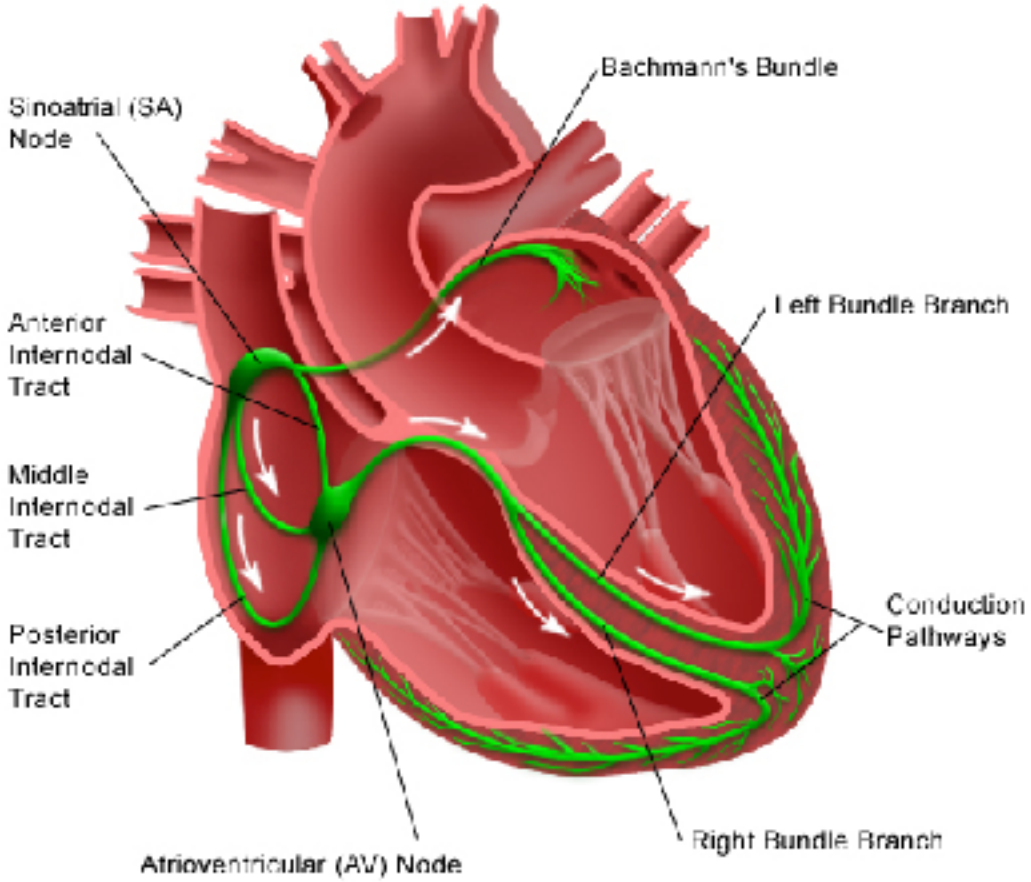
Introduction to Pacemakers and ICDs

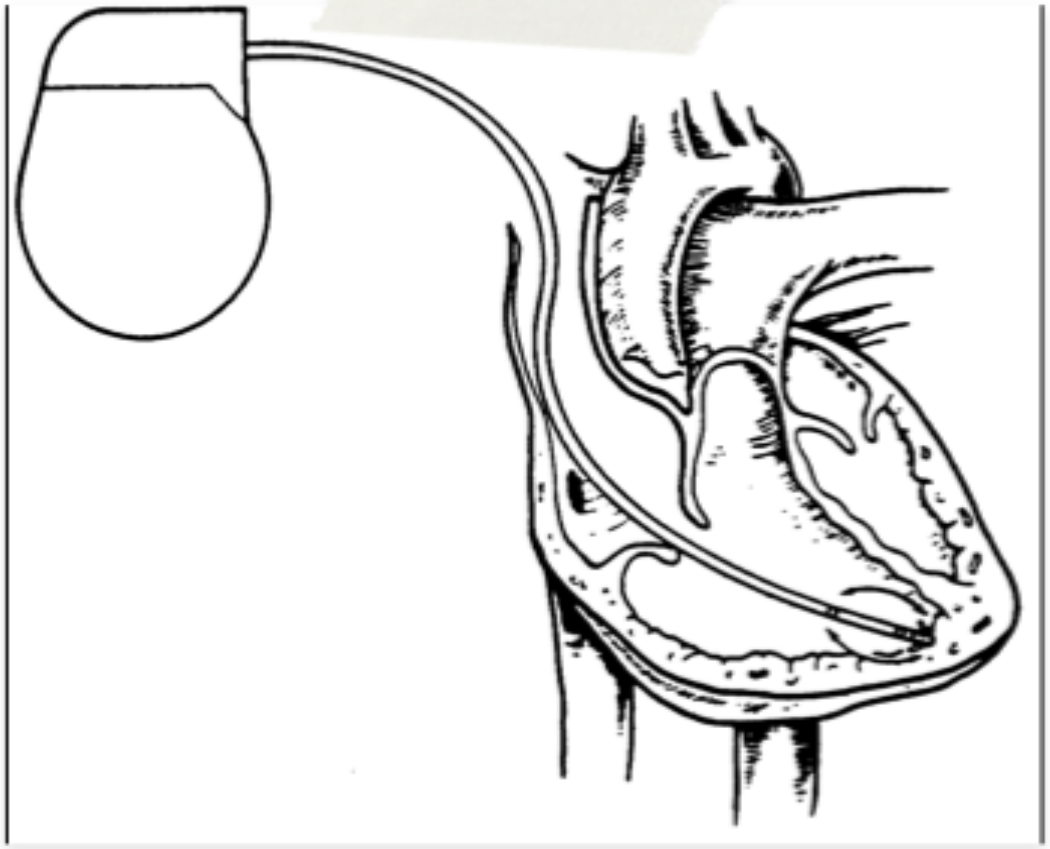
David Perkel MD

9/23/2015

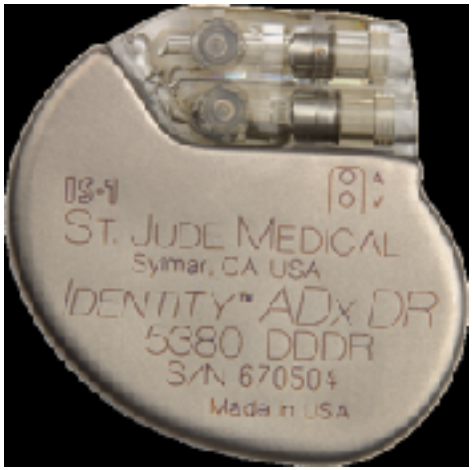
Conduction System



Pacemaker system

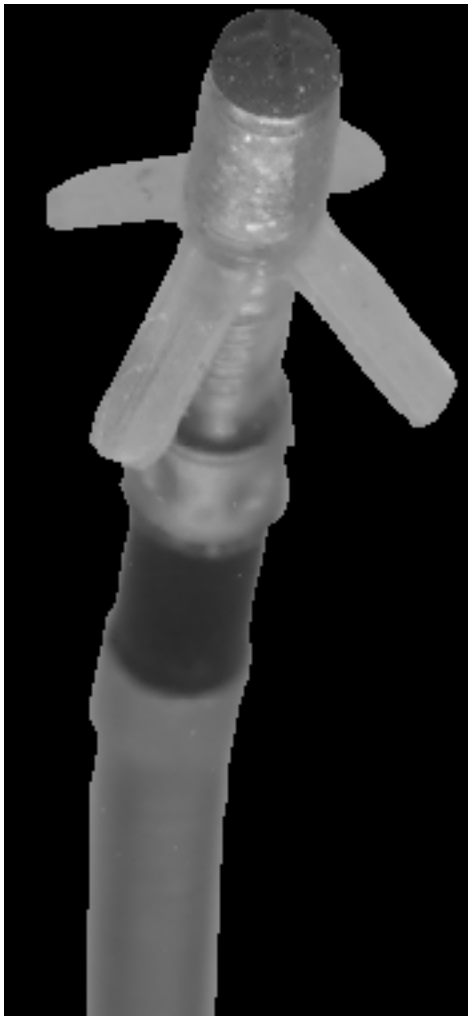


Pulse Generator

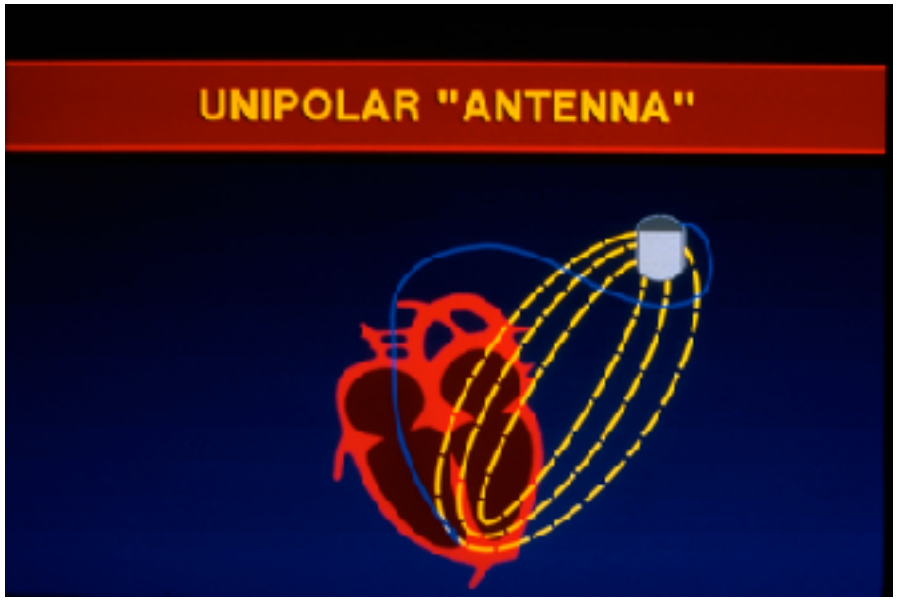


- Composed of clear plastic header titanium casing or “can”
- Volume 10-15 cm^3 pacemakers to 30-35 cm^3 for ICDs
- Includes battery, voltage/supply control unit, microprocessor, ROM, RAM, telemetry control, system controller, rate-adaptive sensors, filters, sensing amplifier, pacing output circuit/control unit
- ICDs also have transformer, capacitor and output circuitry

Leads

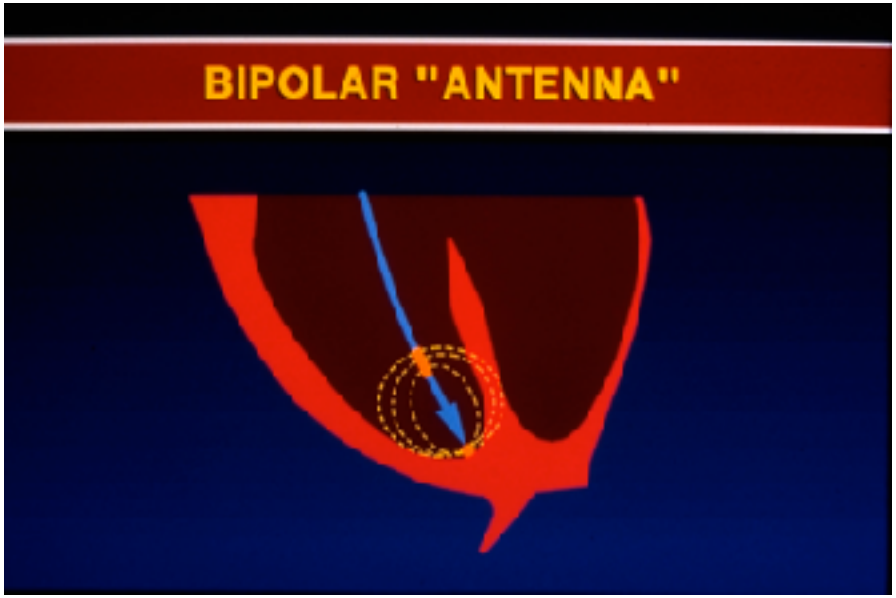


Unipolar Lead



sense and pace between tip and the “housing” can

Bipolar Lead



sense and pace between tip and ring electrode

Types

- Single Chamber
- Dual Chamber
- Biventricular Pacing devices
- Epicardial Leads

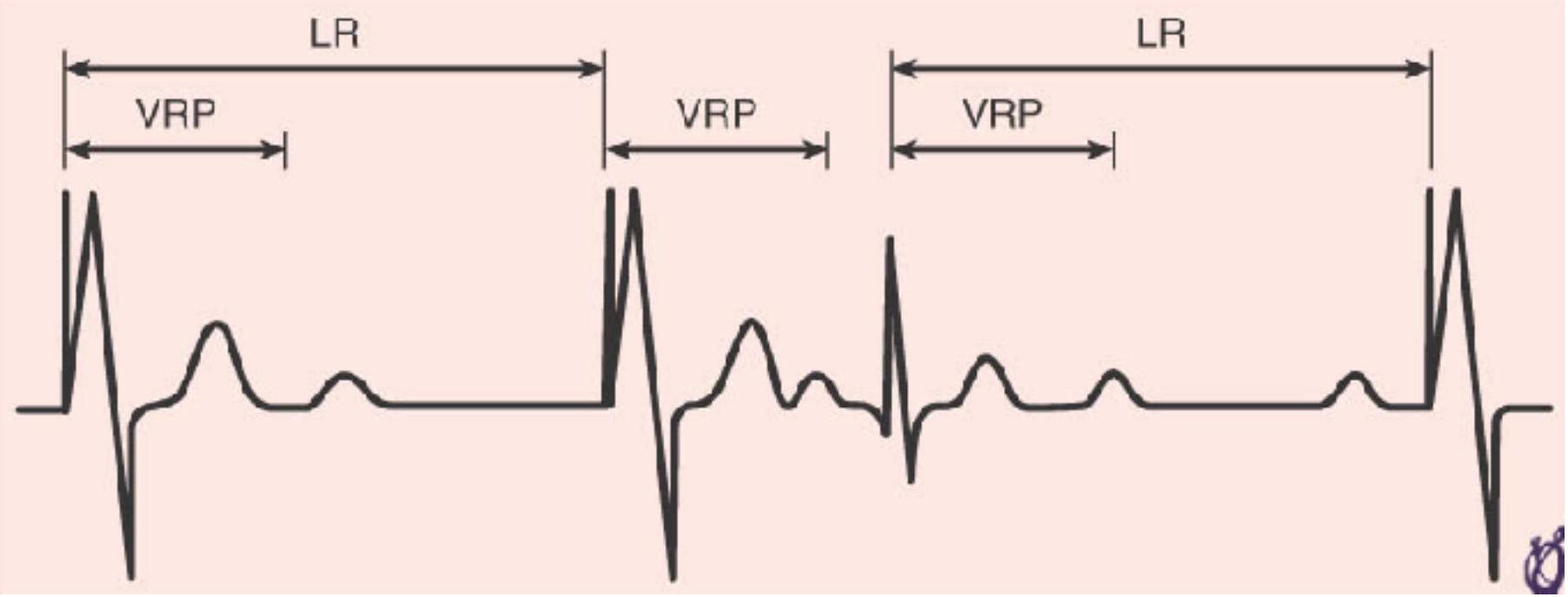
Revised NASPE/BPEG code for pacing

Position:	I	II	III	IV	V
Category:	**Chamber(s) Paced**	**Chamber(s) Sensed**	**Response to Sensing**	**Rate Modulation**	**Multisite Pacing**
	O = None	**O** = None	**O** = None	**O** = None	**O** = None
	A – Atrium	**A** – Atrium	**T** – Triggered	**R** – Rate modulation	**A** – Atrium
	V = Ventricle	**V** = Ventricle	**I** = Inhibited		**V** = Ventricle
	D = Dual (A + V)	**D** = Dual (A + V)	**D** = Dual (T + I)		**D** = Dual (A + V)
Manufacturers' designation only:	**S** = Single (A or V)	**S** = Single (A or V)			

VVI

- Basic single-chamber pacing mode which allows pacing to occur when ventricular rate slows below lower rate limit
- V paced and V sensed, inhibited by native sensed beat
- No AV synchrony (pacemaker syndrome)
- Indicated for patients with chronic atrial fibrillation

VVI Demand pacing



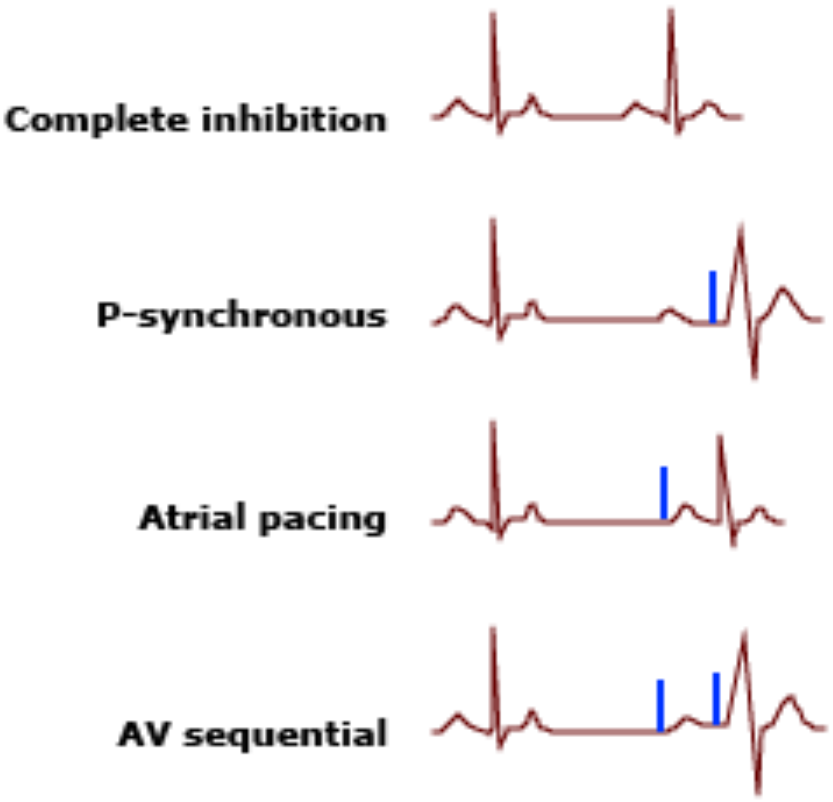
Atrioventricular (AV) synchrony

- Atrial filling occurs throughout diastole when mitral valve is open, concludes with atrial contraction
- Coordination of atrial and ventricular contraction is termed AV synchrony
- AV synchrony increases cardiac output by 25-30%
- Patients with severe diastolic dysfunction benefit from AV synchrony

Pacemaker Syndrome

- Loss of AV synchrony causing atrial contraction against a closed mitral valve
- Worst scenario is retrograde VA conduction with VVI pacing but can also occur with a severe PR prolongation
- Symptoms can range from mild to severe
- Dizziness, syncope, fatigue, cough, dyspnea, orthopnea, PND and throat fullness

Rhythms seen with a normal DDD pacemaker



MOST Trial

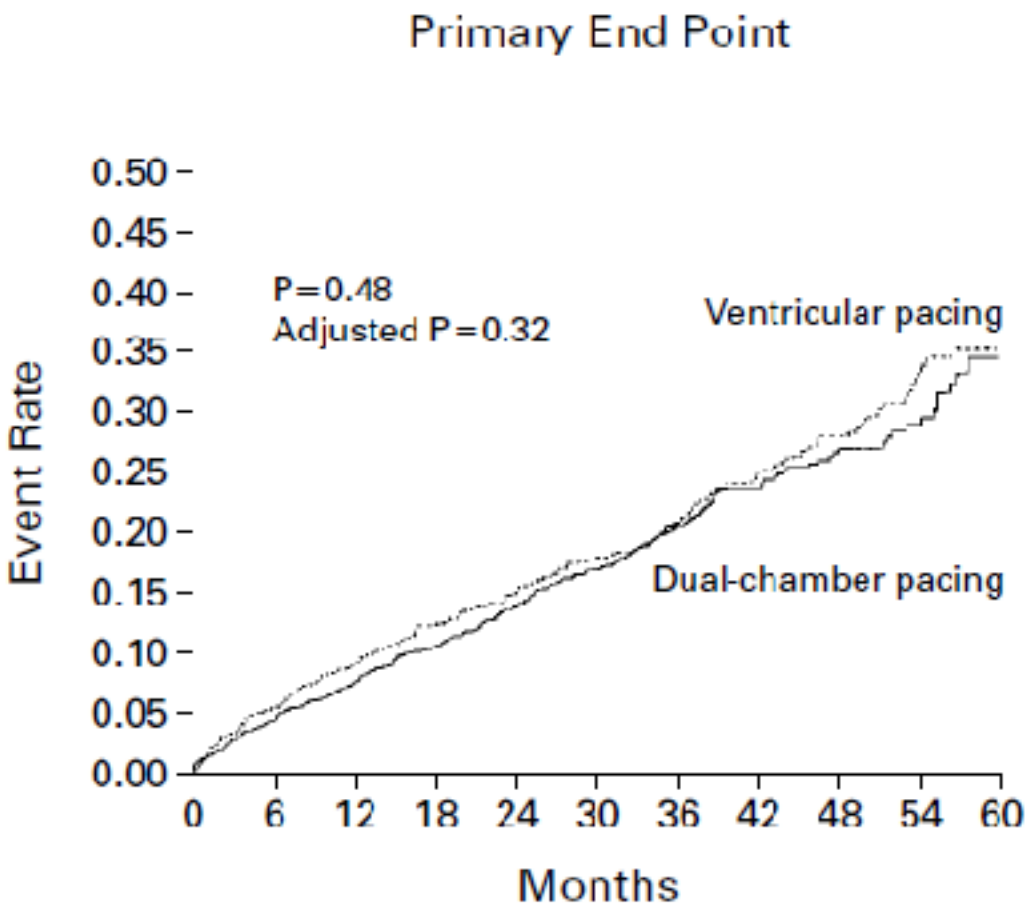
The New England Journal of Medicine

VENTRICULAR PACING OR DUAL-CHAMBER PACING FOR SINUS-NODE DYSFUNCTION

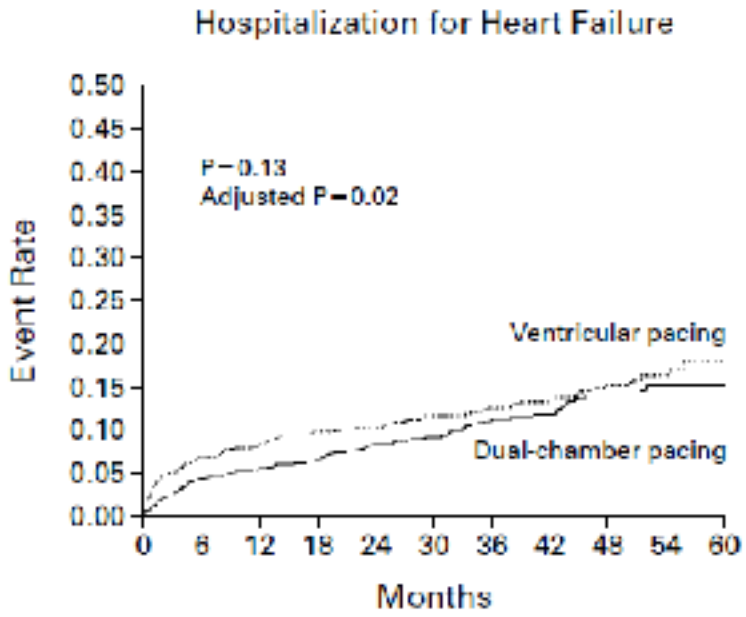
GERVASIO A. LAMAS, M.D., KERRY L. LEE, PH.D., MICHAEL O. SWEENEY, M.D., RUSSELL SILVERMAN, M.D., ANGEL LEON, M.D., RAYMOND YEE, M.D., ROGER A. MARINCHAK, M.D., GREG FLAKER, M.D., ELEANOR SCHRON, M.S., R.N., E. JOHN ORAV, PH.D., ANNE S. HELLKAMP, M.S., AND LEE GOLDMAN, M.D., FOR THE MODE SELECTION TRIAL IN SINUS-NODE DYSFUNCTION*

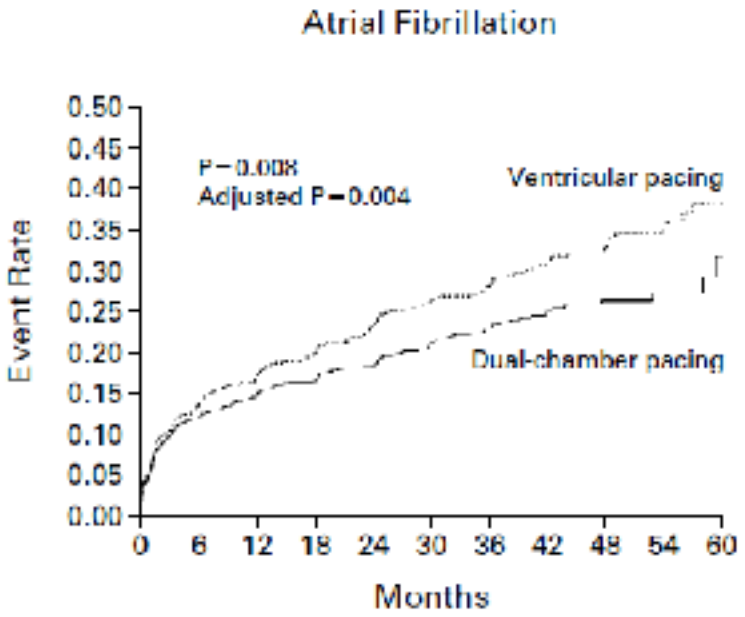
- RCT of DDD vs VVI for sinus node dysfunction patients
- Mode Selection Trial

Incidence of Mortality did not differ



Improved HF and Afib with DDD



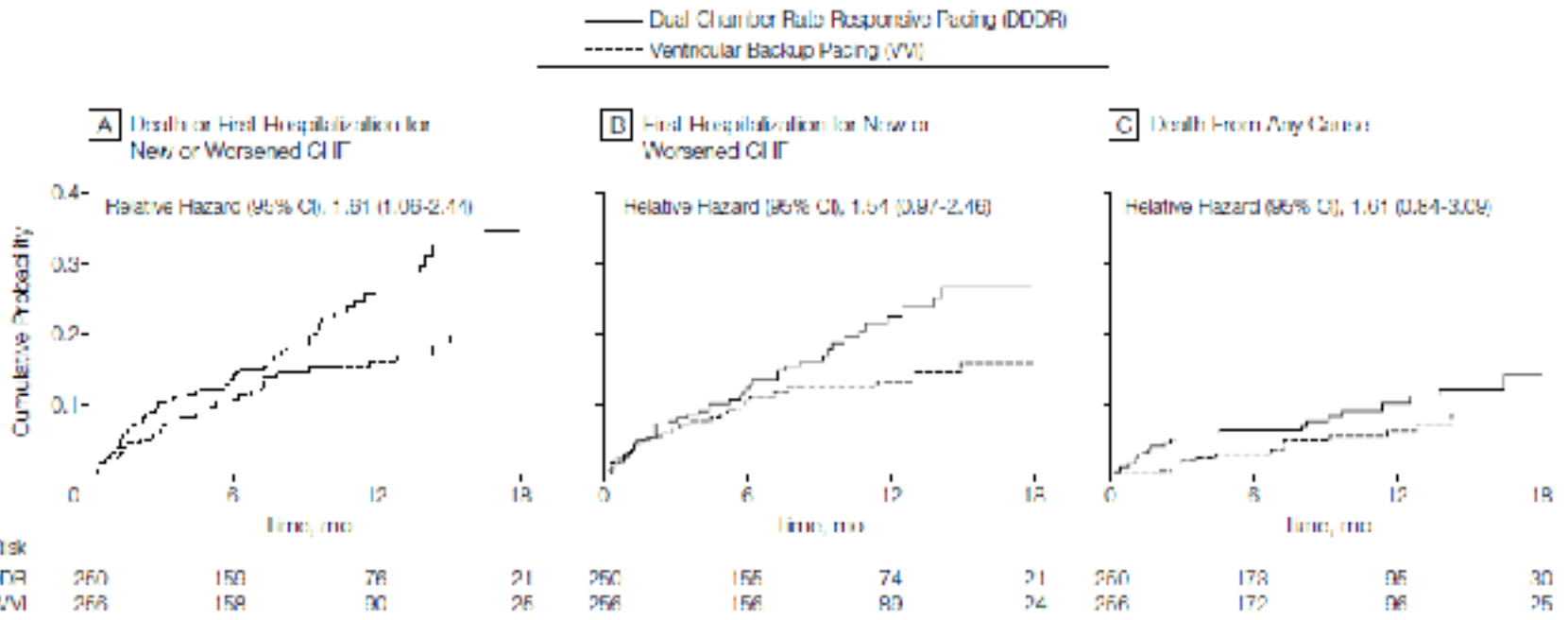


Dual-Chamber Pacing or Ventricular Backup Pacing in Patients With an Implantable Defibrillator

The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial

- ICD patients without indication for antibradycardia pacing
- All patients had dual chamber ICD implanted
- Randomized to VVI 40 versus DDDR 70

Figure 2. Survival to Main End Points in the Trial



For all plots, time zero is the day of randomization. CI indicates confidence interval. A, Survival to death or first hospitalization for congestive heart failure (CHF). Unadjusted $P = .02$; adjusted for sequential monitoring, $P = .03$. B, Survival to first hospitalization for CHF. Patients are censored at death. Log rank $P = .07$. C, Survival to death from any cause. Log rank $P = .15$.

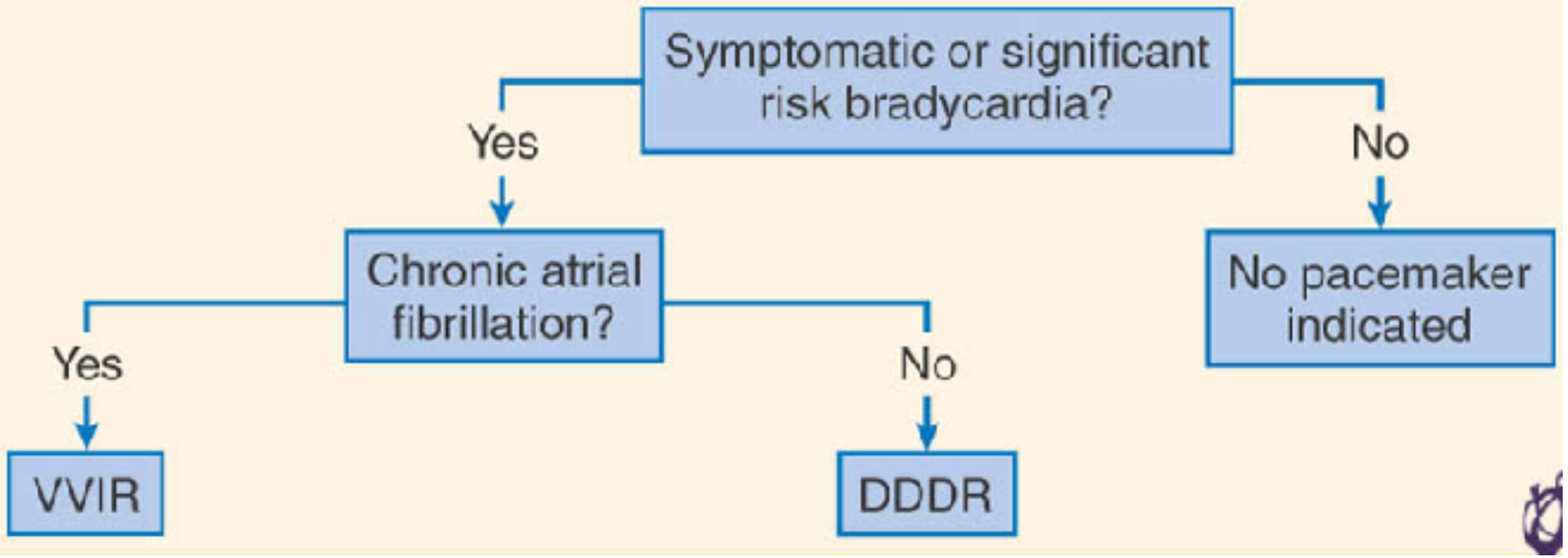
Canadian Trial of Physiological Pacing (CTOPP)

- 2568 patients requiring a pacemaker for symptomatic bradycardia
- Randomized to ventricular (VVI) (n=1474) or physiological pacemaker (AAI/DDD) (n=1094)
- No difference in death/stroke @ mean 6.4 y FU
- ↓ Development of AF in AAI/DDD arm
  - RRR 20.1% (95% CI 5.4 to 32.5; p=0.009)
  - Benefit not apparent until after 2 y
- In the AAI/DDD arm only 5.2% had an atrial pacemaker
- 7% dropout in VVI arm; 25% in AAI/DDD

AAI indicates atrial demand, VVI = ventricular demand, and DDD = fully automatic.

Kerr CR, Connolly SJ, Abdollah H, et al. Canadian Trial of Physiological Pacing: Effects of physiological pacing during long-term follow-up. Circulation 2004;109:357-62.

Pacemaker Algorithm

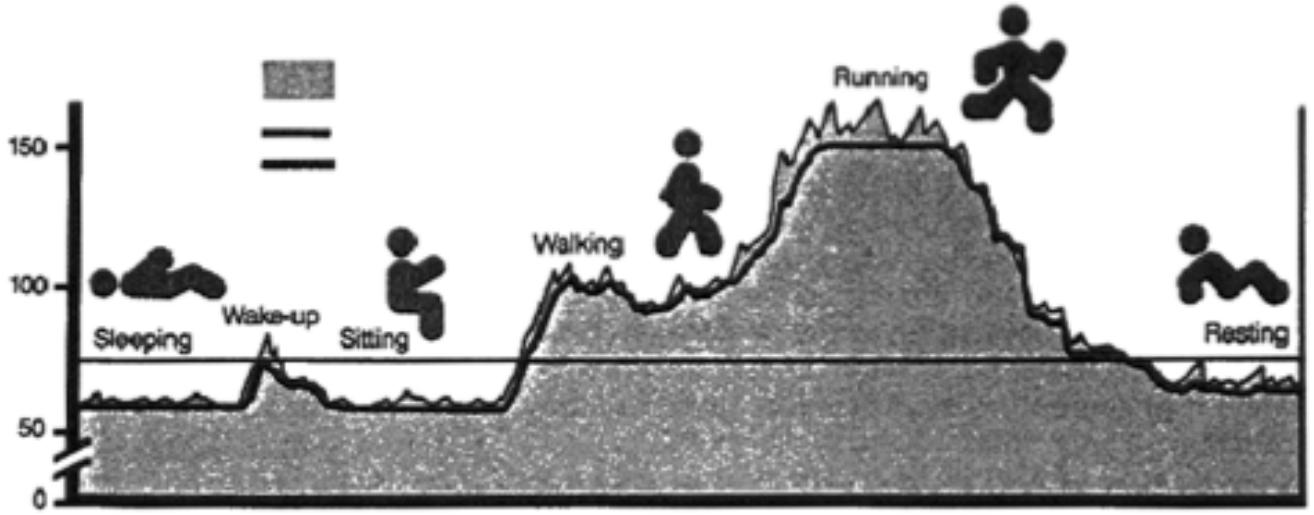


Goals of pacemaker therapy

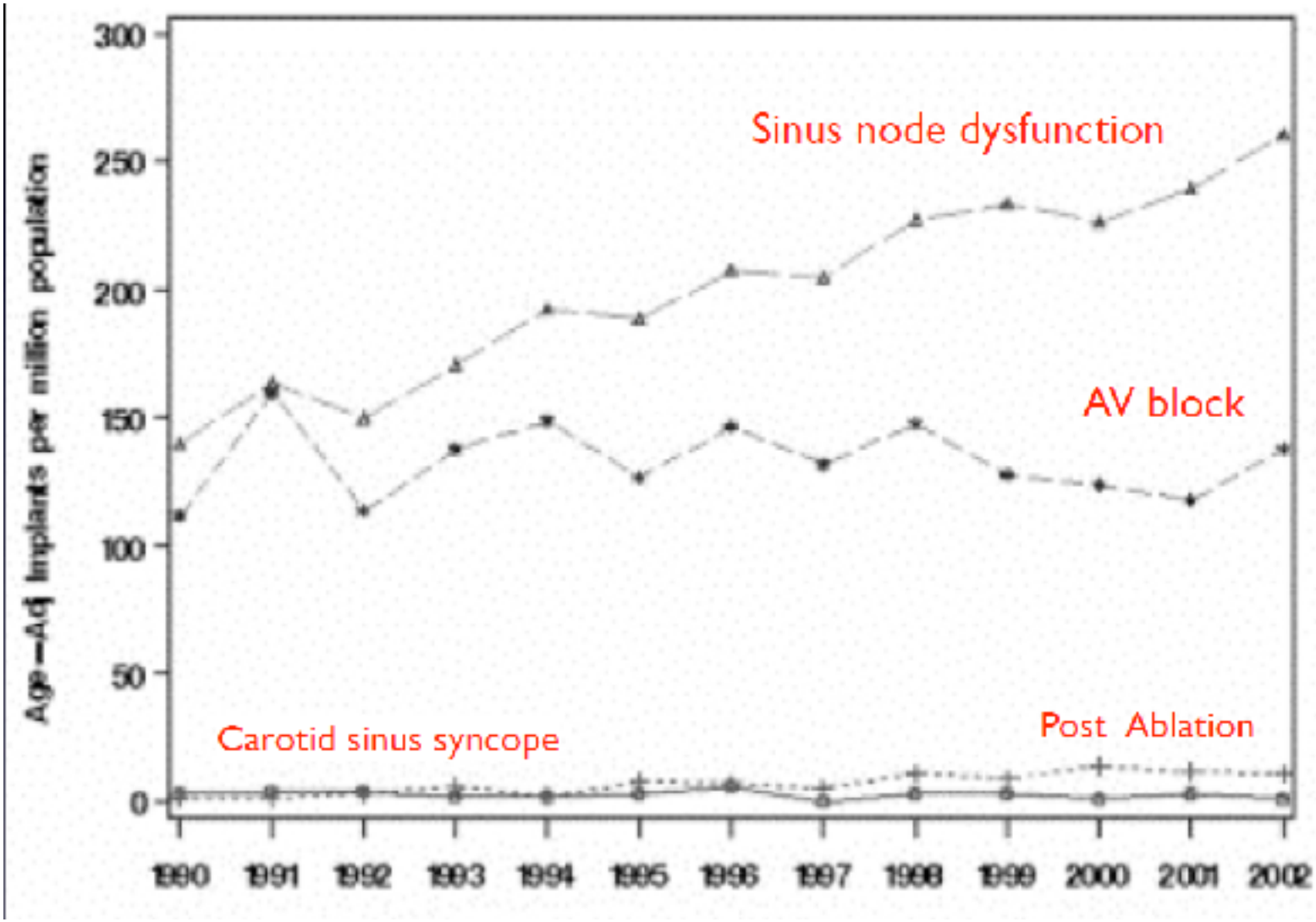
- Bradycardia pacing
- Restoration of AV synchrony

Rate Adaptive Pacing

- Pacing rate is adjusted to metabolic demand
- Sensor in the generator or lead
- Accelerometer vs minute ventilation vs cardiac motion
- Algorithms translate sensor values to pacing rate



Pacemaker Implantation rates



Classification of recommendations

CLASS I	CLASS IIa	CLASS IIb	CLASS III
Benefit >>> Risk	*Benefit >> Risk*	*Benefit ≥ Risk*	*Risk ≥ Benefit*
Procedure/Treatment **SHOULD** be performed/ administered	*Additional studies with focused objectives needed*	*Additional studies with broad objectives needed; additional registry data would be helpful*	Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
	IT IS REASONABLE to perform procedure/administer treatment	Procedure/Treatment **MAY BE CONSIDERED**	

Recommendations for Permanent Pacing in Sinus Node Dysfunction

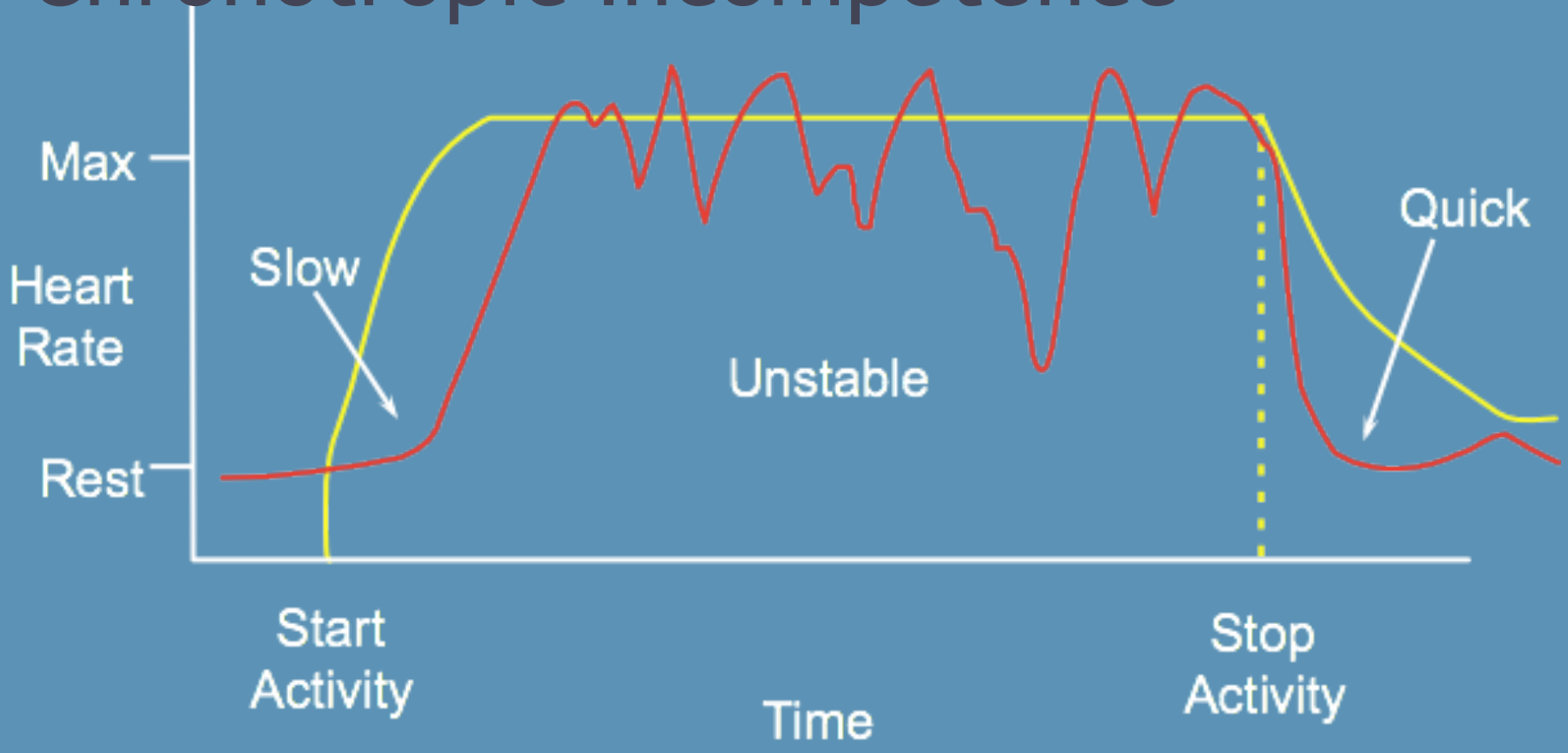
CLASS I

1. Permanent pacemaker implantation is indicated for SND with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms. (*Level of Evidence: C*) (53–55)
2. Permanent pacemaker implantation is indicated for symptomatic chronotropic incompetence. (*Level of Evidence: C*) (53–57)
3. Permanent pacemaker implantation is indicated for symptomatic sinus bradycardia that results from required drug therapy for medical conditions. (*Level of Evidence: C*)

CLASS III

1. Permanent pacemaker implantation is not indicated for SND in asymptomatic patients. (*Level of Evidence: C*)
2. Permanent pacemaker implantation is not indicated for SND in patients for whom the symptoms suggestive of bradycardia have been clearly documented to occur in the absence of bradycardia. (*Level of Evidence: C*)
3. Permanent pacemaker implantation is not indicated for SND with symptomatic bradycardia due to nonessential drug therapy. (*Level of Evidence: C*)

Chronotropic Incompetence

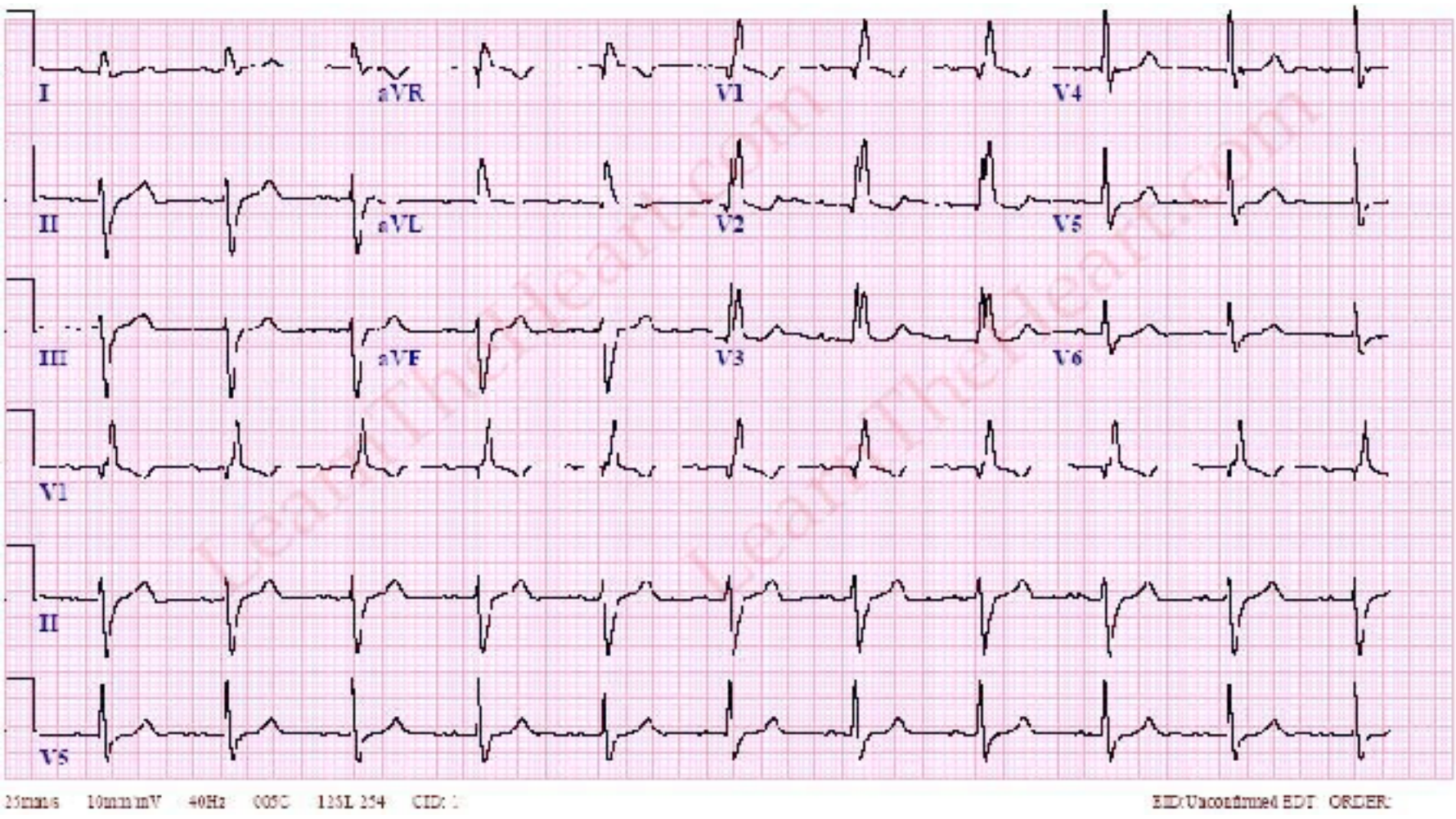


AV Block

- 3rd Degree or advanced 2nd degree AV Block and
  - Symptomatic (even for Wenckebach)
  - Requires bradycardic drugs (BB for afib)
  - Asystole>3 sec in sinus or 5 sec in afib
  - Escape rate <40 bpm or wide QRS escape rhythm
  - AV node ablation, post-op which persists
  - Neuromuscular diseases
- 2nd or 3rd degree with exercise
- 3rd degree block with LV dysfunction or CM

Class III for AV block

- Asymptomatic 1st degree AV block
- Asymptomatic Wenckebach above the His
- AV block expected to resolve and unlikely to recur
  - Drugs
  - Lyme disease
  - Sleep Apnea with nocturnal AV block
  - Early post op cardiac surgery
  - Transient increase in vagal tone


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
II
V5
25mm/s 10mm/mV 40Hz 005C 125L 254 CID: 1
EID:Unconfirmed EDT ORDER:

Bifascicular or Trifascicular block

Indications for PM placement

- intermittent 3rd degree
- 2nd degree type II or advanced AV block
- Alternating bundle branch block

Not Indicated

- Fasicular block without AV block
- Asymptomatic fascicular block with 1st degree

Acute MI

- 3rd degree AV block after a STEMI
- Persistent 2nd degree with alternating BBB
- Transient 2nd or 3rd degree infranodal block and associated BBB
- Persistent, symptomatic 2nd or 3rd degree block

Not Indicated

- Transient block without IVCD
- Acquired LAFB
- Asymptomatic 1st degree with BBB or fasicular

Sinus Node Dysfunction

- Symptomatic bradycardia or sinus pauses
- Symptomatic chronotropic incompetence
- Symptomatic bradycardia from required drug therapy

Not Indicated

- Asymptomatic sinus node dysfunction
- SND with symptoms documented in absence of bradycardia
- SND with symptoms due to non-essential drug therapy

Type II indications

- Chronic heart rate < 40 bpm in a minimally symptomatic patient IIb indication
- Syncope of unknown etiology with SND provoked on EPS in IIa indication

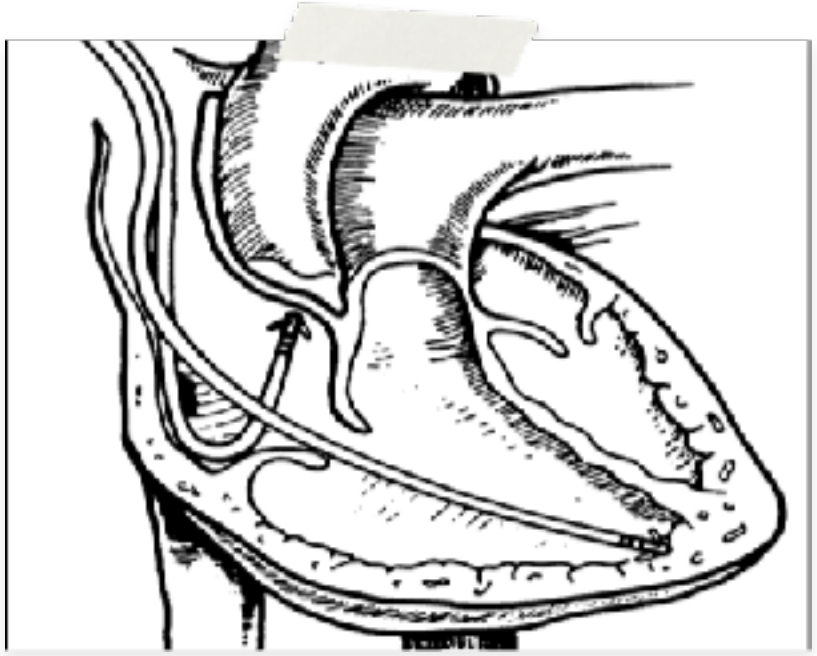
Neuromuscular diseases with AV Block

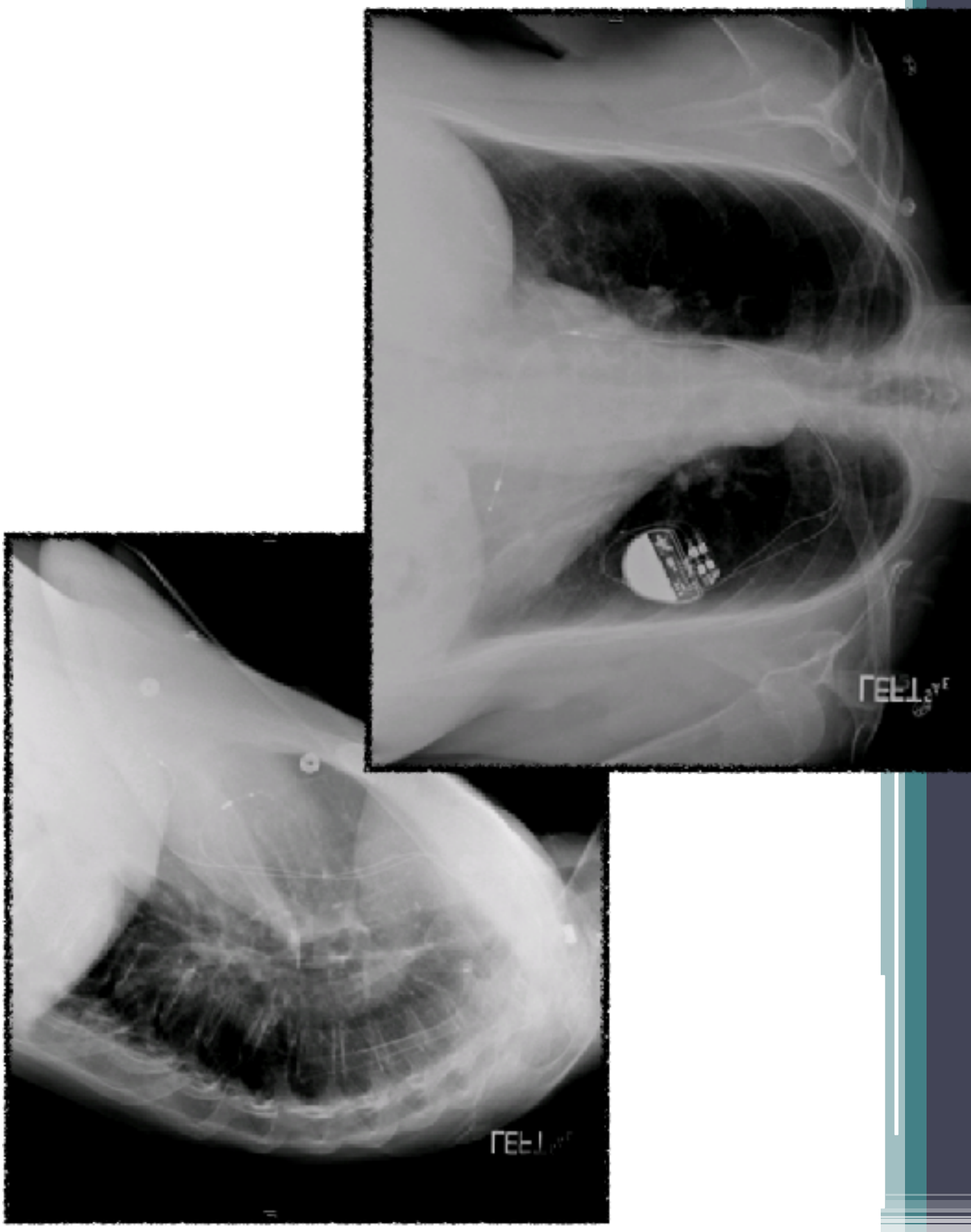
- Myotonic dystrophy
- Kearns-Sayre syndrome
- Erb's dystrophy
- Peroneal muscle atrophy

Pacemakers for Tachycardia

- Antitachycardia Pacing
  - VT
  - SVT
- Pause-dependent VT
- Congential long QT syndrome (high-risk patients)

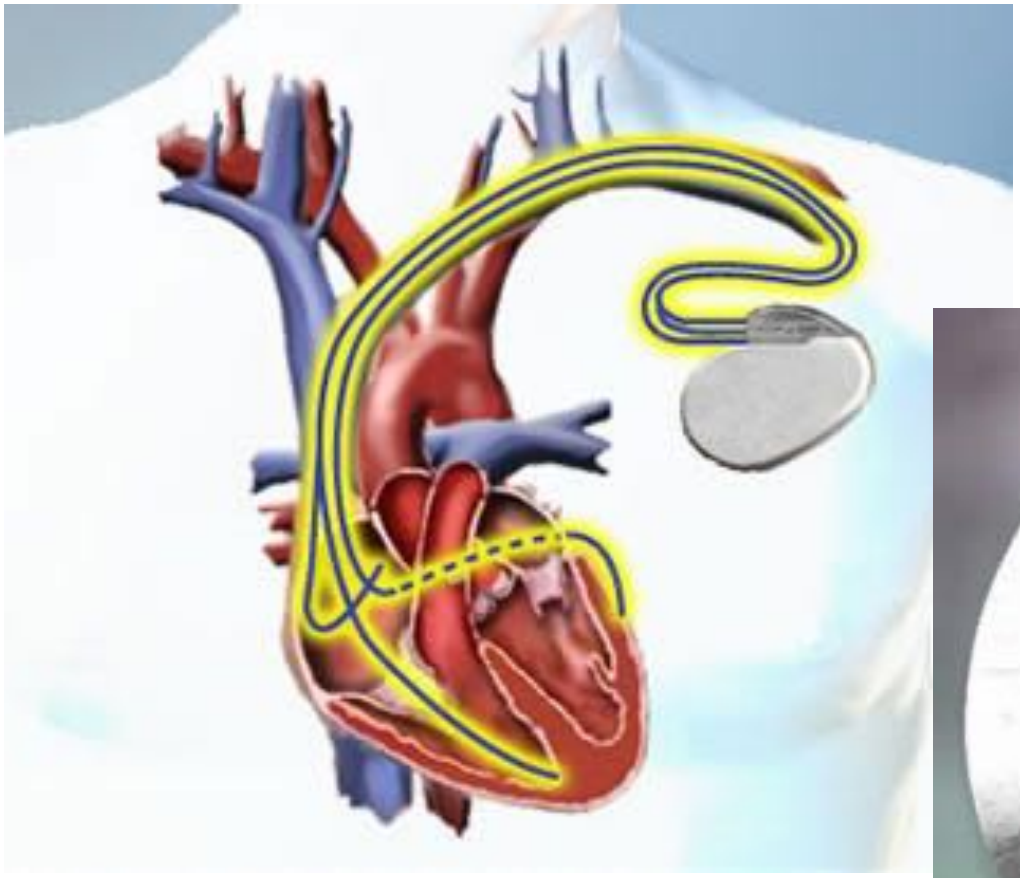
Dual Chamber Device

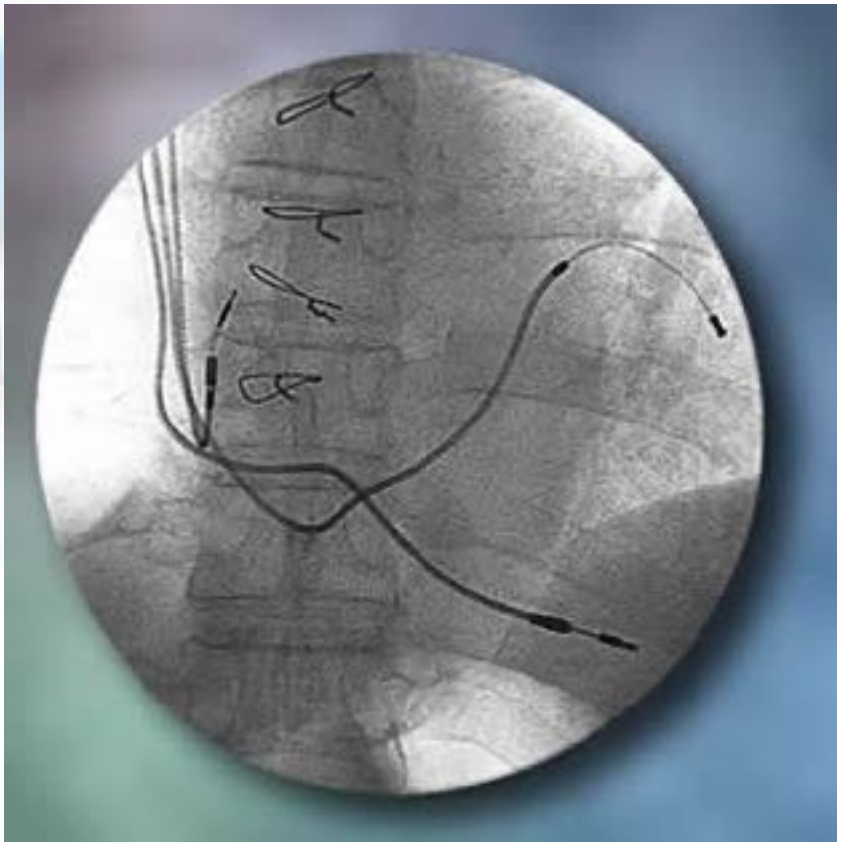




Ventricular Dyssynchrony

- Chronic heart failure patients commonly have several conduction system abnormalities causing:
- Suboptimal ventricular filling
- Reduction in LV contractility
- Prolonged duration of mitral regurgitation
- Paradoxical septal wall motion
- These mechanical manifestations are termed ventricular dyssynchrony



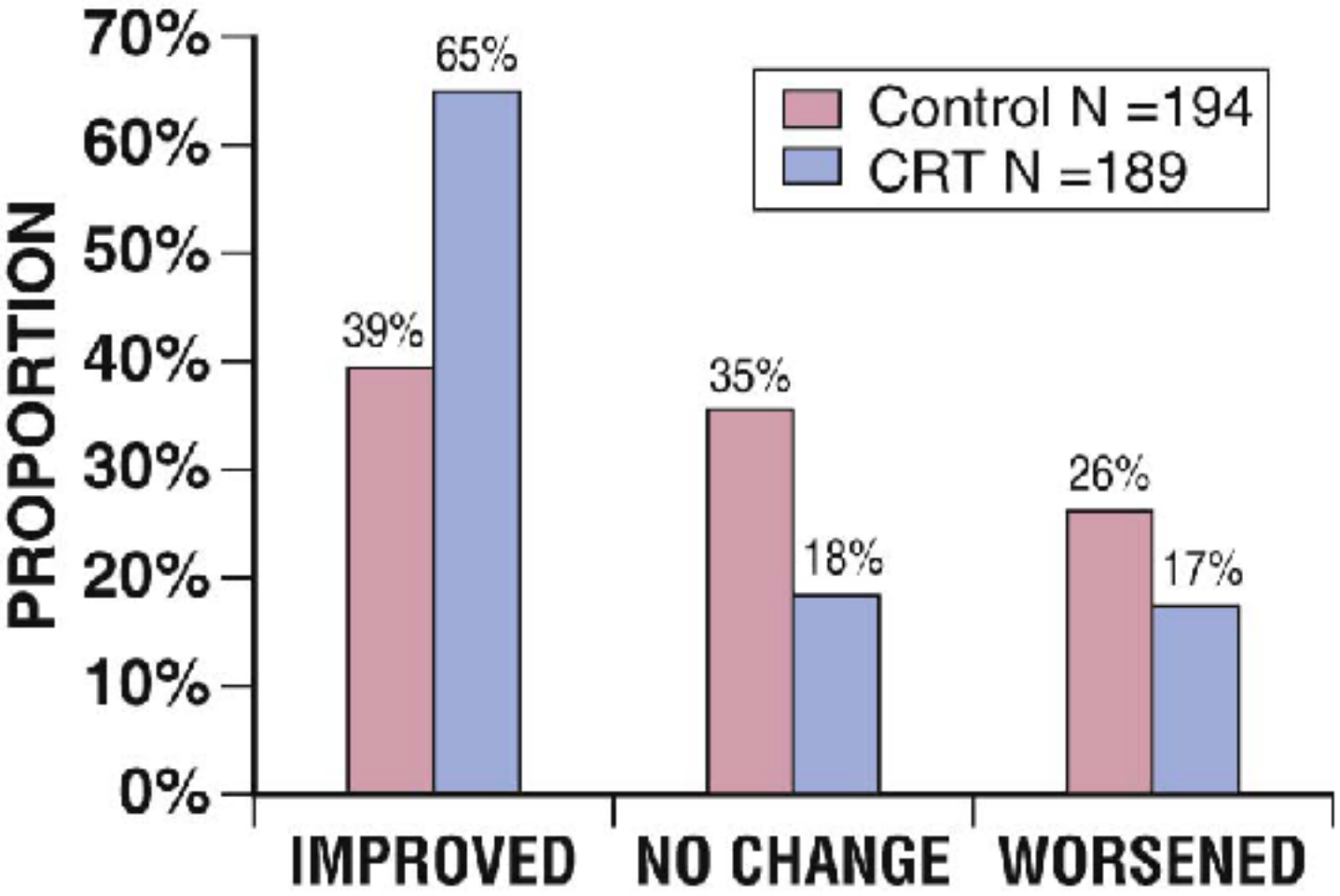


Biventricular pacing trials

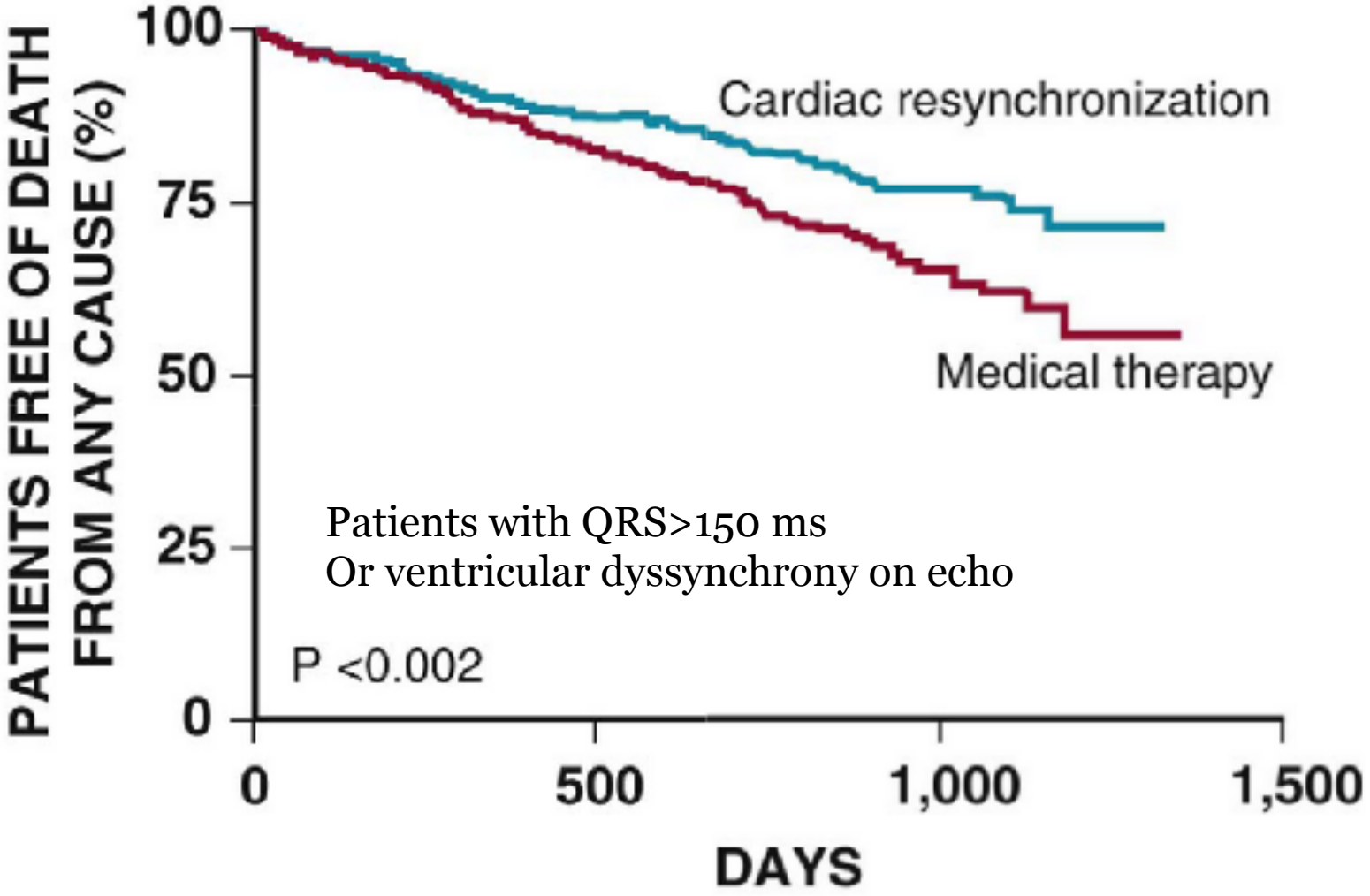
- MUSTIC trial showed significant benefit in exercise tolerance, NYHA class and quality of life

- MIRACLE trial first prospective double-blind RCT included 453 patients with EF<35% and QRS>130 ms
- Clinical Endpoint included death, hospitalization for HF, worsening NYHA class or quality of life

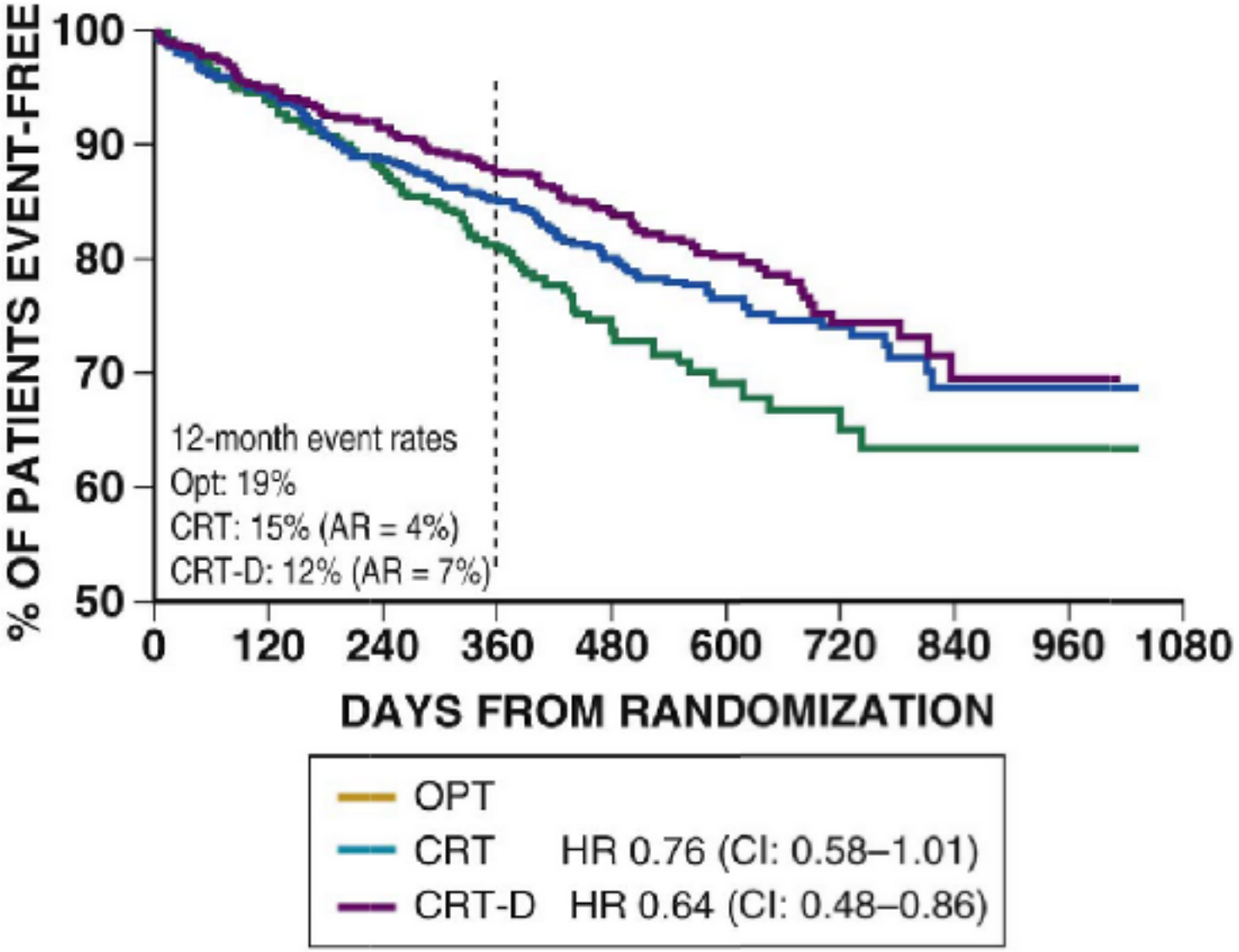
MIRACLE Trial



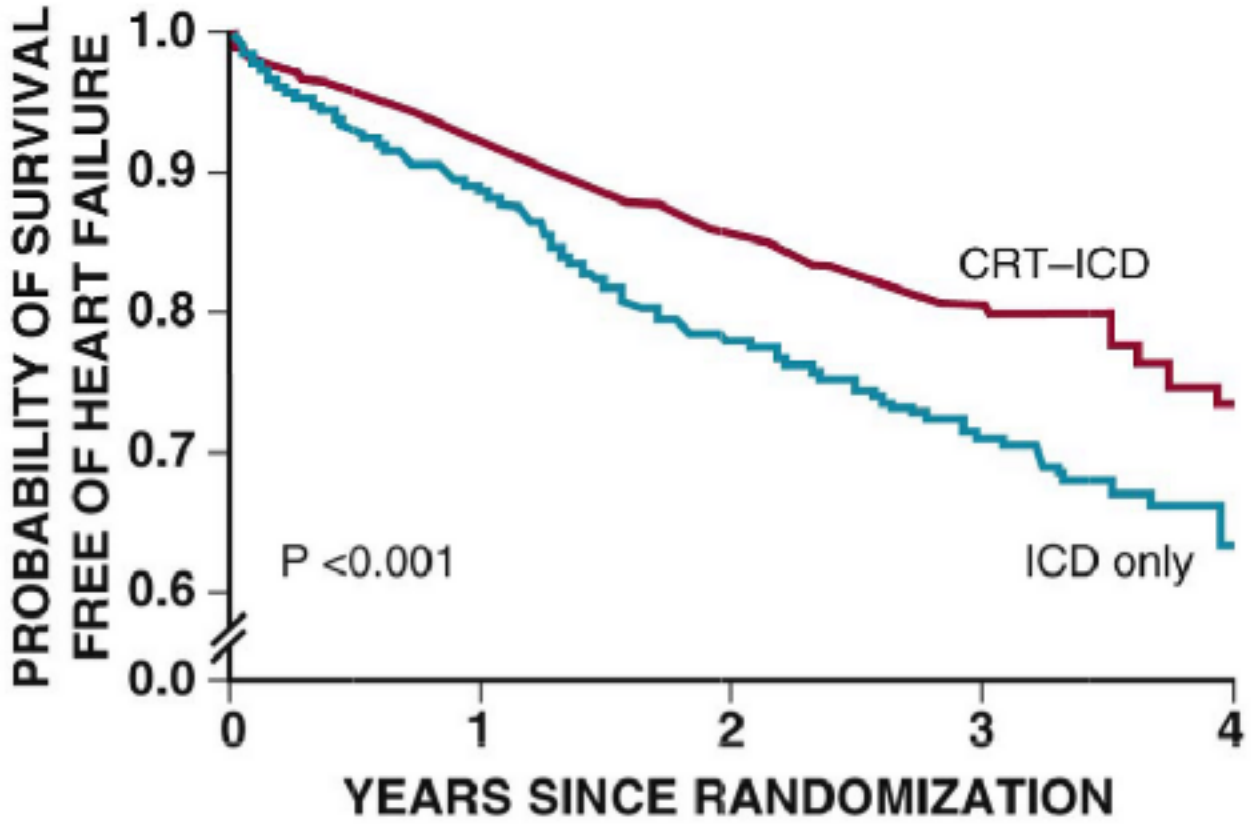
CARE-HF Trial (No ICD)



COMPANION Trial (CRT-ICD)



MADIT-CRT



No. at risk (probability of survival)

ICD only	731	621(0.89)	379(0.78)	173(0.71)	43(0.63)
CRT–ICD	1089	985(0.92)	651(0.86)	279(0.80)	58(0.73)

TABLE 26G-1 ACCF/AHA Guidelines for Cardiac Resynchronization

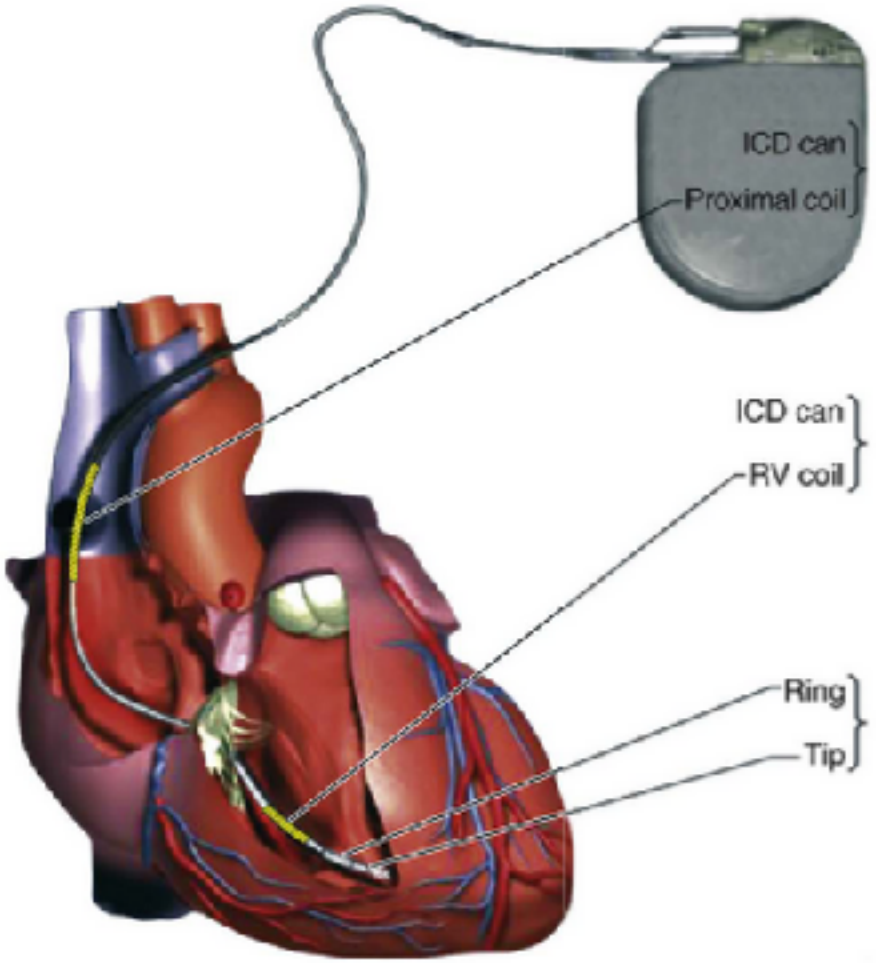
CLASS	INDICATION	LEVEL OF EVIDENCE
I	CRT is indicated for patients who have an LVEF of ≤35%, sinus rhythm, LBBB with a QRS duration of ≥150 milliseconds, and NYHA class II, III, or ambulatory IV symptoms while receiving GDMT	Level of evidence A for NYHA class III/IV, level of evidence B for NYHA class II
IIa	CRT can be useful for patients who have an LVEF of ≤35%, sinus rhythm, a non-LBBB pattern with a QRS duration of ≥150 milliseconds, and NYHA class III/ambulatory class IV symptoms while receiving GDMT	A
	CRT can be useful for patients who have an LVEF of ≤35%, sinus rhythm, LBBB with a QRS duration of 120 to 149 milliseconds, and NYHA class II, III, or ambulatory IV symptoms while receiving GDMT	B
	CRT can be useful in patients with atrial fibrillation and an LVEF of ≤35% while receiving GDMT if (1) the patient requires ventricular pacing or otherwise meets the criteria for CRT and (2) atrioventricular nodal ablation or pharmacologic rate control will allow almost 100% ventricular pacing with CRT	B
	CRT can be useful for patients receiving GDMT who have an LVEF of ≤35% and are undergoing placement of a new or replacement device with an anticipated requirement for significant (>40%) ventricular pacing	C

IIb	CRT may be considered for patients who have an LVEF of ≤35%, sinus rhythm, a non-LBBB pattern with a QRS duration of 120 to 149 milliseconds, and NYHA class III/ambulatory class IV while receiving GDMT	B
	CRT may be considered for patients who have an LVEF of ≤35%, sinus rhythm, a non-LBBB pattern with a QRS duration of ≥150 milliseconds, and NYHA class II symptoms while receiving GDMT	B
	CRT may be considered for patients who have an LVEF of ≤30%, an ischemic cause of heart failure, sinus rhythm, LBBB with a QRS duration of ≥150 milliseconds, and NYHA class I symptoms while receiving GDMT	C
III: No benefit	CRT is not recommended for patients with NYHA class I or II symptoms and a non-LBBB pattern with a QRS duration <150 milliseconds	
	CRT is not indicated for patients whose comorbid conditions and/or frailty limit survival with good functional capacity to <1 year	

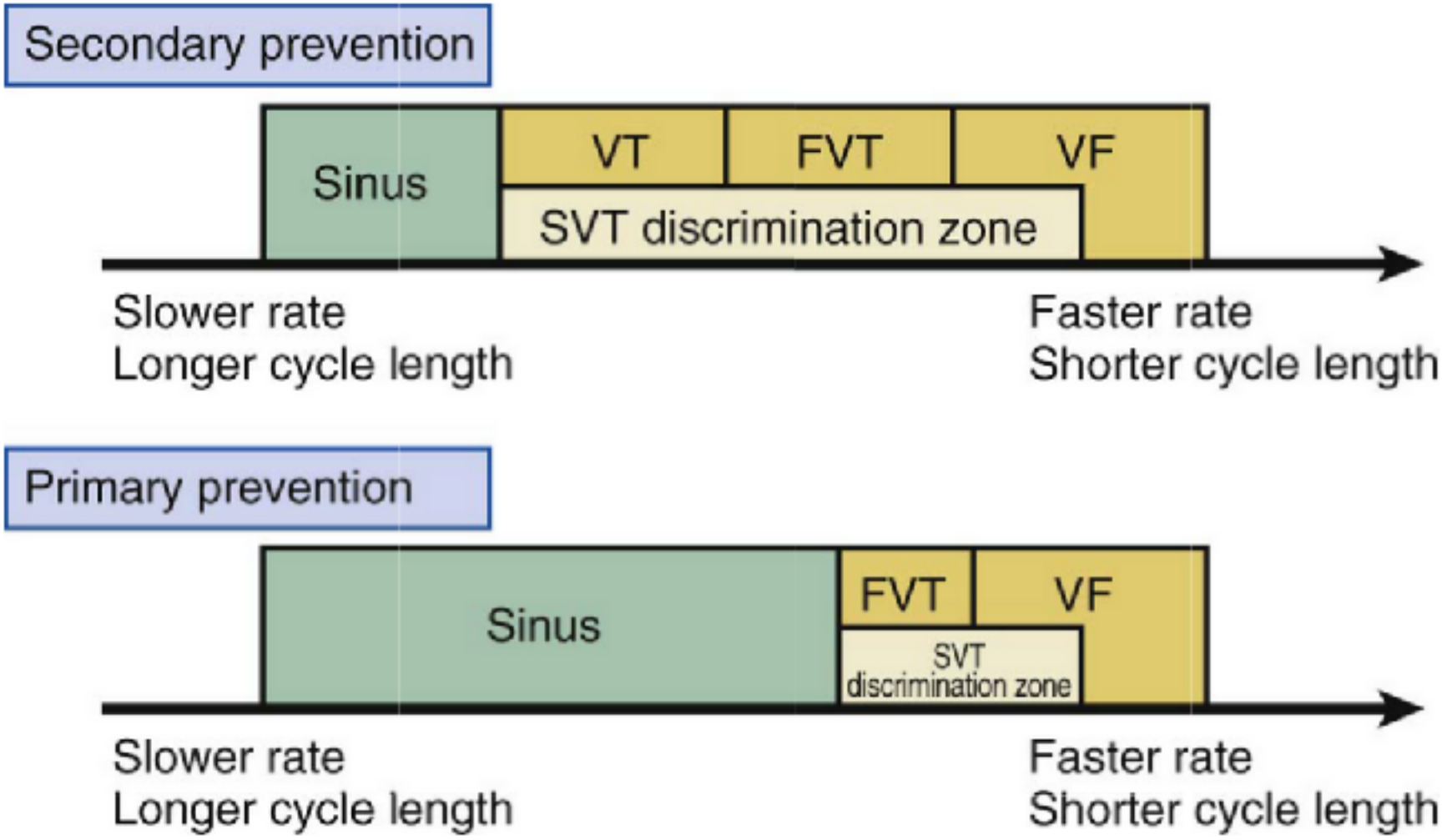
GDMT = guideline directed medical therapy.

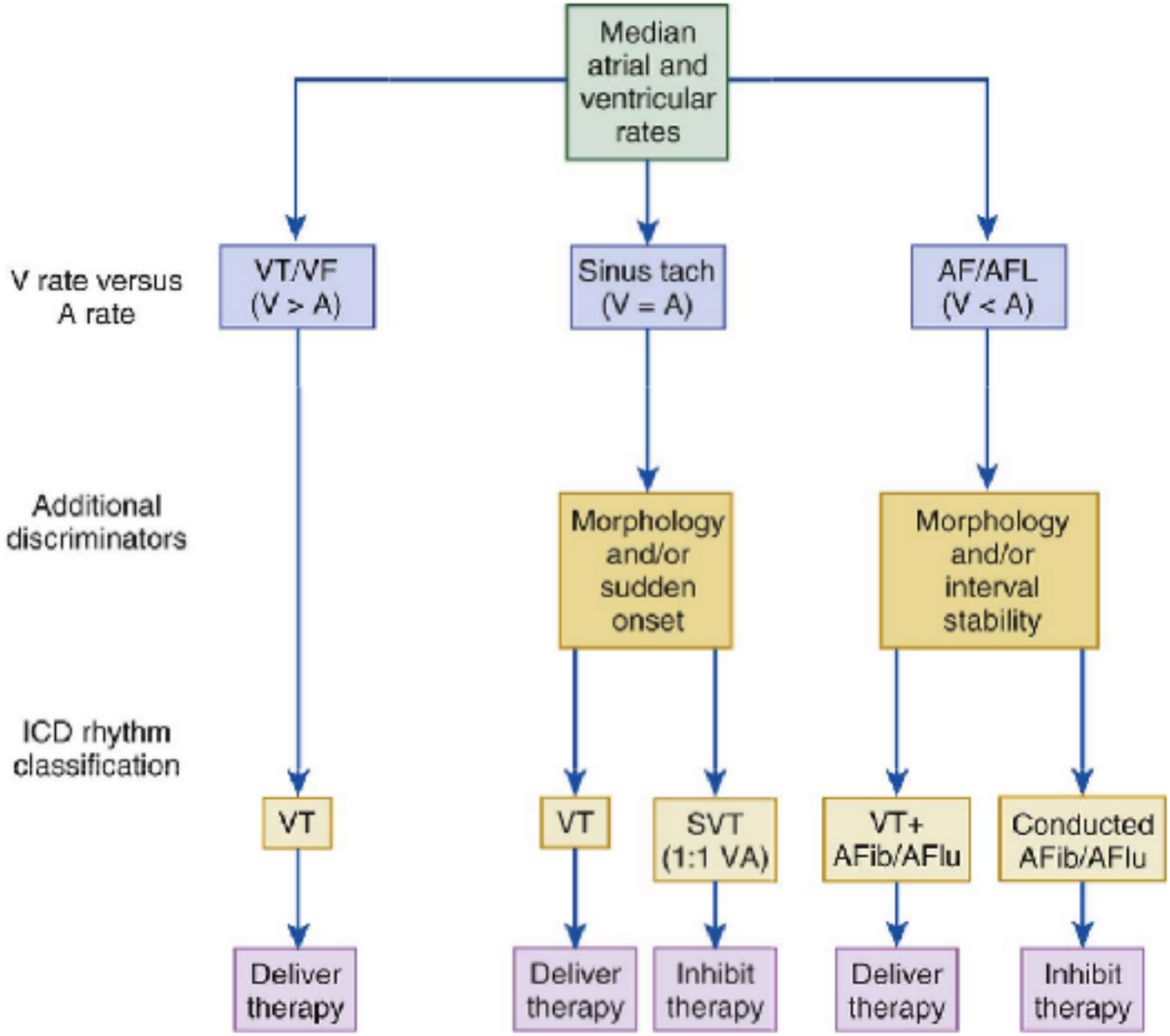
Implantable Cardioverter-Defbrillators

- ICDs can be single-chamber, dual-chamber or BiV devices
- All ICDs have standard anti-bradycardia pacing function
- Goal is prevention of sudden cardiac death



VT/VF Detection Zones



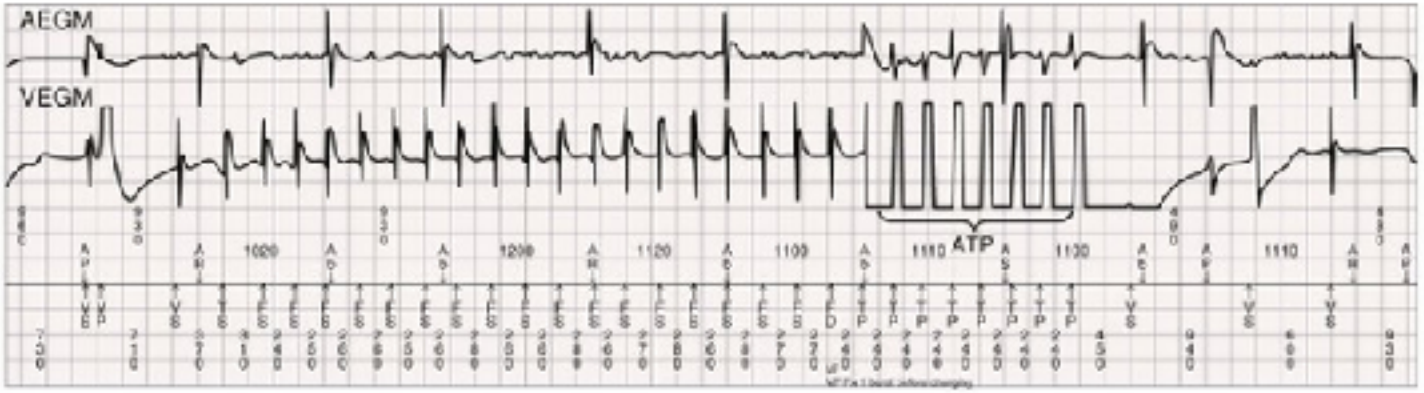

Median atrial and ventricular rates
V rate versus A rate
VT/VF (V > A)
Sinus tach (V = A)
AF/AFL (V < A)
Additional discriminators
Morphology and/or sudden onset
Morphology and/or interval stability
ICD rhythm classification
VT
VT
SVT (1:1 VA)
VT+ AFib/AFlu
Conducted AFib/AFlu
Deliver therapy
Deliver therapy
Inhibit therapy
Deliver therapy
Inhibit therapy

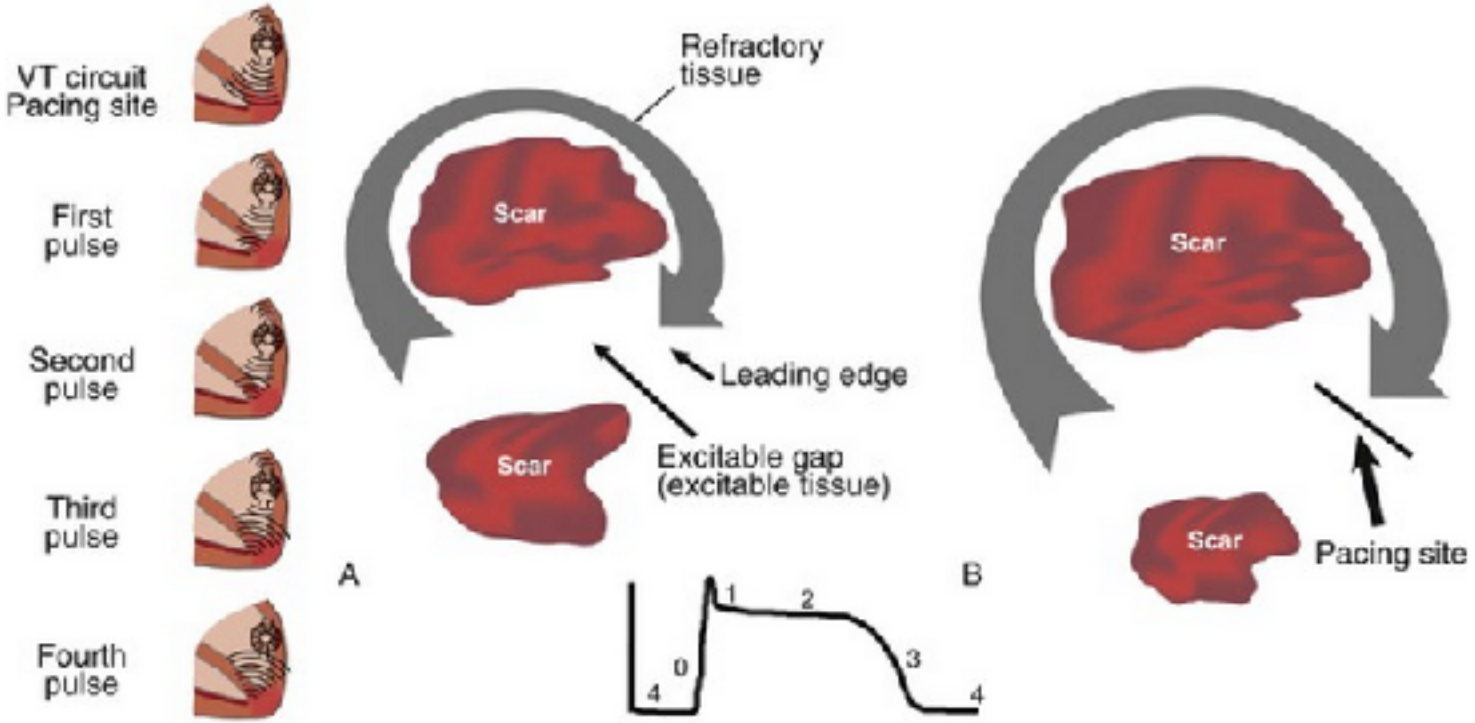
Antitachycardia Pacing

3- to 10-beat trains of pulses at a cycle length shorter than the VT cycle length. In contrast to bradycardia pacing, which is usually delivered with a fixed cycle length, ATP is applied in an adaptive mode with the first pulse set to a percentage of the preceding VT cycle length, typically 85% to 90% for faster VTs and 75% to 85% for slower VTs.

Antitachycardia Pacing

ATP may be delivered in either a “burst” or “ramp” mode. In the burst mode, pulses within a train have a fixed cycle length, which may be decreased by 10 to 30 milliseconds between successive trains if the first train does not terminate the VT. In the ramp mode, sequential pulses within each train are delivered at progressively shorter cycle lengths until a minimum value is reached.

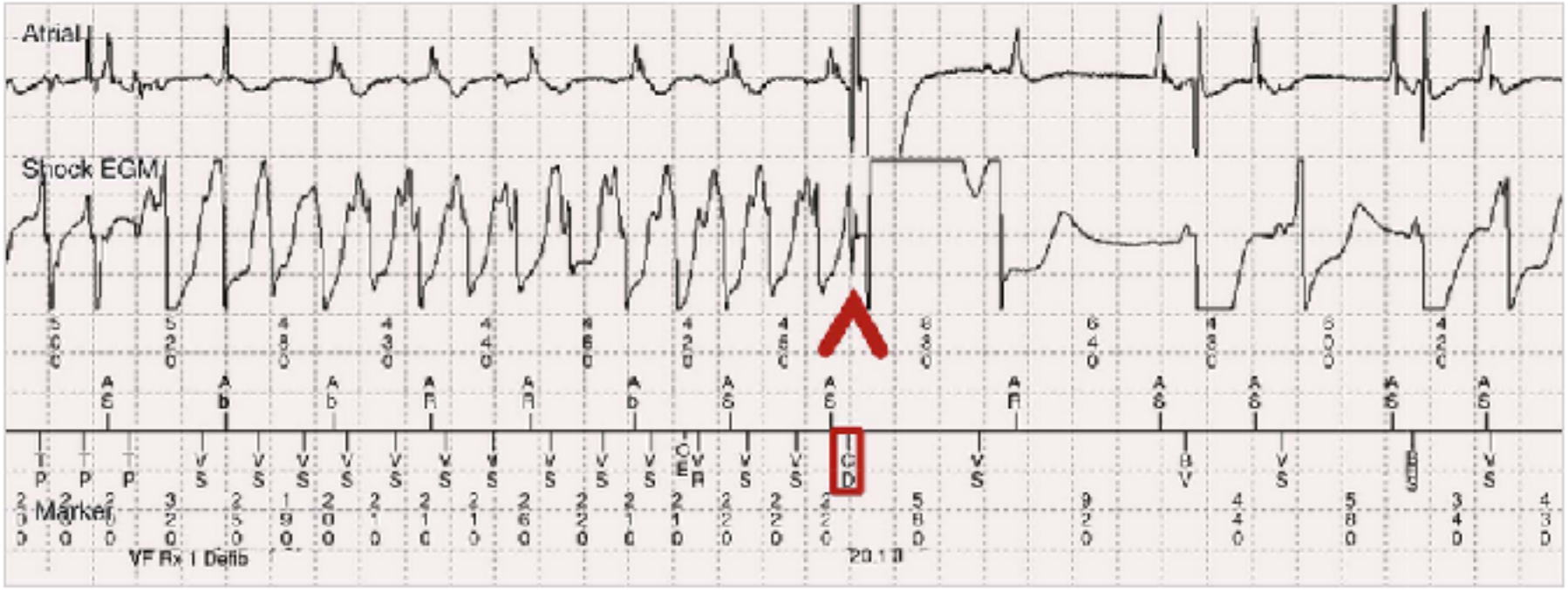

AEGM
VEGM
ATP


VT circuit
Pacing site
First
pulse
Second
pulse
Third
pulse
Fourth
pulse
Refractory
tissue
Scar
Scar
Leading edge
Excitable gap
(excitable tissue)
A
B
0
1
2
3
4
4
Scar
Scar
Pacing site

Defibrillation

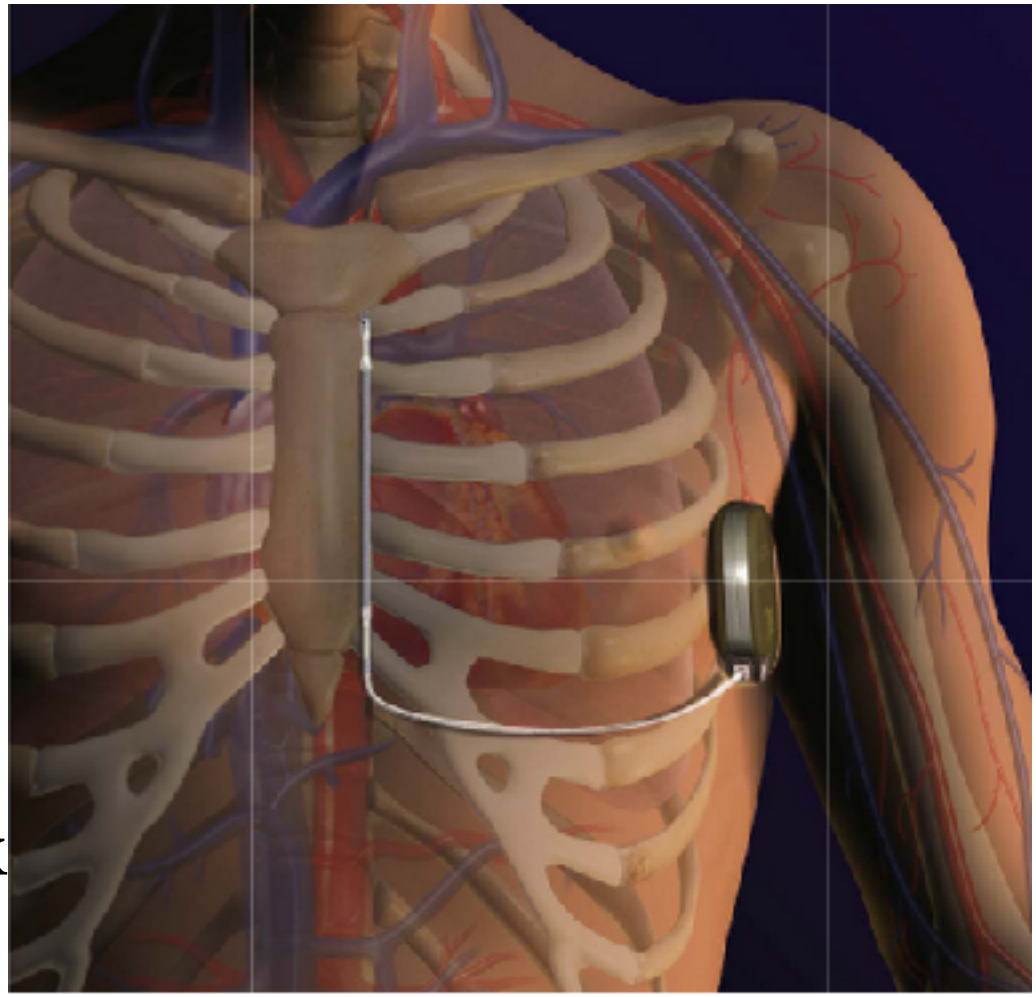
- The high-voltage charging circuit converts the low-voltage output of the battery into the high voltage that charges the shock output capacitor. A special direct current (DC)-to-DC converter/step-up transformer converts the 3.2 V up to the 800 V needed for defibrillation. The charge is stored on a capacitor and then delivered as a single shock. The efficiency of charging circuits is in the range of 50%, and it typically takes 6 to 15 seconds to charge the high-voltage capacitor to maximum voltage (usually 800 to 900 V) and store about 40 J of energy in the capacitor. All ICDs use a biphasic waveform in which the polarity of the waveform is reversed in the middle of the shock.

EGM showing treatment of VT



Subcutaneous ICD

- No venous access
- ICD generator and subq lead on either end of defibrillator coil
- Generator placed anterior axilla at 5th intercostal space
- Delivers 80 J non-programmable shock



Clinical Trials of ICDs

Secondary Prevention Trials

- AVID
- CASH
- CIDS

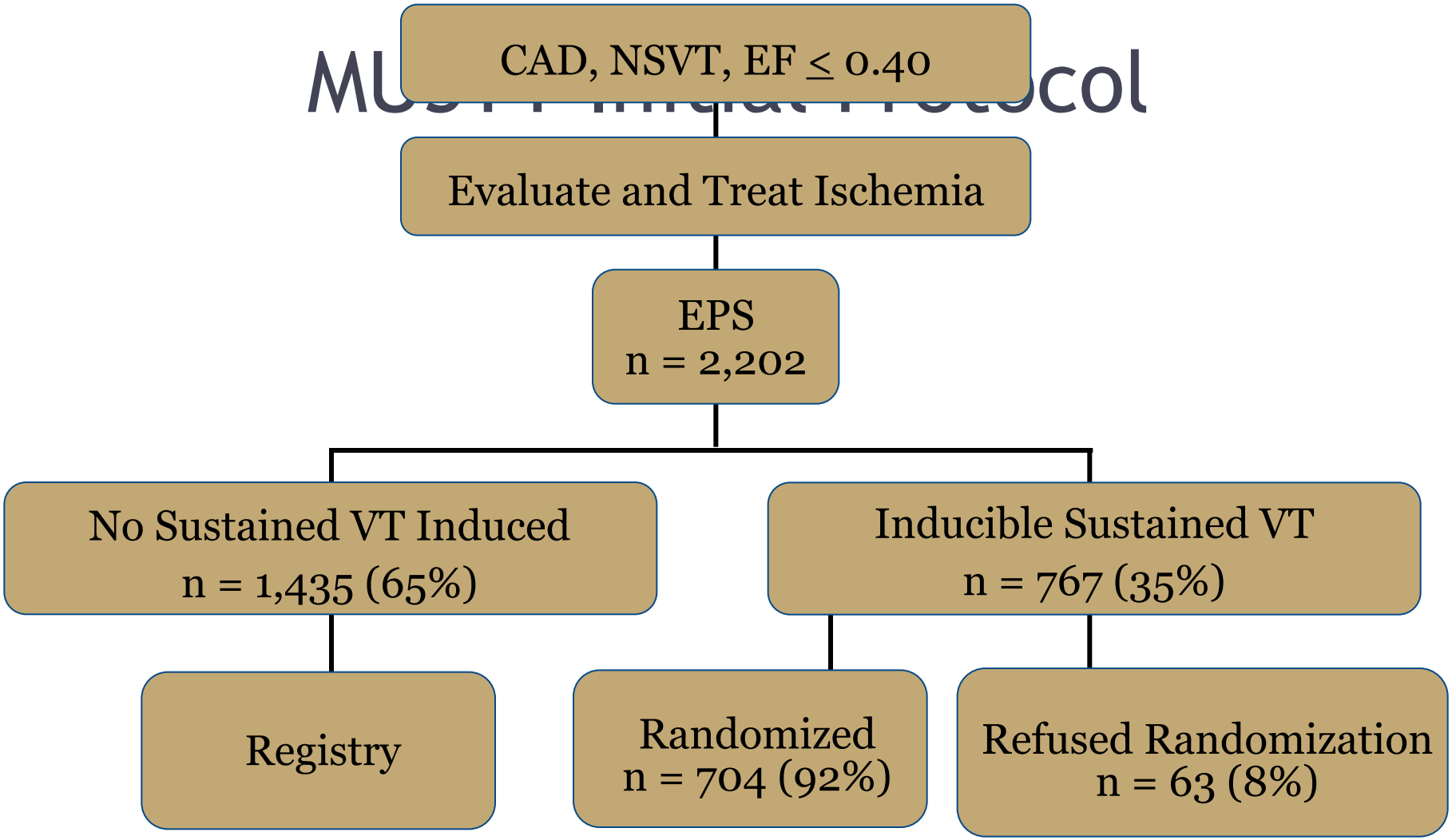
Primary Prevention Trials

- MUSTT
- MADIT-I
- MADIT-II
- SCD-HeFT

Reductions in Mortality with ICDs Compared to Antiarrhythmic Drugs

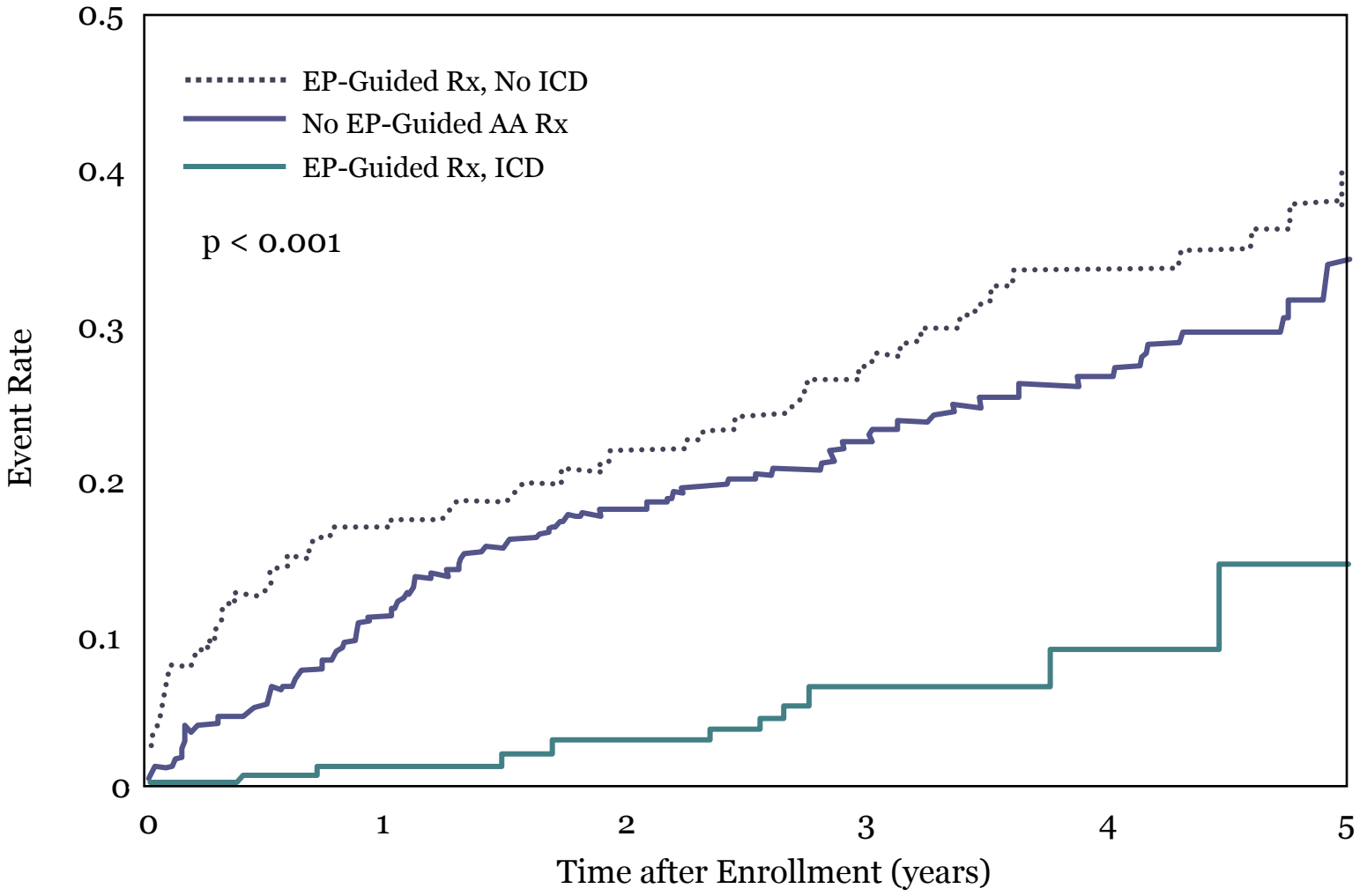
[1] The AVID Investigators. N Engl J Med. 1997;337:1576-1583.
[2] Kuck K. ACC98 News Online. April, 1998. Press release.
[3] Connolly S. ACC98 News Online. April, 1998. Press release.
[4] Moss AJ. N Engl J Med. 1996;335:1933-1940.

MUSTT Initial Protocol



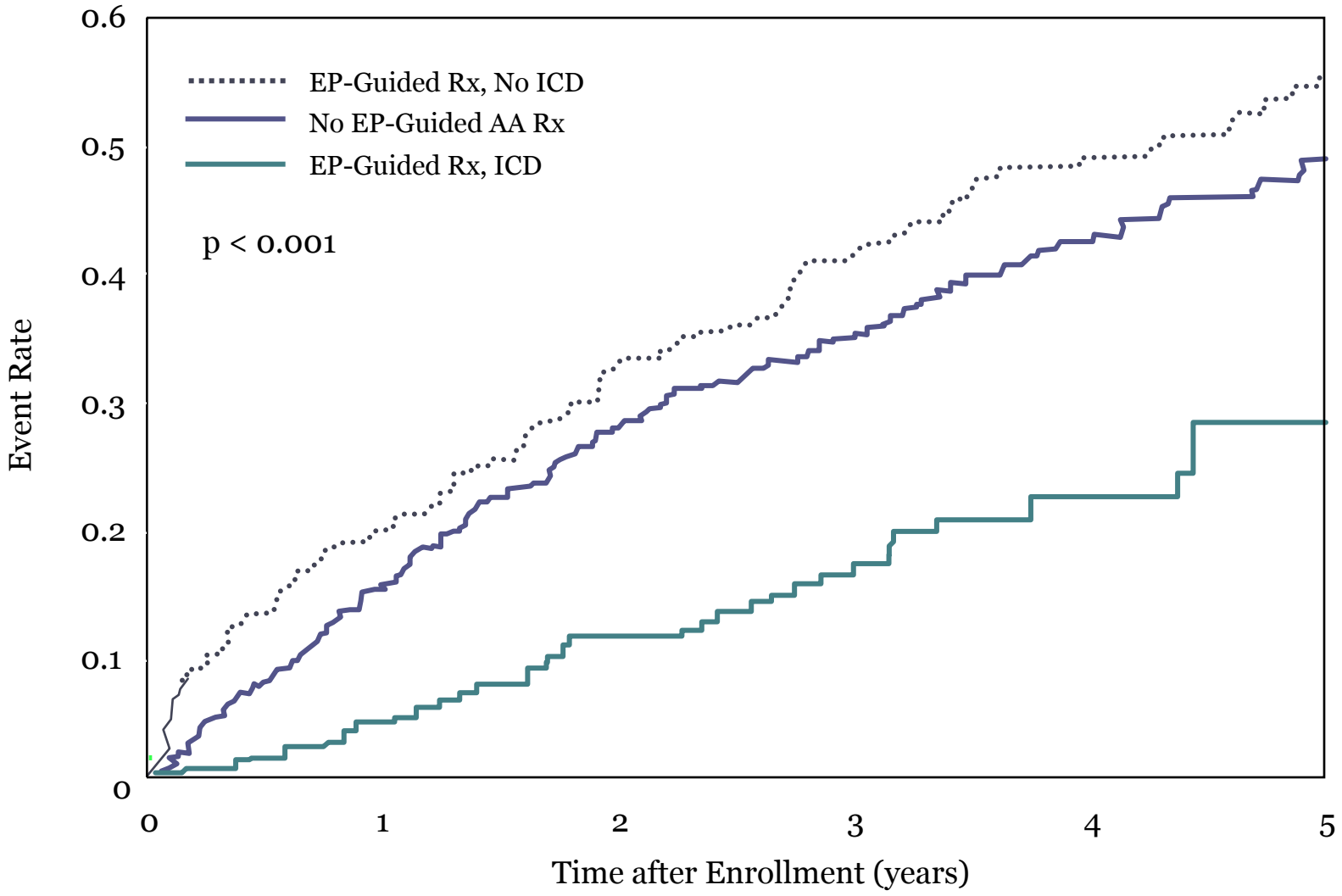
Buxton AE. *N Engl J Med*. 1999;341:1882-1890.
Buxton AE. *N Engl J Med*. 2000;342:1937-1940.

MUSTT Randomized Patient Results: Arrhythmic Death or Cardiac Arrest



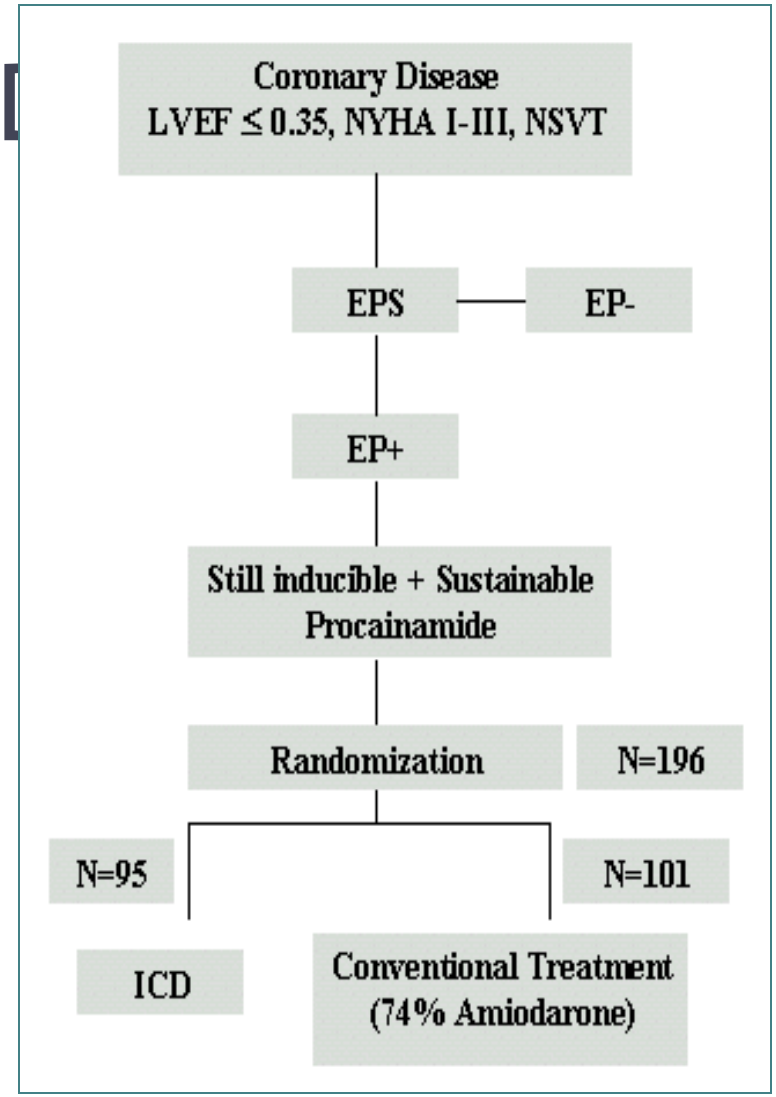
Buxton AE. *N Engl J Med*. 1999;341:1882-1890.

MUSTT Randomized Patient Results: Overall Mortality



Buxton AE. *N Engl J Med*. 1999;341:1882-1890.

MADIT-I



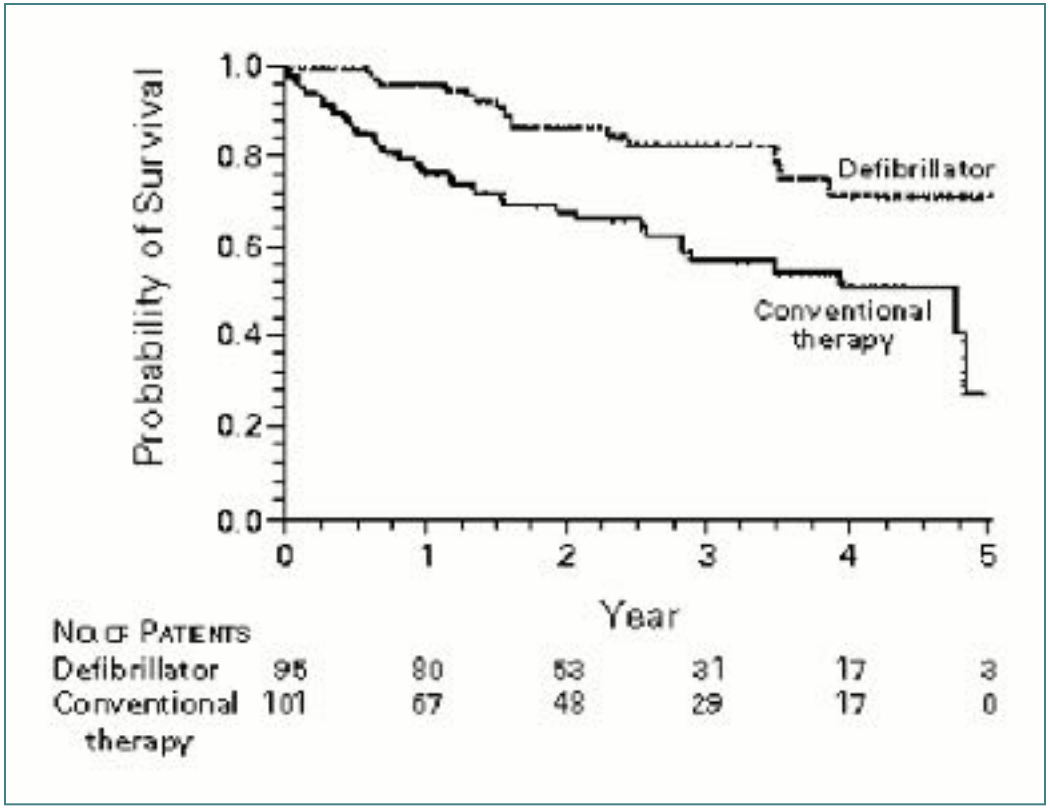
Two patient groups (1:1)

1. Conventional Medical Therapy (CMT)
2. CMT + ICD

Primary endpoint: Mortality

MADIT-I

- Use of ICDs resulted in a 54% reduction in the risk of all-cause mortality rate in the defibrillator group as compared to the CMT group. (p value: 0.009)
- There was no evidence that amiodarone, beta-blockers, or any other antiarrhythmic therapy had a significant influence on the mortality curves.



MADIT II

Multicenter Automatic Defibrillator Implantation Trial II

Status: Completed in 2001

First trial to show the life-saving benefits of ICDs without requiring patients to have a documented history of abnormal heart rhythms

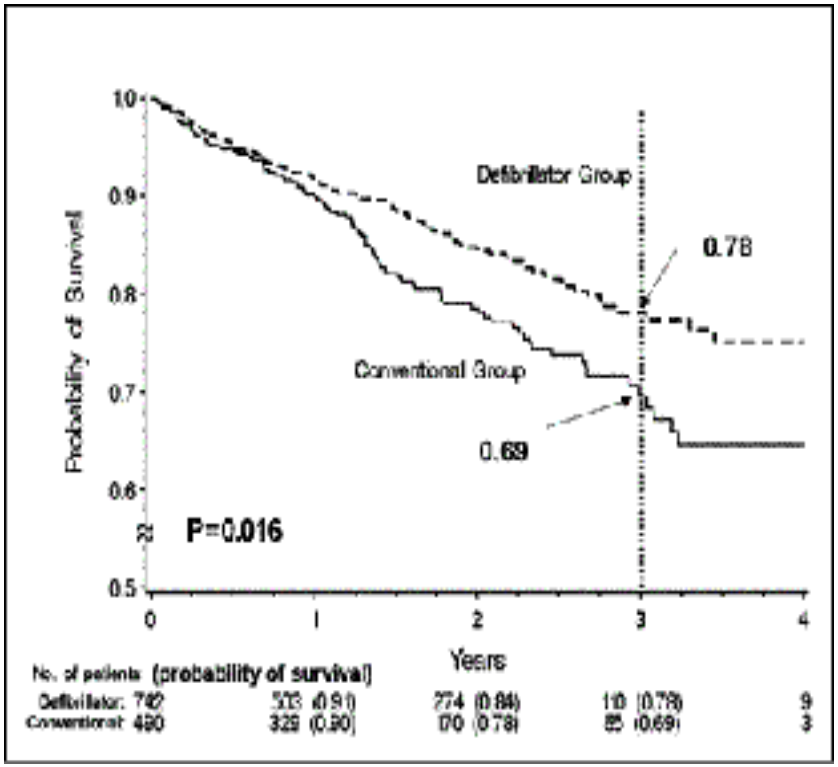
MADIT-II

Mortality over an average follow-up of 20 months

Conventional Group (n=490)	ICD Group (n=742)	Hazard Ratio (95% CI)	*P*-value
19.8 (97)	14.2 (105)	.69 (0.51-0.93)	0.016

- 31% reduction in the risk of death at any interval among patients in the defibrillator group as compared with patients in the conventional-therapy group

- The cumulative survival curves represent a decrease in death rates in the defibrillator group (95% confidence limits; *P*-value) of 12% at 1 year (27 to 40%), 28% at 2 years (4 to 46%), and 29% at 3 years (5 to 46%).



SCD-HeFT

Objective:

- To determine, by intention-to-treat analysis, if amiodarone or an ICD reduces all-cause mortality compared to placebo* in patients with either ischemic or non-ischemic NYHA Class II and III CHF and EF ≤ 35%.

Inclusion Criteria:

- NYHA Class II or III (ischemic or non-ischemic)
- LVEF ≤ 35%
- ≥ 18 years of age; no upper age limitation
- CHF ≥ 3 months
- ACE I and Beta Blocker therapy if tolerated

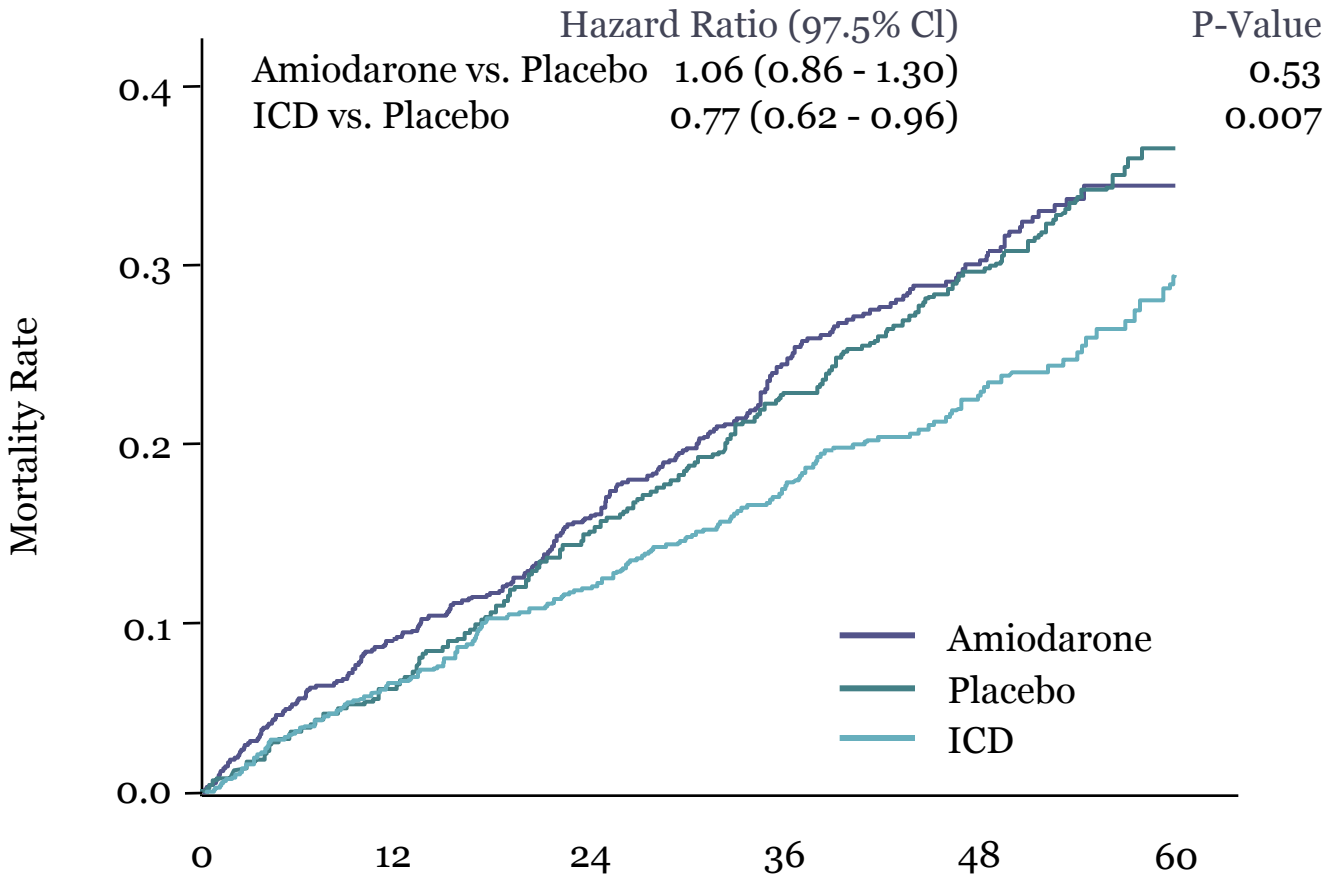
ICD Results:

- In class II or III CHF patients with EF ≤ 35% on good background drug therapy, the mortality rate for placebo-controlled patients is 7.2% per year over 5 years
- ICDs decrease mortality by 23%
- Amiodarone, when used as a primary preventive agent, does not improve survival

* Double-blind for drug therapy

Bardy G. *N Engl J Med.* 2005;352:225-37.

SCD-HeFT Mortality



No. at Risk						
Amiodarone	845	772	715	484	280	97
Placebo	847	797	724	505	304	89
ICD	829	778	733	501	304	103

Bardy GH. *N Engl J Med.* 2005;352:225-237.

ICDs

Class I

1. Survivors of cardiac arrest secondary to ventricular fibrillation (VF) or hemodynamically unstable sustained ventricular tachycardia (VT) after evaluation to define the cause of the event and to exclude any completely reversible causes. *(Level of evidence: A.)*
2. Structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable. *(Level of evidence: B.)*
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiologic study. *(Level of evidence: B.)*
4. LV ejection fraction (LVEF) <35% because of previous myocardial infarction in patients at least 40 days after myocardial infarction and in New York Heart Association (NYHA) functional class II or III. *(Level of evidence: A.)*
5. Nonischemic dilated cardiomyopathy in patients who have an LVEF ≤35% and are in NYHA functional class II or III. *(Level of evidence: B.)*
6. LV dysfunction because of previous myocardial infarction in patients who are at least 40 days after myocardial infarction, have an LVEF <30%, and are in NYHA functional class I. *(Level of evidence: A.)*
7. Nonsustained VT because of previous myocardial infarction, LVEF <40%, and inducible VF or sustained VT at electrophysiologic study. *(Level of evidence: B.)*

Class IIa

1. Unexplained syncope, significant LV dysfunction, and nonischemic dilated cardiomyopathy. *(Level of evidence: C.)*
2. Sustained VT and normal or near-normal ventricular function. *(Level of evidence: C.)*
3. Patients with hypertrophic cardiomyopathy and (a) a family history of sudden death presumably caused by hypertrophic cardiomyopathy in 1 or more first-degree relatives, (b) LV wall thickness ≥30 mm, (c) one or more unexplained syncopal episodes in the last 6 months. *(Level of evidence: C.)*
4. Selected patients with hypertrophic cardiomyopathy and either nonsustained VT (particularly those <30 years of age) or an abnormal blood pressure response with exercise* in the presence of other established risk markers† or potential risk modifiers.‡ *(Level of evidence: C.)*
5. Arrhythmogenic right ventricular dysplasia/cardiomyopathy in patients who have 1 or more risk factors for sudden cardiac death. *(Level of evidence: C.)*
6. Long-QT syndrome in patients who are experiencing syncope and/or VT while receiving beta blockers. *(Level of evidence: B.)*
7. Nonhospitalized patients awaiting transplantation. *(Level of evidence: C.)*
8. Brugada syndrome in patients who have had syncope or documented VT that has not resulted in cardiac arrest. *(Level of evidence: C.)*
9. Catecholaminergic polymorphic VT in patients who have syncope and/or documented sustained VT while receiving beta blockers. *(Level of evidence: C.)*
10. Cardiac sarcoidosis, giant cell myocarditis, or Chagas disease. *(Level of evidence: C.)*

Class IIb

1. Nonischemic heart disease in patients with an LVEF ≤35% and in NYHA functional class I. *(Level of evidence: C.)*
2. Long-QT syndrome and risk factors for sudden cardiac death. *(Level of evidence: B.)*
3. Syncope and advanced structural heart disease in patients in whom thorough invasive and noninvasive investigations have failed to define a cause. *(Level of evidence: C.)*
4. Familial cardiomyopathy associated with sudden death. *(Level of evidence: C.)*
5. LV noncompaction. *(Level of evidence: C.)*
6. Patients with hypertrophic cardiomyopathy and either an abnormal blood pressure response to exercise* or isolated bursts of nonsustained VT in the absence of any other risk factors† or risk modifiers‡ for sudden cardiac death. *(Level of evidence: C.)*

Class III

1. Patients who do not have a reasonable expectation of survival with acceptable functional status for at least 1 year, even if they meet the ICD implantation criteria specified in the class I, IIa, and IIb recommendations. *(Level of evidence: C.)*
2. Incessant VT or VF. *(Level of evidence: C.)*
3. Significant psychiatric illnesses that may be aggravated by device implantation or may preclude systematic follow-up. *(Level of evidence: C.)*
4. Drug-refractory congestive heart failure in patients who are not candidates for cardiac transplantation or CRT-D. *(Level of evidence: C.)*
5. Syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease. *(Level of evidence: C.)*
6. When VF or VT is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with Wolff-Parkinson-White syndrome, right ventricular or LV outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease). *(Level of evidence: C.)*
7. Ventricular tachyarrhythmias caused by a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma). *(Level of evidence: B.)*

References

- Braunwald's Heart Disease 10th Edition
- Epstein AE, DiMarco JP, Ellenbogen KA, et **al.**: ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities

Clinical Trials

- MOST
- DAVID
- CTOPP
- CARE-HF
- Companion
- MUSTT
- MADIT-I
- MADIT-II
- SCD-HeFT
- AVID
- CASH
- CIDS