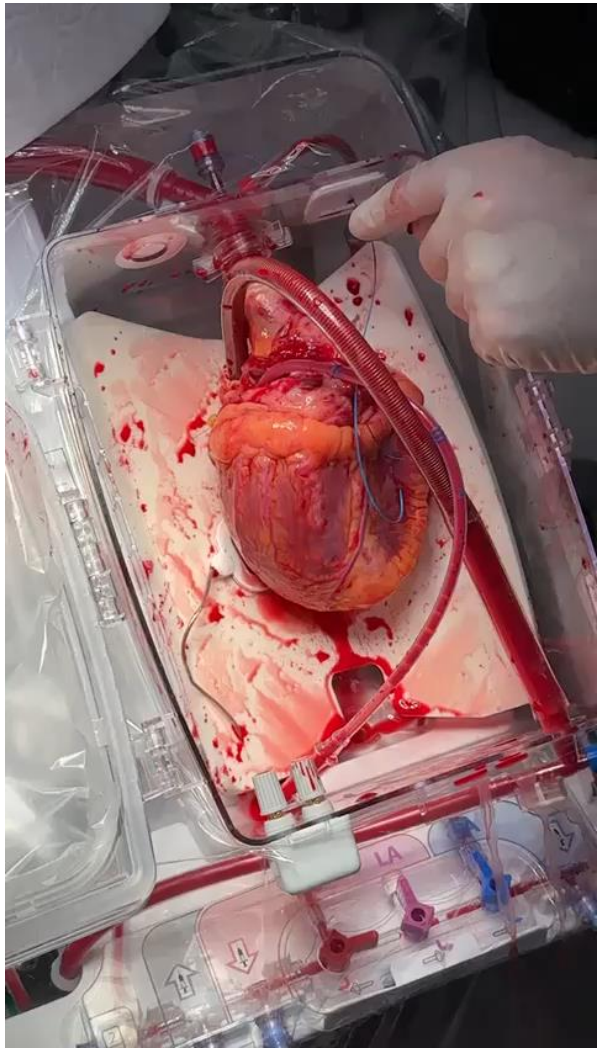
# The Future of Heart Failure Has Just Begun

**Frank Ruschitzka**
**Professor and Chairman of Cardiology**
**University Hospital Zurich**

USZ Universitäts Spital Zürich

# Declaration of Interest

- No personal payments by pharmaceutical companies or device manufacturers
- Remuneration for the time spent in activities, such as participation as member in steering committees of clinical trials were made directly to the University of Zurich
- Research Contracts
  - Payments directly to the University of Zurich and University Hospital of Zurich
  - Postgraduate Heart Failure Course (Abbott, Novartis, Bayer, Servier, AstraZeneca, Roche Diagnostics)



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University of Zurich[UZH]

# 45th Anniversary of the Worlds first PTCA

## Dölf Bachmann and Johannes Grüntzig

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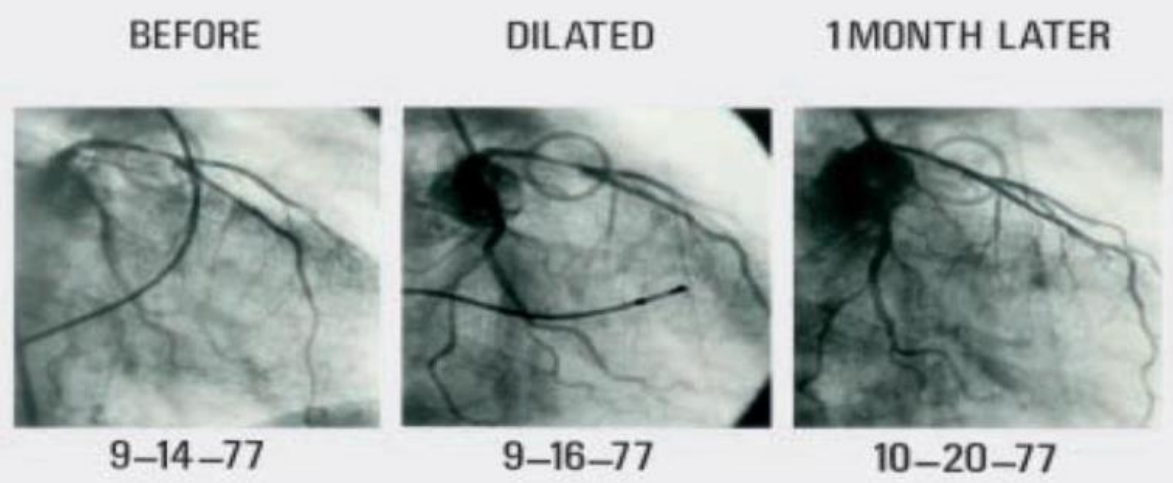
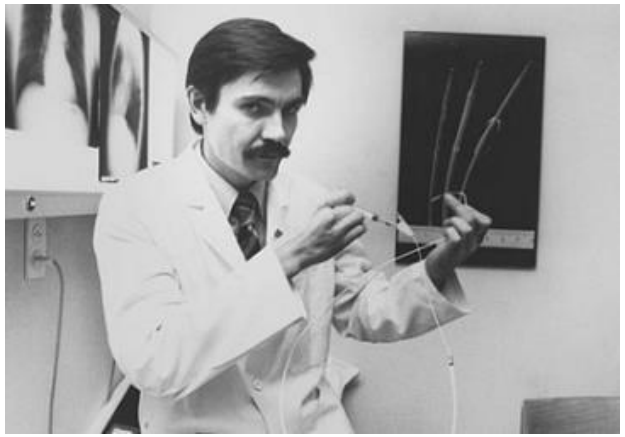
**Zurich, September 16, 2022**

University of Zurich[UZH]

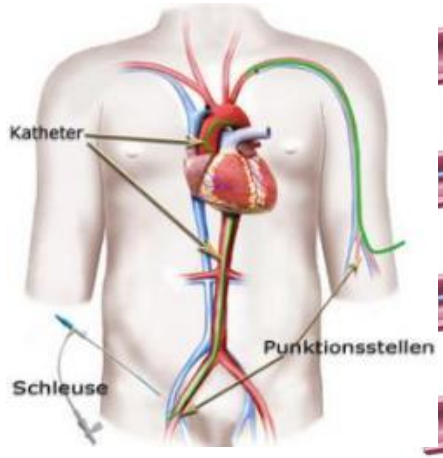
# The Heart Centre of the University Hospital Zurich

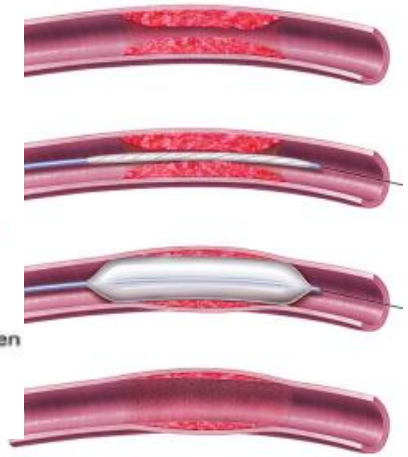
## The Cradle of Interventional Cardiology

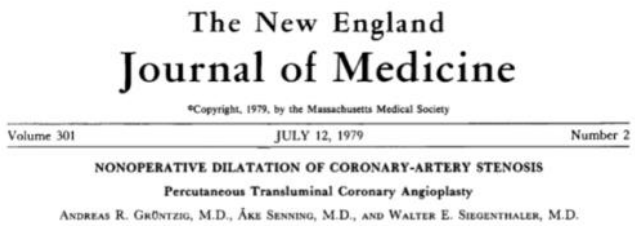


**Andreas Grüntzig**





The New England
Journal of Medicine



Volume 301 JULY 12, 1979 Number 2

NONOPERATIVE DILATATION OF CORONARY-ARTERY STENOSIS

Percutaneous Transluminal Coronary Angioplasty

ANDREAS R. GRÜNTZIG, M.D., ÅKE SENNING, M.D., AND WALTER E. SIEGENTHALER, M.D.

USZ Universitäts Spital Zürich

Grüntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med. 1979 Jul 12;301(2):61-8. doi: 10.1056/NEJM197907123010201. PMID: 449946.

# Percutaneous Coronary Interventions
## The Andreas Grüntzig Legacy

The New England
Journal of Medicine



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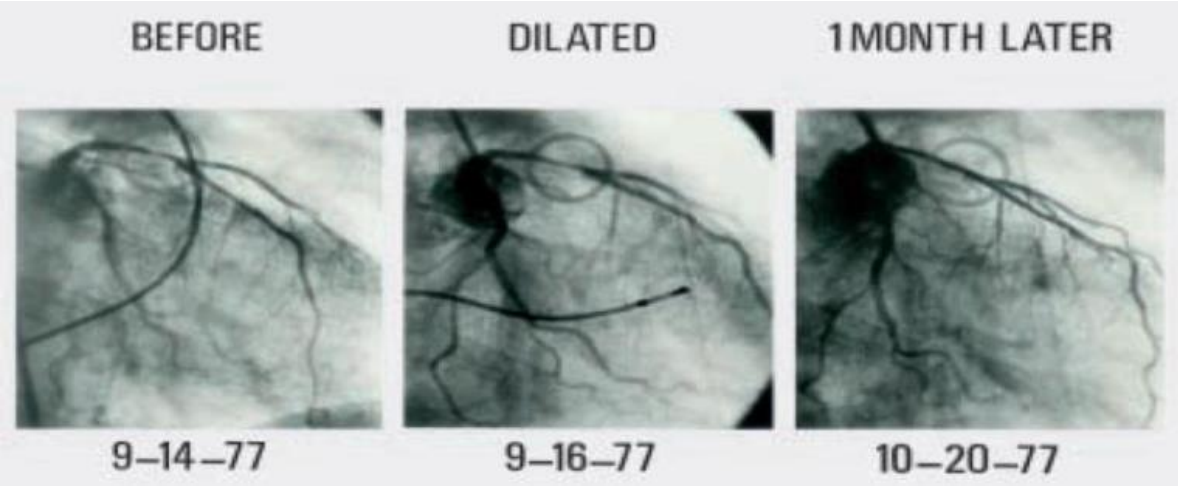



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# Andreas Grüntzig:
## Why we need a new cardiologist

**Andreas Grüntzig**
**(1939-1985)**

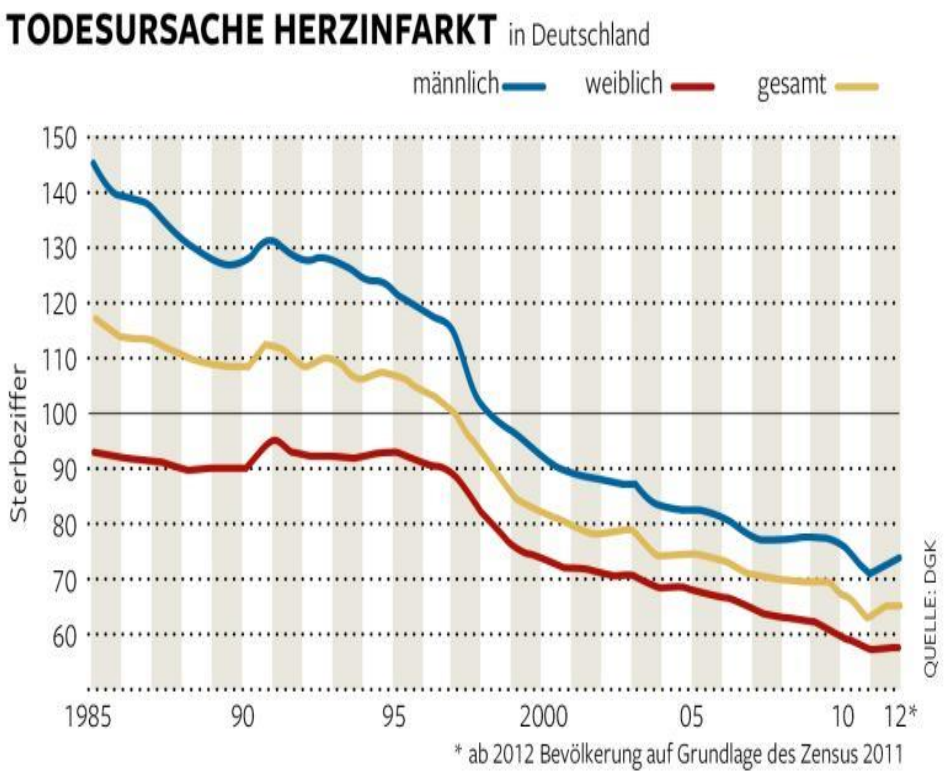
- ***The procedure should be performed by the doctor who has already achieved the patient`s trust***

- ***I don`t want this method to fall into the wrong hands***
  - ***strict indication***
  - ***high quality standards***
  - ***integrity***

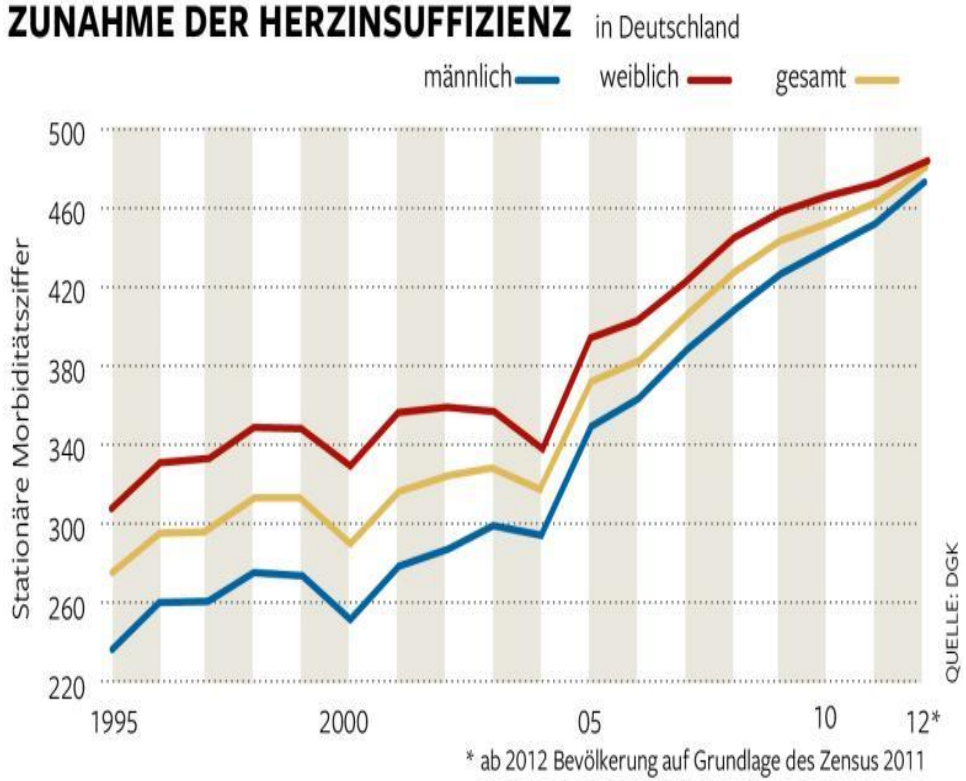
**Zurich, October 22, 1979**

# Heart Failure is Moving Center Stage

## Fatal MI




## Heart Failure




**Heart Report, Germany**

# The Future of Cardiovascular Medicine:
## „Focus on Heart Failure!“

**Eugene Braunwald**
(PCHF Zurich 2015)

- **„PCI has spared lifes, but left survivors with very sick hearts. Heart Failure is therefore the most prevalent, deadly and costly of all heart diseases...“**
- **It’s time for an all-fronts war on heart failure**

# Heart Failure Is Taking Center Stage

## A European Perspective

"Heart failure is moving center stage" was the motto of the Heart Failure 2015 meeting held in Seville (Spain) that I had the honor of co-chairing with Frank Ruschitzka, the inventor of the motto. The complexity of management of patients with heart failure and the continuous therapeutic advances, including drugs, devices, percutaneous interventions, complex cardiac surgery, heart transplantation, mechanical circulatory support, and the patient-centered approach (a key feature in the care of these patients), providing a continuous improvement in survival and quality of life,[1] are perhaps the main reasons why this subspecialty within cardiology is eliciting growing interest among young cardiologists.

**Maria G. Crespo-Leiro, MD, PhD**

**Circulation HF 2019**

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# The Mother of Heart Failure Trials

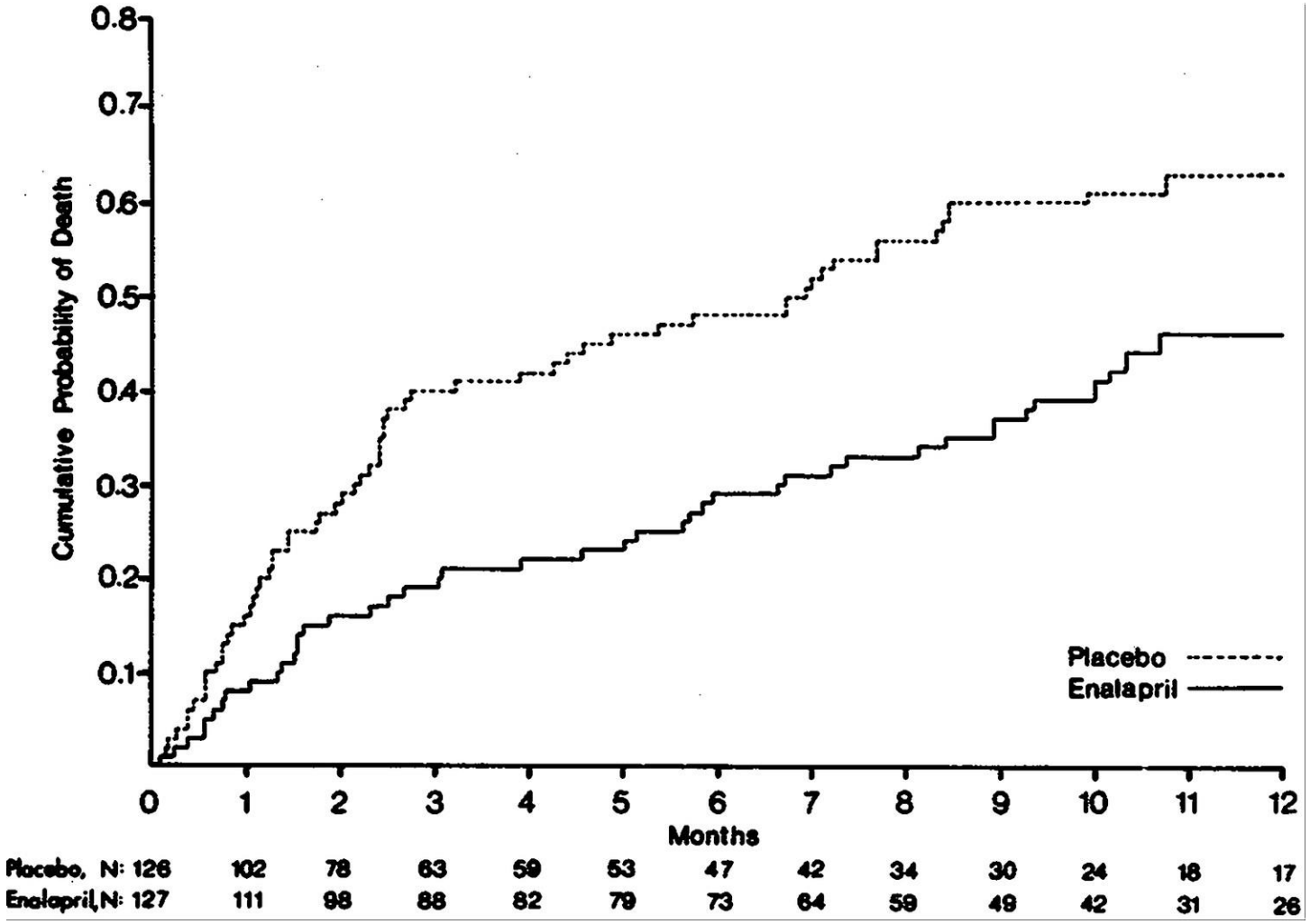


Table 3. Causes of Death.

| Cause | Treatment Group | | P Value (Life-Table Analysis) |
|---|---|---|---|
| | Placebo (N = 126) | Enalapril (N = 127) | |
| | *no. of patients* | | |
| Any cardiac death | 64 | 44 | 0.001 |
| Cardiac death within 24 hours of new symptoms | 19 | 20 | >0.25 |
| Sudden cardiac death (within 1 hour of new symptoms) | 14 | 14 | >0.25 |
| Progression of congestive heart failure | 44 | 22 | 0.001 |
| Other cardiac death | 1 | 2 | |
| Stroke | 2 | 1 | |
| Other cardiovascular deaths* | 2 | 4 | |
| Noncardiovascular death (perforated ulcer) | 0 | 1 | |
| Total mortality | 68 | 50 | 0.003 |

*Includes deaths from renal-artery thrombosis, endocarditis, pulmonary emboli after leg amputation, bronchitis and concomitant heart failure, occlusion of femoral arterial graft, and heart failure in relation to melena (gastric ulcer).

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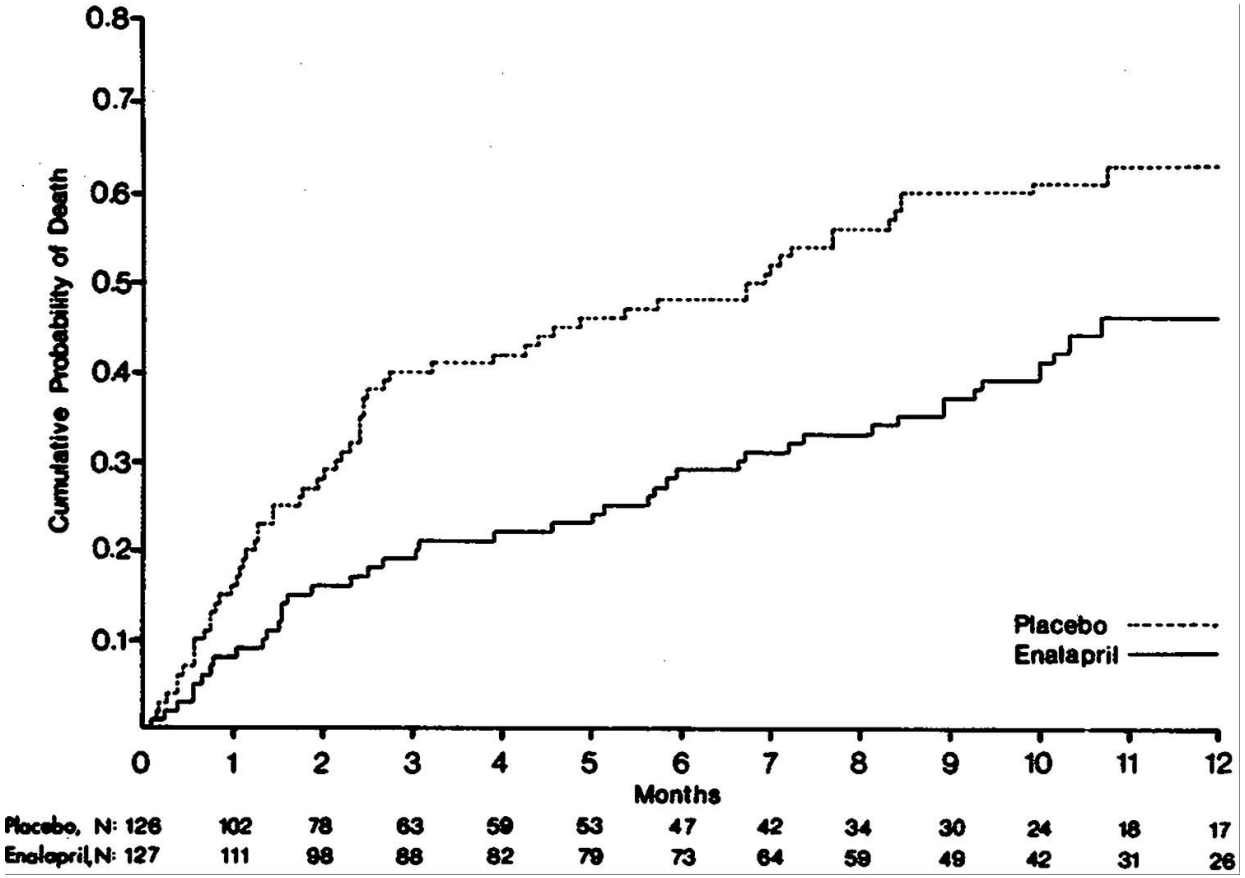
NEJM 1987

University of Zurich[UZH]

# Effects of Enalapril on Mortality in Severe Congestive Heart Failure

Table 1. Base-Line Clinical Characteristics of Patients in the Two Treatment Groups.

| Characteristic | Treatment Group | |
|---|---|---|
| | Placebo (N = 126) | Enalapril (N = 127) |
| | *mean* | |
| Age (yr) | 70 | 71 |
| Weight (kg) | 69 | 66 |
| Heart size (ml/m²) | 853 | 875 |
| Blood pressure (mm Hg) | | |
| Systolic | 121 | 118 |
| Diastolic | 76 | 74 |
| Heart rate | 80 | 79 |
| Serum sodium (mmol per liter) | 137 | 138 |
| Serum potassium (mmol per liter) | 4.1 | 4.0 |
| Serum creatinine (μmol per liter) | 124 | 132 |
| | *percent* | |
| Sex | | |
| Female | 29 | 30 |
| Male | 71 | 70 |
| **Etiologic factors** | | |
| Coronary artery disease | 74 | 72 |
| Previous myocardial infarction | 48 | 47 |
| Cardiomyopathy | 16 | 14 |
| Valvular heart disease | 22 | 23 |
| Hypertension | 19 | 24 |
| Atrial fibrillation | 47 | 53 |
| Diabetes mellitus | 21 | 24 |
| **Drug therapy** | | |
| Digitalis | 94 | 92 |
| Beta-blocker | 2 | 4 |
| Diuretics | | |
| Furosemide (mean dose) | 98 (200 mg) | 98 (210 mg) |
| Spironolactone (mean dose) | 55 (80 mg) | 50 (80 mg) |
| Any other diuretic | 10 | 14 |
| Vasodilators | | |
| Isosorbide dinitrate | 45 | 47 |
| Hydralazine | 2 | 1 |
| Prazosin | 6 | 8 |
| Antiarrhythmic agents | 17 | 13 |
| Anticoagulant agent | 34 | 33 |
| **Duration of heart failure (mo)** | | |
| <6 | 9 | 4 |
| 6–17 | 16 | 24 |
| 18–47 | 21 | 23 |
| ≥48 | 52 | 47 |
| Unknown | 2 | 2 |

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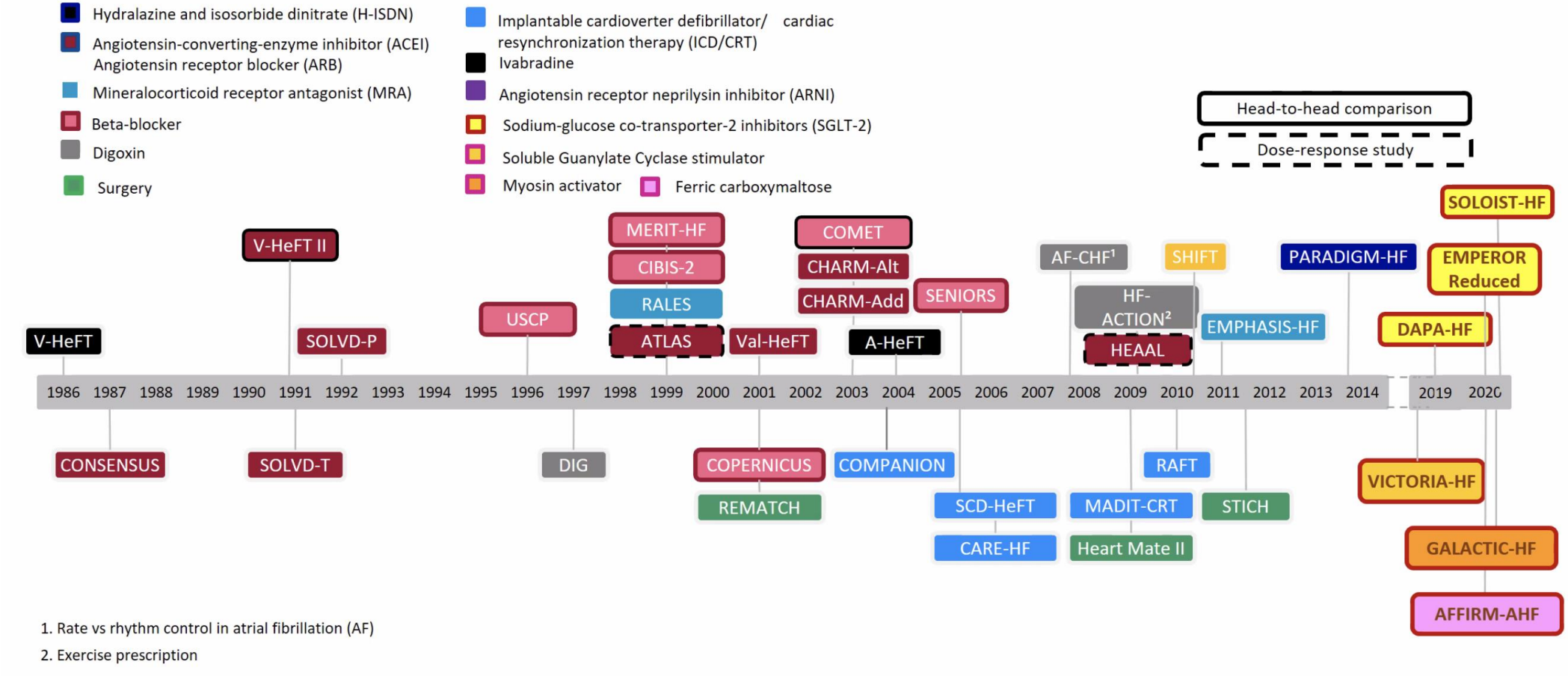
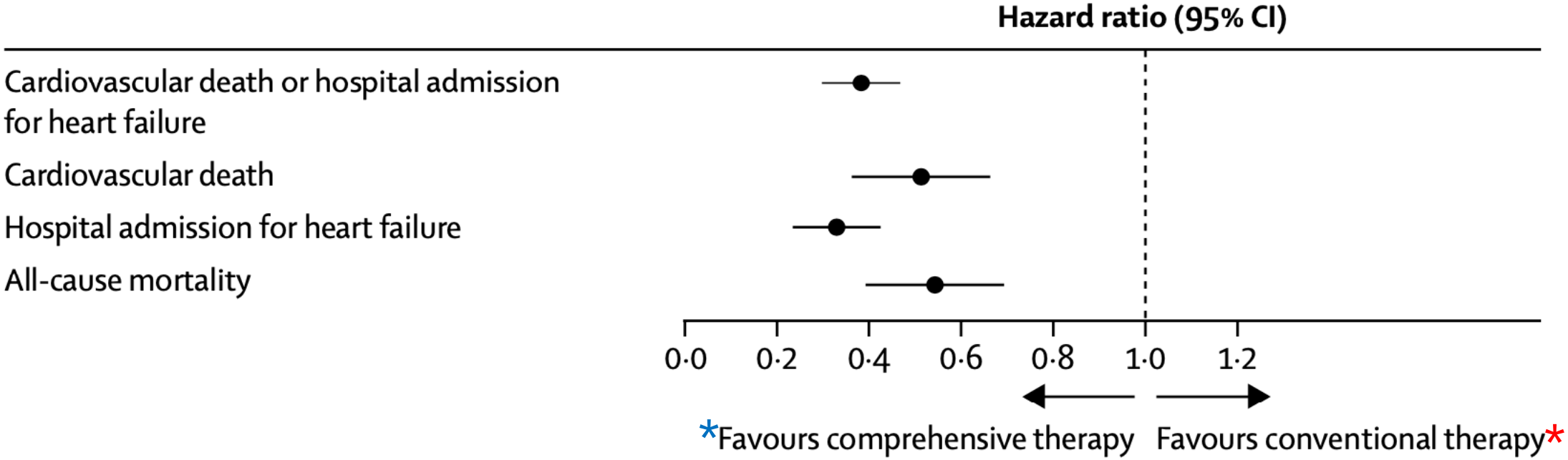
# The (R)evolution in the Treatment of Heart Failure with reduced Ejection Fraction (HFrEF)



# Estimation of Relative Treatment Effects of Comprehensive Disease-modifying Pharmacological Therapy*

## *ARNI, β Blocker, MRA, and SGLT2 inhibitor



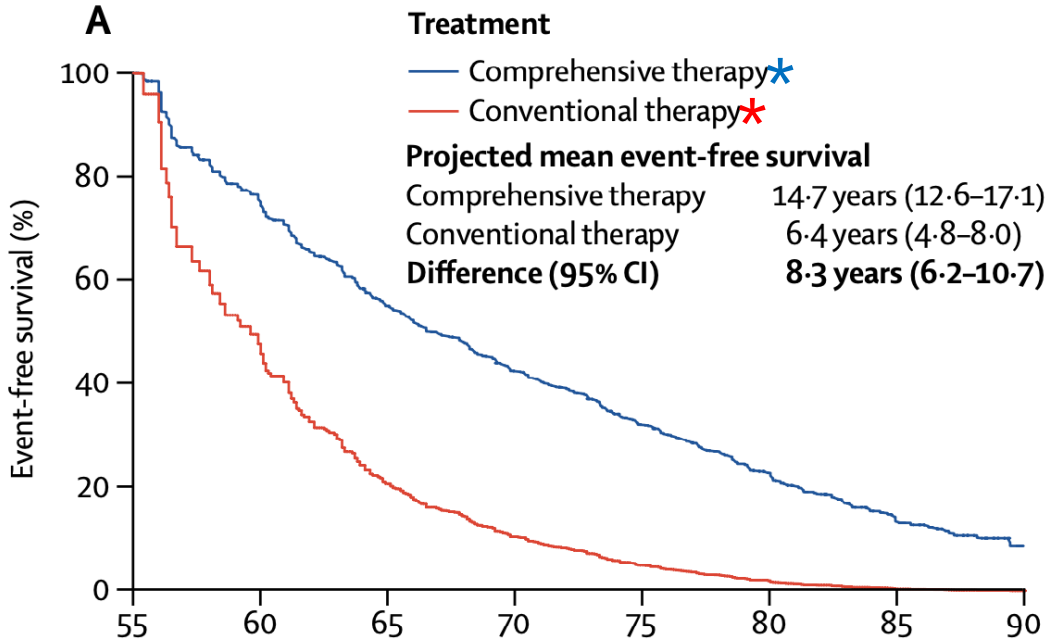

***ARNI, β Blocker, MRA, and SGLT2 inhibitor** vs ***ACE inhibitor or ARB and β blocker**

Vaduganathan Lancet 2020

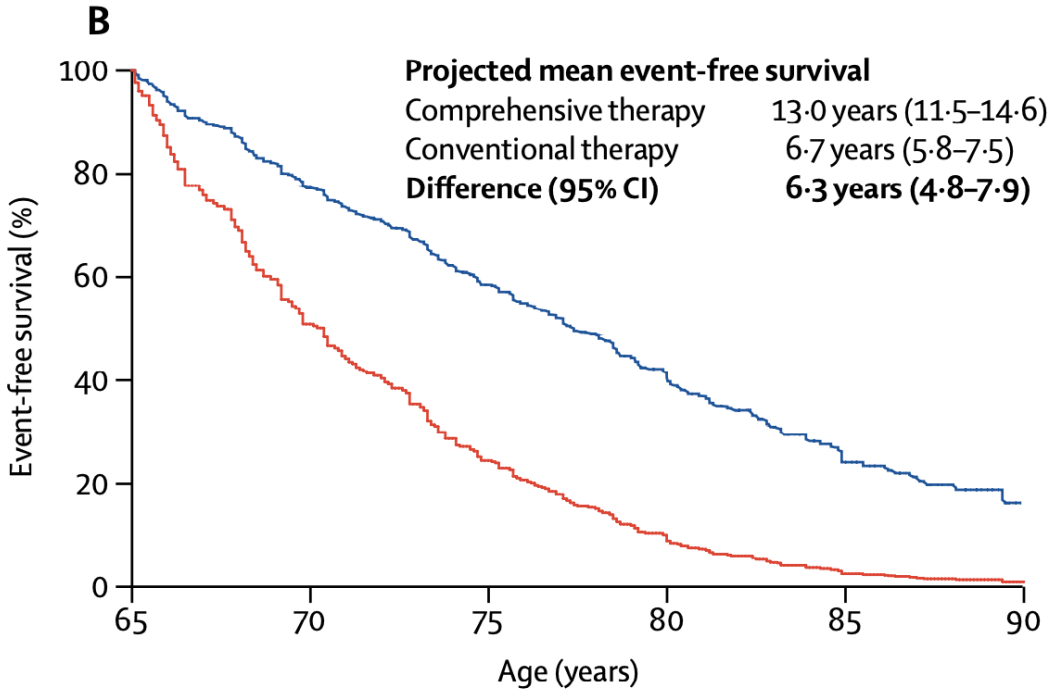
# Lifetime Benefits of Disease-Modifying Comprehensive Pharmacological Therapies in HFrEF

## A Cross-Trial Analysis of PARADIGM-HF DAPA-HF and EMPHASIS-HF

### Patients starting at Age 55 years




### Patients starting at Age 65 years




*ARNI, β Blocker, MRA, and SGLT2 inhibitor vs *ACE inhibitor or ARB and β blocker

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Vaduganathan Lancet 2020

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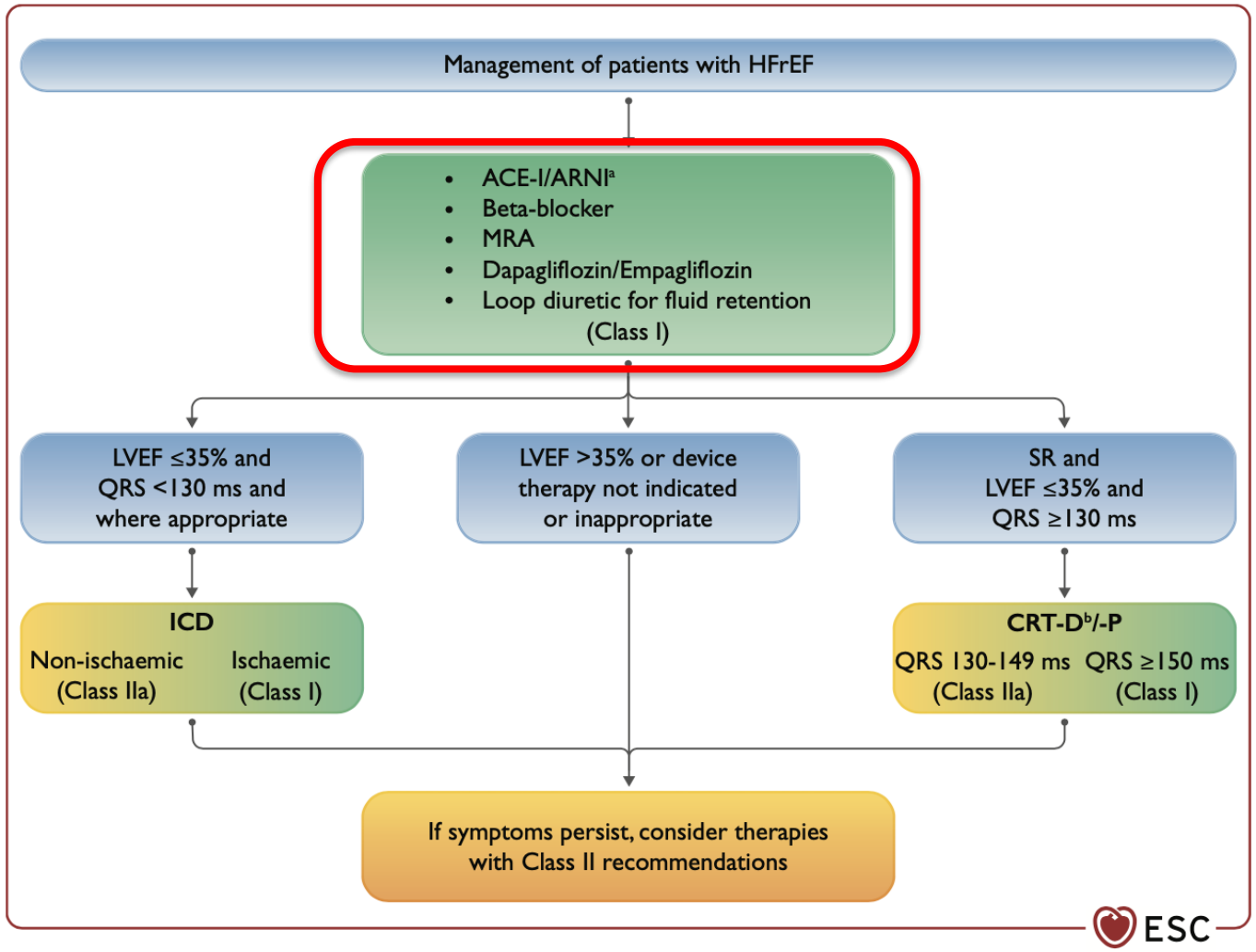
# Therapeutic Algorithm for Symptomatic Heart Failure with reduced Ejection Fraction (HFrEF)




ESC HF Guidelines, McDonagh EHJ 2021

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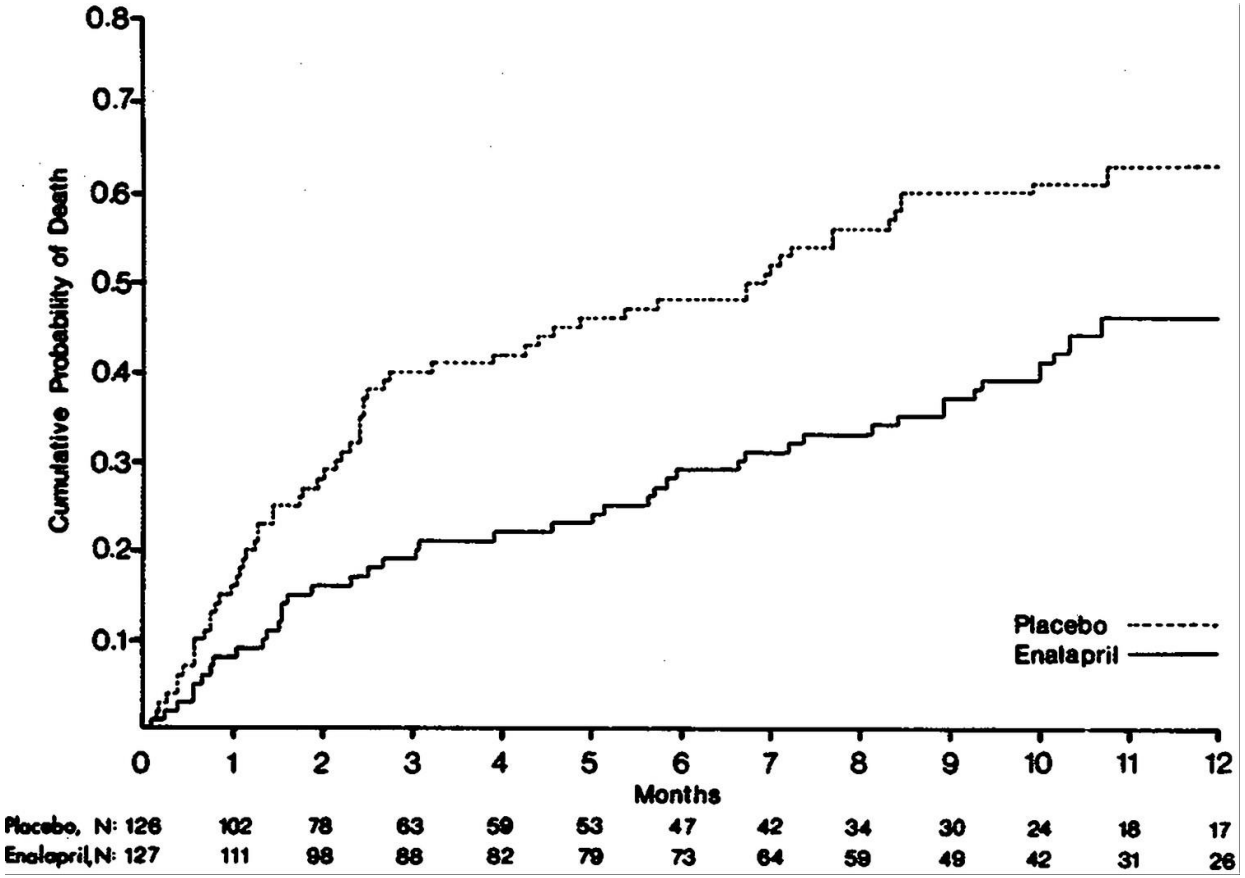


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ESC
European Society of Cardiology
European Heart Journal (2021) 00, 1–128
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

# 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

## Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

## With the special contribution of the Heart Failure Association (HFA) of the ESC

**Authors/Task Force Members: Theresa A. McDonagh* (Chairperson) (United Kingdom), Marco Metra * (Chairperson) (Italy), Marianna Adamo (Task Force Coordinator) (Italy), Roy S. Gardner (Task Force Coordinator) (United Kingdom), Andreas Baumbach (United Kingdom), Michael Böhm (Germany), Haran Burri (Switzerland), Javed Butler (United States of America), Jelena Čelutkienė (Lithuania), Ovidiu Chioncel (Romania), John G.F. Cleland (United Kingdom), Andrew J.S. Coats (United Kingdom), Maria G. Crespo-Leiro (Spain), Dimitrios Farmakis (Greece), Martine Gilard (France), Stephane Heymans (Netherlands), Arno W. Hoes (Netherlands), Tiny Jaarsma (Sweden), Ewa A. Jankowska (Poland), Mitja Lainscak (Slovenia), Carolyn S.P. Lam (Singapore), Alexander R. Lyon (United Kingdom), John J.V. McMurray (United Kingdom), Alex Mebazaa (France), Richard Mindham (United Kingdom), Claudio Muneretto (Italy), Massimo Francesco Piepoli (Italy), Susanna Price (United Kingdom), Giuseppe M.C. Rosano (United Kingdom), Frank Ruschitzka (Switzerland), Anne Kathrine Skibelund (Denmark), ESC Scientific Document Group**

# The 2021 Heart Failure Guidelines

## The Swan Song of the Left Ventricular Ejection Fraction

### 3.1 Definition of heart failure

- Heart Failure (HF) is not a single pathological diagnosis, but a clinical syndrome consisting of cardinal symptoms (e.g., breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in **elevated intracardiac pressures** and/or inadequate cardiac output at rest and/or during exercise.

# The Main Terminology Used to Describe Heart Failure is Historical and Based on Measurement of LVEF

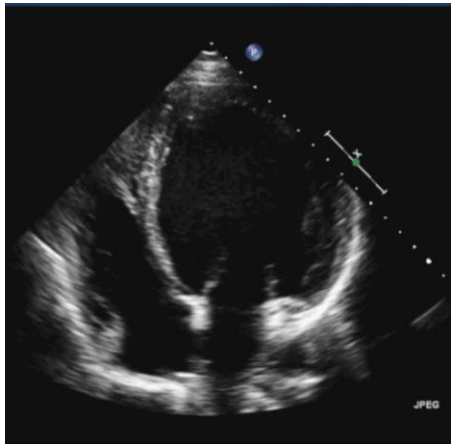
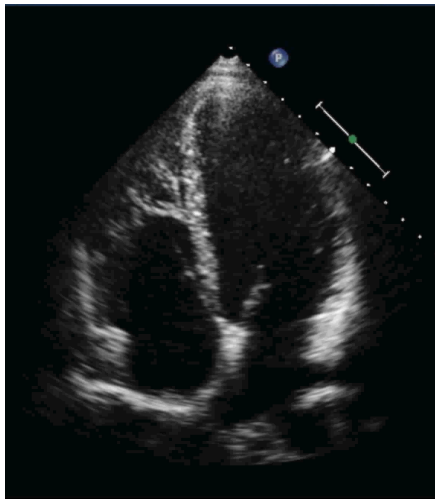


**Table 3.1** Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

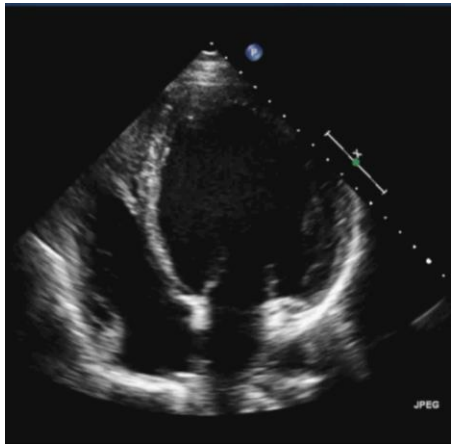
| Type of HF | | HFrEF | HFmrEF | HFpEF |
|---|---|---|---|---|
| CRITERIA | 1 | Symptoms ± Signs[a] | Symptoms ± Signs[a] | Symptoms ± Signs[a] |
| | 2 | LVEF <40% | LVEF 40–49% | LVEF ≥50% |
| | 3 | – | 1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2). | 1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2). |



ESC HF Guidelines 2016; Ponikowski EHJ 2016

# The old ESC-Heart Failure Guideline Classification 2016

## Heart failure with preserved, *mid-range* and reduced Ejection Fraction



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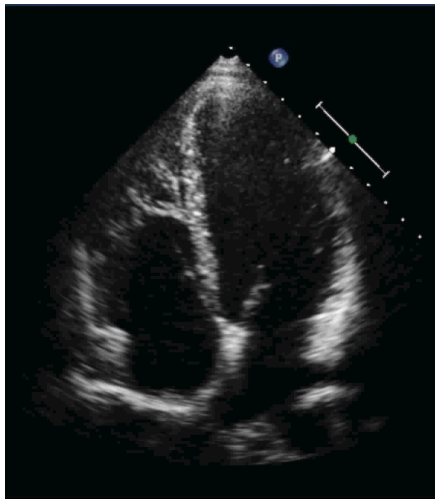
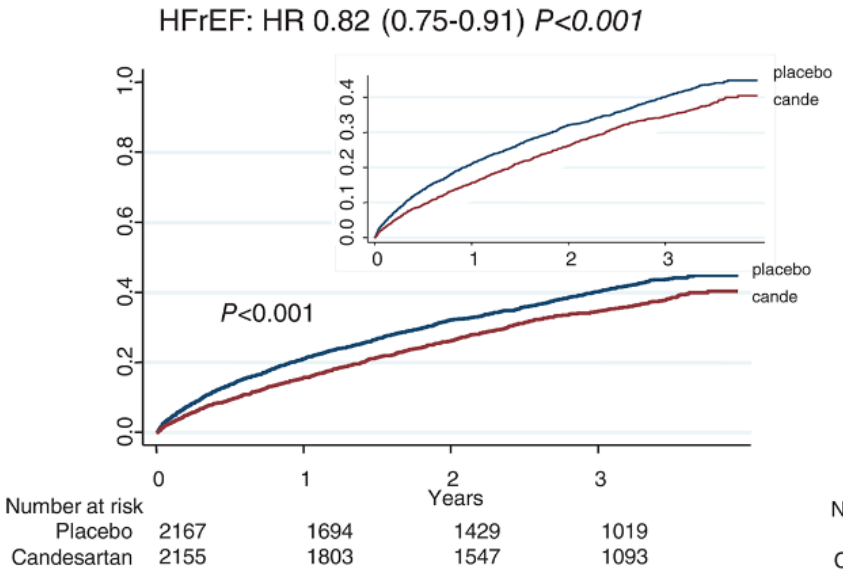
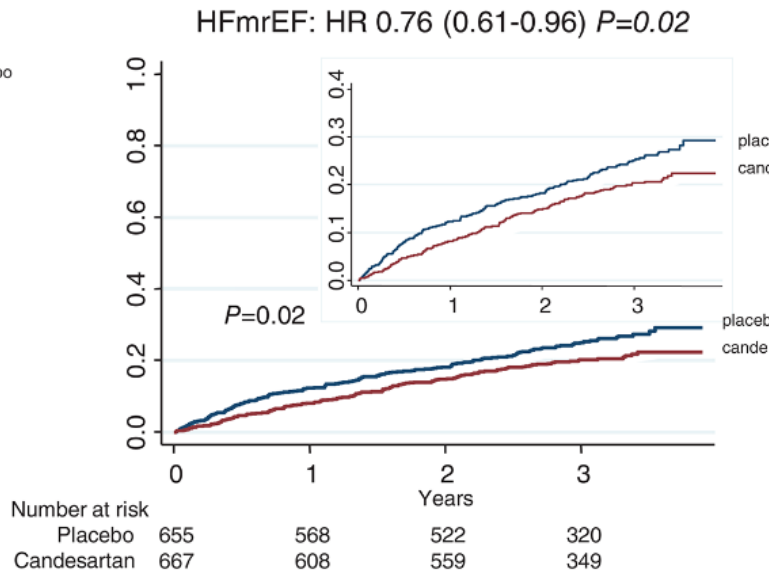


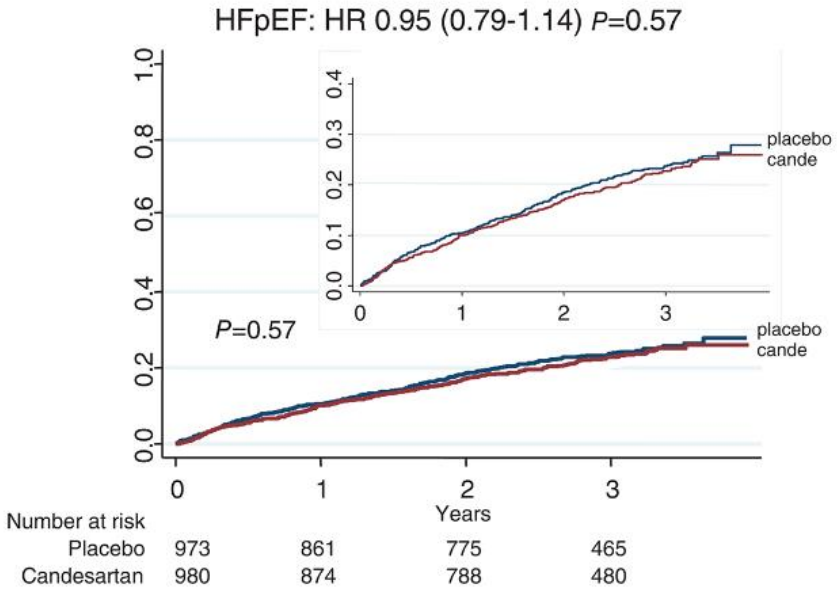
ESC HF Guidelines 2016; Ponikowski EHJ 2016

# HFmrEF resembles HFrEF (but not HFpEF)

## Candesartan Improves Outcomes in HFmrEF




**n=7598 patients**
**1322 HFmrEF patients**

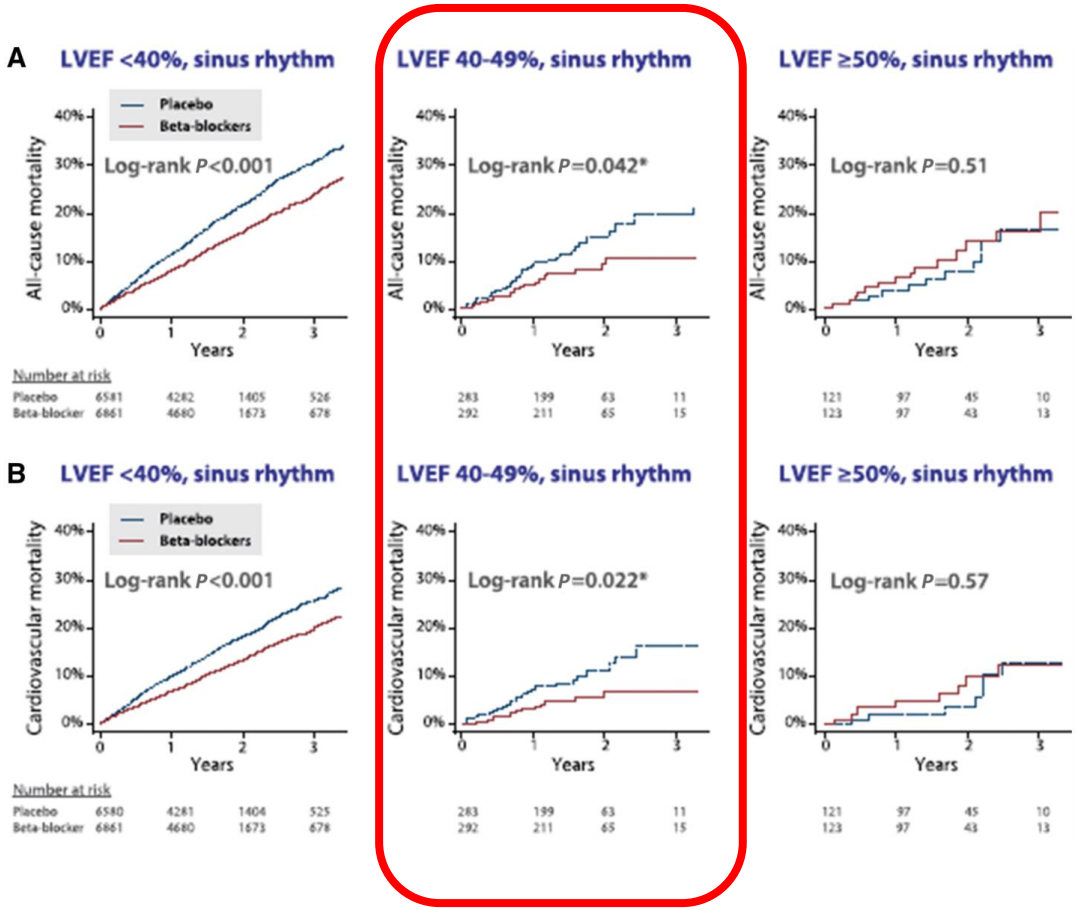
# HFmrEF resembles HFrEF (but not HFpEF)

## Beta-Blockers Improve Outcomes in HFmrEF

Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials.

**Mortality**

**CV Mortality**



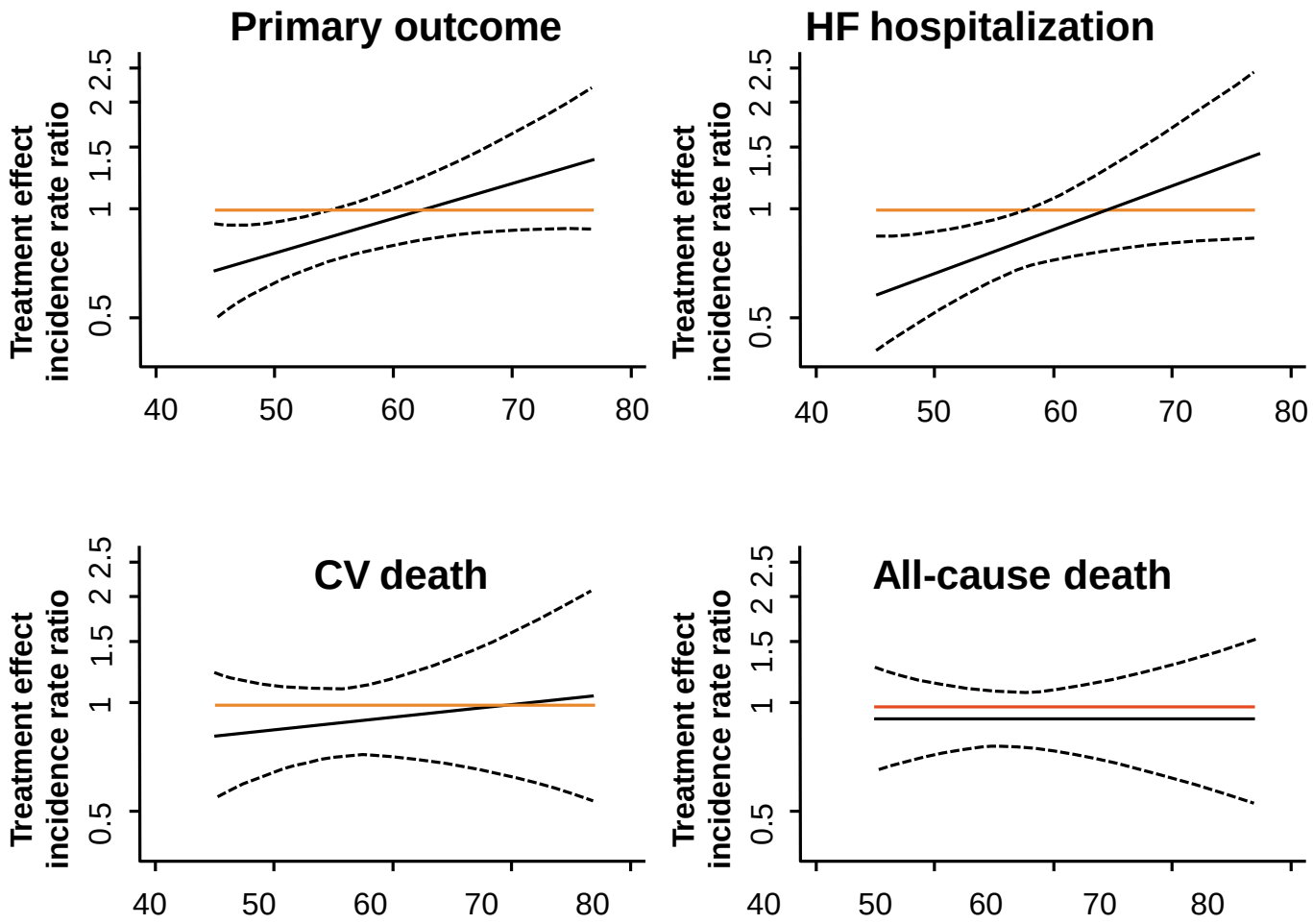

**Cleland EHJ 2017**

# Treatment Effect of Spironolactone as a Function of Ejection Fraction: *A post-hoc Analysis of TOPCAT*

**Patients with LVEF ≥45%**

**[range 44% to 85%]**

**n=3444**




CV, cardiovascular; EF, ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction

Dashed lines represent 95% CI; primary outcome: composite of CV death, aborted cardiac arrest, or hospitalization for HF

**Solomon Eur Heart J. 2016**

UniversityHospital Zurich

University of Zurich[UZH]

/

# We Now Renamed HFmrEF (…*formerly known as mid-range*) as Heart Failure with mildly reduced Ejection Fraction…

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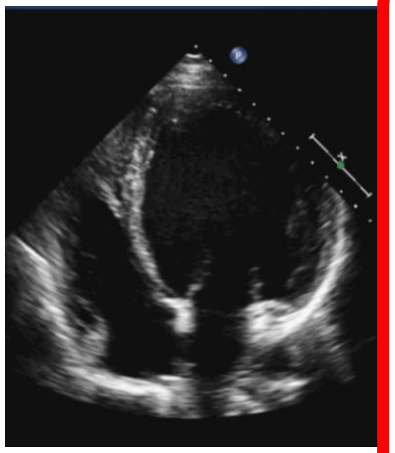
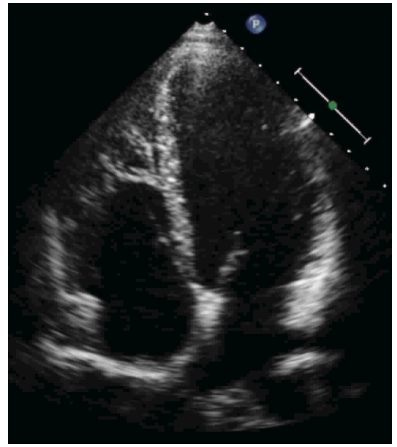
| | 3 | – | 1. Elevated levels of natriuretic peptides[b];<br>2. At least one additional criterion:<br>a. relevant structural heart disease (LVH and/or LAE),<br>b. diastolic dysfunction (for details see Section 4.3.2). | 1. Elevated levels of natriuretic peptides[b];<br>2. At least one additional criterion:<br>a. relevant structural heart disease (LVH and/or LAE),<br>b. diastolic dysfunction (for details see Section 4.3.2). |

# The New Definition of Heart Failure with reduced and mildly reduced Ejection Fraction and preserved Ejection Fraction



| Type of HF | | HFrEF | HFmrEF | HFpEF |
|---|---|---|---|---|
| CRITERIA | 1 | Symptoms ± Signs[a] | Symptoms ± Signs[a] | Symptoms ± Signs[a] |
| | 2 | LVEF ≤40% | LVEF 41-49%[b] | LVEF ≥50% |
| | 3 | - | - | Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c] |



**ESC HF Guidelines 2021; McDonagh EHJ 2021**

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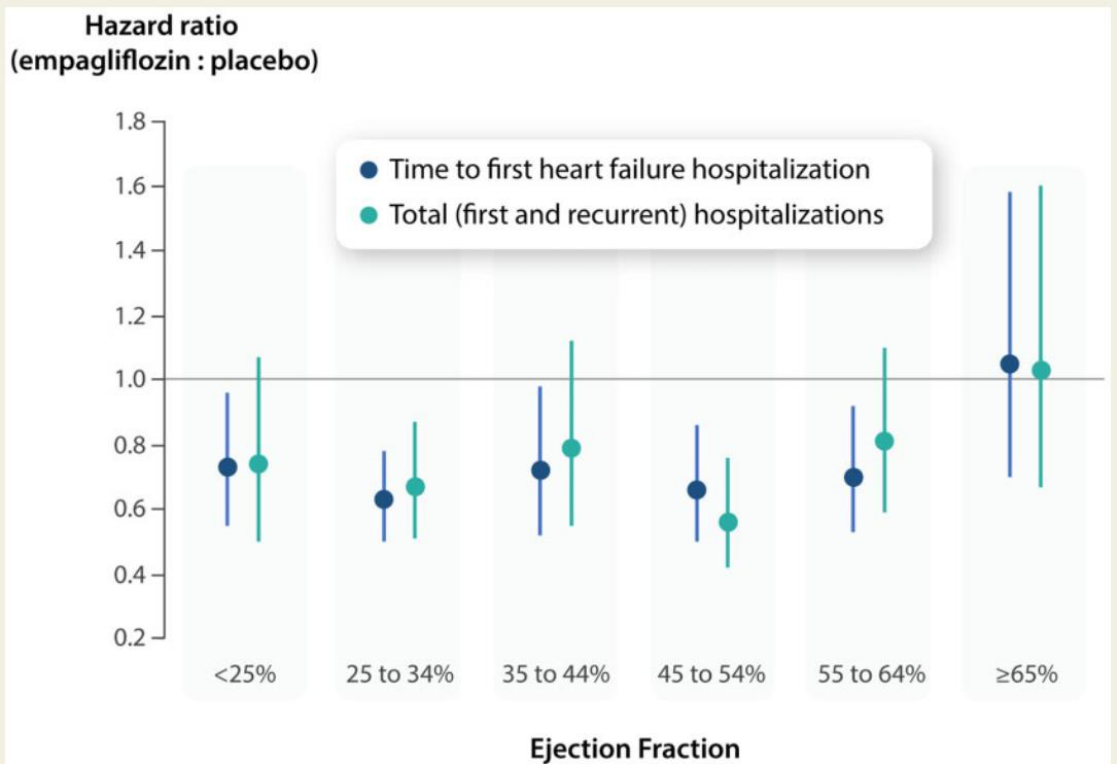
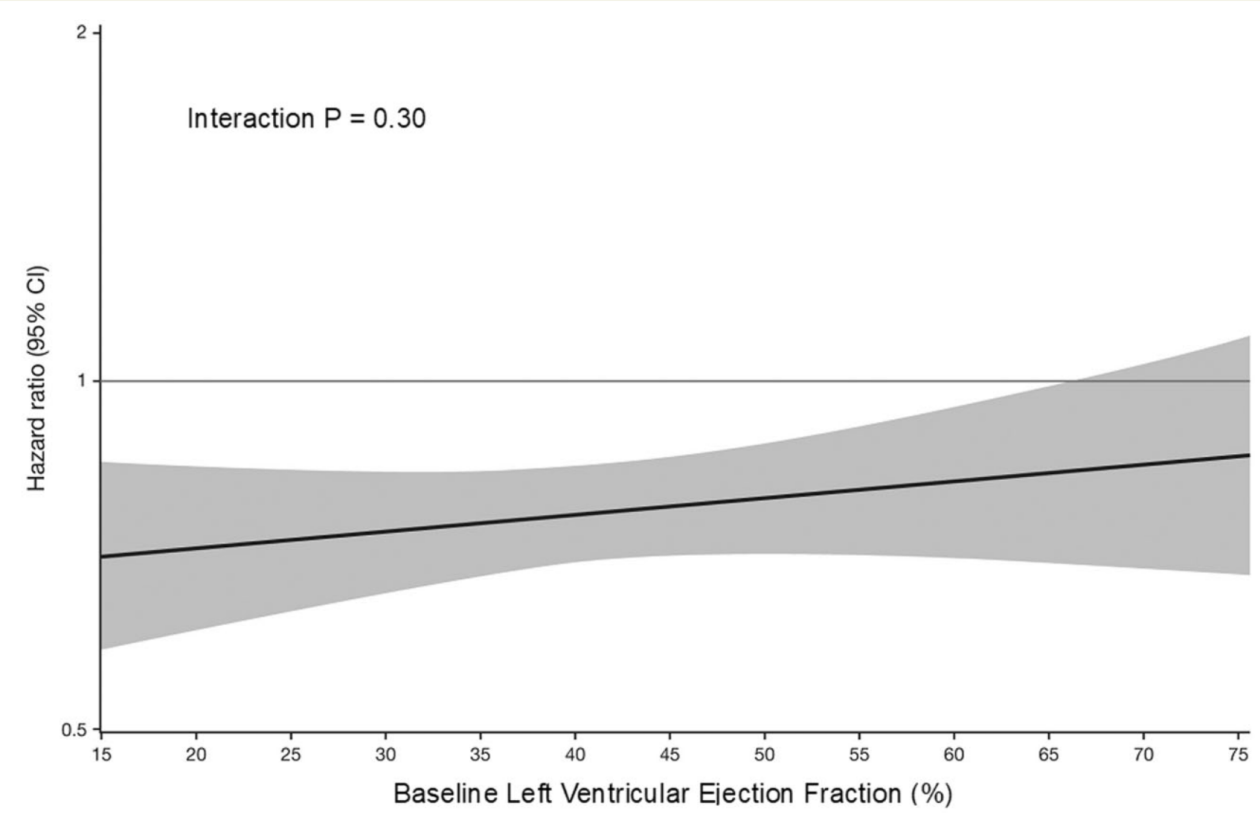
# Effect of Empagliflozin in Patients with Heart Failure across the Spectrum of Left Ventricular Ejection Fraction

## Clinically Meaningful and Similar Benefit up to EF 65%

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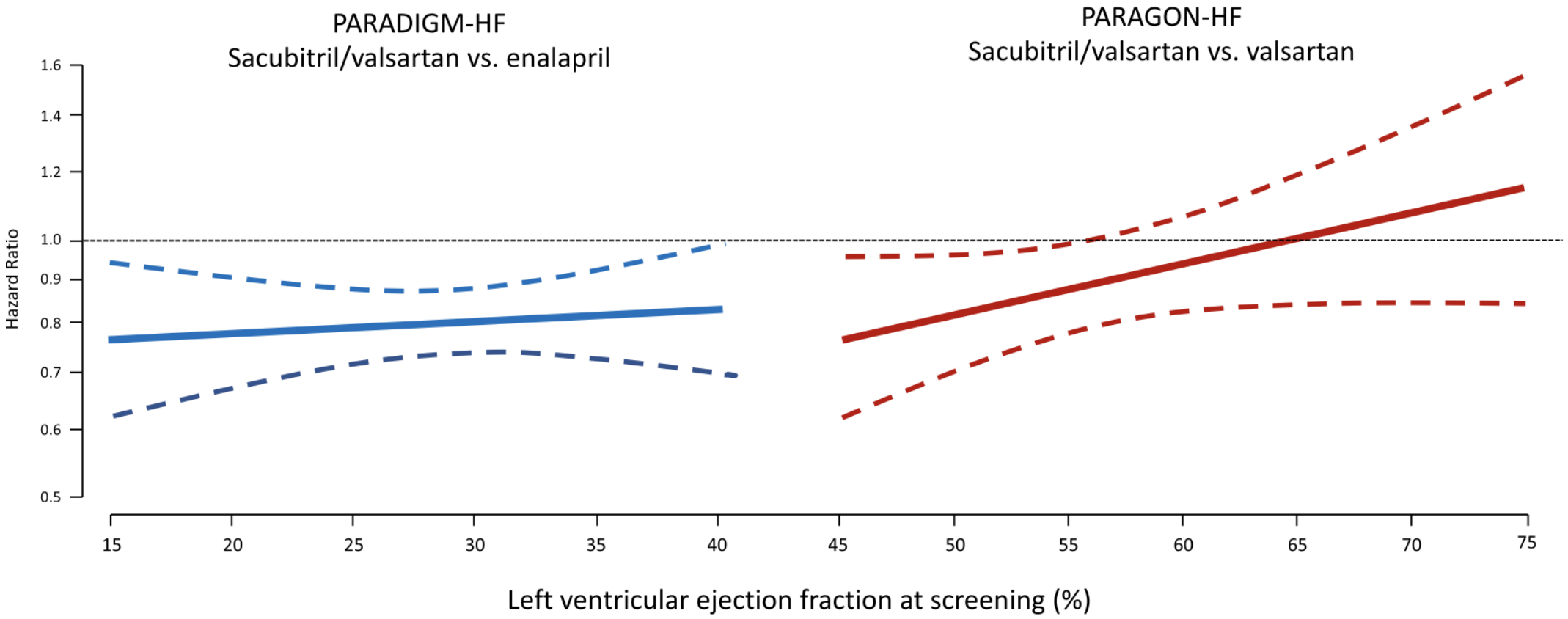
**Butler EHJ 2022**

# Gradient to the Treatment effect* in PARADIGM and PARAGON Is 60 the new 40?

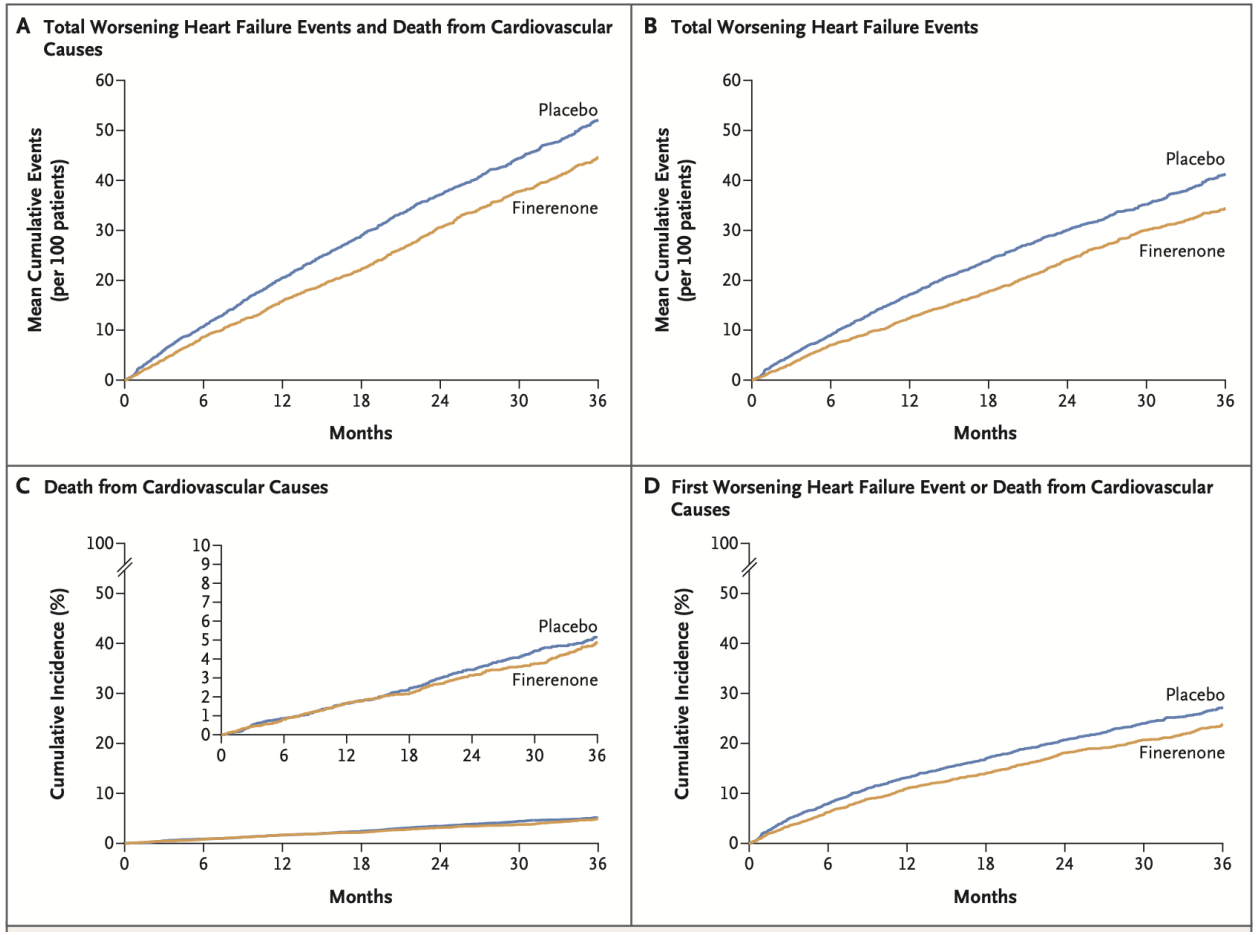



***Cardiovascular death or Heart Failure Hospitalization**

Solomon&McMurray J Card Failure 2021

# Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

## Primary Outcome and Its Components

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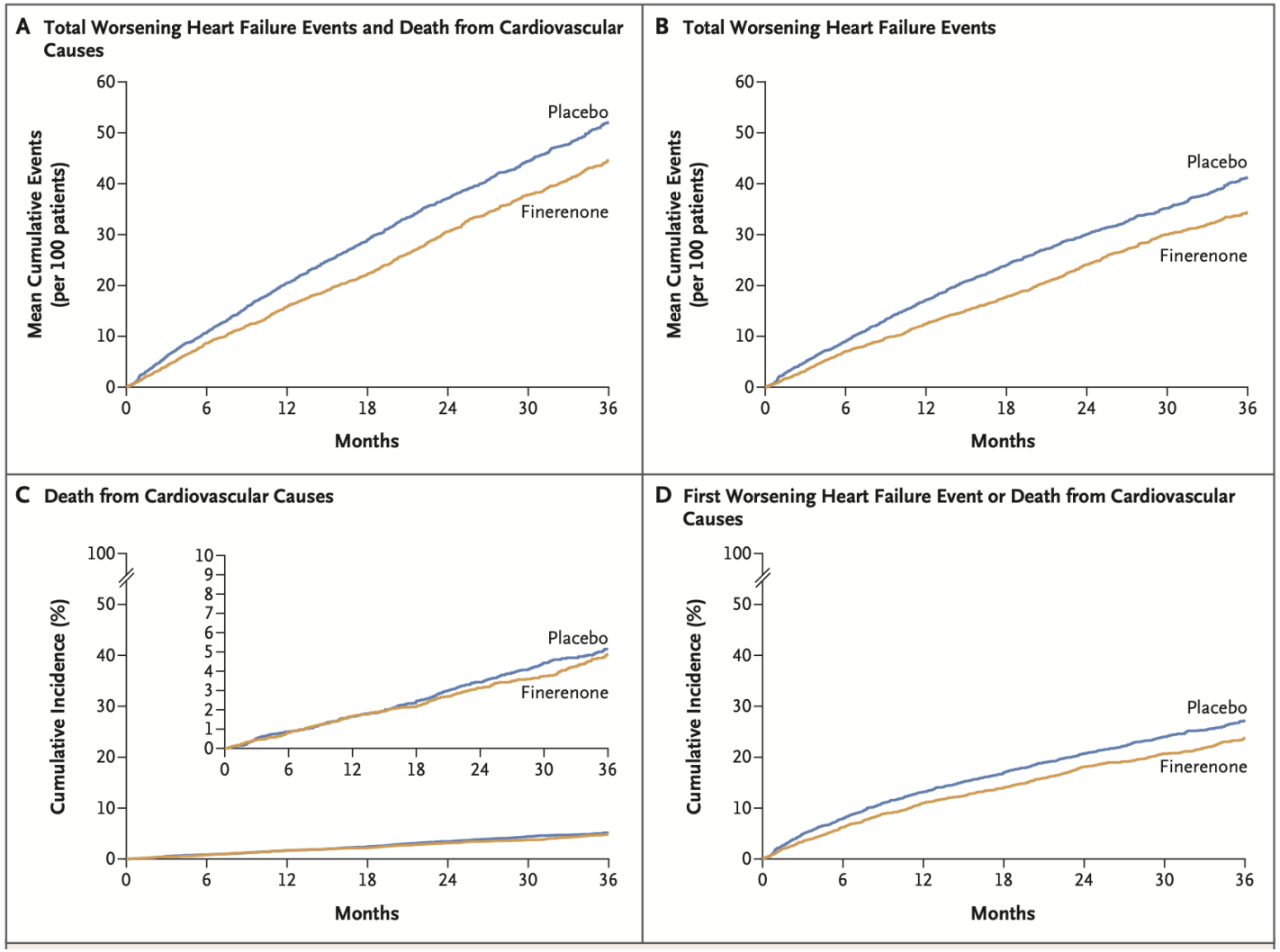
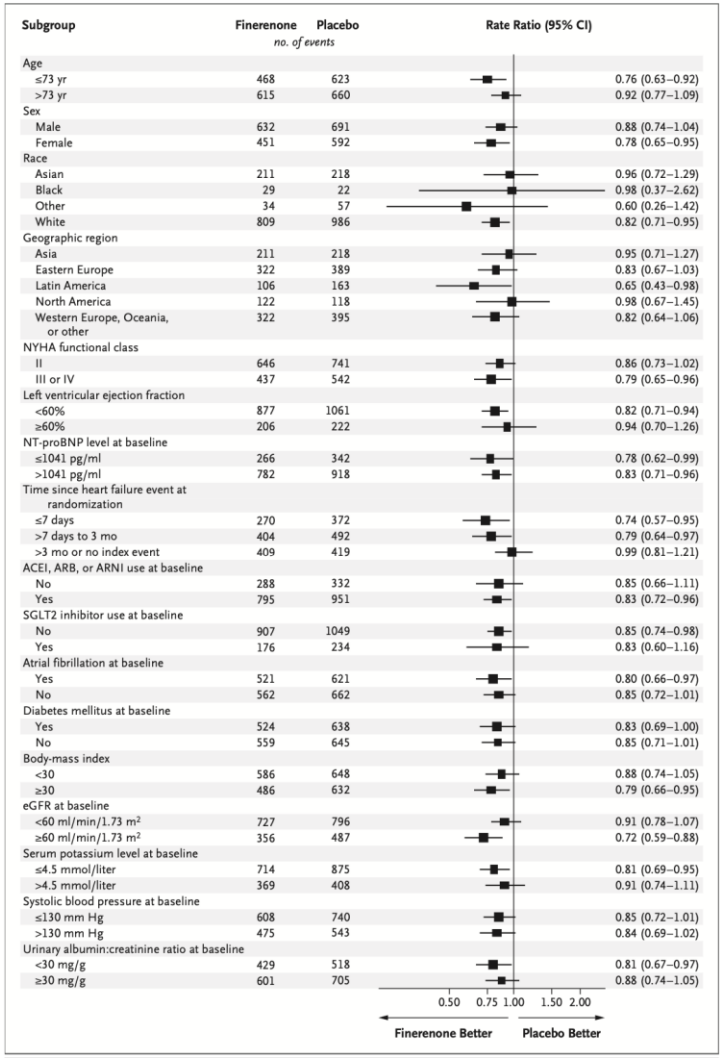
Solomon NEJM 2024

# Finerenone in HFpEF

## Subgroup Analysis of the Primary Outcome



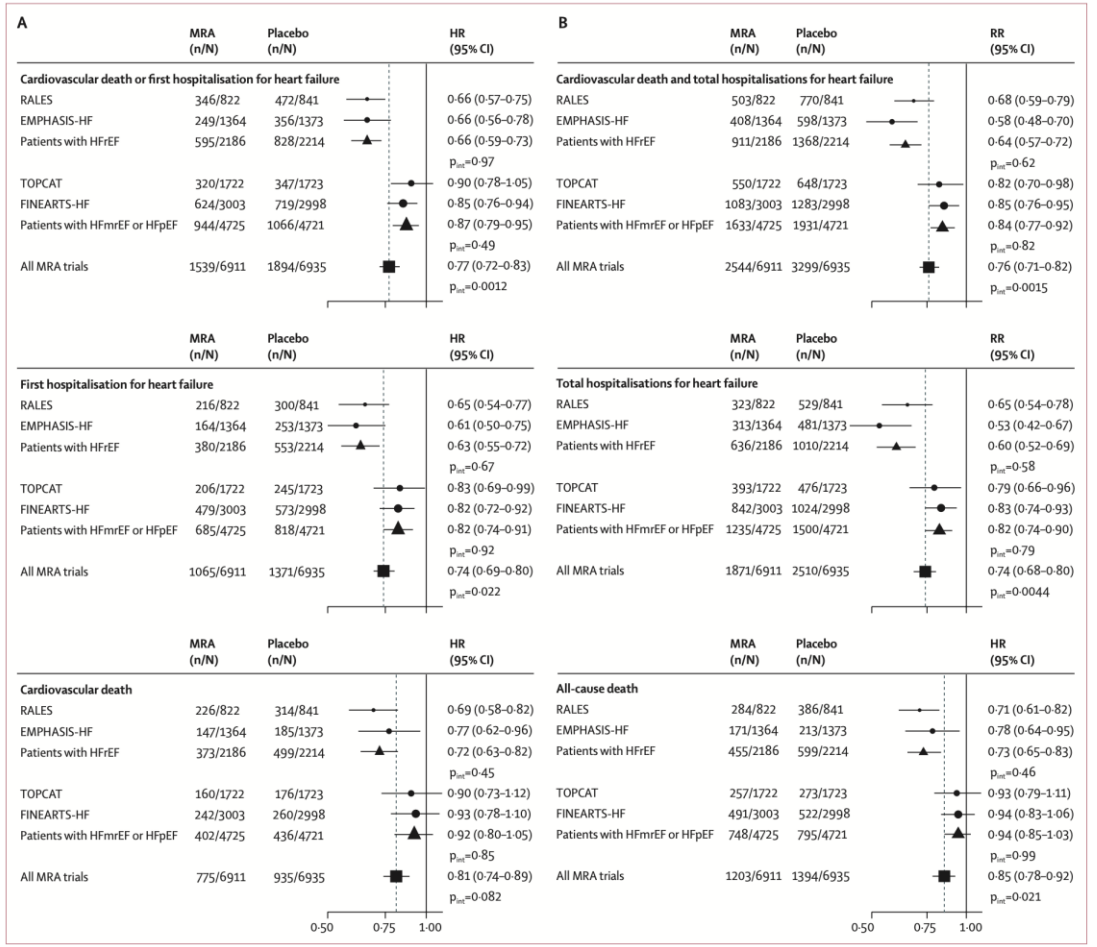
| Subgroup | Finerenone (no. of events) | Placebo (no. of events) | Rate Ratio (95% CI) |
|---|---|---|---|
| Age | | | |
| ≤73 yr | 468 | 623 | 0.76 (0.63–0.92) |
| >73 yr | 615 | 660 | 0.92 (0.77–1.09) |
| Sex | | | |
| Male | 632 | 691 | 0.88 (0.74–1.04) |
| Female | 451 | 592 | 0.78 (0.65–0.95) |
| Race | | | |
| Asian | 211 | 218 | 0.96 (0.72–1.29) |
| Black | 29 | 22 | 0.98 (0.37–2.62) |
| Other | 34 | 57 | 0.60 (0.26–1.42) |
| White | 809 | 986 | 0.82 (0.71–0.95) |
| Geographic region | | | |
| Asia | 211 | 218 | 0.95 (0.71–1.27) |
| Eastern Europe | 322 | 389 | 0.83 (0.67–1.03) |
| Latin America | 106 | 163 | 0.65 (0.43–0.98) |
| North America | 122 | 118 | 0.98 (0.67–1.45) |
| Western Europe, Oceania, or other | 322 | 395 | 0.82 (0.64–1.06) |
| NYHA functional class | | | |
| II | 646 | 741 | 0.86 (0.73–1.02) |
| III or IV | 437 | 542 | 0.79 (0.65–0.96) |
| Left ventricular ejection fraction | | | |
| <60% | 877 | 1061 | 0.82 (0.71–0.94) |
| ≥60% | 206 | 222 | 0.94 (0.70–1.26) |
| NT-proBNP level at baseline | | | |
| ≤1041 pg/ml | 266 | 342 | 0.78 (0.62–0.99) |
| >1041 pg/ml | 782 | 918 | 0.83 (0.71–0.96) |
| Time since heart failure event at randomization | | | |
| ≤7 days | 270 | 372 | 0.74 (0.57–0.95) |
| >7 days to 3 mo | 404 | 492 | 0.79 (0.64–0.97) |
| >3 mo or no index event | 409 | 419 | 0.99 (0.81–1.21) |
| ACEI, ARB, or ARNI use at baseline | | | |
| No | 288 | 332 | 0.85 (0.66–1.11) |
| Yes | 795 | 951 | 0.83 (0.72–0.96) |
| SGLT2 inhibitor use at baseline | | | |
| No | 907 | 1049 | 0.85 (0.74–0.98) |
| Yes | 176 | 234 | 0.83 (0.60–1.16) |
| Atrial fibrillation at baseline | | | |
| Yes | 521 | 621 | 0.80 (0.66–0.97) |
| No | 562 | 662 | 0.85 (0.72–1.01) |
| Diabetes mellitus at baseline | | | |
| Yes | 524 | 638 | 0.83 (0.69–1.00) |
| No | 559 | 645 | 0.85 (0.71–1.01) |
| Body-mass index | | | |
| <30 | 586 | 648 | 0.88 (0.74–1.05) |
| ≥30 | 486 | 632 | 0.79 (0.66–0.95) |
| eGFR at baseline | | | |
| <60 ml/min/1.73 m² | 727 | 796 | 0.91 (0.78–1.07) |
| ≥60 ml/min/1.73 m² | 356 | 487 | 0.72 (0.59–0.88) |
| Serum potassium level at baseline | | | |
| ≤4.5 mmol/liter | 714 | 875 | 0.81 (0.69–0.95) |
| >4.5 mmol/liter | 369 | 408 | 0.91 (0.74–1.11) |
| Systolic blood pressure at baseline | | | |
| ≤130 mm Hg | 608 | 740 | 0.85 (0.72–1.01) |
| >130 mm Hg | 475 | 543 | 0.84 (0.69–1.02) |
| Urinary albumin:creatinine ratio at baseline | | | |
| <30 mg/g | 429 | 518 | 0.81 (0.67–0.97) |
| ≥30 mg/g | 601 | 705 | 0.88 (0.74–1.05) |





Solomon NEJM 2024

# Effect estimates from the individual patient level meta-analysis of MRAs and prespecified efficacy outcomes

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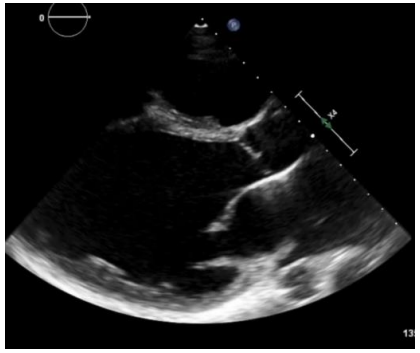
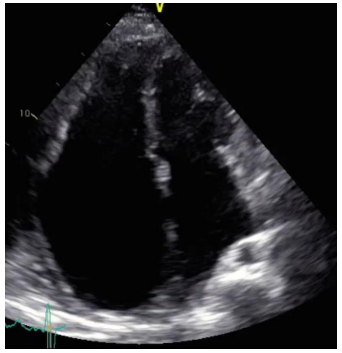
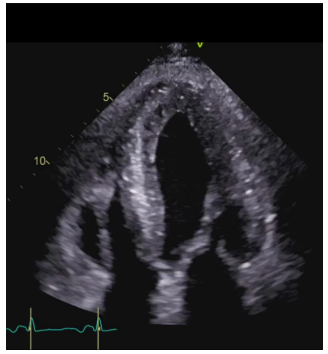
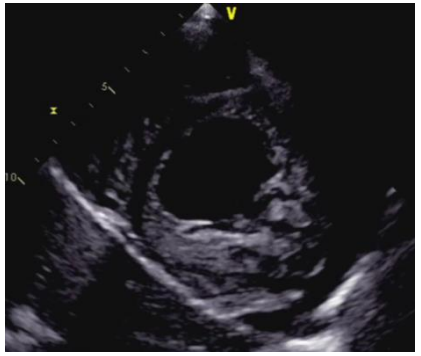
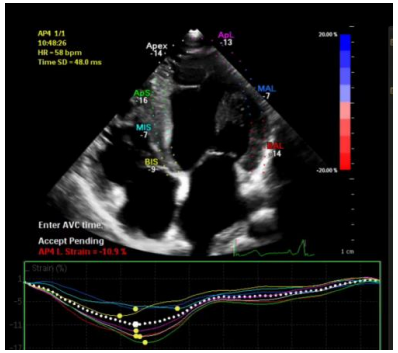
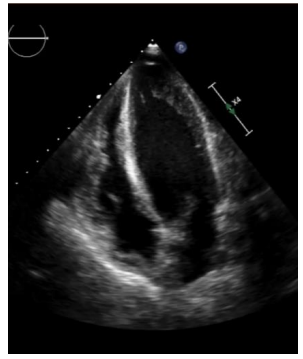
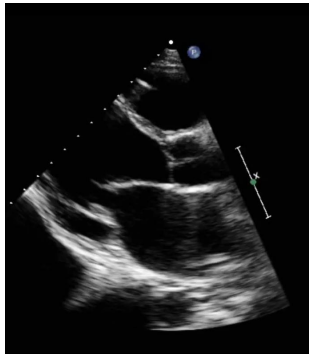
**Jhund Lancet 2024**

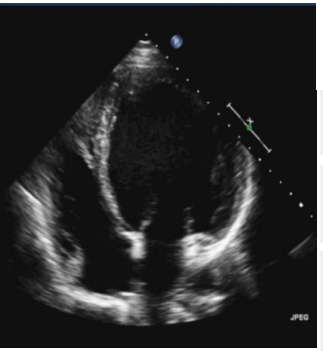
# LV Ejection Fraction - the Threshold Value to Define ‘Normal’ vs. ‘Reduced’ EF is Arbitrary


courtesy Johan Jervoe

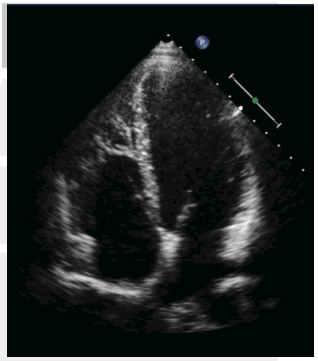
# *Simplicity is the Ultimate Sophistication…*

## *Heart Failure with reduced or normal Ejection Fraction*



| HFrEF | | HFnEF |
|---|---|---|
| Symptoms ± Signs[a] | Symptoms ± Signs[a] | Symptoms ± Signs[a] |
| LVEF ≤40% | LVEF 41–49%[b] | LVEF ≥50% |
| – | – | Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c] |



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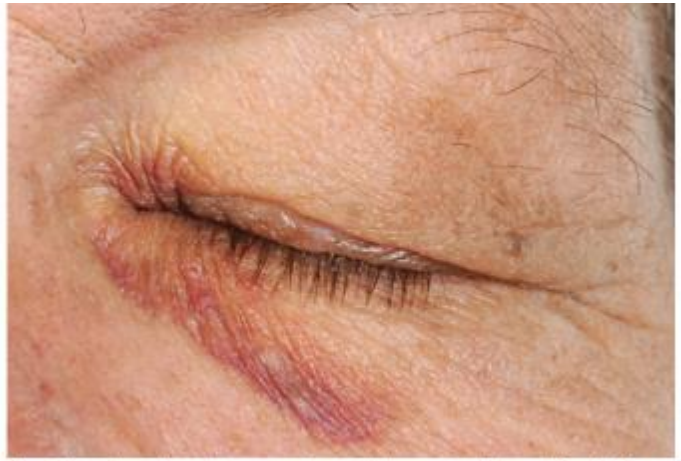
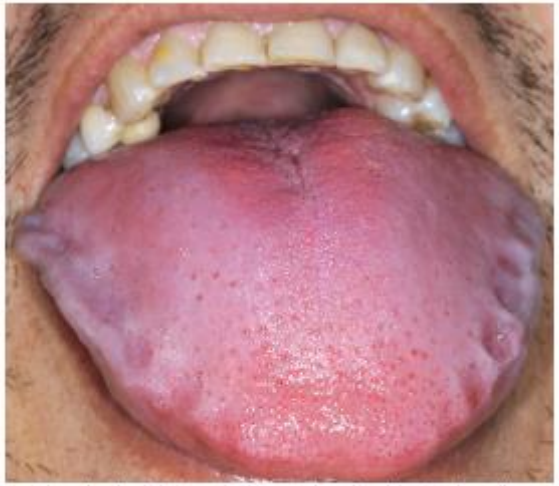
Proposed new Classification Ruschitzka ESC 2023

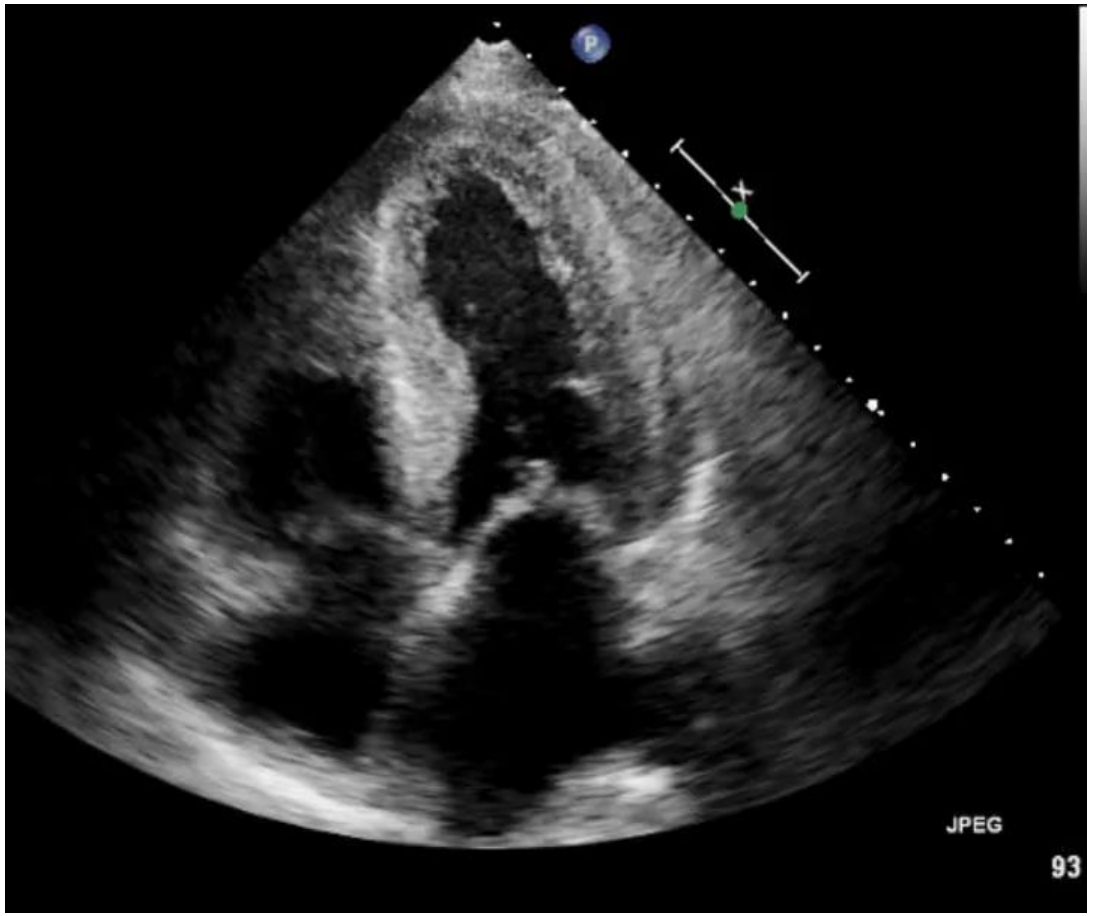
# Let`s Shift our Focus from Dichotomizing Heart Failure by Ejection Fraction to a better Understanding of Etiology and Pathophysiology



Klassische, schon etwas ältere spontane Einblutungen in die Augenlider. Meist bilateral ('Waschbärenaugen').



Typische Makroglossie bei AL-Amyloidose mit lateralen Abdrücken durch die Zahnreihen.

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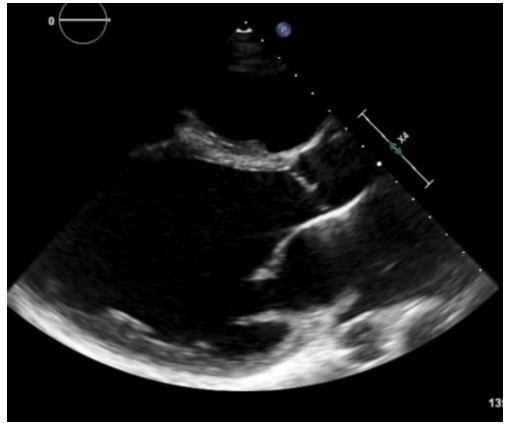
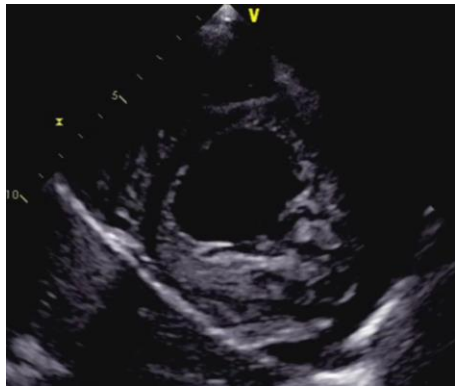
# HEART FAILURE

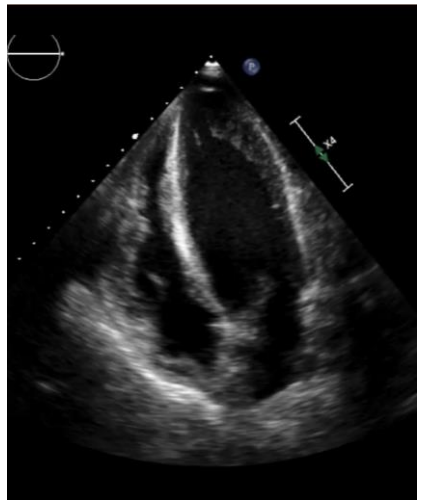
Dilative Cardiomyopathy

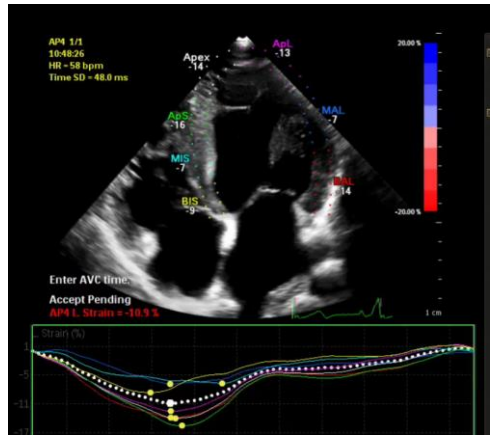


NonCompaction

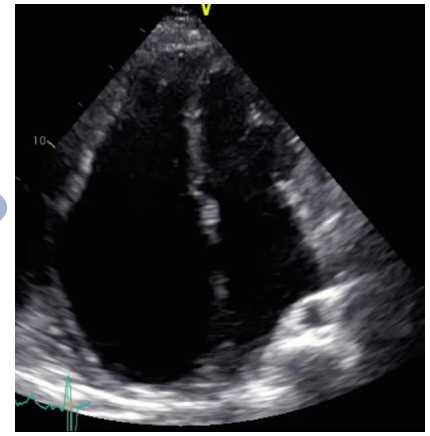


Myocarditis



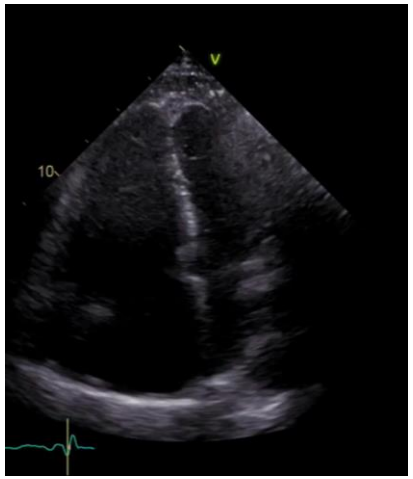



Hypertrophic Cardio-myopathy

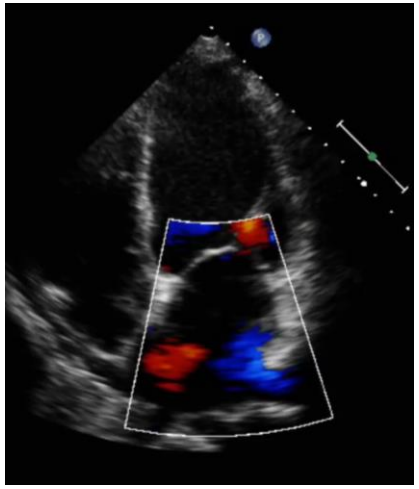


Restrictive Cardio-myopathy

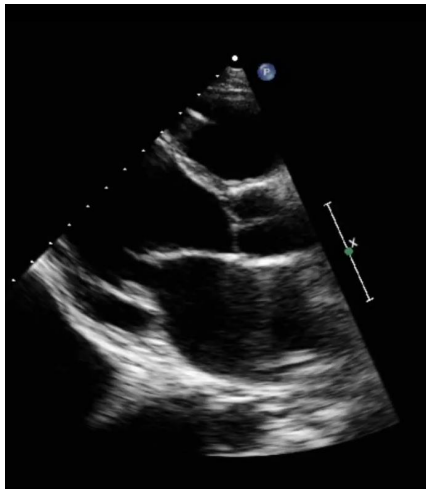
Right Ventricular Dysfunction

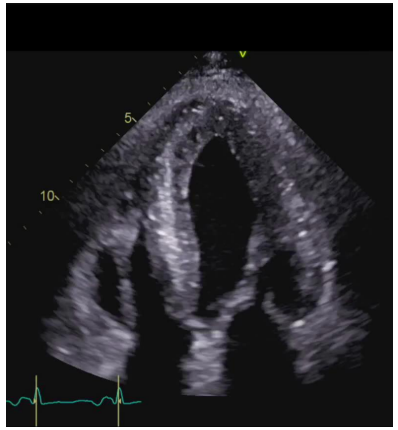


Mitral Regurgitation



„Left Atrial Disease“





Amyloidosis

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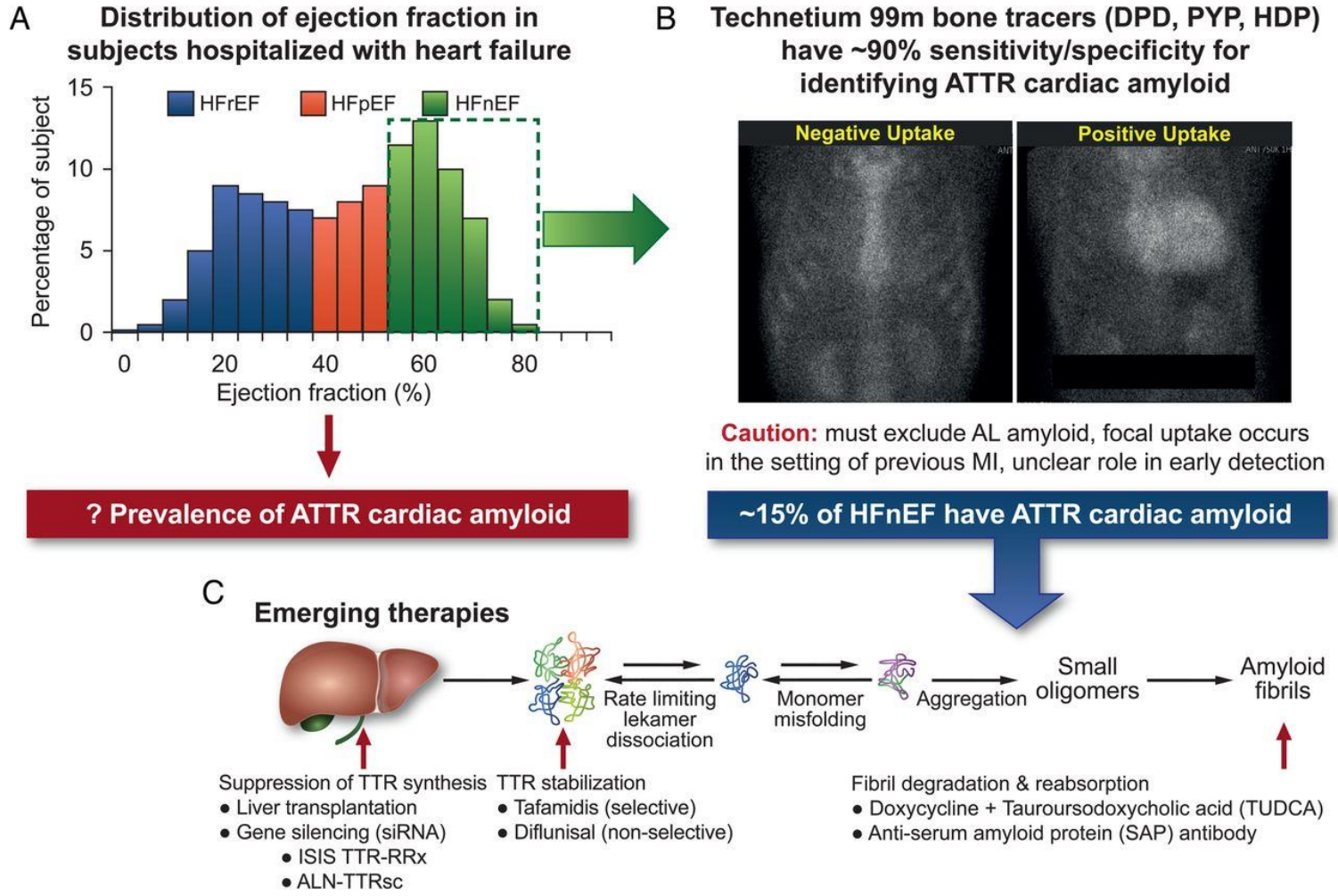
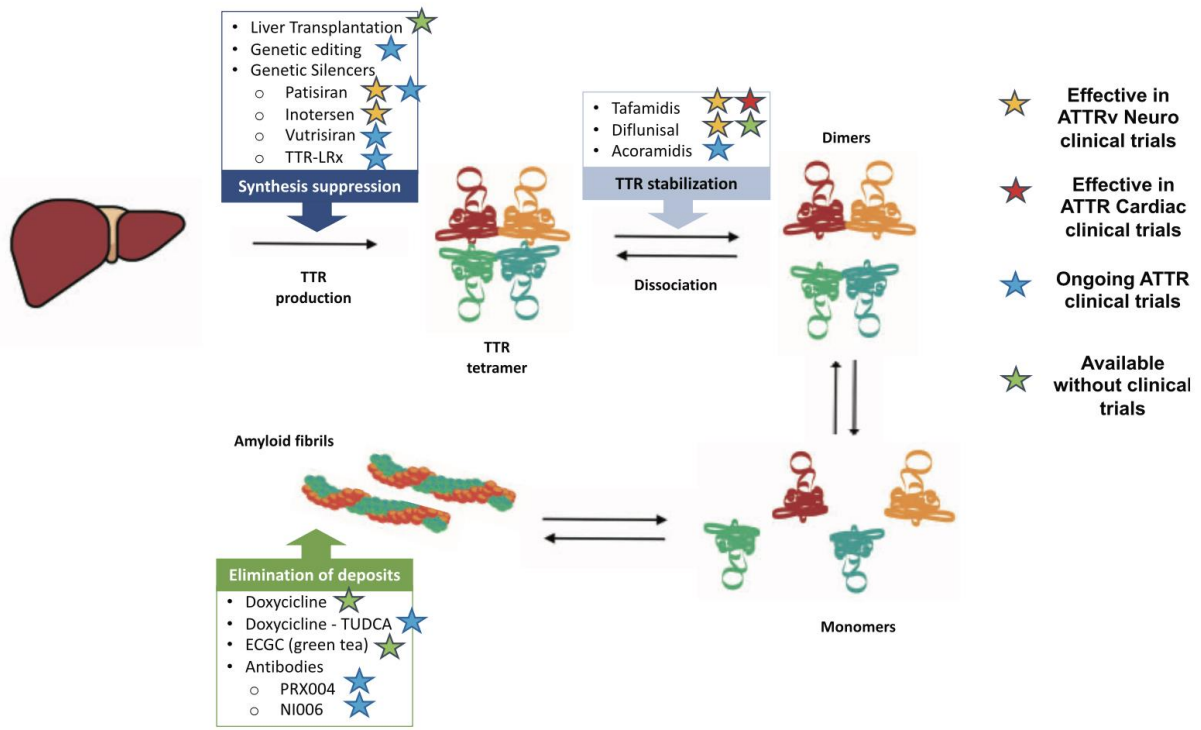
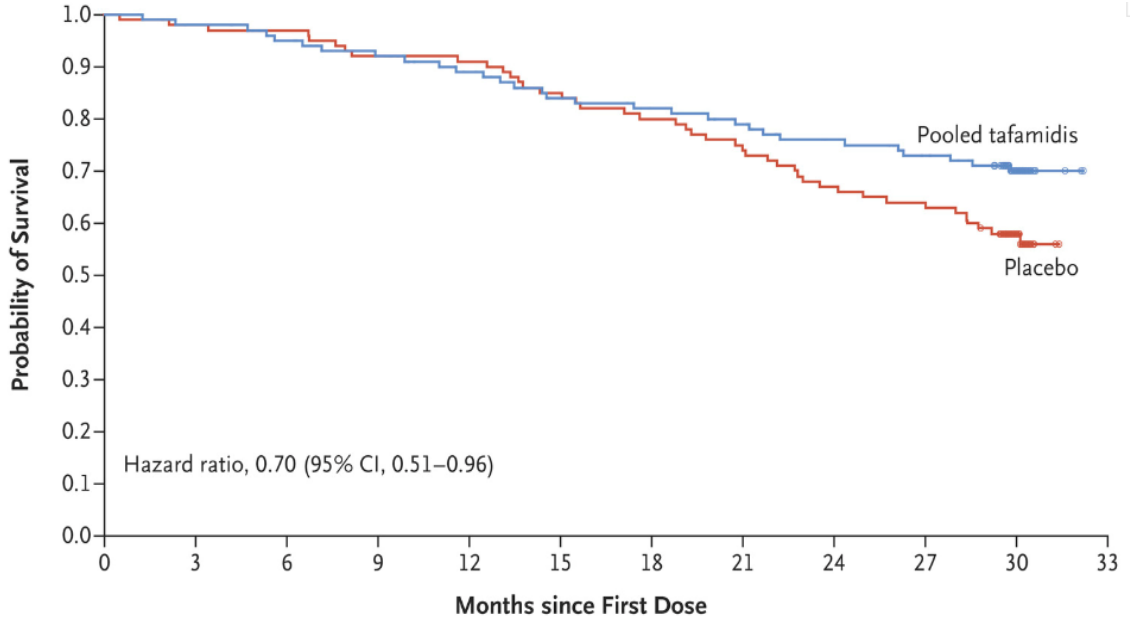
# Unveiling Transthyretin amyloid (ATTR) as a Potentially Modifiable Cause of Heart Failure




Adam Castaño Eur Heart J 2015

# Stabilizing Molecules (Tafamidis) and Genetic Silencers (Patisiran, Inotersen) as Specific Pharmacologic Treatments for Transthyretin Amyloid Cardiomyopathy




**No. at Risk (cumulative no. of events)**

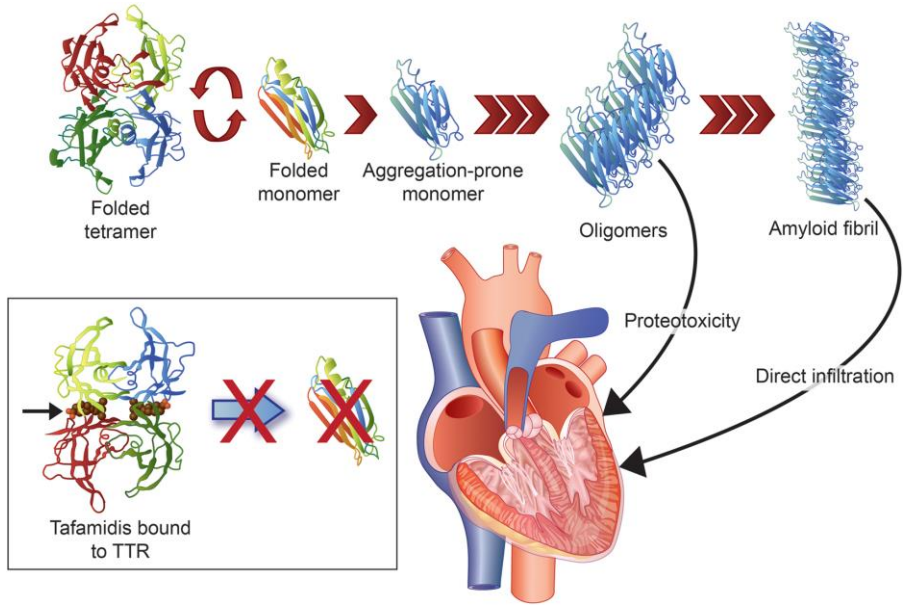
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pooled tafamidis | 264 (0) | 259 (5) | 252 (12) | 244 (20) | 235 (29) | 222 (42) | 216 (48) | 209 (55) | 200 (64) | 193 (71) | 99 (78) | 0 (78) |
| Placebo | 177 (0) | 173 (4) | 171 (6) | 163 (14) | 161 (16) | 150 (27) | 141 (36) | 131 (46) | 118 (59) | 113 (64) | 51 (75) | 0 (76) |

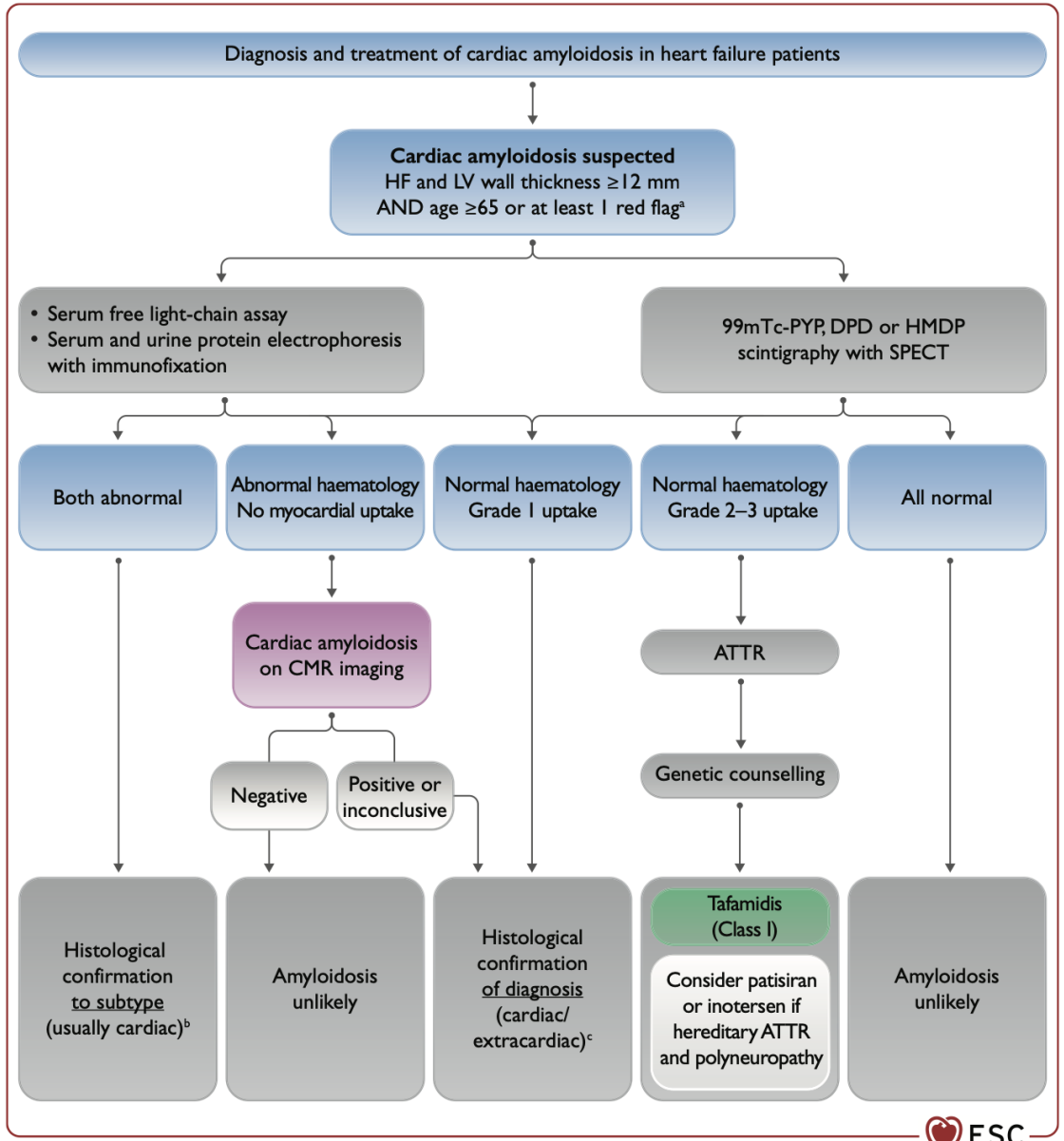
USZ Universitäts Spital Zürich

**ATTR-ACT Study: Maurer NEJM 2018**
**Garcia-Pavia EHJ 2021**

# TTR-Amyloidosis – Diagnosis and Treatment

## Effect of tafamidis on the transthyretin (TTR) tetramer




Falk RH et al, EHJ 2019
ESC Guidelines EHJ 2021

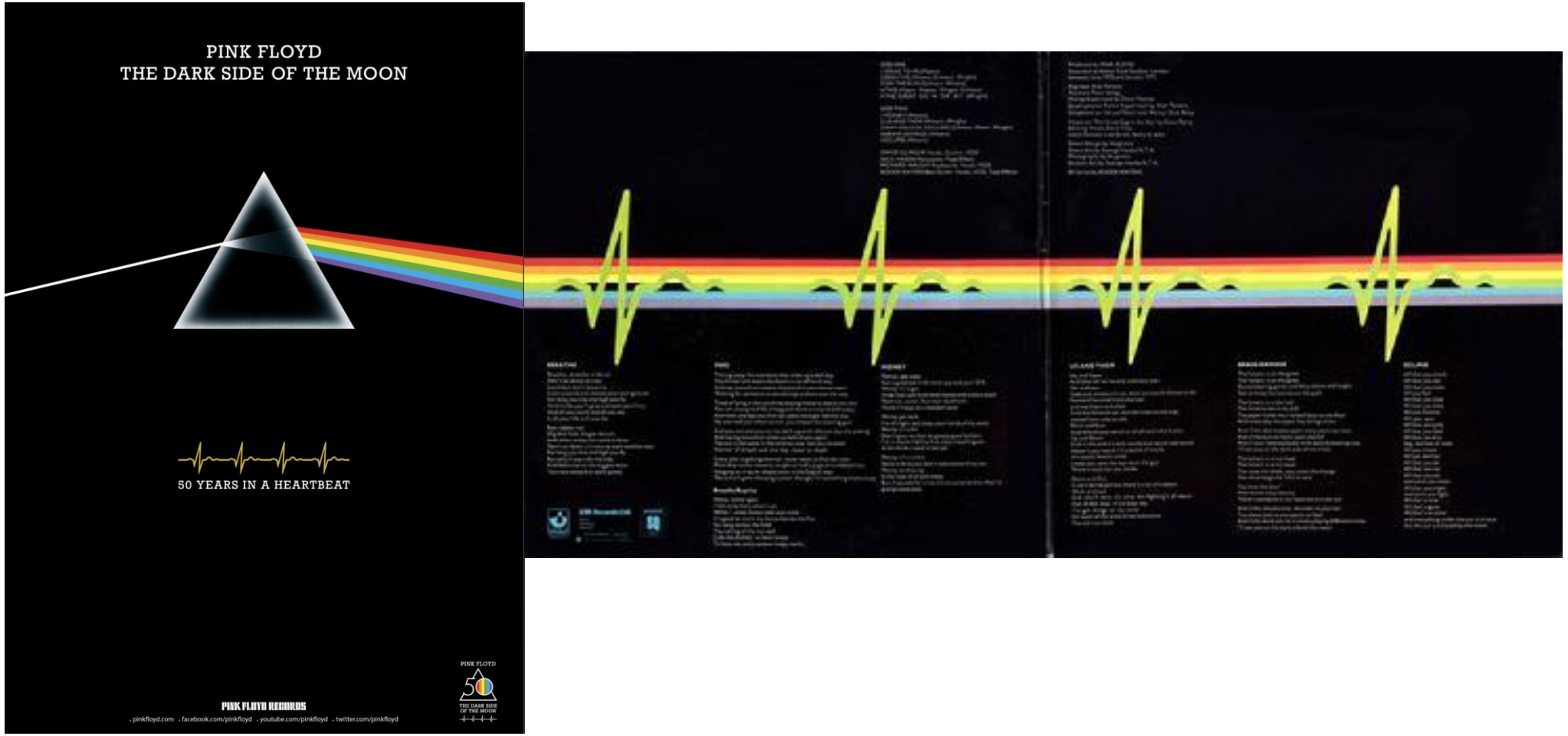
USZ Universitäts Spital Zürich

# Cardiology is Invasive, Interventional Physiology

## The Need for Deep Phenotyping

# Cardiology is Invasive, Interventional Physiology

## The Need for Deep Phenotyping

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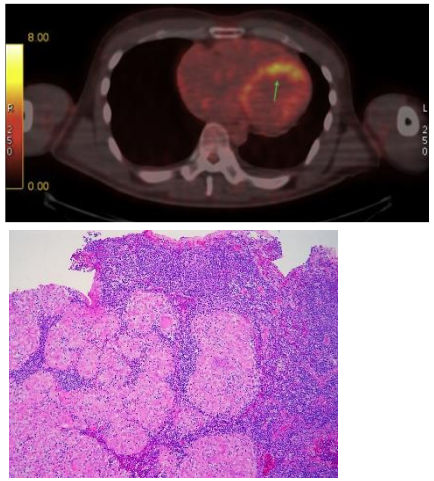
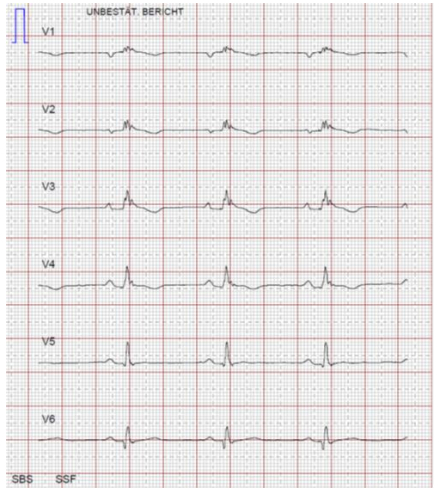
University of Zurich[UZH]

# Differential Diagnosis Cardiac Sarcoidosis (histologically proven)

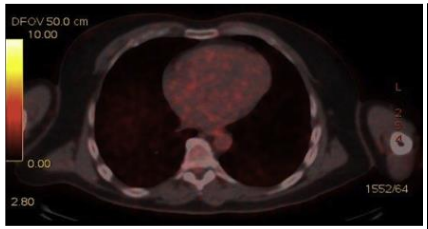
- CS often involves the RV apex and septum, whereas ARVC typically affects subtricuspid region and leads to RVOT dilation
- AVB, longer QRS duration (>96ms), and positive 18F-FDG PET favor a diagnosis of CS

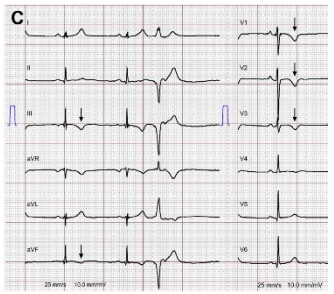


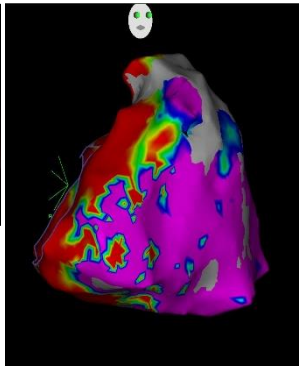



Cardiac sarcoid

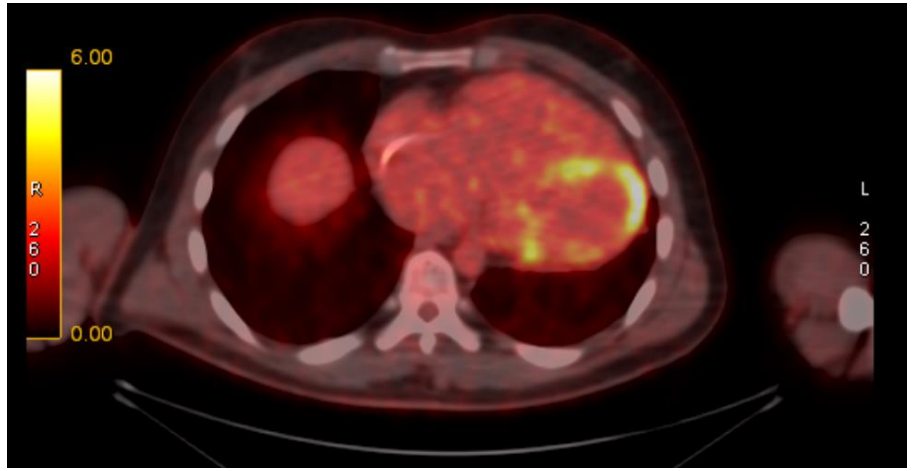


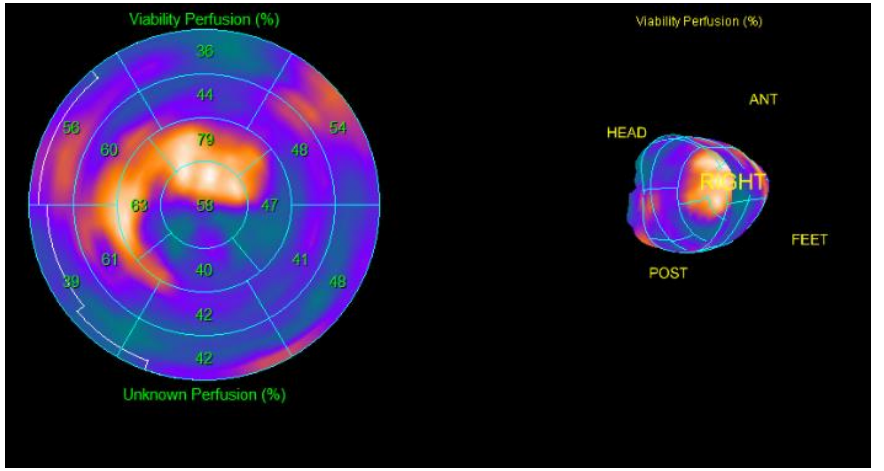



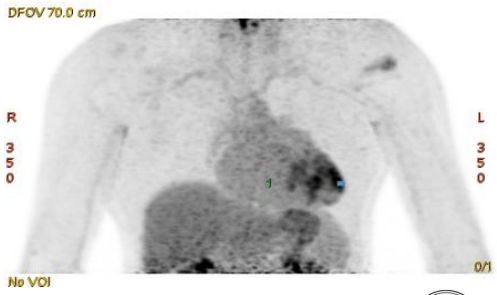
ARVC

# FDG-PET Cardiac Sarcoid mimicking ARVC



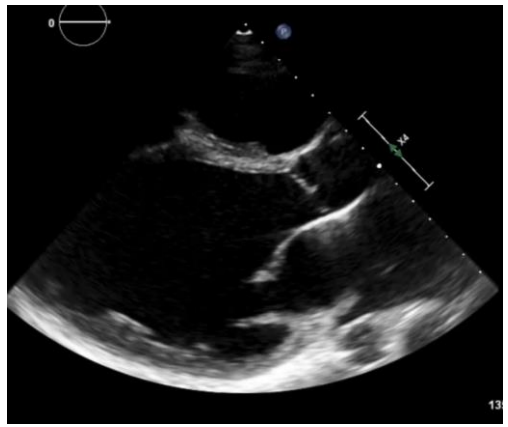

- Fokale metabolische Aktivität im Septum (basal bis apikal) sowie LV anteroapikal und basolateral, vereinbar mit myokardialer Inflammation
- Keine extrakardiale Inflammation



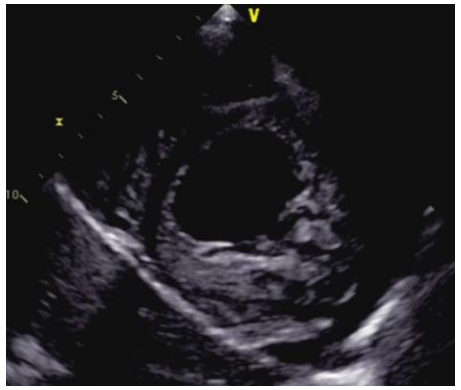

Saguner AM et al. Heart Rhythm 2021

# HEART FAILURE

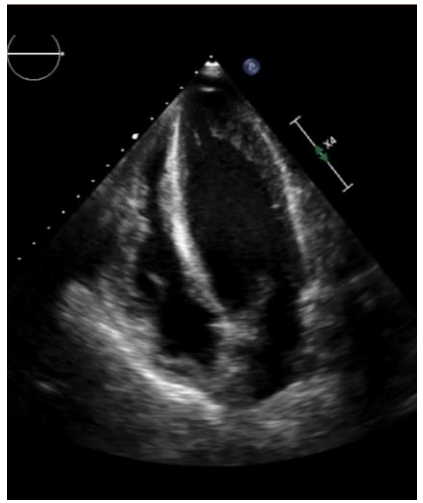
Dilative Cardiomyopathy

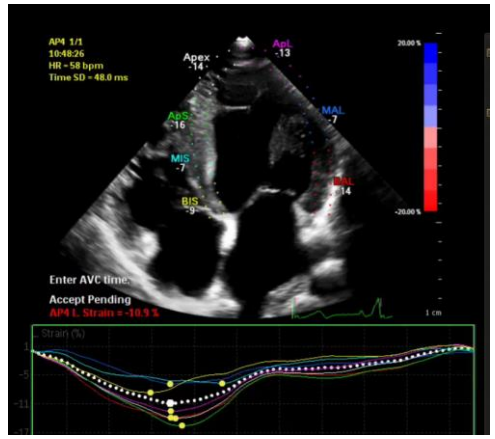


NonCompaction



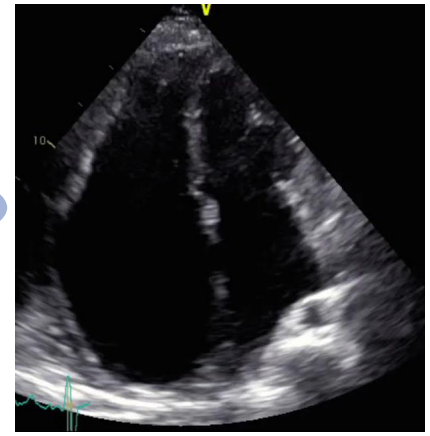
Myocarditis



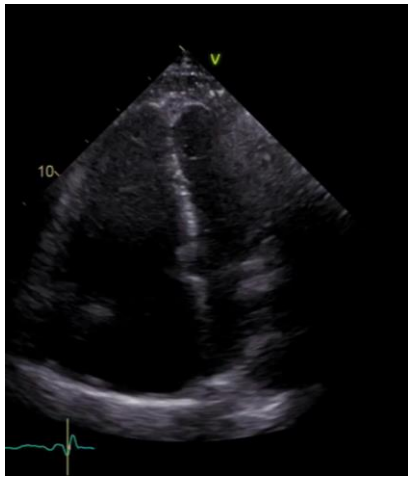



Hypertrophic Cardio-myopathy

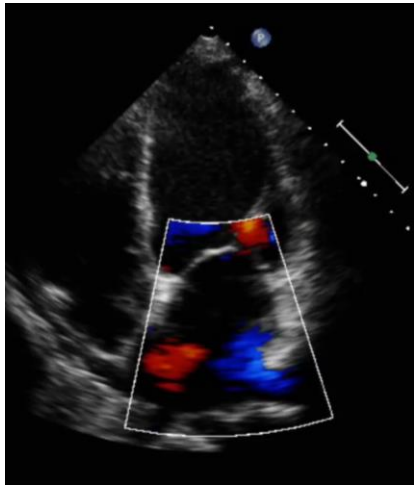
Restrictive Cardio-myopathy



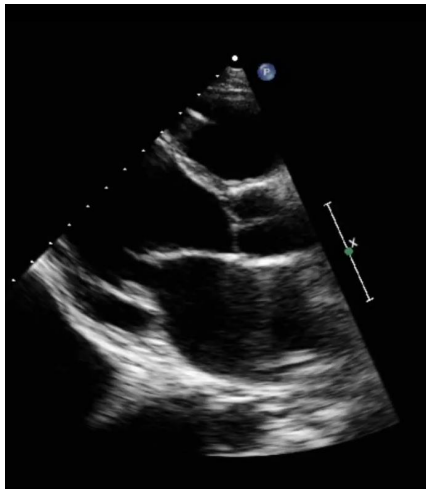
Right Ventricular Dysfunction

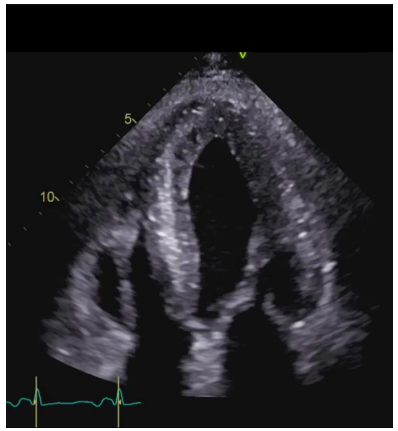


Mitral Regurgitation



HFpEF





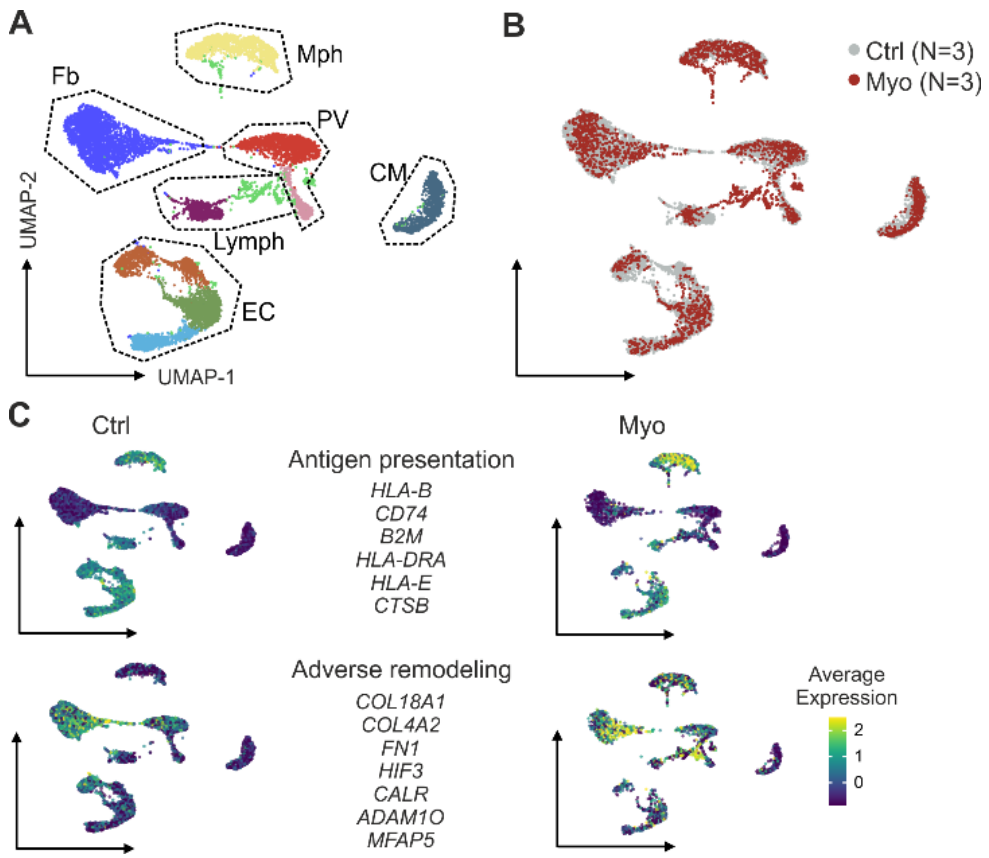
Amyloidosis

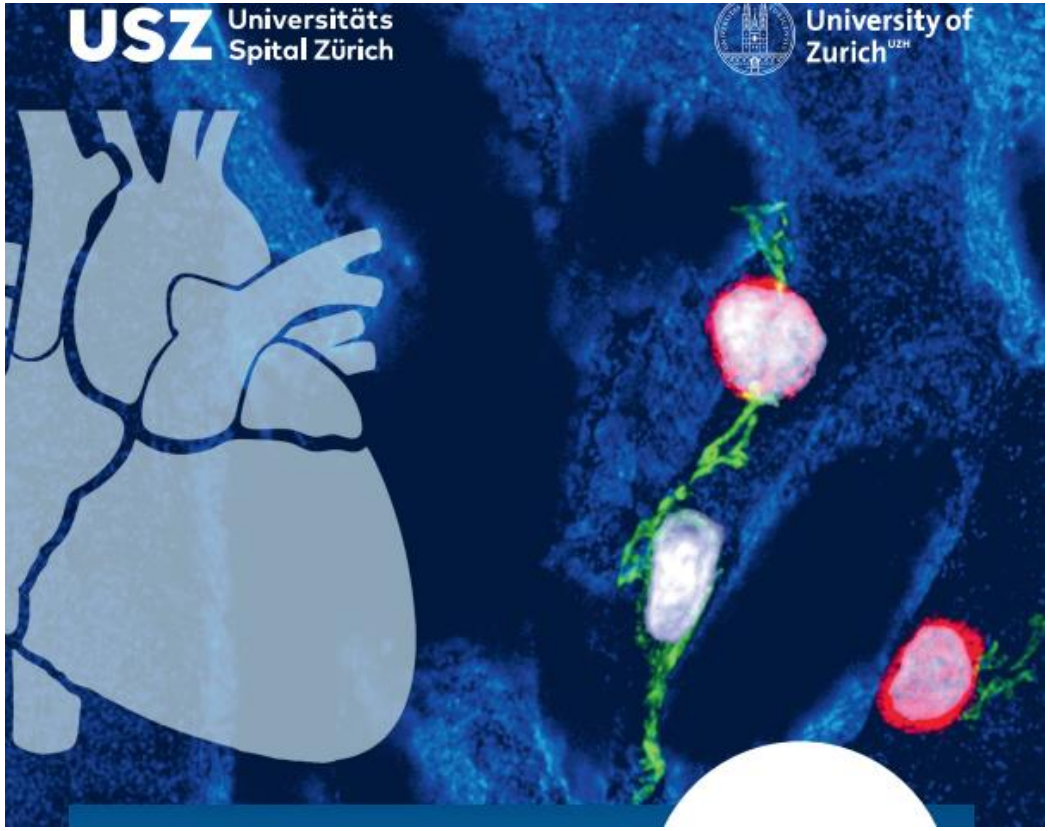
USZ Universitäts Spital Zürich

University of Zurich[UZH]

# The Need for Deeper Phenotyping in Cardiology

## Single cell transcriptomics analysis of cardiac cells




**Endothelial cells (EC), perivascular cells (PV), cardiomyocytes (CM), fibroblasts (Fb), macrophages (Mph), lymphocytes (lymph).**

**courtesy Burkhard Ludewig**

# Volume 3 Issue 3, March 2024

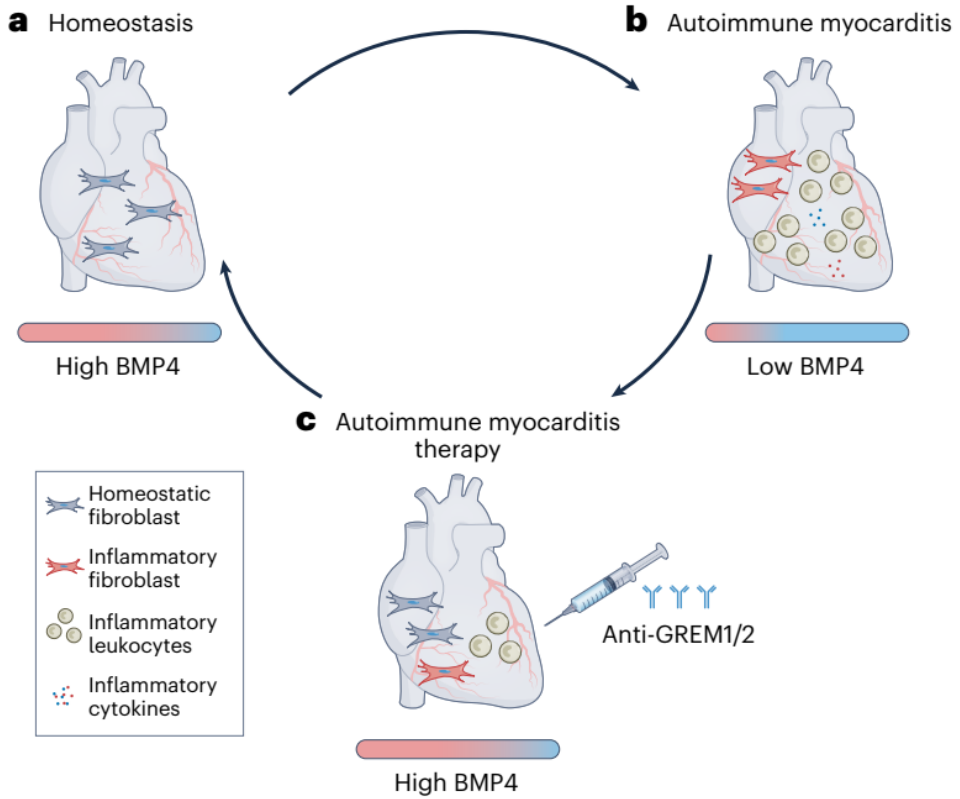

UniversityHospital Zurich

News & views

Autoimmune myocarditis

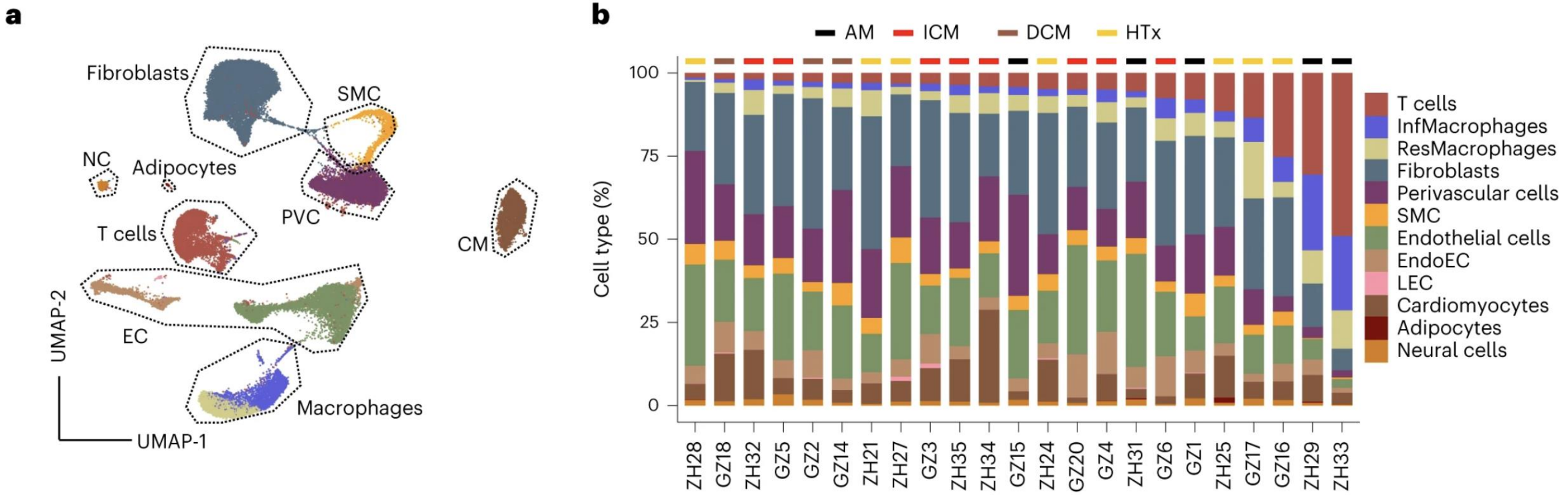
## BMP4 mediates myocardial inflammation and fibrosis

Pilar Martín



# The Need for Deeper Phenotyping in Cardiology

## snRNA-seq from Left or Right Ventricular Endomyocardial Biopsies from Heart Failure Patients



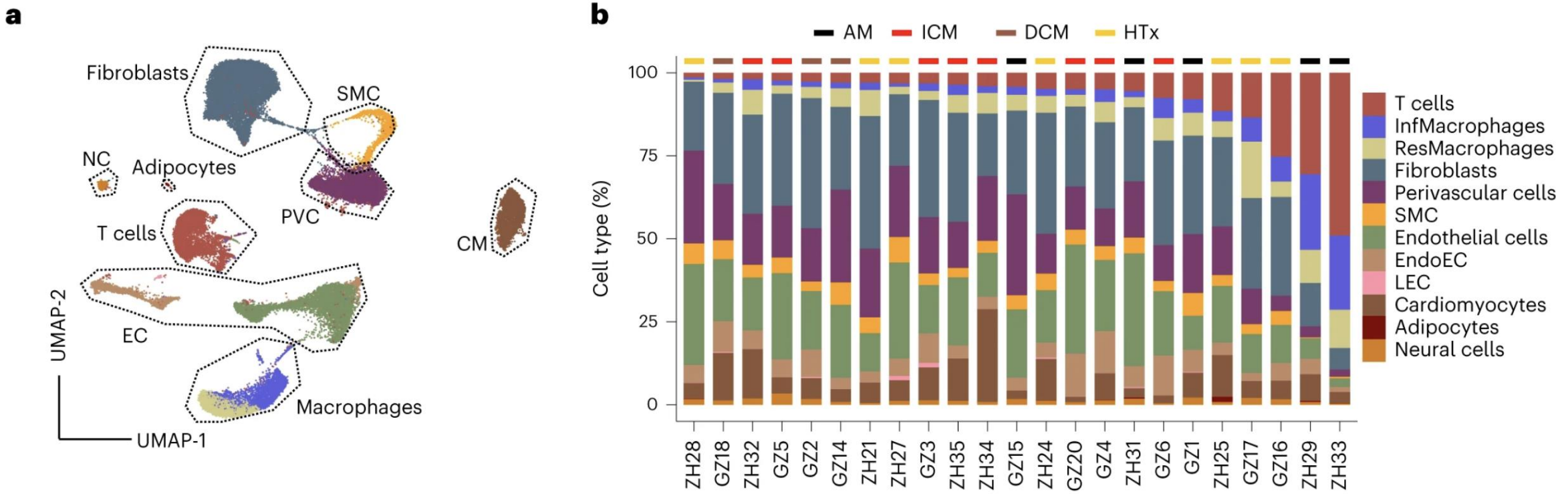

**Acute myocarditis (AM) (*n* = 5)**
**Inflammatory cardiomyopathy (ICM) (*n* = 8)**

**Dilated cardiomyopathy (DCM) (*n* = 3)**
**Heart transplantation (HTx) (*n* = 7)**

USZ Universitäts Spital Zürich

**Perez-Shibayama Nature Cardiovascular Research 2024**

# snRNA-seq from Left or Right Ventricular Endomyocardial Biopsies from Heart Failure Patients

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**Heart transplantation (HTx) (*n* = 7)**

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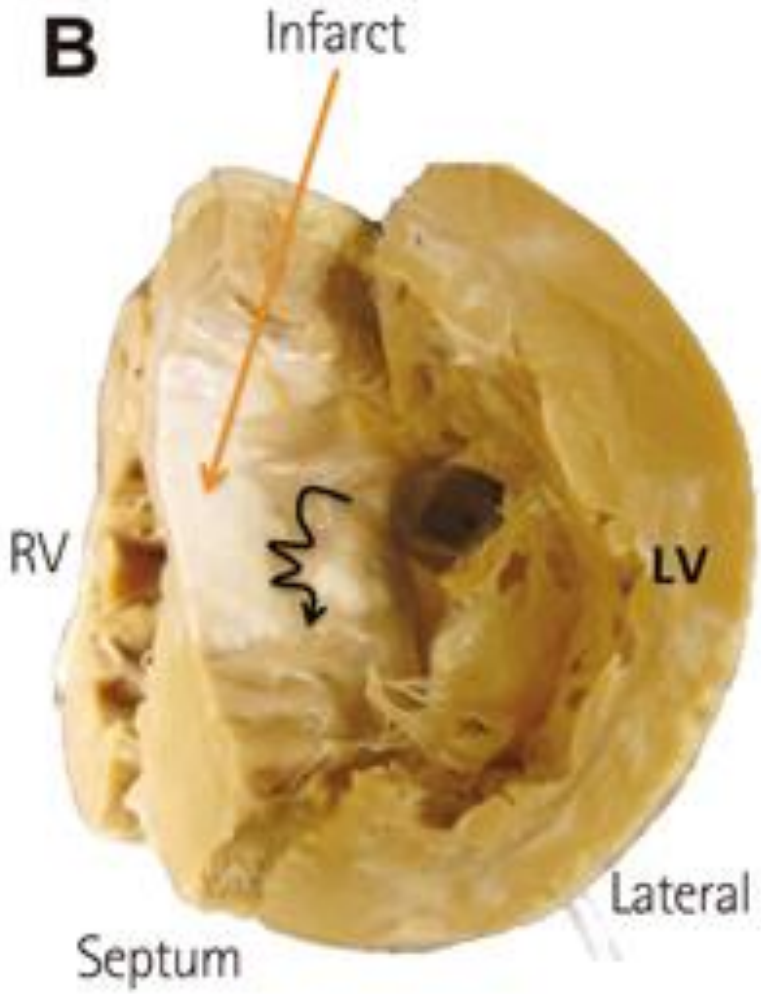
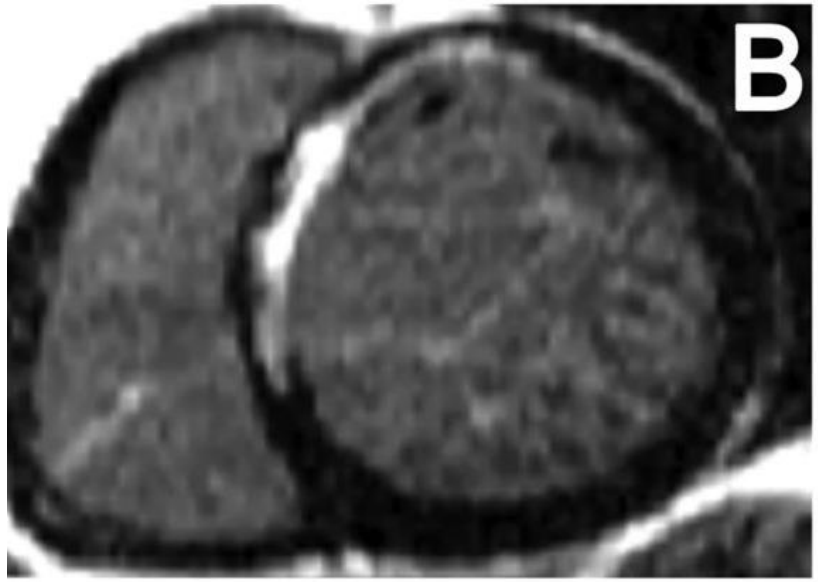
**Perez-Shibayama Nature Cardiovascular Research 2024**

# VT Substrate after Myocardial Infarction




LGE on MRI

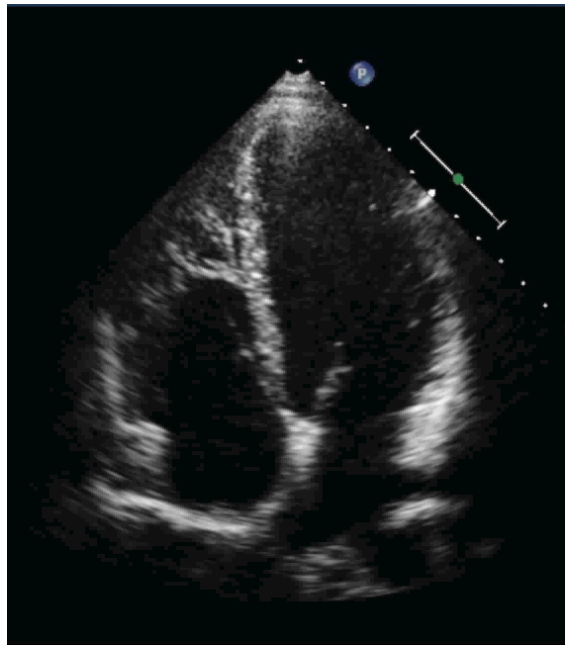


Gerstenfeld et al. Korean Circ J. 2014 Jul;44(4):210-217.

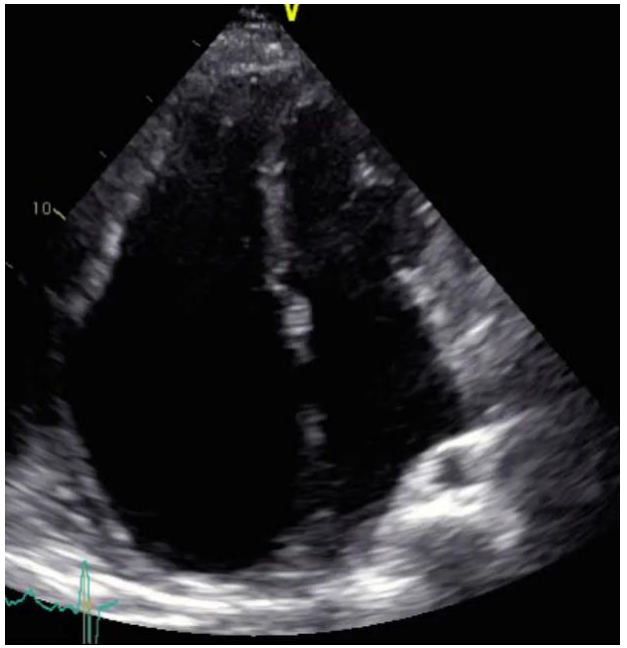
# „*Lone*“ AFib does not exist!

## In Every AFib Patient a Cause, an Atrial Substrate is Present

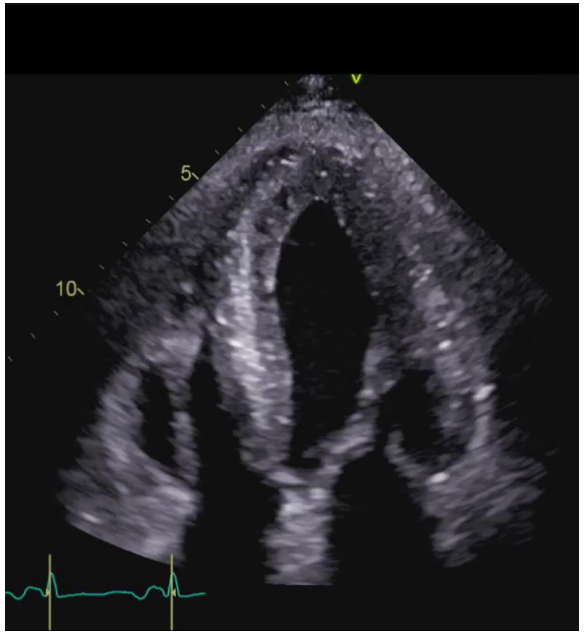
**HFpEF**



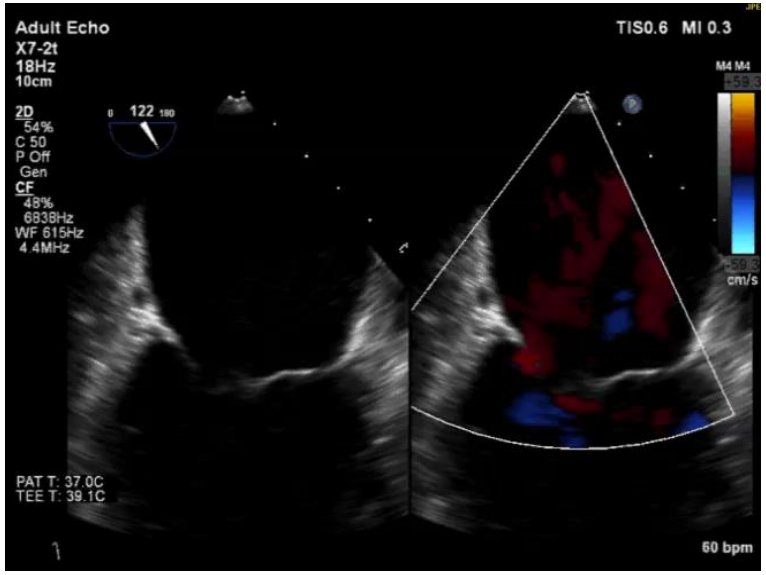
**Restrictive Cardiomyopathy**



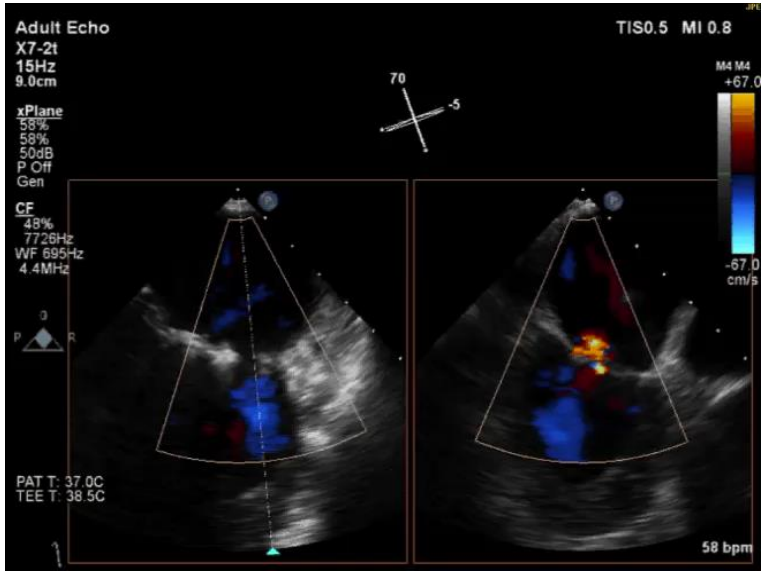
**Cardiac Amyloidosis**



# FMR is Called Secondary MR for a Reason
## It`s a Myocardial, not only a Leaflet Disease




**Severe FMR**
**Patient remains in NYHA III despite optimal drug and CRT therapy**

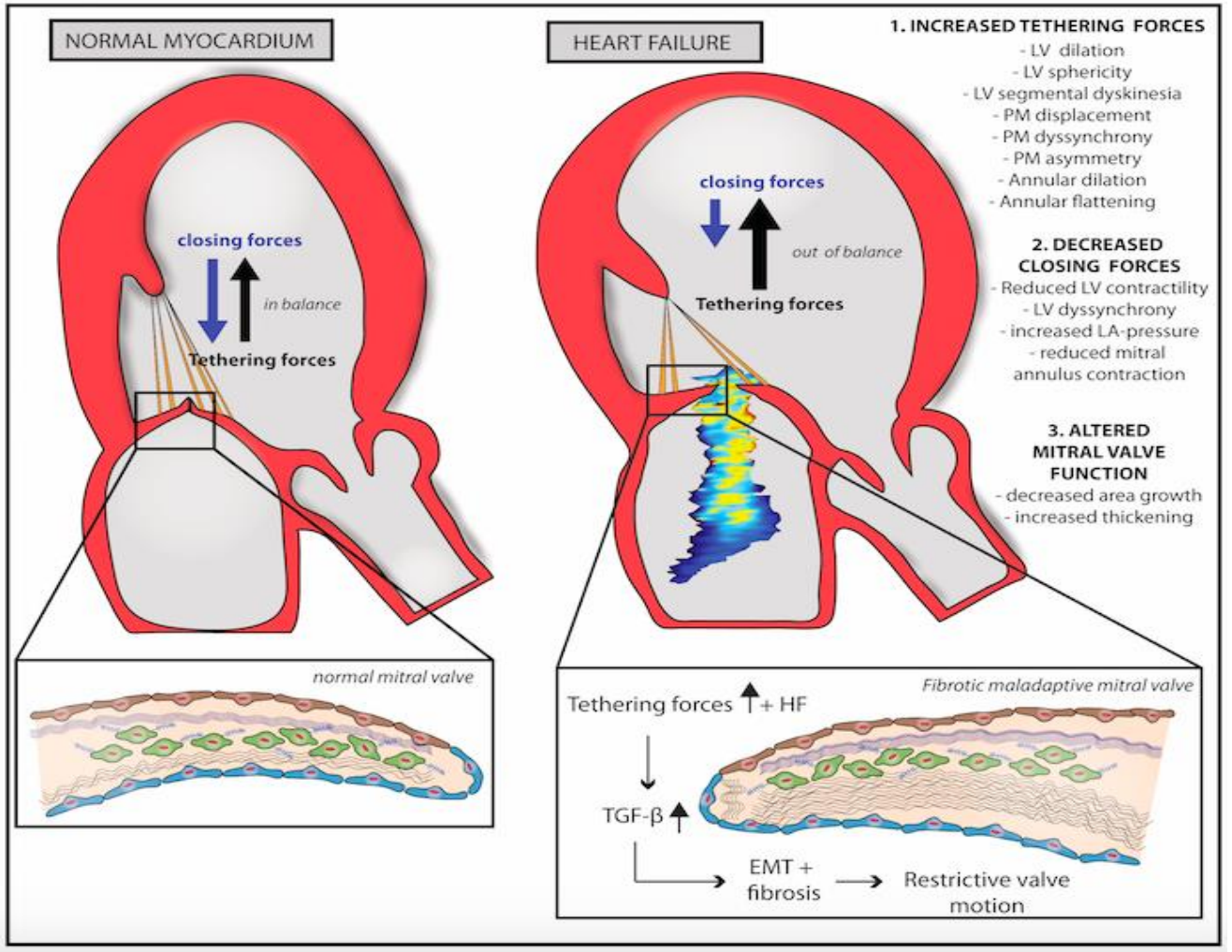



**Result after successful percutaneous MitraClip Implantation**

courtesy Felix Tanner

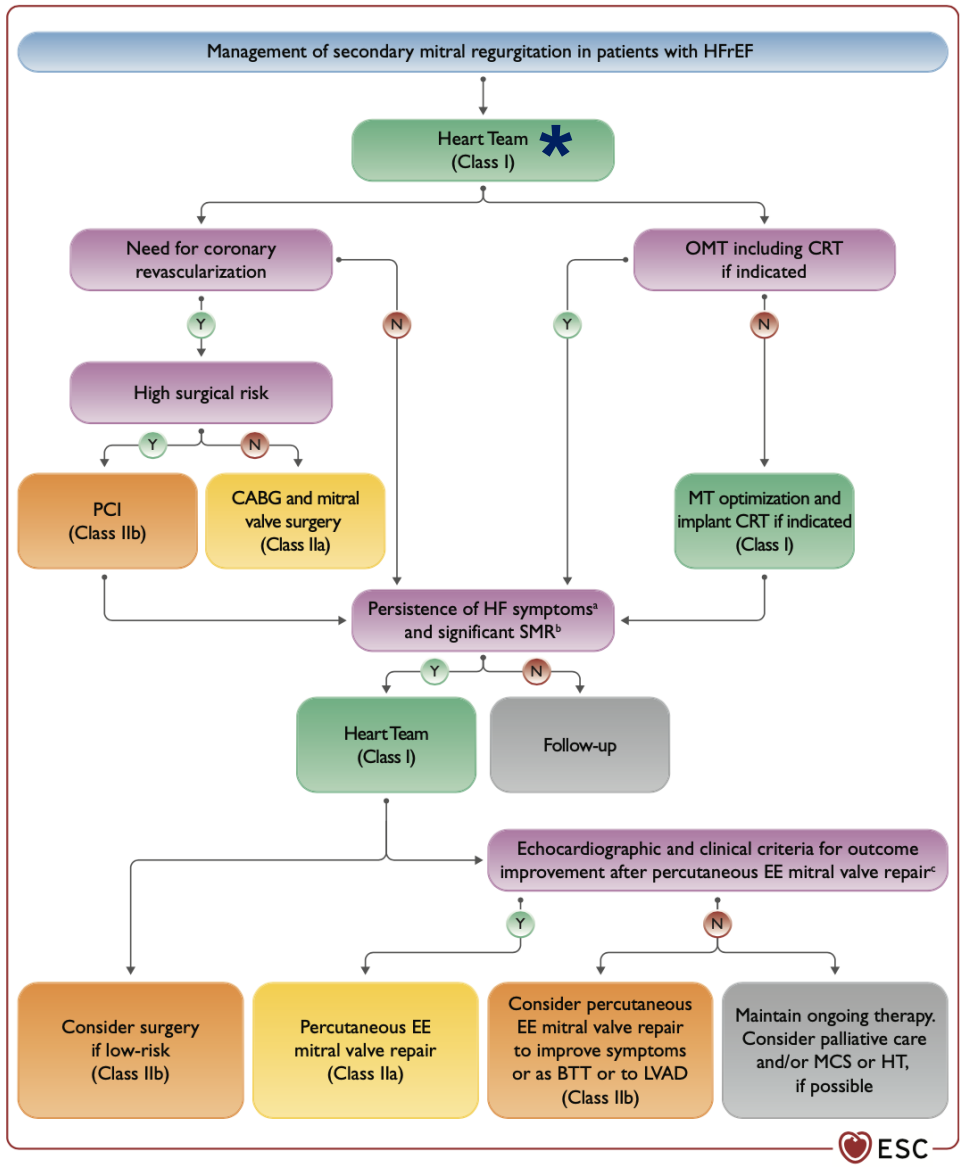
# Functional = Secondary Mitral Regurgitation

## It`s a Disease of the Left Ventricle, not only a Leaflet Disease




Mullens Circulation 2019

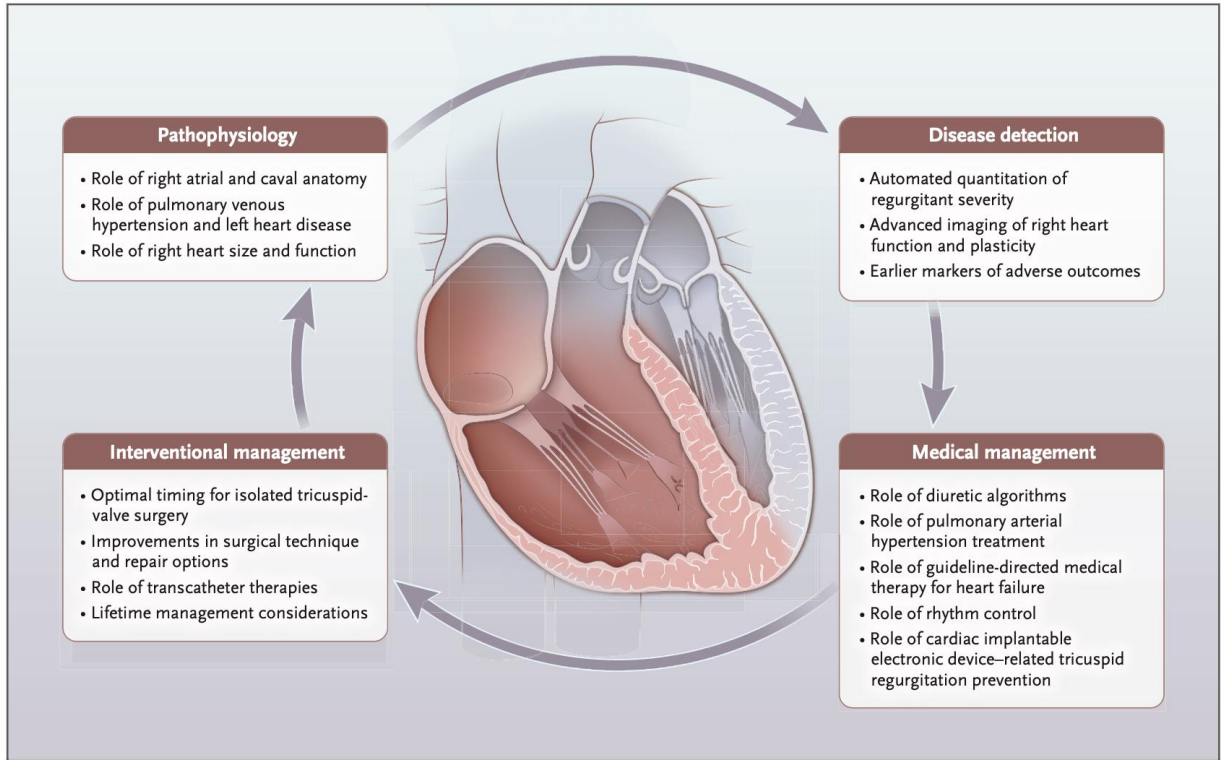
# Management of Secondary Mitral Regurgitation




*
- Heart Failure Specialist
- CV Imager
- Interventionalist
- Surgeon (if primary MR)

ESC HF Guidelines, McDonagh EHJ 2021

# Cardiology is Interventional Physiology


## The "*Dark*" Side of the Moon

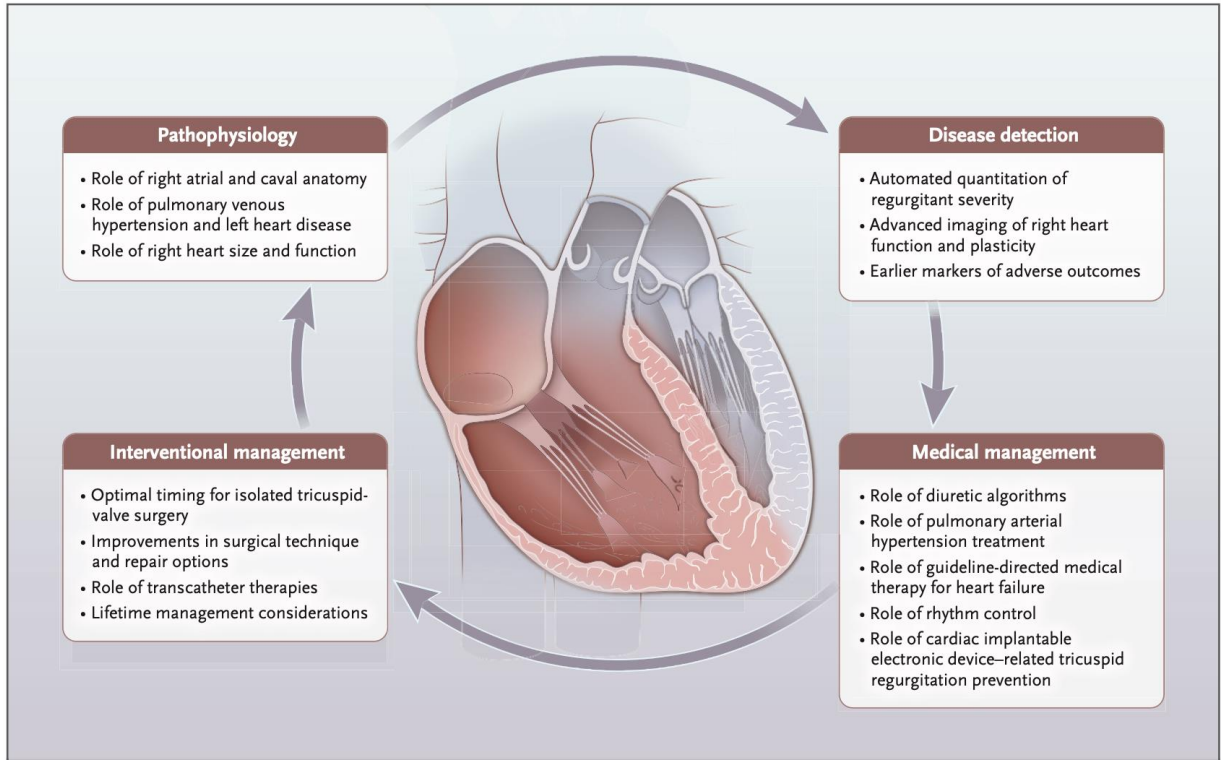
https://www.nasa.gov

Hahn NEJM 2023

USZ Universitäts Spital Zürich

University of Zurich[UZH]

# Understanding the Physiology of the Right Ventricle is Essential for the Adequate Management of Tricuspid Regurgitation


## The "*Dark*" Side of the Moon

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https://www.nasa.gov

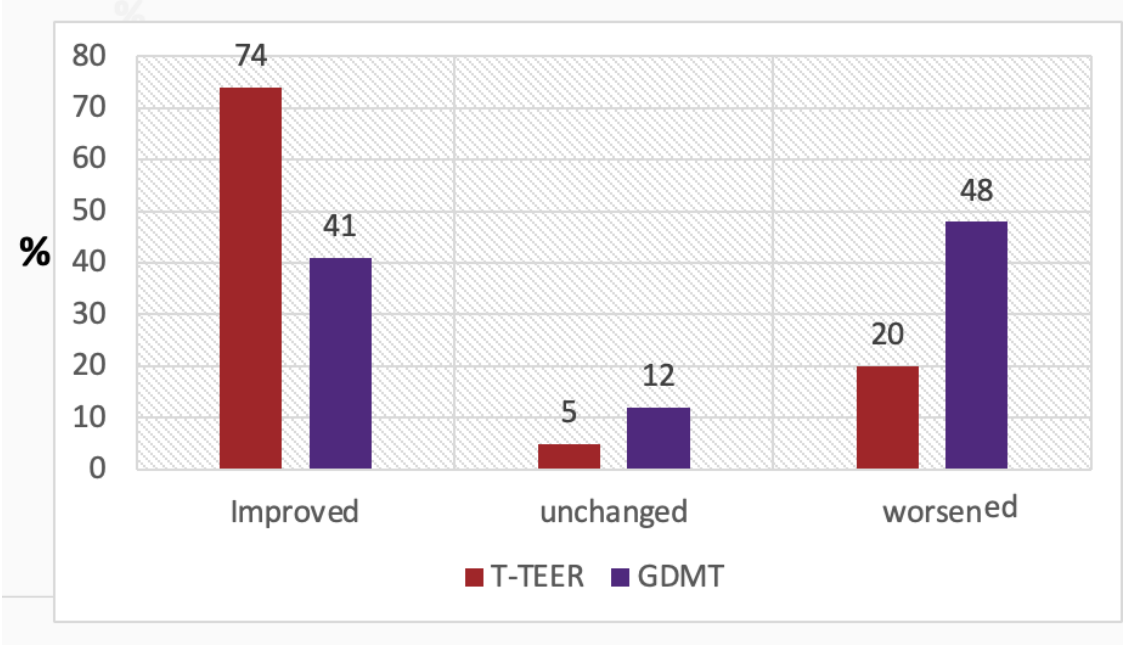
Hahn NEJM 2023

University of Zurich[UZH]

# TRI-Fr: Primary Endpoint

## Hierarchical Clinical Composite Endpoint *driven by an improvement in quality of life (*TEER is not a blinded procedure)

| Hierarchical Clinical Composite Endpoint | Control N = 148 | T-TEER N = 152 |
|---|---|---|
| **Improved** | | |
| Favorable change in NYHA class , n | 39 | 70 |
| Mild, moderate or marked improvement on PGA (< 4) , n | 19 | 39 |
| **Worsened** | | |
| Unscheduled hospitalization for HF , n | 20 | 15 |
| Died, n | 8 | 5 |
| Unfavorable change in NYHA-class at last visit, n | 15 | 3 |
| Slight, moderate or marked worsening on PGA (> 4), n | 25 | 7 |
| **Unchanged**: none of the above, n | 17 | 8 |
| Missing | 5 | 5 |

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Donal et al. presented at ESC 2024

# Hierarchical Composite Endpoint/MCE

## No differences in the incidence of death or hospitalization for heart failure at 1 year

| Hierarchical Clinical Composite Endpoint | Control N = 148 | T-TEER N = 152 |
|---|---|---|
| **Improved** | | |
| Favorable change in NYHA class , n | 39 | 70 |
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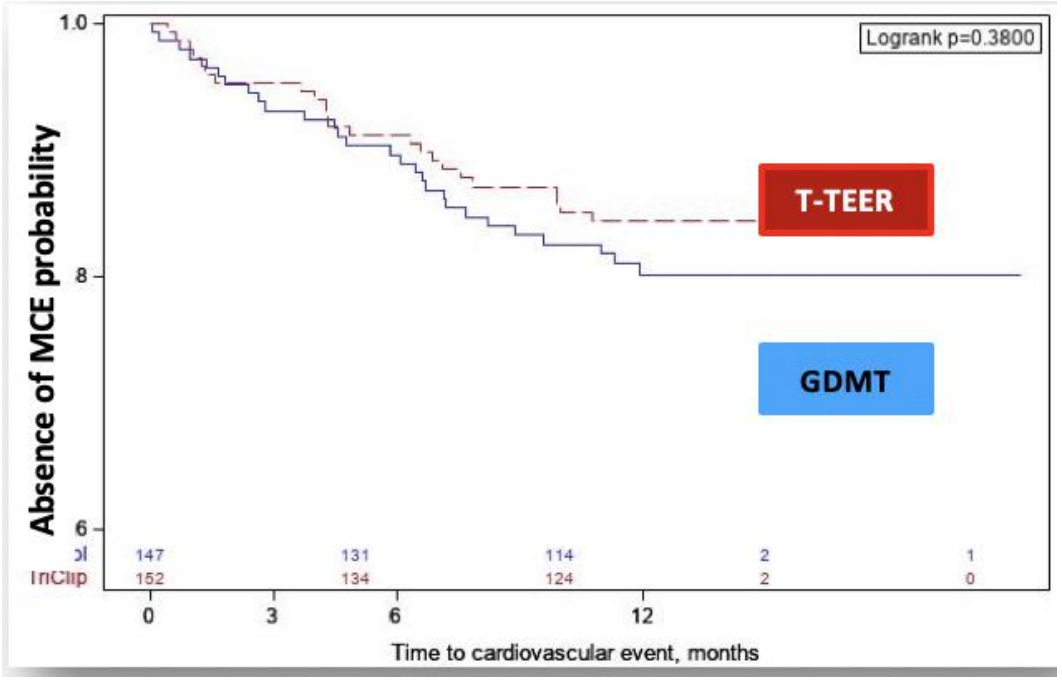


**one-year mortality 3.4%**

**Major cardiovascular events during the one-year follow-up** (MCE): myocardial infarction, or unstable angina, or revascularization, or stroke, or cardiovascular death, or heart failure hospitalization

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**Donal et al. presented at ESC 2024**

# TRI-Fr included Patients with HFpEF, HFmrEF, HFimpEF

| Baseline Characteristics | Overall N = 300 | GDMT N = 148 | T-TEER N = 152 |
|---|---|---|---|
| **Gender**, Male, no (%) | 109 (36.3) | 55 (37.2) | 54 (35.5) |
| **Age**, years | 78.5 ± 6.37 | 78.7 ± 6.39 | 78.3 ± 6.39 |
| Body Mass Index, Kg/m² | 25.1[22.7; 28.7] | 25.0[22.8;28.9] | 25.2[22.4; 28.7] |
| Heart Rate, beat per minute | 73.7 ± 14.5 | 74.9 ± 13.3 | 72.5 ± 15.4 |
| New York Heart Association classification, n (%) | | | |
| II (%) | 170 (56.7) | 77 (52.0) | 93 (61.2) |
| III (%) | 122 (40.7) | 64 (43.2) | 58 (38.2) |
| Severe renal failure (eGFR < 30 mL/min), n (%) | 19 (6.63) | 6 (4.05) | 13 (8.55) |
| Arterial hypertension, n (%) | 208 (69.3) | 102 (68.9) | 106 (69.7) |
| Prior (< 1 year) heart failure hospitalization, n (%) | 121 (40.3) | 66 (44.6) | 55 (36.2) |
| **Permanent pacemaker** (PM/CRT/ICD), n (%) | 44 (14.7) | 23 (15.5) | 21 (13.8) |
| **Atrial fibrillation**, n (%) | 285 (95.0) | 142 (95.9) | 143 (94.1) |
| Any prior mitral intervention, n (%) | 33 (11.0) | 16 (10.8) | 17 (11.2) |
| Any prior aortic intervention, n (%) | 32 (10.7) | 14 (9.46) | 18 (11.8) |
| **Right heart catheterization** | | | |
| Mean Pulmonary Artery Pressure, mm Hg | 22.4 ± 6.58 | 22.6 ± 6.69 | 22.2 ± 6.44 |
| Mean Right Atrial Pressure, mm Hg | 9.48 ± 4.98 | 10.0 ± 5.54 | 8.93 ± 4.31 |
| **Six-minute Walk Test** , m | 305 ± 108 | 309 ± 112 | 302 ± 104 |
| Massive or Torrential Tricuspid regurgitation, n (%) | 269 (89.7) | 135 (91.2) | 134 (88.2) |
| Left Ventricle Ejection Fraction, % | 57 [50; 64] | 58[50; 65] | 57[50; 63] |

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**Donal presented at ESC 2024**

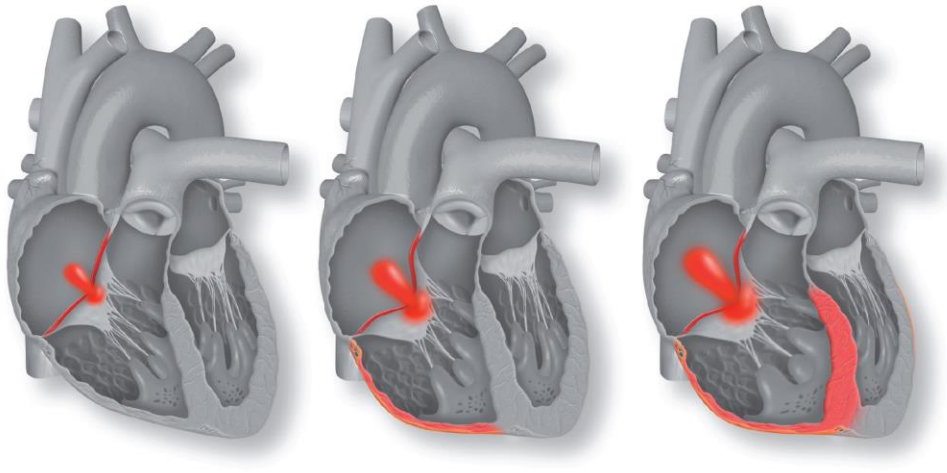
**Inclusion criterion LVEF>35%**

# Secondary Tricuspid Regurgitation

## The underlying LV pathology is commonly missed, and heart failure symptoms are wrongly attributed to TR

**Secondary Tricuspid Regurgitation**

**HFpEF / HFmrEF / HFrEF**



**Phase I**
- Increased RV systolic pressure
- sPAP ↑
- RV dilatation
- TV annular dilatation

**Phase II**
- Progressive RV dilatation
- RA dilatation
- TV annular dilatation

**Phase III**
- RV dilatation and distortion
- sPAP ↑
- RA dilatation
- TV annular dilatation
- Tethering of TV leaflets

**Bartko PE et al, EHJ 2020**

| Baseline Characteristics | Overall N = 300 | GDMT N = 148 | T-TEER N = 152 |
|---|---|---|---|
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**Donal presented at ESC 2024**

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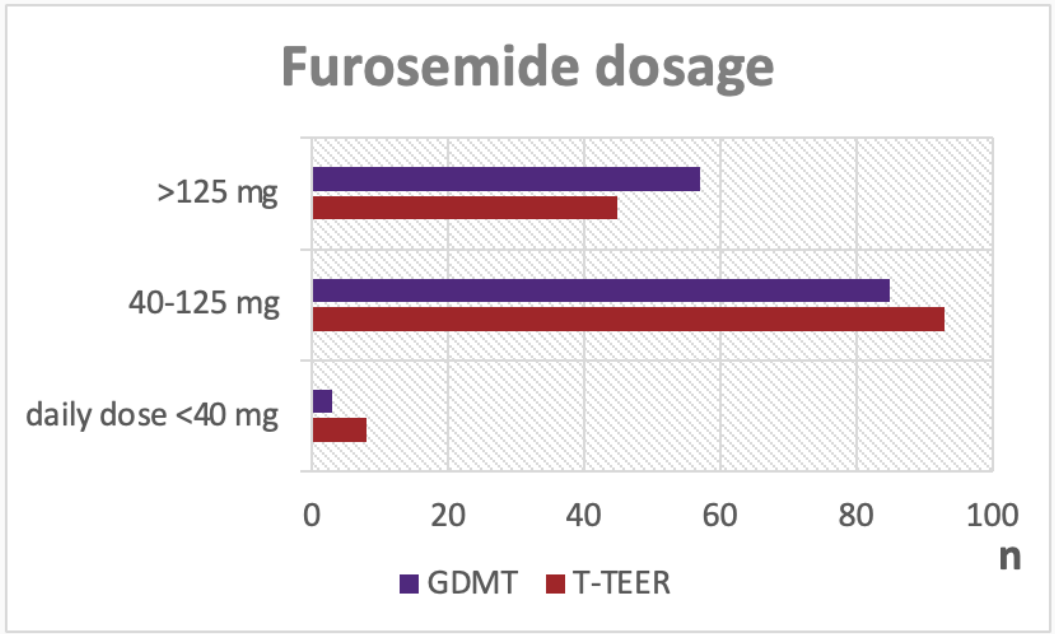
# TRI-Fr: Medical Treatment

| Number of patients receiving | GDMT | T-TEER |
|---|---|---|
| MRA | 80 | 70 |
| ACE-i/ARA-II/ARNI | 61 | 56 |
| Post rando | 15 | 17 |
| BBlocker | 110 | 107 |
| SGLT2-I | 23 | 16 |
| Post rando | 14 | 15 |
| Diuretics (Furosemide /hydrochlorothiazide) | 143 /17 | 145 /14 |



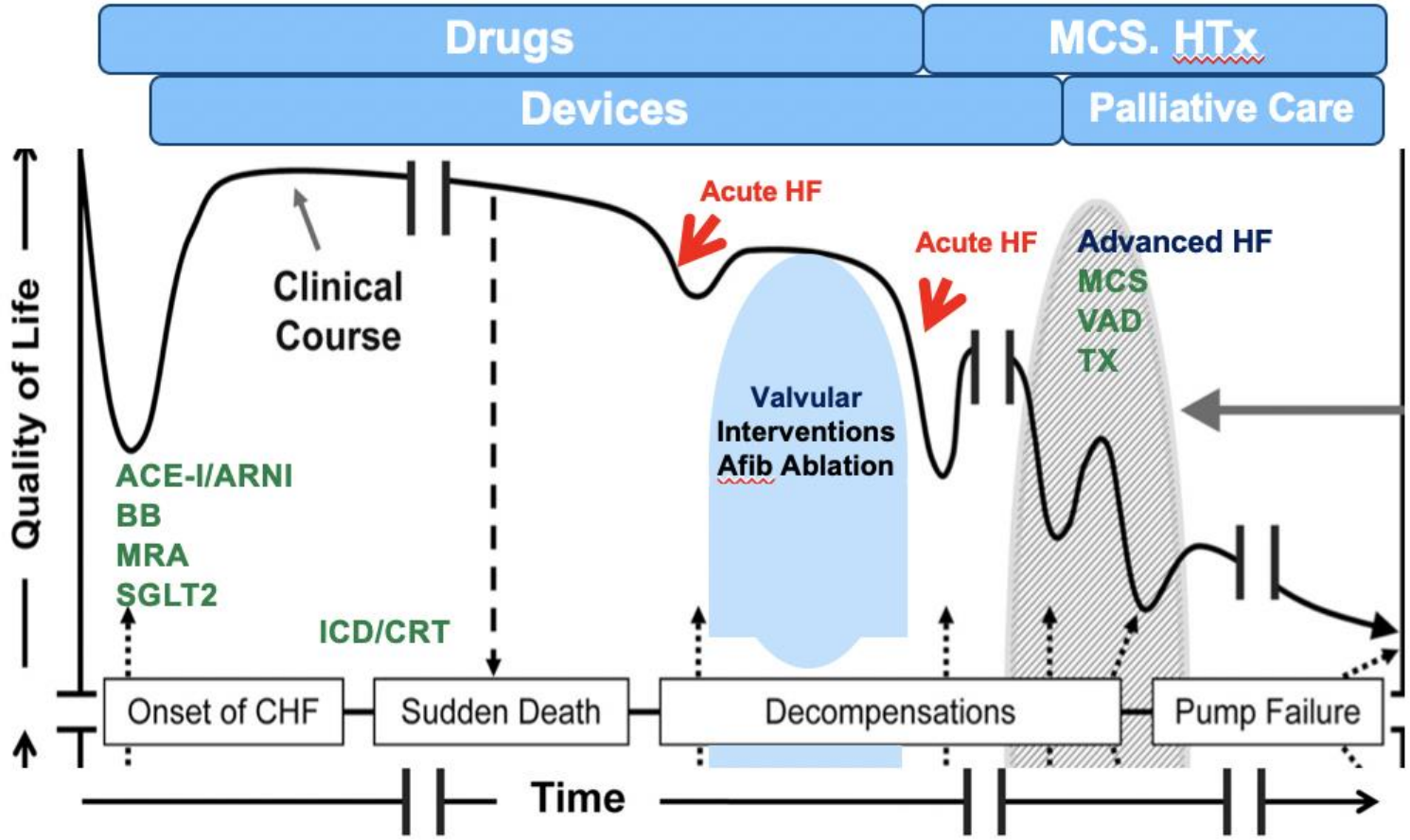

- Relatively low number of patients receiving SGLT2 and/or MRA
- **Change of Average Total Daily Equivalent Dosage (mg) vs Baseline?**



**Donal presented at ESC 2024**

# The 8 Rights in Heart Failure

## Right Patient, Right Drug, Right Device, Right Intervention, Right Dose, Right Route, Right Time, Right Doctor(s), Right Heart




Ruschitzka HFA Advanced HF Course Vienna 2023
mod. after Allen Circulation 2012

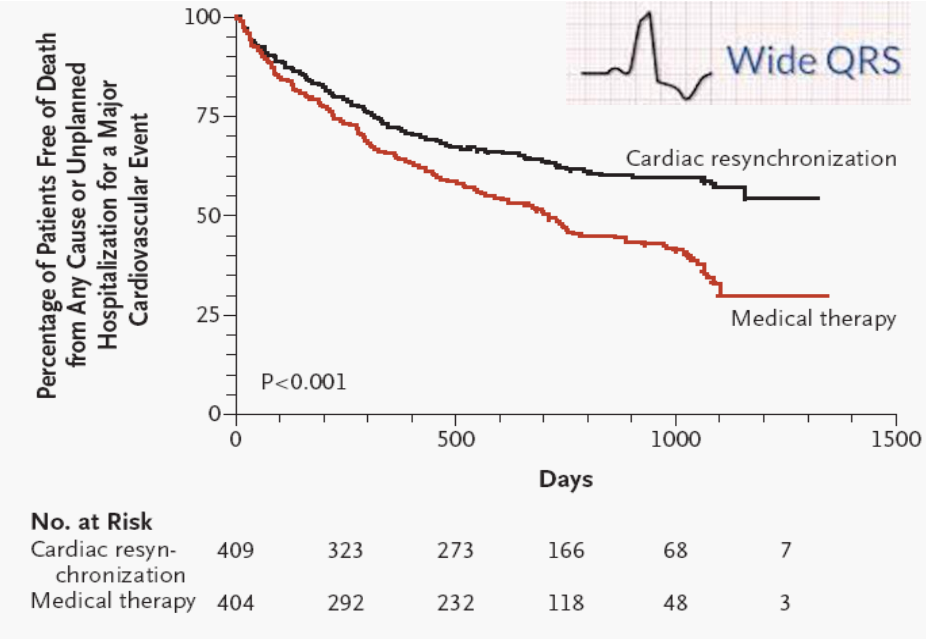
USZ Universitäts Spital Zürich

University of Zurich[UZH]

# Lessons Learned from Cardiac Resynchronisation Therapy

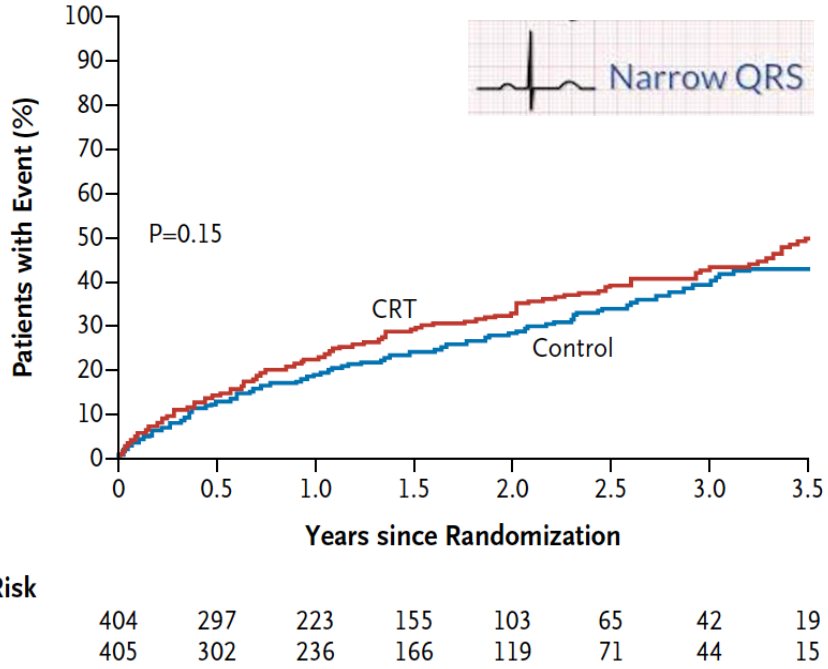
## Deep Phenotyping, Define the Sweet Spot for Benefit and Team Up!

### CARE-HF




Cleland J, et al. NEJM 2005

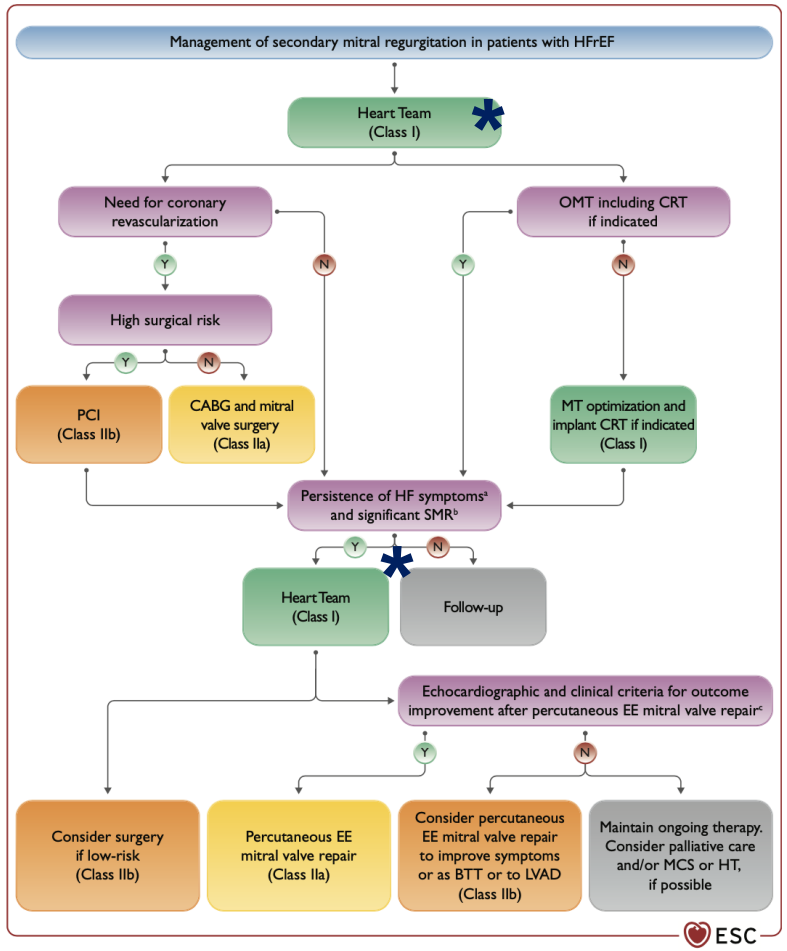
### EchoCRT



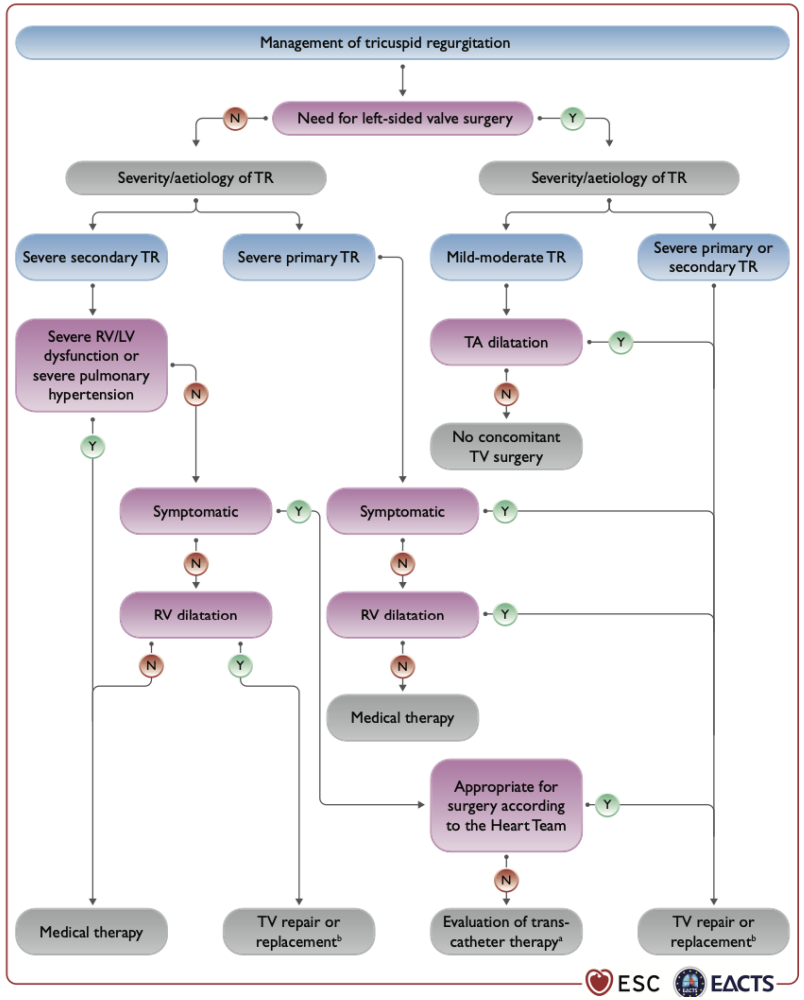

Ruschitzka F., et al. NEJM 2013

# Synergy of Drugs, Device and Interventions in Heart Failure

## Collaborative heart teams provide the best possible care




* Heart Failure Specialist
CV Imager
Interventionalist
Surgeon (if primary MR)




ESC HF Guidelines, McDonagh EHJ 2021

# Thank you

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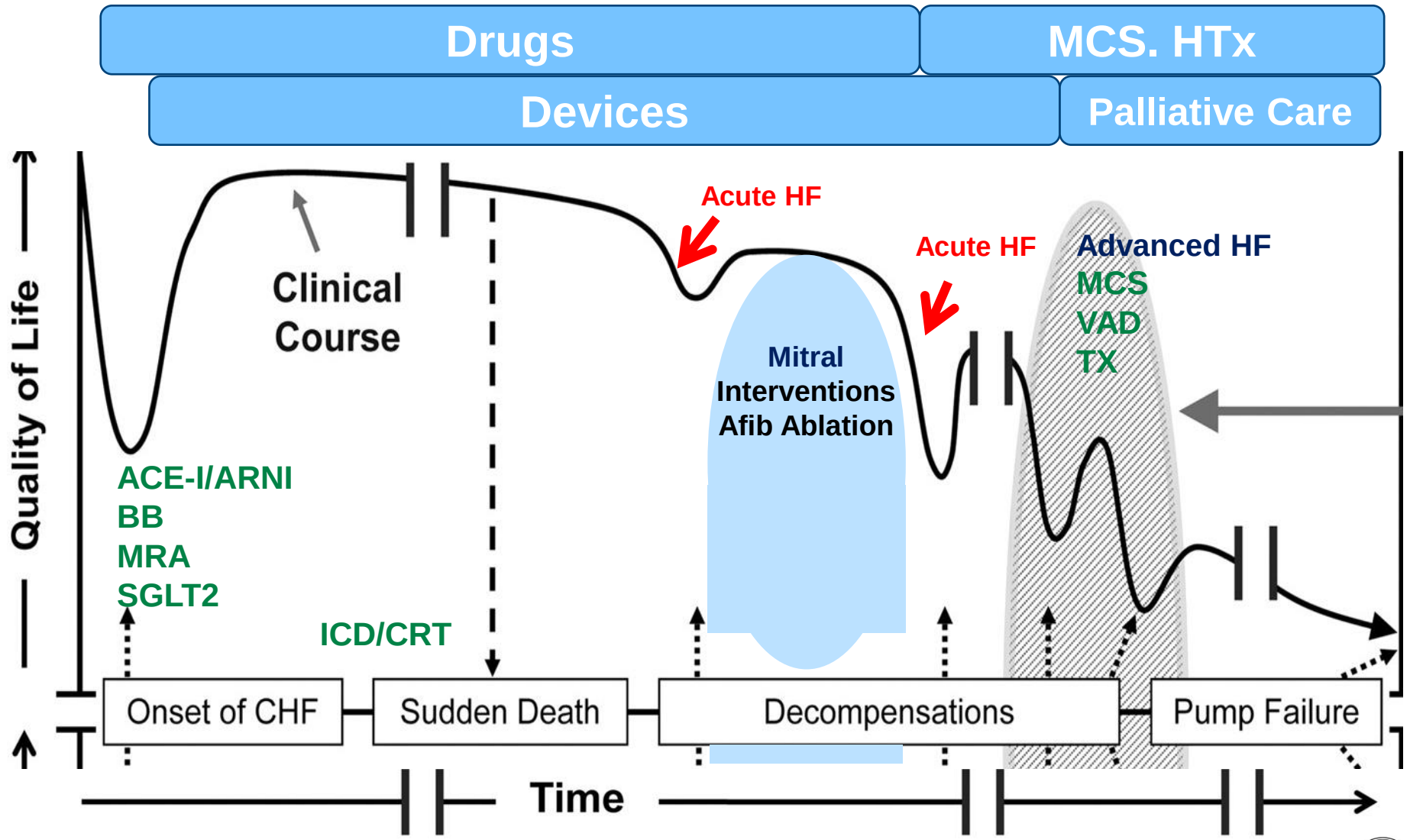
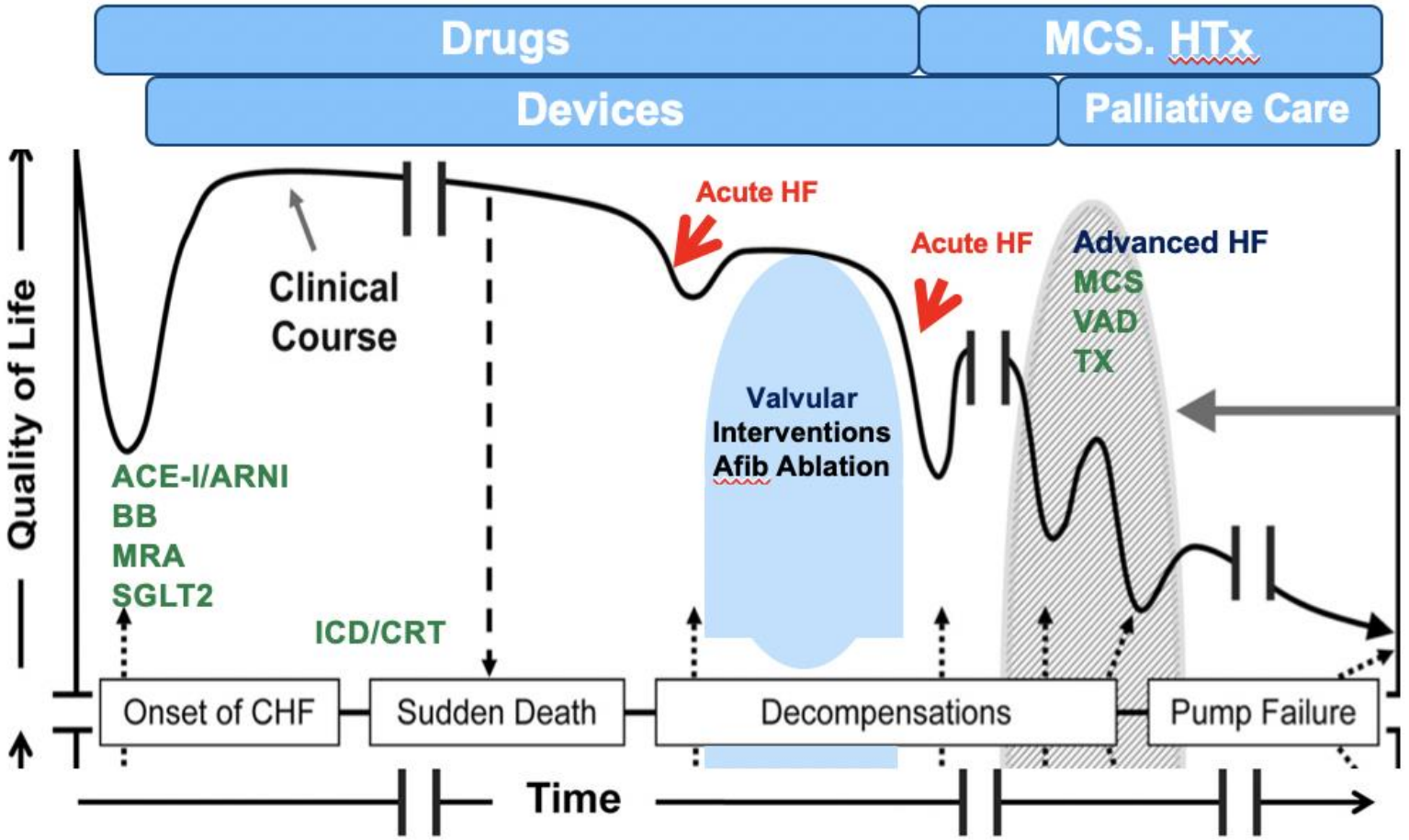
# Synergy of Drugs, Device and Interventions in Heart Failure




Ruschitzka ESC 2021
mod. after Allen Circulation 2012

# Management of Heart Failure is an Art

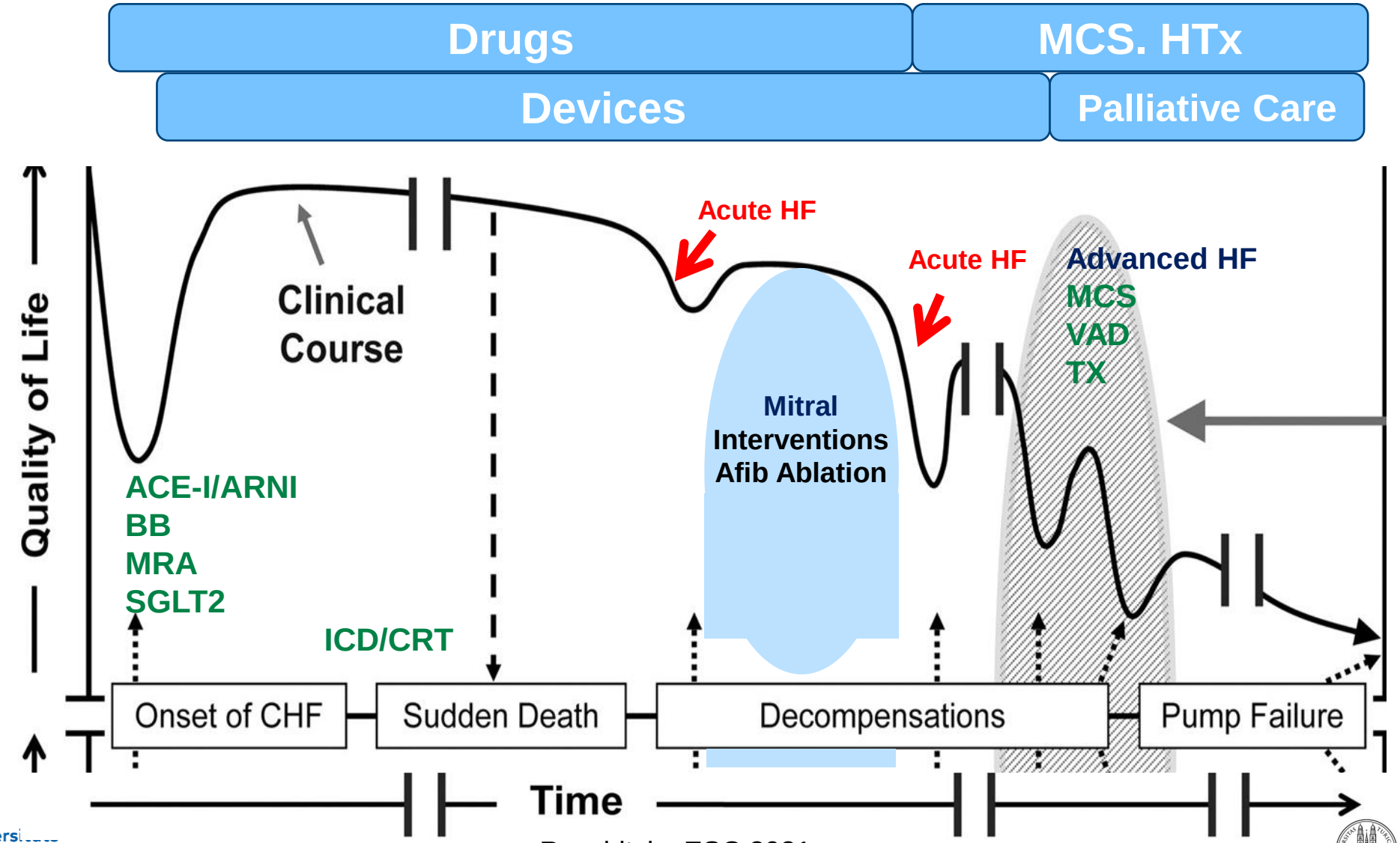
## Synergy of Drugs, Device and Interventions



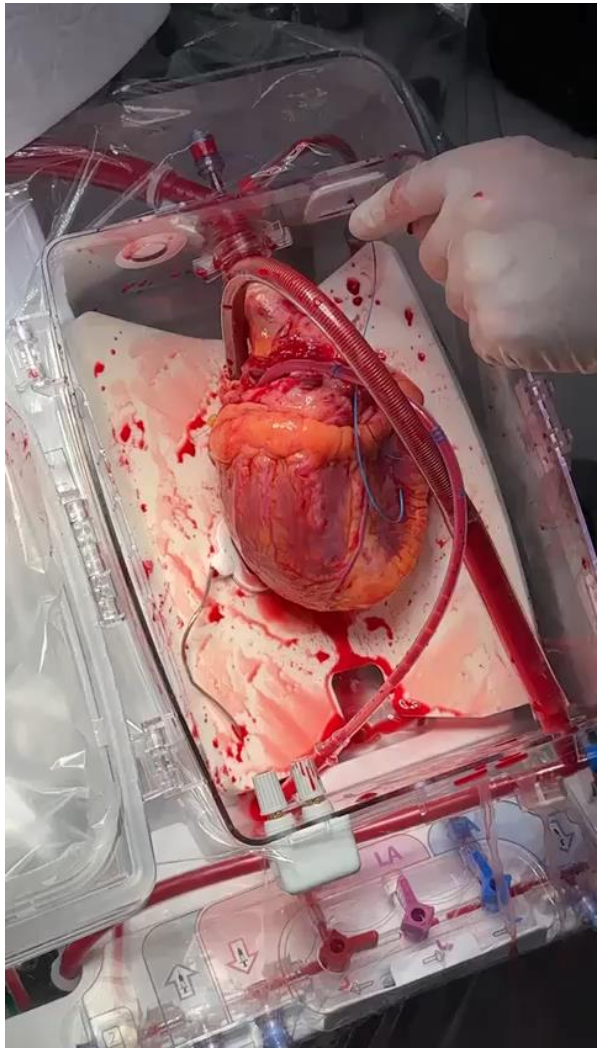

Ruschitzka ESC 2018
mod. after Allen Circulation 2012

# Synergy of Drugs, Device and Interventions in Heart Failure

## Team up, Deep Phenotype and Define the Sweet Spot for Benefit!




Ruschitzka ESC 2021
mod. after Allen Circulation 2012



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# Multicentric Randomized Evaluation of a Tricuspid Valve Percutaneous Repair System in the Treatment of Severe Tricuspid Regurgitation (TRI-Fr): *Discussant*


**Frank Ruschitzka**
**Professor and Chairman, Department of Cardiology**
**University Hospital Zurich, Switzerland**


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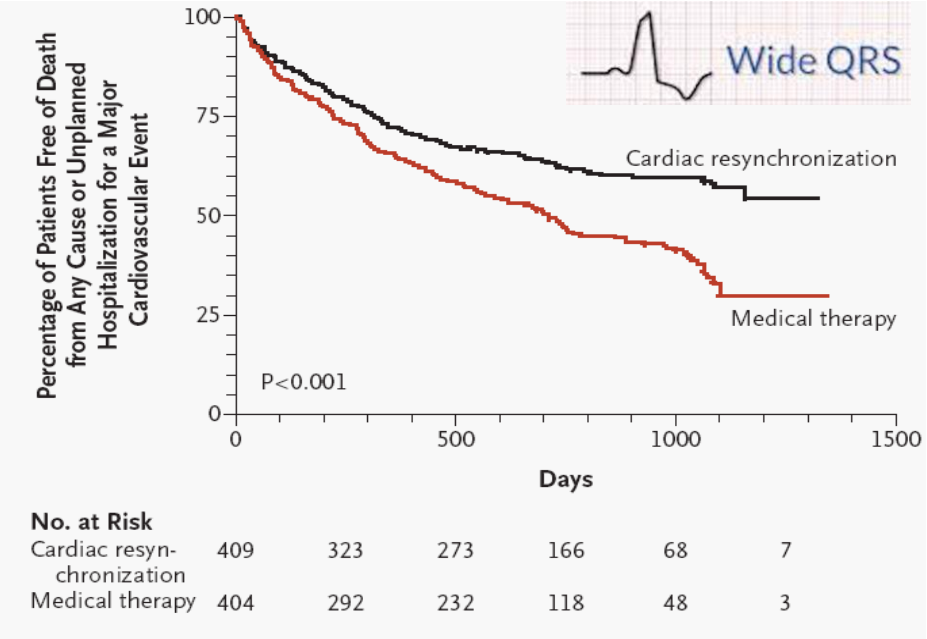
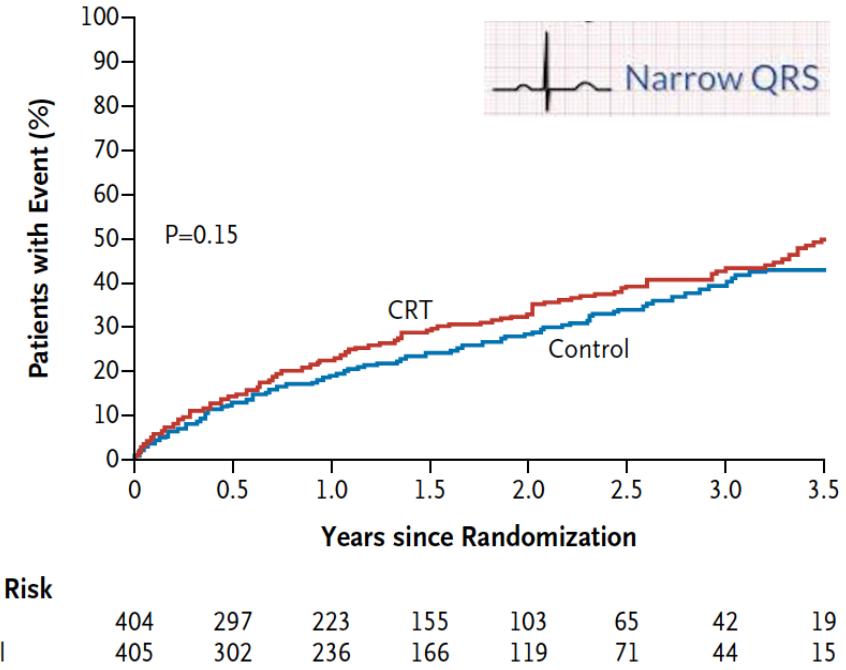
# Cardiac Resynchronisation Therapy (CRT)
## Live Saving Therapy in Wide QRS

### CARE-HF




Cleland J, et al. NEJM 2005

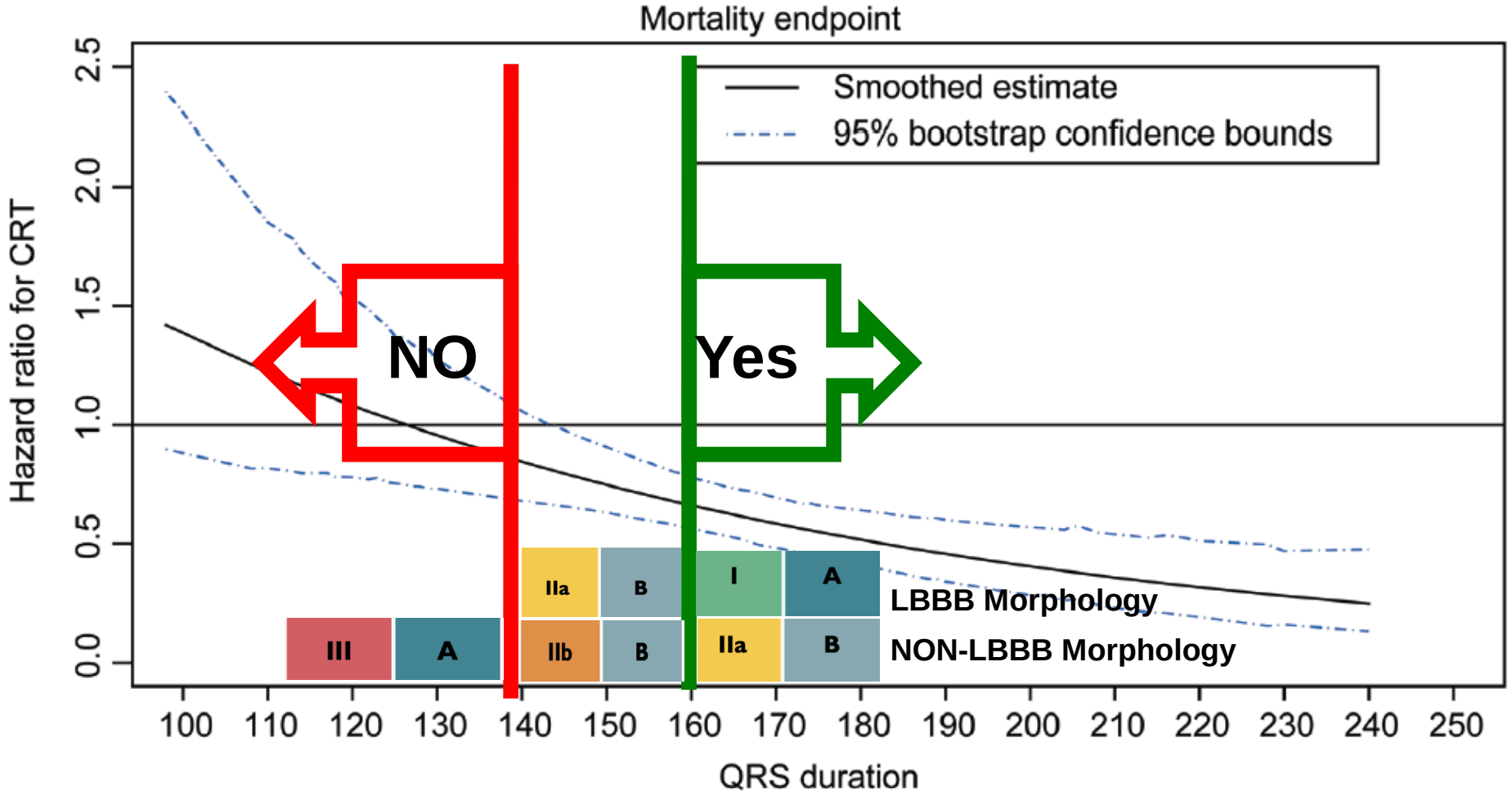
### EchoCRT




Ruschitzka F., et al. NEJM 2013

# Lessons Learned from CRT

## Lesson I: Define the Sweet Spot for Benefit!




Ruschitzka NEJM 2013
Cleland EHJ 2013
McDonagh EHJ 2021

# *In Medicine, There Is No Such Thing as an Unmitigated Good...*

"this 'all or nothing' is in my opinion necessary for religious communities and useful for political parties...but for science I consider it harmful"

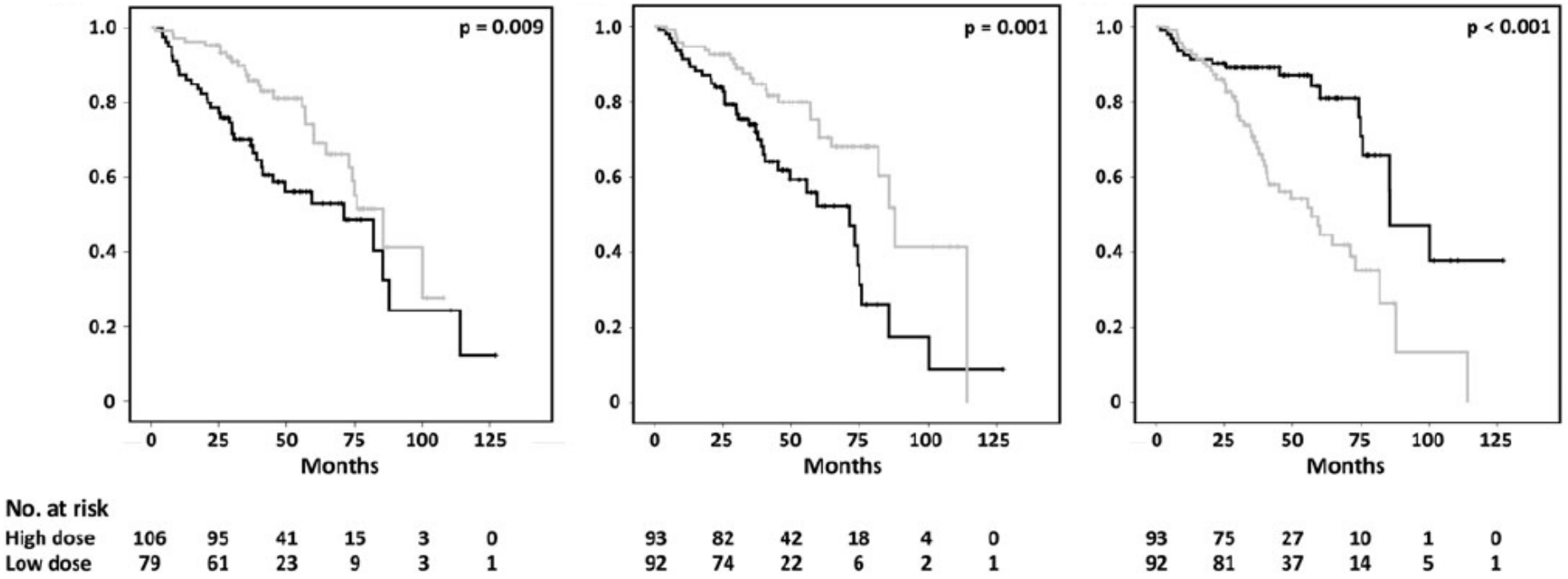
*(Eugen Bleuler, Zürich, 1911*
*...in a letter to Sigmund Freud)*


Obtained with image and/or portrait rights

# Lessons Learned from CRT

## Lesson II: Team Up! Synergy of Drugs, Devices and Interventions

**ACE-Inhibitors** **Betablockers** **Diuretics**

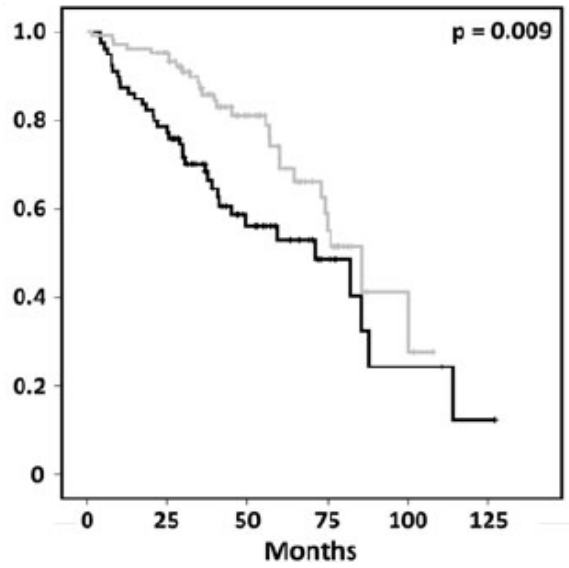



Steffel EHJ 2014

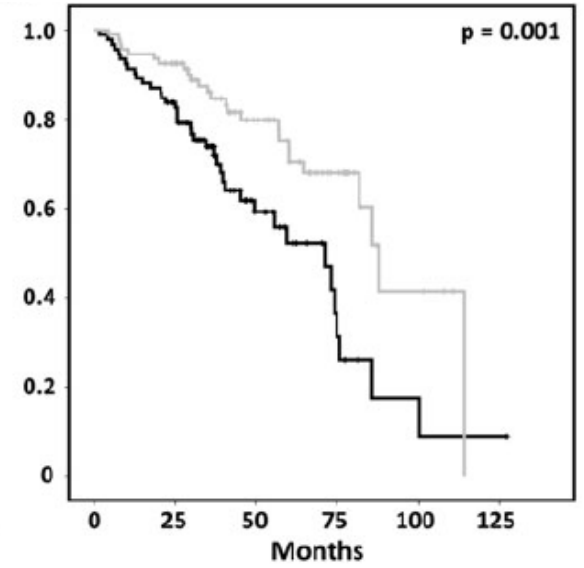
# Lessons Learned from CRT

## Higher dosages of heart failure medication are associated with improved outcome following CRT

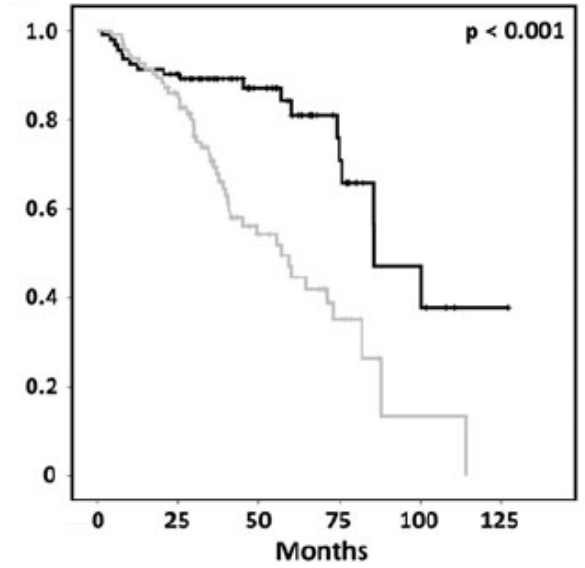
### ACE-Inhibitors




### Betablockers




### Diuretics

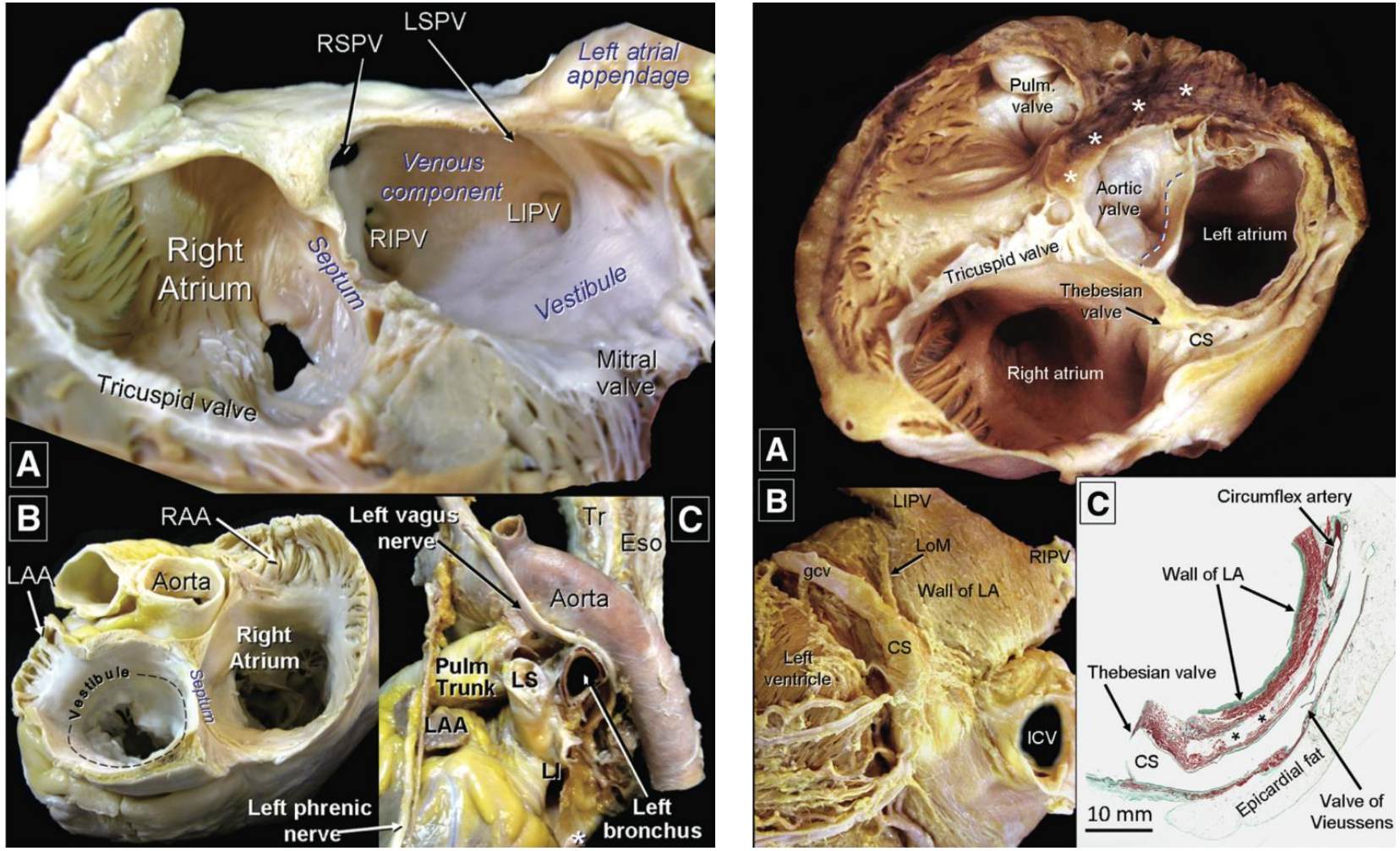



| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| High dose | 106 | 95 | 41 | 15 | 3 | 0 | 93 | 82 | 42 | 18 | 4 | 0 | 93 | 75 | 27 | 10 | 1 | 0 |
| Low dose | 79 | 61 | 23 | 9 | 3 | 1 | 92 | 74 | 22 | 6 | 2 | 1 | 92 | 81 | 37 | 14 | 5 | 1 |

Steffel EHJ 2014

# The Left Atrium is Prime Real Estate

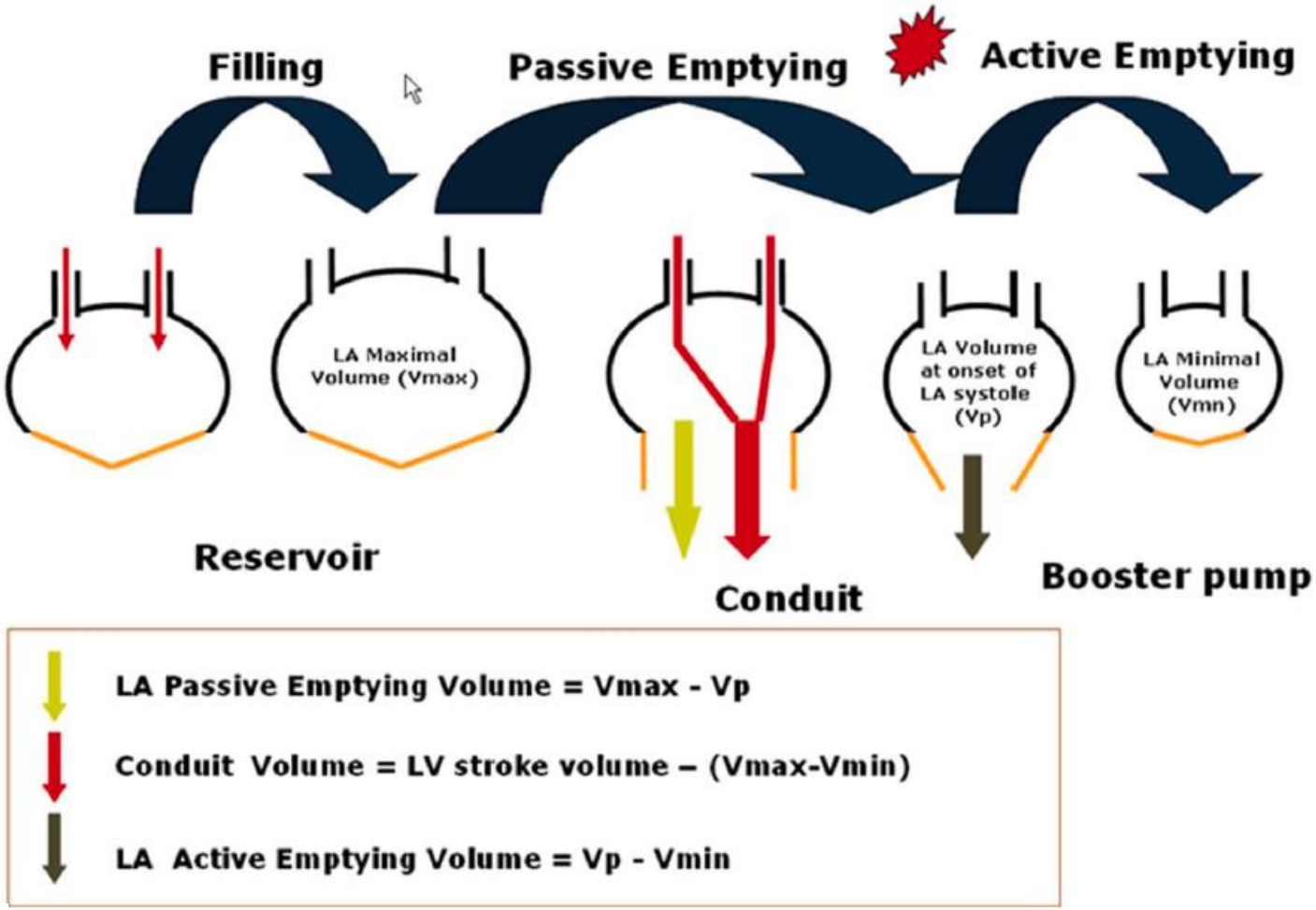
## Reservoir, Conduit, "Contractile Chamber"




Ho Circ EP 2012

# The Left Atrium is a Multitasker

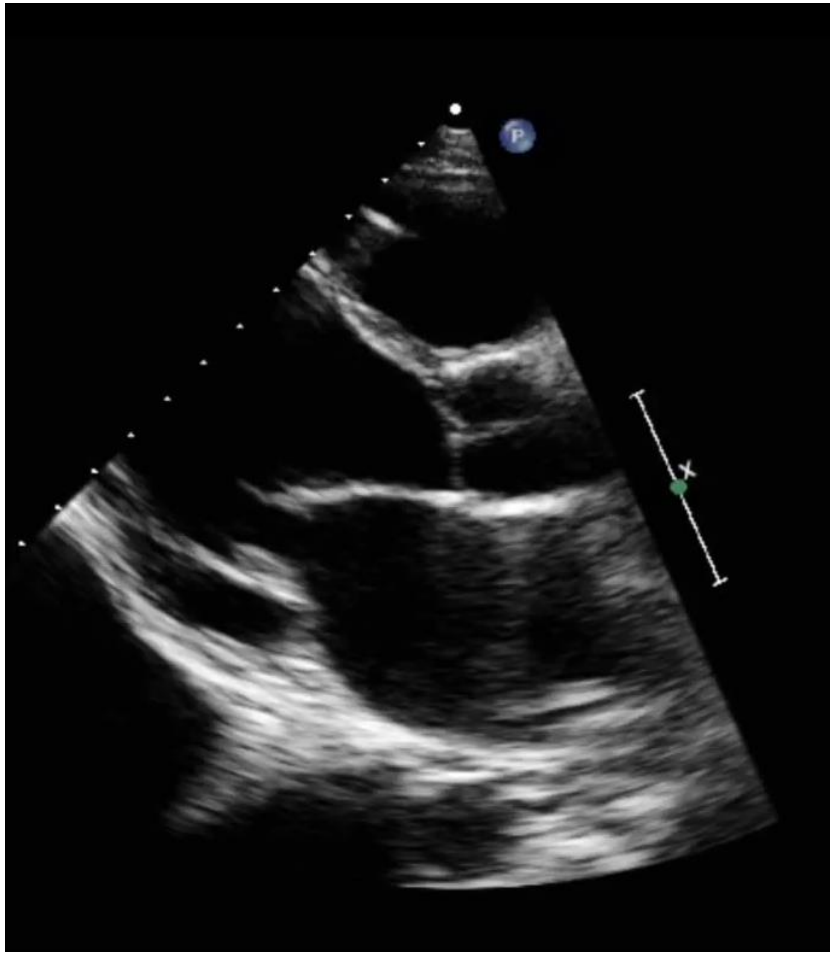
## Reservoir, Conduit, “Contractile Chamber”

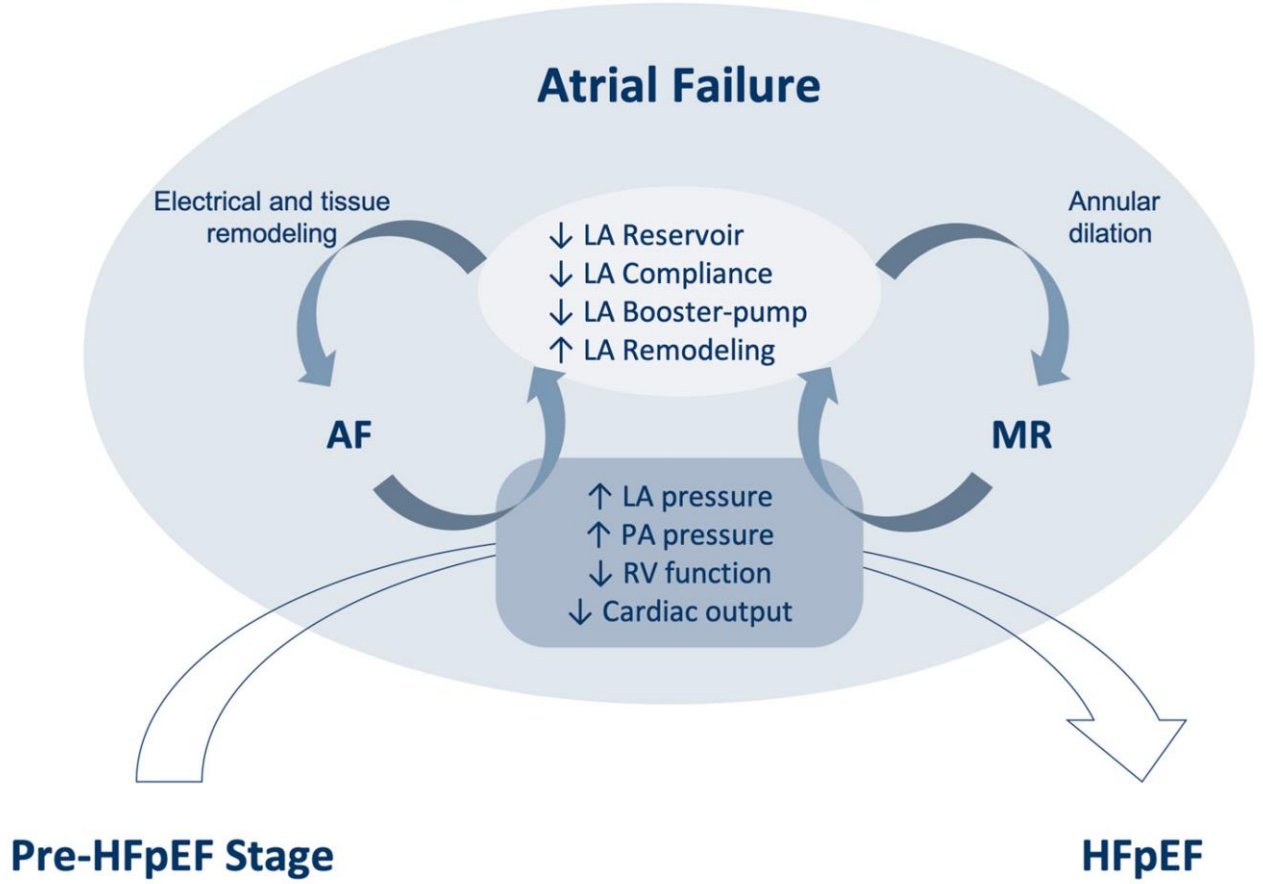



Rossi Circ HF 2014

# Left Atrial Disease

## Time to Move to a Substrate Concept of Atrial Fibrillation






Ruschitzka HFA 2017
HFA Consensus Paper EHJ 2022
Bayes-Genis A et al, J Cin Med 2020

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# Declaration of Interest

- No personal payments by pharmaceutical companies or device manufacturers
- Remuneration for the time spent in activities, such as participation as member in steering committees of clinical trials were made directly to the University of Zurich
- Research Contracts
  - Payments directly to the University of Zurich and University Hospital of Zurich
  - Postgraduate Heart Failure Course (Abbott, Novartis, Bayer, Servier, AstraZeneca, Roche Diagnostics)

# Merci

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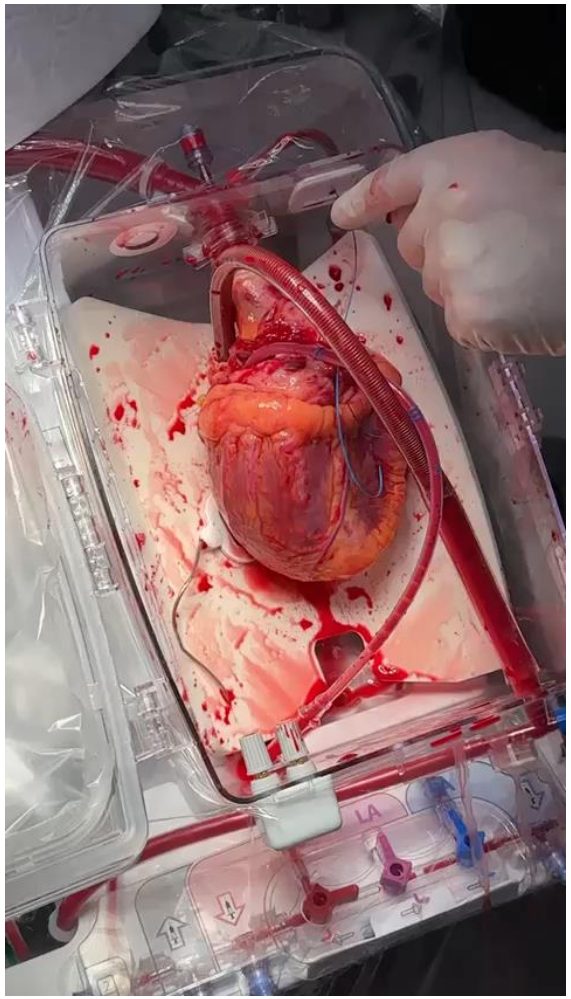
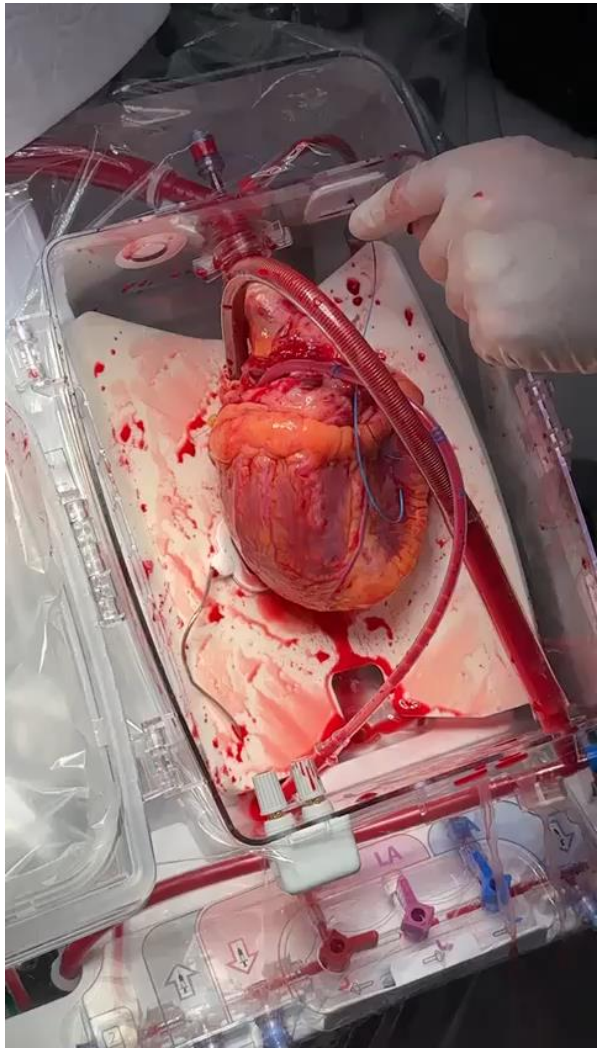
# Unser Herz - Ein Wunderwerk der Natur



**100`000 Schläge/Tag**
**>3`000`000`000 beats per life**

**6000 l/Tag**
**>180`000`000 liter per life**

**Herzgewicht:**
**300-350 g bei Männern**
**250-300 g bei Frauen**



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# Mehr Herz …

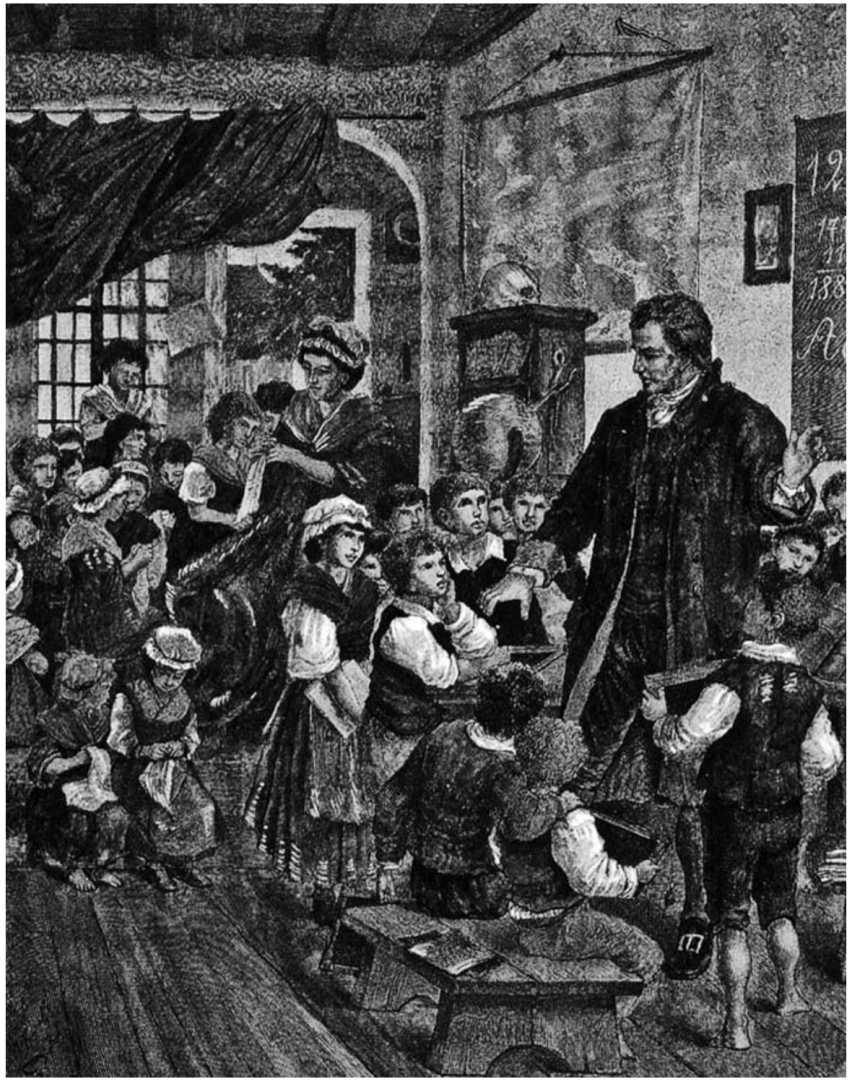

31'334 likes

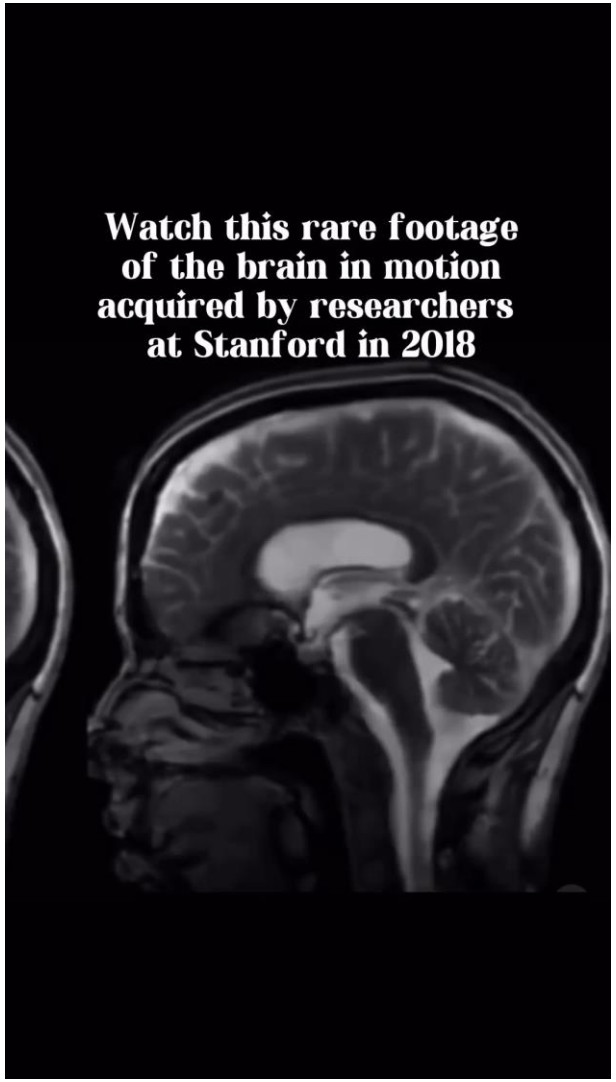
ynwagram #Klopp's gesturing the players to show heart in the final few minutes of the game... more

# Mit Kopf, Herz und Hand

# Der Mensch wird zum Menschen, indem er sein Herz, seine handwerklichen Fähigkeiten und seinen Geist bildet

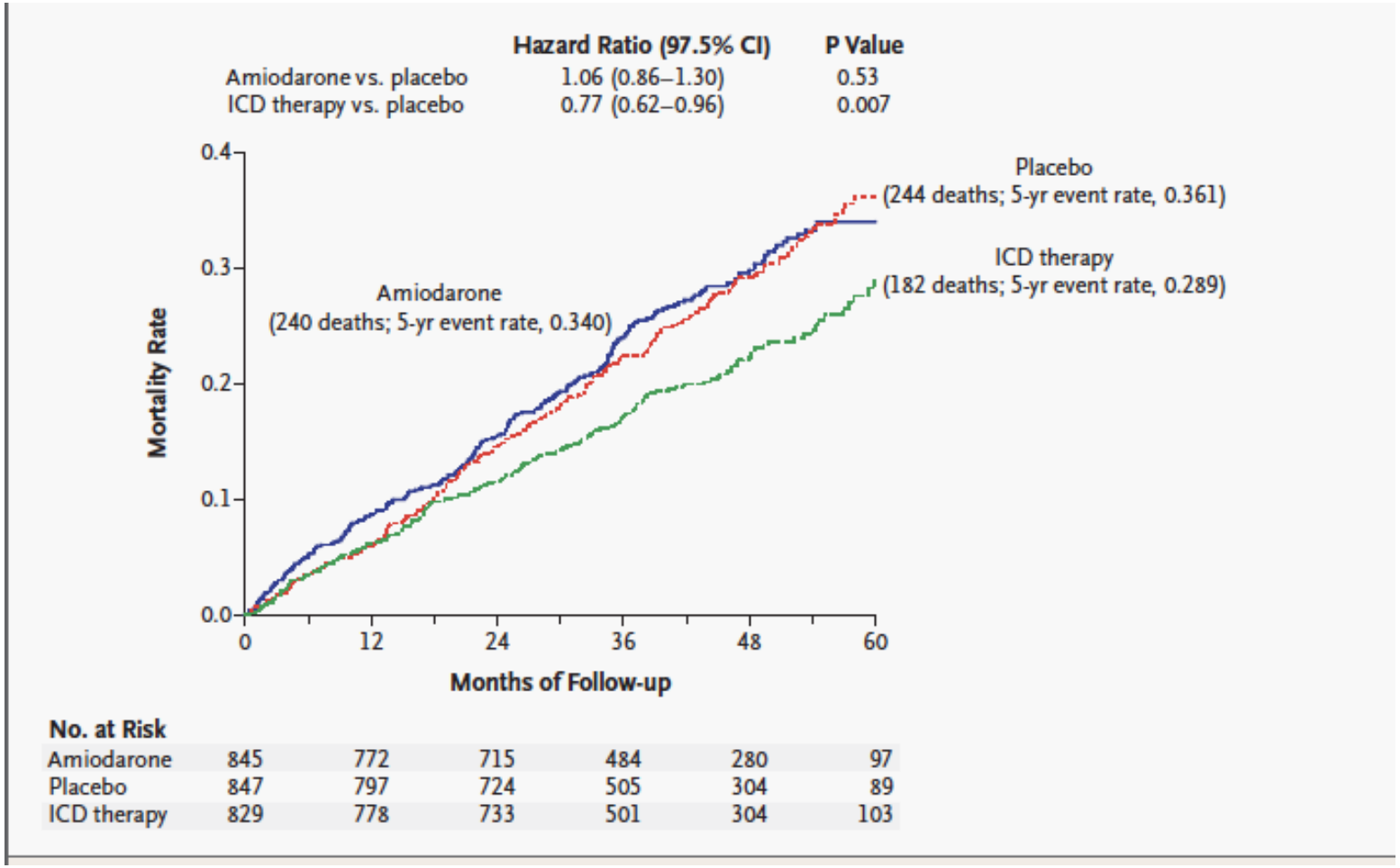
# Mit Kopf, Herz und Hand





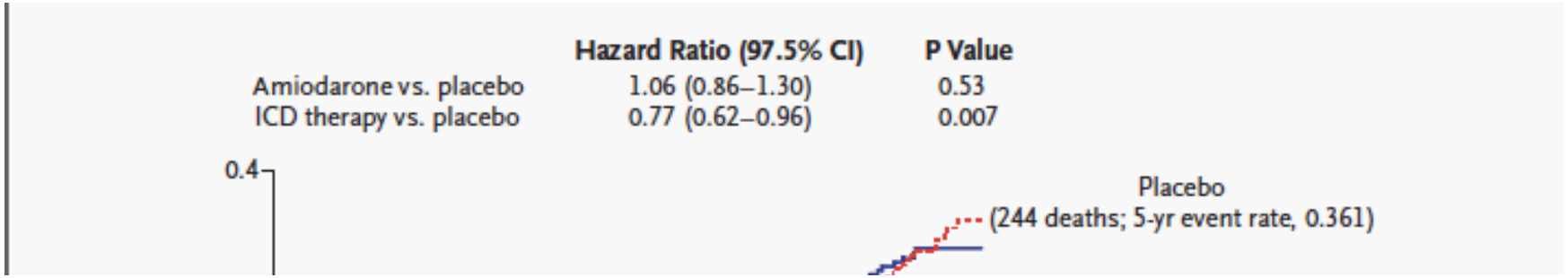
# Sudden Cardiac Death Heart Failure Trial (SCD HeFT)

## Death from Any Cause

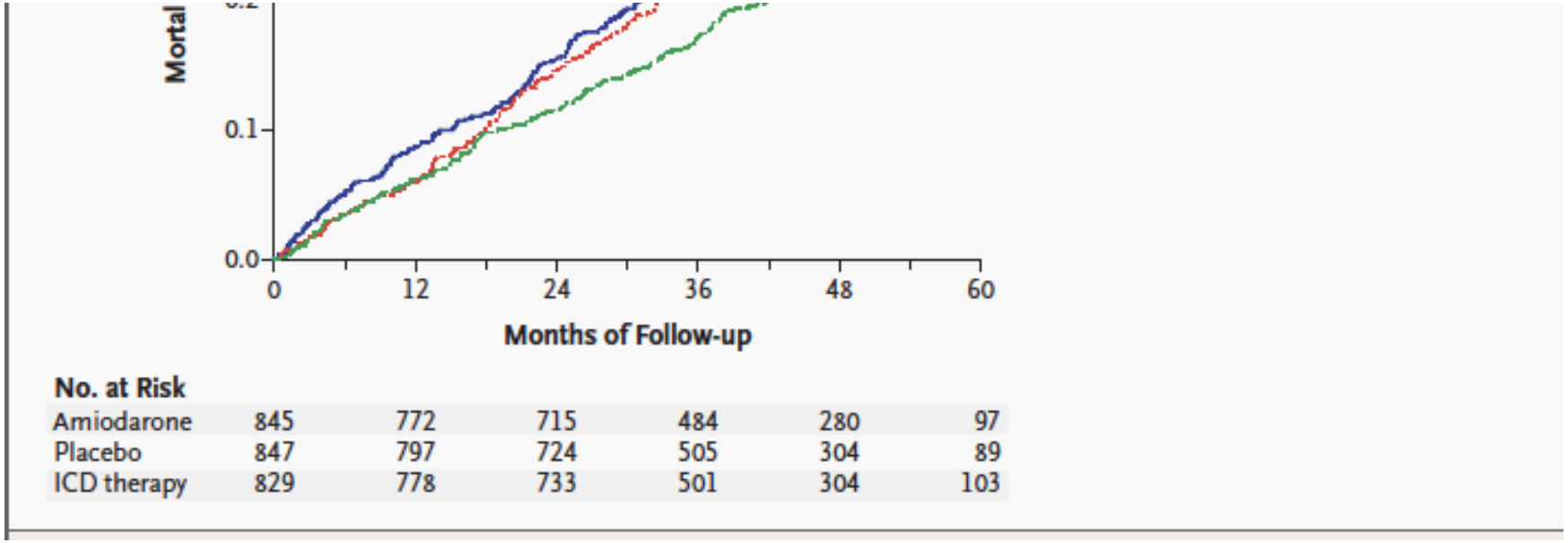



Bardy NEJM 2005

# SCD HeFT: Death from Any Cause

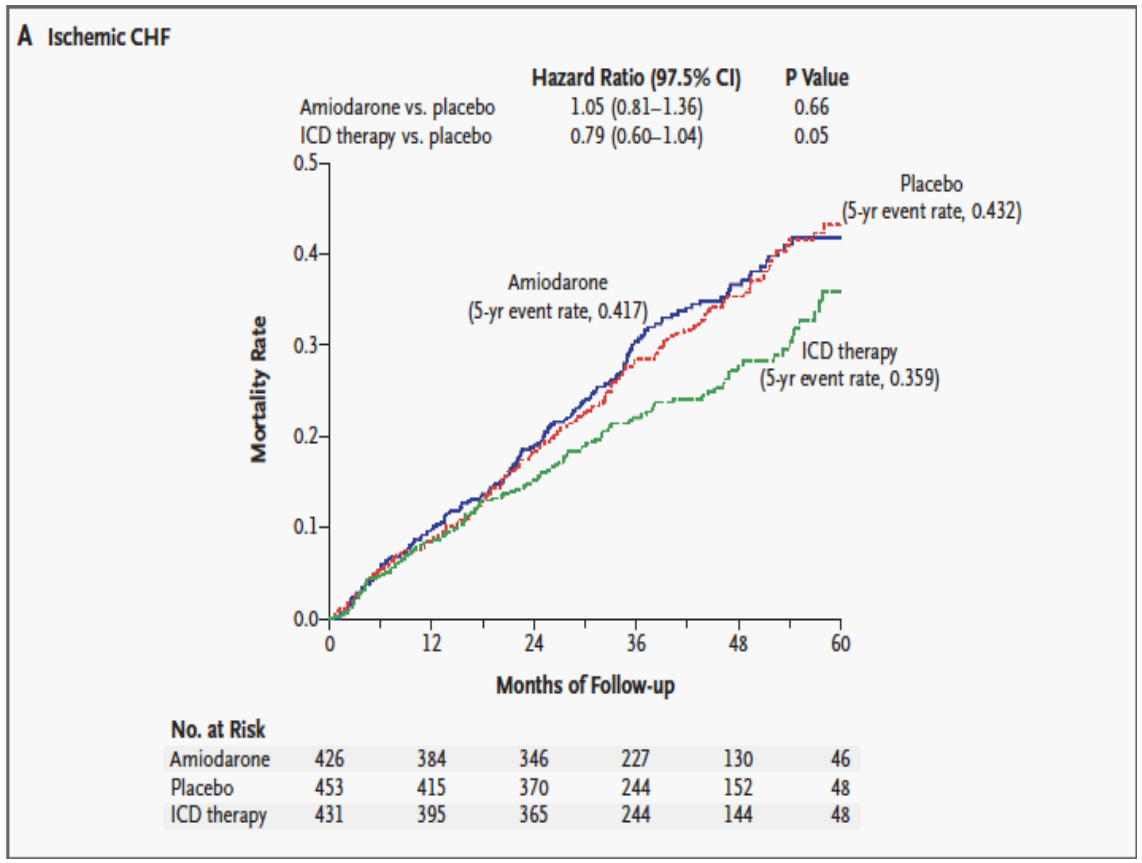


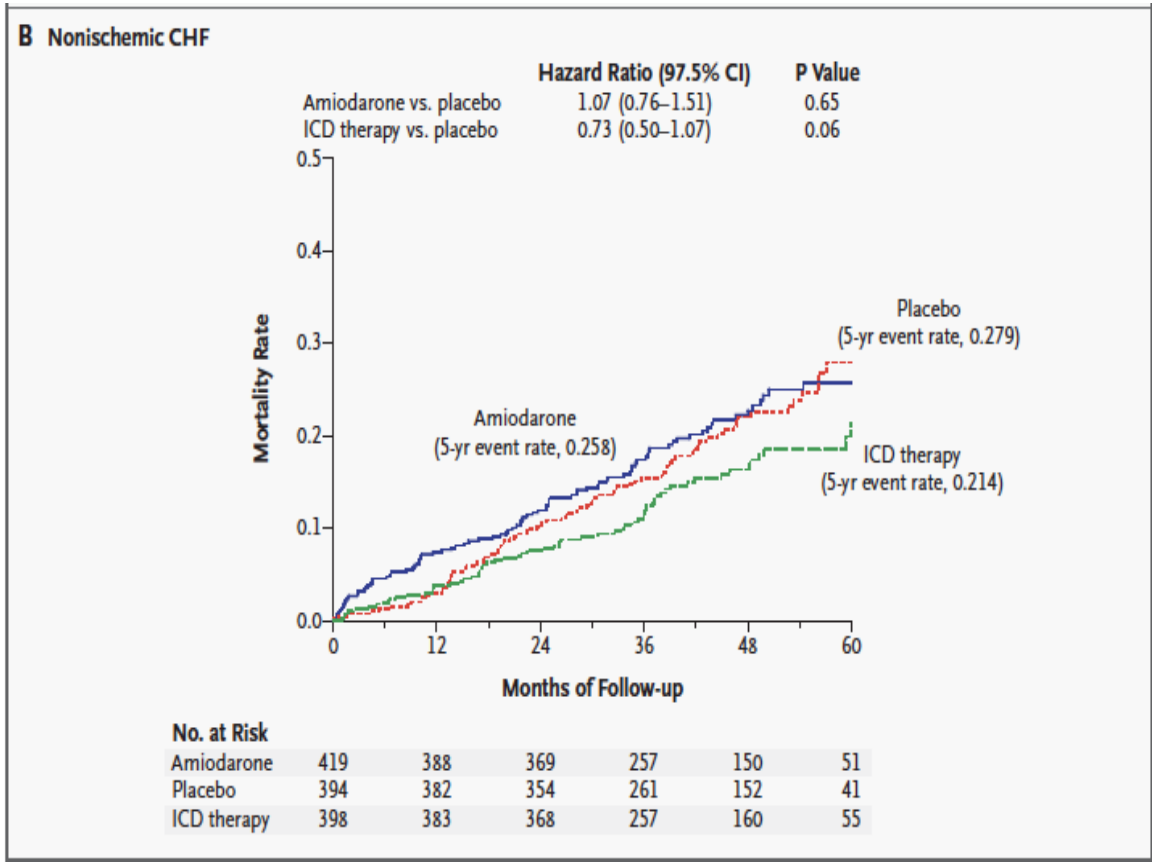

**ARR in mortality with an ICD was 6.9%**
**NNT (for 45.5 months to prevent one death) of 14**




Bardy NEJM 2005

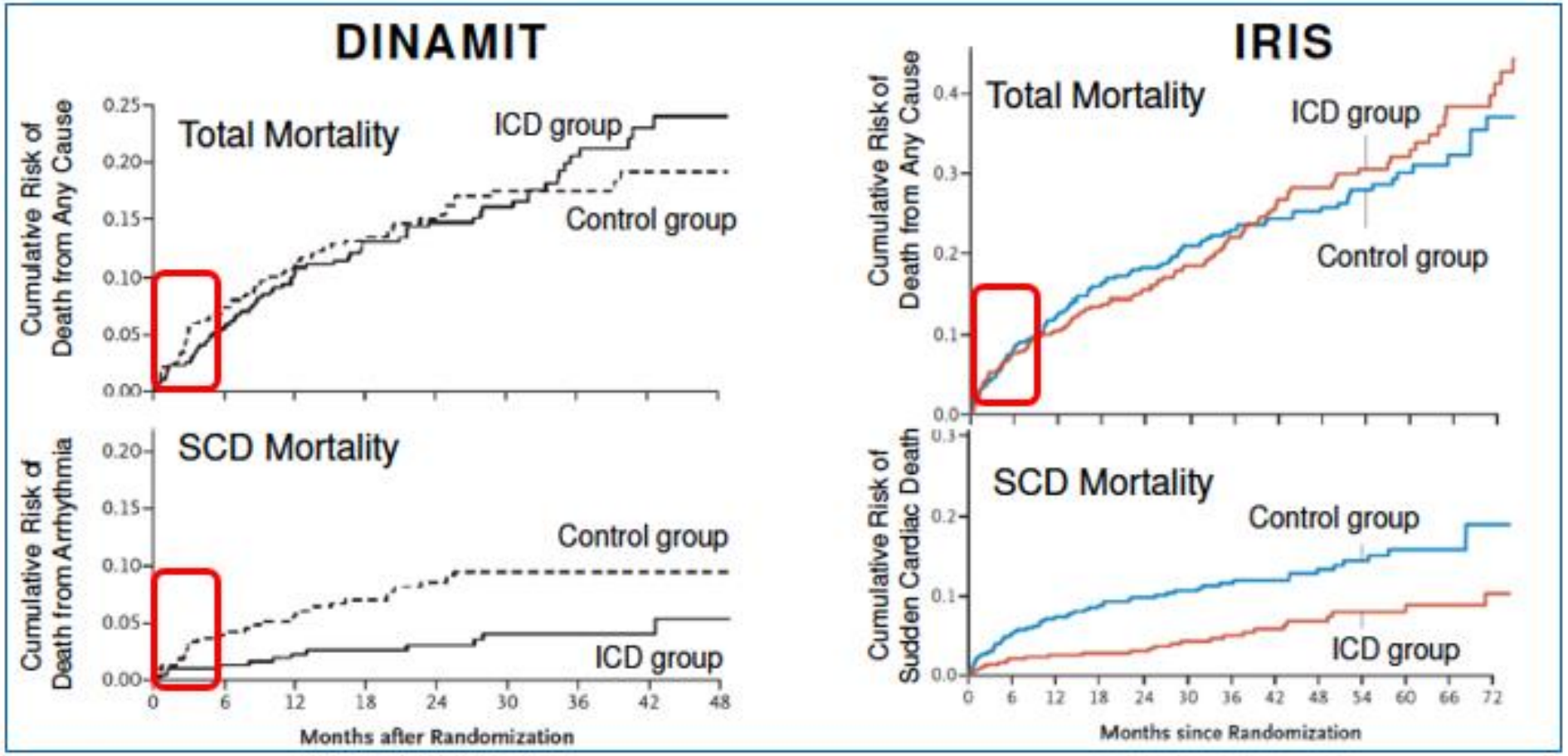
# SCD HeFT: Death from Any Cause
## Ischemic vs Nonischemic Aetiology




Bardy NEJM 2005

# No Benefit early post-MI for ICDs




**Hohnloser NEJM 2004**
**Steinbeck NEJM 2009**

# Randomized Controlled Trials of VT Ablation

## *Is Timing everything…*

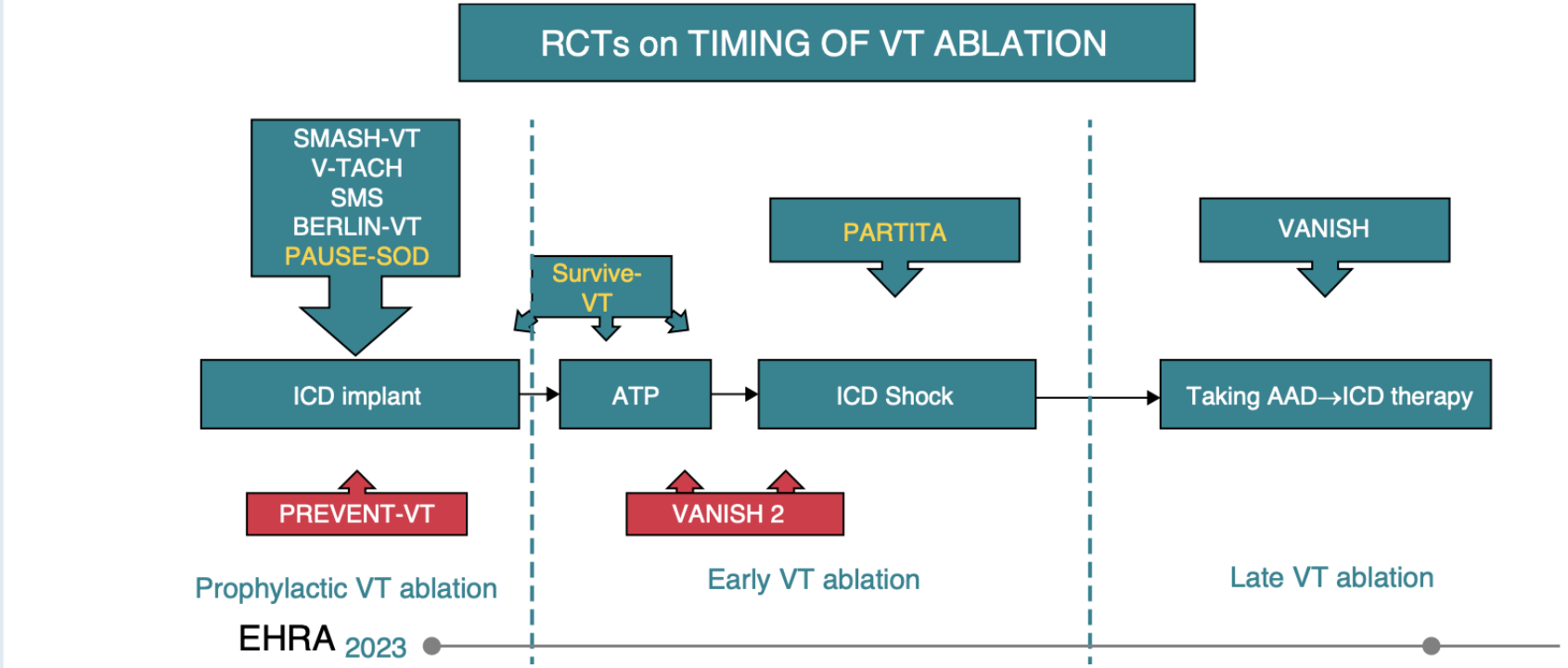



**Figure 3** Randomized controlled trial describing the timing for VT ablation.

# VTACH Study

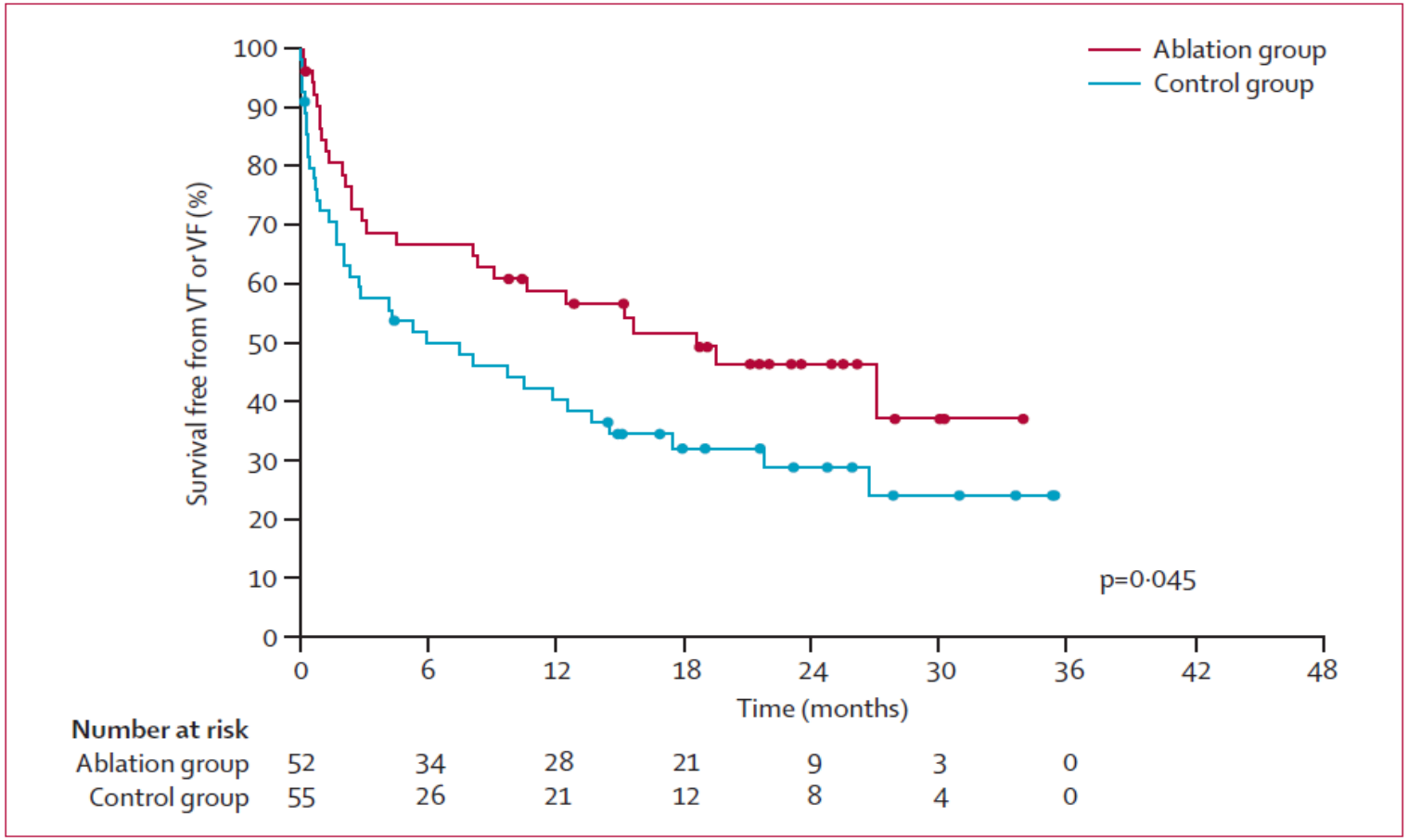



*Figure 2*: **Kaplan-Meier curves for the primary endpoint**
Estimates for survival free from ventricular tachycardia (VT) or ventricular fibrillation (VF). Censored patients are indicated by dots. The p value was calculated by log-rank test.

- **RRR 39% vs. no Ablation**
- **AAD allowed**
- **LVEF >30% most benefit**

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**Kuck KH et al Lancet 2010**

# SMASH-VT: Prophylactic Substrate-based Catheter Ablation Reduced the Incidence of ICD Therapies in Patients with a History of Myocardial Infarction

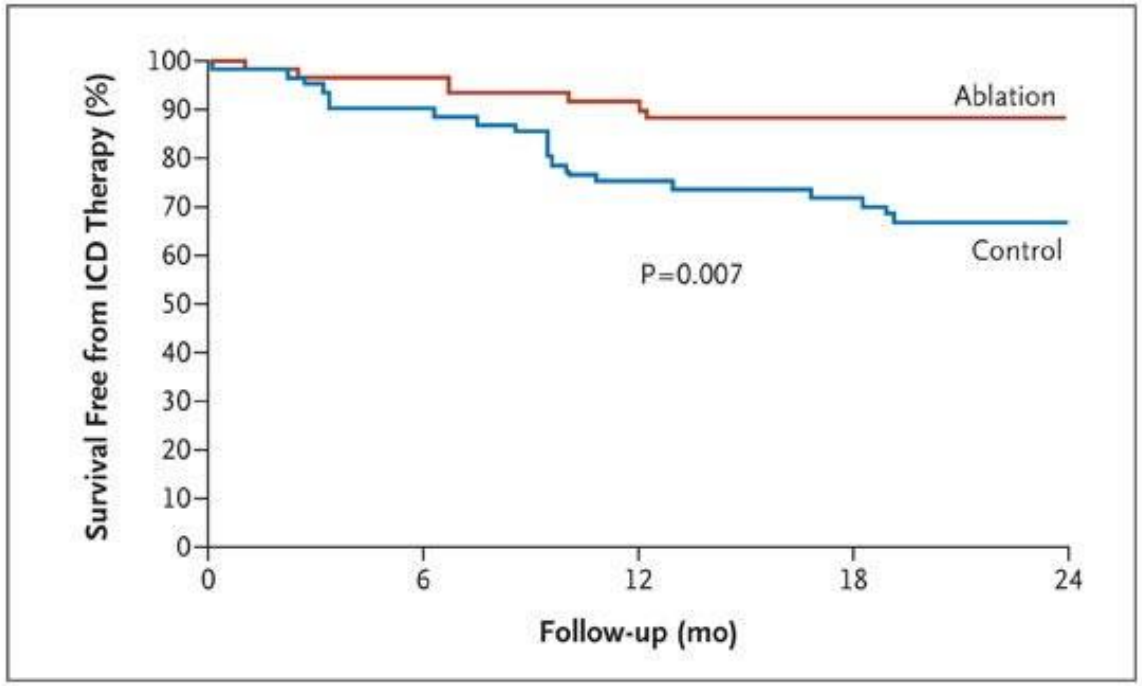



**Table 2. End Points.***

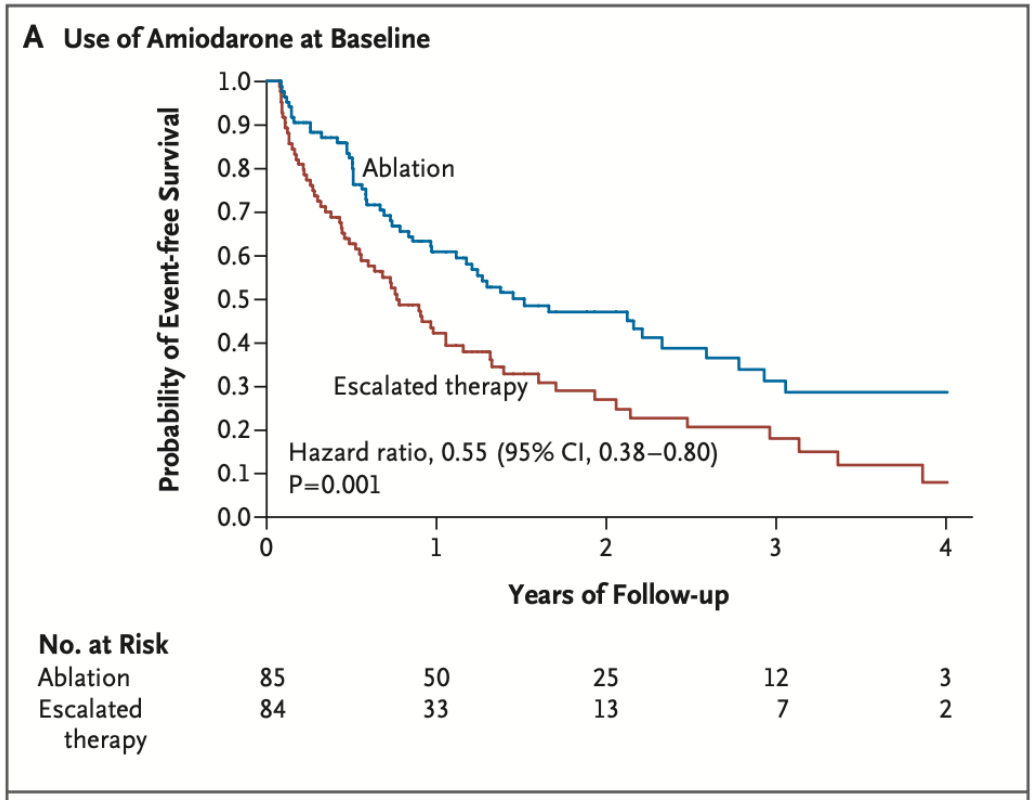
| Variable | Ablation Group (N=64) | Control Group (N=64) | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of patients (%)* | | | |
| ICD events* | 8 (12) | 21 (33) | 0.35 (0.15–0.78) | 0.007† |
| ICD shocks | 6 (9) | 20 (31) | 0.27 (0.11–0.67) | 0.003† |
| ICD storms | 4 (6) | 12 (19) | 0.30 (0.09–1.00) | 0.06‡ |
| Death | 6 (9) | 11 (17) | 0.59 (0.22–1.59) | 0.29† |
| Congestive heart failure | 3 (5) | 6 (9) | | |
| Ventricular tachycardia storm | 0 | 1 (2) | | |
| Cancer | 1 (2) | 0 | | |
| Pulmonary embolism | 1 (2) | 0 | | |
| Unknown | 1 (2) | 4 (6) | | |

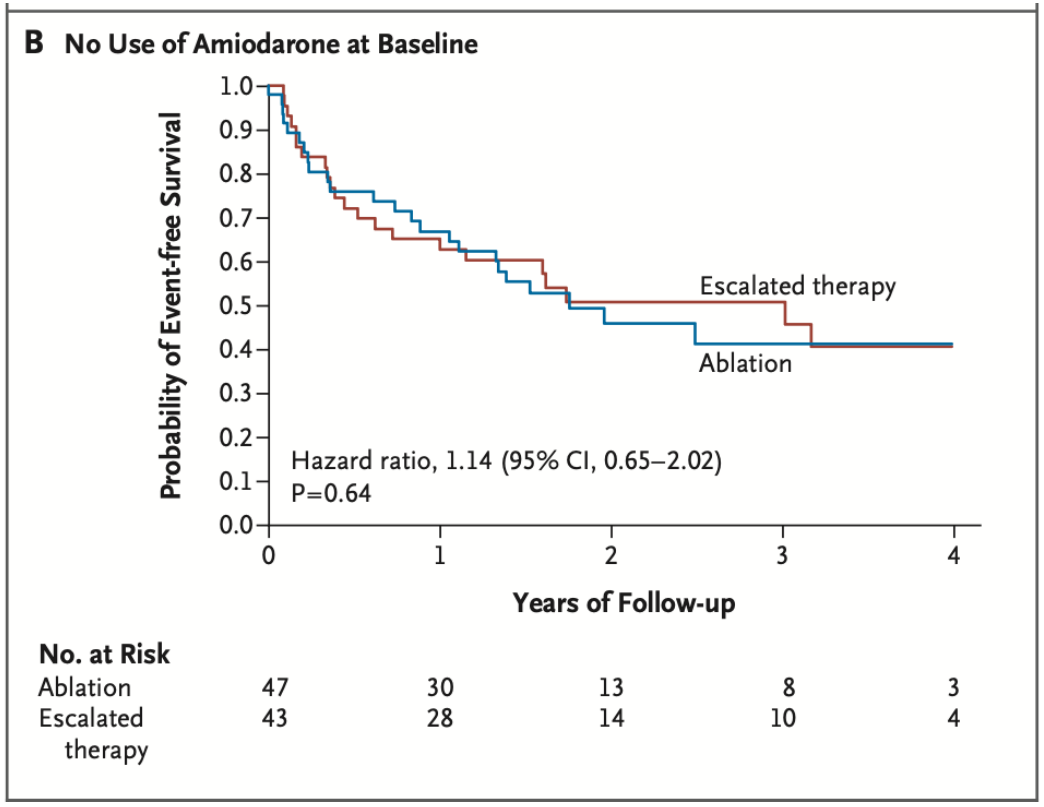


Reddy NEJM 2007

# VANISH Trial: VT Ablation versus AAD Escalation

## Benefit of catheter ablation only among patients in whom the index arrhythmia had occurred despite amiodarone therapy at baseline

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Sapp NEJM 2016

# VANISH Trial: VT Ablation versus AAD Escalation

## Treatment-Attributed Adverse Events

| Event# | AAD Group (n=127) No. (%) | Catheter Ablation Group (n=132) No. (%) | P |
|---|---|---|---|
| **Catheter Ablation Related** | | | |
| Vascular injury‡ | | 3 (2.3) | 0.25 |
| Major Bleeding | 1 (0.8) | 3 (2.3) | 0.62 |
| Cardiac Perforation | 1 (0.8) | 2 (1.5) | 1.00 |
| Endocarditis | 1 (0.8) | | 0.49 |
| Heart Block | 1 (0.8)* | | 0.49 |
| **Antiarrhythmic Drug Related** | | | |
| Death | | | |
| Pulmonary toxicity | 2 (1.6) | | 0.24 |
| Liver toxicity/multiorgan failure | 1 (0.8) | | 0.49 |
| Pulmonary Infiltrate | 2 (1.6)** | | 0.24 |
| Shortness of Breath | 3 (2.4) | 1 (0.8) | 0.36 |
| Heart Failure Admission | 1 (0.8) | 3 (2.3) | 0.62 |
| Hyperthyroidism | 5 (3.9) | 3 (2.3) | 0.49 |
| Hypothyroidism | 5 (3.9)† | 2 (1.5) | 0.27 |
| Hepatic Dysfunction | 6 (4.7) | | 0.013 |
| Tremor/Ataxia | 6 (4.7) | | 0.013 |
| Drug Therapy Change | 6 (4.7) | | 0.013 |
| Other adverse events no. (%) | 6 (4.7)†† | 4 (3.0) | 0.53 |
| TOTAL PATIENTS | 39 (30.7) | 20 (15.2) | 0.0031 |
| TOTAL EVENTS | 51 | 22 | 0.0023 |

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Sapp NEJM 2016

# Catheter Ablation of VT in the 2022 ESC Guidelines

## Ischemic

| | | |
|---|---|---|
| In patients with CAD and recurrent, symptomatic SMVT, or ICD shocks for SMVT despite chronic amiodarone therapy, catheter ablation is recommended in preference to escalating AAD therapy.[471] | I | B |
| Catheter ablation should be considered in patients with CAD and recurrent, symptomatic SMVT, or ICD shocks for SMVT despite beta-blockers or sotalol treatment.[471] | IIa | C |
| Catheter ablation is recommended in patients presenting with incessant VT or electrical storm due to SMVT refractory to AADs.[330,331] | I | B |

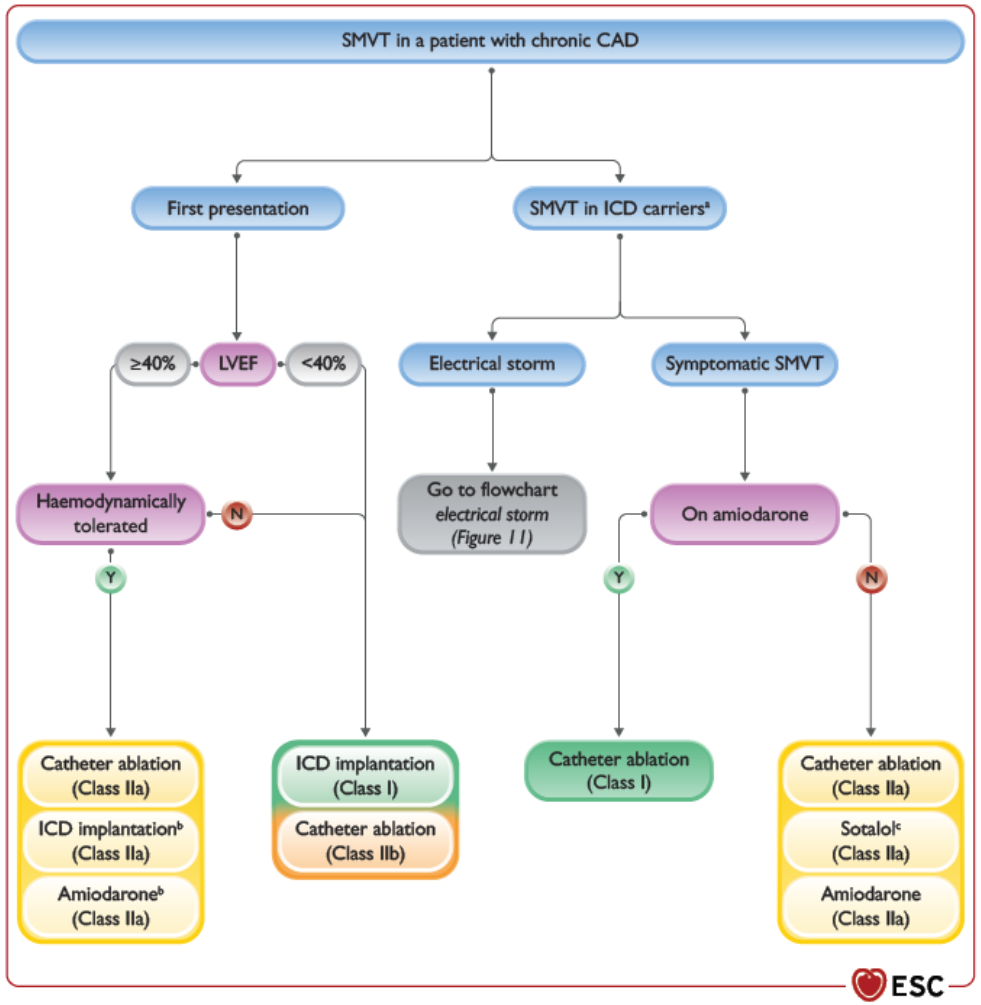
## Non-ischemic

| | | |
|---|---|---|
| Catheter ablation in specialized centres should be considered in patients with DCM/HNDCM and recurrent, symptomatic SMVT or ICD shocks for SMVT, in whom AADs are ineffective, contraindicated, or not tolerated.[481,497,664,669] | IIa | C |
| In patients with ARVC and recurrent, symptomatic SMVT or ICD shocks for SMVT despite beta-blockers, catheter ablation in specialized centres should be considered.[482,709,714] | IIa | C |



Zeppenfeld ESC Guidelines on VA EHJ 2022

# Algorithm for the management of sustained monomorphic ventricular tachycardia in patients with chronic coronary artery disease




Zeppenfeld ESC Guidelines on VA EHJ 2022

# Catheter Ablation of VT in the 2022 ESC Guidelines
## More Questions than Answers

**Ischemic**

| | | |
|---|---|---|
| In patients with CAD and recurrent, symptomatic SMVT, or ICD shocks for SMVT despite chronic amiodarone therapy, catheter ablation is recommended in preference to escalating AAD therapy.[471] | I | B |
| Catheter ablation should be considered in patients with CAD and recurrent, symptomatic SMVT, or ICD shocks for SMVT despite beta-blockers or sotalol treatment.[471] | IIa | C |
| Catheter ablation is recommended in patients presenting with incessant VT or electrical storm due to SMVT refractory to AADs.[330,331] | I | B |

- **Indication in patients with structural heart disease and recurrent VT episodes causing ICD interventions.**
- **No survival benefit from CA**
  - **Timing: prophylactic at the time of ICD implant**
  - **after the first shock**
  - **after recurrent VT episodes**
  - **or even after electrical storm**
- **Does the prevention of VT impact survival, or affect the occurrence of heart failure?**
  - **Many patients after ICD implant might never have a recurrent arrhythmia**



**Zeppenfeld ESC Guidelines on VA EHJ 2022**

# Randomized Controlled Trials of VT Ablation

## *Is Timing everything…*

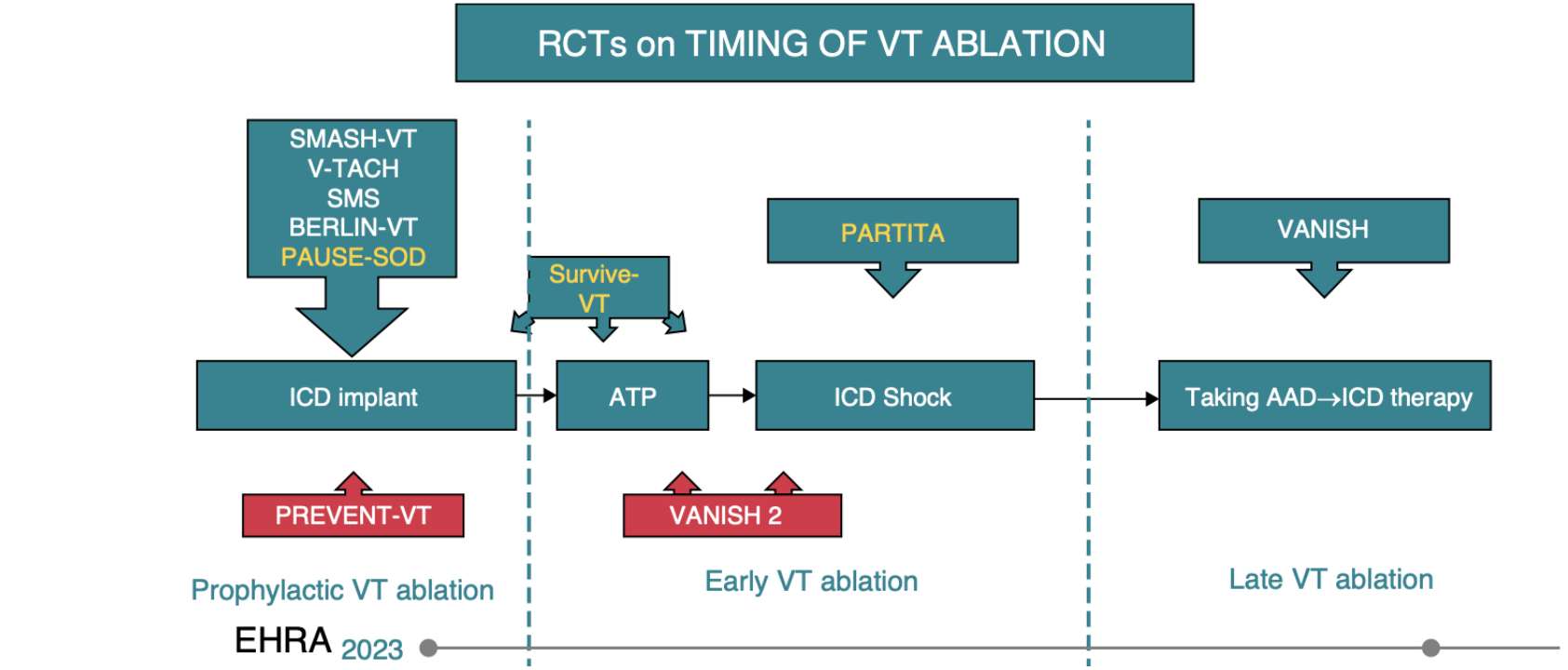



**Figure 3** Randomized controlled trial describing the timing for VT ablation.

# SURVIVE-VT: Substrate Ablation vs AAD with recurrent post-infarction Ventricular Tachycardia after an ICD implant

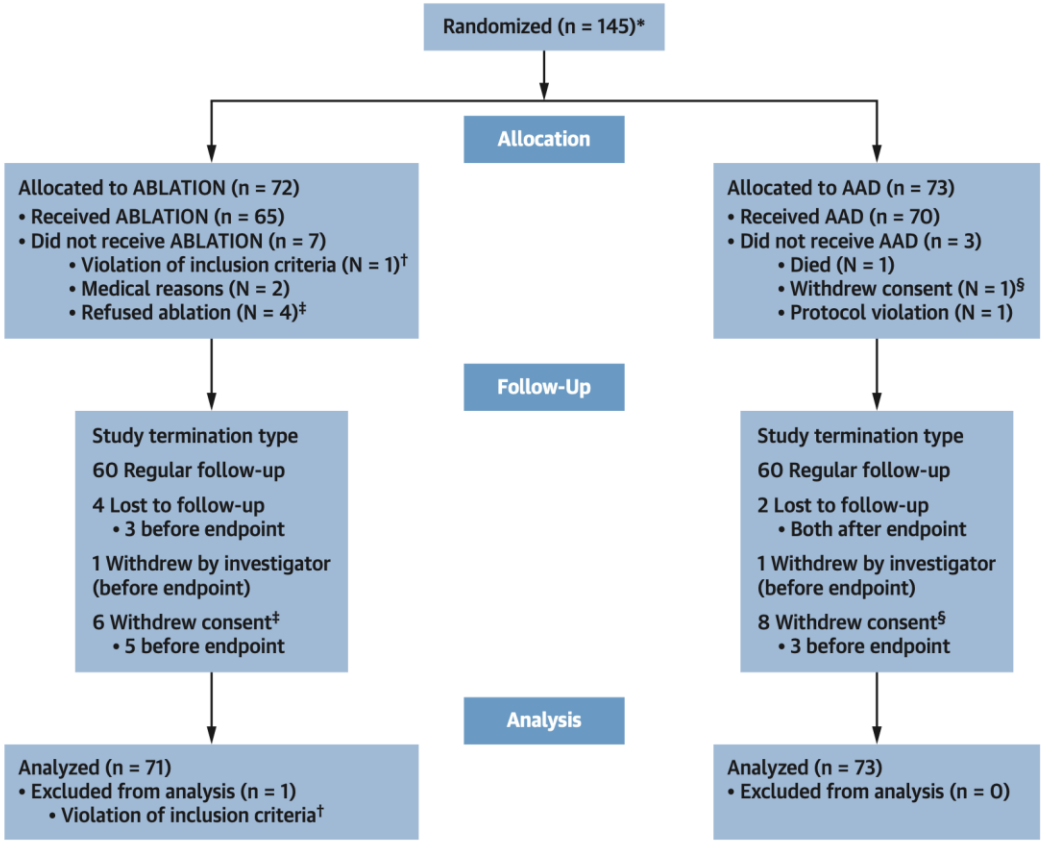



**TABLE 1 Baseline Demographic Characteristics**

| | Ablation (n = 71) | AAD (n = 73) |
|---|---|---|
| Age, y | 70 (63-75) | 71 (64-76) |
| Male | 70 (98.6) | 68 (93.2) |
| BMI, kg/m$^2$ | 27.3 (25.2-31.6) | 27.6 (25.9-30.0) |
| Hypertension | 56 (78.9) | 47 (64.4) |
| Diabetes | 21 (29.6) | 15 (20.5) |
| Renal insufficiency | 8 (11.3) | 7 (9.6) |
| Creatinine, mg/dL | 1.05 (0.87-1.28) | 1.02 (0.88-1.15) |
| Creatinine ≥1.5 mg/dL | 11 (16.2) | 7 (9.7) |
| Time since last myocardial infarction, y | 14 (6-24) | 14 (7-23) |
| Infarction location | | |
| Anterior | 25 (35.2) | 31 (42.5) |
| Inferior | 46 (64.8) | 40 (54.8) |
| Lateral | 6 (8.5) | 12 (16.4) |
| Previous CABG | 18 (26.5) | 12 (17.1) |
| Previous PCI | 26 (38.2) | 26 (37.1) |
| No revascularization | 25 (36.8) | 33 (47.1) |
| Ejection fraction, % | 35 (26-41) | 33 (25-40) |
| LVEF ≤30% | 31 (43.7) | 36 (49.3) |
| NYHA functional class | | |
| I | 31 (44.3) | 31 (42.5) |
| II | 33 (47.1) | 37 (50.7) |
| III | 6 (8.6) | 5 (6.8) |
| AF or atrial flutter | 9 (13.6) | 8 (12.3) |
| Medical therapy | | |
| Beta-blockers | 69 (97.2) | 62 (86.1) |
| ACE inhibitors or ARBs | 70 (98.6) | 65 (90.3) |
| RAAS inhibitors | 39 (55.7) | 42 (60.9) |
| Follow-up, mo | 23.8 (16.6-24.0) | 23.3 (9.4-23.9) |

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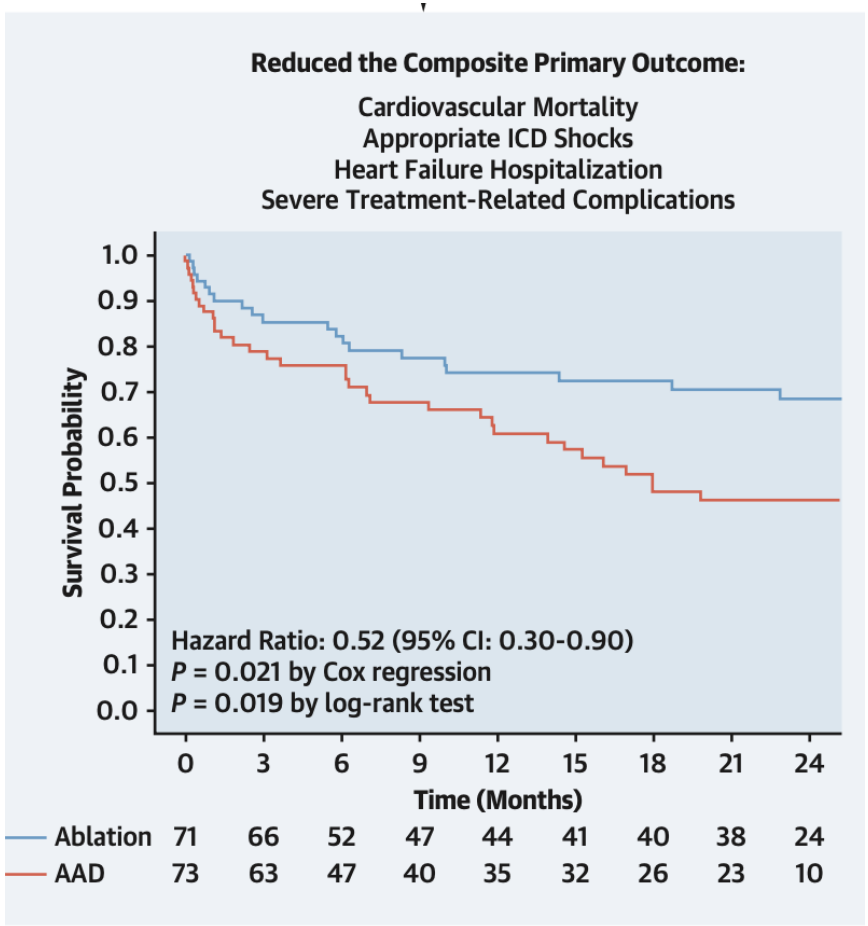
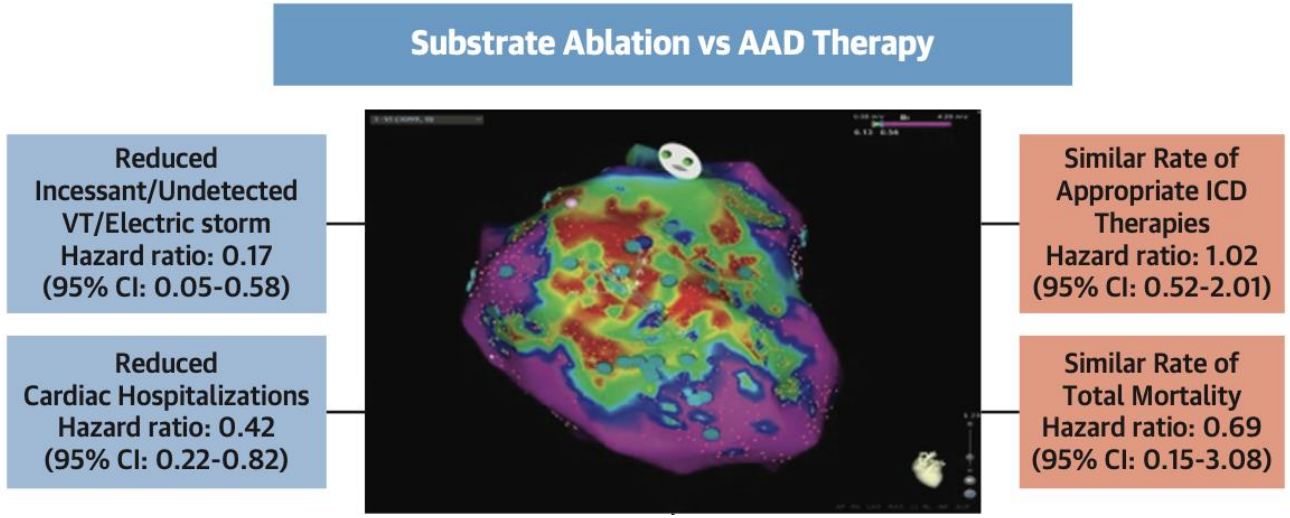
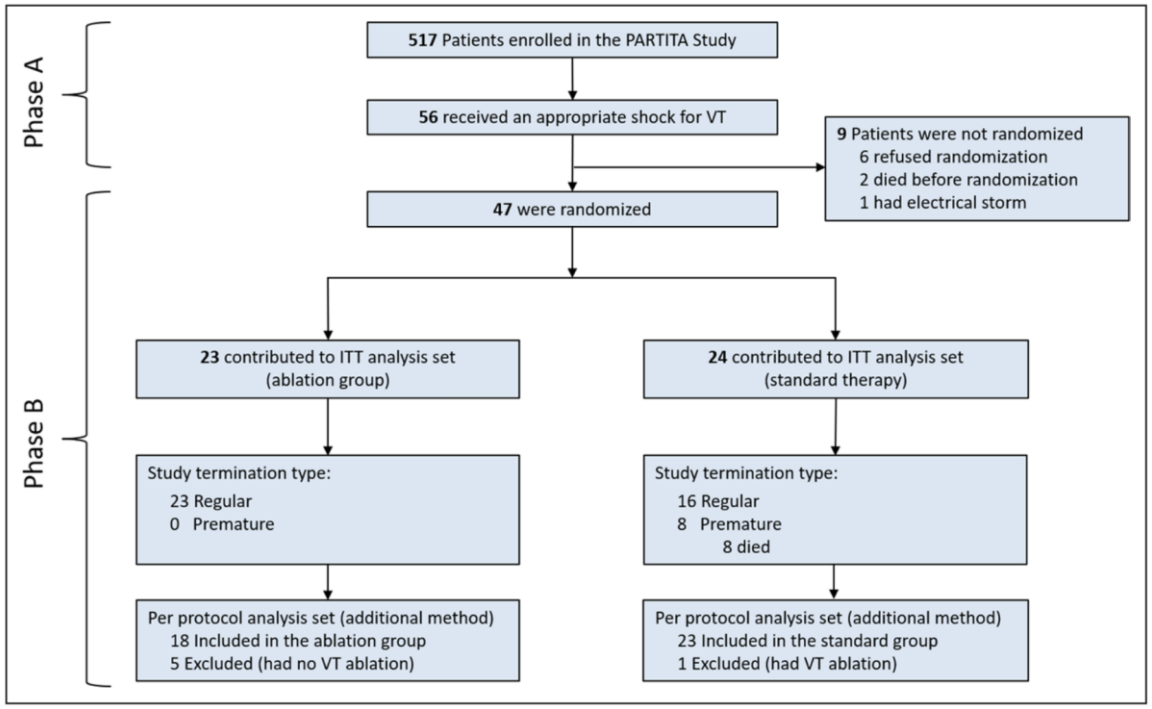
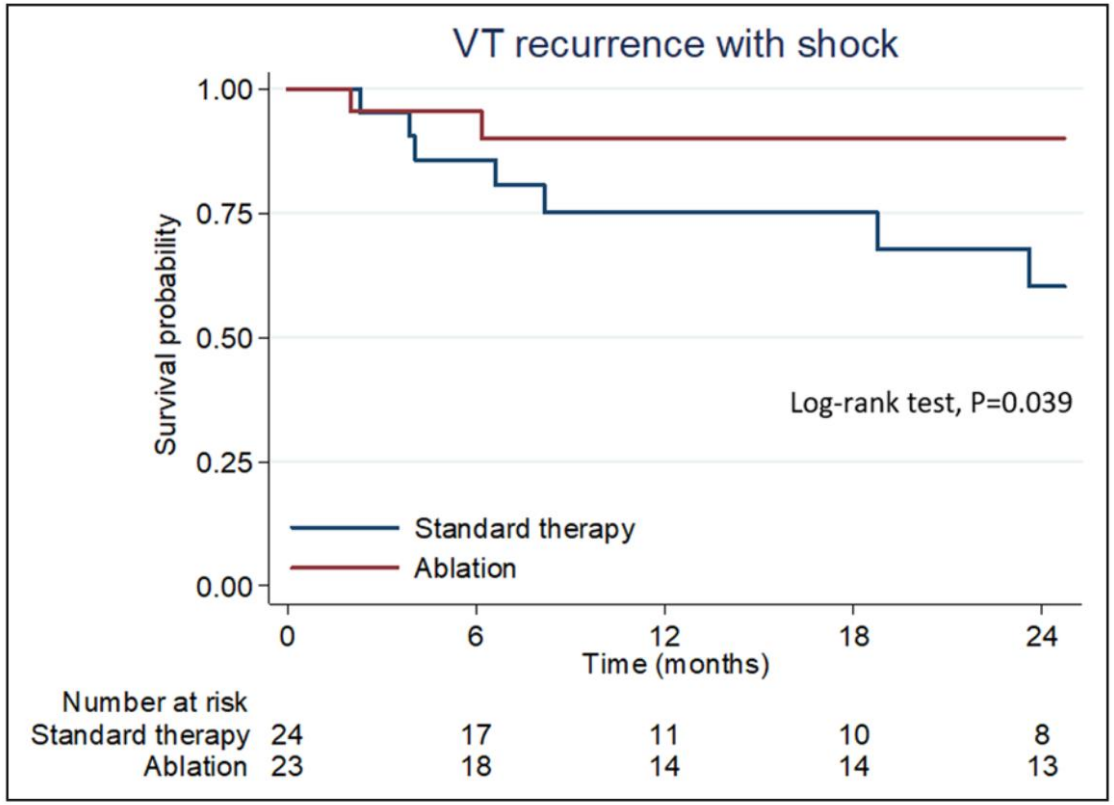
# SURVIVE-VT: Substrate Ablation vs Antiarrhythmic Drug Therapy for Symptomatic Ventricular Tachycardia



# PARTITA Trial: VT ablation after the first appropriate ICD shock, and before use of amiodarone, was associated with lower mortality

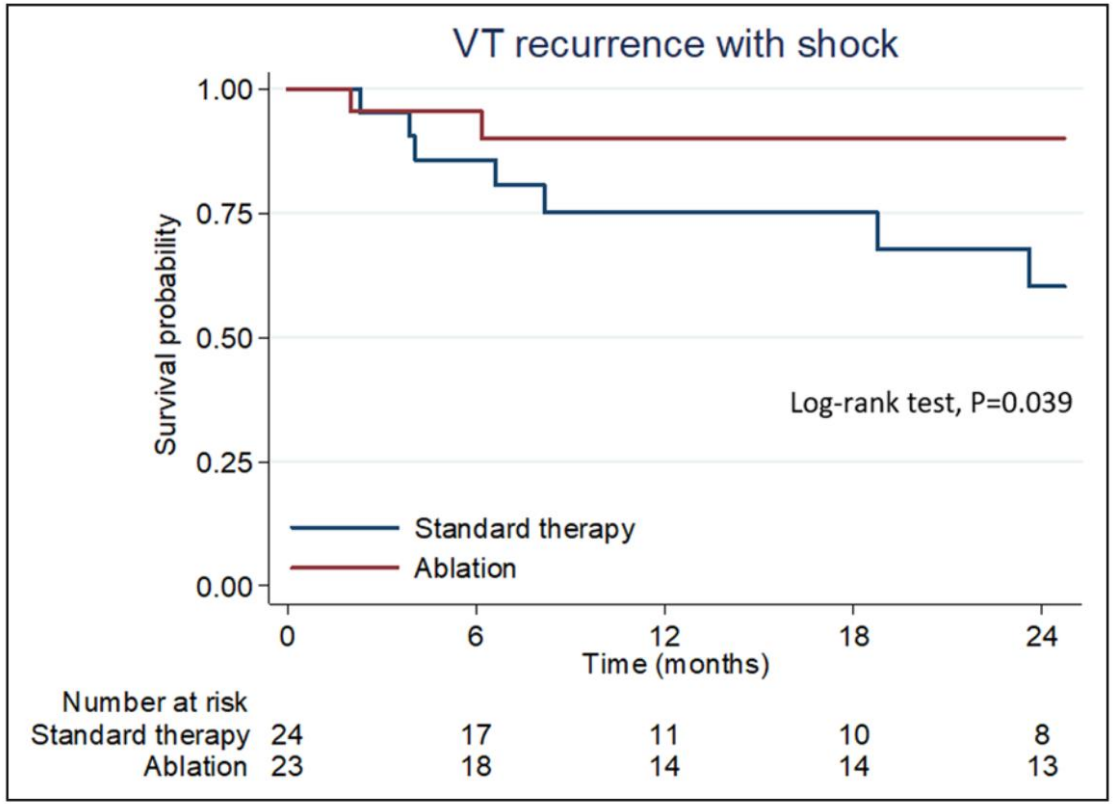


# PARTITA Trial: VT ablation after the first appropriate ICD shock, and before use of amiodarone, was associated with lower mortality

**Table 4. Percentage of Patients With Secondary Outcomes and Comparison Between Ablation and Standard Therapy Group by Log-Rank Test**

| Outcomes | Ablation (n=23) | Standard therapy (n=24) | *P* value |
|---|---|---|---|
| All-cause death | 0 (0) | 8 (33.3) | 0.004 |
| Worsening HF hospitalization | 1 (4.3) | 4 (16.7) | 0.159 |
| Worsening HF hospitalization or cardiac death | 1 (4.3) | 6 (25.0) | 0.053 |
| Cardiac death | 0 (0) | 3 (12.5) | 0.087 |
| Recurrent VT | 7 (30.4) | 12 (50.0) | 0.434 |
| Recurrent VT with ATP | 7 (30.4) | 11 (45.8) | 0.639 |
| Recurrent VT with shock | 2 (8.7) | 10 (41.7) | 0.039 |
| Electrical storm | 0 (0) | 2 (8.3) | 0.280 |

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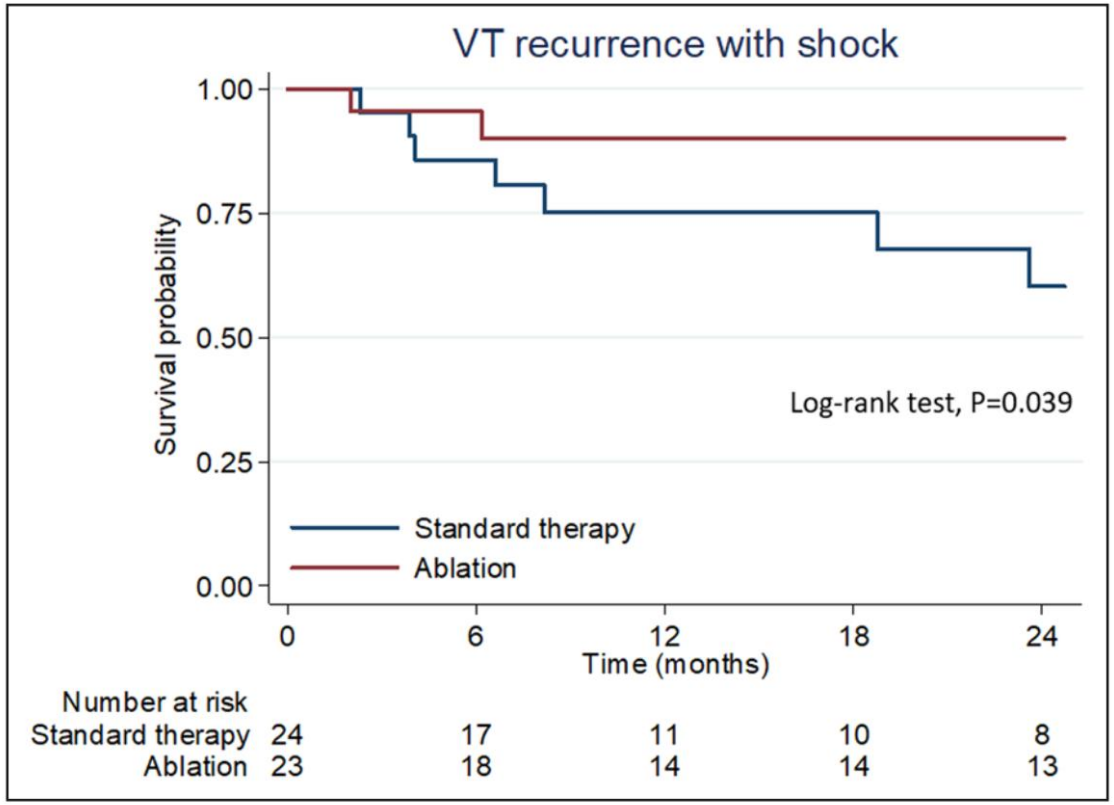
# PARTITA Trial: VT ablation after the first appropriate ICD shock, and before use of amiodarone, was associated with lower mortality

**Table 1. Patient Characteristics**

| Characteristics | Overall (n=517) | Randomized (n=47) | Ablation (n=23) | Standard therapy (n=24) | *P* value* |
|---|---|---|---|---|---|
| Male | 449 (87) | 40 (85) | 19 (83) | 21 (88) | 0.7 |
| Age, y | 67.3 (10.7) | 68.4 (9.3) | 71.2 (8.1) | 65.6 (9.6) | 0.059 |
| NYHA class | | | | | 0.5 |
| I | 95 (20) | 8 (18) | 3 (13) | 5 (24) | |
| II | 291 (62) | 29 (66) | 17 (74) | 12 (57) | |
| III | 82 (17) | 7 (16) | 3 (13) | 4 (19) | |
| IV | 1 (0.2) | 0 (0) | 0 (0) | 0 (0) | |
| LV ejection fraction, % | 34.0 (9.5) | 32.2 (8.6) | 31.9 (9.0) | 32.4 (8.3) | >0.9 |
| QRS duration, ms | 120.8 (31.1) | 123.6 (30.1) | 126.3 (35.0) | 120.9 (25.2) | >0.9 |
| Device | | | | | 0.5 |
| Single-chamber ICD | 177 (35) | 13 (28) | 5 (22) | 8 (33) | |
| Dual-chamber ICD | 209 (41) | 19 (40) | 11 (48) | 8 (33) | |
| CRT-D | 123 (24) | 15 (32) | 7 (30) | 8 (33) | |
| ICD indication | | | | | 0.5 |
| Primary prevention | 403 (79) | 35 (74) | 16 (70) | 19 (79) | |
| Secondary prevention | 107 (21) | 12 (26) | 7 (30) | 5 (21) | |
| Cardiomyopathy | | | | | 0.5 |
| Ischemic | 397 (78) | 38 (81) | 20 (87) | 18 (75) | |
| Idiopathic dilated | 114 (22) | 9 (19) | 3 (13) | 6 (25) | |
| Drug therapy | | | | | |
| ACE inhibitors | 327 (67) | 34 (72) | 17 (74) | 17 (71) | 0.8 |
| ARB | 79 (16) | 8 (17) | 3 (13) | 5 (21) | 0.7 |
| Aspirin | 326 (67) | 32 (68) | 16 (70) | 16 (67) | 0.8 |
| β-blockers | 423 (97) | 47 (100) | 23 (100) | 24 (100) | – |
| Diuretics | 381 (78) | 40 (85) | 20 (87) | 20 (83) | >0.9 |
| Statins | 343 (70) | 36 (77) | 17 (74) | 19 (79) | 0.7 |
| Amiodarone | 56 (13) | 5 (12) | 1 (5) | 4 (21) | 0.2 |

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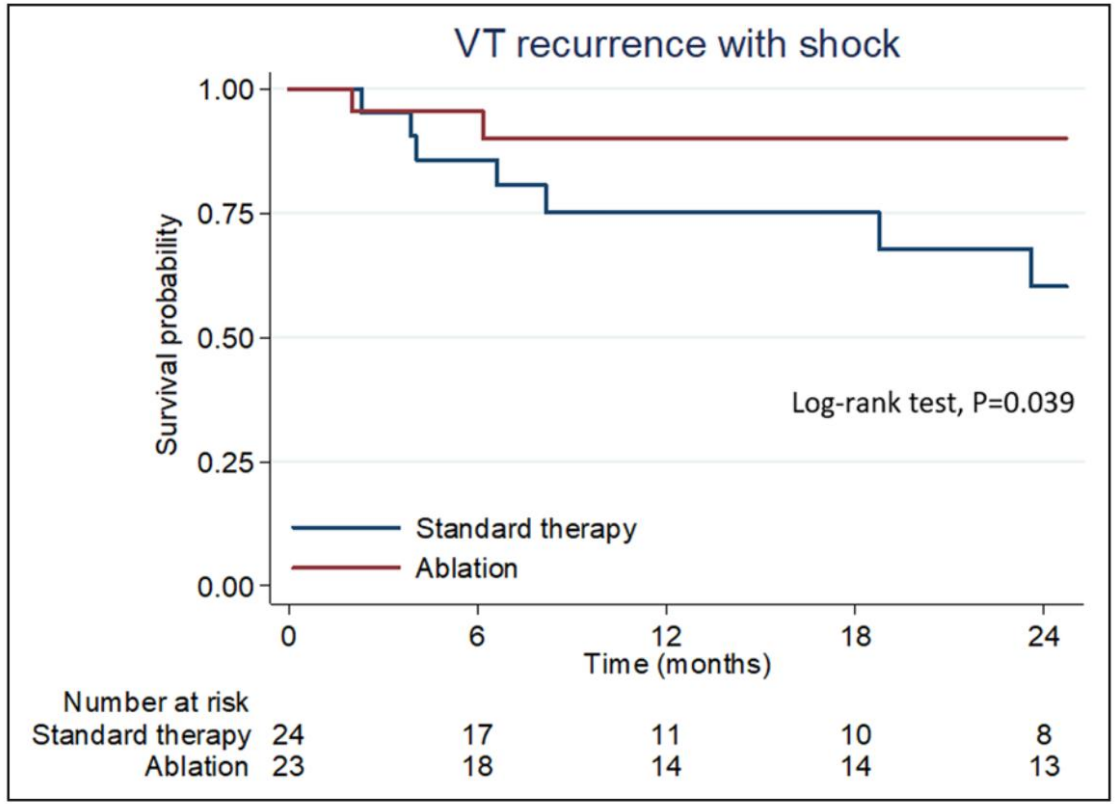
# PARTITA Trial: Does Timing of Ventricular Tachycardia Ablation Affect Prognosis in Patients With an Implantable Cardioverter Defibrillator?




After an initial episode of sustained VT that warrants ICD implantation

- programming should be optimized to minimize the chance of ICD shocks
- When VT recurs, particularly with ICD shocks, it is reasonable to consider catheter ablation at that time to prevent further VT
- particularly for patients with ischemic heart disease or arrhythmogenic right ventricular cardiomyopathy.
- More studies are needed to clarify whether reducing VT with catheter ablation reduces hospitalizations and improves survival
- ablating VT *before* using amiodarone may provide benefit

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# VANISH2: Is Ablation Superior to AAD as First Line Therapy for Patients with Ischemic Cardiomyopathy and VT

Trial Designs

## A randomized clinical trial of catheter ablation and antiarrhythmic drug therapy for suppression of ventricular tachycardia in ischemic cardiomyopathy: The VANISH2 trial

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**ABSTRACT**

**Background** Recurrent ventricular tachycardia (VT) in patients with prior myocardial infarction is associated with adverse quality of life and clinical outcomes, despite the presence of implanted defibrillators (ICDs). Suppression of recurrent VT can be accomplished with antiarrhythmic drug therapy or catheter ablation. The Ventricular Tachycardia Antiarrhythmics or Ablation In Structural Heart Disease 2 (VANISH2) trial is designed to determine whether ablation is superior to antiarrhythmic drug therapy as first line therapy for patients with ischemic cardiomyopathy and VT.

**Methods** The VANISH2 trial enrolls patients with prior myocardial infarction and VT (with one of: ≥1 ICD shock; ≥3 episodes treated with antitachycardia pacing (ATP) and symptoms; ≥5 episodes treated with ATP regardless of symptoms; ≥3 episodes within 24 hours; or sustained VT treated with electrical cardioversion or pharmacologic conversion). Enrolled patients are classified as either sotalol-eligible, or amiodarone-eligible, and then are randomized to either catheter ablation or to that antiarrhythmic drug therapy, with randomization stratified by drug-eligibility group. Drug therapy, catheter ablation procedures and ICD programming are standardized.

All patients will be followed until two years after randomization. The primary endpoint is a composite of mortality at any time, appropriate ICD shock after 14 days, VT storm after 14 days, and treated sustained VT below detection of the ICD after 14 days. The outcomes will be analyzed according to the intention-to-treat principle using survival analysis techniques

**Results** The results of the VANISH2 trial are intended to provide data to support clinical decisions on how to suppress VT for patients with prior myocardial infarction.

Clinicaltrials.gov registration NCT02830360. (Am Heart J 2024;274:1–10.)

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**Am Heart Journal 2024**