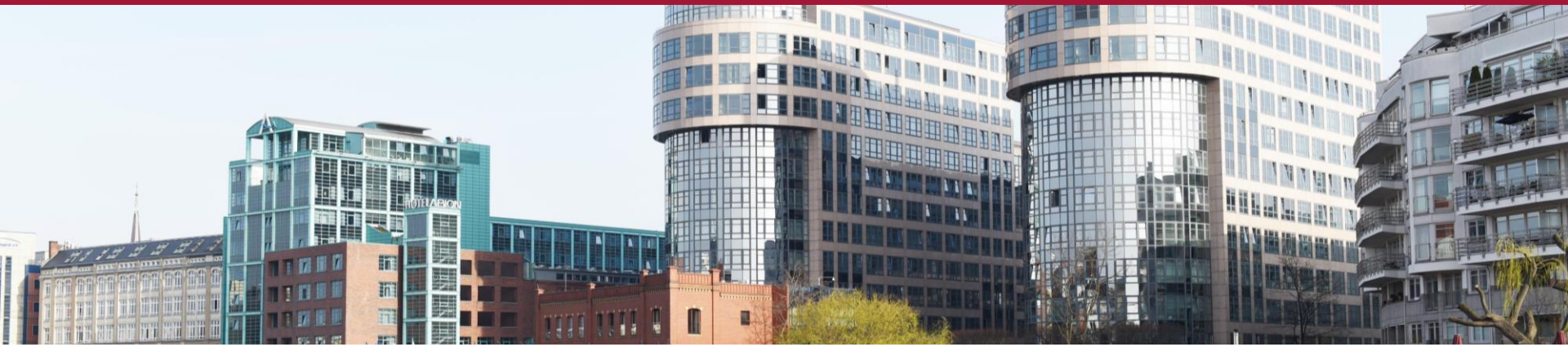


Antiarrhythmic effects of CRT, assist devices, sacubitril, exercise and others in HFrEF

W. Haverkamp

SPREE-BOGEN
Kardiologie im Spreebogen
Berlin, Germany

DRZB
Deutsches Rhytmuszentrum
Berlin-Brandenburg

Definitions

- **Antiarrhythmic effect**: treatment modality (mode of action) that leads to the termination or the prevention of an arrhythmia.
- **Antifibrillatory effect**: treatment modality (mode of action) that leads to the termination or the prevention of atrial/ventricular fibrillation.

Definitions

- **Antiarrhythmic drugs**: drugs that aims to terminate an existing arrhythmia and/or to prevent future arrhythmic events by ***directly interacting*** with the arrhythmia mechanism/s or the electrophysiological properties of the arrhythmogenic substrate.

Traditional antiarrhythmic drugs

Modified Vaughan Williams Classification of Antiarrhythmic Drugs

Class	Examples	Mechanism
Ia	Quinidine Procainamide	Na^+ channel blockers (intermediate association/dissociation)
Ib	Lidocaine Phenytoin	Na^+ channel blockers (fast association/dissociation)
Ic	Flecainide Propafenone	Na^+ channel blockers (slow association/dissociation)
II	Propranolol Metoprolol	Beta blockers (propanolol also shows some class I action)
III	Amiodarone Sotalol	K^+ channel blockers (sotalol is also a beta blocker; amiodarone has Class I, II, III, and IV activity)
IV	Verapamil Diltiazem	Ca^{2+} channel blockers

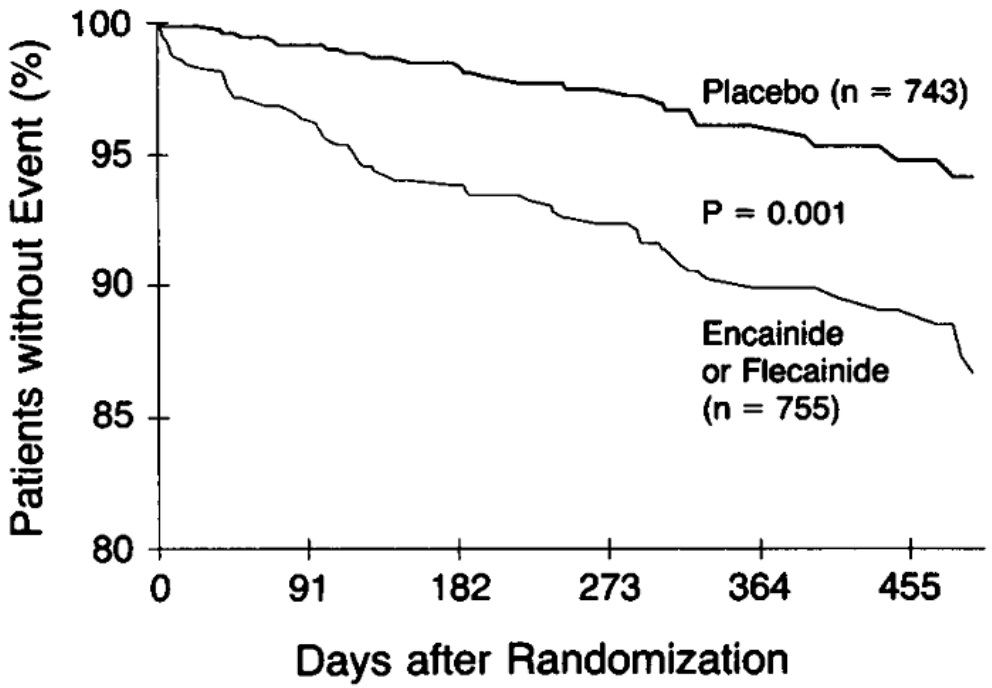
Vaughan Williams EM. Classification of antiarrhythmic drugs. In: Sandoe E, Flensted-Jensen E, Olesen K II, eds. *Symposium on Cardiac Arrhythmias.* Stockholm, Sweden: Astra 1970; 449- 472.

Harrison DC. Is there a rational basis for the modified classification of antiarrhythmic drugs? Morganroth J, Moore EN, eds. *Cardiac Arrhythmias: New Therapeutic Drugs and Devices.* Boston, Mass: Nijhoff 1985; 36- 47.

Traditional antiarrhythmic drugs

- **Major limitation of traditional antiarrhythmic drugs**: all may produce proarrhythmia.
- **Proarrhythmia**: Drug-induced provocation of a new arrhythmia or a significant increase in the frequency of a preexisting arrhythmia.

CAST



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

CAST Investigators, 4/1989

Definitions

- **Drugs with an indirect antiarrhythmic effect**: drugs that reduce the likelihood of future arrhythmic events ***without directly interacting*** with the arrhythmia mechanism/s or the electrophysiological properties of the arrhythmogenic substrate.

Classification of antiarrhythmic drugs

Circulation

SYSTEMATIC REVIEW

Modernized Classification of Cardiac Antiarrhythmic Drugs

BACKGROUND: Among his major cardiac electrophysiological contributions, Miles Vaughan Williams (1918–2016) provided a classification of antiarrhythmic drugs that remains central to their clinical use.

METHODS: We survey implications of subsequent discoveries concerning sarcolemmal, sarcoplasmic reticular, and cytosolic biomolecules, developing an expanded but pragmatic classification that encompasses approved and potential antiarrhythmic drugs on this centenary of his birth.

Ming Lei, BM, MSc, DPhil
Lin Wu, BM, MSc, MD
Derek A. Terrar, BSc, MA, PhD
Christopher L.-H. Huang, MA, BMBCh, DM, DSc, PhD, MD, ScD

Modified classification of antiarrhythmic drugs

Drug class	Mode of action
Class 0	HCN channel blockers
Class I	Voltage-gated Na+ channel blockers
Class II	Autonomic inhibitors and activators
Class III	K+ channel blockers and openers
Class IV	Ca2+ handling modulators
Class V	Mechanosensitive channel blockers
Class VI	Gap junction channel blockers
Class VII	Upstream target modulators

Lei et al. 2018

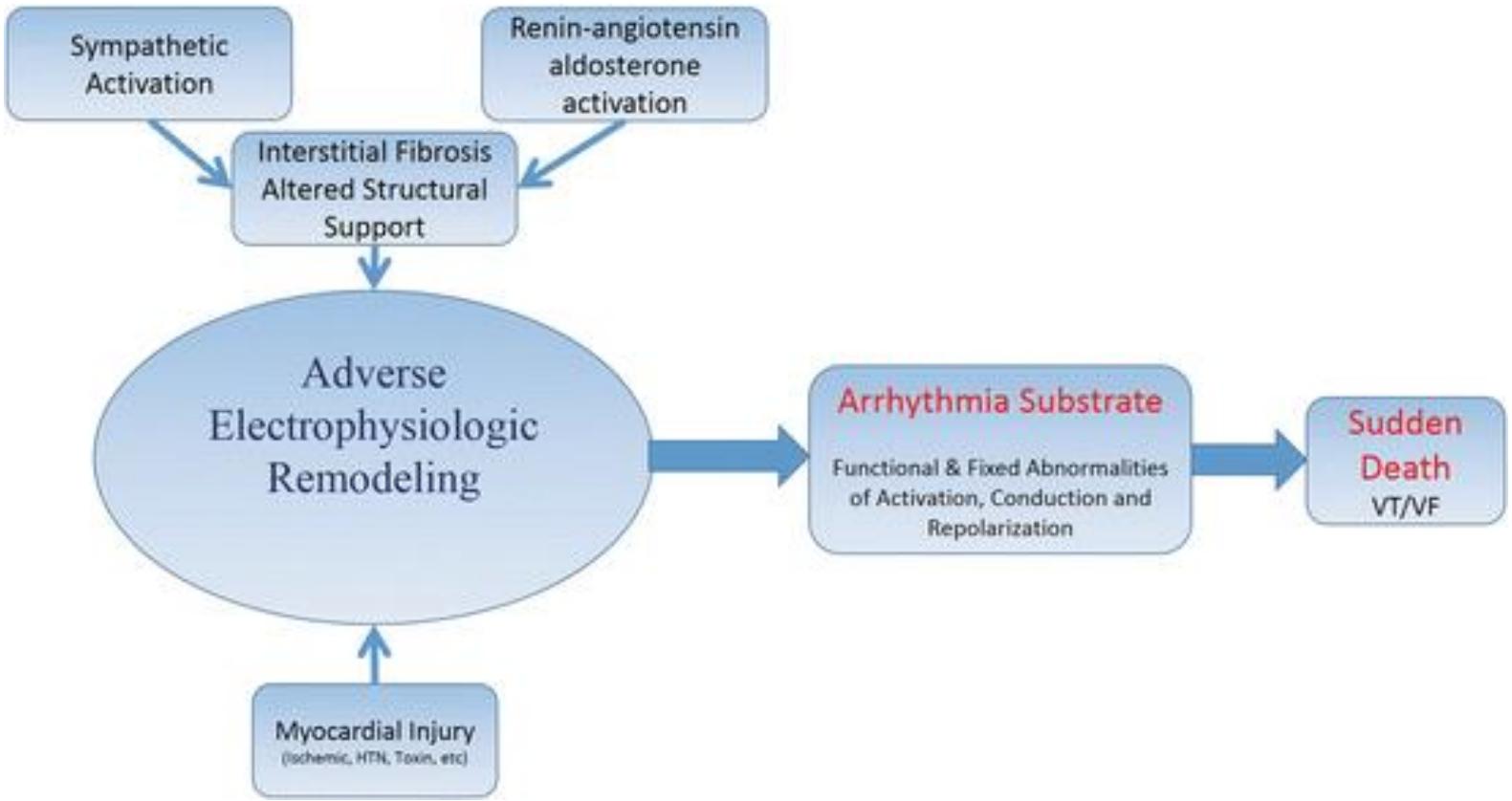
Class VII: Drugs acting on upstream modulatory targets

The introduction of a **Class VII** results from the need to encompass **tissue structure remodeling processes** and their consequently **longer-term changes** that contrast with the primary preoccupation with the short-term effects of particular drugs on specific ion channels in the original Vaughan Williams classification. […]

Experimental studies have demonstrated that **renin-angiotensin-aldosterone inhibitors**, **omega-3 fatty acids**, and **statins** prevent such electrophysiological and/or structural remodeling.

Lei et al. 2018

Arrhythmias in systolic heart failure



Adamson et al. 2015

DANISH: ICD in non-ischemic cardiomyopathy

The NEW ENGLAND JOURNAL of MEDICINE

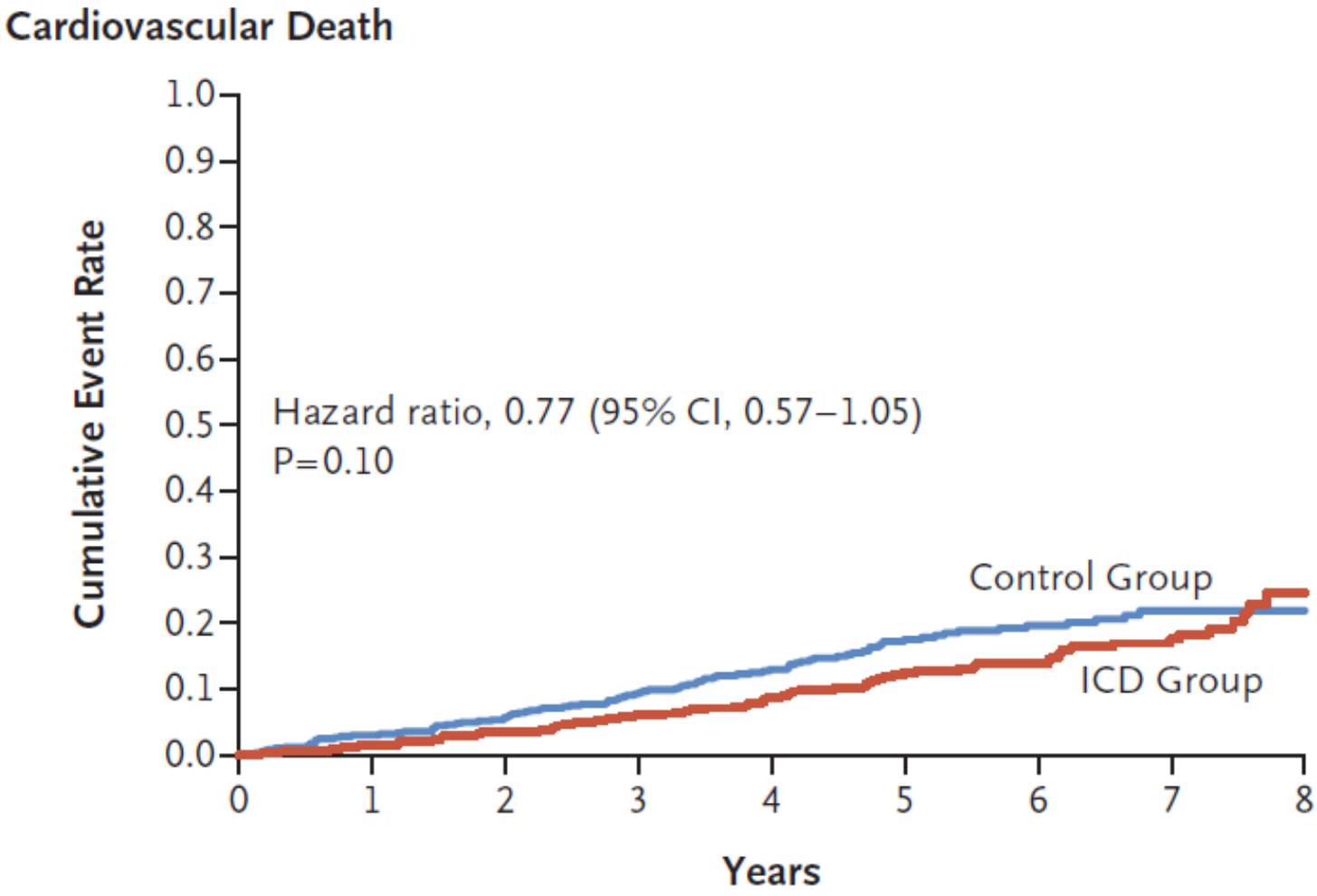
ORIGINAL ARTICLE

Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure

Lars Køber, M.D., D.M.Sc., Jens J. Thune, M.D., Ph.D.,
Jens C. Nielsen, M.D., D.M.Sc., Jens Haarbo, M.D., D.M.Sc.,
Lars Videbæk, M.D., Ph.D., Eva Korup, M.D., Ph.D., Gunnar Jensen, M.D., Ph.D.,
Per Hildebrandt, M.D., D.M.Sc., Flemming H. Steffensen, M.D.,
Niels E. Bruun, M.D., D.M.Sc., Hans Eiskjær, M.D., D.M.Sc., Axel Brandes, M.D.,
Anna M. Thøgersen, M.D., Ph.D., Finn Gustafsson, M.D., D.M.Sc.,
Kenneth Egstrup, M.D., D.M.Sc., Regitze Videbæk, M.D.,
Christian Hassager, M.D., D.M.Sc., Jesper H. Svendsen, M.D., D.M.Sc.,
Dan E. Høfsten, M.D., Ph.D., Christian Torp-Pedersen, M.D., D.M.Sc., and
Steen Pehrson, M.D., D.M.Sc., for the DANISH Investigators*

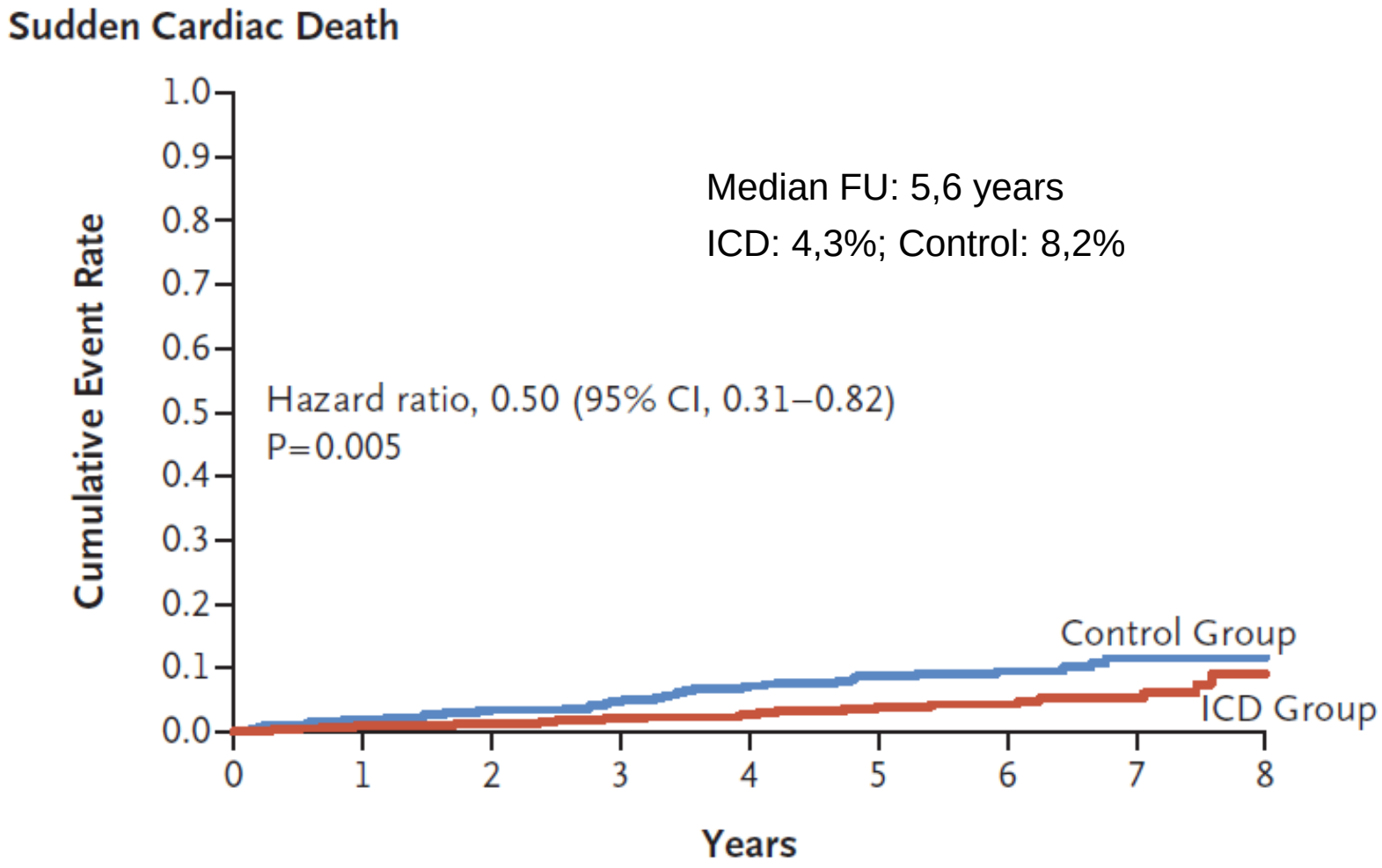
Kober et al. 2016

DANISH: ICD in non-ischemic cardiomyopathy



Kober et al. 2016

DANISH: ICD in non-ischemic cardiomyopathy



Median FU: 5,6 years

ICD: 4,3%; Control: 8,2%

Kober et al. 2016

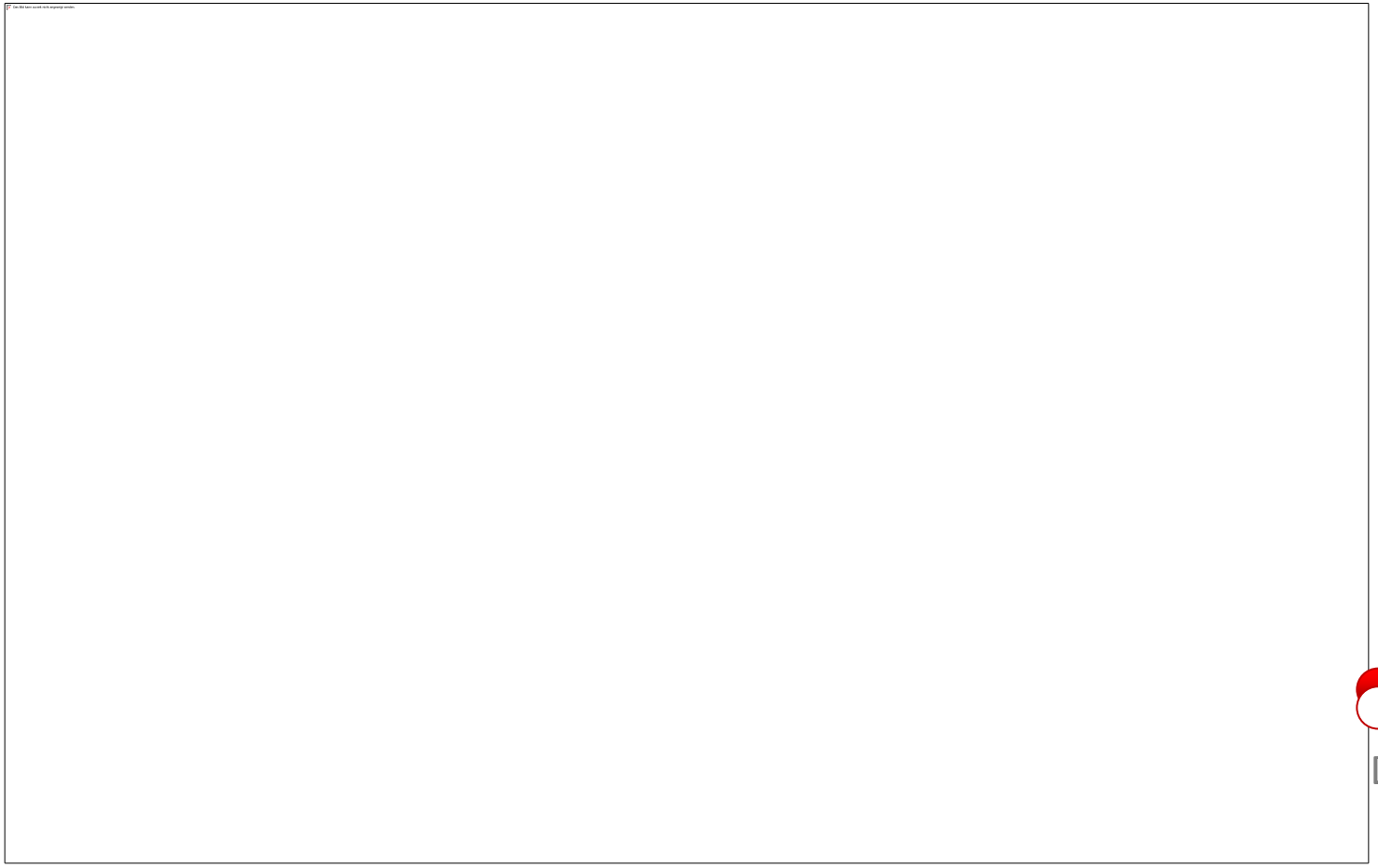
DANISH: ICD in non-ischemic cardiomyopathy

Kober et al. 2016

Declining sudden death rates in systolic heart failure

Shen et al. 2017

Declining sudden death rates in systolic heart failure



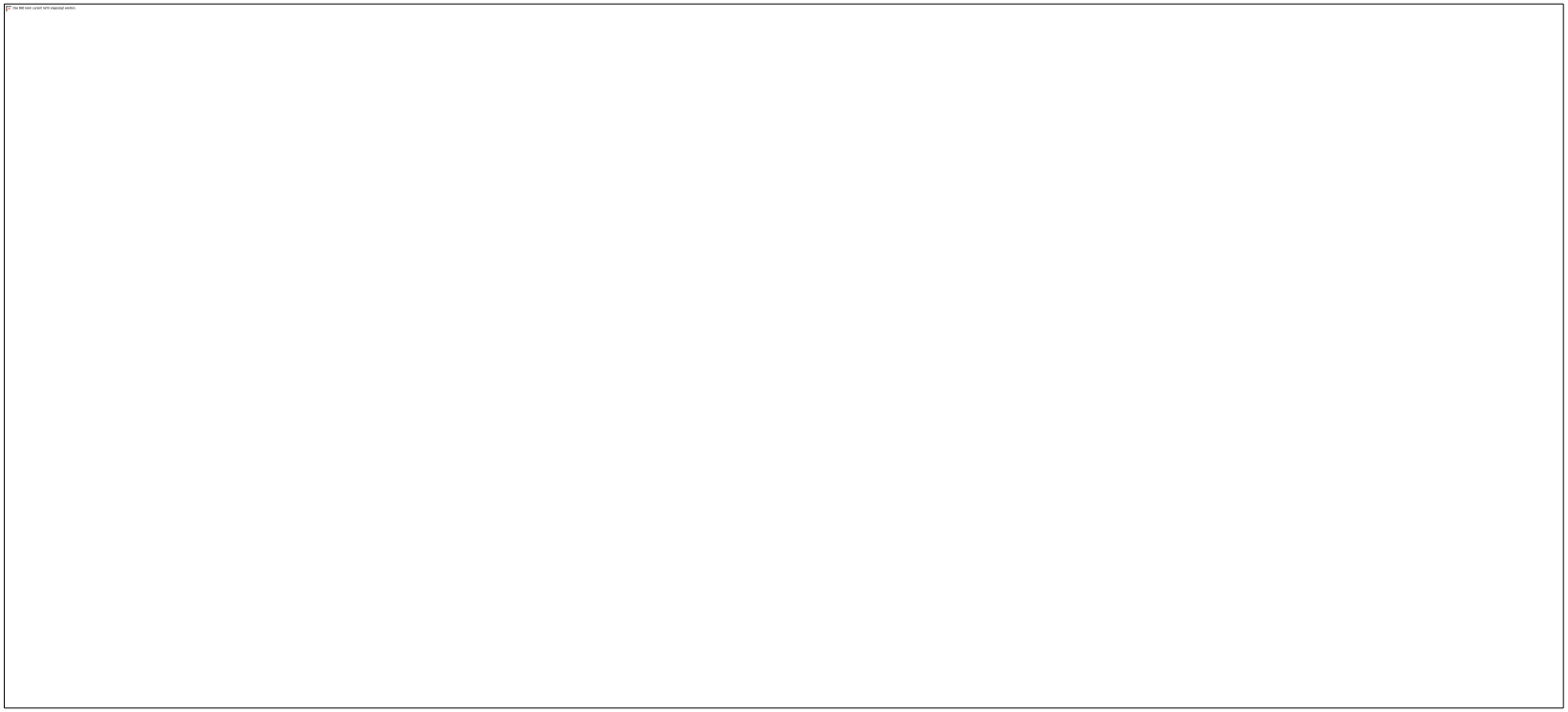
DANISH

Shen et al. 2017

Antiarrhythmic effects

- ***CRT***
- ***Assist devices***
- ***Sacubitril***
- ***Exercise***

Cardiac resynchronization therapy



The effect of CRT-defibrillator on sustained VA was compared with ICD-only therapy. Thirteen studies were inluded (4,631 subjects).

Ventricular arrhythmias: ventricular tachycardia or fibrillation episodes that stop only after antitachycardia pacing and/or shocks (or did not otherwise stop spontaneously), as documented by device interrogations.

VA: CRT-D vs. ICD

Patients with CRT had a significantly lower incidence of VA compared with patients with ICD only (odds ratio: 0.754; confidence interval: 0.594 to 0.959).

Saini et al. 2016

VA: CRT responders vs. non responders

CRT responders had a significantly lower risk of VA (odds ratio: 0.436; confidence interval: 0.323 to 0.589). **CRT nonresponders** had an elevated risk of VA compared with ICD-only subjects (odds ratio: 1.497; confidence interval: 1.225 to 1.829).

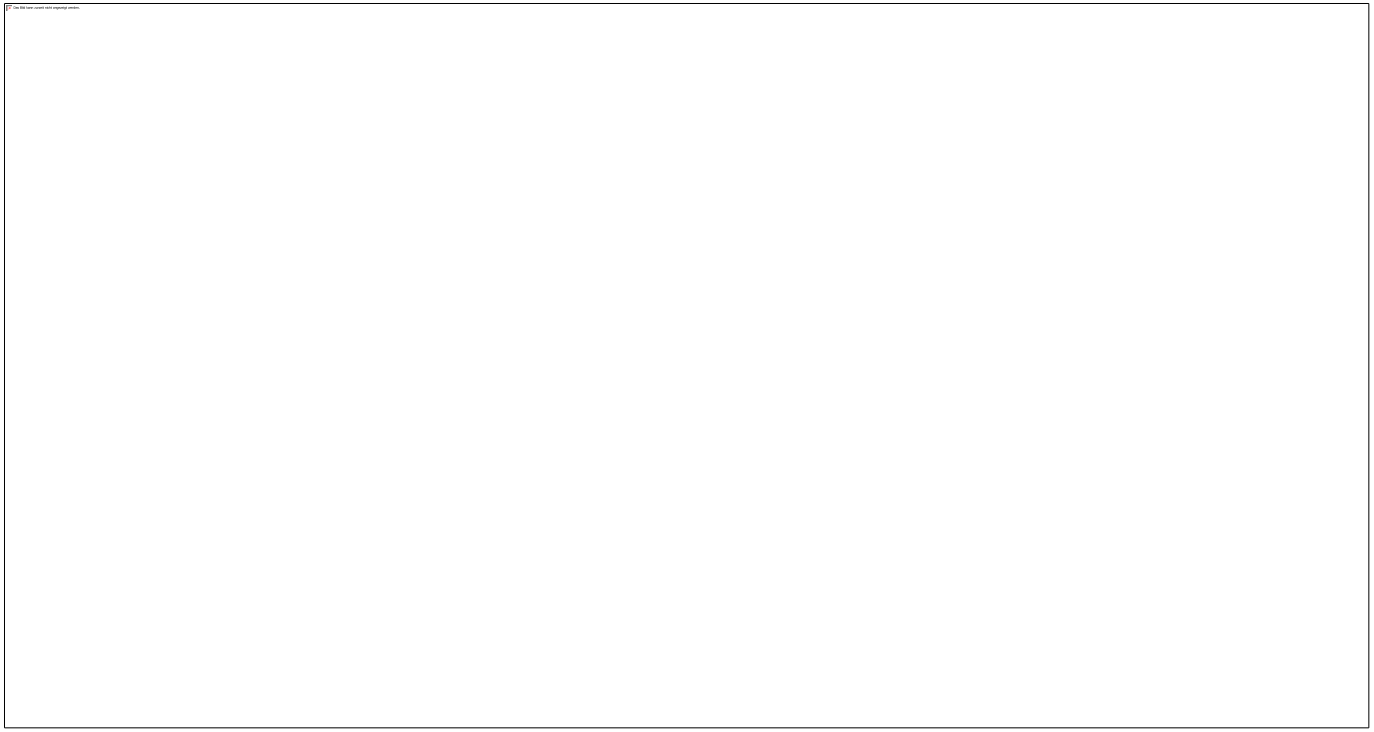
⟶ Hemodynamic improvement and reverse remodling

Saini et al. 2016

Antiarrhythmic effects

- ***CRT***
- ***Assist devices***
- ***Sacubitril***
- ***Exercise***

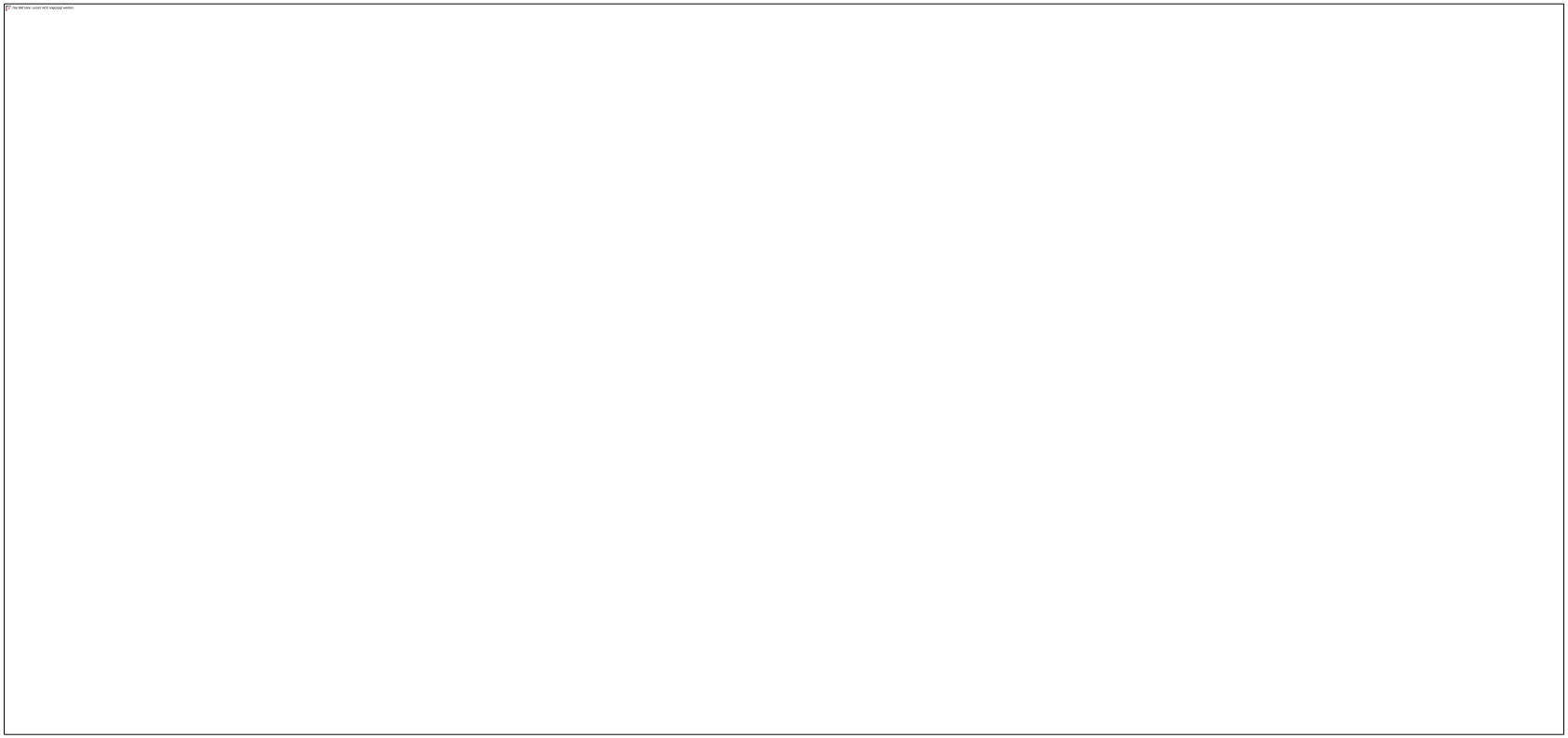
LVAD in refractory VA



Arrhythmias in patients with LVADs

Moss 2016

„Stable“ VT is not tolerated indefinitely



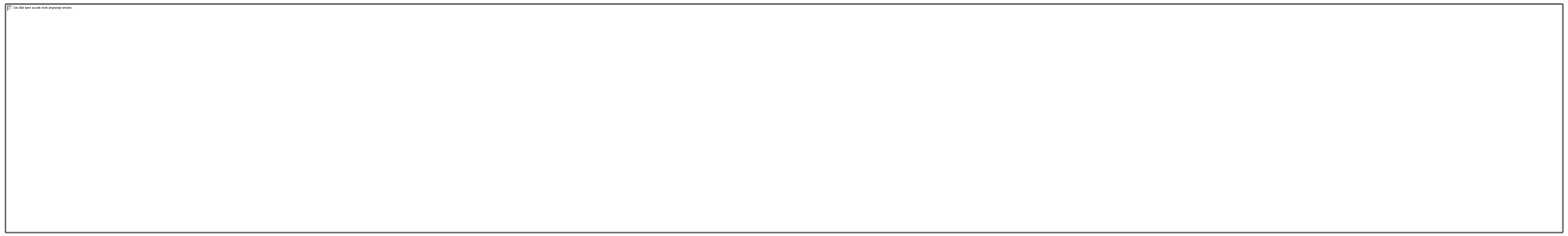
Moss 2016

Arrhythmia mechanisms in LVAD patients

- Use of inotropic drugs post-operatively
- Inflow cannula contact with the endocardium
- Suction events in continuous flow devices
- Persistent or recurrent myocardial ischaemia
- Apical scarring from LVAD inflow site
- Intrinsic arrhythmogenicity due to fibrosis or myocyte remodelling
- QTc prolongation from unloading of cardiomyopathic hearts
- Changes in ion channel and gap junction regulation

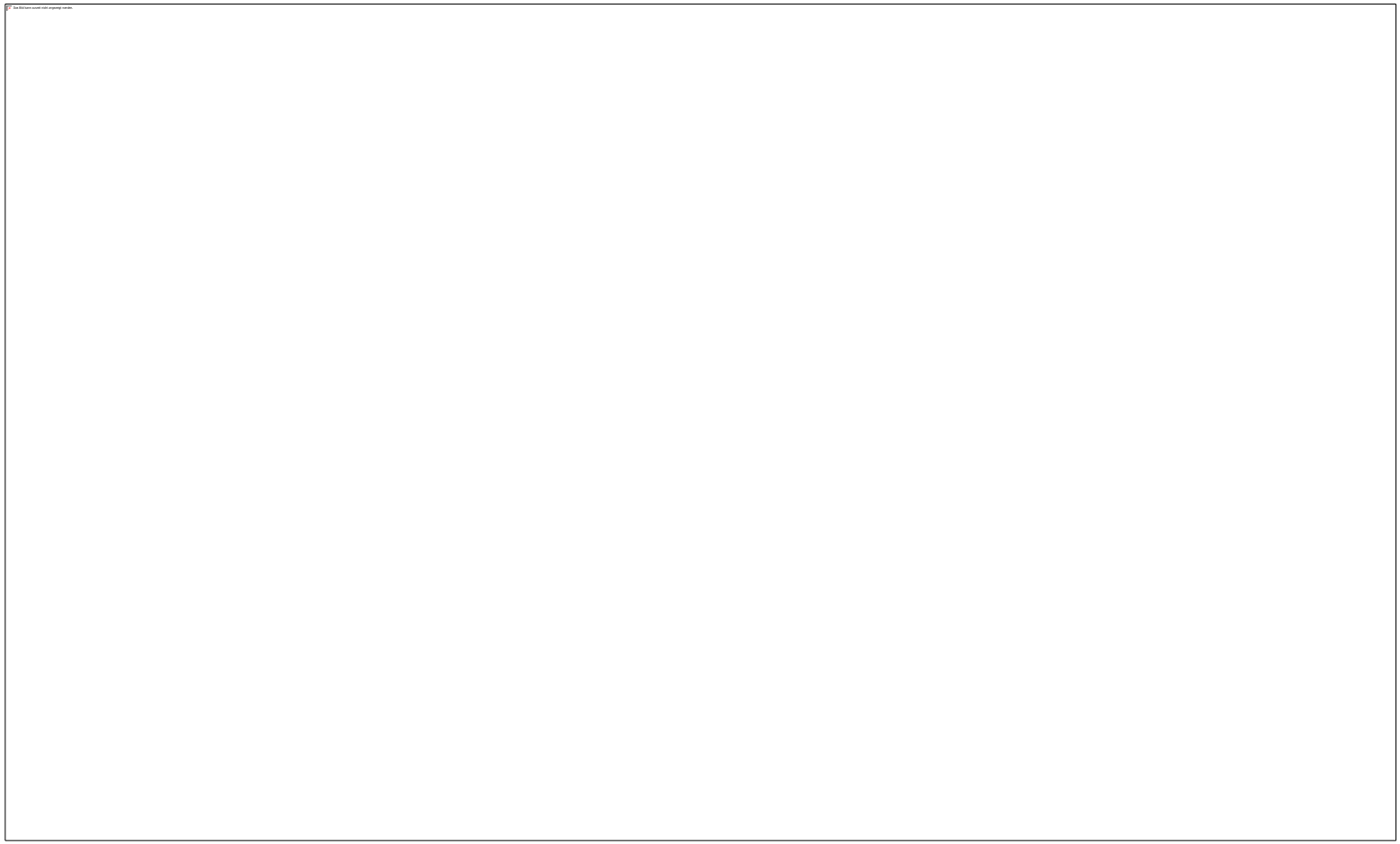
Shirazi et al. 2013

Arrhythmias in patients with LVADs

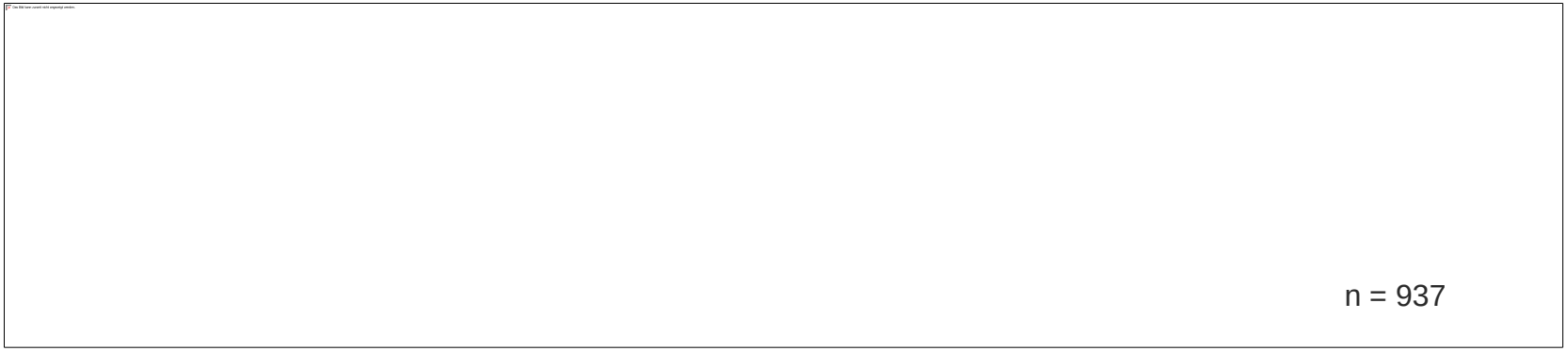


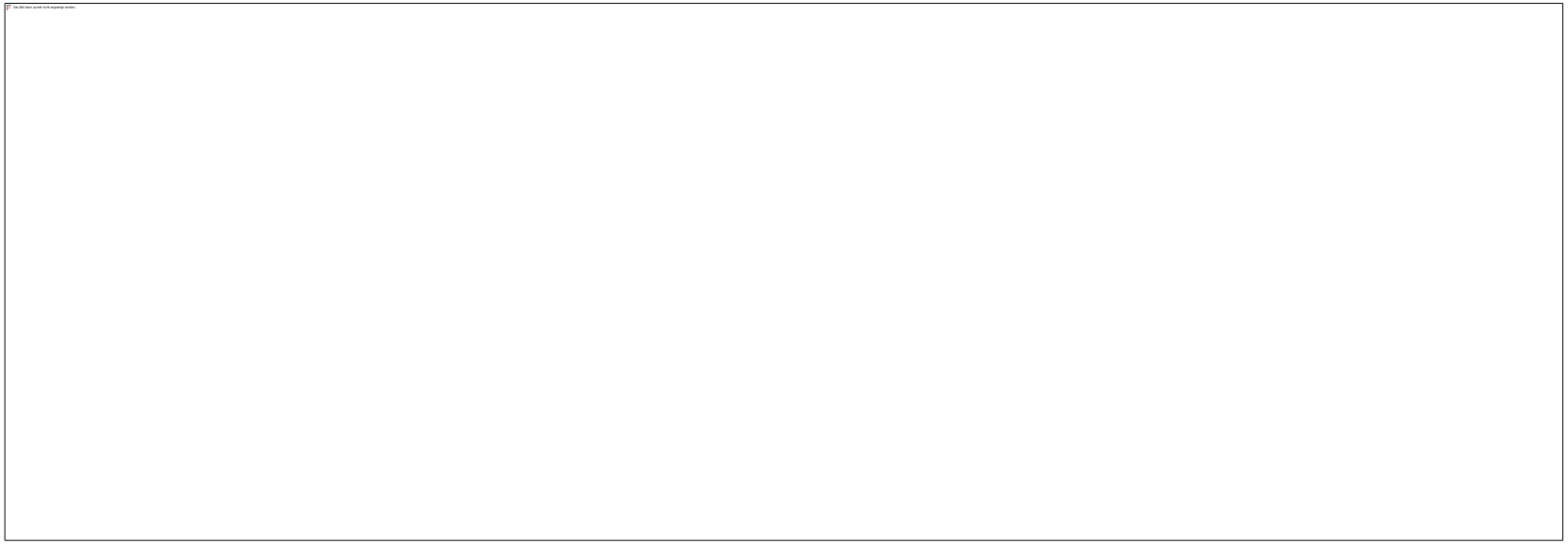
Shirazi et al. 2013

VA post -LVAD is associated with higher risk of death



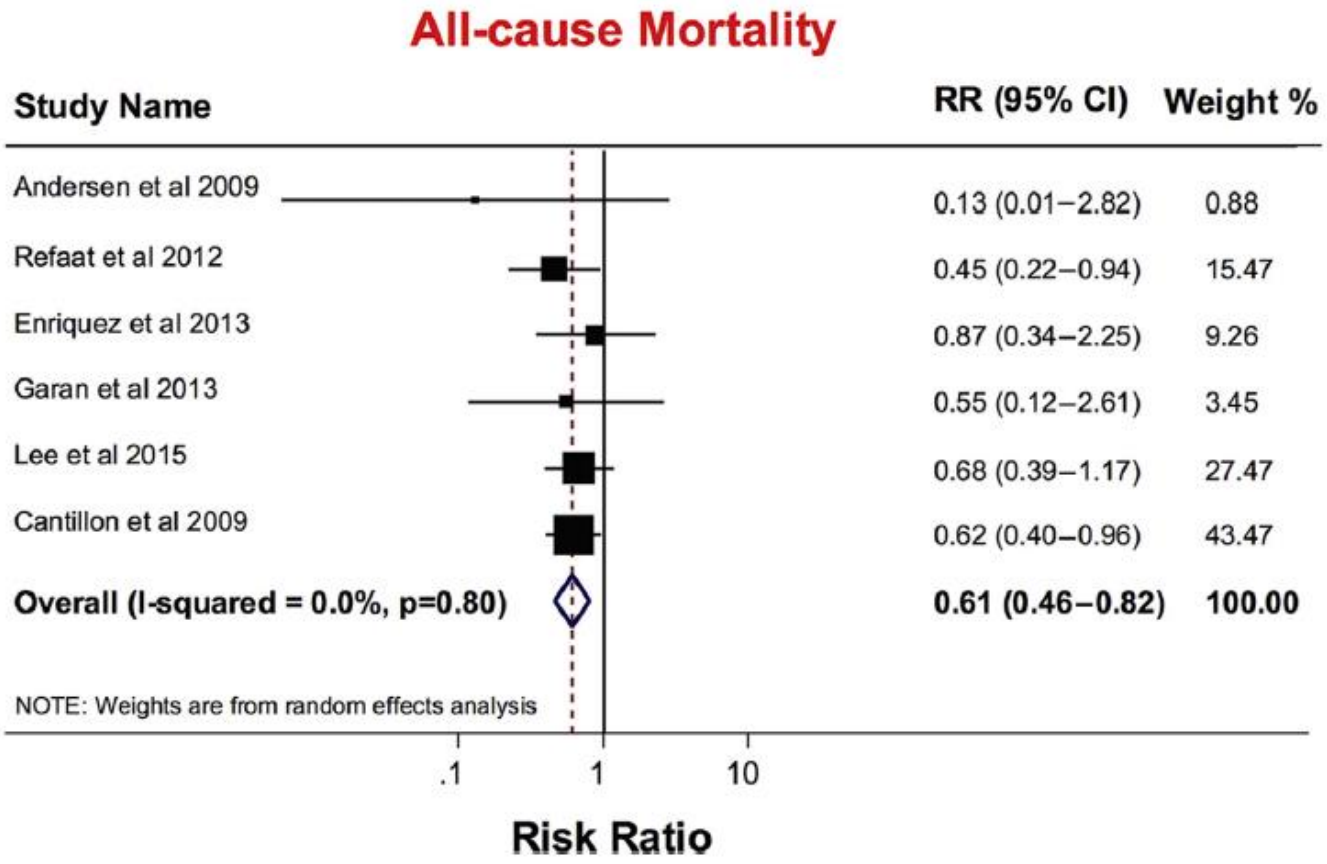
ICD vs. no ICD in LVAD patients





Vakil et al. 2016

ICD vs. no ICD in LVAD patients

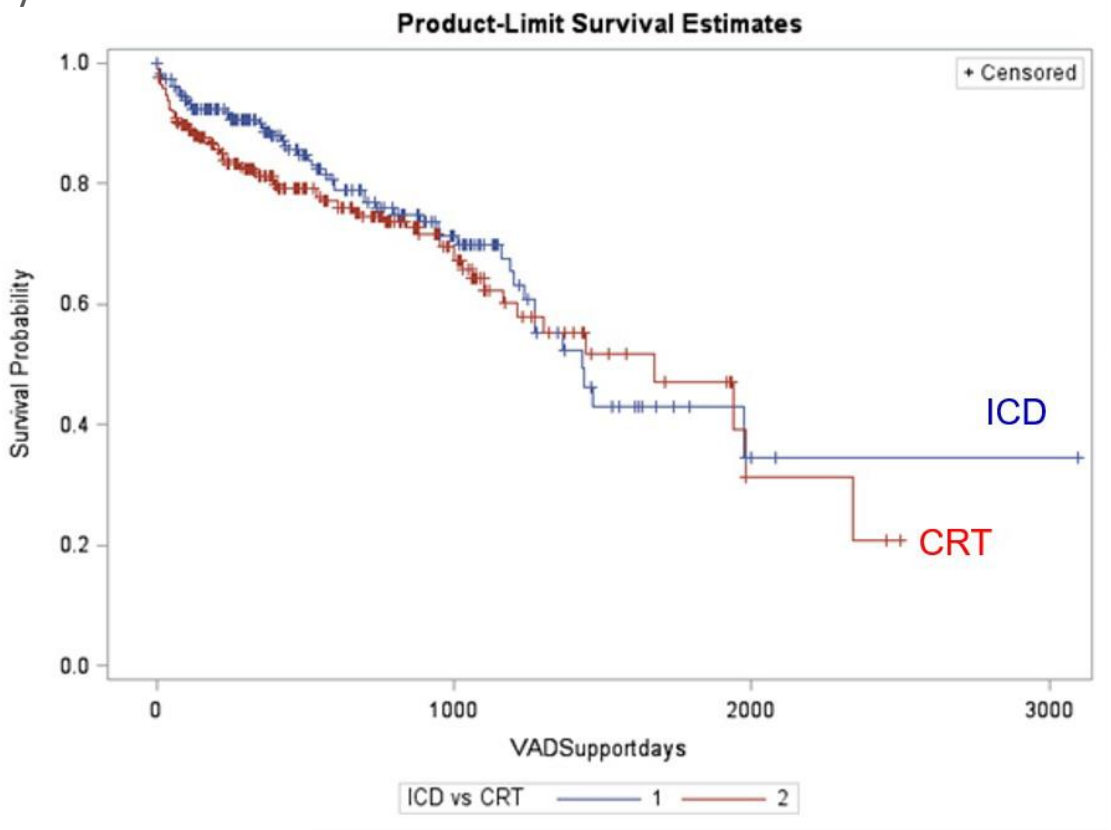


Vakil et al. 2016

LVAD pts: ICD vs. CRT

Cardiac Resynchronization Therapy and Clinical Outcomes in Continuous Flow Left Ventricular Assist Device Recipients

non-randomized study
n = 488



Gopinathannair et al. 2018

Antiarrhythmic effects

- ***CRT***
- ***Assist devices***
- ***Sacubitril***
- ***Exercise***

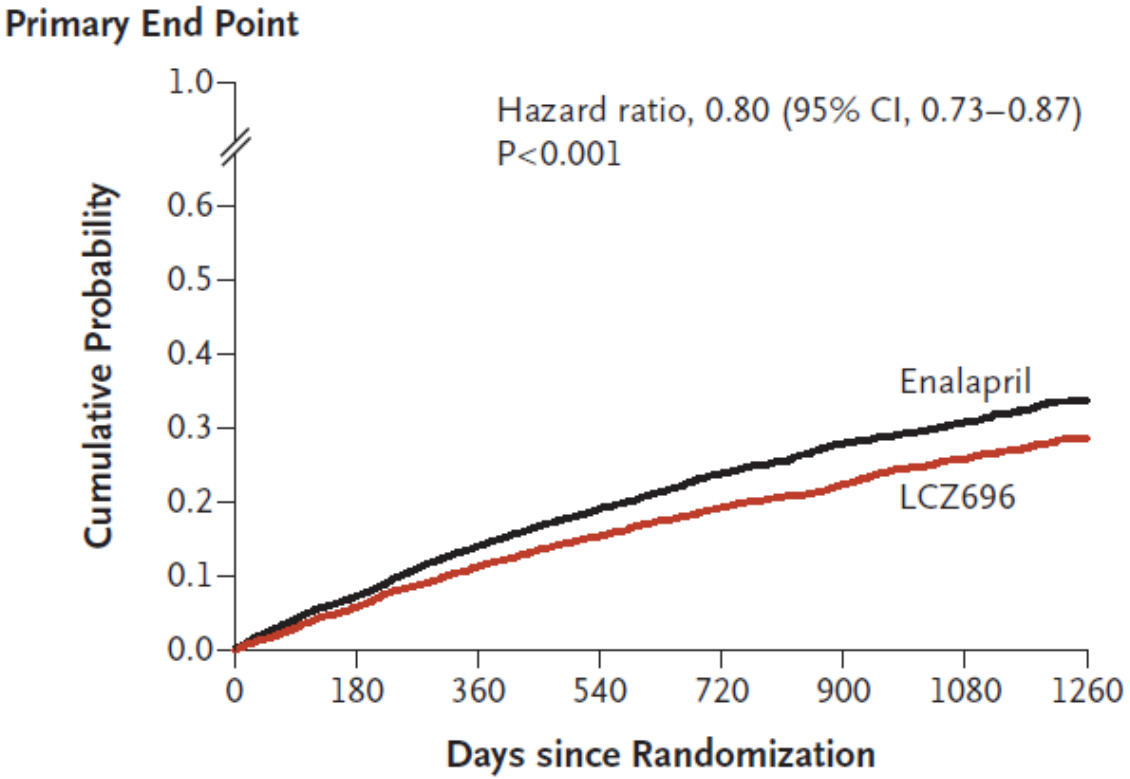
PARADIGM-HF: Mode of death

A Comparison of Angiotensin Receptor-Neprilysin Inhibition (ARNI) With ACE Inhibition in the Long-Term Treatment of Chronic Heart Failure With a Reduced Ejection Fraction

PARADIGM-HF was the first study to compare the long-term efficacy and safety of the **angiotensin-receptor–neprilysin inhibitor** (**ARNI**), sacubitril/valsartan (previously known as LCZ696), against standard care with the angiotensin-converting enzyme (ACE) inhibitor, enalapril, in patients (8.000+) with chronic symptomatic heart failure and reduced ejection fraction (HFREF). The trial was stopped early due to benefit.

PARADIGM-HF: Primary endpoint

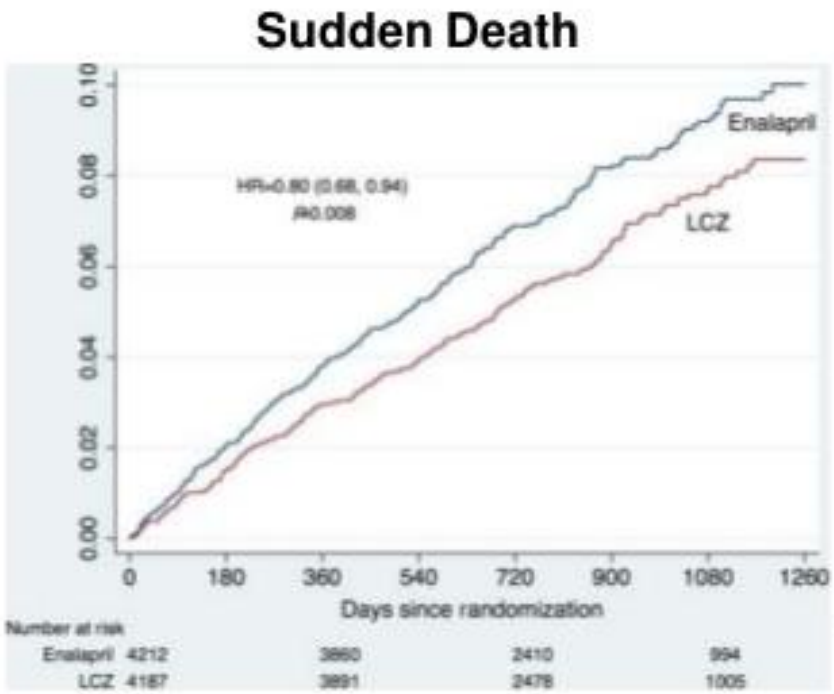
Primary outcome: composite of death from cardiovascular causes or hospitalization for heart failure



No. at Risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

McMurray et al. 2014

PARADIGM-HF: Mode of death



Desai et al. Eur Heart J 2015;36(30):1990-7

Sacubitril/Valsartan

Circulation

ON MY MIND

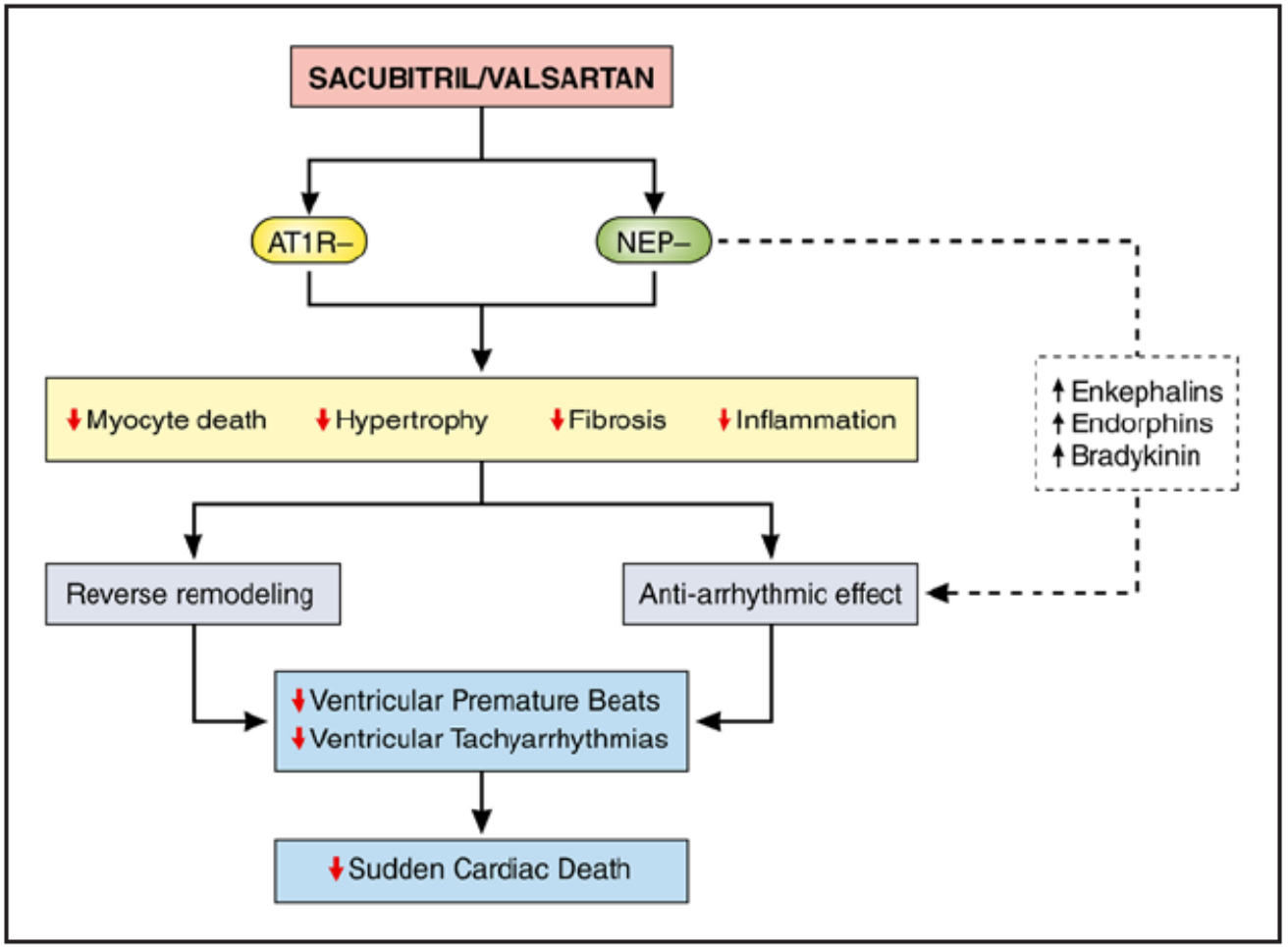
Is Sacubitril/Valsartan (Also) an Antiarrhythmic Drug?

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

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 Morbidity in Heart Failure),[1] published in 2014, 8442 patients with heart failure (HF)

Circulation. 2018;138:551–553. DOI: 10.1161/CIRCULATIONAHA.118.034755

Sacubitril/Valsartan



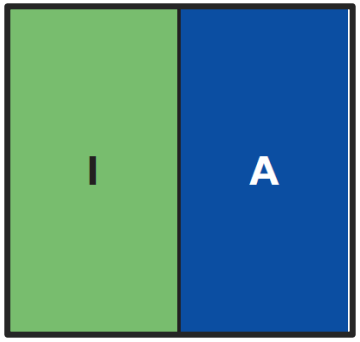
Sarria und Bayes-Genis, 2018

Sudden cardiac death in HFrEF

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

EUROPEAN SOCIETY OF CARDIOLOGY®

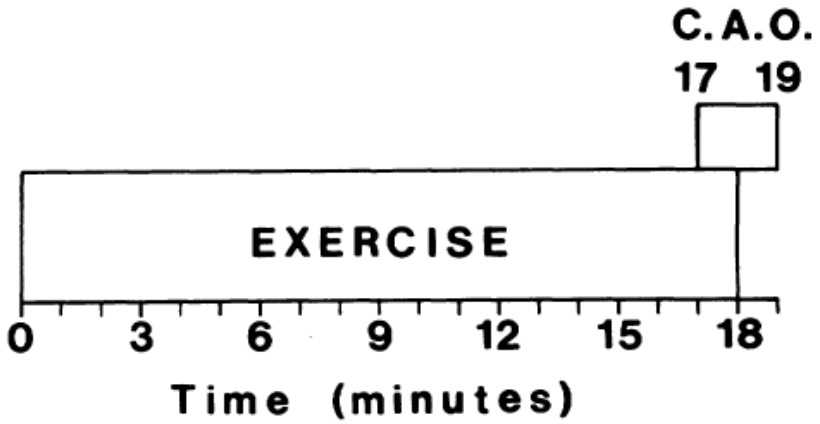
- Treatment with **beta-blocker**, **MRA** and **sacubitril/valsartan** reduces the risk of sudden death and is recommended for patients with HFrEF and ventricular arrhythmias.

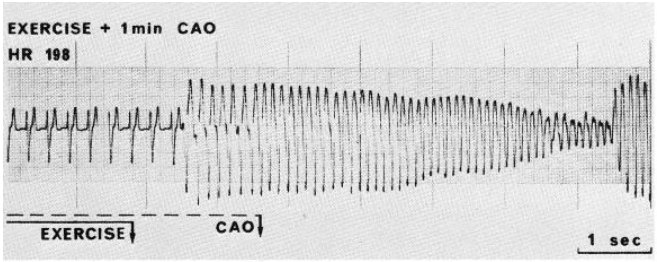


Antiarrhythmic effects

- ***CRT***
- ***Assist devices***
- ***Sacubitril***
- ***Exercise***

Exercise-induced VT/VF





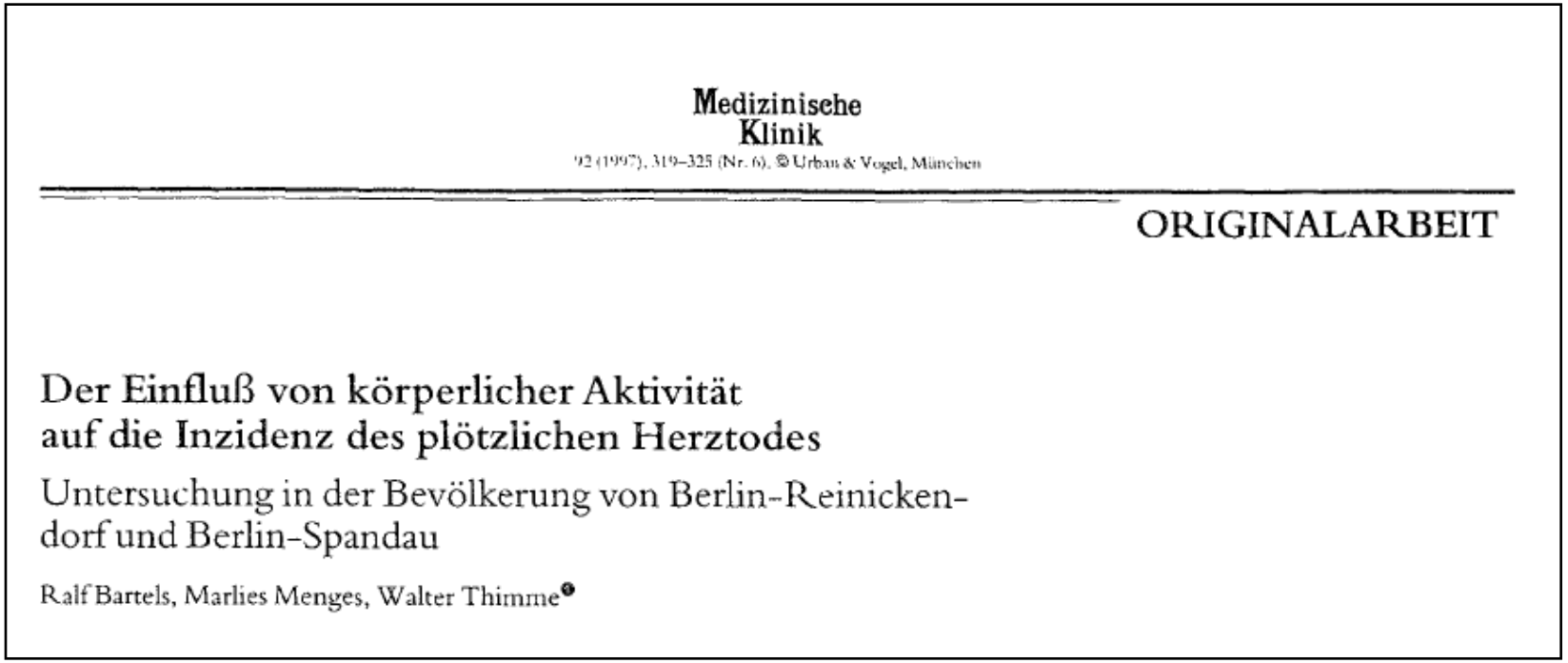
Experimnetal model: **2 min. of coronary artery occlusion (CAO) in dogs**

CAO only: No VF in 33 dogs

CAO + Exercise: VF in 21 out of 33 dogs (64%)

Schwartz et al, 1984

Physical activity and incidence of sudden cardiac death



Medizinische
Klinik
92 (1997), 319–325 (Nr. 6), © Urban & Vogel, München

ORIGINALARBEIT

Der Einfluß von körperlicher Aktivität auf die Inzidenz des plötzlichen Herztodes

Untersuchung in der Bevölkerung von Berlin-Reinicken-dorf und Berlin-Spandau

Ralf Bartels, Marlies Menges, Walter Thimme

Influence of regular physical activity and sudden extrenious situations on the incidence of sudden cardiac death in two different Berlin districts with a total population of 219,251 in the examined age-groups. All cases of scd which occurred outside of the hospital and were documented as been induced from ventricular fibrillation were examined over a time period of 18 months.

Bartels et al, 1997

Physical activity and incidence of sudden cardiac death

Belastungs-gruppe	Plötzliche Herztode (n=) (n=77)	Herztode/10 000 Personenjahre
1	47	4,69
2	7	4,25
3	4	2,63
4	9	0,92

Tabelle 1. Inzidenz des plötzlichen Herztodes in Abhängigkeit von der regelmäßig ausgeführten körperlichen Aktivität (Erklärung der Belastungsgruppen siehe Text).

1: little or no physical activity.
2: physically active - 30 min - 1 h per week
3: physically active - 1 - 2 hrs per week
4: physically active - > 2 hrs per week

Bartels et al, 1997

Physical activity and incidence of sudden cardiac death

Belastungs-gruppe	Tote bei Belastung (n=)	Tote in Ruhe (n=)	Inzidenz des plötzlichen Herztodes bei Belastung*	Inzidenz des plötzlichen Herztodes in Ruhe*	Relatives Risiko für den plötzlichen Herztod
1	7	40	(836,9)	2,1	(398,5)
2	3	4	195,2	1,3	150
3	0	4	–	3,3	–
4	4	15	1,6	0,4	4,0

*Anzahl der plötzlichen Herztode in 10^5 Personenstunden.

Tabelle 2. Inzidenz des plötzlichen Herztodes (pHT) in Ruhe und bei körperlicher Belastung ≥ 6 MET und das relative Risiko für den plötzlichen Herztod bei Belastung im Vergleich zur Ruhe in Abhängigkeit von der regelmäßig ausgeführten körperlichen Aktivität.

Bartels et al, 1997

Physical activity and incidence of sudden cardiac death

art-health/dont-worry-about-sudden-cardiac-arrest-during-exercise

Suchen

noak-wiki.de | arrhythmie-syndrome... | ekg-wiki.de | kardiologie-wiki.de | inSuite | Conga-Register | Fokus-Herzrhythmuss... | UpToDate

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Harvard Heart Letter

Don't worry about sudden cardiac arrest during exercise

Updated: July 17, 2015 Published: July, 2015

New findings may help allay fears about sports-related heart death.

You've probably heard at least one account of a middle-aged man who suddenly collapsed and died while exercising. One famous example is James F. Fixx, author of *The Complete Book of Running*, who in 1984 died of a heart attack at age 52 while jogging.

These anecdotes might give you pause as you lace up your workout shoes. But a new study offers reassurance that exercise-related heart deaths are quite rare, accounting for just 5% of sudden cardiac arrest cases.

"These deaths grab our attention because they're rare and counterintuitive. But there's absolutely no question that regular, moderate-intensity exercise is the best way to prevent sudden cardiac arrest," says Dr. Aaron L. Baggish, associate director of the Cardiovascular Performance Program at Harvard-affiliated Massachusetts General Hospital. The paradox is that if you are going to have a heart-related event, it's more likely to occur when you're exercising than when you're not, he explains.

Getting regular exercise is the best way to prevent most types of heart disease —including sudden cardiac arrest.

Images: Thinkstock

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6-Week Plan For Healthy Eating: eLearning Course
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Related Articles

December 2011 references and further reading
Putting heart attack, stroke triggers in perspective

Antiarrhythmic effects of exercise

Am J Physiol Heart Circ Physiol 310: H1360–H1370, 2016.
First published March 4, 2016; doi:10.1152/ajpheart.00858.2015.

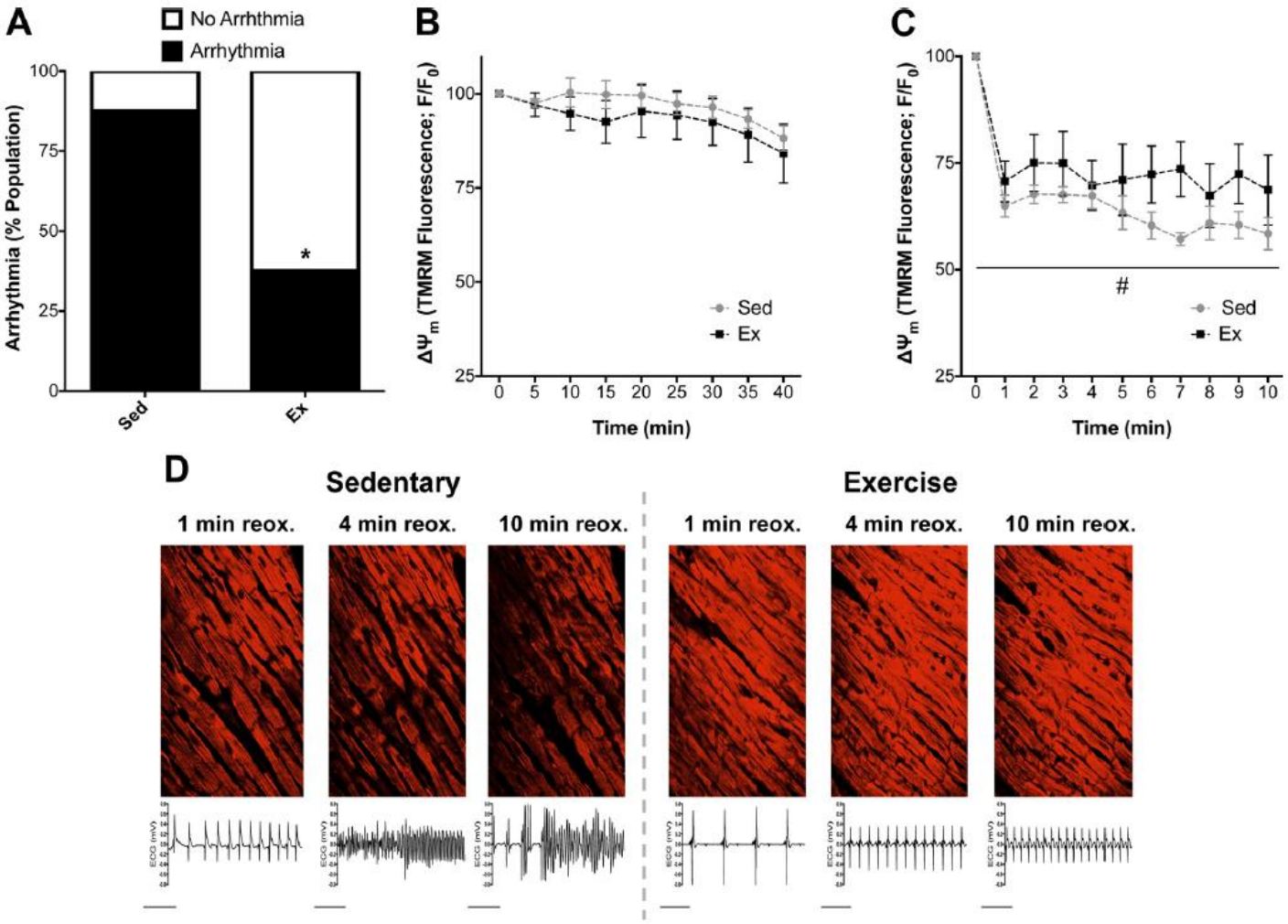
Exercise-induced protection against reperfusion arrhythmia involves stabilization of mitochondrial energetics

Rick J. Alleman,[1,2] Alvin M. Tsang,[1,2] Terence E. Ryan,[1,2] Daniel J. Patteson,[1,2] Joseph M. McClung,[1,2] Espen E. Spangenburg,[1,2] Saame Raza Shaikh,[2,3] P. Darrell Neufer,[1,2] and David A. Brown[1,2]

[1]*Department of Physiology, Brody School of Medicine, East Carolina University, Greenville, North Carolina;* [2]*East Carolina Diabetes and Obesity Institute, Brody School of Medicine, East Carolina University, Greenville, North Carolina; and* [3]*Department of Biochemistry and Molecular Biology, Brody School of Medicine, East Carolina University, Greenville, North Carolina*

Submitted 6 November 2015; accepted in final form 26 February 2016

Antiarrhythmic effects of exercise



Beneficial effects of physical activity

- Antiatherogenic effects
- Anti-inflammatory effects
- Effects on vascular endothelial function
- Effects on blood clotting
- Autonomic functional changes
- Anti-ischemic effects
- Antiarrhythmic effects
- Reduction in age-related disability

Conclusions

- Antiarrhythmic therapy means more than just prescribing traditional antiarrhythmic drugs …