MHIF FEATURED STUDY:

Exact Trial

OPEN AND ENROLLING:

EPIC message to *Research MHIF Patient Referral*

CONDITION:	PI:	RESEARCH CONTACTS:	SPONSOR:
Refractory Angina	Jay Traverse, MD Ben Sun, MD	Jake Jensen – Jacob.Jensen@allina.com | 612-863-3818 Kari Thomas – Kari.M.Thomas@allina.com | 612-863-7493	Xylocor Therapeutics, Inc

DESCRIPTION: an early phase, non-randomized, study evaluating direct administration of a modified adenovirus vector expressing multiple isoforms of the VEGF (human vascular endothelial growth factor) gene.

The route of administration will be one-time intramyocardial injections directly into the free wall of the left ventricle via TECAP.

CRITERIA LIST/ QUALIFICATIONS:

Inclusion:

- Diagnosis of Chronic angina due to obstructive coronary artery disease
  - CCS Angina class II-IV
- History of reversible left ventricular ischemia

Exclusion:

- Current electrocardiographic abnormalities that would interfere with ST-segment analysis
- Severe Congestive heart failure defined as NYHA III or IV, or LVEF less than 25%

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Sudden Cardiac Death After Myocardial Infarction

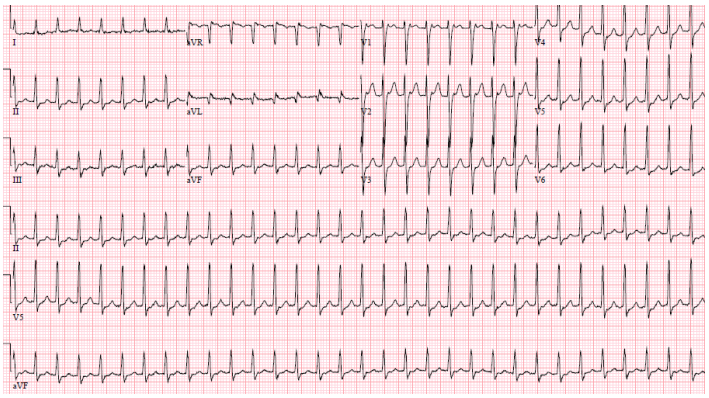
Minneapolis Heart Institute Grand Rounds
February 18, 2020

Rob Fraser, MD
Cardiology Fellow

Today's Outline

- Case 1
- Case 2
- Review of sudden cardiac death after myocardial infarction
  - Epidemiology
  - Pathogenesis
  - Primary prevention therapies
- Case 3

Case 1: Cardiology office consultation



41 year old female with palpitations

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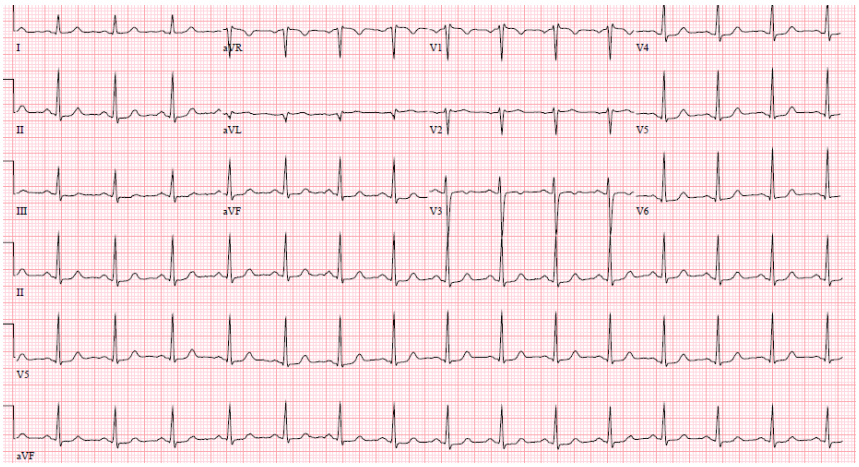
Baseline



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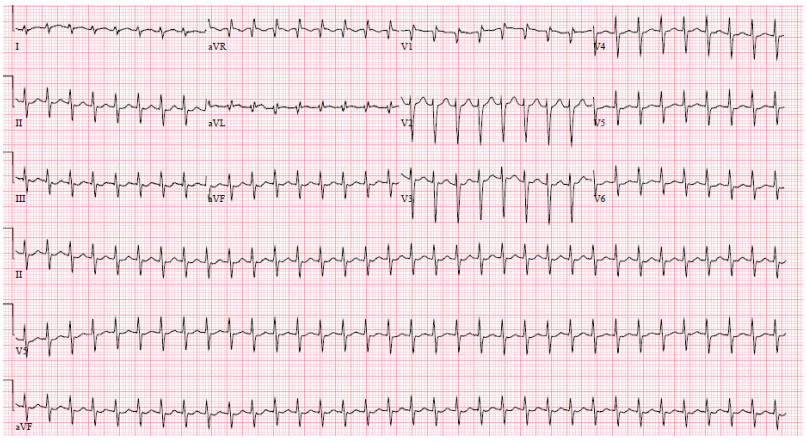
Assessment

- Paroxysmal SVT, probable AVNRT

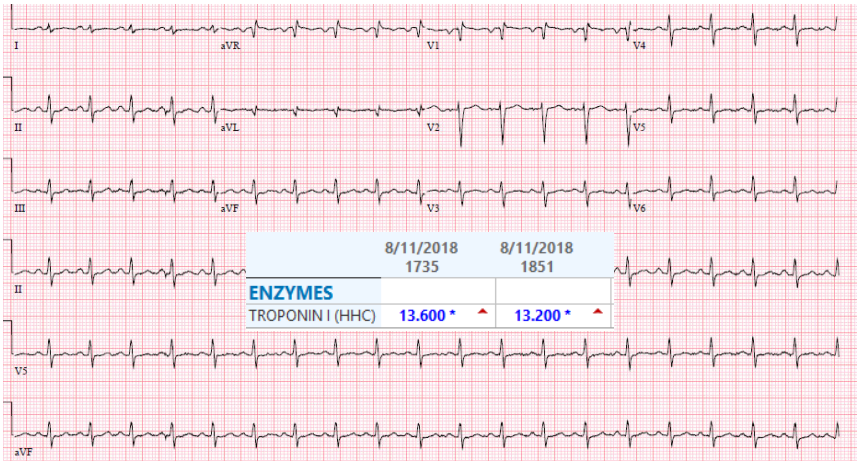
Plan

- Start metoprolol 25 bid
- EP consultation for consideration of ablation

48 hours later in Hutchinson ED



Adenosine



	8/11/2018 1735	8/11/2018 1851
ENZYMES		
TROPONIN I (HHC)	13.600 *	13.200 *

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Overnight transfer

Assessment

- Recurrent SVT aborted with adenosine
- Type 2 myocardial infarction due to sustained arrhythmia

Plan

- Transfer to ANW for:
  - Echocardiogram
  - Coronary CTA
  - EP consultation

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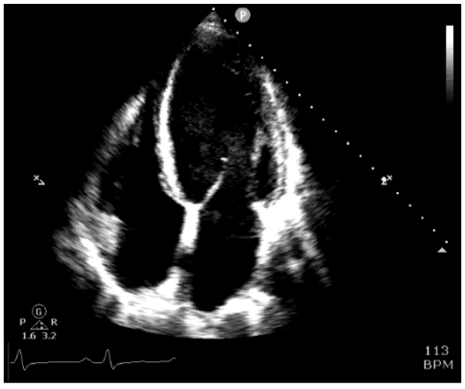
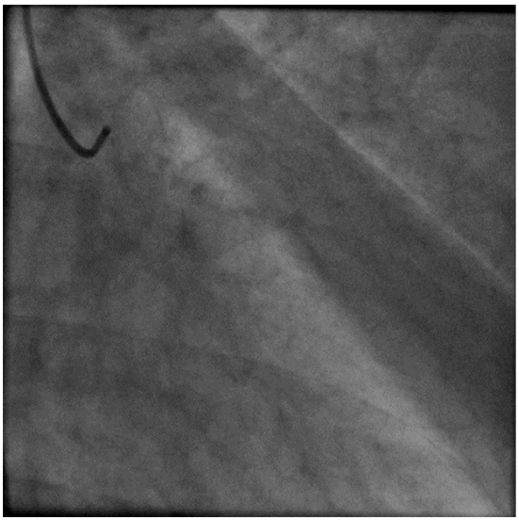
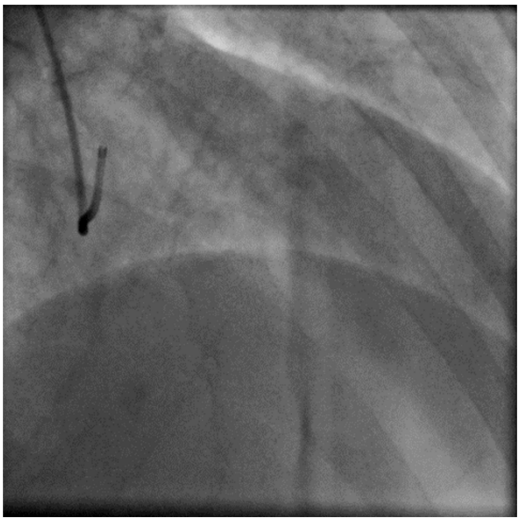
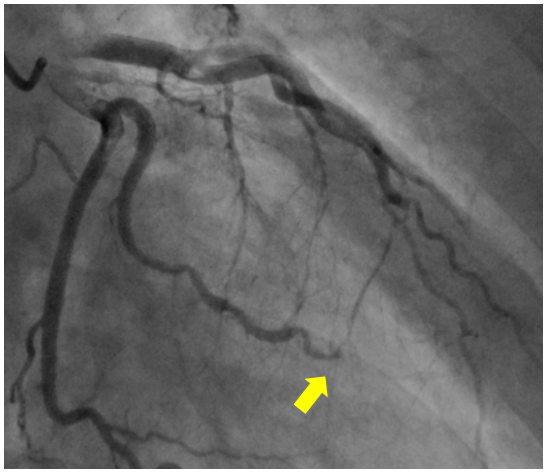
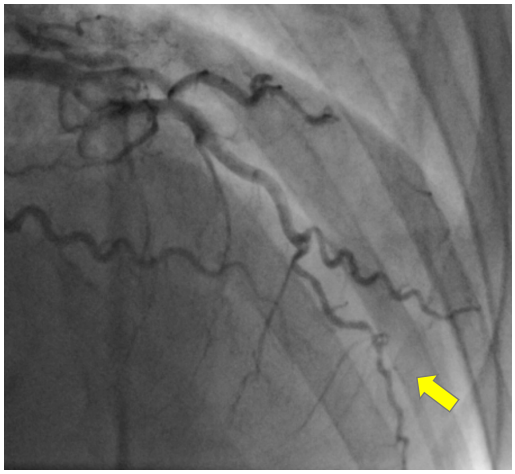
118
BPM


113
BPM









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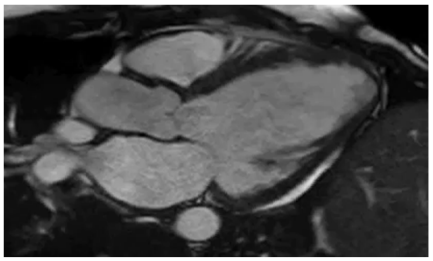

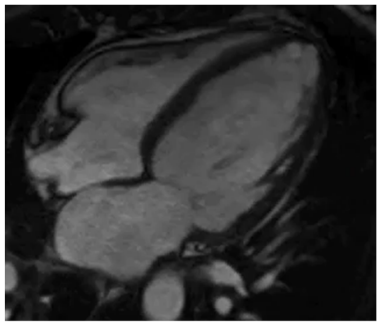

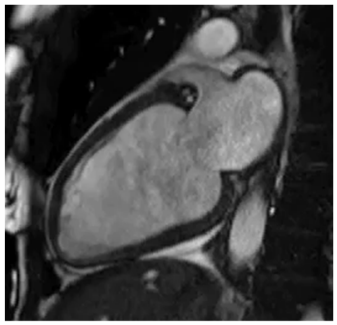

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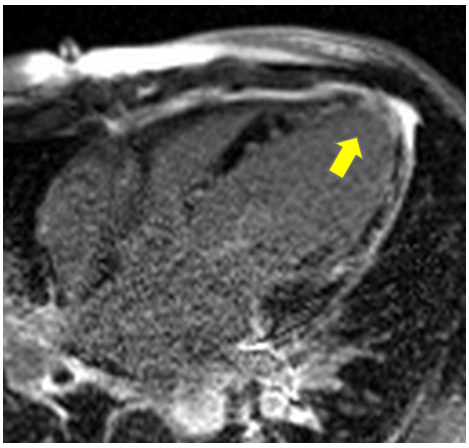

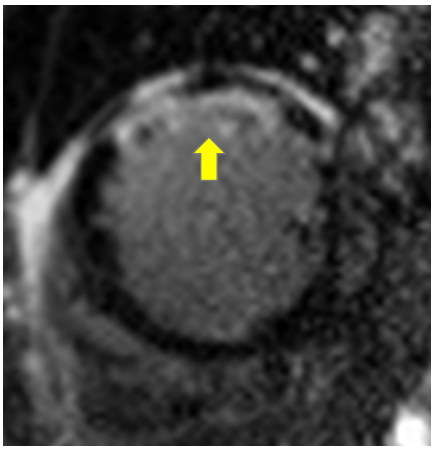

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Discharged on Hospital Day #8

Cardiology Problem List

- NSTEMI due to SCAD or vasculitis
- Mixed ischemic/non-ischemic cardiomyopathy
- Paroxysmal SVT

Plan

- DAPT, statin, BB, ACEi
- HF clinic follow up in 1 week
- SVT ablation once rheumatologic disease stable

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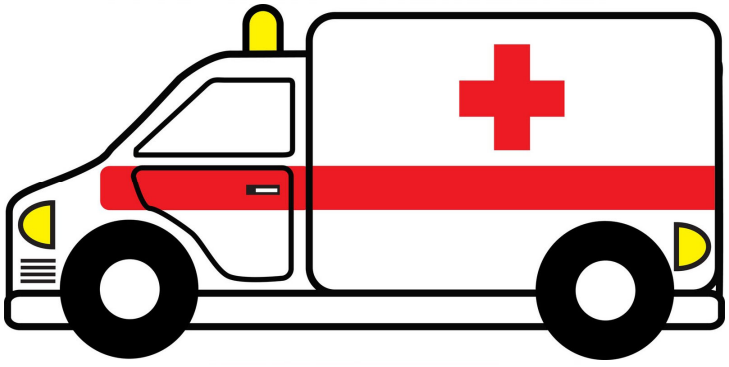

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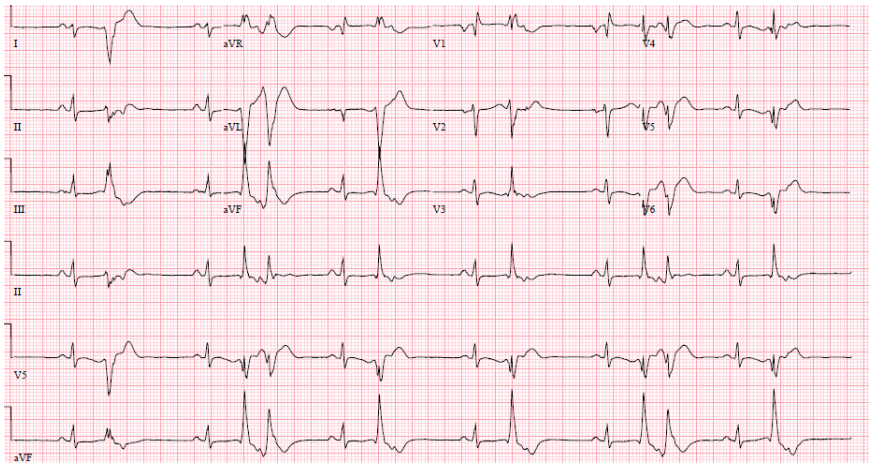
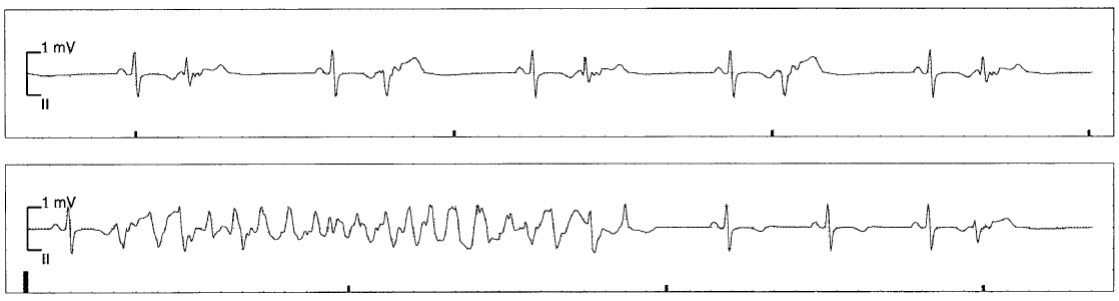
5 days after discharge





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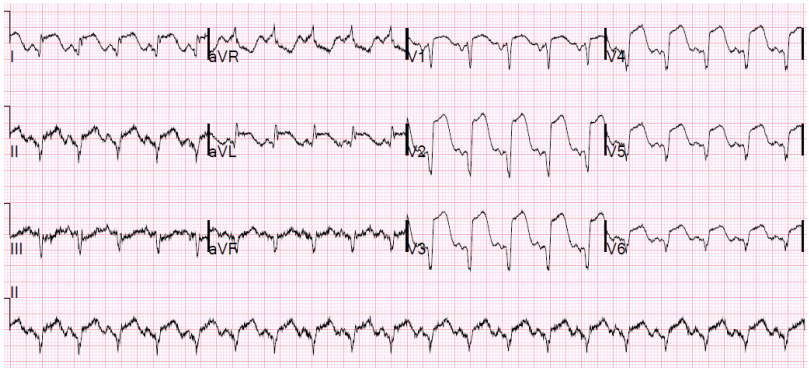
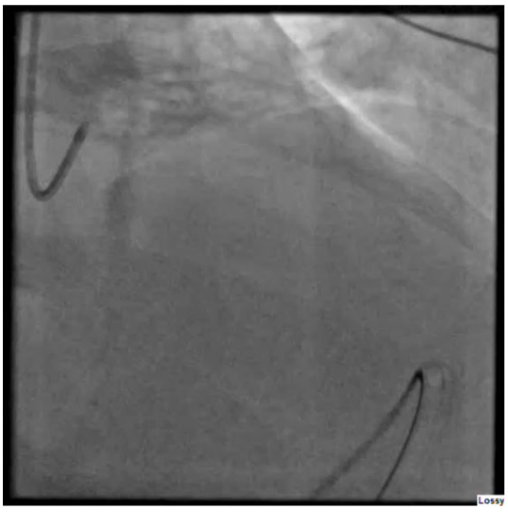
Case 2: Emergency room consultation



58 year old female with 2 days of CP



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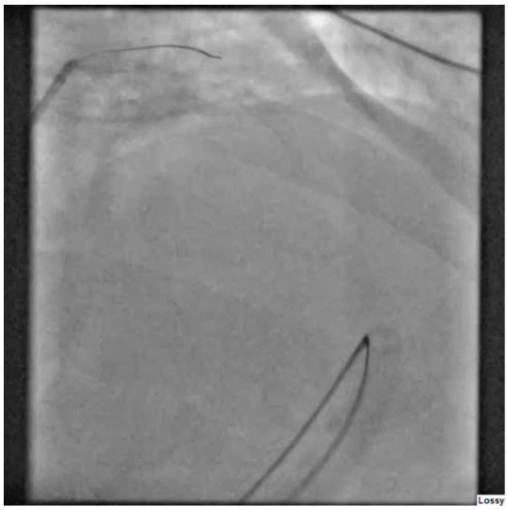

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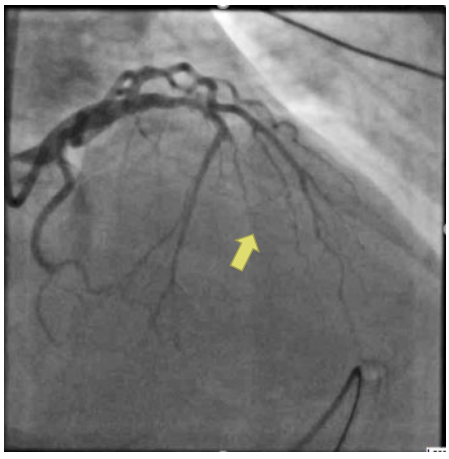

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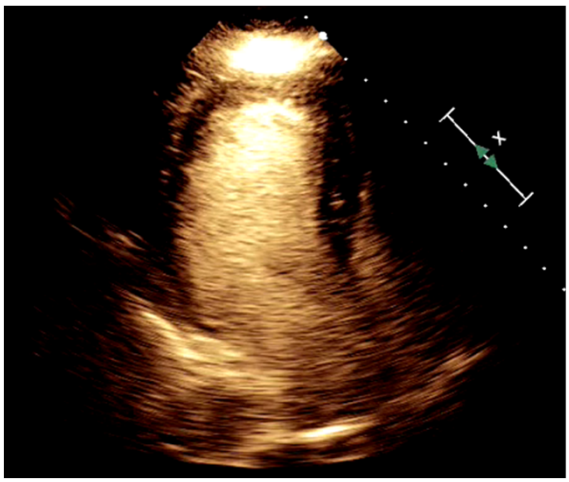

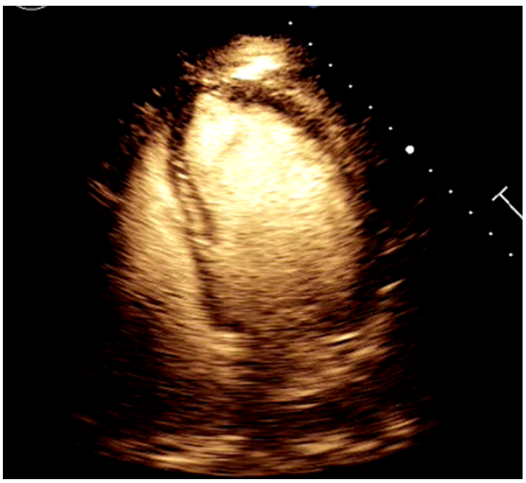

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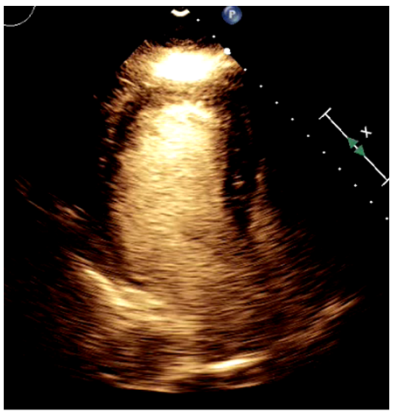
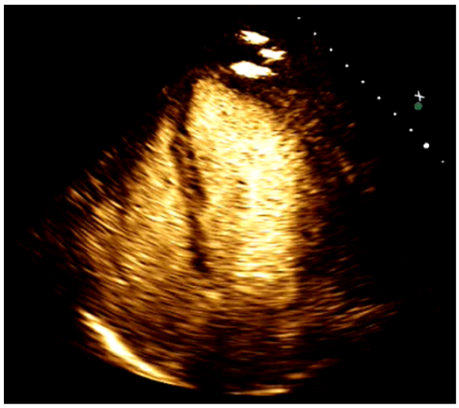
3 days later





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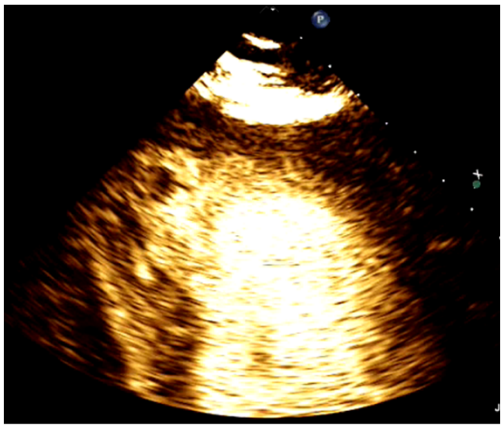


Hennepin County Medical Center

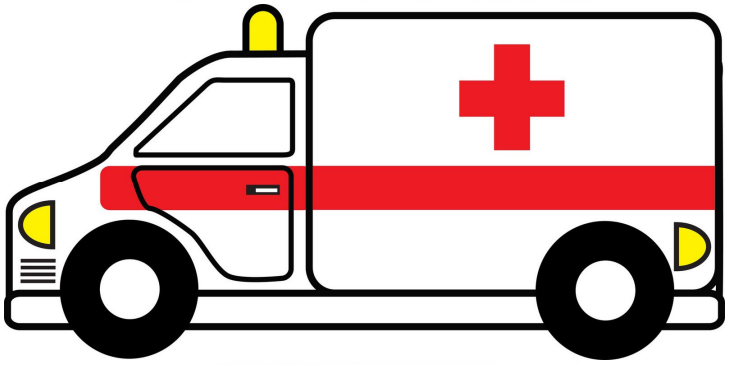
Discharged on Hospital Day #5

Cardiology Problem List

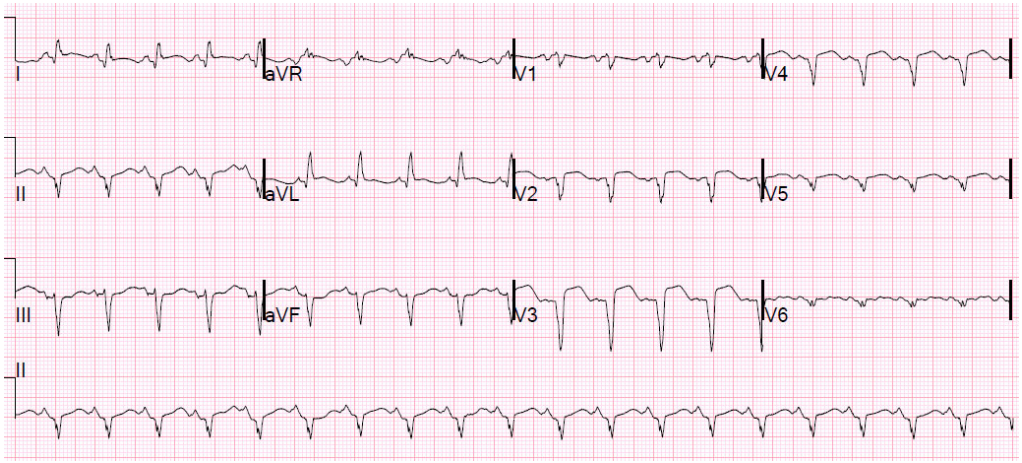
- Anterior STEMI
- Ischemic cardiomyopathy
- LV thrombus

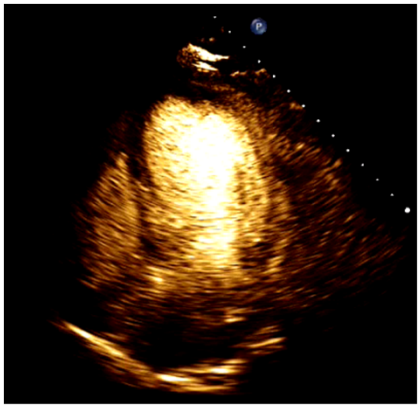
Plan

- BB, ACEi, ARA, statin
- Short term triple therapy (DES + LV thrombus)
- Cardiology clinic in 1 week

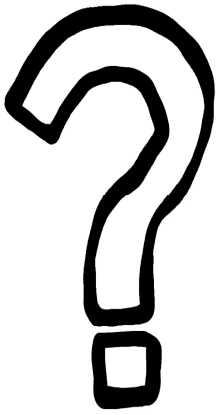


3 Days After Discharge





Hennepin County Medical Center



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Objectives

- Define sudden cardiac death
- Review SCD epidemiology and pathogenesis
- Review *pharmacologic* and *device* therapies for prevention of *early* SCD after acute myocardial infarction

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Sudden Cardiac Death
Definition and Epidemiology

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CLINICAL PRACTICE GUIDELINE

2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

Term	Definition or Description
Sudden cardiac arrest (S2.2.2-2)	SCA is the sudden cessation of cardiac activity such that the victim becomes unresponsive, with either persisting gasping respirations or absence of any respiratory movements, and no signs of circulation as manifest by the absence of a perceptible pulse. An arrest is presumed to be of cardiac etiology unless it is known or likely to have been caused by trauma, drowning, respiratory failure or asphyxia, electrocution, drug overdose, or any other noncardiac cause.
Sudden cardiac death (S2.2.2-2)	Sudden and unexpected death occurring within an hour of the onset of symptoms, or occurring in patients found dead within 24 h of being asymptomatic and presumably due to a cardiac arrhythmia or hemodynamic catastrophe.

JACC 2018;72(14)

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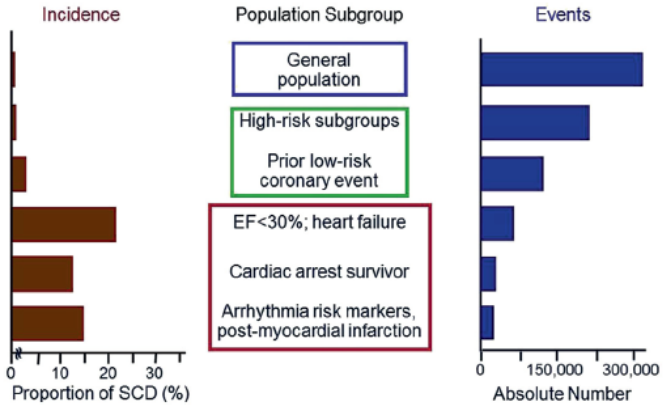
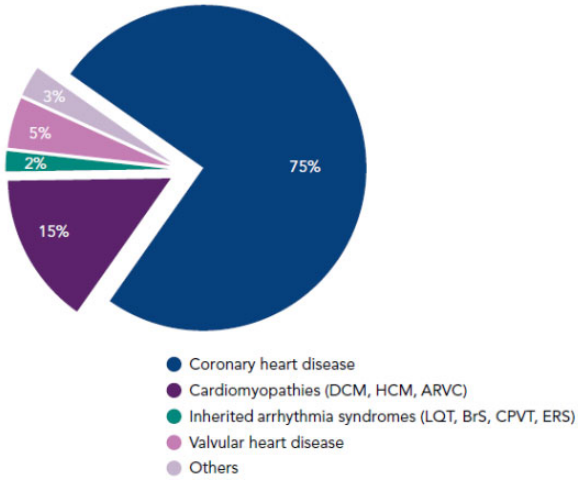
FIGURE 1A SCD Incidence and Total Events (S2.2.2-1)

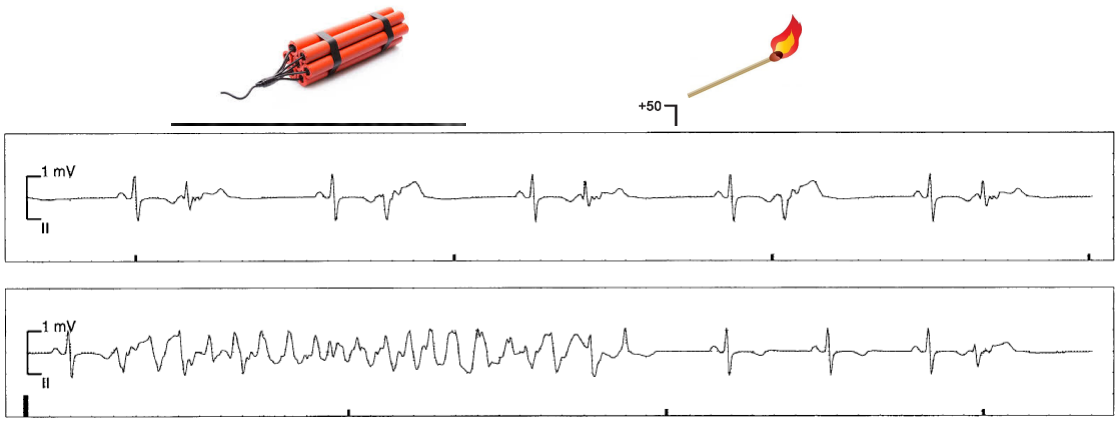


JACC 2018;72(14)

Figure 2: Causes of Sudden Cardiac Death



AER 2018;7(2)



Edema
Scar

- repolarization
- autonomic modulation

Adv Physiol Educ 2017(41)

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 23, 2005 VOL. 352 NO. 25

Sudden Death in Patients with Myocardial Infarction and Left Ventricular Dysfunction, Heart Failure, or Both

VALIANT 2003

Valsartan v captopril
AM
EF < 40% or clinical HF

NEJM 2003;349(20)
NEJM 2005;352(25)

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7% had SCD within 3 years of AMI

Highest SCD rate early after AMI

First 30 days:
1.4% SCD rate

2 year monthly steady-state:
0.14% SCD rate

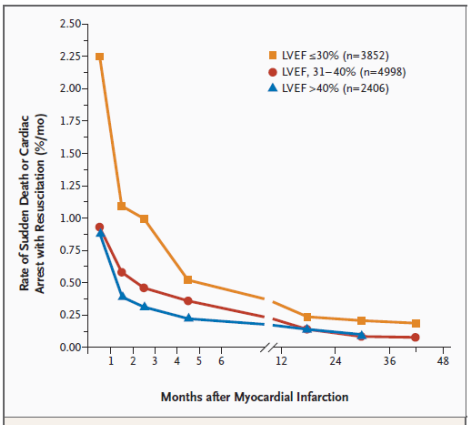


Figure 2. Rate of Sudden Death or Cardiac Arrest with Resuscitation over the Course of the Trial in the Three Categories of Left Ventricular Ejection Fraction (LVEF).
The analysis was restricted to patients for whom data on LVEF were available. The average rate (percentage per month) is shown at the midpoint of each period.

NEJM 2005;352(25)

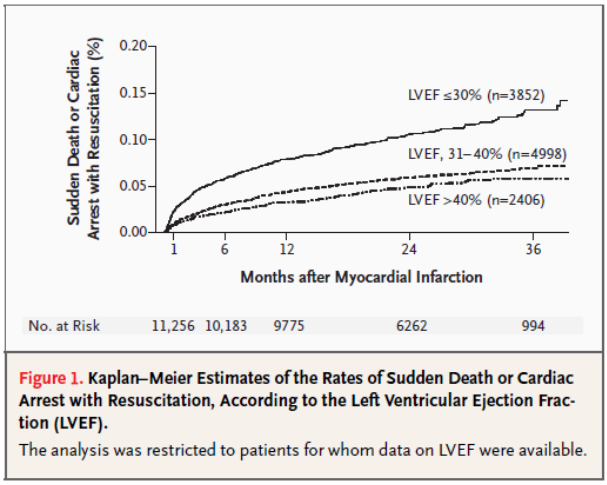


Figure 1. Kaplan–Meier Estimates of the Rates of Sudden Death or Cardiac Arrest with Resuscitation, According to the Left Ventricular Ejection Fraction (LVEF).
The analysis was restricted to patients for whom data on LVEF were available.

Lower EF = Higher SCD rate

Predictors of SCD
- Old age
- Higher HR
- Lower EF
- BB intolerance
- Prolonged QRS
- Abnormal HR variability
- NSVT
- Sustained VT on EPS
- Late potentials

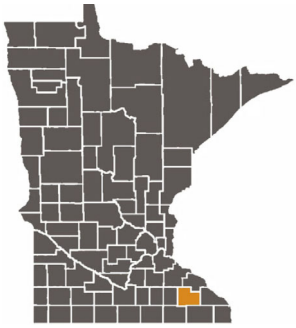
NEJM 2005;352(25)

Original Contribution

November 5, 2008

Sudden Death After Myocardial Infarction

A. Selcuk Adabag, MD, MS; Terry M. Therneau, PhD; Bernard J. Gersh, MB, ChB, DPhil; et al



JAMA. 2008;300(17)

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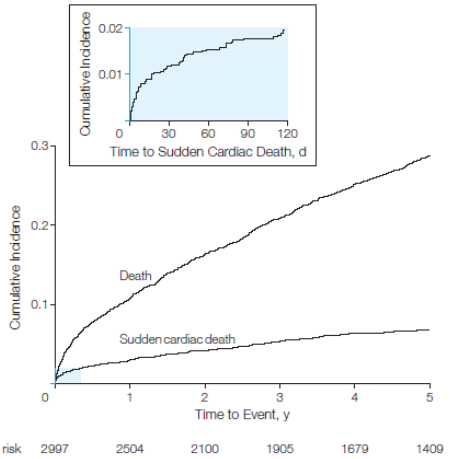
First 30 days:
1.2% SCD rate

Monthly steady-state:
0.12% SCD rate

Figure 1. Cumulative Incidence of Sudden Cardiac Death and All-Cause Mortality After Myocardial Infarction Among Residents of Olmsted County, Minnesota



The blue area on the plot represents the cumulative incidence of sudden death during the first 120 days after the index myocardial infarction.

JAMA 2008;300(17)

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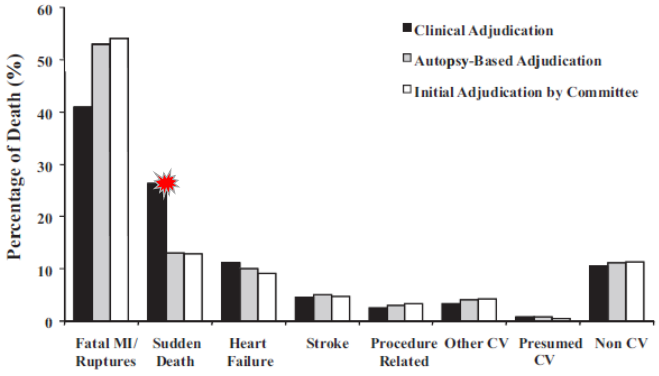
VALIANT: clinical adjudication versus autopsy

15% of deaths underwent autopsy

42% of arrhythmic deaths reclassified

- 26% recurrent MI
- 12% cardiac rupture
- 4% pump failure



Circulation. 2010;122:597-602

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OPTIMAAL: clinical adjudication versus autopsy

19% of deaths underwent autopsy

62% of arrhythmic deaths reclassified

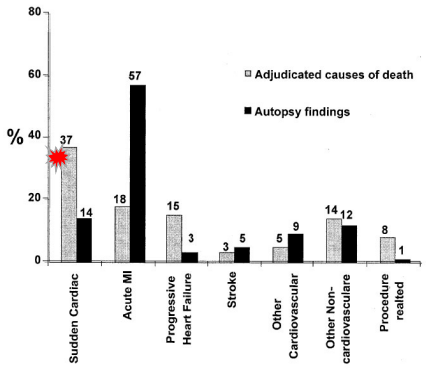

Figure 1 Causes of death in all autopsied patients (n = 180) before and after the result of autopsy was used to determine cause of death.

AJM 2005;118:752-758

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Early Post-AMI Sudden Cardiac Arrest Pharmacologic Primary Prevention

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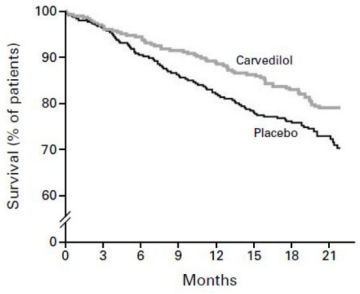
BB



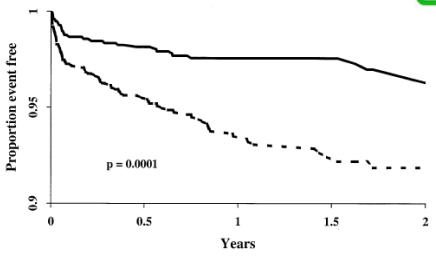


Figure 2. Survival free of any ventricular arrhythmia. **Dotted line** = placebo; **solid line** = carvedilol.

CAPRICORN 2005

AMI within 21d

EF < 40%

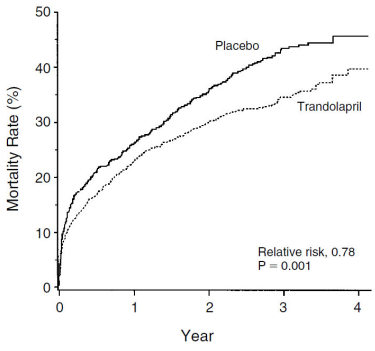
JACC 2005;45(4)

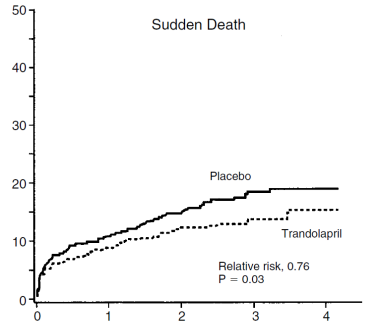
ACEi

TRACE 1995

AMI within 7d

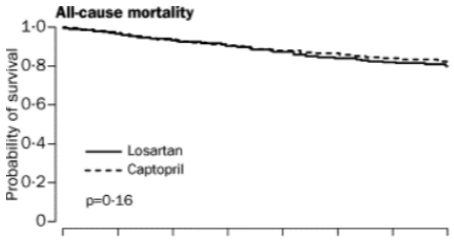
EF < 35%

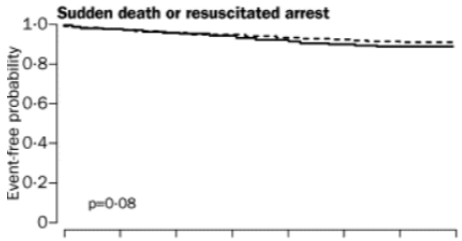




NEJM 1995;333:1670-1677

ARB



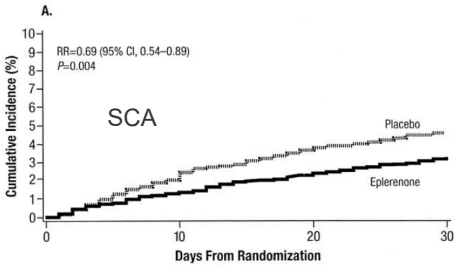


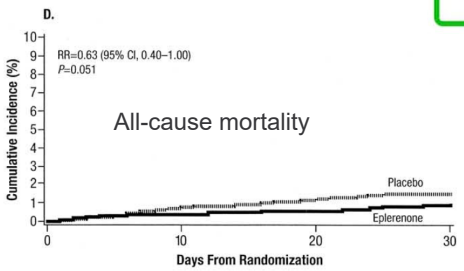
OPTIMAAL 2003

AMI within 10d
EF < 35%

Lancet 2002;360
NEJM 2003;349

ARA



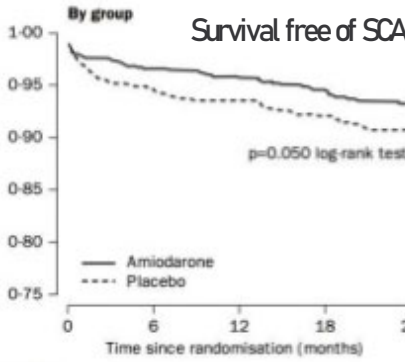


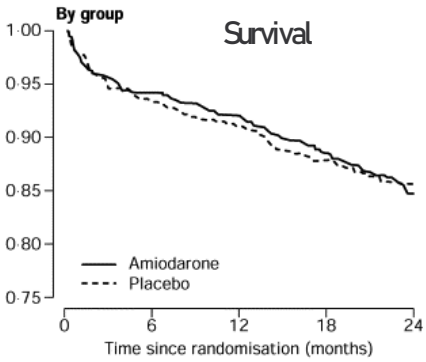
EPHESUS 2005

AMI within 3–14d
EF < 40%

JACC 2005;46

Amiodarone





EMAT 1997

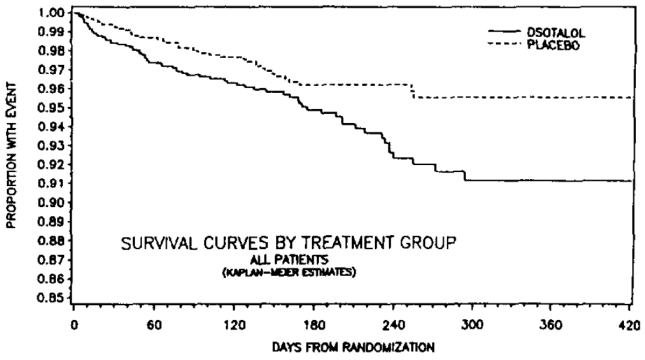
AM during hospitalization
EF < 40%

Lancet 1997;350

Sotalol

SWORD 1996

AM within 42d
EF < 40%

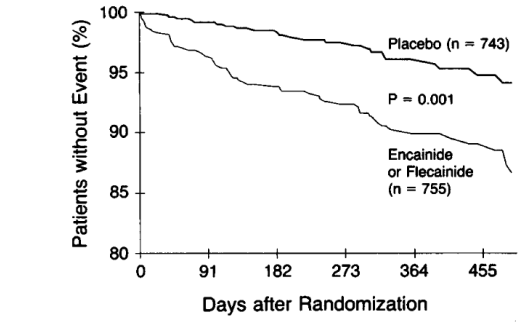


Lancet 1996;348(924)

Class IC

CAST 1991

AM with 6d – 2yrs
EF < 40%
PVCs



Placebo	743	625	516	412	292	181
Active drug	755	619	507	392	286	186

NEJM 1991(324)12:781-788

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Pharmacologic Therapy Summary

Medication	Decreases Early SCD	Decreases Early All-Cause Mortality
BB	Yes	Yes
ACEi	Yes	Yes
ARB	Yes	Yes
ARA	Yes	Yes
Amiodarone	Yes	No
Sotalol	No	No
Class IC	No	No

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Pharmacologic Therapy Summary

Medication	Decreases Early SCD	Decreases Early All-Cause Mortality
BB	Yes	Yes
ACEi	Yes	Yes
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Sotalol	No	No
Class IC	No	No

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Remote Post-AMI Sudden Cardiac Arrest Device Primary Prevention

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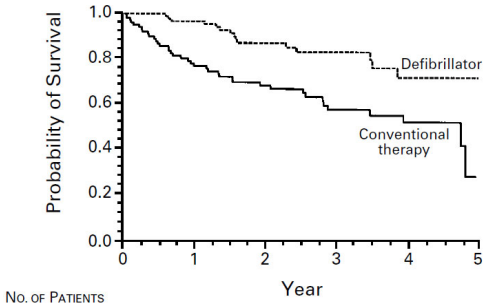
ORIGINAL ARTICLE

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

MADIT I 1996

ICM with EF < 35%
NSVT
EPS



No. of Patients						
Defibrillator	95	80	53	31	17	3
Conventional therapy	101	67	48	29	17	0

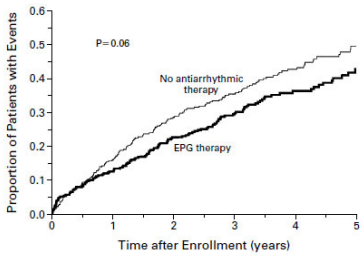
NEJM 1996;335:1933-40

ORIGINAL ARTICLE

Electrophysiologic Testing to Identify Patients with Coronary Artery Disease Who Are at Risk for Sudden Death

MUSTT 1999

ICM with EF < 40%
NSVT
EPS



No. at Risk						
No antiarrhythmic therapy	353	296	248	185	122	71
EPG therapy	351	306	270	203	121	70

Figure 2. Kaplan–Meier Estimates of the Rates of Death from All Causes. EPG denotes electrophysiologically guided.

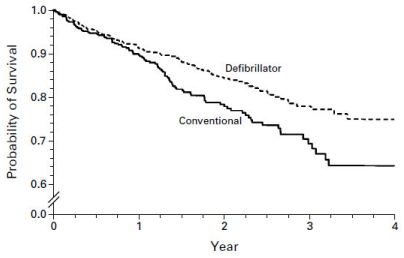
NEJM 1999;341:1882-90

MADIT II 2002

ICM with EF < 30%

ORIGINAL ARTICLE

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



No. at Risk					
Defibrillator	742	503 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

Figure 2. Kaplan–Meier Estimates of the Probability of Survival in the Group Assigned to Receive an Implantable Defibrillator and the Group Assigned to Receive Conventional Medical Therapy.
The difference in survival between the two groups was significant (nominal P=0.007, by the log-rank test).

NEJM 2002;346:877-83

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Remote Post-MI ICD Evidence

Trial	Inclusion	Why not applicable
MADIT 1996	ICM with EF < 35% NSVT EPS	Required > 3 weeks from AMI Required > 2 months from CABG Required > 3 months from PCI
MUSTT 1999	ICM with EF < 40% NSVT EPS	84% > 30 days out from AMI 50% > 3 years out from AMI
MADIT II 2002	ICM with EF < 30%	Required > 1 month from AMI Required > 3 month from revasc

NEJM 2002;346:877-83
NEJM 1996;335:1933-40
NEJM 1999;341:1882-90

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NEJM 2002;346:877-83
NEJM 1996;335:1933-40
NEJM 1999;341:1882-90

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Early Post-AMI Sudden Cardiac Arrest Device Primary Prevention

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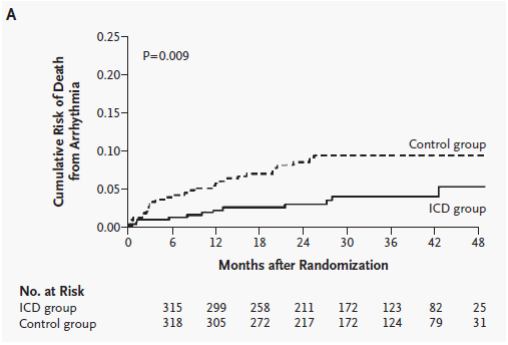
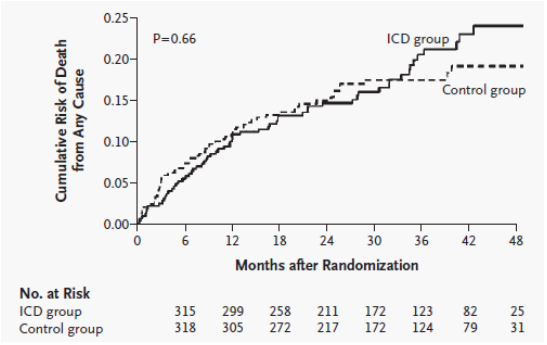
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 9, 2004 VOL. 351 NO. 24

Prophylactic Use of an Implantable Cardioverter–Defibrillator after Acute Myocardial Infarction

DINAMIT 2004

6–40 days post MI
EF < 35%
Abn HR variability





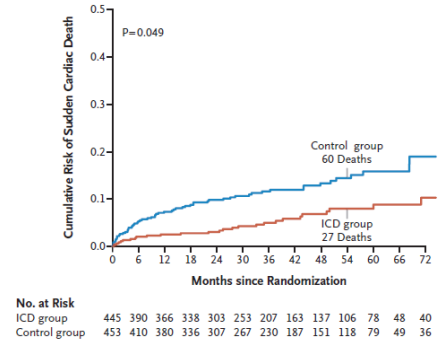
NEJM 2004;351:2481-8

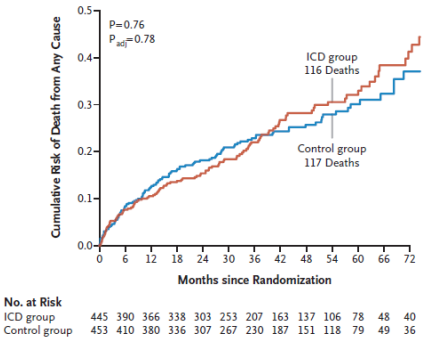
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 8, 2009 VOL. 361 NO. 15

Defibrillator Implantation Early after Myocardial Infarction

IRIS 2009

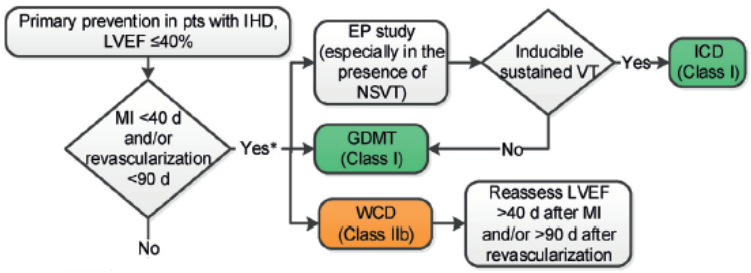
5–31 days post MI
EF < 40%
NSVT
Elevated resting HR





NEJM 2009;361:1427-36

FIGURE 4 Primary Prevention of SCD in Patients With Ischemic Heart Disease



Trial	Criteria	Translation to guideline
DINAMIT (-)	Enrolled **6-40** days after AMI	Must be > **40** days from AMI
MADIT II (+)	Enrolled **90** days after revascularization	Must be > **90** days from revascularization

JACC 2018;72(14)
NEJM 2009;361:1427-36
NEJM 2004;351:2481-8

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National Coverage Determination (NCD) for Implantable Automatic Defibrillators (20.4)

AMI + Low EF = ICD unless

- AMI within 40 days
- Revascularization within 90 days
- NYHA IV heart failure
- Revascularization candidate

2. Patients with a prior
   - New York He
   - Had a Coron
   (3) months;
   - Had an MI w
   - Clinical symp

e:

asty and/or stenting, within the past three

For these patients i
1861(r)(1) of the So
specialist as define
making encounter n

and a physician (as defined in Section
tant, nurse practitioner, or clinical nurse
D implantation. The shared decision

CMS.gov accessed 1/24/20

HOPE DISCOVERED HERE | Minneapolis Heart Institute Foundation

PACE 2004; 27:4–9

Zoll.com accessed 1/22/2020

Wearable Cardioverter-Defibrillator Use in Patients Perceived to Be at High Risk Early Post-Myocardial Infarction

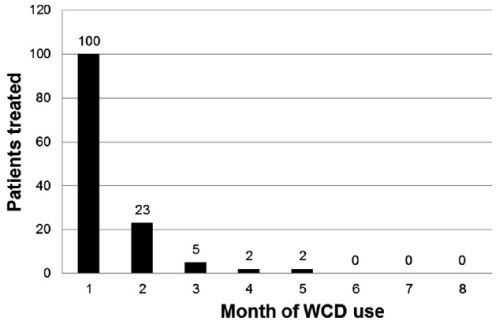
8453 patients

1.6% received appropriate shocks

1.2% received appropriate shocks within 30 days of AMI

1.1% received inappropriate shocks

91% survived event to emergency room
- Average of 2 shocks per event



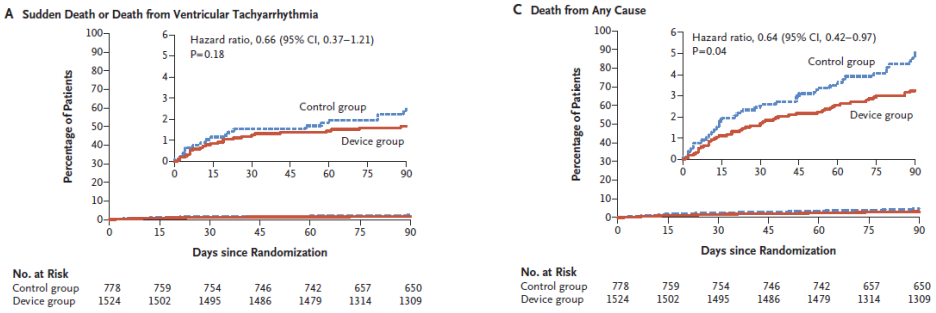
JACC 2013;62:2000–7

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 27, 2018 VOL. 379 NO. 13

Wearable Cardioverter–Defibrillator after Myocardial Infarction

VEST 2018

AMI
EF < 35%
< 7 days after discharge



NEJM 2018;379:1205-15

Table 3. Primary, Secondary, and Other Outcomes.*

Event	Device Group (N=1524)	Control Group (N=778)	Relative Risk (95% CI)	P Value
Arrhythmic death				
No. of patients (%)†	25 (1.6)	19 (2.4)	0.67 (0.37–1.21)	0.18
Device worn at time of death or event leading to death — no.	9	0	NA	
Death from any cause				
No. of patients (%)	48 (3.1)	38 (4.9)	0.64 (0.43–0.98)	0.04
Device worn at time of death or event leading to death — no.	12	0	NA	

- 1.4% received appropriate shocks
  - 100% converted VT/VF
  - 70% survived event (30% developed PEA, bradyarrhythmia, asystole)
  - 65% survived to trial conclusion
- 0.6% received inappropriate shocks
- 4.5% aborted shock by pressing response button

NEJM 2018;379:1205-15

LifeVest Wearable Defibrillator Reduces Total Mortality By 36 Percent At 90 Days

The Landmark VEST Trial Shows 90-Day Use of LifeVest WCD Reduces Total Mortality After Heart Attack

Zoll.com accessed 1/22/2020

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Recommendations for Wearable Cardioverter-Defibrillator
References that support the recommendations are summarized in Online Data Supplement 56.

COR	LOE	RECOMMENDATIONS
IIa	B-NR	1. In patients with an ICD and a history of SCA or sustained VA in whom removal of the ICD is required (as with infection), the wearable cardioverter-defibrillator is reasonable for the prevention of SCD (S11.2-1–S11.2-4).
IIb	B-NR	2. In patients at an increased risk of SCD but who are not ineligible for an ICD, such as awaiting cardiac transplant, having an LVEF of 35% or less and are within 40 days from an MI, or have newly diagnosed NICM, revascularization within the past 90 days, myocarditis or secondary cardiomyopathy or a systemic infection, the wearable cardioverter-defibrillator may be reasonable (S11.2-1–S11.2-5).

JACC 2018;72(14)

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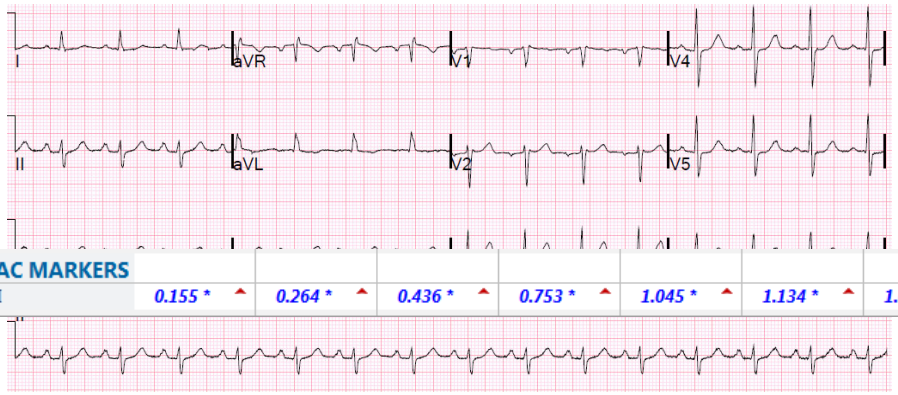
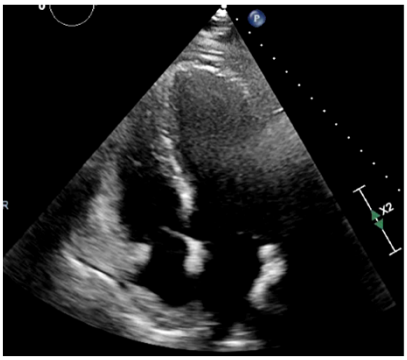
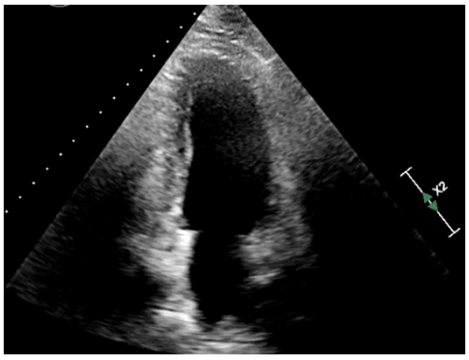
Case 3: Inpatient consult



CARDIAC MARKERS							
Troponin I	0.155 *	0.264 *	0.436 *	0.753 *	1.045 *	1.134 *	1.083 *

60M with HTN and T2DM admitted with syncope





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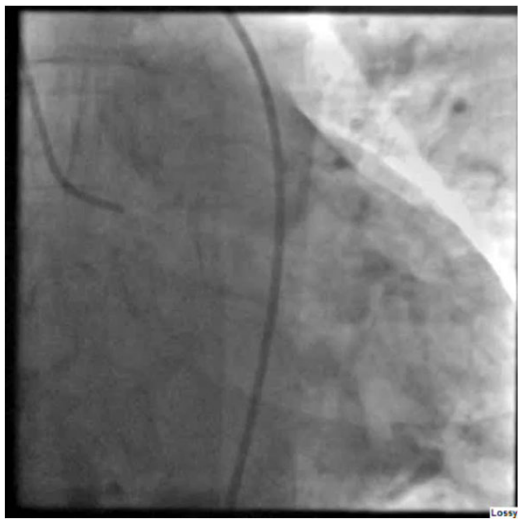
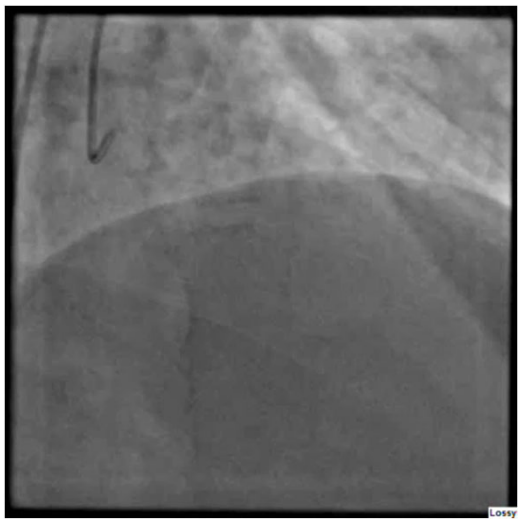

Lossy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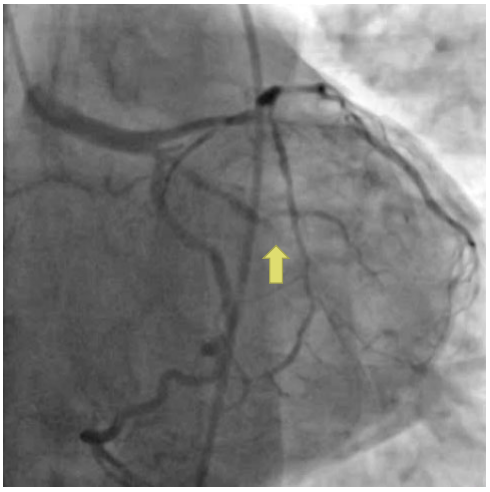

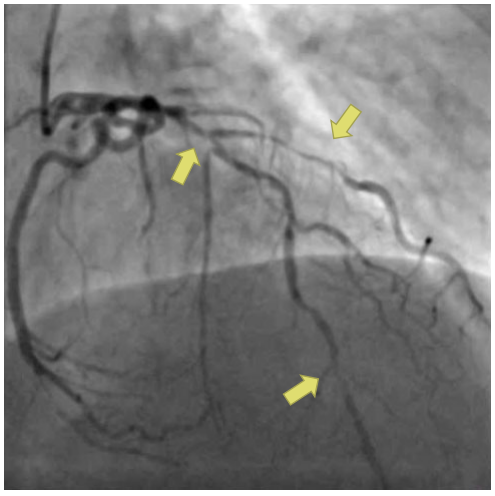

Discharged on hospital day #3

Problem List

- Multivessel coronary disease awaiting surgical revascularization
- High risk syncope, cannot rule out ventricular arrhythmia
- HTN, T2DM

Plan

- Asa, statin, BB, ARB
- WCD
- Follow up with cardiology in 3 days (at home in Texas)

Summary

- Sudden cardiac death is a messy clinical endpoint without autopsy
- The vast majority of SCD is attributed to ischemic heart disease
- Risk of SCD is highest in 1st month after AMI
- BB*, ACEi, ARB, and ARA* have best evidence for early post-AMI SCD prevention
- ICD therapy is mostly not available in early post-AMI period

Summary

- WCD requires patient participation
- WCD data is cloudy
- WCD successfully aborts lethal ventricular arrhythmias
  - Despite this 30% do not survive event
- WCD risks inappropriate shocks
  - 3 aborted shocks for every 1 appropriate shock
- WCD is assigned a class 2b recommendation: ("may be reasonable") in ACC/AHA/HRS 2017 VA guideline

Sudden Cardiac Death After Myocardial Infarction

Minneapolis Heart Institute Grand Rounds
February 18, 2020

@RobFraserMD

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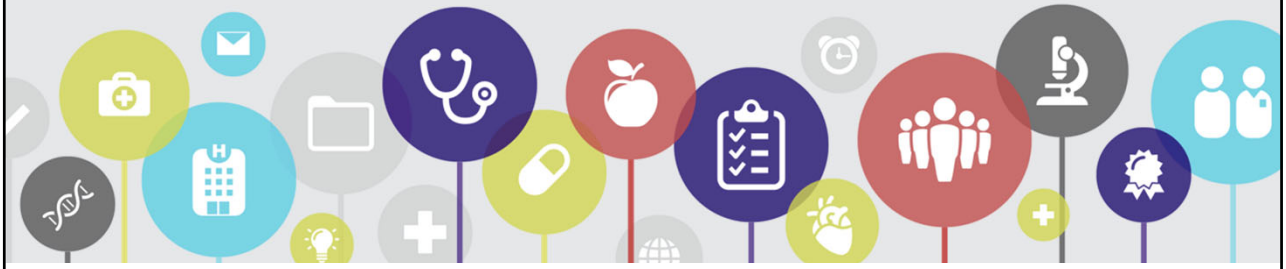

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