ACC Late Breaking Clinical Trials 2018

UCSF
University of California
San Francisco

Vest Prevention of **E**arly **S**udden Death **T**rial (VEST)

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On behalf of the VEST Investigators

Disclosures

- **ClinicalTrials.gov registration:** NCT01446965
- **Funding**
  - NHLBI (U01HL089458 & U01HL089145) funded Coordinating Centers until 2012
  - ZOLL funded study throughout and Coordinating Centers after 2012

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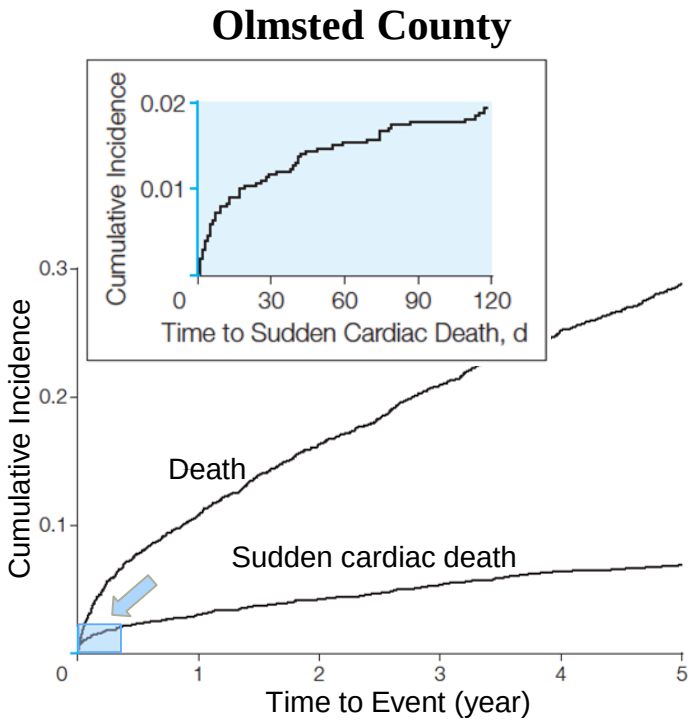
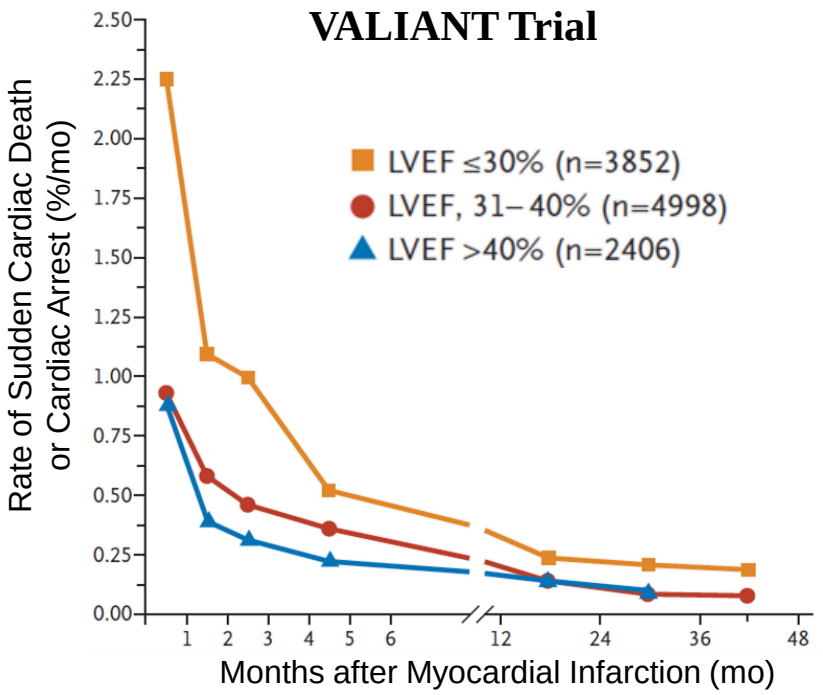
Background: SCD is high after MI



Adabag, *et al.* JAMA 2008



VALIANT—Solomon, *et al.* NEJM 2005

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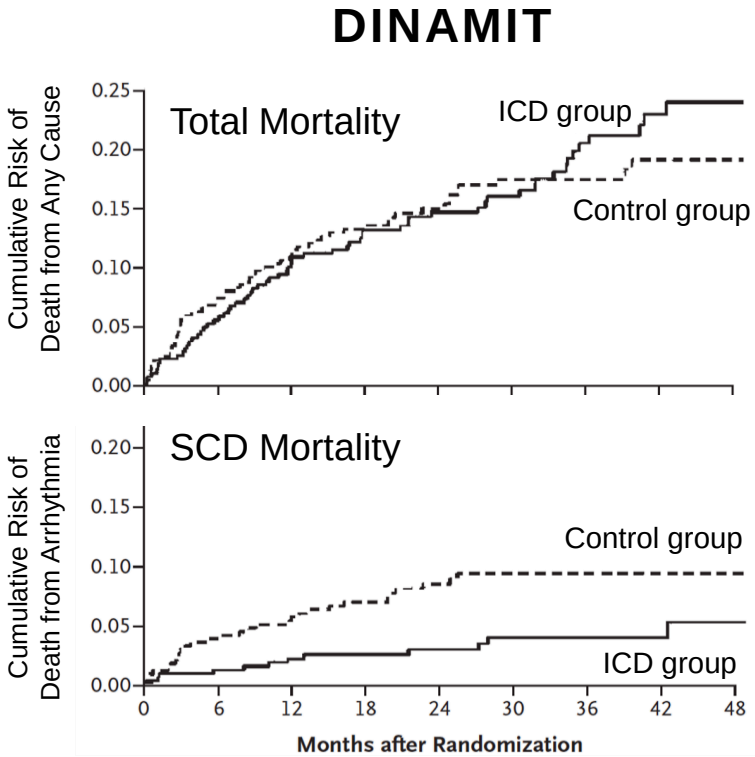
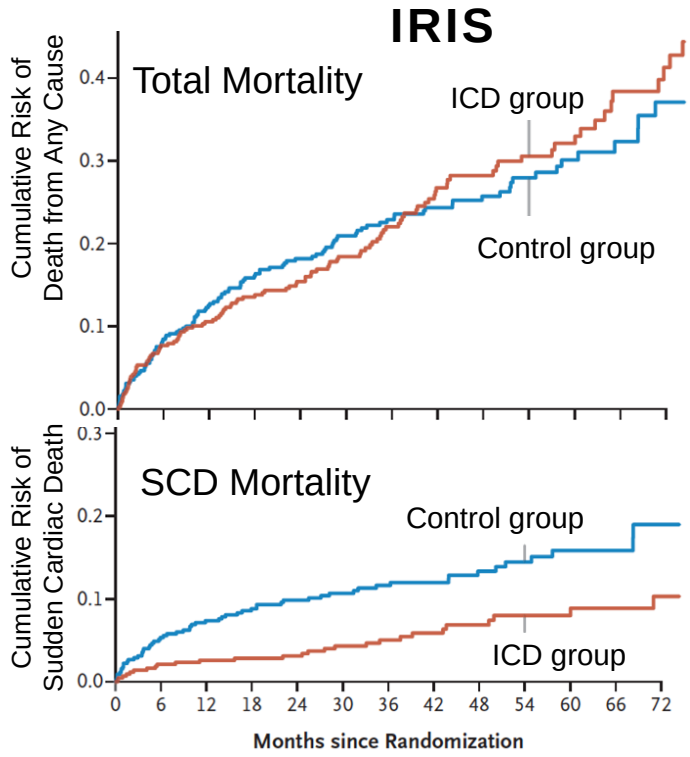
Background: No benefit from early ICD



DINAMIT: Hohnloser, *et al.* NEJM 2004



IRIS: Steinbeck, *et al.* NEJM 2009

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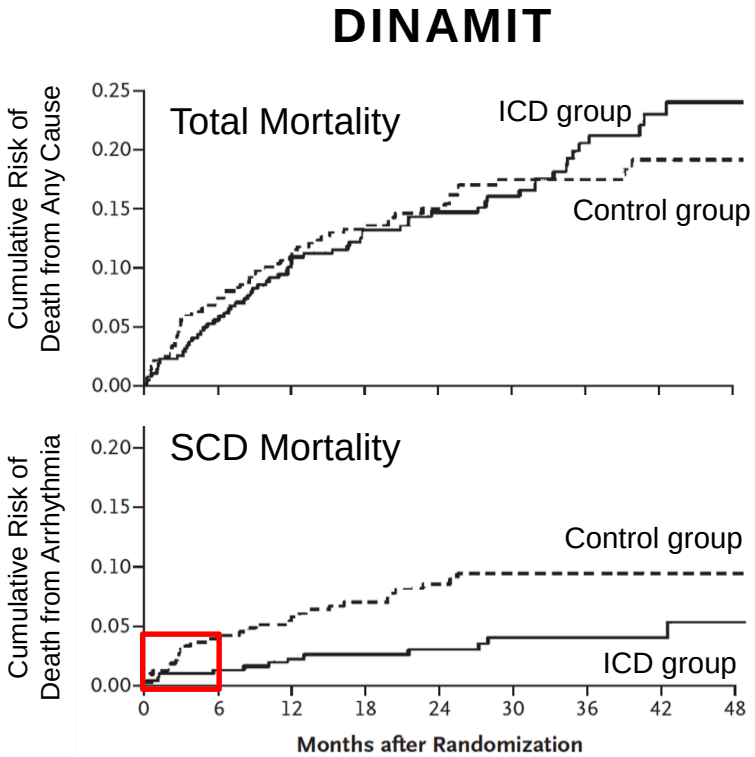
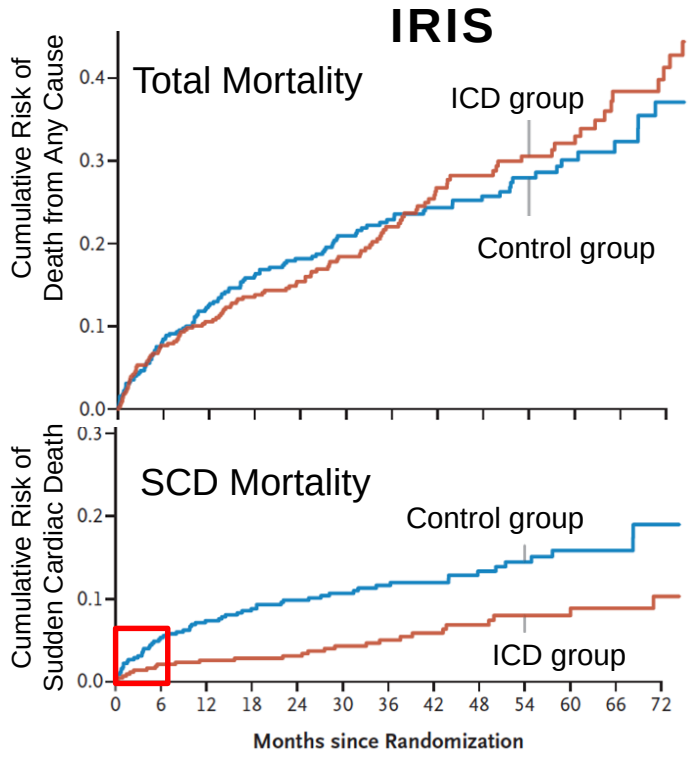


DINAMIT: Hohnloser, *et al.* NEJM 2004



IRIS: Steinbeck, *et al.* NEJM 2009

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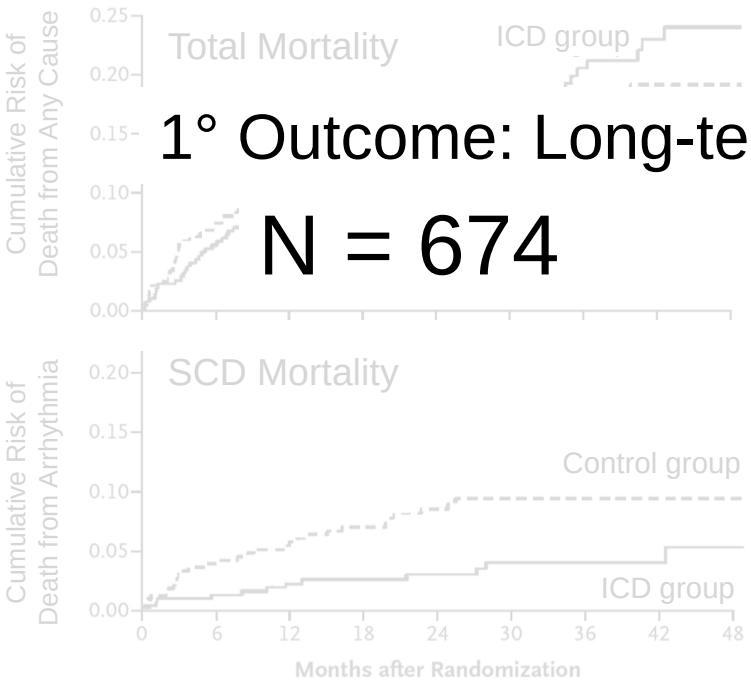
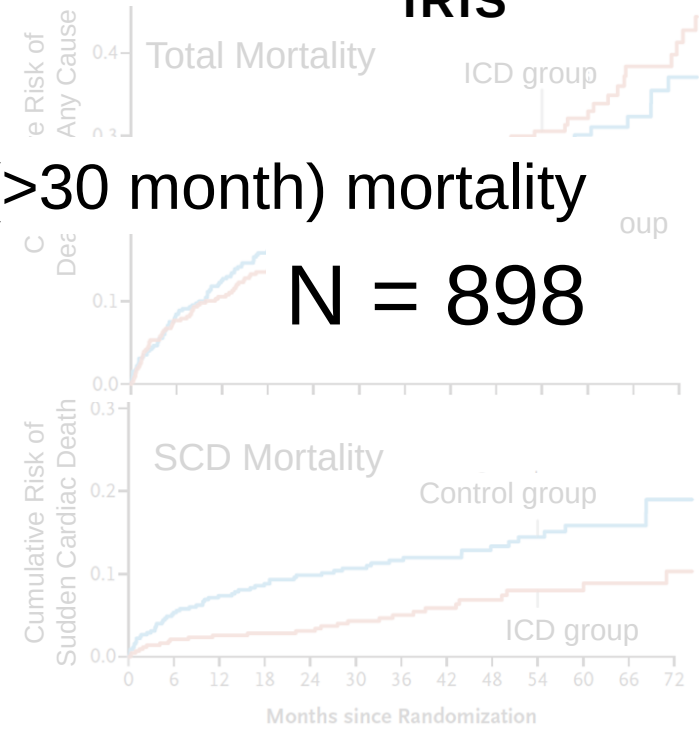
DINAMIT



IRIS



1° Outcome: Long-term (>30 month) mortality

N = 674

N = 898

DINAMIT: Hohnloser, *et al.* NEJM 2004

IRIS: Steinbeck, *et al.* NEJM 2009

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Background: Guideline recommendations

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Al-Khatib SM, et al.
2017 VA/SCD Guidelines

6.1.2. Primary Prevention of SCD in Patients with Ischemic Heart Disease

Recommendations for Primary Prevention of SCD in Patients With Ischemic Heart Disease		
COR	**LOE**	**Recommendations**
I	A	1. In patients with LVEF of 35% or less that is due to ischemic heart disease who are at least 40 days post-MI and at least 90 days post revascularization, and with NYHA class II or III HF despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected (1,2).

2017 ACC/AHA/HRS Guideline for Management of Patients With Ventricular Arrhythmias. JACC 2017

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Background: VEST rationale

- ICD not indicated in immediate post-MI period
- Some early mortality not due to arrhythmias immediately post-MI, thus not preventable by ICD
- LVEF may recover over 3 months post-MI

Can a wearable cardioverter defibrillator (WCD) reduce SD mortality in the immediate post-MI period (<90 days) in patients with reduced LVEF, as a bridge to evaluation for ICD?

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Methods: Study design

- **Multi-center, randomized, open-label trial**
- **Participants enrolled within 7 days of hospital d/c with acute MI and EF≤35%**
- **Randomized 2:1 to receive:**
  - Wearable cardioverter defibrillator (WCD) + guideline-directed therapy **or**
  - Guideline-directed medical therapy alone
- **MD's & sites blinded to detected arrhythmias**
- **Crossovers & ICDs prohibited (except for secondary prevention during follow-up)**

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Methods: Inclusion & exclusion

Inclusion Criteria

- ≤7 days of hospital discharge for acute MI
- EF ≤35% assessed:
  - ≥8 hrs after MI
  - ≥8 hrs after PCI
  - ≥48 hrs after CABG

Exclusion Criteria

- Existing ICD
- Significant valve disease
- Unipolar pacing system
- Chronic hemodialysis
- Chest too small/large for WCD
- Discharge to SNF for >7 days
- Pregnancy

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Methods: Screening & enrollment

- **Screening & enrollment between 2008—2017**
- **108 enrolling sites**
  - 76 US sites
  - 6 German sites
  - 24 Polish sites
  - 2 Hungarian sites

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Methods: Intervention-WCD

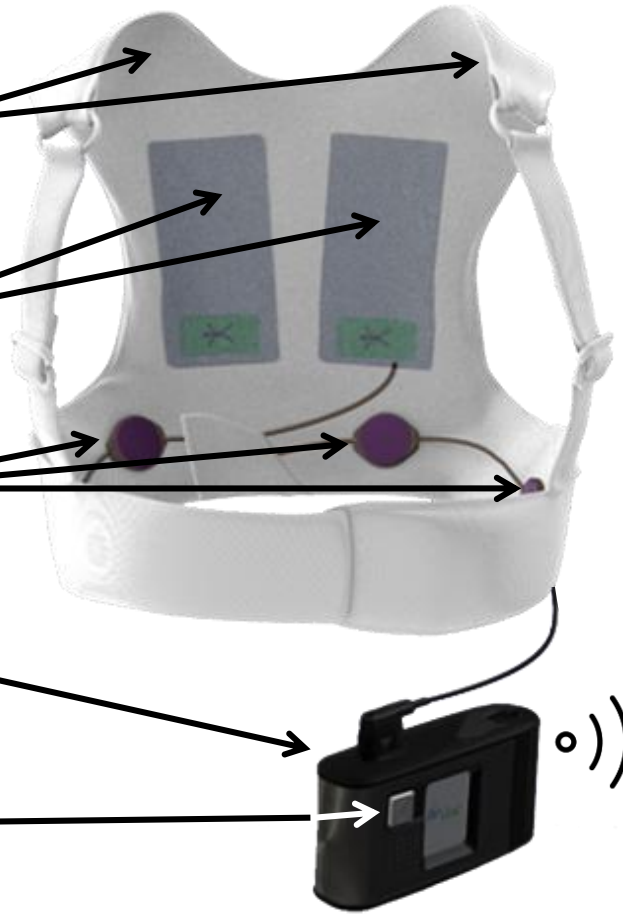
Washable-Interchangeable Garment

Self-Gelling Defibrillation Electrodes

Dry ECG Electrodes

Rechargeable Monitor & Battery Pack

Response Buttons



Monitors
- Wear-time
- Noise
- Device warning
- Asystole
- VT/VF

Treatment
- VT/VF

Investigators blinded to data

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Methods: Outcomes

- **Follow-up at 1 month & 3 months**
- **Search NDI at end of study**
- **Primary Outcome: SCD & death due to ventricular arrhythmias**
- **Secondary outcomes**
  - Total mortality & Non-sudden death
  - Cause-specific death
  - Non-fatal outcomes
    - CV Hospitalizations
    - WCD compliance
    - Adverse events

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Methods: Analysis plan

- **Primary Analysis: Intention-to-treat**
  - Participants with indeterminate causes of death or unknown vital status are treated as not having primary outcome
- **Secondary Analyses**
  - Weighted sensitivity analyses excluding unknown vital status and indeterminate causes of death from denominator

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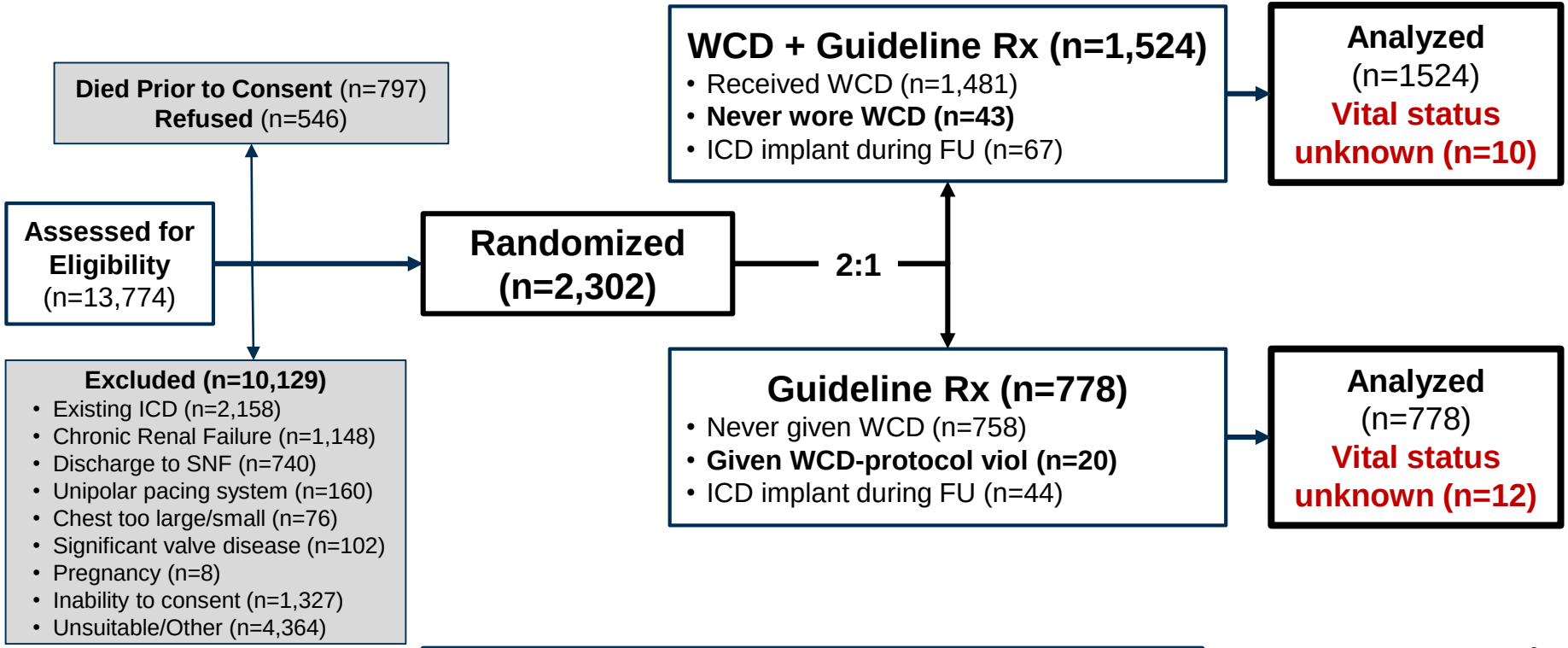
Results: CONSORT diagram



Mean Follow-up = 84.3 ± 15.6 days

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Results: Participant characteristics

Characteristic	WCD Group (N=1524)	Control Group (N=778)
Age, mean ± SD	60.9 ± 12.6	61.4 ± 12.3
Men, n (%)	1107 (72.8%)	577 (74.7%)
Body mass index, Mean ± SD	28.4 ± 5.5	28.6 ± 6.6
Smoker, n(%)	561 (36.9%)	273 (35.5%)
Race n (%)		
White	1278 (84.1%)	636 (82.6%)
Black	143 (9.4%)	75 (9.7%)
Asian	23 (1.5%)	14 (1.8%)
Native American/Alaskan	25 (1.7%)	12 (1.6%)
Pacific Islander/Hawaiian	1 (0.1%)	0 (0%)
Mixed	20 (1.3%)	14 (1.8%)
Hispanic, n (%)	85 (5.6%)	34 (4.4%)

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Results: Prior history

Characteristic	WCD Group (N=1524)	Control Group (N=778)
Diabetes Mellitus, n (%)	496 (32.6%)	246 (31.7%)
Hypertension, n(%)	993 (65.3%)	501 (64.6%)
Prior MI, n (%)	380 (25.1%)	193 (24.9%)
Prior CABG, n (%)	133 (8.8%)	70 (9.0%)
Prior PCI, n (%)	374 (24.6%)	202 (26.0%)
Prior CHF, n (%)	246 (16.2%)	146 (18.9%)
NYHA Classification, n (%)		
I	691 (45.5%)	326 (42.1%)
II	528 (34.8%)	286 (36.9%)
III	211 (13.9%)	116 (15.0%)
IV	46 (3.0%)	18 (2.3%)

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Results: Characteristics of index MI

Characteristic	WCD Group (N=1524)	Control Group (N=778)
LVEF	28.2 ± 6.1%	28.2 ± 5.9%
PCI during MI hospitalization	1272 (84.2%)	650 (84.1%)
Thrombolytics during MI hospitalization	118 (7.8%)	71 (9.2%)
CABG during index hospitalization	14 (0.9%)	12 (1.5%)
Cardiac Arrest/VF	169 (11.2%)	70 (9.1%)
Pulmonary Edema requiring Intubation	162 (10. 7%)	88 (11.4%)
Intra-aortic Balloon Pump	173 (11.5%)	93 (12.0%)
Cardiogenic Shock	136 (9.0%)	79 (10.2%)

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Results: Medical treatment

Characteristic	WCD Group (N=1524)	Control Group (N=778)
ASA	1328 (87.1%)	677 (87.0%)
Other antiplatelet	1378 (90.4%)	679 (87.3%)
Statin	1384 (90.8%)	695 (89.3%)
Beta blocker (including carvedilol)	1407 (92.3%)	716 (92.0%)
ACEI/ARB	1330 (87.3%)	665 (85.5%)
Eplerenone/spironolactone	661 (43.4%)	342 (44.0%)
Other diuretic	736 (48.3%)	384 (49.4%)
Amiodarone	106 (7.0%)	55 (7.1%)

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Results: Crossover treatment

Characteristic	WCD Group (N=1524)	Control Group (N=778)
WCD received, n (%)	**1455 (95.5%)**	20 (2.6%)*
Average hours/day WCD worn	**14.1 ± 9.3**	0.8 ± 3.9*
ICD during follow up (<90 days), n (%)	67 (4.4%)	44 (5.7%)
ICD Implant timing (days since randomization), median (IQR)	62 (24-81)	58 (25-77)

*P <0.001

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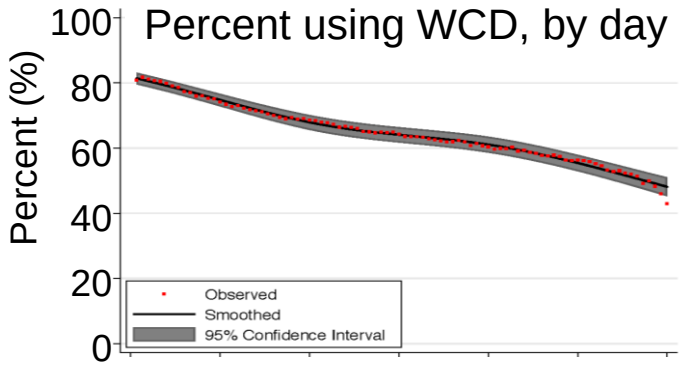
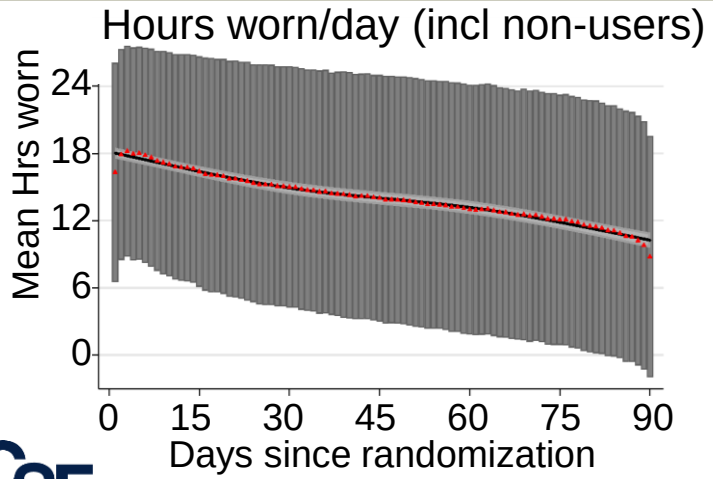
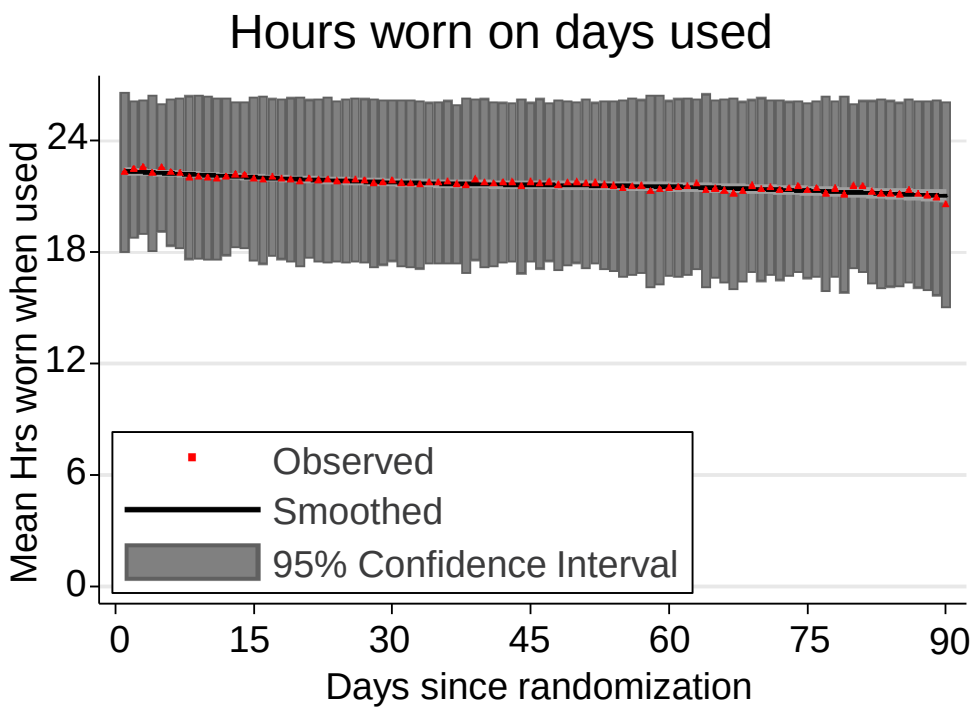
Results: WCD wear-time







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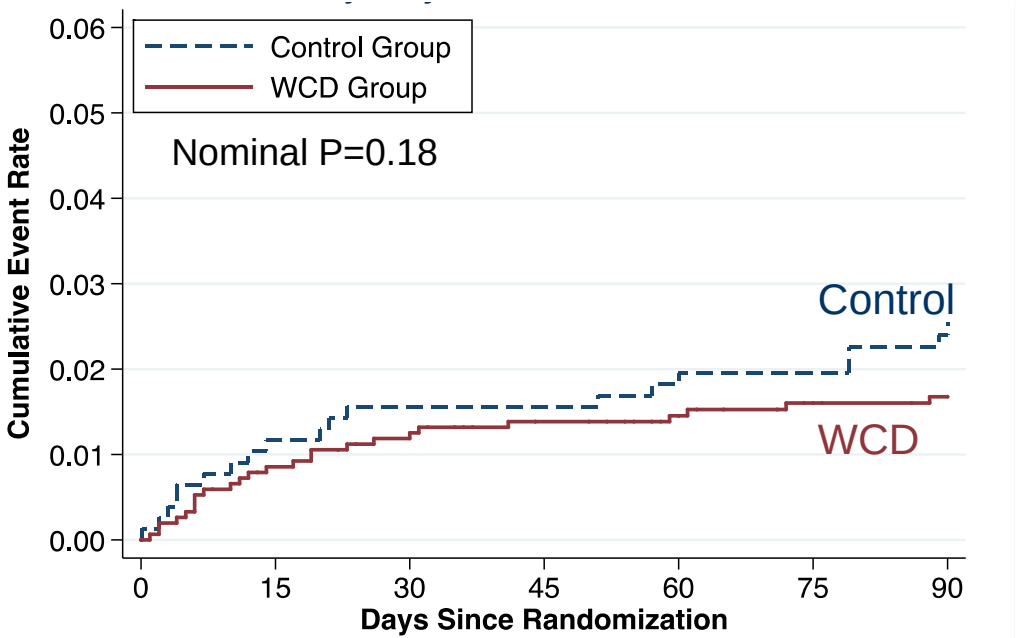
Results: Outcomes, intention-to-treat

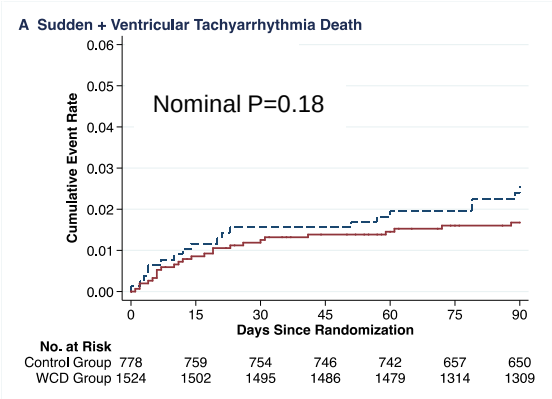
A Sudden + Ventricular Tachyarrhythmia Death



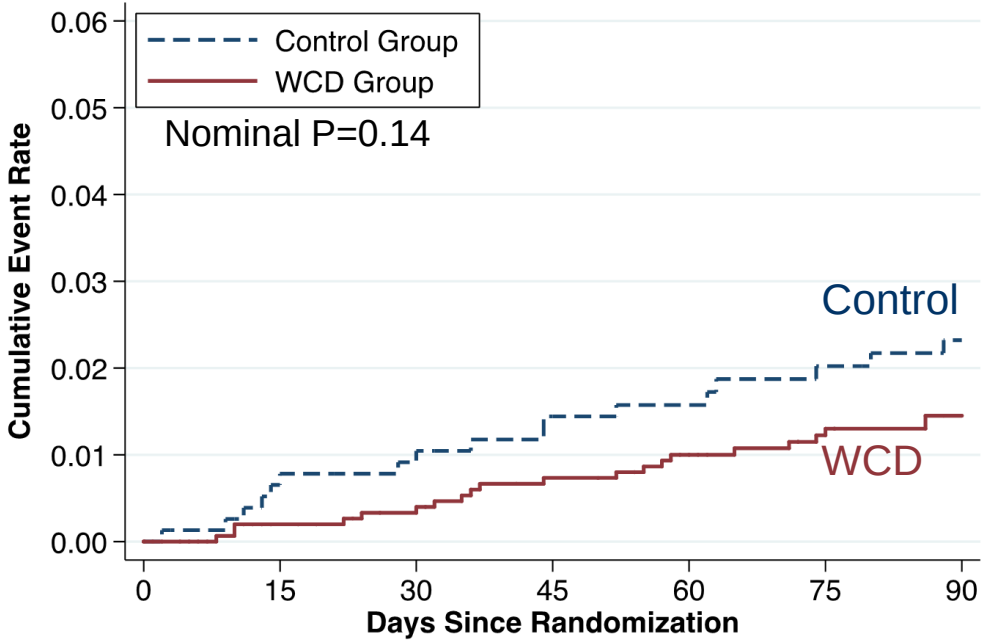
No. at Risk

Control Group	778	759	754	746	742	657	650
WCD Group	1524	1502	1495	1486	1479	1314	1309

Results: Outcomes, intention-to-treat



B Non-sudden Death



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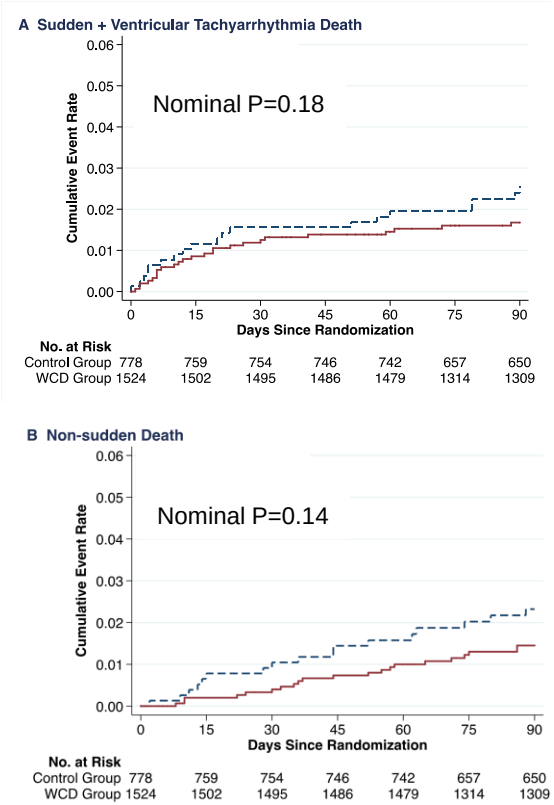
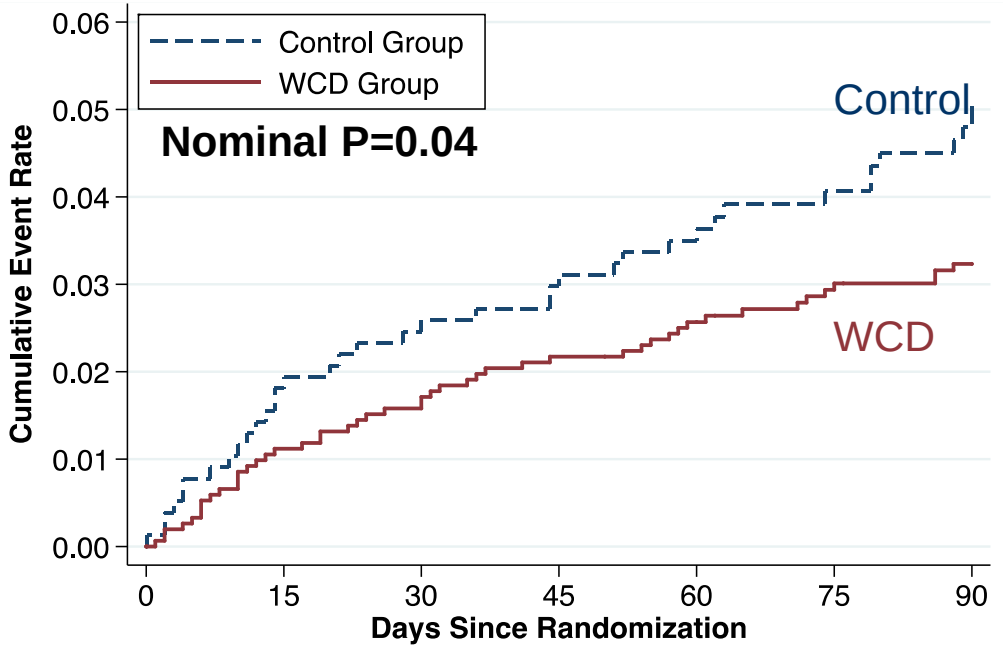


C Death from Any Cause



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Results: Cause-specific death

Clinical event type	WCD (N=1524)	Control (N=778)	P value*
FATAL EVENTS, n (%)			
Sudden Death (1° outcome)	25 (1.6%)	19 (2.4%)	0.18
Non-sudden death	21 (1.4%)	17 (2.2%)	0.15
Congestive heart failure death	10 (0.7%)	5 (0.6%)	1.0
Recurrent MI death	1 (0.1%)	1 (0.1%)	1.0
Stroke death	0 (0.0%)	**4 (0.5%)**	**0.01**
Other cardiovascular death	5 (0.3%)	3 (0.4%)	1.0
Other death	5 (0.3%)	4 (0.5%)	0.72
Indeterminate death	2 (0.1%)	2 (0.3%)	0.83
Death, any cause	48 (3.1%)	**38 (4.9%)**	**0.04**
NON-FATAL EVENTS, n (%)			
Rehospitalization, cardiovascular	334 (22%)	174 (22%)	0.81
Rehospitalization, any cause	475 (31%)	253 (33%)	0.51

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Results: WCD therapies & events

Therapies	WCD Group (N=1524)	Control Group (N=778)
Appropriate shocks (p=0.002)		
1 appropriate shock	**13 (0.9%)**	0 (0%)
≥2 appropriate shocks	**7 (0.5%)**	1 (0.1%)
Inappropriate shocks (p=0.05)		
1 inappropriate shock	**8 (0.5%)**	0 (0%)
≥2 inappropriate shocks	**2 (0.1%)**	0 (0%)
Aborted shocks (p<0.001)		
1 aborted shock	**43 (2.8%)**	0 (0%)
≥2 aborted shocks	**12 (0.8%)**	0 (0%)
>5 aborted shocks	**15 (1.0%)**	0 (0%)

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Results: Pre-specified symptoms

Characteristics	WCD	Control	P value
Fatigue	36.0%	38.8%	0.21
Back pain	20.0%	19.4%	0.73
Trouble sleeping	39.0%	37.3%	0.47
Dizziness	24.3%	23.5%	0.66
Fainting	4.2%	5.1%	0.34
Nausea	9.4%	12.0%	0.06
Headache	18.3%	19.1%	0.66
Palpitations	23.1%	25.7%	0.18
Chest pain	18.7%	21.4%	0.14
Shortness of breath	38.7%	**45.4%**	**0.003**
Rash in any location	**15.2%**	7.1%	**<0.001**
Rash on torso	**12.9%**	3.8%	**<0.001**
Itch in any location	**17.2%**	6.4%	**<0.001**
Itch on torso	**14.5%**	3.1%	**<0.001**

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Discussion: Sudden vs total mortality

- **Possible misclassification of sudden deaths**
  - Reducing power for SD outcome but not total mortality
  - 14 of 20 participants who received an appropriate shock survived to 90 days
- **WCD may confer additional protection beyond SD**
  - Earlier care for bradycardia, NSVT or aborted shocks
- **Reduced anxiety or increased medication compliance**
  - More shortness of breath in controls

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Discussion: Limitations

- **Participants and investigators not blinded**
  - Differences in shortness of breath between groups
  - No differences in prescribing guideline-directed Rx
- **Crossovers**
  - 20 participants in Control group received the WCD
  - 19% in WCD group did not use the WCD
  - Should bias results toward the null, but still found a difference in total mortality

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Conclusions

- VEST represents the first randomized controlled trial of the WCD
- The WCD did not statistically significantly reduce sudden death mortality, our primary outcome
- The WCD was associated with lower total mortality in the first 90 days post-MI in patients with LVEF ≤35%
- Prescribing the WCD is reasonable to protect high-risk patients with a low LVEF post-MI until evaluation for an ICD at 40-90 days

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Thank you: VEST Investigators

- **Jeffrey Olgin** UCSF
- **Mark Pletcher** UCSF
- **Eric Vittinghoff** UCSF
- **Jerzy Wranicz** Medical Univ Lodz
- **Rajesh Malik** McLeod Regional
- **Daniel Morin** Ochsner
- **Steven Zweibel** Univ of CT
- **Alred Buxton** Beth Israel
- **Claude S Elayi** Univ of KY
- **Eugene Chung** Univ of MI
- **Eric Rashba** Stoney Brook
- **Martin Borggrefe** Univ Mannheim
- **Stephen Hulley** UCSF
- **Byron Lee** UCSF

On Behalf of the VEST Investigators

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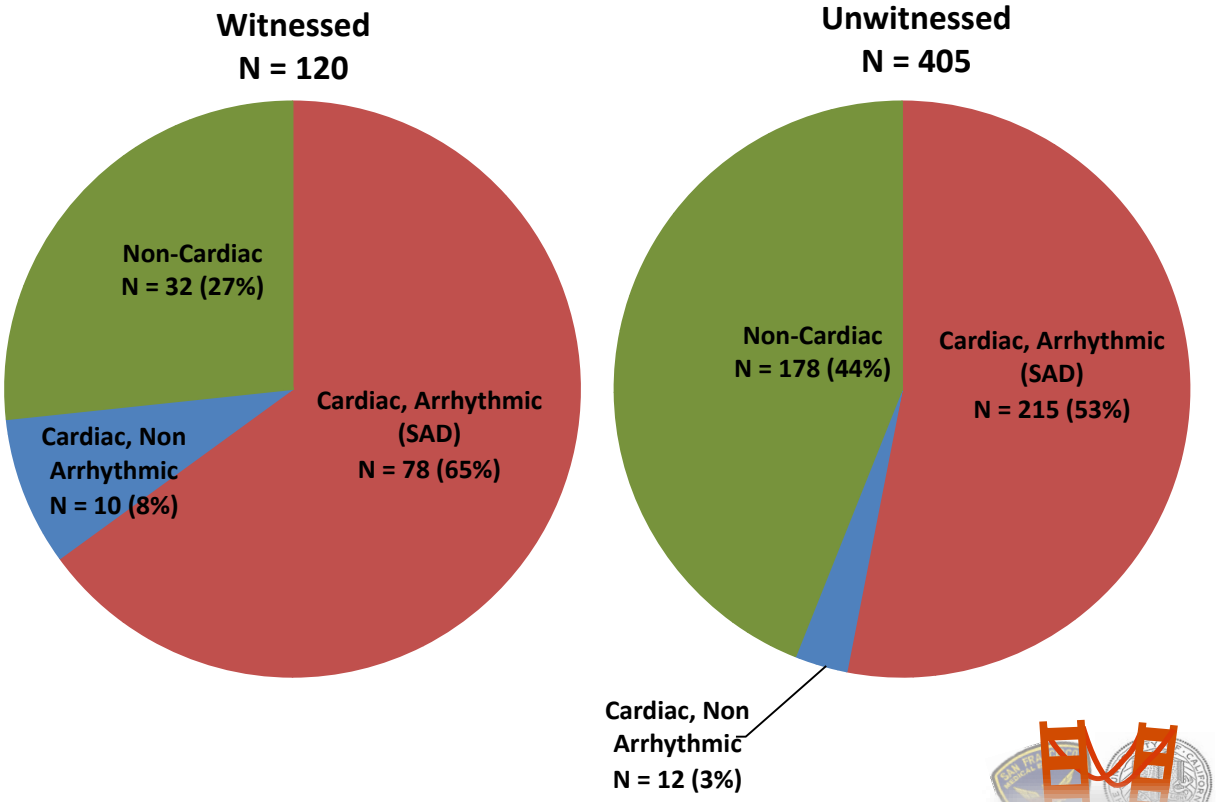
Thank you

Discussion: Sudden death etiology

- Autopsy-proven cause of death
- 525 consecutive ”sudden deaths” in SF County
- 98% autopsy rate.



Tseng, Z. *et al* Circulation, in press

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POST SCD

Results: ICD implants

	WCD (n=67)	Control (n=44)
TIMING OF ICD IMPLANT:		
Days since randomization, med (IQR)	62 (24-81)	58 (25-77)
REASON FOR EARLY ICD IMPLANT:		
Cardiac arrest/WCD shock	15	6
Sustained VT	4	1
Bradycardia	0	1
HF treatment (required CRT)	5	1
Syncope and inducible VT	0	1
Protocol violation	24	18
Unknown reason	19	16

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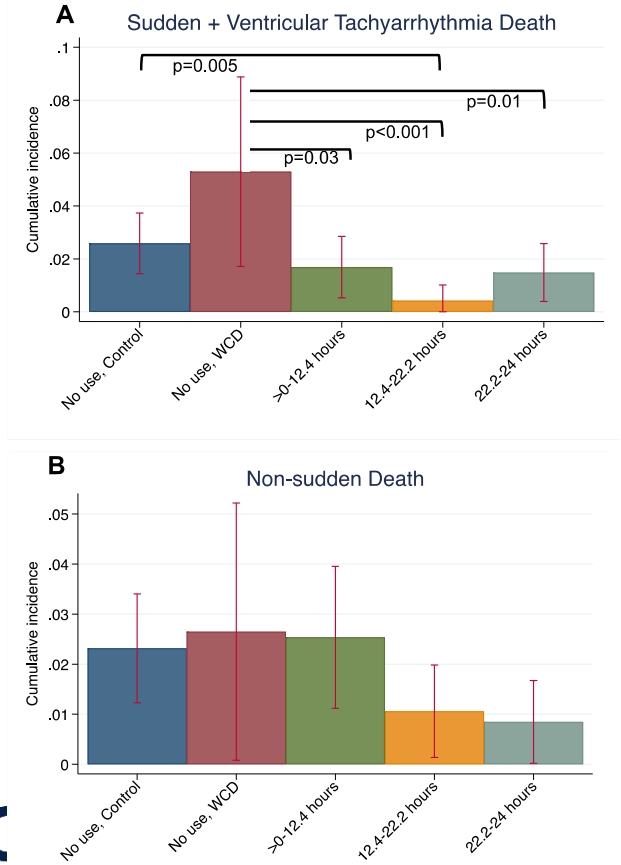
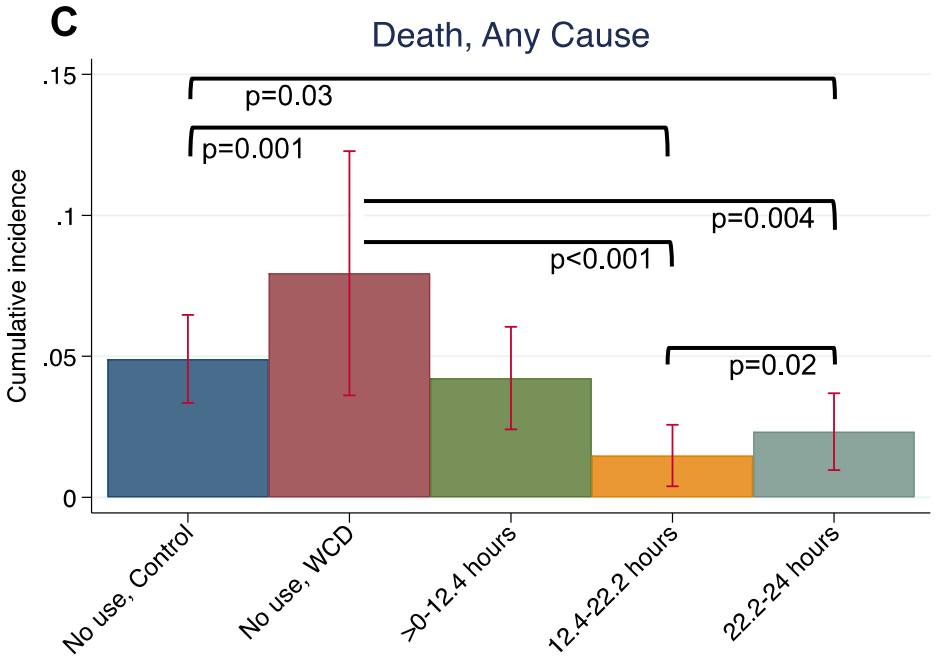
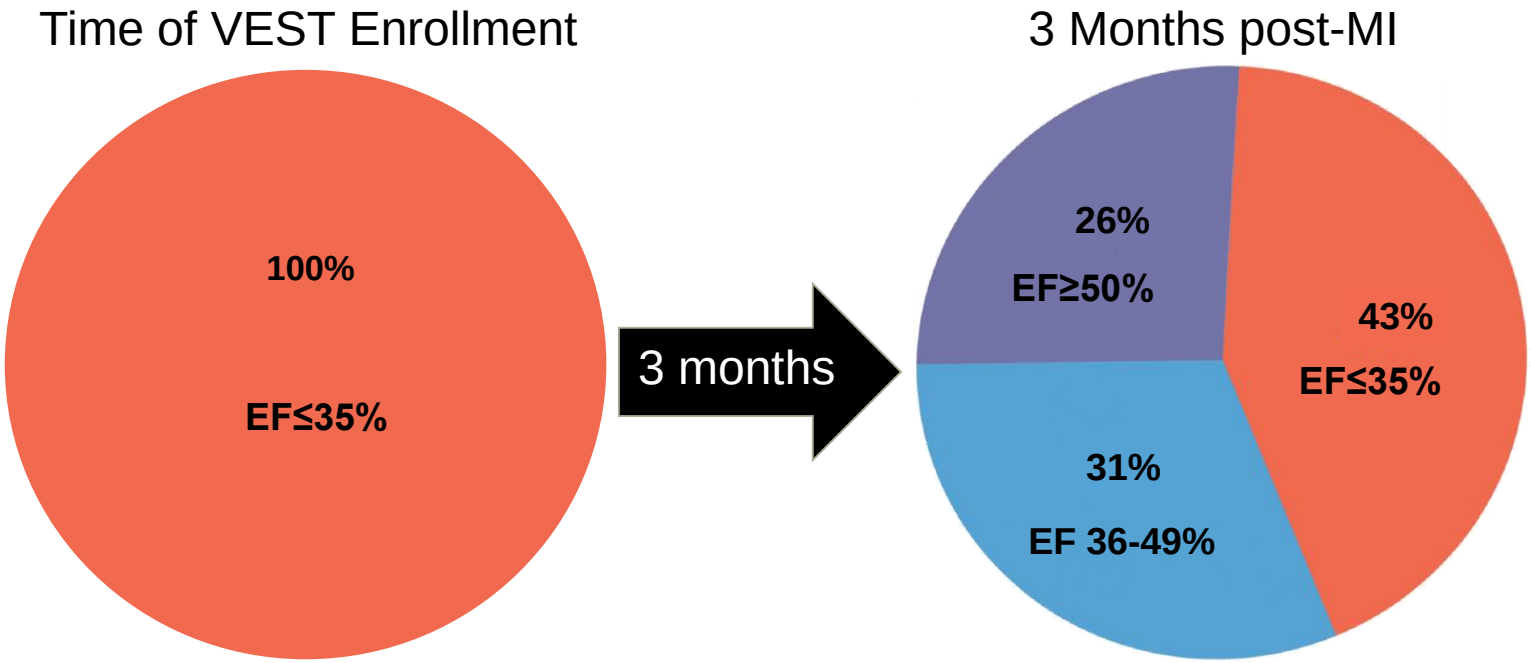
Results: Outcomes, as-treated



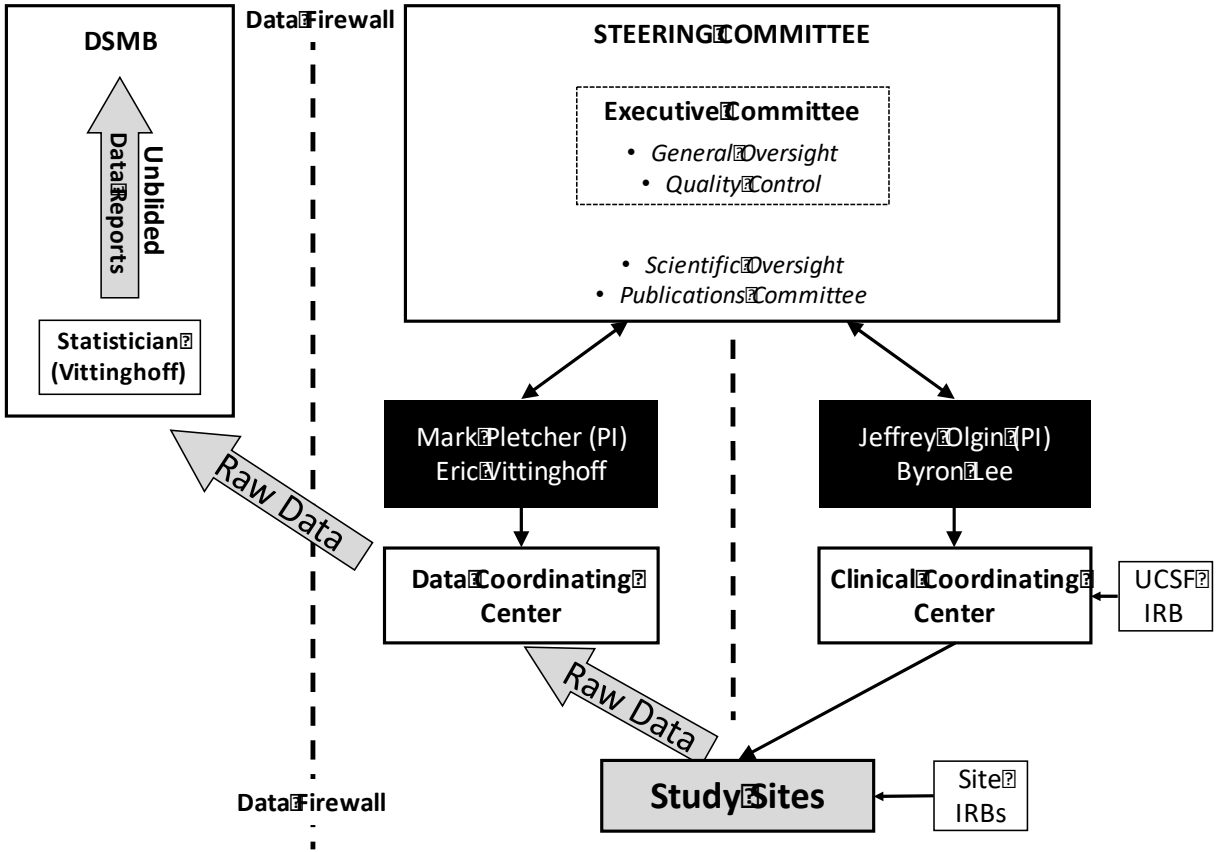


Background: EF improves over time



PREDICTS: Brooks, *et al.* JACC 2016

Methods: Study governance & oversight



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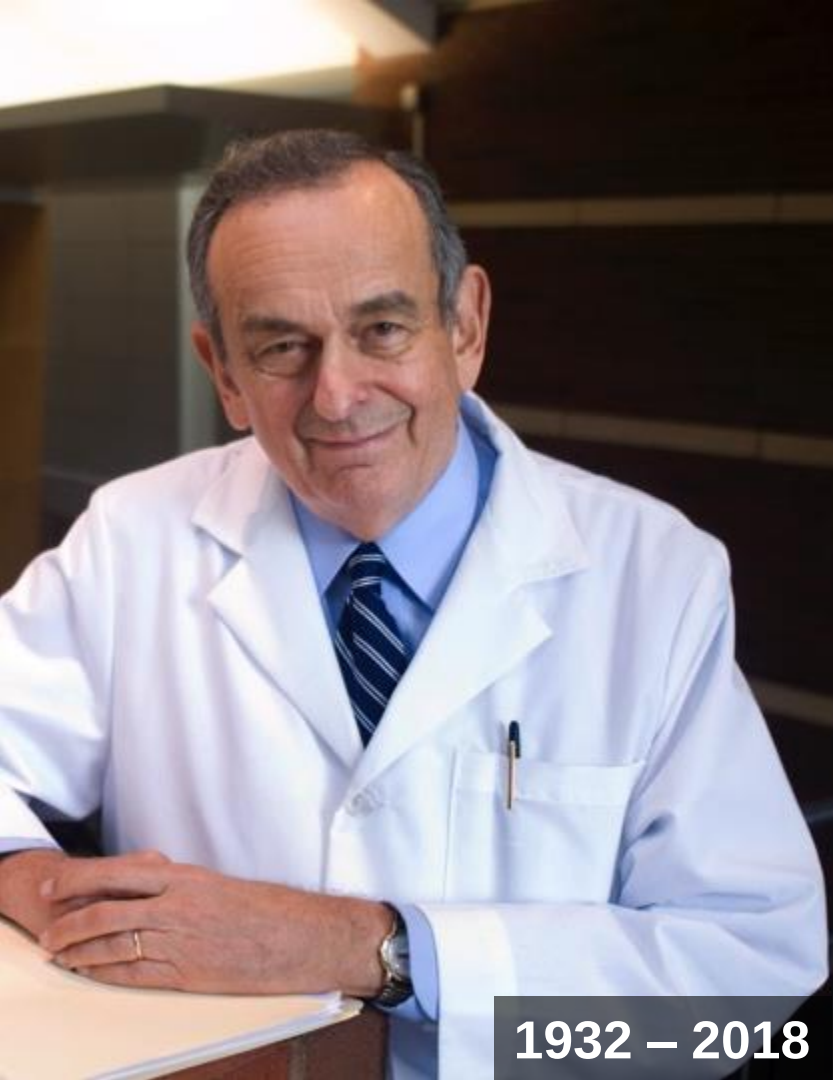

MADIT

Multicenter Automatic Defibrillator Implantation Trials

The NEW ENGLAND JOURNAL of MEDICINE

Improved Survival with an Implanted Defibrillator in Patients with Coronary Disease at High Risk for Ventricular Arrhythmia

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Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction

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Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events

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Reduction in Inappropriate Therapy and Mortality through ICD Programming

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