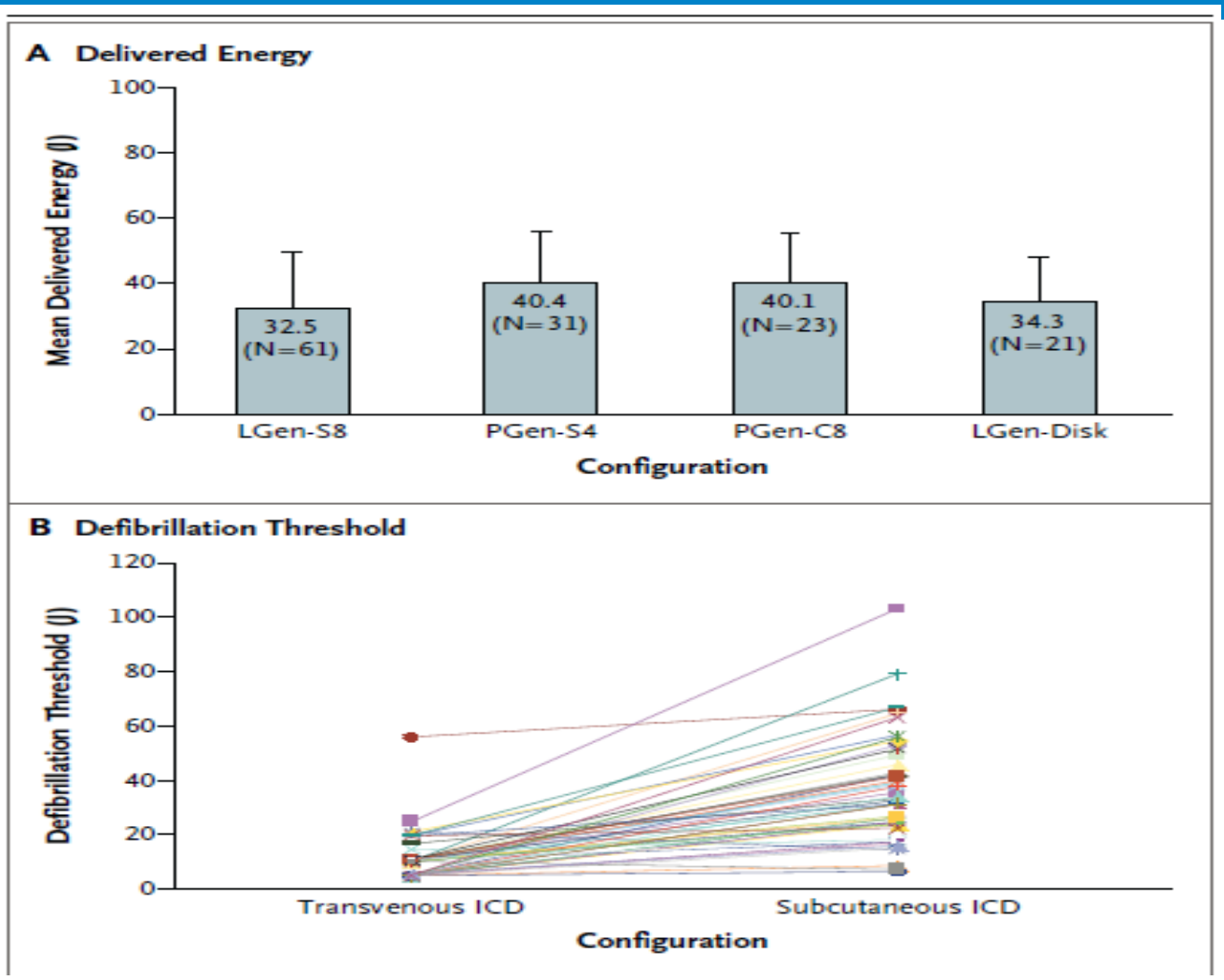


Figure 1. Four Configurations of a Subcutaneous Implantable Cardioverter–Defibrillator.
The four lead systems that were tested to select the best of these candidates were a left lateral pulse generator with an 8-cm coil electrode positioned at the left parasternal margin, designated LGen-S8 (Panel A); a left pectoral pulse generator with a left parasternal 4-cm coil electrode at the inferior sternum, designated PGen-S4 (Panel B); a left pectoral pulse generator with an 8-cm coil electrode curving from the left inferior parasternal line across to the inferior margin of the left sixth rib, designated PGen-C8 (Panel C); and a left lateral pulse generator with a left parasternal 5-cm² oval disk, designated LGen-S5 (Panel D).

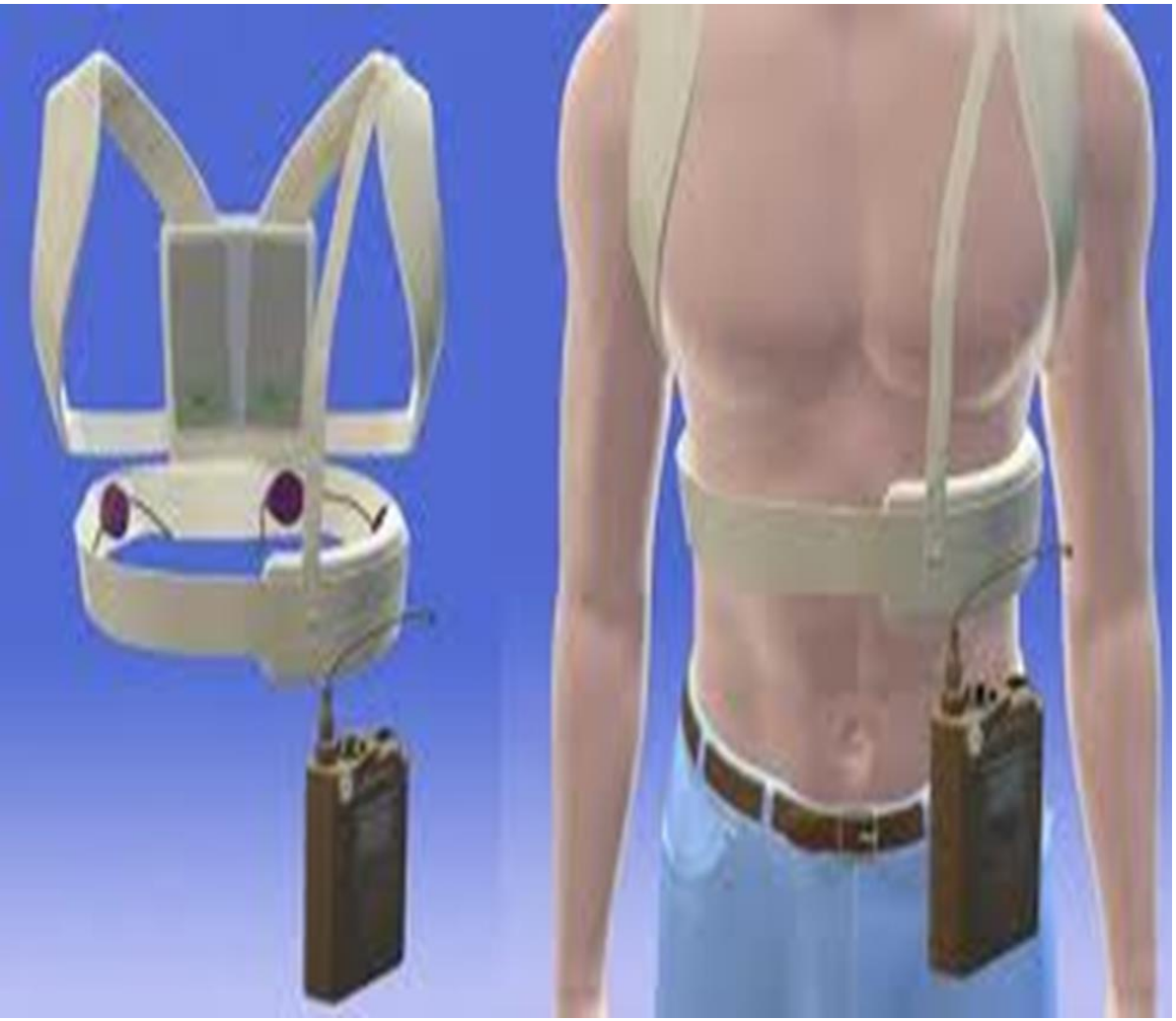
Bardy GH et al. NEJM 2010; DOI:10.1056

Vector DER



Bardy GH et al. NEJM 2010; DOI:10.1056

LifeVest System



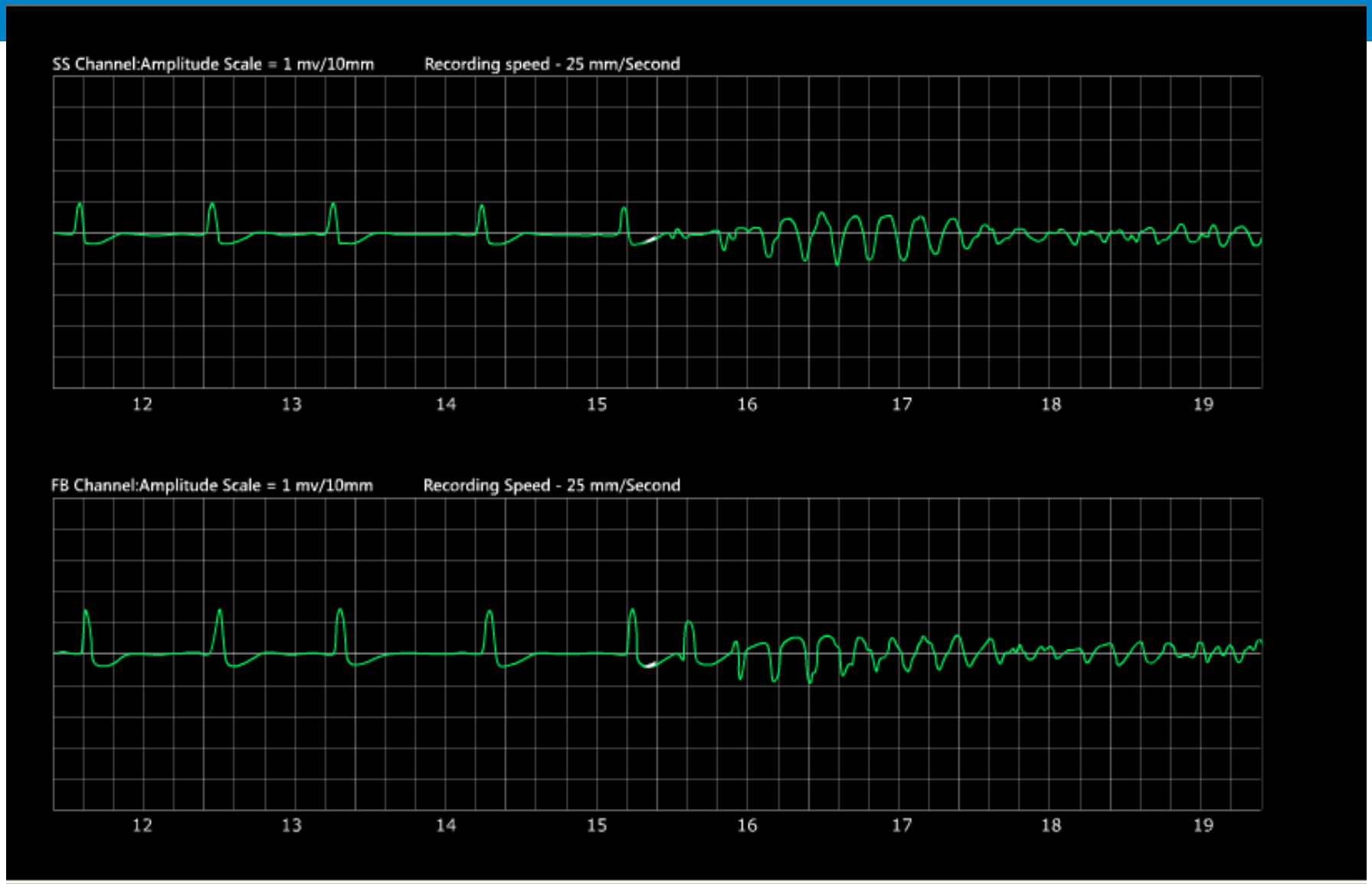
Shock energy 150 Joule

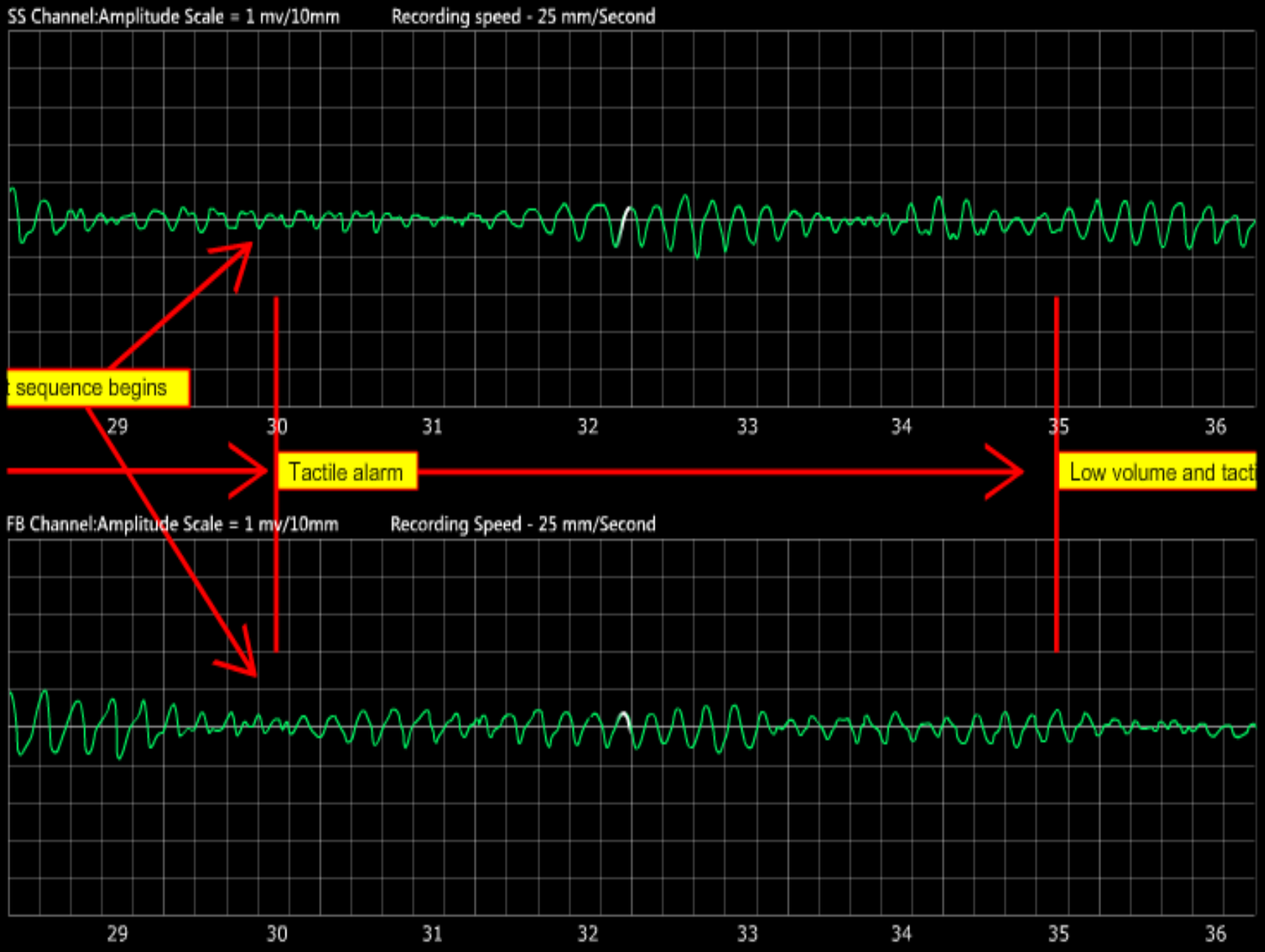
Biphasic shock

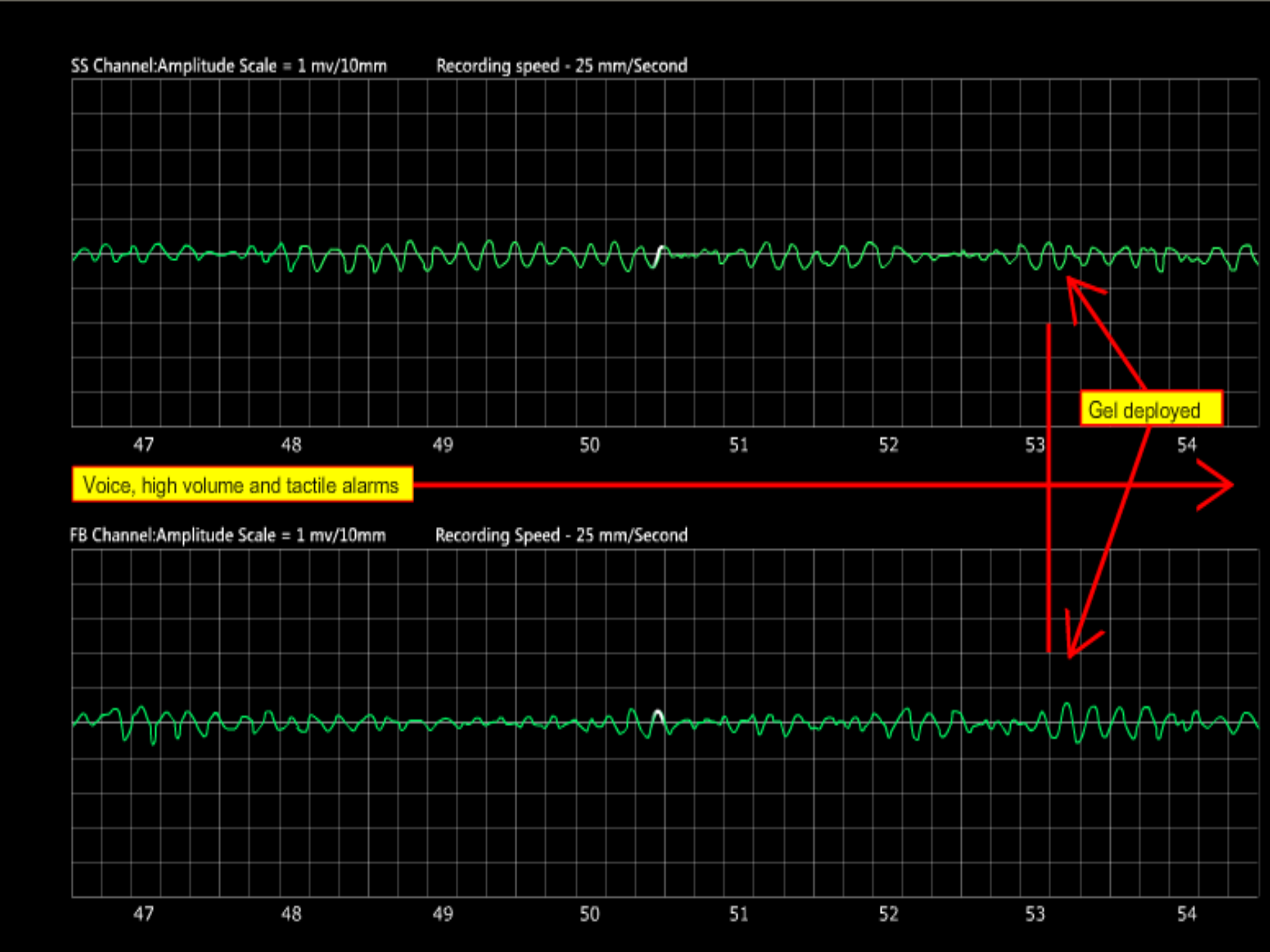
Detection time is approx. 15 seconds

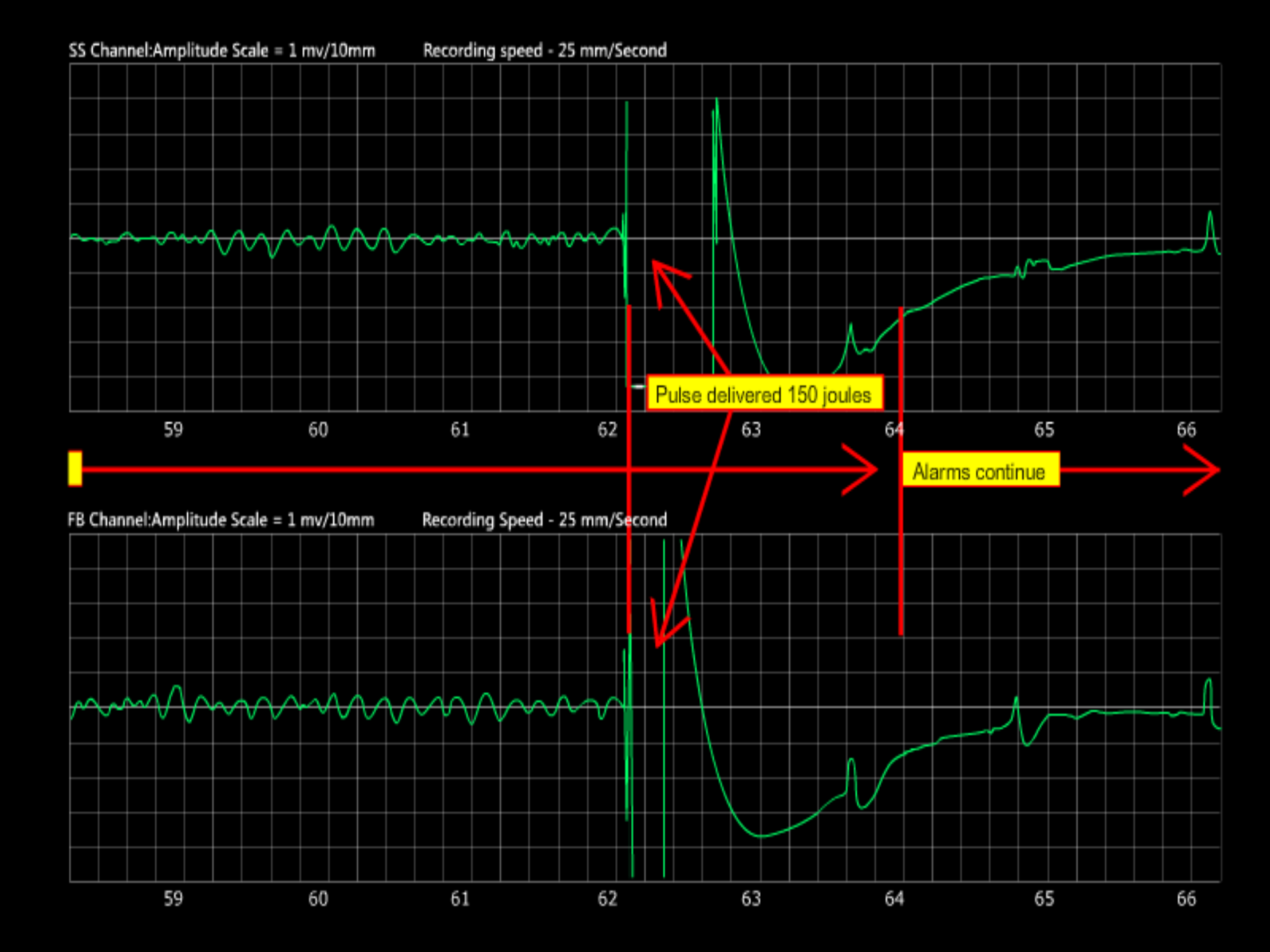
Charge time is less than 10 seconds to maximum output

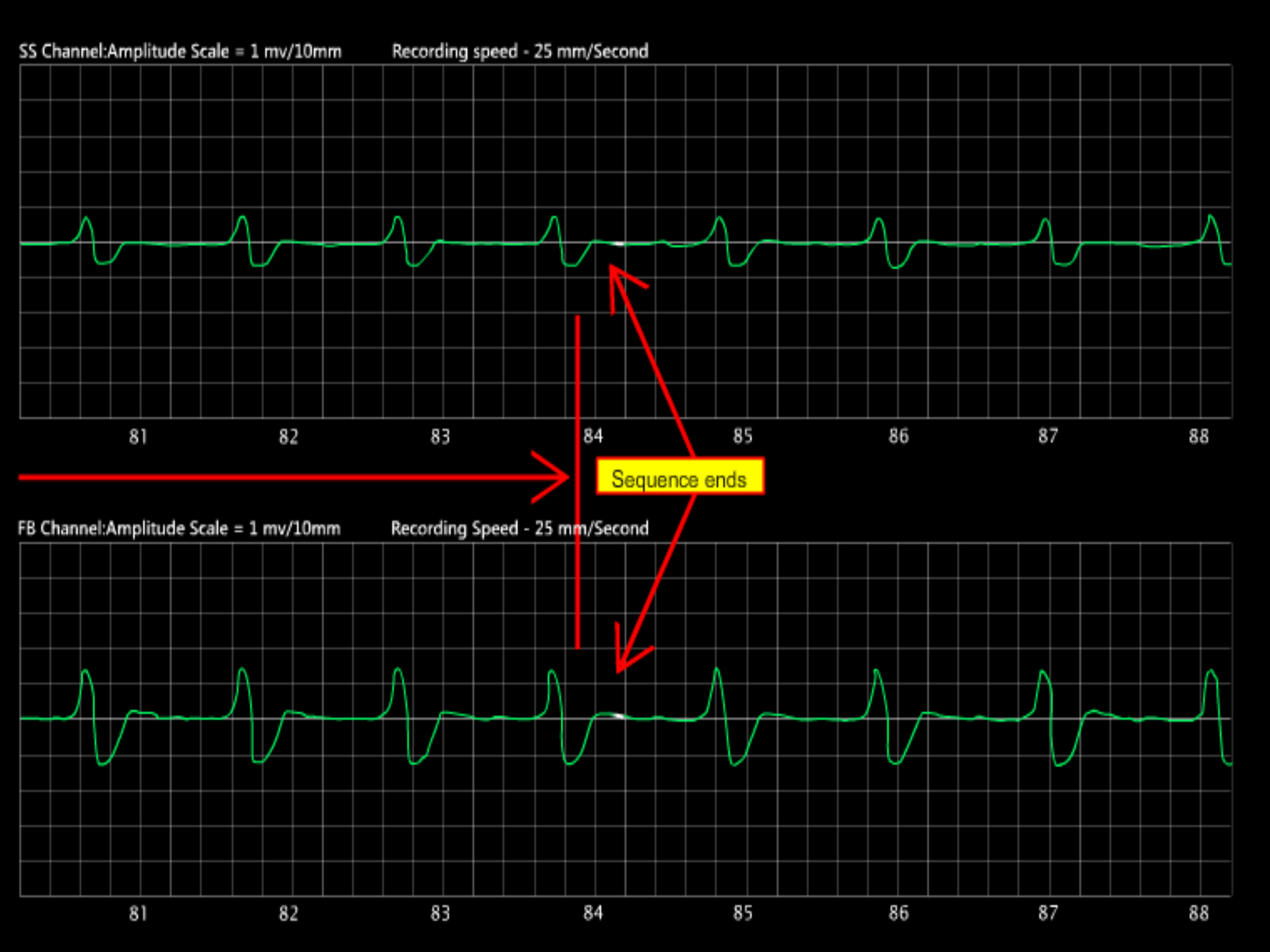
LifeVest Sensing




SS Channel:Amplitude Scale = 1 mv/10mm
Recording speed - 25 mm/Second
sequence begins
29
30
31
32
33
34
35
36
Tactile alarm
Low volume and tact
FB Channel:Amplitude Scale = 1 mv/10mm
Recording Speed - 25 mm/Second
29
30
31
32
33
34
35
36


SS Channel:Amplitude Scale = 1 mv/10mm
Recording speed - 25 mm/Second
47
48
49
50
51
52
53
54
Gel deployed
Voice, high volume and tactile alarms
FB Channel:Amplitude Scale = 1 mv/10mm
Recording Speed - 25 mm/Second
47
48
49
50
51
52
53
54

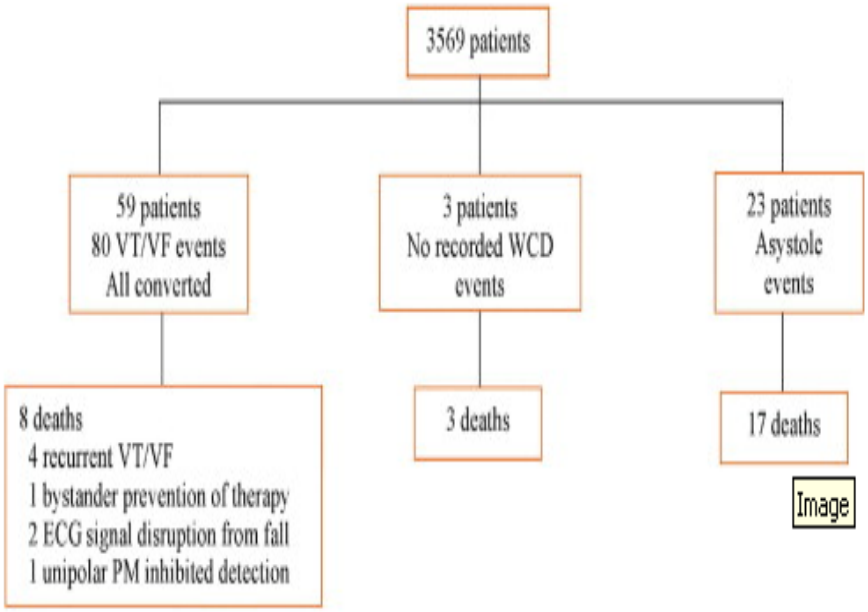

SS Channel:Amplitude Scale = 1 mv/10mm
Recording speed - 25 mm/Second
Pulse delivered 150 joules
59
60
61
62
63
64
65
66
Alarms continue
FB Channel:Amplitude Scale = 1 mv/10mm
Recording Speed - 25 mm/Second
59
60
61
62
63
64
65
66

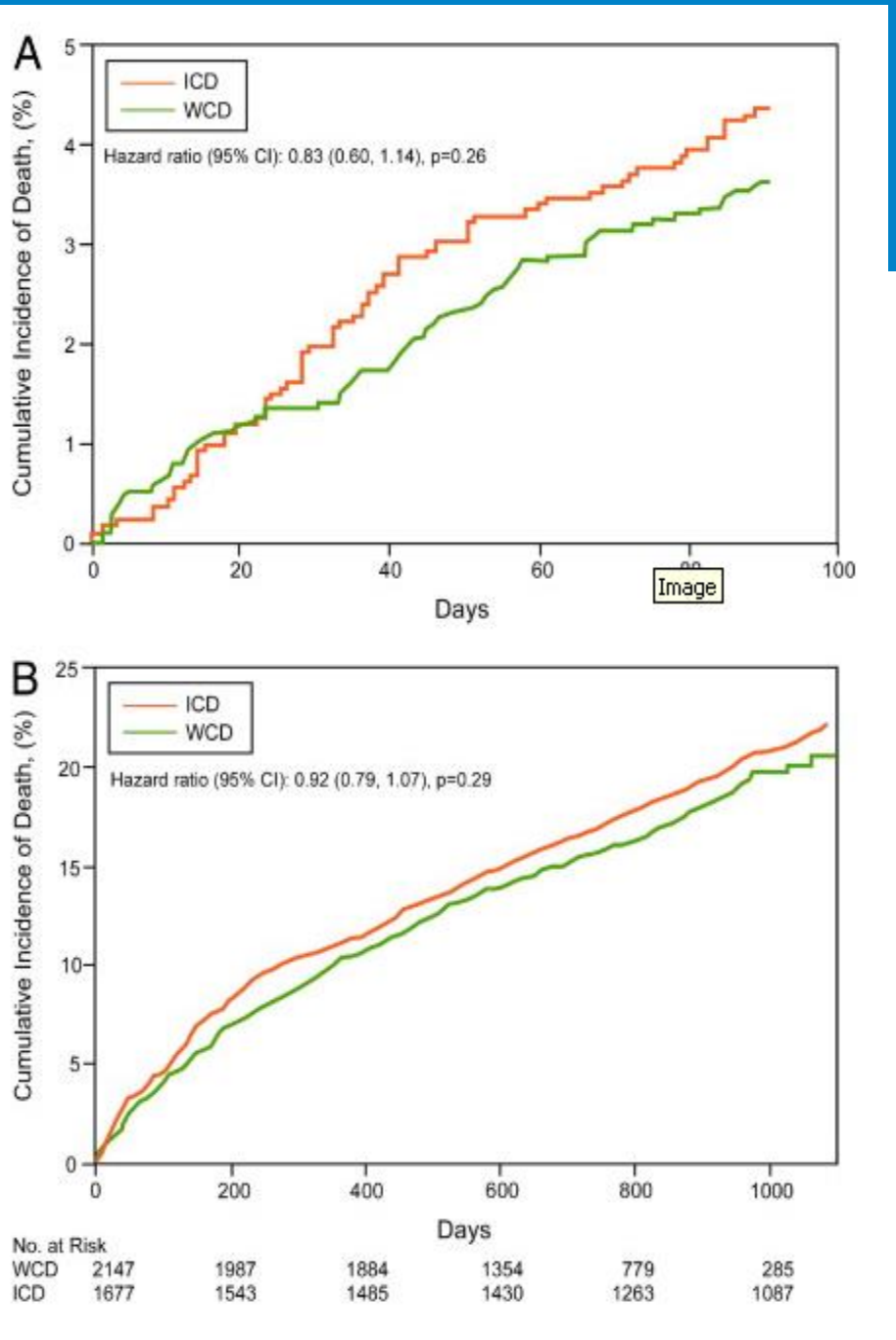

SS Channel:Amplitude Scale = 1 mv/10mm
Recording speed - 25 mm/Second
81
82
83
84
85
86
87
88
Sequence ends
FB Channel:Amplitude Scale = 1 mv/10mm
Recording Speed - 25 mm/Second
81
82
83
84
85
86
87
88

Aggregate National Experience with Wearable Cardioverter Defibrillator:

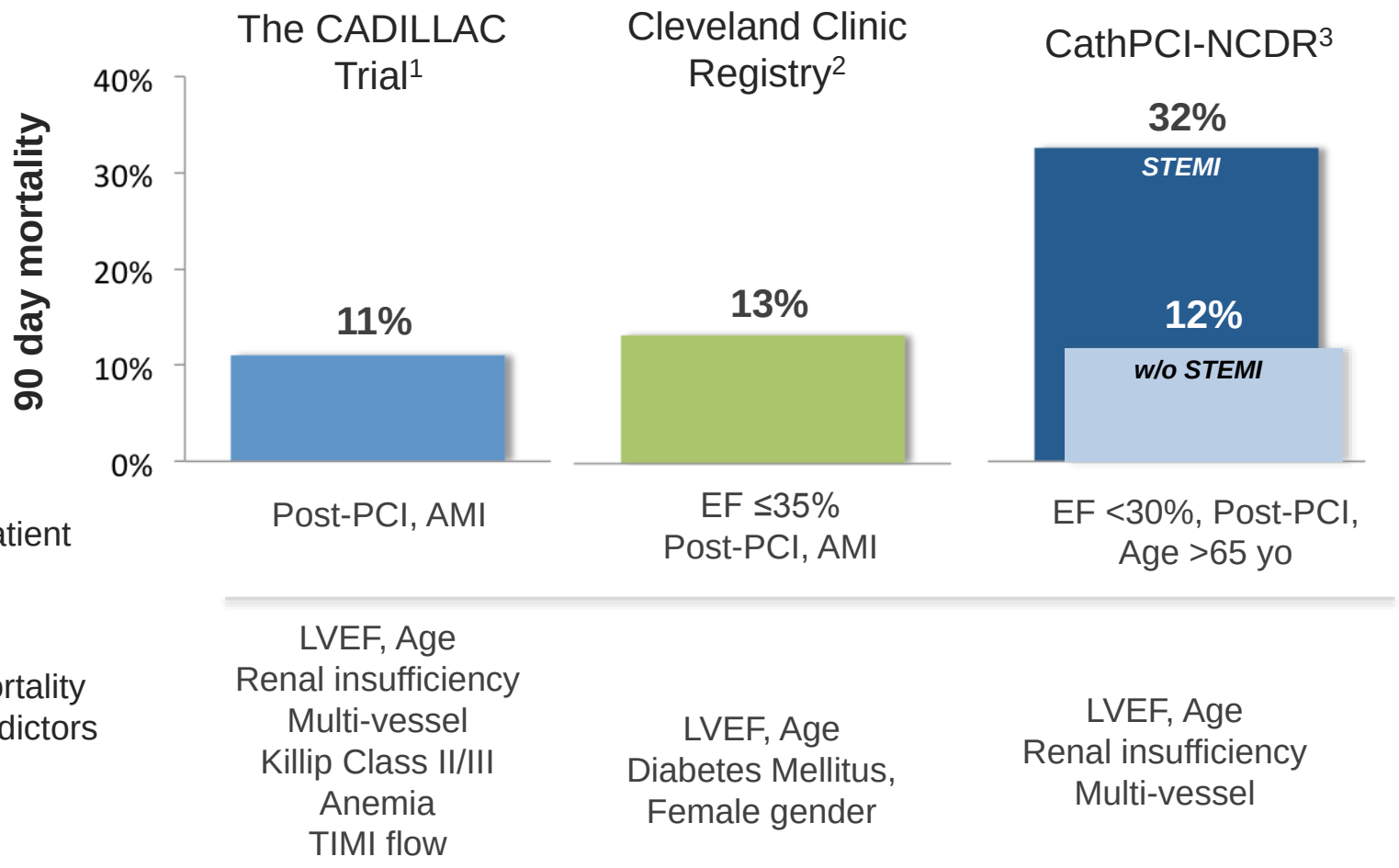
Event rates, Compliance, Survival

Chung et al. JACC 2010; 5(3): 194.





Wealth of Evidence Supports Post-PCI Risk



[1] Halkin, A et al. Prediction of Mortality After Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction: CADILLAC Risk Score. JACC 2005;45:1397-1405.
[2] Zishiri ET, et al. Early Risk of Mortality after Coronary Artery Revascularization in Patients with Left Ventricular Dysfunction and Potential Role of the Wearable Cardioverter Defibrillator. Circulation: Arrhythmia and Electrophysiology; 2013;6: 117-128
[3] Weintraub et al. Prediction of Long-Term Mortality After Percutaneous Coronary Intervention in Older Adults: Results From the National Cardiovascular Data Registry. Circulation 2012;125:1501-1510.

The CADILLAC Trial
Prediction of Mortality Post-PCI

- **Objective**
  - Develop a simple risk score for predicting mortality after primary PCI
- **Methodology**
  - Use of CADILLAC trial database: 2,082 post-MI post-PCI patients
    - Randomized, double-blind, multicenter study
  - Validation of results to Stent-PAMI trial
- **SCD risk analysis**
  - Goal was to develop a simple risk score for predicting mortality after primary PCI

Halkin, A et al. Prediction of Mortality After Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction: CADILLAC Risk Score. JACC 2005;45:1397-1405.

The CADILLAC Trial
Mortality Risk Factors

- **The CADILLAC Risk Score defines low-, medium-, and high-risk groups**
  - High risk group defined as a score ≥6
  - 20% of post-PCI patients
  - Baseline LVEF is the most powerful predictor of mortality
  - Other risk factors include renal insufficiency, Killip class II/III, age >65 y, anemia, and three vessel disease.

- **Low LVEF plus any other risk factor = HIGH risk**

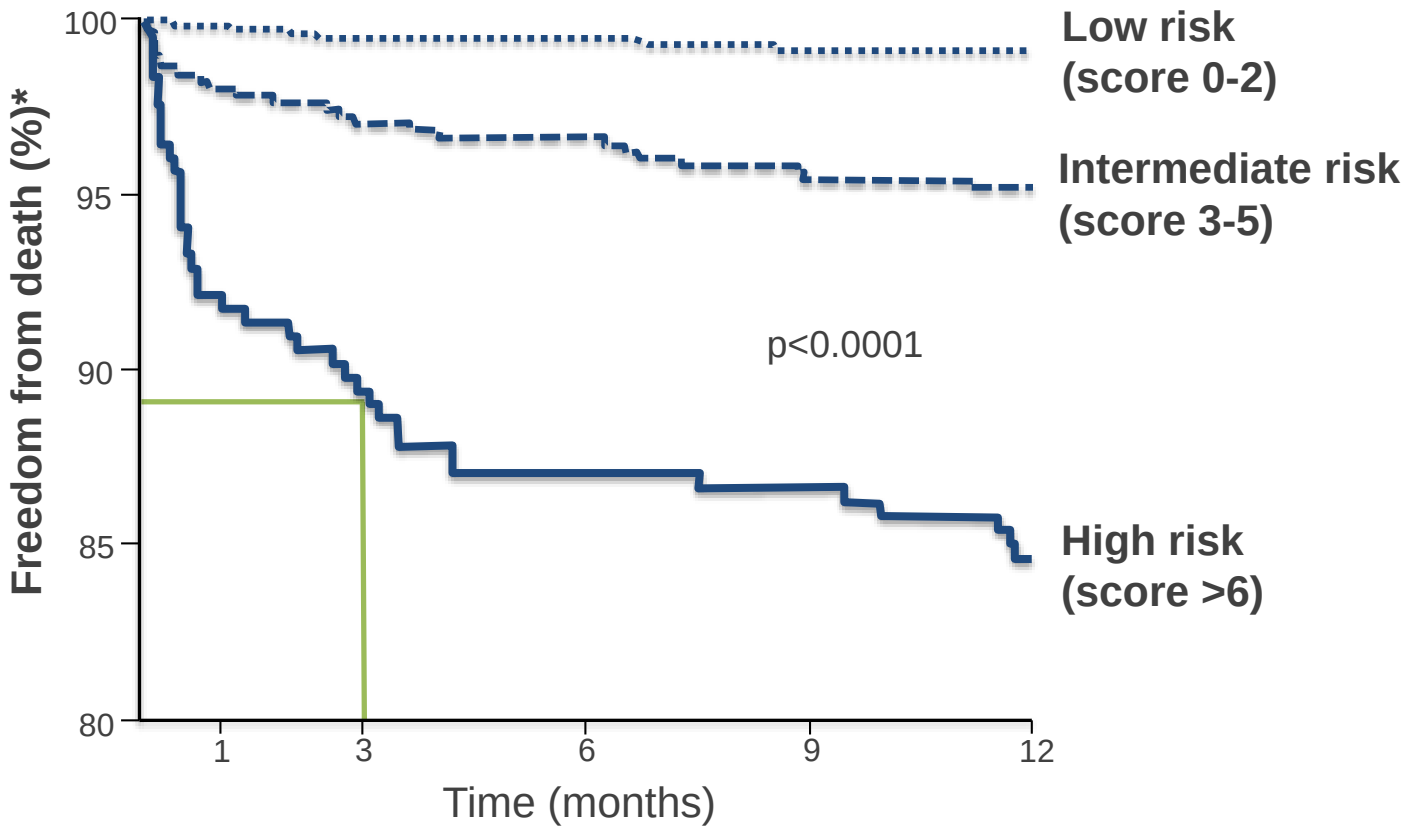
Risk Factors	Score
Baseline LVEF <40%	4
Renal Insufficiency	3
Killip Class II/III	3
Age >65	2
Final TIMI flow 0-2	2
Three-Vessel Disease	2
Anemia	2

CADILLAC Risk Score	Risk Category
Score ≥6	High
Score 3-5	Intermediate
Score 0-2	Low

Halkin, A et al. Prediction of Mortality After Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction: CADILLAC Risk Score. JACC 2005;45:1397-1405.

The CADILLAC Trial

High Early Mortality Post-PCI



** 60% of mortality due to SCD[1]*

[1]Stone, G et al. "Prevention of Sudden Cardiac Arrest Post PTCA in High-Risk Patients." April 2011. Available at http://www.theheart.org/article/1202823.do.

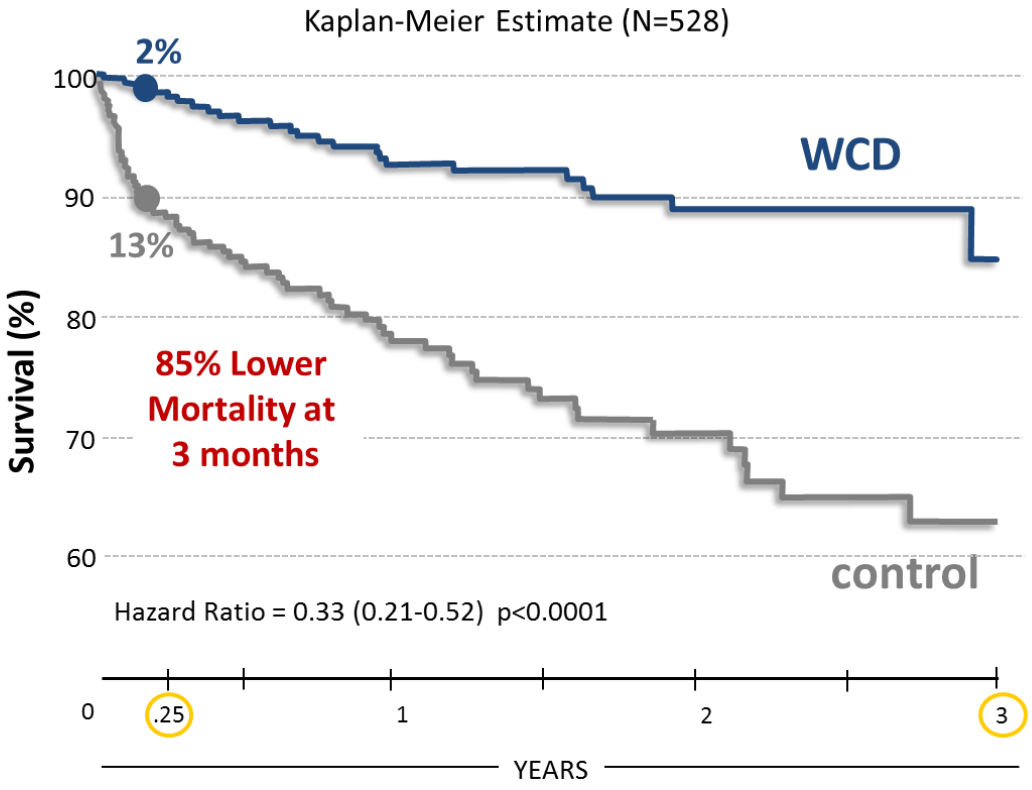
Cleveland Clinic Post-PCI Registry
Objectives and Methodology

- **Objective**
  - Assess difference between early vs. late mortality in patients with EF≤35% post-PCI
  - Determine if WCD use is associated with better survival in post-PCI patients with EF≤35%
- **Methodology**
  - Retrospective study
    - Cleveland Clinic registry (n=1951)
    - WCD national database users (n=288)
  - 2,239 low EF post-PCI patients from Aug 2002 – Dec 2009
  - Kaplan-Meier analysis used to determine difference in survival for both cohorts
  - Propensity score matching used to mitigate bias in data by selecting non-WCD patients similar to patients prescribed the LifeVest WCD

Zishiri ET, et al. Early Risk of Mortality after Coronary Artery Revascularization in Patients with Left Ventricular Dysfunction and Potential Role of the Wearable Cardioverter Defibrillator. Circulation: Arrhythmia and Electrophysiology; 2013;6: 117-128

Cleveland Clinic Post-PCI Registry

LifeVest use associated with improved survival



LifeVest	264	210	172	82	19
control	264	186	134	65	31

- **Post-PCI low EF (≤35%) patients prescribed the LifeVest had an 85% lower 90-day mortality** (2%) compared to a matched cohort of patients not prescribed the LifeVest (13%)
- **WCD use associated with a 57% lower risk of death** (p<0.0001) over a mean follow-up of over 3 years in the total post-PCI cohort

Zishiri ET, et al. Early Risk of Mortality after Coronary Artery Revascularization in Patients with Left Ventricular Dysfunction and Potential Role of the Wearable Cardioverter Defibrillator. Circulation: Arrhythmia and Electrophysiology; 2013;6: 117-128

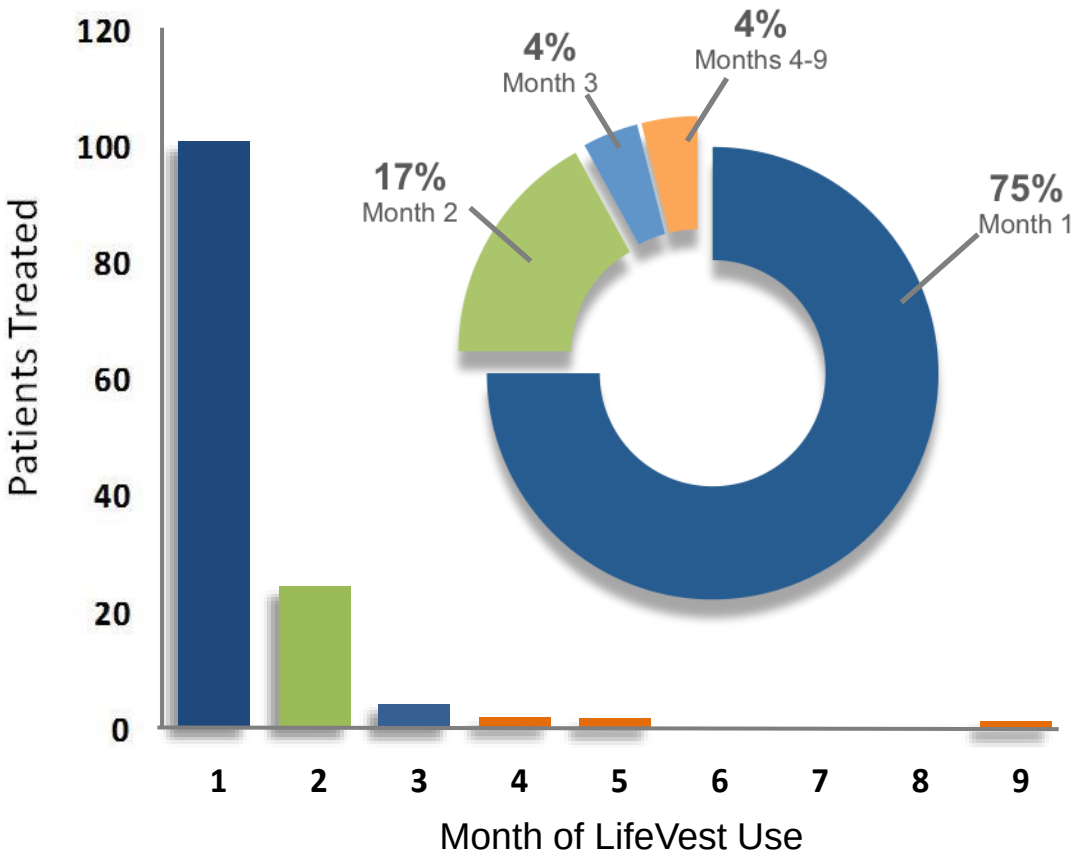
Cleveland Clinic Post-PCI Registry
Conclusions

- **Patients with LVEF ≤35% have higher early compared to late mortality after coronary revascularization**
- **Post-PCI patients with EF ≤35% who were prescribed the WCD had:**
  - 85% lower 90-day total mortality (2%) compared to a matched cohort of patients not prescribed the WCD (13%)
- **WCD use associated with significant reduction in total mortality in patients with EF ≤35% following PCI**
  - 57% lower risk of death ($p<0.0001$) over a mean follow-up of over 3 years in the total post-PCI cohort
  - Following the end of WCD use, a persistent survival benefit was observed out to 3 years

Zishiri ET, et al. Early Risk of Mortality after Coronary Artery Revascularization in Patients with Left Ventricular Dysfunction and Potential Role of the Wearable Cardioverter Defibrillator. Circulation: Arrhythmia and Electrophysiology; 2013;6: 117-128

WCD Use Post-MI
Results

75% of Treated Patients Received Therapy during the first 30 days post-MI[1]



- **1.6% of patients treated by WCD**
- **Median time to treatment was 16 days in all patients**
  - Revasc.: 14 days
- **96% received therapy in first 3 months**
- **WCD use resulted in post-event survival of 91%**
  - Revasc.: 95%
  - No Revasc.: 84%

[1] Epstein AE, Abraham WT, Bianco N, Kern KB, Mirro M, Rao SV, Rhee EK, Solomon SD, Szymkiewicz S, Wearable Cardioverter-Defibrillator Use in Patients Perceived to be at High Risk Early Post Myocardial Infarction, *Journal of the American College of Cardiology* (2013), doi:10.1016/j.jacc.2013.05.086.

Eighteen Month Results From the Prospective Registry And Follow-up Of Patients Using the LifeVest Wearable Defibrillator (WEARIT-II Registry)

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From the Cardiology Division of the Department of Medicine (I.G., HK, WZ, A.J.M) University of Rochester Medical Center, Rochester, N.Y.; Sheba Medical Center and Tel Aviv University, Israel (I.G.); and ZOLL, Pittsburgh, PA (SS, CW).

Presentation adapted from:

Goldenberg IL et al., Eighteen Month Results From The Prospective Registry And Follow-up Of Patients Using The LifeVest Wearable Defibrillator (WEARIT-II Registry), presented as Late Breaking Clinical Trial at Heart Rhythm, **May 10, 2013.** Available at *ow.ly/kZngG*.

Background

- **MADIT II**
  - Only one third of patients received an appropriate ICD therapy over 4 years of follow-up[1]

- **MADIT RIT**
  - Rate of appropriate ICD shocks was only 4% -- the overall appropriate shock rate was 3 events / 100 patient years[2]

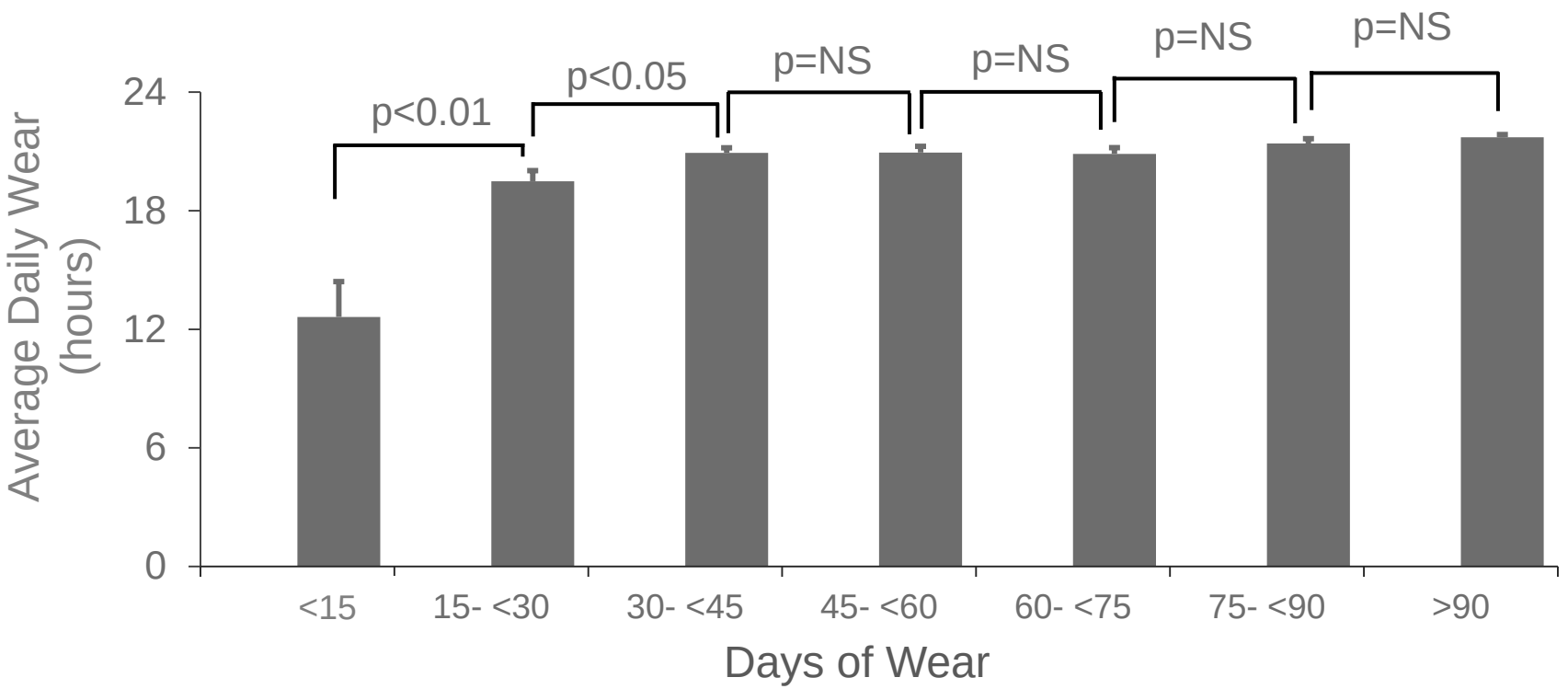
1. Moss AJ, Zareba W, Hall WJ, et al. (2002) Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 346: 877–883.

2. Moss AJ, Schuger C, Beck CA, et al. (2012) Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 367(24):2275-83.

WEARIT-II
Clinical Characteristics

	All patients N=882
Age, yrs	61 ± 12
Female	31%
LVEF, %	25 ± 11
Renal disease	8%
Diabetes	29%
Afib	28%
Prior cardiac arrest	22%
Beta-blockers	85%
ACE-I/ARBs	74%
Amiodarone	13%

WEARIT-II: Compliance



- **Daily wear time**
  - **Mean: 21 ± 3 hours**
  - **Median: 22 hours (IQ range 22-23 hours)**

WEARIT-II: Arrhythmic Events

	Patients	Events	Event Rate (per 100 pt/yrs)
WCD Therapy for VT/VF	10	17	9
Sustained VT (untreated)*	11	53	27
NSVT	9	93	47
Atrial arrhythmias/SVT	21	126	64
Asystole	2	5	3

* Spontaneously terminated; response button use/extended detection time

- Average wearing days: 81 ± 52

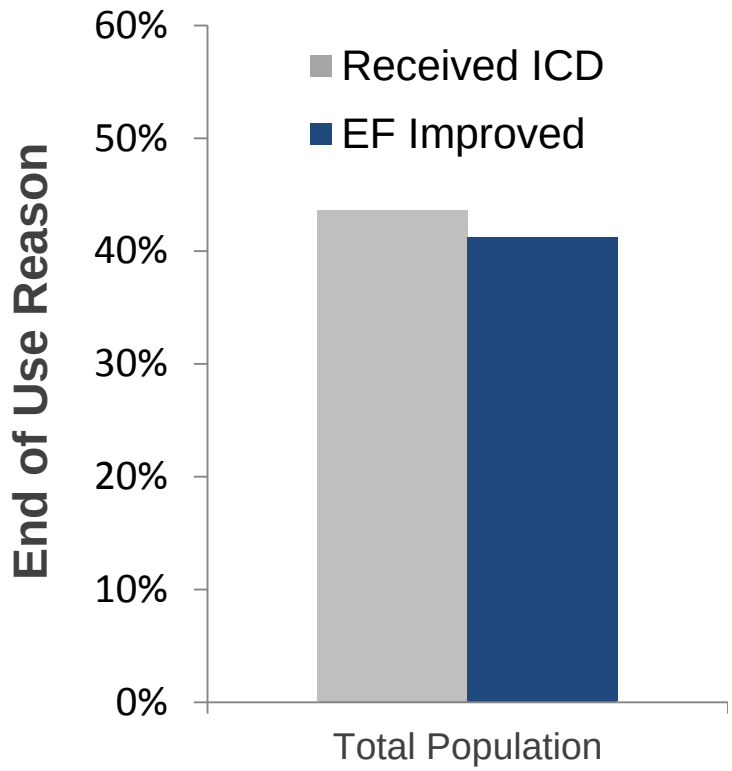
WEARIT-II: Adverse Events
Low occurrence of inappropriate therapies

TYPE	TOTAL POPULATION N=882
Inappropriate Rx, n (%)	3 (0.3%)
Death,* n (%)	4 (0.5%)

*3 deaths without wearing the WCD during hospitalization; 1 with WCD (asystole)

WEARIT-II
Outcomes following WCD use

- LV function improved in 41% of patients and did not need an ICD
- 43% of patients demonstrated persistent arrhythmic risk and received an ICD

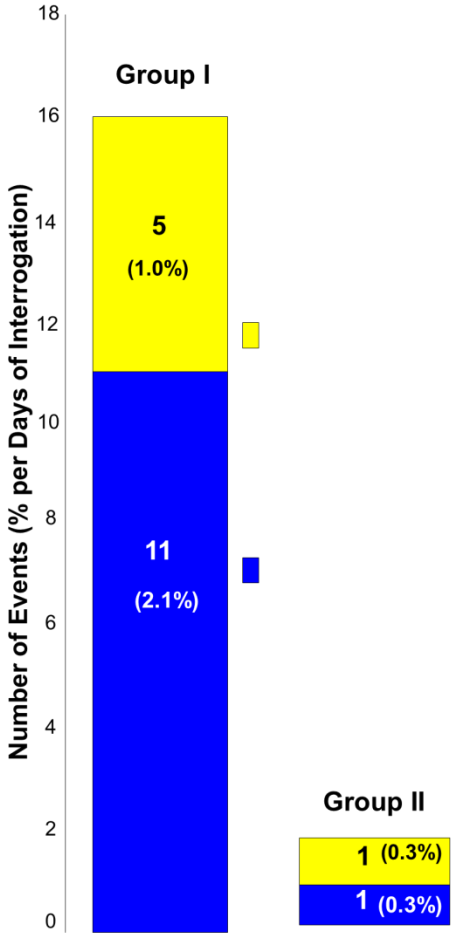


WEARIT-II: Conclusions

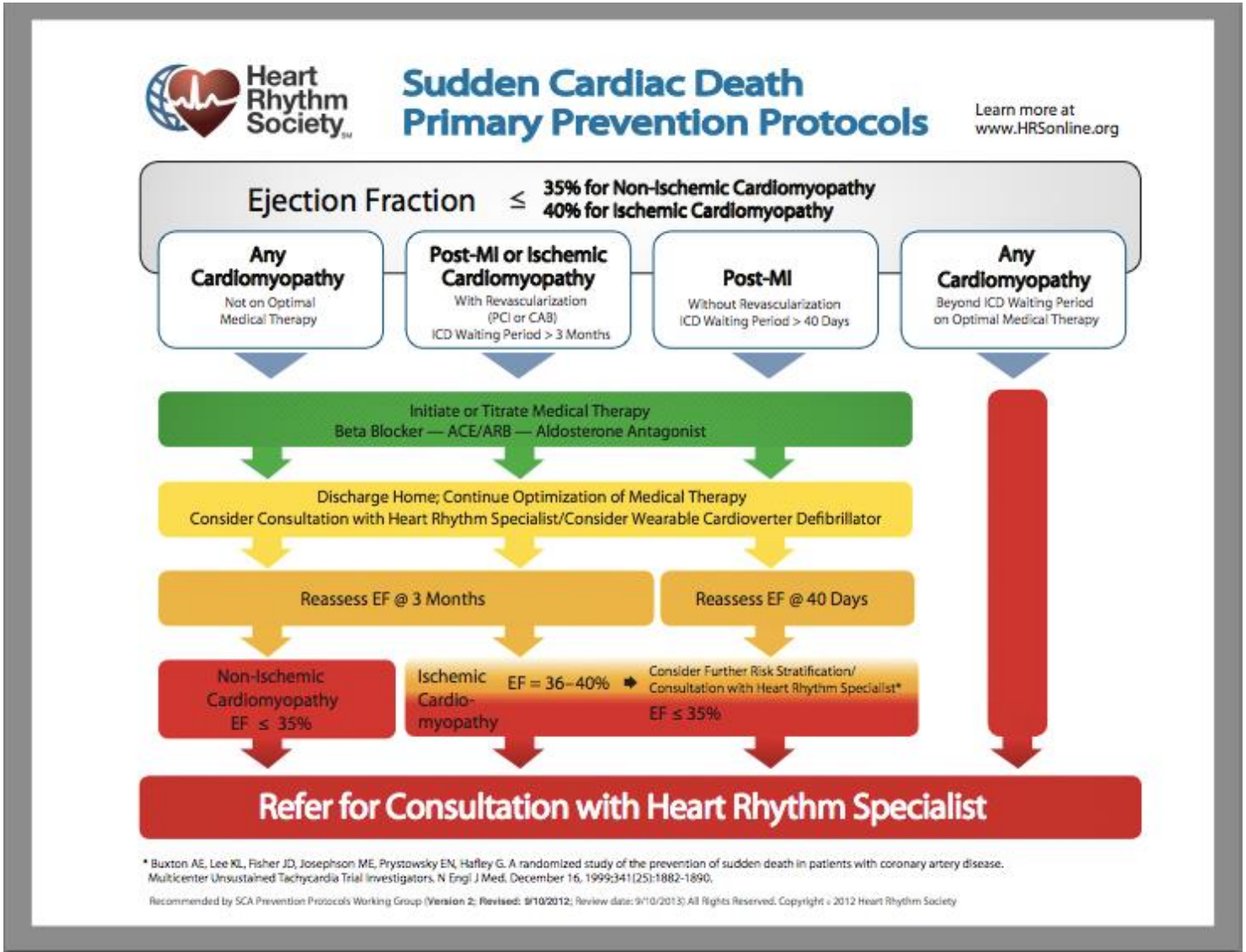
- **The LifeVest WCD can be used as part of a real world strategy for managing patients at risk of SCA**
  - Safe termination of life-threatening arrhythmic events
  - Avoidance of unnecessary therapies for non-life-threatening arrhythmias
  - Low rate of inappropriate therapies

Use of WCD is more common in patients with history of CIED Infection compared to post MI

	Group I	Group II
Total Number of Patients	10	11
Average age	70 +/- 11	60 +/- 15
Indication for WCD:		
-CIED Infection requiring extraction	10	-
-History of VT/VF	-	7
-New NICM, Requiring Medical Optimization	-	2
-Syncope and High-Risk of VT/VF - Takotsubo CM or Congenital Malformation	-	2
Patients with an CIED prior to WCD use	9	3
CIED Indication: Primary Prevention	8	3
CIED Indication: Secondary Prevention	1	0
History of Congestive Heart Failure	10	9
History of ICM	9	7
History of NICM	1	2
Average EF%	29.6 +/-9.4%	33.1 +/- 20.8%
Total Number of Interrogation Days	515	387
Total VA events Detected by WCD	**11**	**1**
Average% of VA events per Interrogation Days	**2.1%**	**0.3%**
Average Interrogation Days Per Group	51.5 +/- 39.3	48.4 +/- 25.7
Total Number of Shocks	**5**	**1**
% of Shocks per Interrogation Days	**1.0%**	**0.3%**



Heart Rhythm Society
Sudden Cardiac Death Primary Prevention Protocols



Conclusions

- **Patients are at the highest risk of SCD in the first 30 days after an MI**
- **1 in 5 post-AMI patients is at high risk of dying following their PCI procedure**
- **The majority of mortality in AMI patients post-PCI occurs in the first 3 months:**
  - 1 in 10 high-risk patients die, with about 60% of this mortality due to SCD
- **Tools like the HRS SCD Screening protocol can identify those patients at the highest risk**
- **The WCD is an effective tool to protect these patients from SCD while long-term risk is being determined**

Questions