Malignant arrhythmia in heart failure: role of medical therapy

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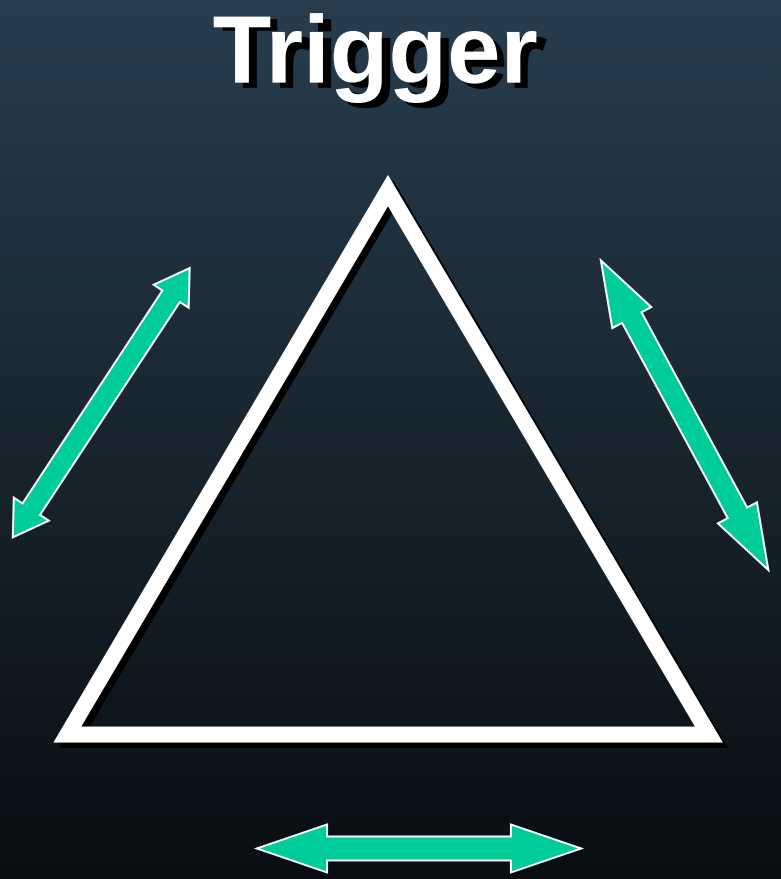
Malignant Arrhythmias in Heart Failure

Annual arhhythmias incidence in HF	
Non Sustained VT	50-80%
Sustained VT	5%

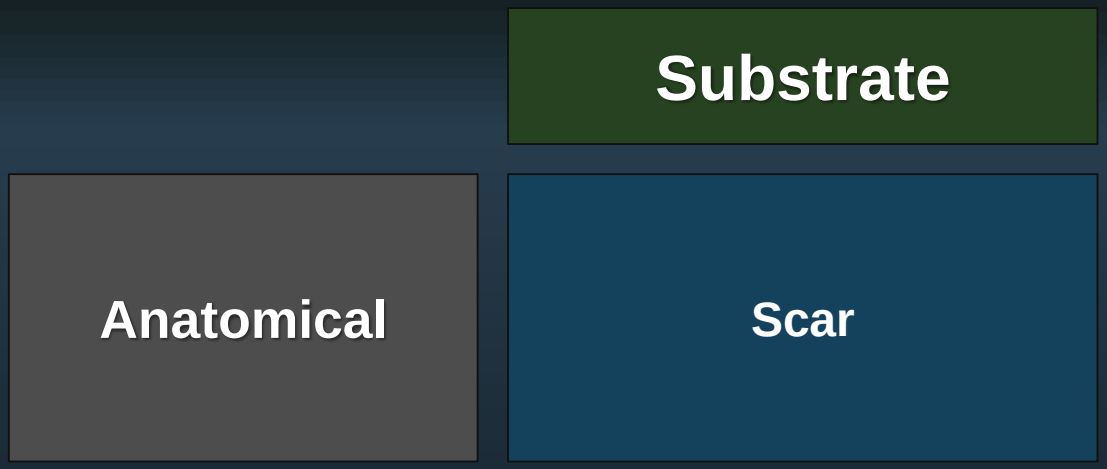
Lifelong risk of sudden cardiac death if untreated	
SCD as cause of death	40%

Teerlink Criculation 2000
Mainerz AJC 1984
Singh Jaacc 1998
Packer, Eur J Heart Fail 2019

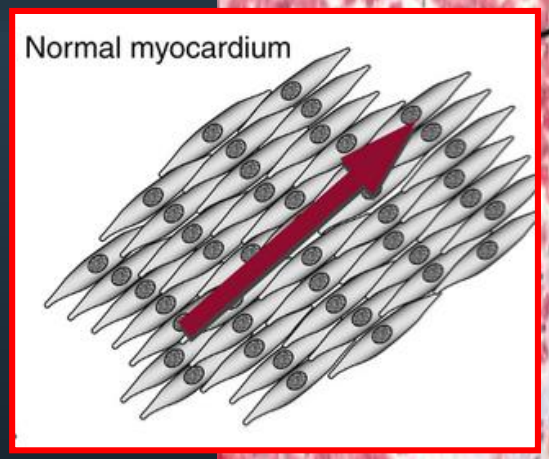
Arrhythmias: physyopathology

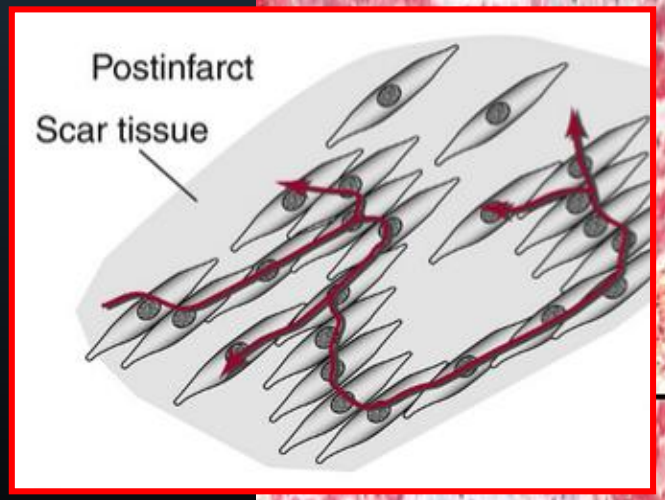


Physyopathology: remodeling



Scar Hystology





Danciu, atlas of pathology 2014

Physyopathology: remodeling

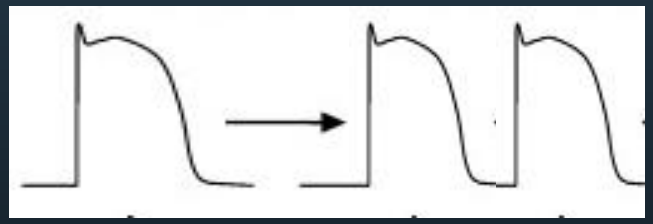
	Substrate
Anatomical	**Scar**
	Gap junction anomalies
Functional	**Stretch**

Functional Remodeling

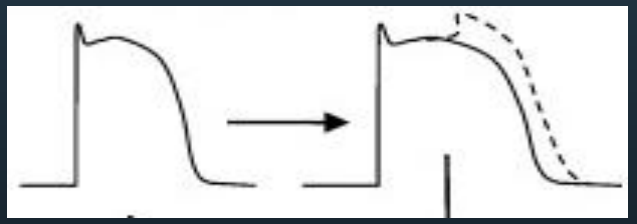
Cronical stretch

Electric Remodeling

↓ effective refractory period



↓ or ↑ action potential duration



Disomogeneity

Acute stretch

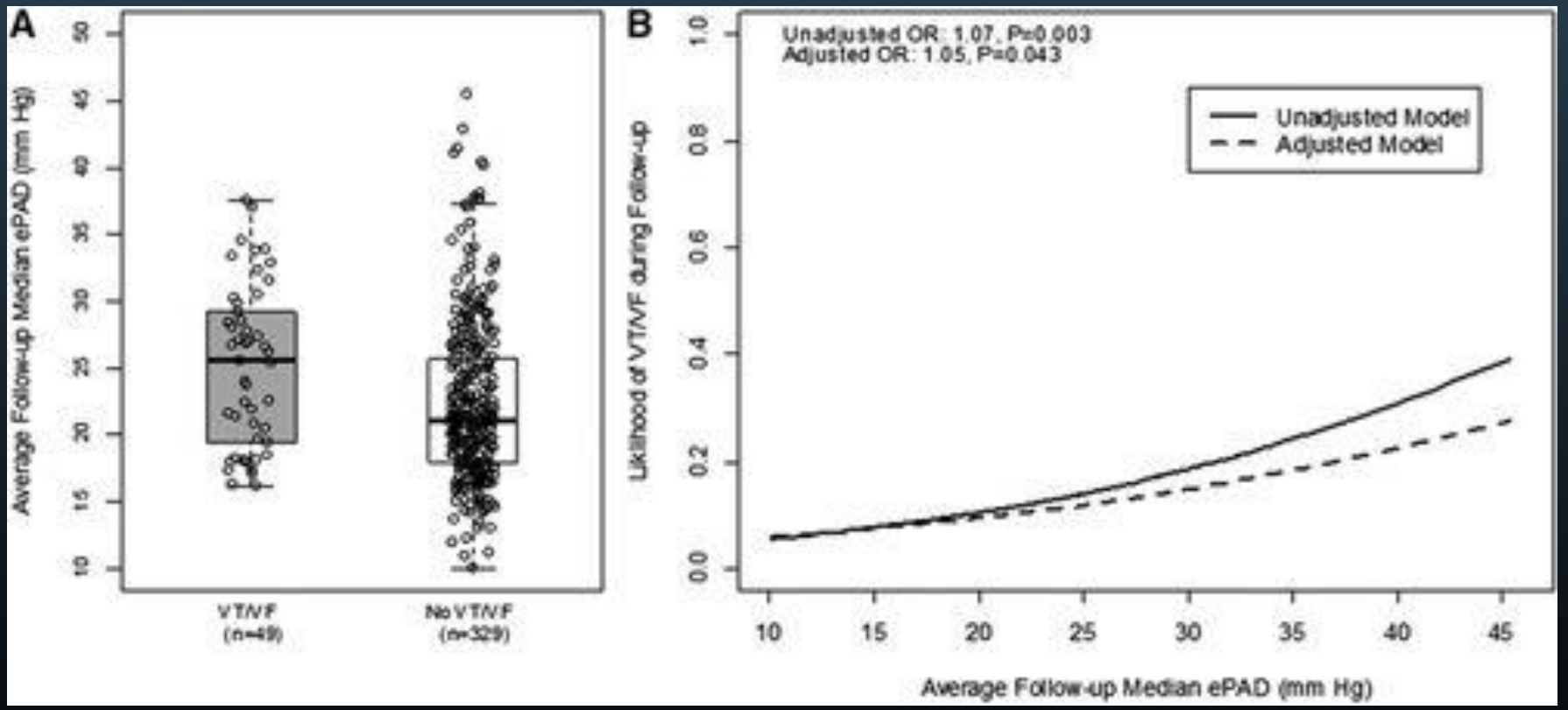
Stretch activated membrane channels

Franz, Cardiovasc Res, 1989

Functional Remodeling

Acute stretch

Stretch activated membrane channels



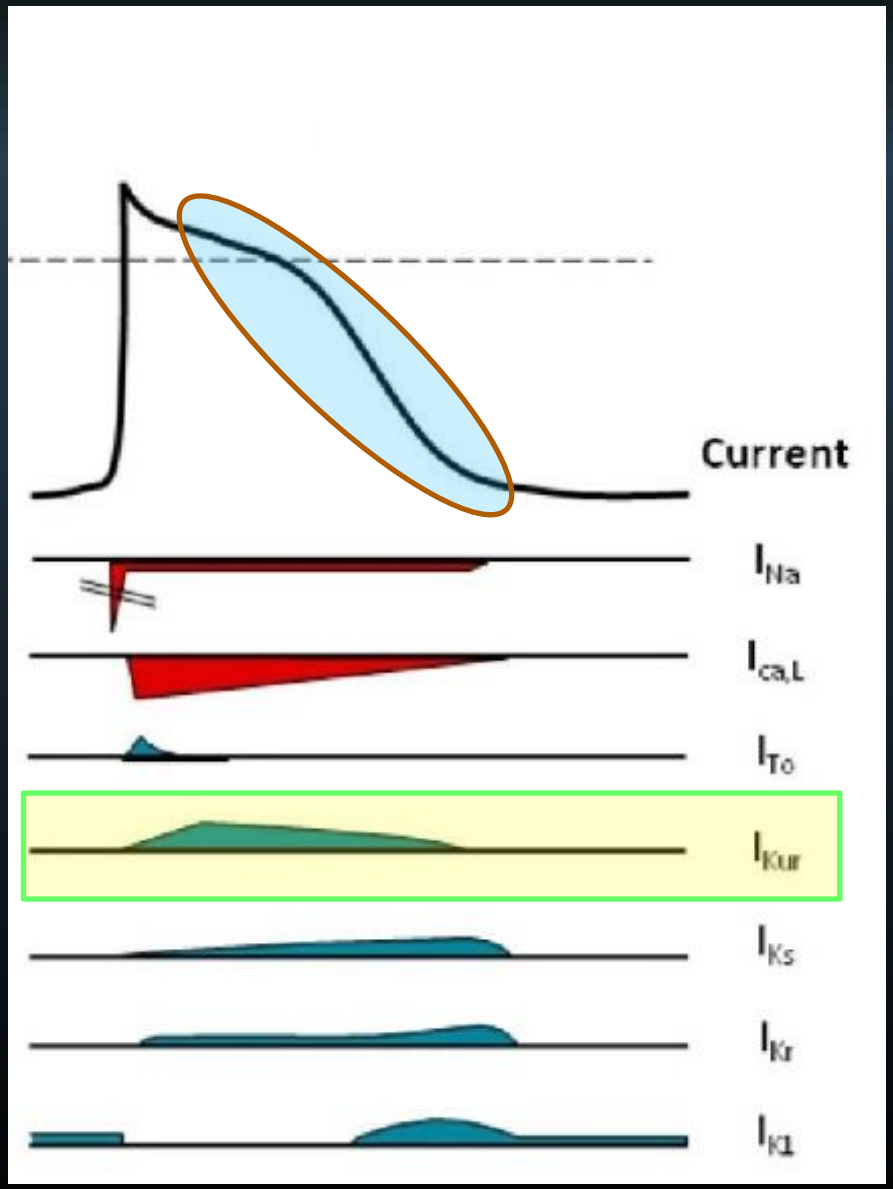
ICD with invasive pulmonary artery diastolic pressure monitor

Reiter. Circulation: Arrhythmia and Electrophysiology, 2013

Physyopathology: remodeling

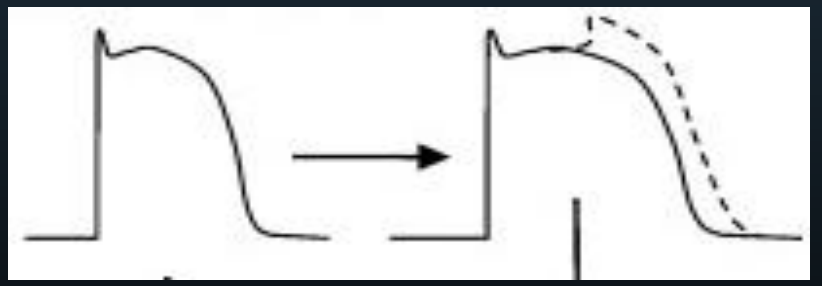
	Substrate	Trigger
Anatomical	Scar	
	Gap junction anomalies	
Functional	Stretch chronical	Stretch acute
Electrical		

Electrical Remodeling



Downregulation inward rectifier potassium current

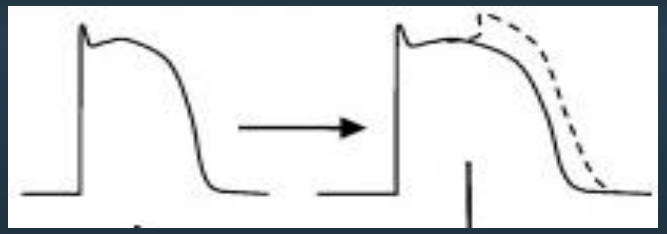
Prolongation of action potential duration



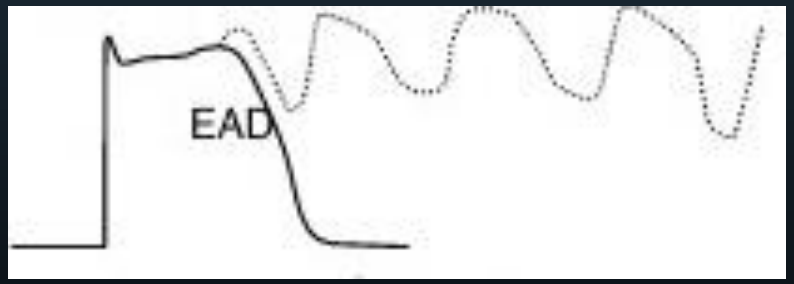
Franz, Cardiovasc Res, 1989

Electrical Remodeling

Prolongation of action potential duration

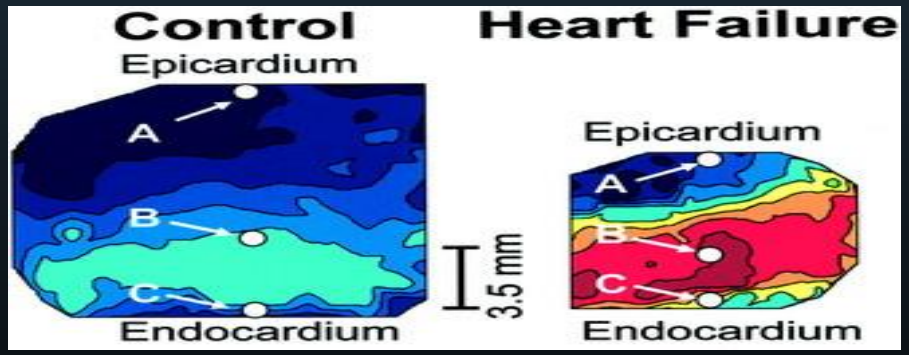


Early After Depolarization



Trigger

Eterogeneous: dispersion of repolarization



Substrate

Akar, Circ Res, 2003

Physyopathology: remodeling

	Substrate	Trigger
Anatomical	Scar	
	Gap junction anomalies	
Functional	Stretch chronical	Stretch acute

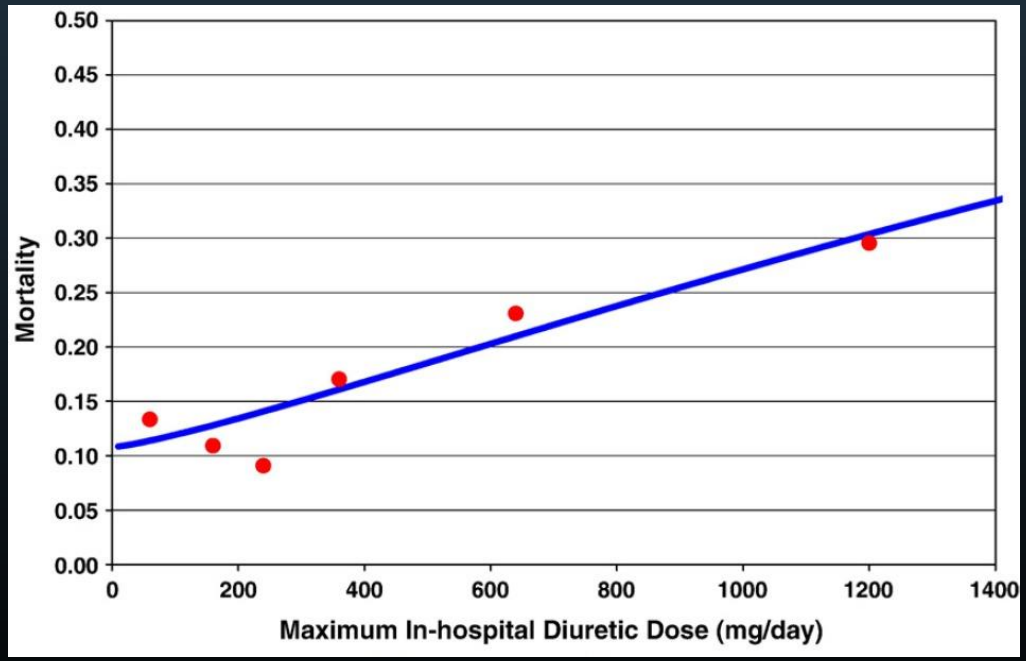
If we fight clinical decompensation and heart failure progression, do we prevent ventricular arrhythmias?

HF drugs

Diuretics

No reduction in SCD-VT

Increased mortality with higher diuretic dose



Electrolite imbalace?

Selection Bias?

Hasselblad, Eur J Heart Fail 2007

HF drugs

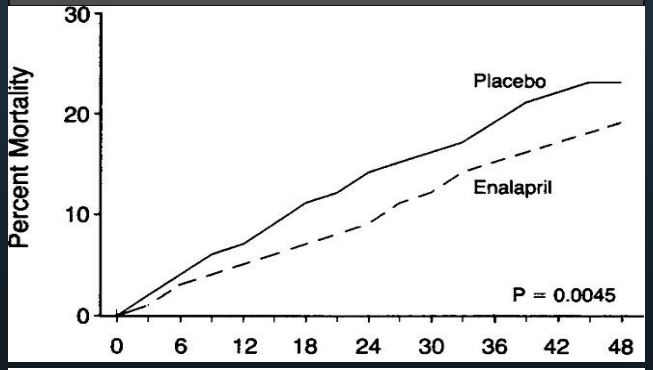
Diuretics

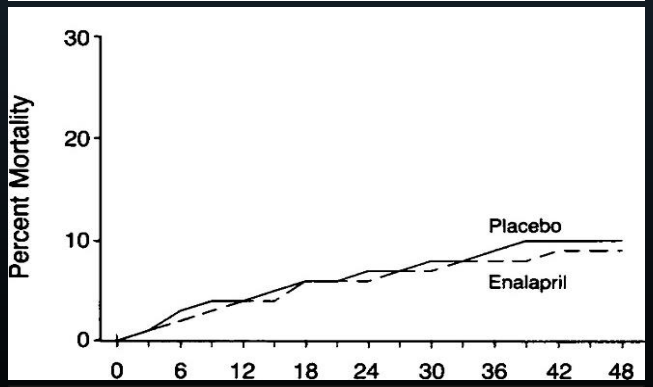
ACE-I

Lack of Long-Term Ventricular Arrhythmia Reduction by *Enalapril* in Heart Failure

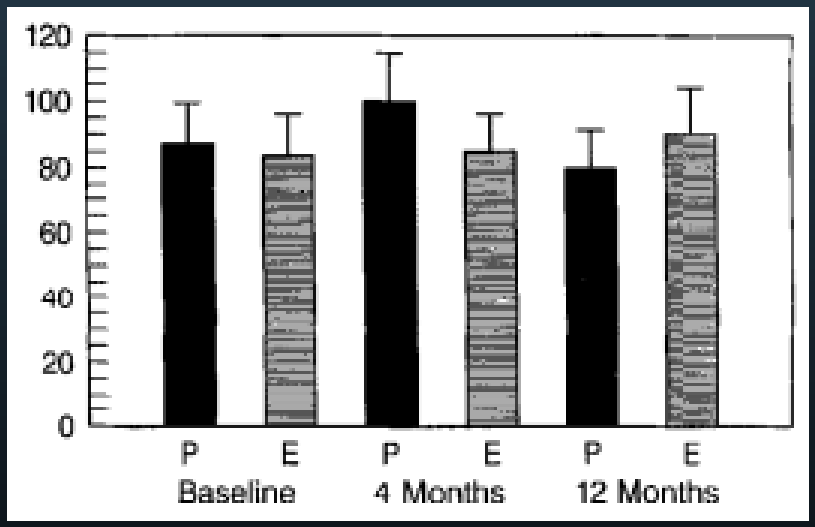
Craig M. Pratt, MD, Martin Gardner, MD, Carl Pepine, MD, Robert Kohn, MD, James B. Young, MD, Barry Greenberg, MD, Robert Capone, MD, John Kostis, MD, Milena Henzlova, MD, Gilbert Gosselin, MD, Melvin Weiss, MD, Marilyn Francis, RN, Dawn Stewart, Ed Davis, PhD, and Salim Yusuf, MD, for the SOLVD Investigators

SOLVD: total mortality





SOLVD: SCD



SOLVD: 1 year observation

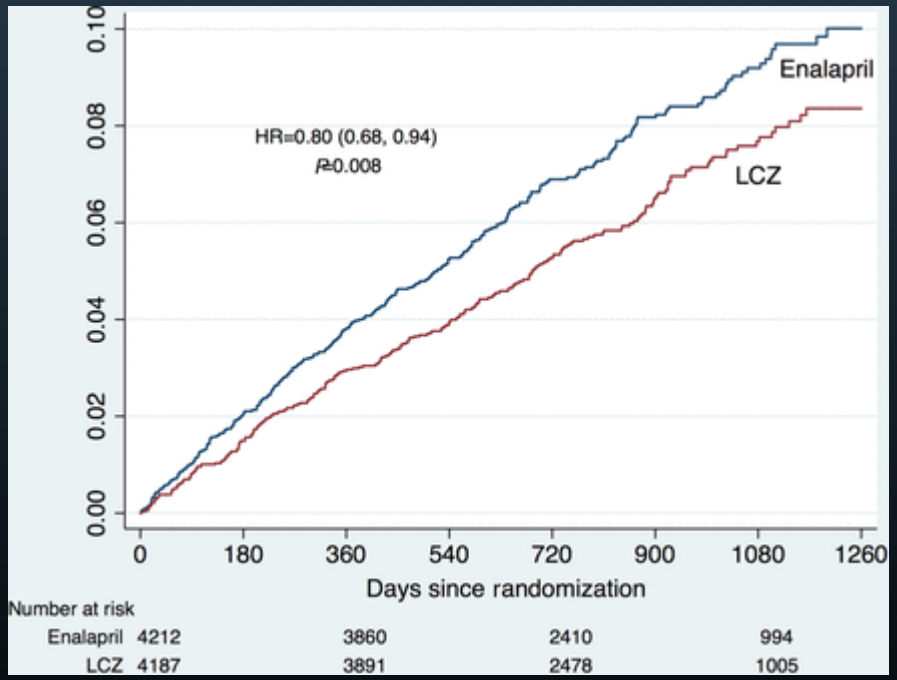
Yusuf, NEJM 1991

Pratt, JACC 1995

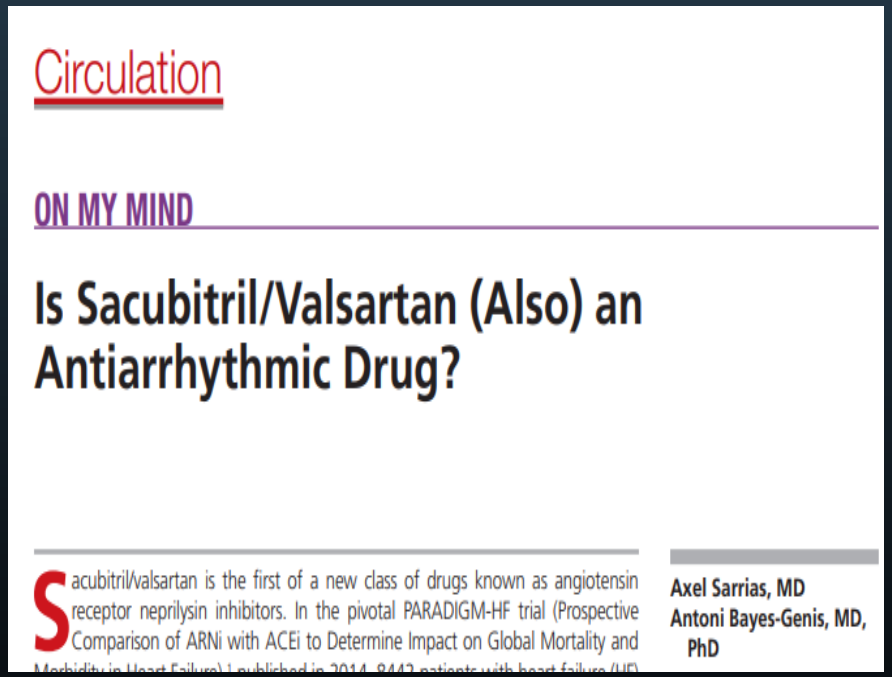
HF drugs

Diuretics

ACE-I | **ARB** | **ARNI**



PARADIGM HF Sudden death



Circulation

ON MY MIND

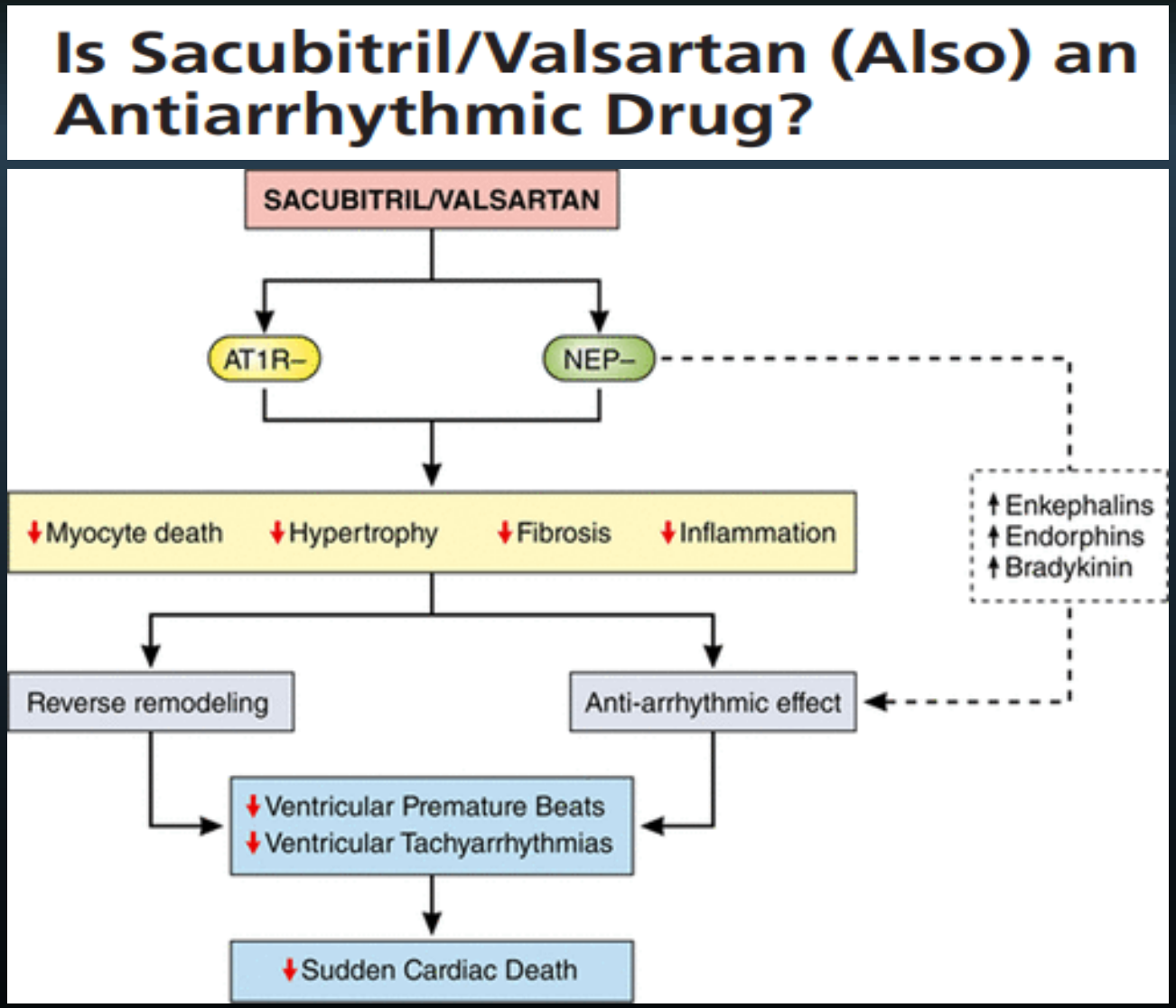
Is Sacubitril/Valsartan (Also) an Antiarrhythmic Drug?

Sacubitril/valsartan is the first of a new class of drugs known as angiotensin receptor neprilysin inhibitors. In the pivotal PARADIGM-HF trial (Prospective Comparison of ARNi with ACEi to Determine Impact on Global Mortality and

Axel Sarrias, MD
Antoni Bayes-Genis, MD, PhD

McMurray NEJM 2014

HF drugs



Sarrias, Circulation 2018

HF drugs

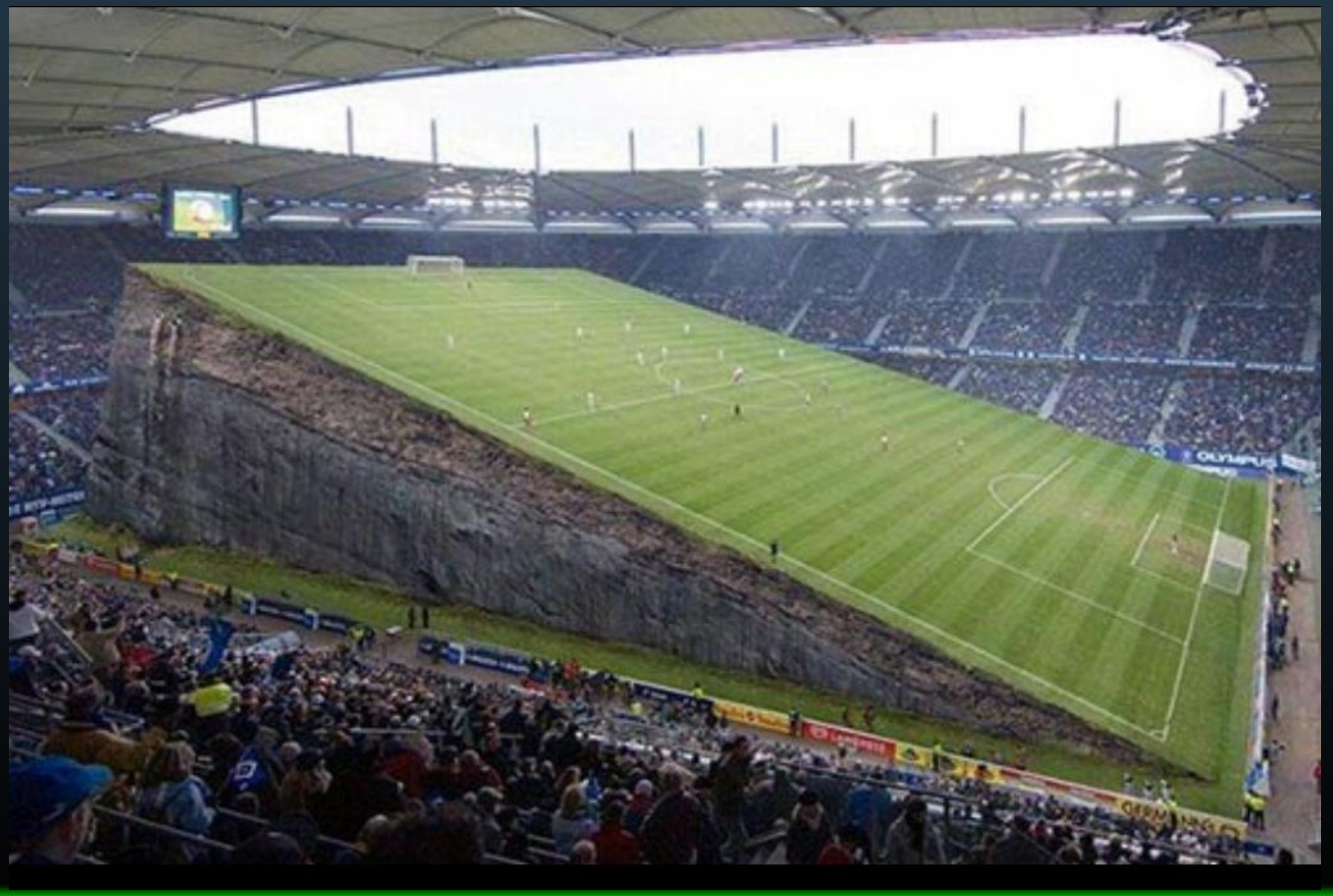
Diuretics

ACE-I

ARB

ARNI

Beta blockers

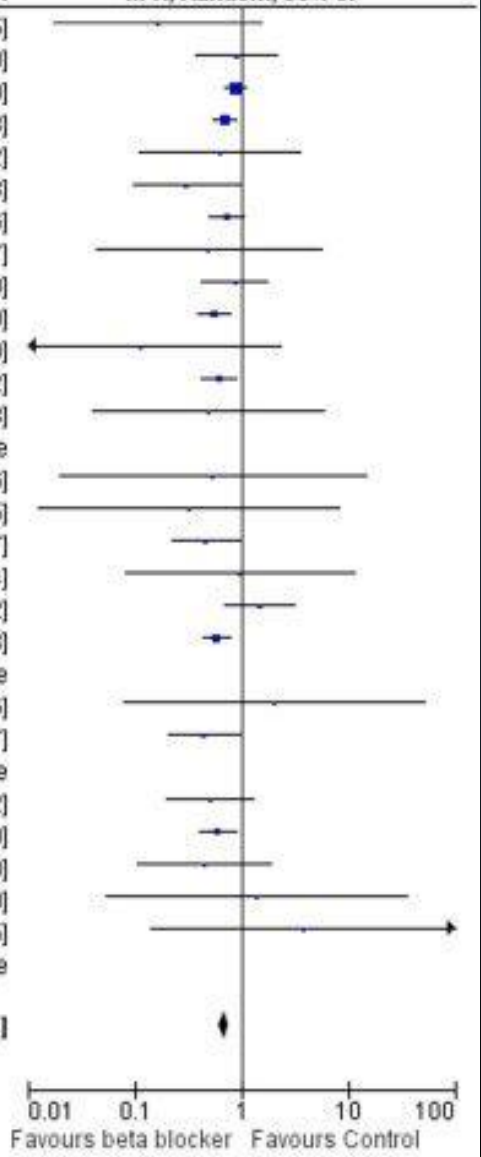


Beta Blockers and Sudden Death in HF

A

Study or Subgroup	Beta blockers Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Anderson et al	1	25	5	25	0.2%	0.17 [0.02, 1.55]
Australia/New Zealand	10	207	11	208	1.4%	0.91 [0.38, 2.19]
BEST	182	1354	203	1354	23.2%	0.88 [0.71, 1.09]
BHAT	129	1916	180	1921	19.5%	0.70 [0.55, 0.88]
Bristow et al.	4	105	2	34	0.4%	0.63 [0.11, 3.62]
Bristow et al.,	6	261	6	84	0.8%	0.31 [0.10, 0.98]
CAPRICORN	51	975	69	984	7.8%	0.73 [0.50, 1.06]
CELICARD	1	62	2	62	0.2%	0.49 [0.04, 5.57]
CIBIS	15	320	17	321	2.1%	0.88 [0.43, 1.79]
CIBIS II	48	1327	83	1320	8.2%	0.56 [0.39, 0.80]
Colucci et al.,	0	232	2	134	0.1%	0.11 [0.01, 2.39]
COPERNICUS	45	1156	69	1133	7.3%	0.62 [0.43, 0.92]
de Milliano et al.	2	43	1	11	0.2%	0.49 [0.04, 5.93]
ELANDD	0	57	0	59		Not estimable
Englmeier et al.	0	9	1	16	0.1%	0.54 [0.02, 14.76]
Fisher et al.	0	25	1	25	0.1%	0.32 [0.01, 8.25]
Hansteen V. et al	11	278	23	282	2.0%	0.46 [0.22, 0.97]
Krum et al.	2	33	1	16	0.2%	0.97 [0.08, 11.54]
MDC	18	194	12	189	1.9%	1.51 [0.71, 3.22]
MERIT-HF	79	1990	132	2001	13.2%	0.59 [0.44, 0.78]
Metra et al.	0	20	0	20		Not estimable
Olsen et al.	1	36	0	24	0.1%	2.07 [0.08, 52.96]
Packer et al.	12	696	15	398	1.8%	0.45 [0.21, 0.97]
Pollock et al.	0	12	0	7		Not estimable
RESOLVD	7	214	13	212	1.2%	0.52 [0.20, 1.32]
Seniors	44	1067	70	1061	7.2%	0.61 [0.41, 0.90]
Sturm et al.	3	51	6	49	0.5%	0.45 [0.11, 1.90]
UHLIR et al.	1	62	0	28	0.1%	1.39 [0.05, 35.19]
Wisenbaugh et al.	1	11	0	13	0.1%	3.86 [0.14, 104.65]
Woodley et al.	0	30	0	20		Not estimable
Total (95% CI)		**12768**		**12011**	**100.0%**	**0.69 [0.62, 0.77]**
Total events	673		924			

Heterogeneity: Tau² = 0.00; Chi² = 23.06, df = 25 (P = 0.57); I² = 0%
Test for overall effect: Z = 6.98 (P < 0.00001)



↓ automaticity

↓ excitability

↓ conduction speed

↓ DAD

Anti Ischemic

31% sudden death reduction in HF

NNT 43

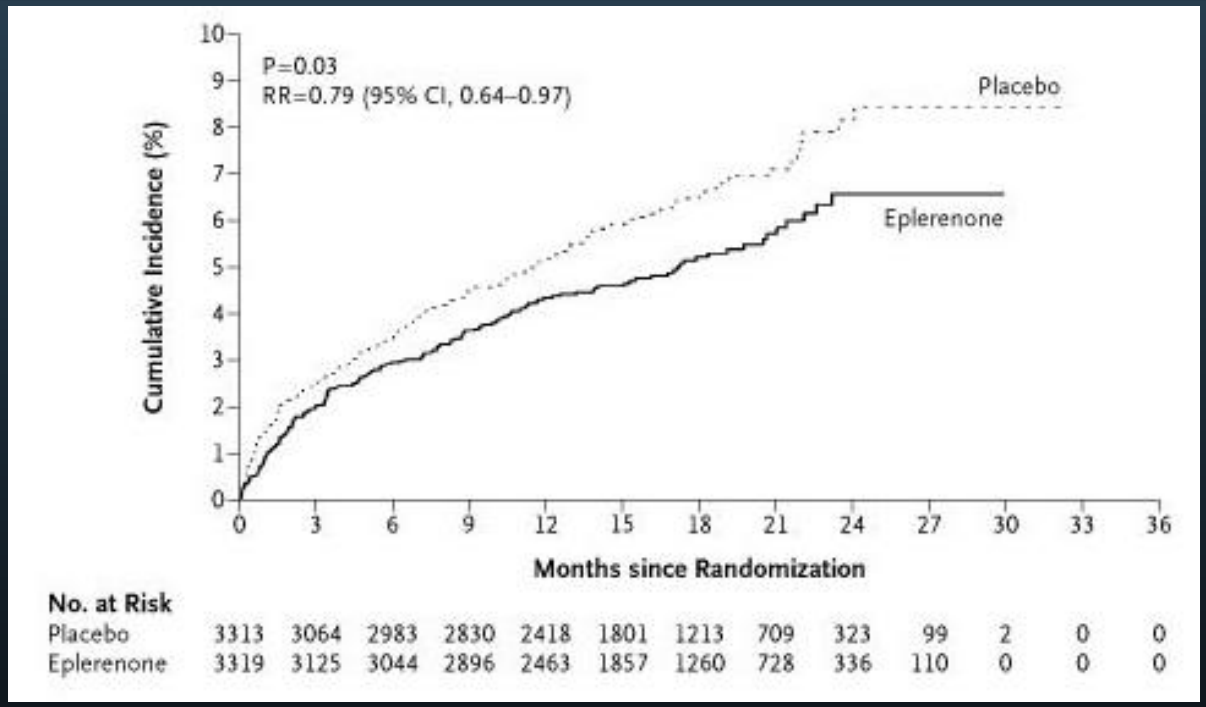
Al Gobari, BMC Cardiovasc Disord 2013

HF drugs

- Diuretics
- ACE-I
- ARB
- ARNI
- Beta blockers
- MRA

HF drugs

Eplerenone: EPHESUS trial



Sudden death in Ephesus: eplerenone vs placebo

On top of optimal therapy (75% betablockers)

NNT 50

Fibrosis reduction?

Protection from hypokaliemia?

Pitt, NEJM 2003

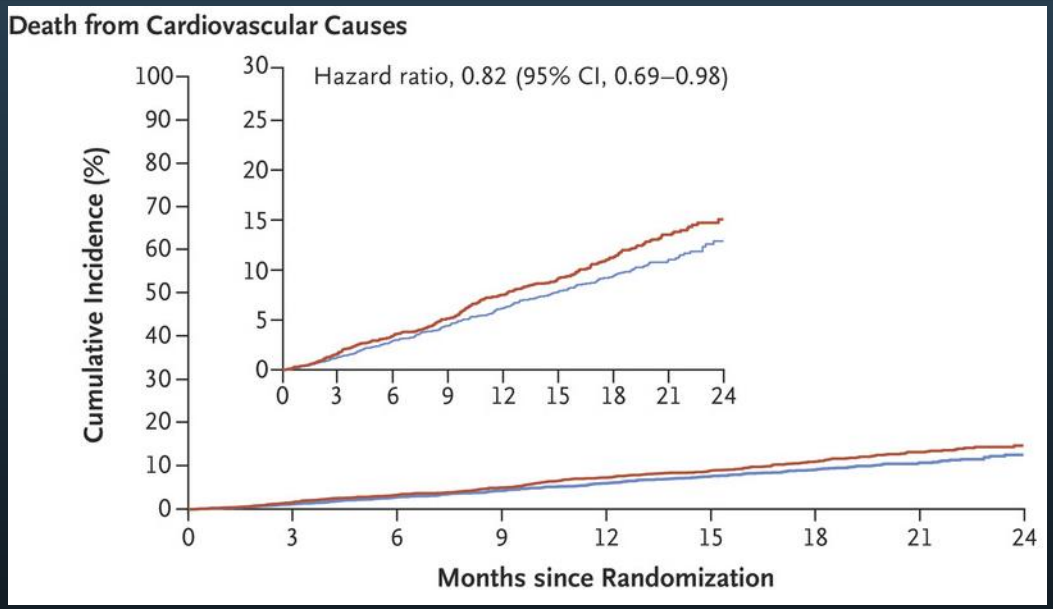
HF drugs

- Diuretics
- ACE-I
- ARB
- ARNI
- Beta blockers
- MRA
- Dapagliflozin

HF drugs

Dapaglifozin DAPA HF

Reduction of death from cardiovascolar causes



Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. DOI: 10.1056/NEJMoa1911303

McMurray, NEJM 2019

HF drugs

Supplementary Appendix

TABLE S1: A) Adverse events of interest and B) serious adverse events

	Number (%) of patients[a]	
	DAPA 10 mg (N=2368)	Placebo (N=2368)
Sudden death	19 (0.8)	10 (0.4)
Sudden cardiac death	18 (0.8)	27 (1.1)
Cardiac disorders	520 (22.0)	634 (26.8)
Cardiac failure	262 (11.1)	351 (14.8)
Cardiac failure congestive	65 (2.7)	70 (3.0)
Cardiac failure acute	42 (1.8)	59 (2.5)
Acute myocardial infarction	37 (1.6)	38 (1.6)
Ventricular tachycardia	34 (1.4)	54 (2.3)
Cardiac failure chronic	27 (1.1)	33 (1.4)
Atrial fibrillation	26 (1.1)	39 (1.6)
Angina unstable	21 (0.9)	30 (1.3)
Myocardial infarction	16 (0.7)	17 (0.7)
Angina pectoris	12 (0.5)	12 (0.5)
Ventricular fibrillation	11 (0.5)	6 (0.3)

P=NS

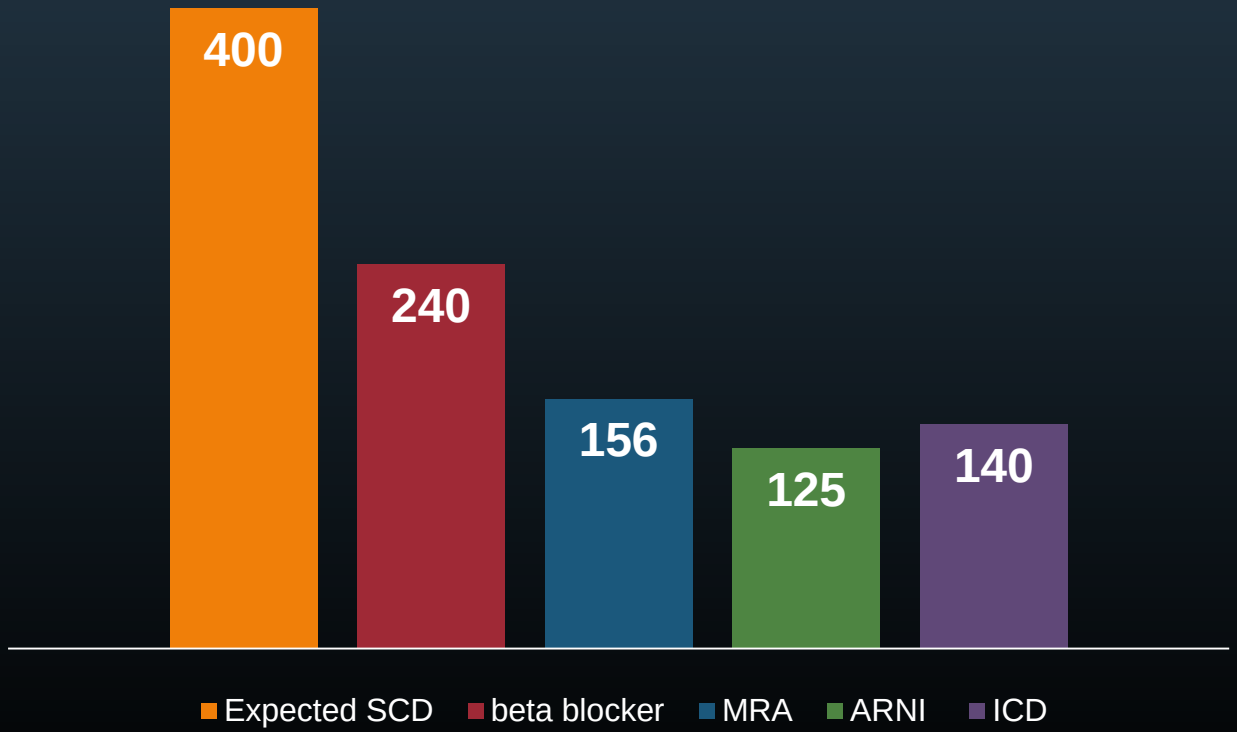
McMurray, NEJM 2019

HF drugs

	Beta blockers	MRA	ARNI
RR sudden death reduction	35-45%	35%	20%

Hypotetic coohort 1.000 HF patients

Untreated 400 deaths



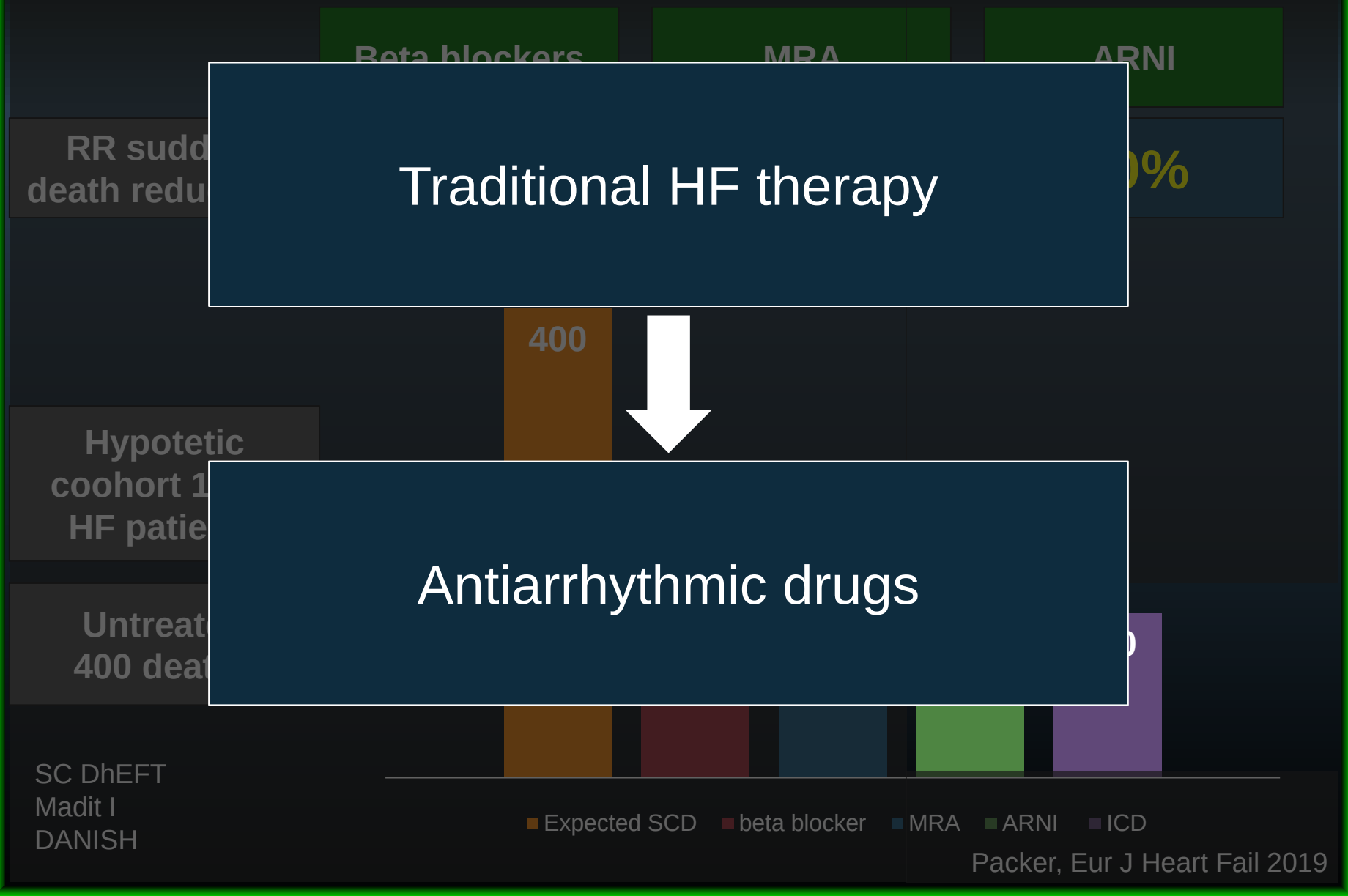
SC DhEFT
Madit I
DANISH

Packer, Eur J Heart Fail 2019

HF drugs

Traditional HF therapy

Antiarrhythmic drugs



Physyopathology: remodeling

	Substrate	Trigger
Anatomical	Scar	
	Gap junction anomalies	
Functional	Stretch chronical	Stretch acute
Electrical	Heterogenous lenghtening ap duration, transmural gradient	Downregulation ik→EAD
		Ca alteration→DAD

HF antiarrhytmic drugs

I	Ia	Quinidine

Scarse data on efficacy

High proarrhythmic effect

HF antiarrhytmic drugs

I | Ia | Quinidine | Dysopiramide

Negative inotropic effect

HF antiarrhytmic drugs

I	Ia	Quinidine	Dysopiramide	Procainamide

Negative inotropic effect

No oral formulation

HF antiarrhytmic drugs

I	Ia	Quinidine	Dysopiramide	Procainamide
	Ib	Lidocaine	Mexiletine	
		More efficent on high rate VT		

HF antiarrhytmic drugs

I	Ia	Quinidine	Dysopiramide	Procainamide
	Ib	Lidocaine	Mexiletine	
	Ic	Propafenone	Flecainide	

CAST

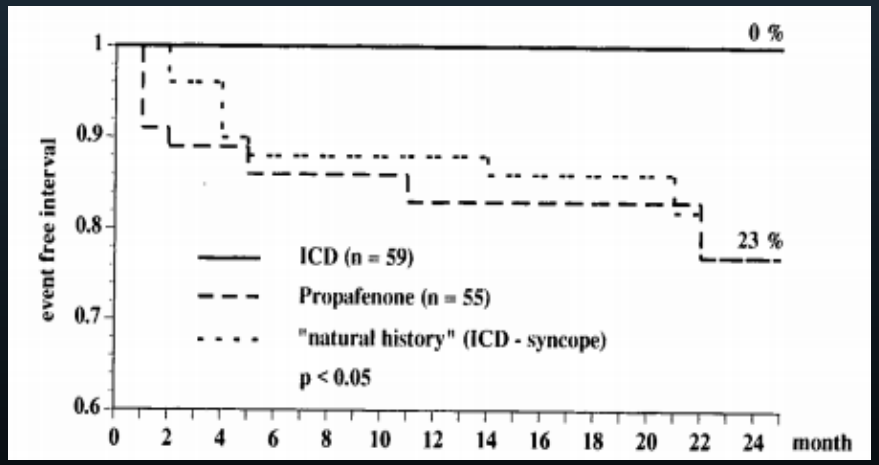
The New England Journal of Medicine

Owned and Published by the Massachusetts Medical Society

THE CARDIAC ARRHYTHMIA SUPPRESSION TRIAL (CAST)

NEJM 1989

CASH

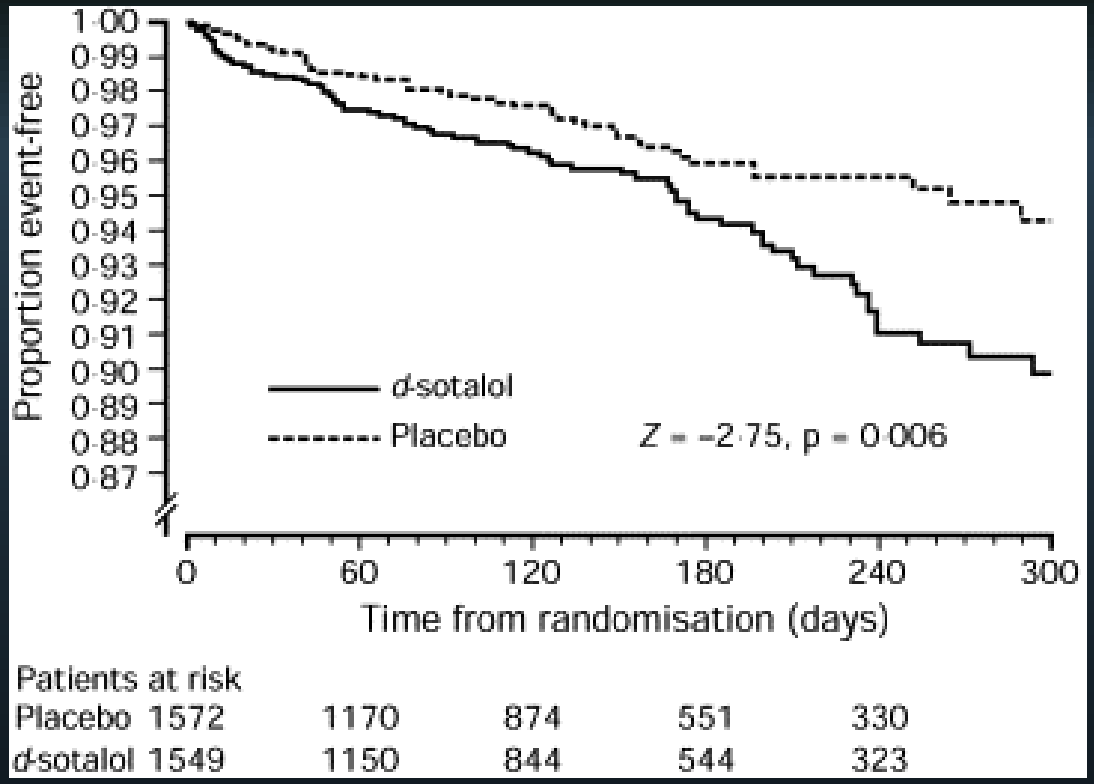


Kuck Circ 2000

HF antiarrhytmic drugs

I	Ia	Quinidine	Dysopiramide	Procainamide
	Ib	Lidocaine	Mexiletine	
	Ic	Propafenone	Flecainide	
II	Beta blockers			
III	Sotalol	Amiodarone		
IV	Ca antagonist			

Sotalol: SWORD trial



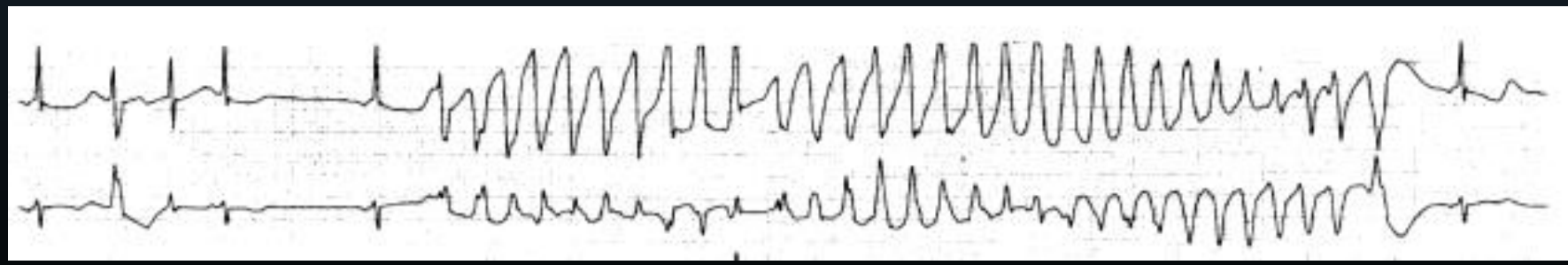
D- Sotalol vs placebo

Primary prevention

3121 patients FE < 40

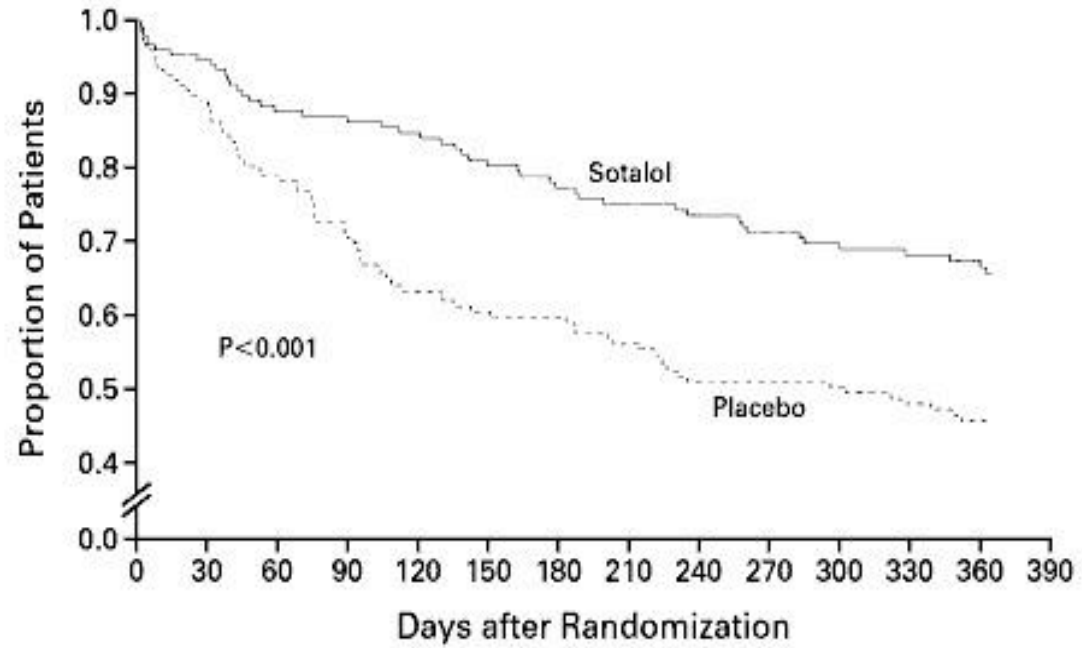
Anticipated interruption for mortality eccess

	d-sotalol (n=1549)	Placebo (n=1572)	Log-rank p*
All causes	78	48	0·006
Cardiac deaths			
All cardiac	73	45	0·008
Arrhythmic (presumed)	56	32	0·008



Waldo, Lancet 1996

D-L Sotalol



Racemic mixture D and L

Secondary prevention

302 ICD patients randomized to sotalol vs placebo

Time to death for any cause or appropriate ICD shock

Subgroup FE < 30% → p 0.02

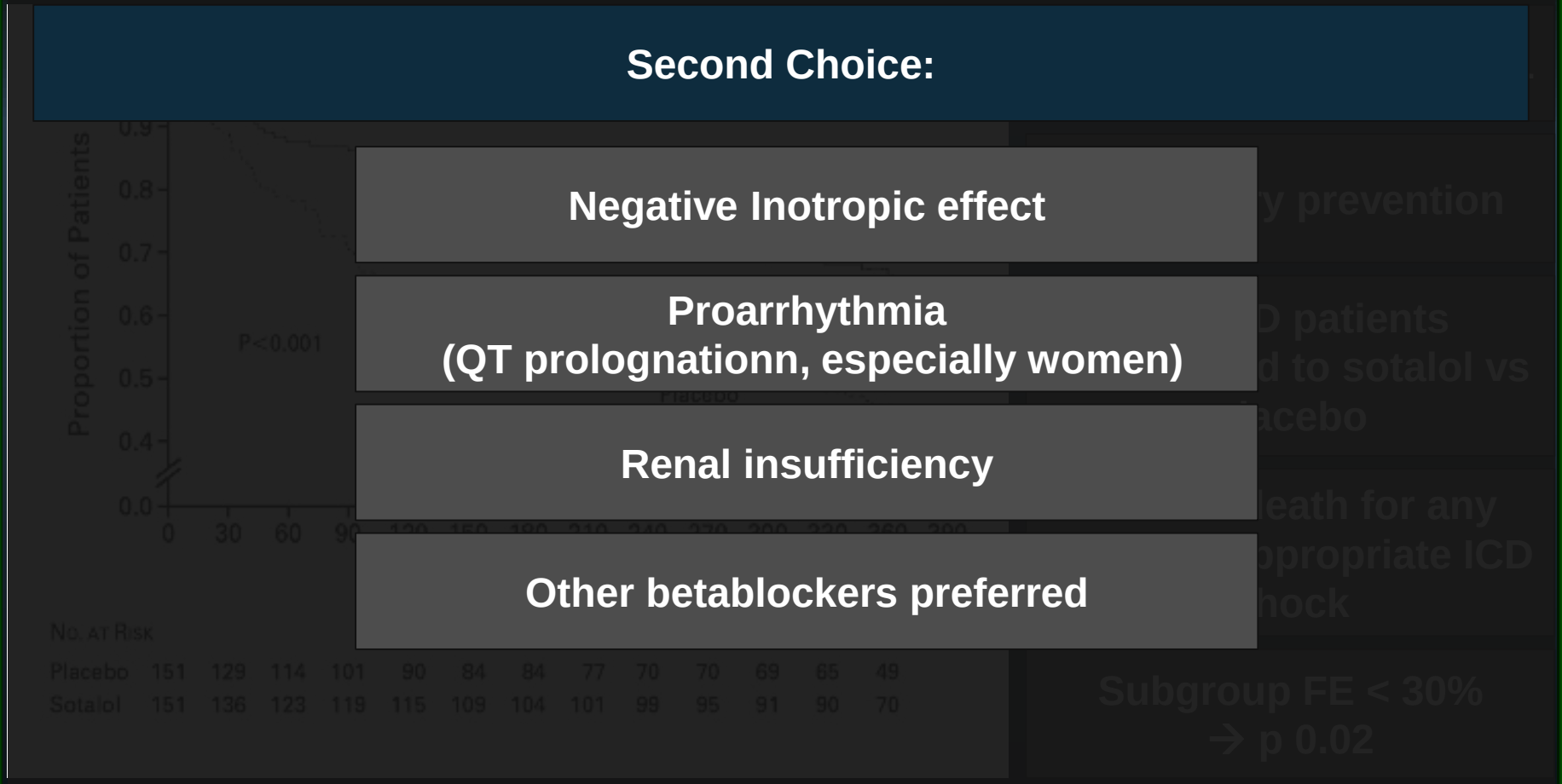
Sotalol reduced ICD shock in secondary prevention in HF patients

Pacifico, NEJM 1999

D-L Sotalol

Second Choice:

- **Negative Inotropic effect**
- **Proarrhythmia (QT prolognationn, especially women)**
- **Renal insufficiency**
- **Other betablockers preferred**



Sotalol reduced ICD shock in secondary prevention in HF patients

Pacifico, NEJM 1999

HF antiarrhytmic drugs

I	Ia	Quinidine	Dysopiramide	Procainamide
	Ib	Lidocaine	Mexiletine	
	Ic	Propafenone	Flecainide	
II		Beta blockers		
III		Sotalol		
IV		Ca antagonist		

HF antiarrhytmic drugs

I	Ia	Quinidine	Dysopiramide	Procainamide
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HF antiarrhytmic drugs

I	Ia	Quinidine	Dysopiramide	Procainamide
	Ib	Lidocaine	Mexiletine	
	Ic	Propafenone	Flecainide	
II		Beta blockers		
III		Sotalol	Amiodarone	
IV		Ca antagonist		

Amiodarone

SCD reduced of 32%

No effect on overall mortality

Proarrhythmia

Toxicity (thyroid 3.2%, lung 1.4%, liver 1.1%)

Discontinuation 10 % (up to 40%)

Indicated in secondary prevention until tolerated

Piccini, EHJ 2009

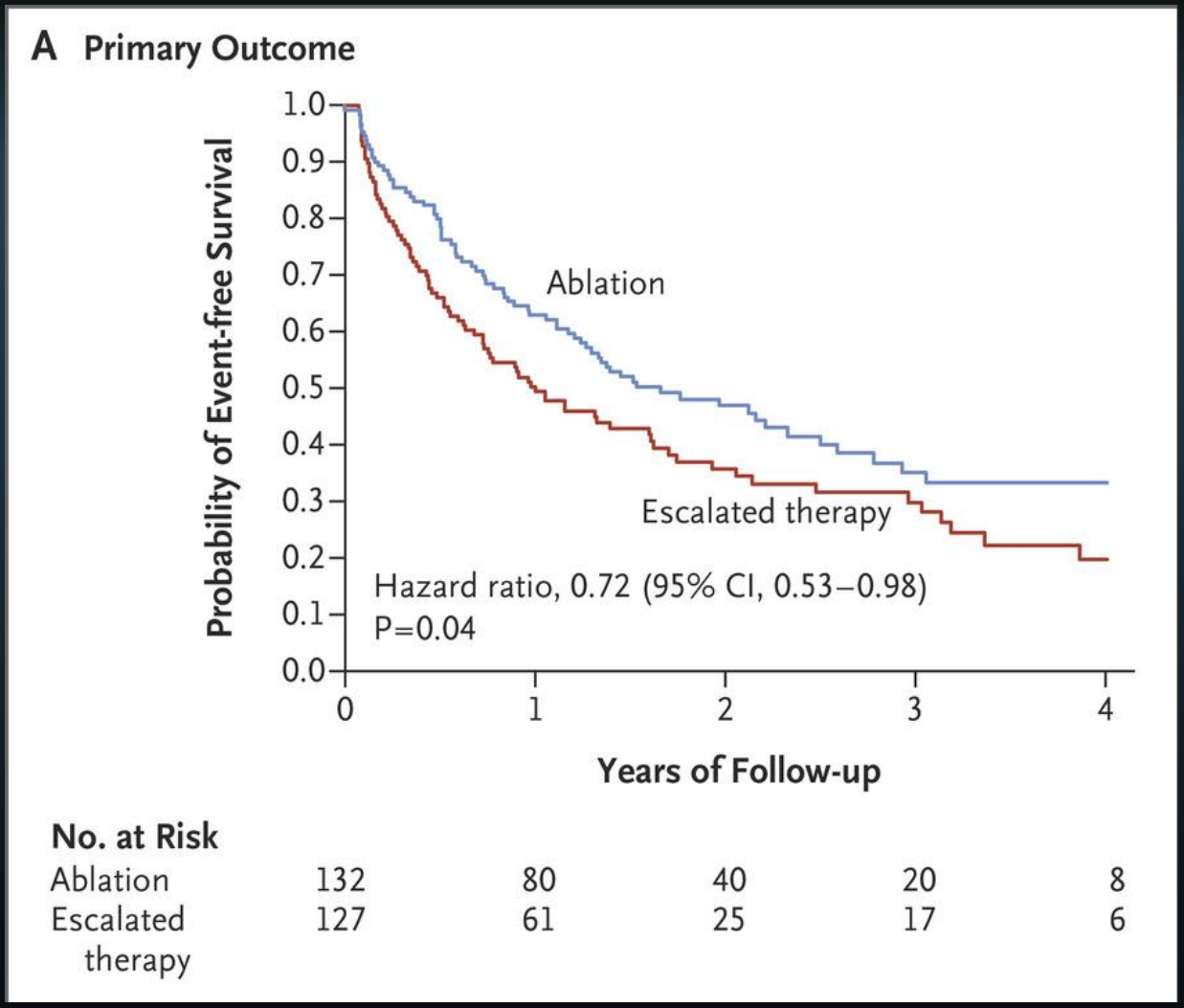
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ventricular Tachycardia Ablation versus Escalation of Antiarrhythmic Drugs

John L. Sapp, M.D., George A. Wells, Ph.D., Ratika Parkash, M.D., William G. Stevenson, M.D., Louis Blier, M.D., Jean-Francois Sarrazin, M.D., Bernard Thibault, M.D., Lena Rivard, M.D., Lorne Gula, M.D., Peter Leong-Sit, M.D., Vidal Essebag, M.D., Ph.D., Pablo B. Nery, M.D., Stanley K. Tung, M.D., Jean-Marc Raymond, M.D., Laurence D. Sterns, M.D., George D. Veenhuyzen, M.D., Jeff S. Healey, M.D., Damian Redfearn, M.D., Jean-Francois Roux, M.D., and Anthony S.L. Tang, M.D.

Amiodarone: VANISH trial



Death + Storm + ICD Shock

Sapp N Engl J Med 2016

Conclusions

Standard HF therapy has a very **good efficacy** against sudden death, mainly due to ventricular arrhythmias

When standard therapy is not enough, in **secondary prevention** antiarrhytmic drugs may be added (**Amiodarone, Mexiletine** for fast VT or, rarely, **Sotalol**)

When even antiarrhythmic drugs is not tolerated or fails to prevent arrhythmic episodes, **interventional therapy** must be considered