



**CONGRESSO**

ROMA, 25 - 27 Giugno 2026

**HFrEF di nuova diagnosi: quando  
è davvero il momento giusto  
dell'ICD?**

**C.Colaiaco**  
**Roma**

**SEDE DEI LAVORI**

A. Roma Lifestyle Hotel  
Via Giorgio Zoega 59, Roma



# Prevenzione primaria della morte cardiaca improvvisa nello HFrEF.

## Se la domanda non fosse più «*quando*» ma «*se*» dobbiamo ancora impiantare il defibrillatore?

American Heart Journal Plus: Cardiology Research and Practice 27 (2023) 100281

Contents lists available at ScienceDirect  
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Cardiology Research and Practice  
journal homepage: www.elsevier.com/locate/ahjplus  
STATE-OF-THE-ART REVIEW

ELSEVIER

Review Article

Sudden cardiac death prevention in the e:  
failure medications

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### Revisiting ICD Therapy for Primary Prevention in Patients With Heart Failure and Reduced Ejection Fraction

Amin Yehya, MD, MS,<sup>a</sup> Jose Lopez, MD,<sup>b</sup> Andrew J. Sauer,  
Nastien E. Ibrahim, MD, MPH,<sup>c</sup> Roderick Tung, MD,<sup>d</sup> Biyi  
Sana M. Al-Khatib, MD, MHS<sup>e</sup>

REVIEW ARTICLE | Originally Published 24 February 2020 | Open Access | Check for updates

### Time to Shock the System: Moving Beyond the Current Paradigm for Primary Prevention Implantable Cardioverter-Defibrillator Use

Faisal M. Merchant, MD<sup>a</sup>, Wayne C. Levy, MD, and Daniel

Journal of the American Heart Association • Volume 9, Number 1, January 14, 2020

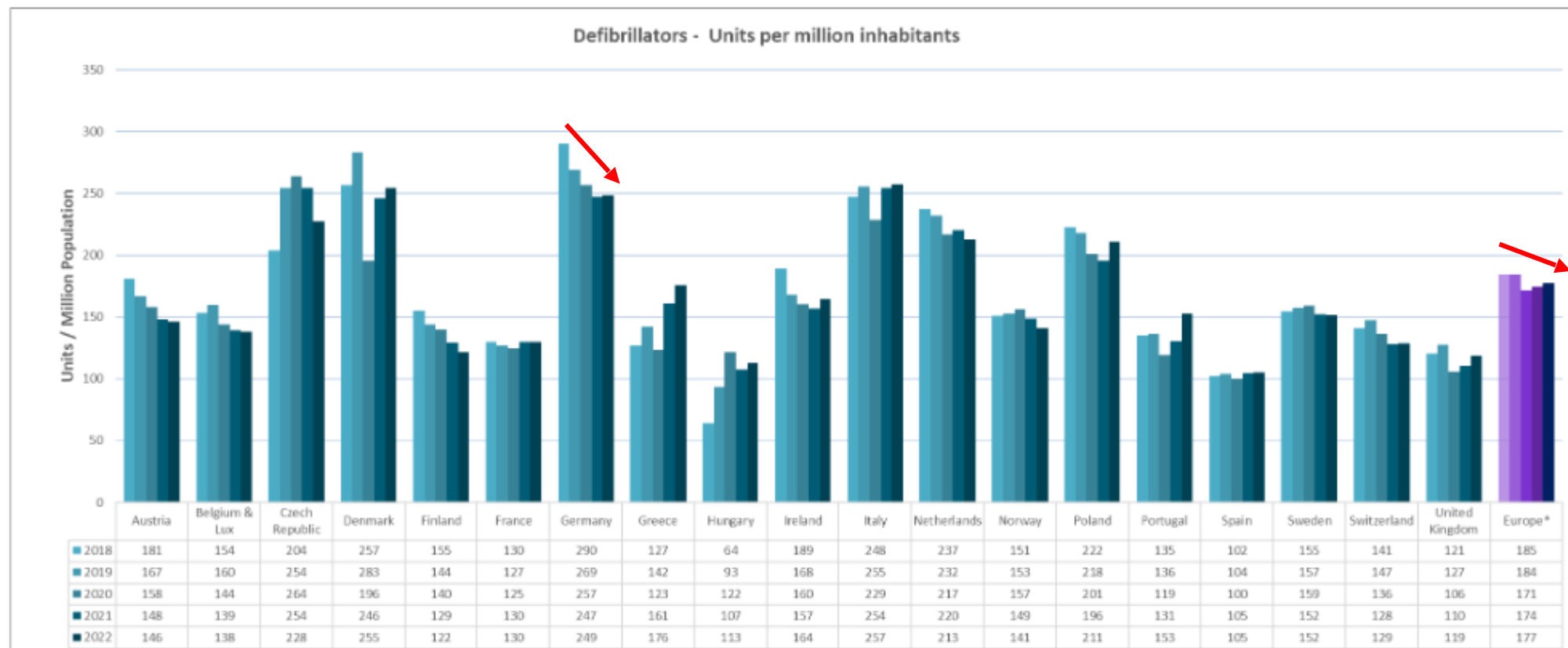
**HIGHLIGHTS**

- ICD therapy is guideline recommended for primary prevention in patients with heart failure and reduced ejection fraction.
- Contemporary GDMT reduces the risk of SCD.
- Shared decision making is important when considering ICD therapy.
- Trials are being conducted to appropriately evaluate the current era of GDMT for heart failure.

Prevention of sudden cardiac death:  
will heart failure drugs replace ICDs ?

*“..in many patients, the **reversal of cardiac remodeling** produced by broad-spectrum **neurohormonal antagonists** may be sufficiently great to **fully obviate the need for an ICD...**”*

# 2018 - 2022



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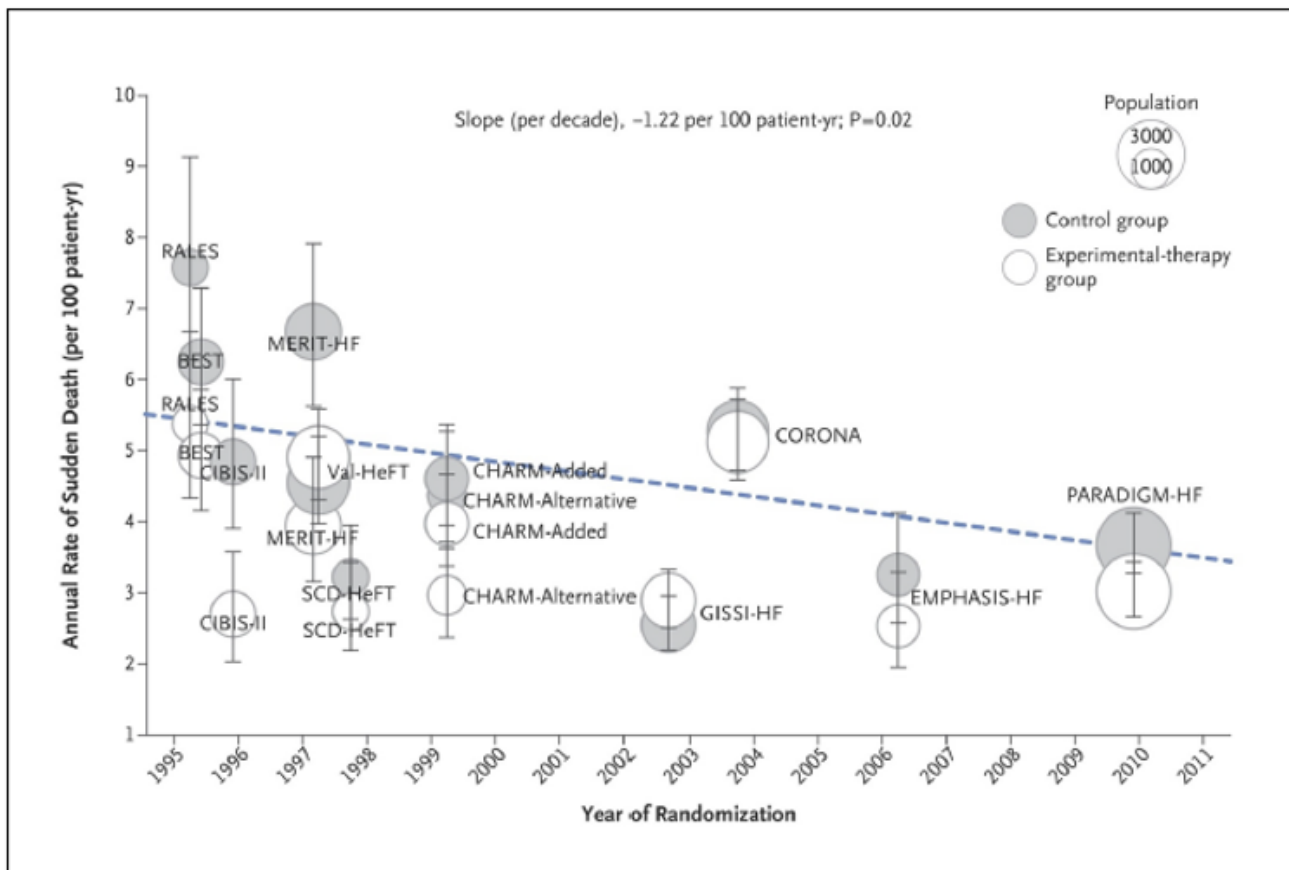
Source population data: Eurostat

Units: MedTech Europe, based on reports from major manufacturers

\*Europe represents total of listed countries

[www.medtecheurope.org](http://www.medtecheurope.org)

# Declining Risk of Sudden Death in Heart Failure



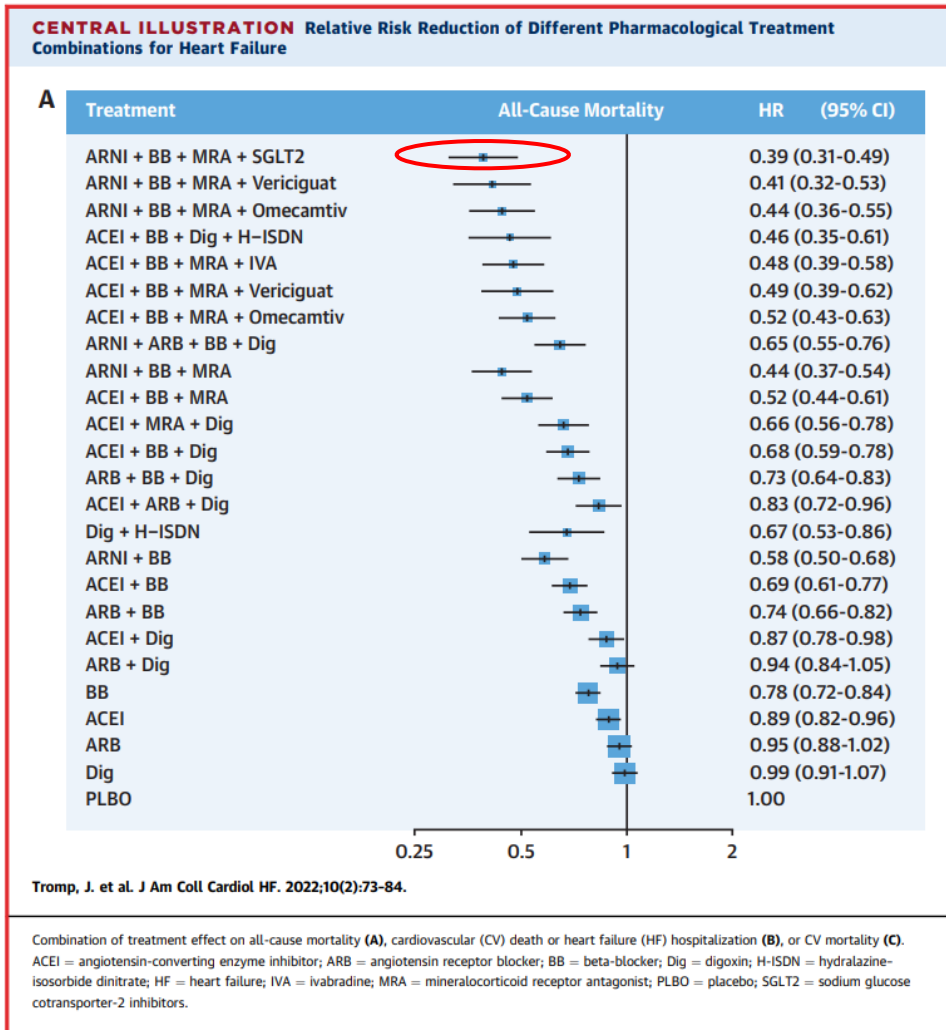
*'... the rate of sudden death ... has fallen over the past two decades,*

*a finding that is consistent with a cumulative benefit of evidence-based medications on sudden death.'*

Shen Li, et al. N Engl J Med 2017; 377:41-51

- **40.195** pazienti con HF provenienti da **12 RCT** condotti **tra il 1995 ed il 2014**.

# I "Fantastici 4"



## A Systematic Review and Network Meta-Analysis of Pharmacological Treatment of Heart Failure With Reduced Ejection Fraction

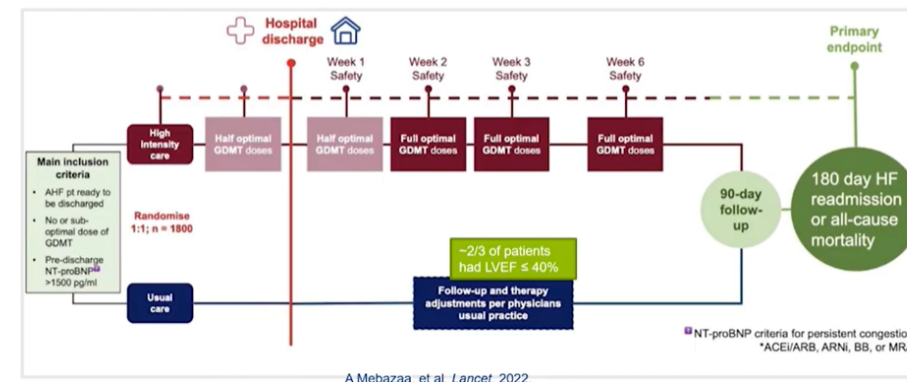


Jasper Tromp, MD, PhD,<sup>a,b,c,\*</sup> Wouter Ouwerkerk, PhD,<sup>b,d,\*</sup> Dirk J. van Veldhuisen, MD, PhD,<sup>a</sup> Hans L. Hillege, MD, PhD,<sup>a</sup> A. Mark Richards, MBChB, PhD,<sup>e,f,g</sup> Peter van der Meer, MD, PhD,<sup>a</sup> Inder S. Anand, MD,<sup>h</sup> Carolyn S.P. Lam, MBBS, PhD,<sup>a,b,c</sup> Adriaan A. Voors, MD, PhD<sup>a</sup>

Il maggior beneficio totale stimato per la **combinazione** di ARNI, BB, MRA e SGLT2i

Maggior beneficio se la titolazione avviene **velocemente**

Safety, tolerability and efficacy of up-titration or GDMT for acute HF (STRONG-HF): a multinational, open-label, randomized trial



# «Un approccio più riflessivo....»

Le ragioni per cui stiamo assistendo ad una sorta di revisionismo...

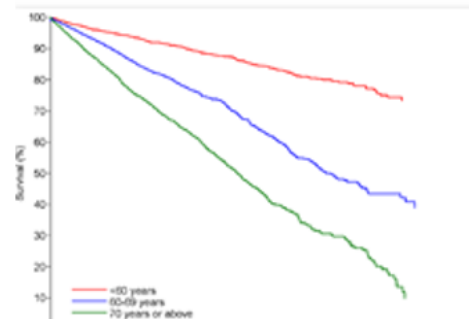
Chiara **CONSAPEVOLEZZA** dei benefici dell'ICD, ma maggiore attenzione anche alle possibili complicanze.



Limits of T-ICD: the weak part is the lead

High voltage leads are not eternal.....

'Younger' ICD recipients generally have a better life expectancy and survive longer than their TV-ICD lead and the greatest risk of complications with a TV system is related to the ICD lead<sup>2</sup>



**Lead infections**



25% lead failure at 10 years (OPTUM database)

OPTUM database showed that:  
**1 IN 4**

**10%**

Lead failure<sup>2</sup>

**6.5%**

Lead Placement issues\*\*2

**3%**

Infection<sup>2</sup>

# Vale la pena aspettare?

## HF-OPT Study - Patients with *de novo* HFrEF (LVEF $\leq 35\%$ )

### Population



598 patients with *de novo* HFrEF

### Intervention



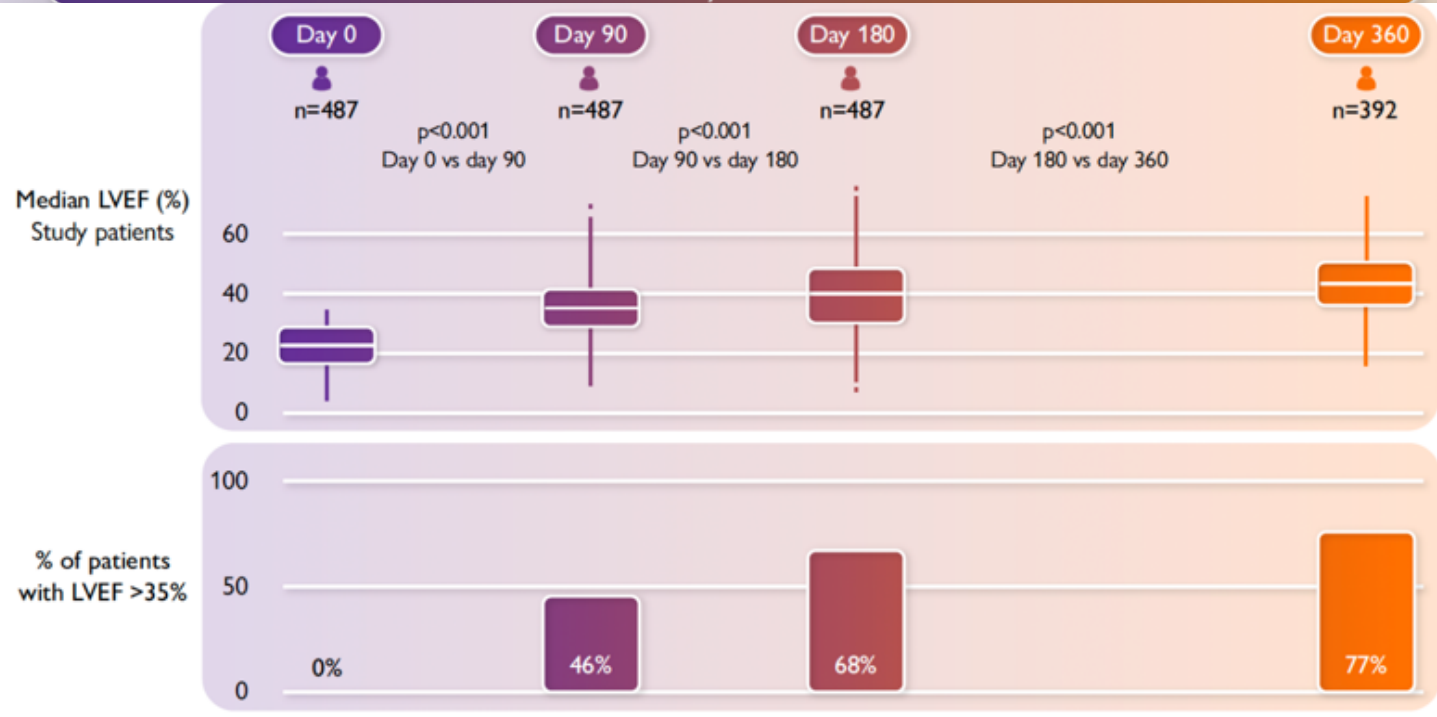
Optimised GRMT + WCD

### Time points



Echocardiographic evaluation at baseline, 90/180/365 days

### Primary outcome



### Therapy duration and improvement of ventricular function in *de novo* heart failure: the Heart Failure Optimization study

Christian Veltmann<sup>1,2,\*†</sup>, David Duncker<sup>1†</sup>, Michael Doering<sup>3</sup>, Siva Gummadu<sup>4</sup>, Michael Robertson<sup>5</sup>, Thomas Wittlinger<sup>6</sup>, Byron J. Colley<sup>7</sup>, Christian Perings<sup>8</sup>, Orvar Jonsson<sup>9</sup>, Johann Bauersachs<sup>1</sup>, Robert Sanchez<sup>10</sup>, and Lars S. Maier<sup>11</sup>; for the Heart Failure Optimization Study (HF-OPT) Investigators

- 46% dei pazienti ha mostrato un recupero della FE > 35% a 3 mesi
- 68% dei pazienti ha mostrato un recupero della FE > 35% a 6 mesi



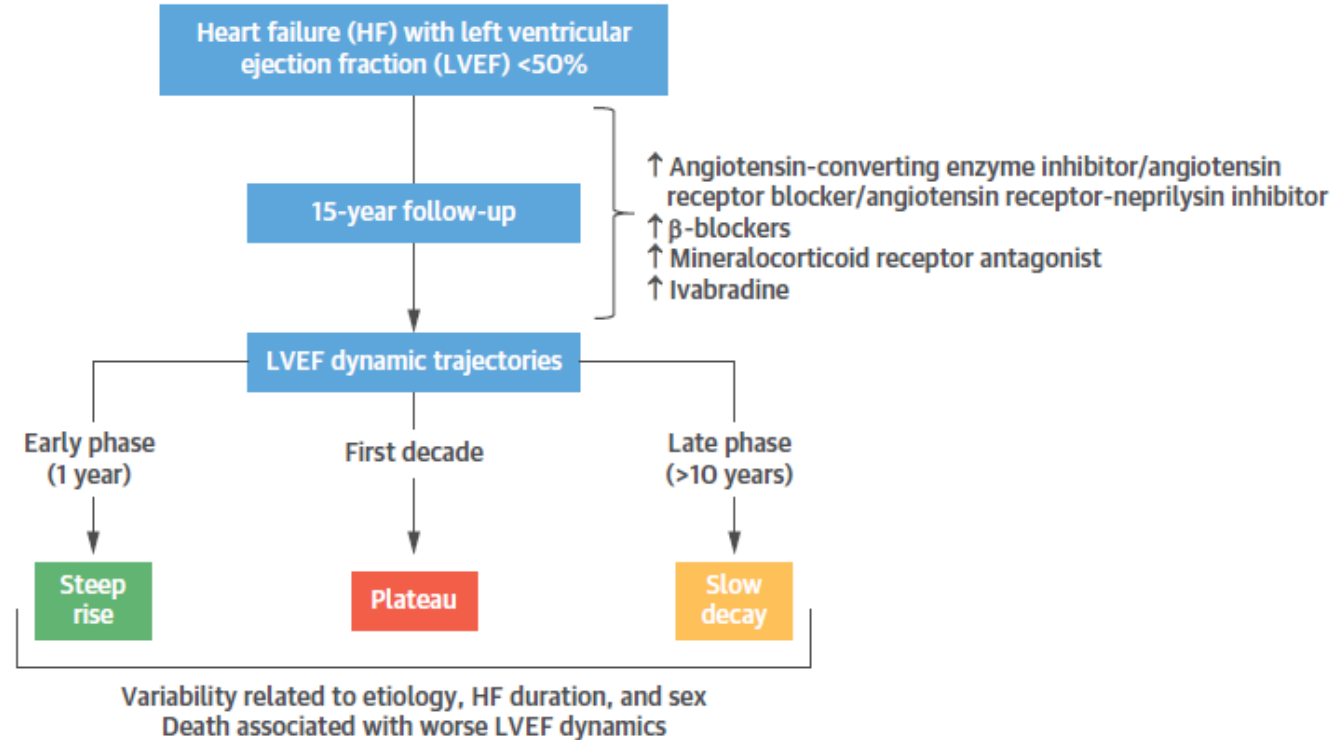
89% dei pazienti ha mostrato un recupero della FE > 35% quando BB, ARNI e MRA erano alla **dose massima** a 6 mesi

- SGLT2 inhibitors were not included within the study.

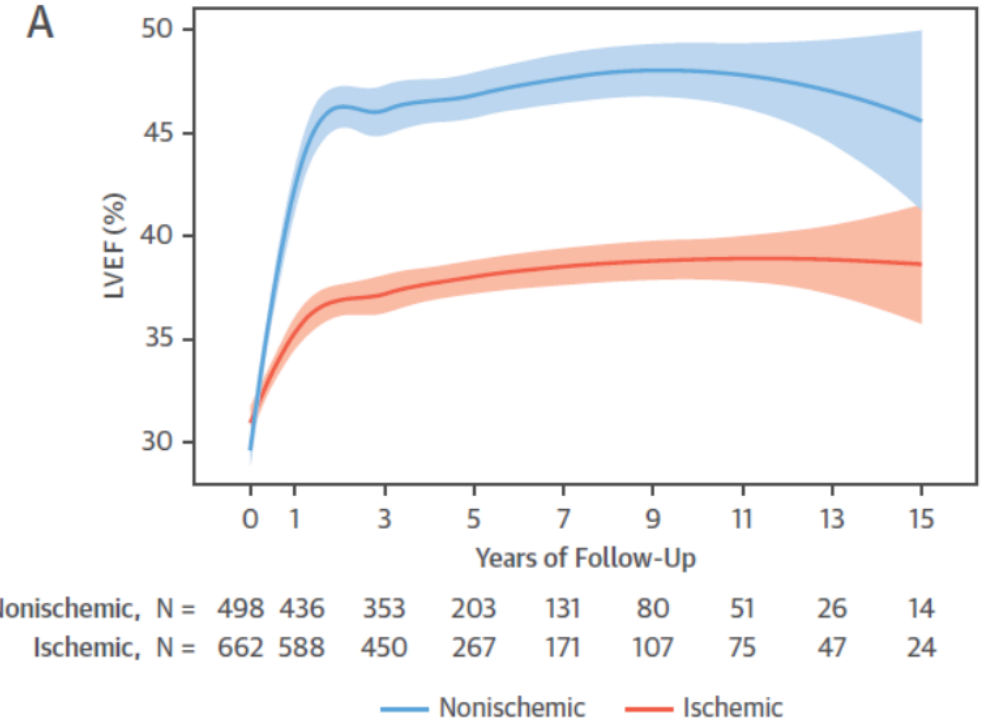


Josep Lupón, MD, PhD,<sup>a,b,c,d,e,f,g,h,i,j,k,l,m,n,o,p,q,r,s,t,u,v,w,x,y,z</sup> Giovana Gavidia-Bovadilla, MSc,<sup>a,f</sup> Elena Ferrer, MD,<sup>b</sup> Marta de Antonio, MD, PhD,<sup>a,b</sup> Alexandre Perera-Lluna, PhD,<sup>c,d,e</sup> Jorge López-Ayerbe, MD,<sup>b</sup> Mar Domingo, MD, PhD,<sup>a</sup> Julio Núñez, MD, PhD,<sup>d,i,j</sup> Elisabet Zamora, MD, PhD,<sup>a,b,c,d,e</sup> Pedro Moliner, MD,<sup>a,b</sup> Patricia Díaz-Ruata, MSc,<sup>f,g</sup> Javier Santesmases, MD,<sup>a</sup> Antoni Bayés-Genís, MD, PhD,<sup>a,b,c,d,e,f,g,h,i,j,k,l,m,n,o,p,q,r,s,t,u,v,w,x,y,z</sup>

# EF trajectory - Is it worth waiting?



Lupón, J. et al. J Am Coll Cardiol. 2018;72(6):591-601.



## Sudden cardiac death in newly diagnosed non-ischaemic or ischaemic cardiomyopathy assessed with a wearable cardioverter-defibrillator: the German nationwide SCD-PROTECT study

• **Elevata incidenza di VT/VF** fin dalla dimissione (6 vs 8,4 eventi/100 anni-paziente nei pazienti non ischemici e ischemici), **2–3 volte superiore** rispetto all'HFrEF cronico con ICD.

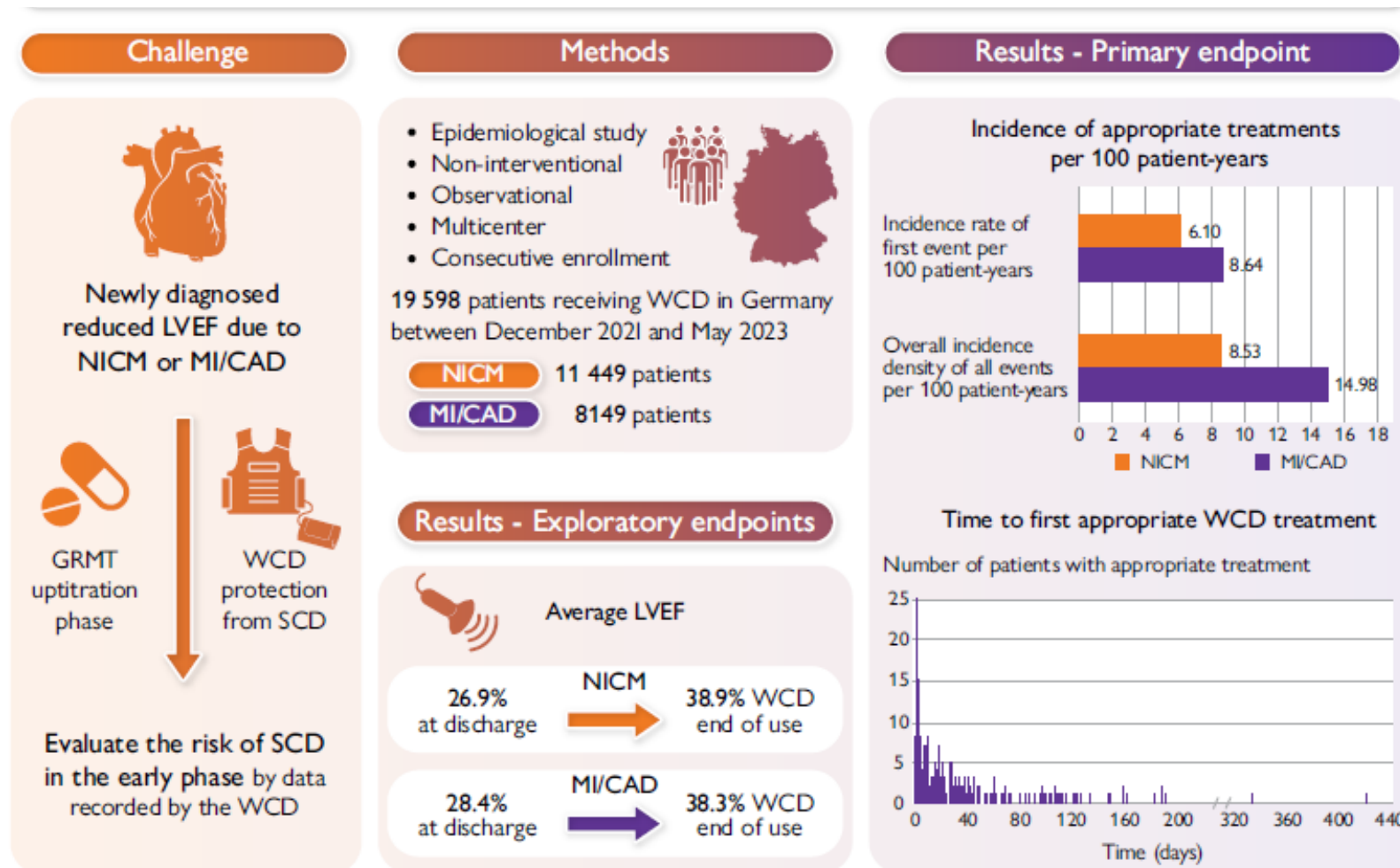
• **Massima vulnerabilità precoce:** circa 1/3 degli eventi si verifica entro i **primi 10 giorni**; il rischio è concentrato nei **primi 30–90 giorni**.

• **Recupero della funzione ventricolare:** 53% dei pazienti raggiunge **LVEF >35%**.

• **Solo il 36%** richiede successivamente un **ICD definitivo**.

• **Il WCD** colma il periodo ad alto rischio fino all'effetto della GDMT.

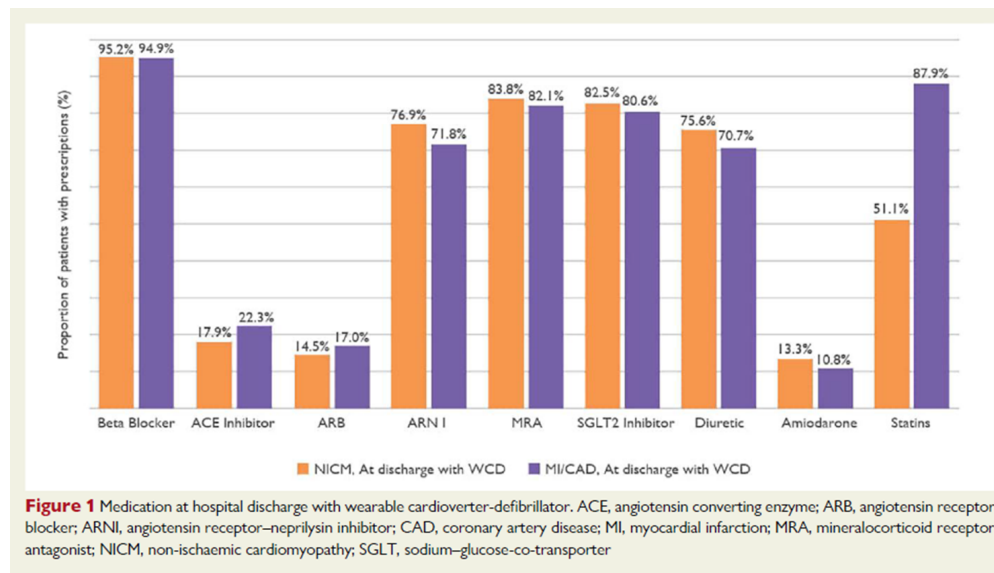
## SCD-PROTECT: Sudden cardiac arrest in patients with newly diagnosed non-ischaemic cardiomyopathy or coronary artery disease



GRMT, guideline-recommended medical therapy; LVEF, left ventricular ejection fraction; MI/CAD, myocardial infarction/coronary artery disease; NICM, non-ischaemic cardiomyopathy; SCA/SCD, sudden cardiac arrest/death; WCD, wearable cardioverter defibrillator

Duncker, D, et al. *European Heart Journal*.

# SCD-PROTECT: Sudden cardiac arrest in patients with newly diagnosed non-ischaemic cardiomyopathy or coronary artery disease



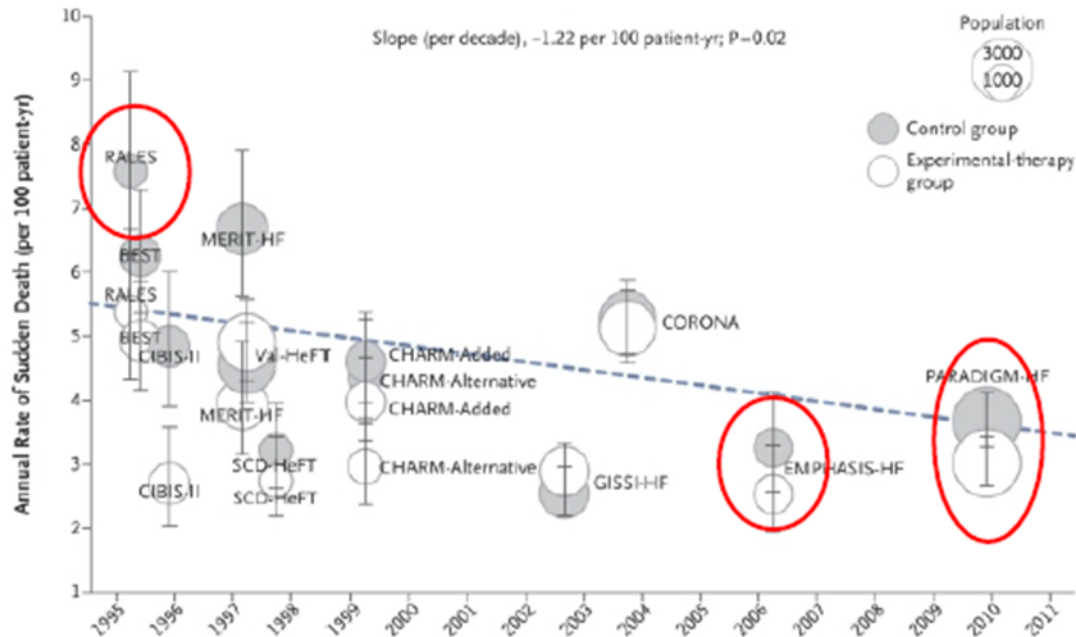
**GDMT al momento della  
dimissione >80% per tutti e  
quattro i pilastri**



**I pazienti hanno  
indossato il  
dispositivo per  
un periodo di  
due mesi con  
>22h/die di  
wearing time**

**I tassi di SCD stanno davvero diminuendo nei trial clinici?**

# Declining Risk of Sudden Death in Heart Failure



|                 | RALES | EMPHASIS-HF | PARADIGM-HF |
|-----------------|-------|-------------|-------------|
| NYHA III/IV (%) | 99.6  | 0           | 25.5        |
| LVEF (%)        | 25.2  | 26.1        | 29.4        |

In control groups

L'inclusione del livello basale di **NT-ProBNP** nell'**analisi multivariata NON** ha fatto emergere differenze significative nei tassi di SCD tra lo studio **Val-HeFT** (condotto nel 1995) il recente **PARADIGM-HF** cardiaca improvvisa (SCD)

Shen Li, et al. N Engl J Med 2017; 377:41-51

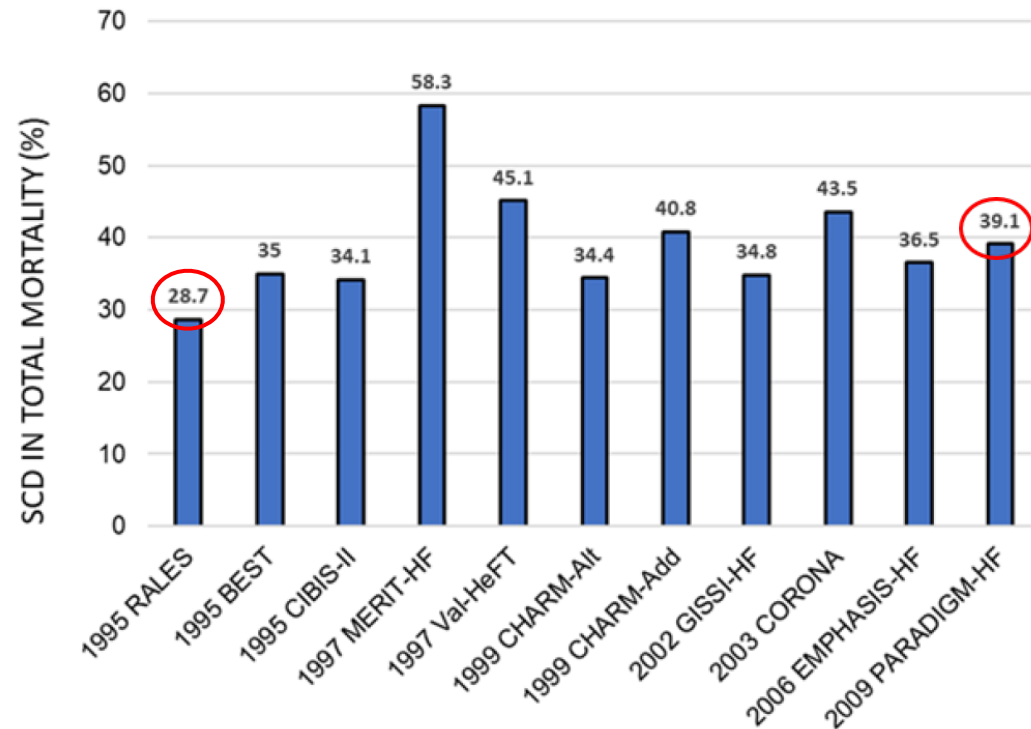
1. Esclusione dei pazienti con ICD
2. Marcata eterogenità dei RCTs
3. Esclusione di 30 RCTs per mancanza dati

-->**GRAVITA'** dei pazienti arruolati

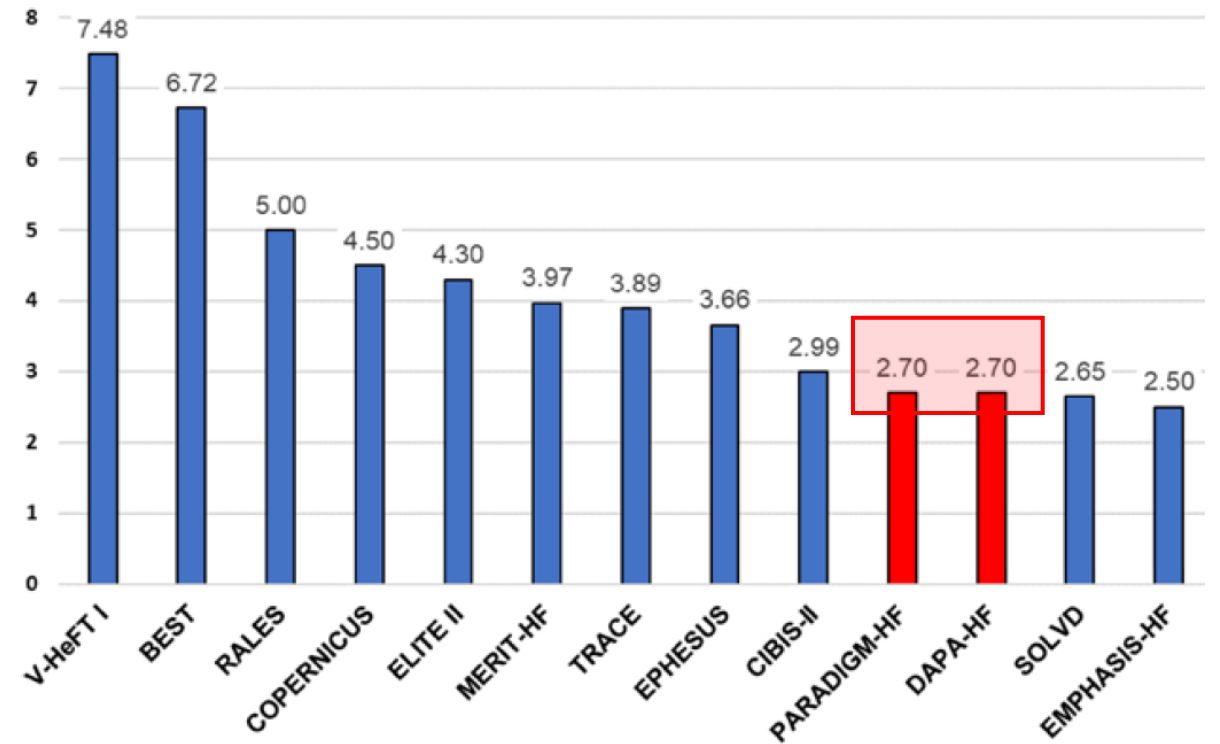
## PRIMER

## Declining Risk of Sudden Cardiac Death in Heart Failure: Fact or Myth?

Francisco Leyva, MD; Carsten W. Israel, PhD; Jagmeet Singh, MD, PhD



**SCD rate as a percentage of total mortality in HF trials**



**Residual risk of SCD in HF trials.**

The graph shows SCDs (%) per 100 patient years in the intervention arm in HF trials.

**Qual è il “rischio accettabile”  
di morte cardiaca improvvisa?**

# PARADIGM-HF: Sacubitril / Valsartan and SCD

N = 8399

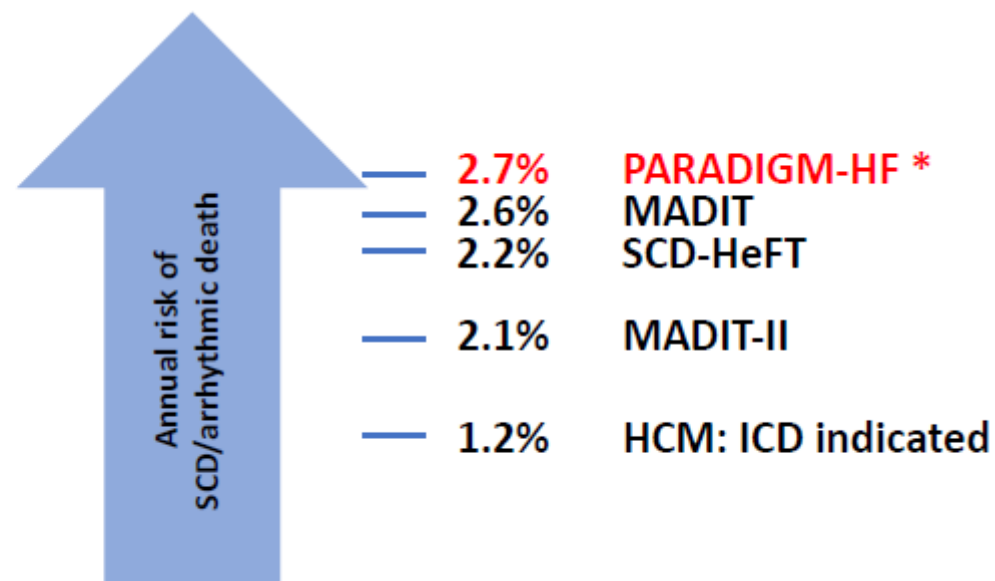
Median follow-up: 27 months (2.25 yrs)

| LCZ                  |     |               |
|----------------------|-----|---------------|
|                      | N   | % of patients |
| Total deaths         | 711 | 17.0          |
| Cardiovascular death | 558 | 13.3          |
| Sudden death         | 250 | 6.0           |
| Last contact <1 h    | 167 | 4.0           |
| 1–24 h               | 83  | 2.0           |

In treatment arm:

**SD annual event rate: 2.7%**

**5-year event rate: 13.5%**



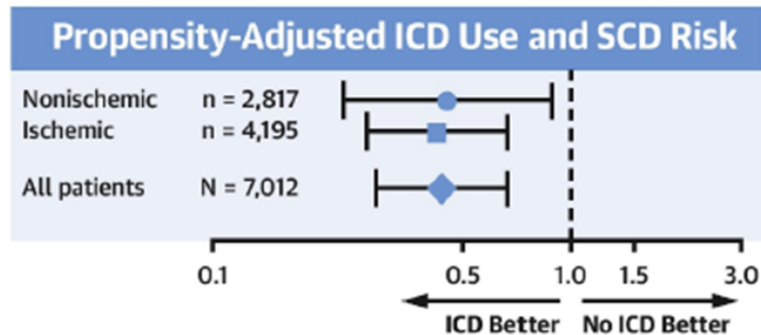
Desai AS, et al. Eur Heart J 2015;1990–1997

\* Rohde LE, et al. JACC Heart Fail. 2020;8:844-855

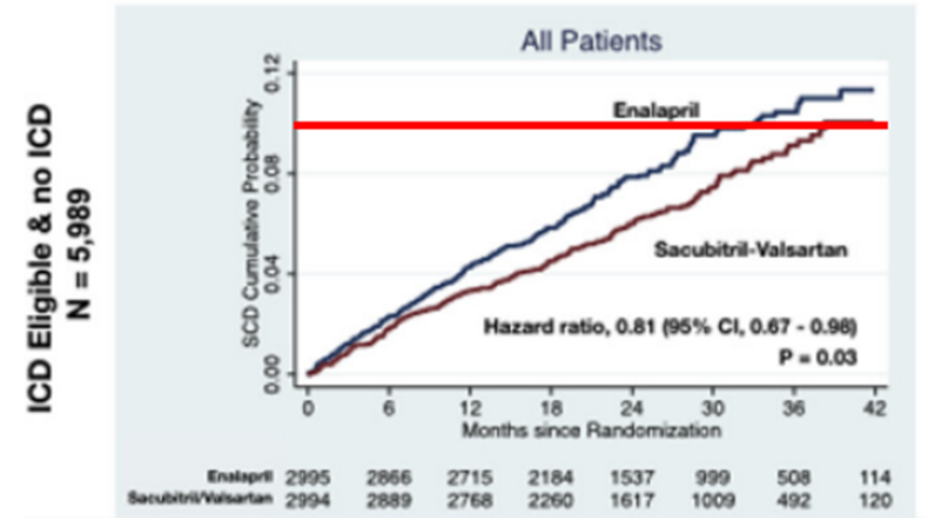
# Sacubitril/Valsartan and Sudden Cardiac Death According to Implantable Cardioverter-Defibrillator Use and Heart Failure Cause

A PARADIGM-HF Analysis

- **15%** had ICDs
- **85%** (7,145) were eligible for ICDs \*



- **DAPA-HF**: 26.2% received an ICD despite LVEF <40%.
- **EMPEROR-Reduced**: 31.4% with ICD, though 73% had LVEF ≤30%.



**SCD: 1/3 of total mortality**

Analisi aggiustata per propensity score: **ICD riduzione del 56% rischio SCD** (HR 0,44; P<0,01)

**Is this relevant to current practice?**

# Effect on SCD risk: ACEi

## Captopril (SAVE)

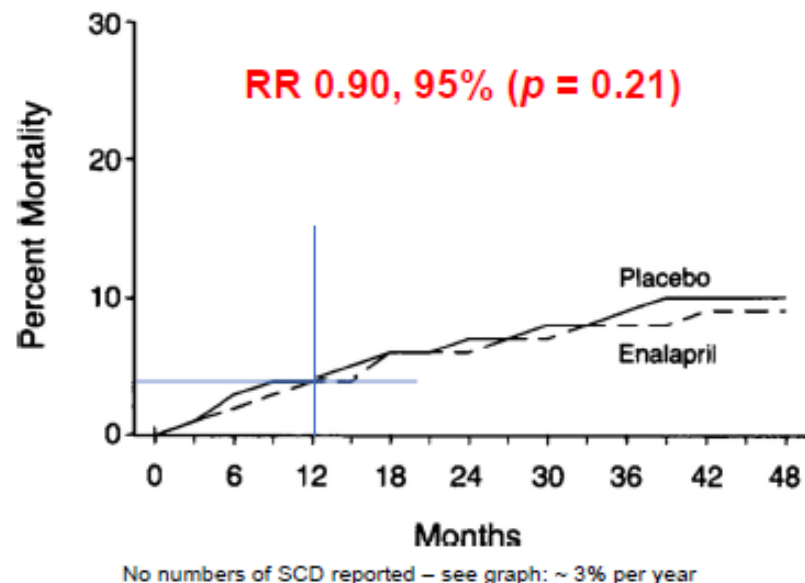
| CAUSE OF DEATH                         | no. of deaths |           | RISK REDUCTION<br>(95% CI)<br>percent | P VALUE |
|----------------------------------------|---------------|-----------|---------------------------------------|---------|
|                                        | PLACEBO       | CAPTOPRIL |                                       |         |
| <b>Cardiovascular</b>                  | 234           | 188       | 21 (5-35)                             | 0.014   |
| Atherosclerotic heart disease          | 222           | 174       | 23 (6-37)                             | 0.009   |
| Progressive heart failure†             | 58            | 38        | 36 (4-58)                             | 0.022   |
| Sudden, with preceding symptoms        | 50            | 43        | —                                     | NS      |
| Sudden, unexpected                     | 75            | 62        | —                                     | NS      |
| Acute myocardial infarction            | 25            | 24        | —                                     | NS      |
| Cardiac procedure                      | 9             | 5         | —                                     | NS      |
| Other cardiac                          | 5             | 2         | —                                     | NS      |
| Vascular                               | 12            | 14        | —                                     | NS      |
| <b>Noncardiovascular</b>               | 41            | 40        | —                                     | NS      |
| Cancer                                 | 20            | 14        | —                                     | NS      |
| Infection or gastrointestinal bleeding | 18            | 16        | —                                     | NS      |
| Traumatic or unknown                   | 3             | 10        | —                                     | NS      |
| <b>All</b>                             | 275           | 228       | 19 (3-32)                             | 0.019   |

56% of deaths were SCD

Pfeffer MA, et al. N Eng J Med;1992;327:669-677.

## Enalapril (SOLVD)

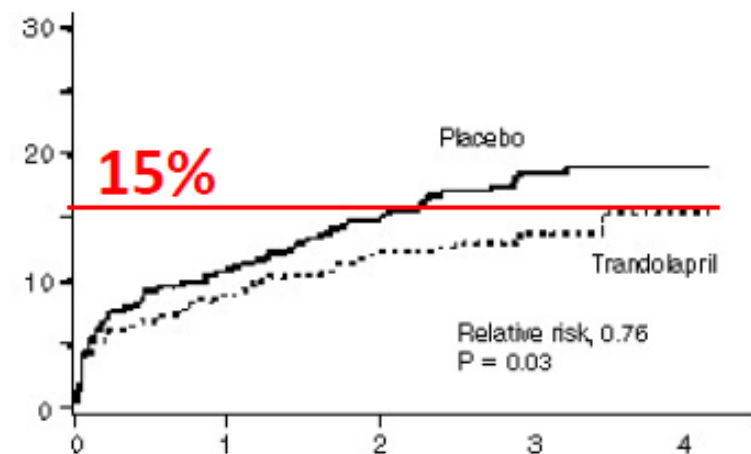
### Arrhythmic Death



The SOLVD investigators. N Engl J Med 1991; 325:293-302

## Trandolapril (TRACE)

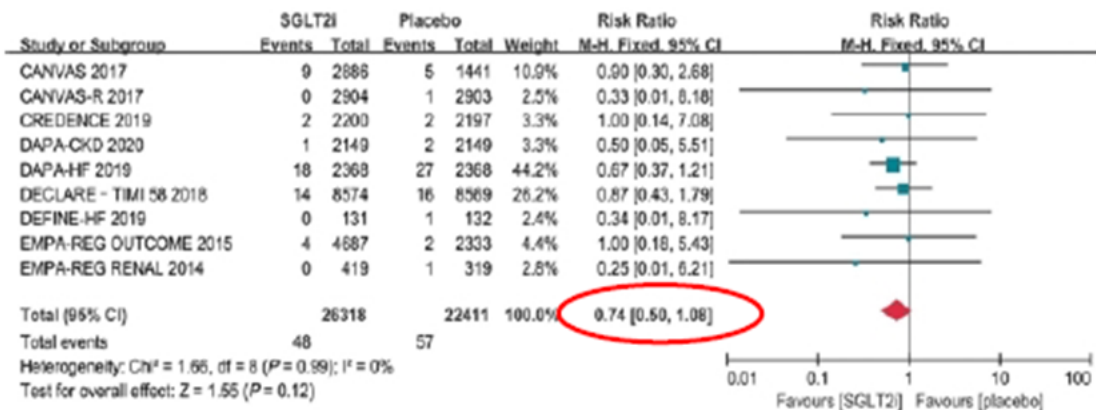
### SCD



Kober L, et al. TRACE study. N Eng J Med 1995; 333:1670-1

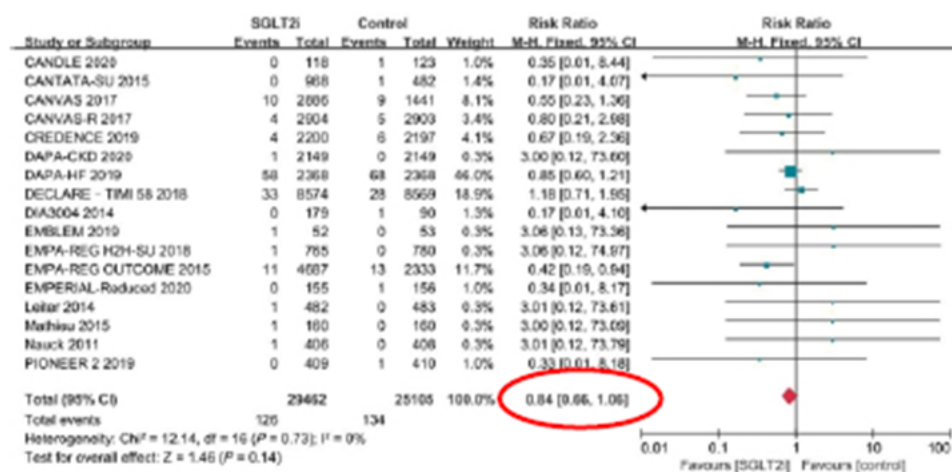
# SGLT-2i and SCD / ventricular arrhythmias

## SCD



**NO EFFECT**

## VENTRICULAR ARRHYTHMIAS



**NO EFFECT**

‘... there is no plausible explanation as to why low-dosage SGLT2i therapy might decrease the incidence of VAs’

# Effect on SCD risk: beta-blockers

## PERSPECTIVE

### Compelling First-Line Drug and Device Therapies for the Prevention of Sudden Death in Patients With Chronic Heart Failure and a Reduced Ejection Fraction Who Are Candidates for an Implantable Cardioverter-Defibrillator

Packer M. Circ Arrhythm Electrophysiol. 2019;12:e007430

#### ' $\beta$ -Adrenergic Receptor Blockers

$\beta$ -Blockers have decreased the risk of SCD by 35% to 45% of patients with chronic HFrEF in large-scale trials,<sup>2</sup> in whom ICDs were rarely used.'

#### COPERNICUS (carvedilol)

|                          |          |          |       |
|--------------------------|----------|----------|-------|
| Sudden death             | 69 (6.1) | 45 (3.9) | 0.016 |
| Ventricular tachycardia  | 26 (2.3) | 12 (1.0) | 0.019 |
| Ventricular fibrillation | 23 (2.0) | 12 (1.0) | 0.053 |

**SCD:** 4.5% per yr  
22.5% per 5 yrs.

**SCD/VA:** 6.81% per yr  
34.1% per 5 yrs

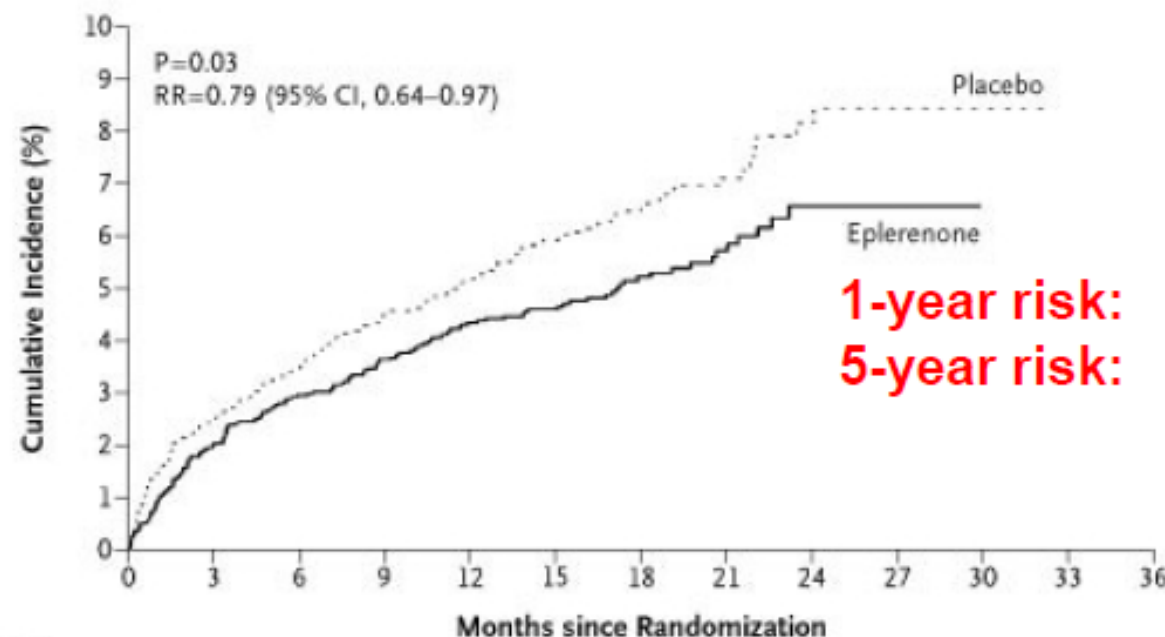
# Effect on SCD: MRAs

“In large-scale trials, spironolactone and eplerenone have been shown to reduce the risk of SCD by  $\approx 20\%$  in patients with chronic HF, who generally did not have an ICD.”

Packer M. Circ Arrhythm Electrophysiol. 2019;12:e007430

## EPHESUS TRIAL: EPLERENONE

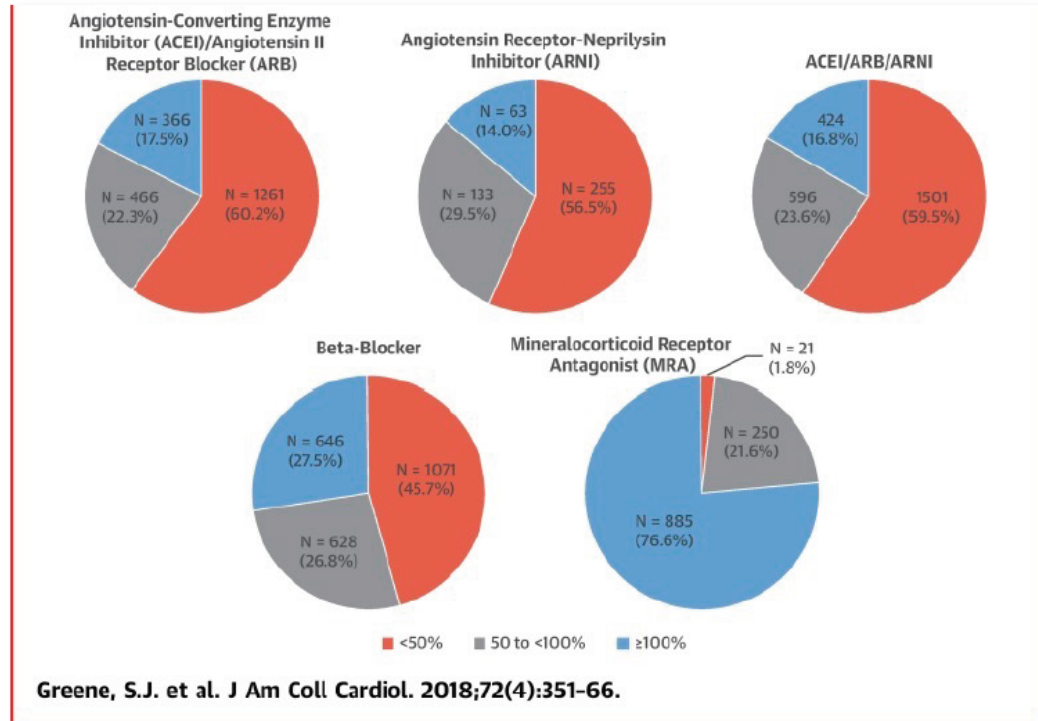
### Sudden Cardiac Death



\*, 162 SCDs/3319= 4.88% over mean follow-up of 16 months; = 3.66% per year = 18.3% 5-year risk

**I tassi di SCD stanno davvero diminuendo nella “real life”?**

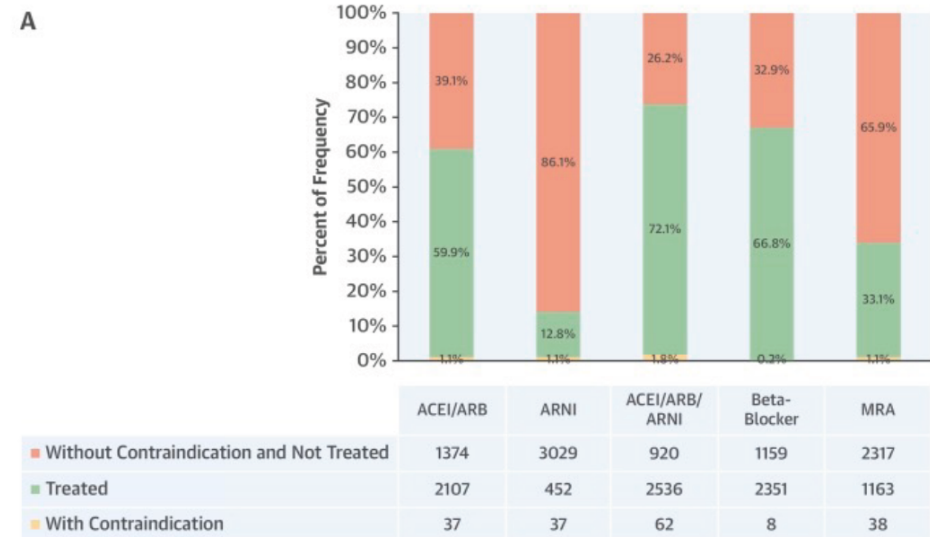
# Ottimizzazione della terapia medica nella “real life”



“Significant gaps in guideline directed use and dosing of evidence-based medications”

→ **Heart failure medication is most commonly underdosed.**

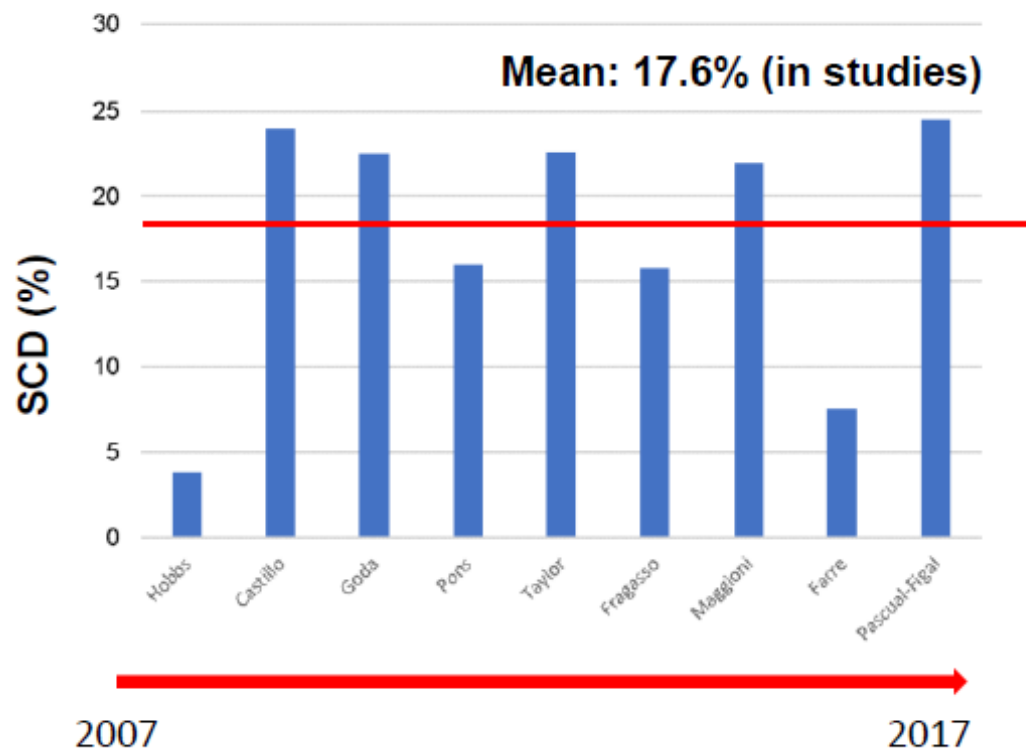
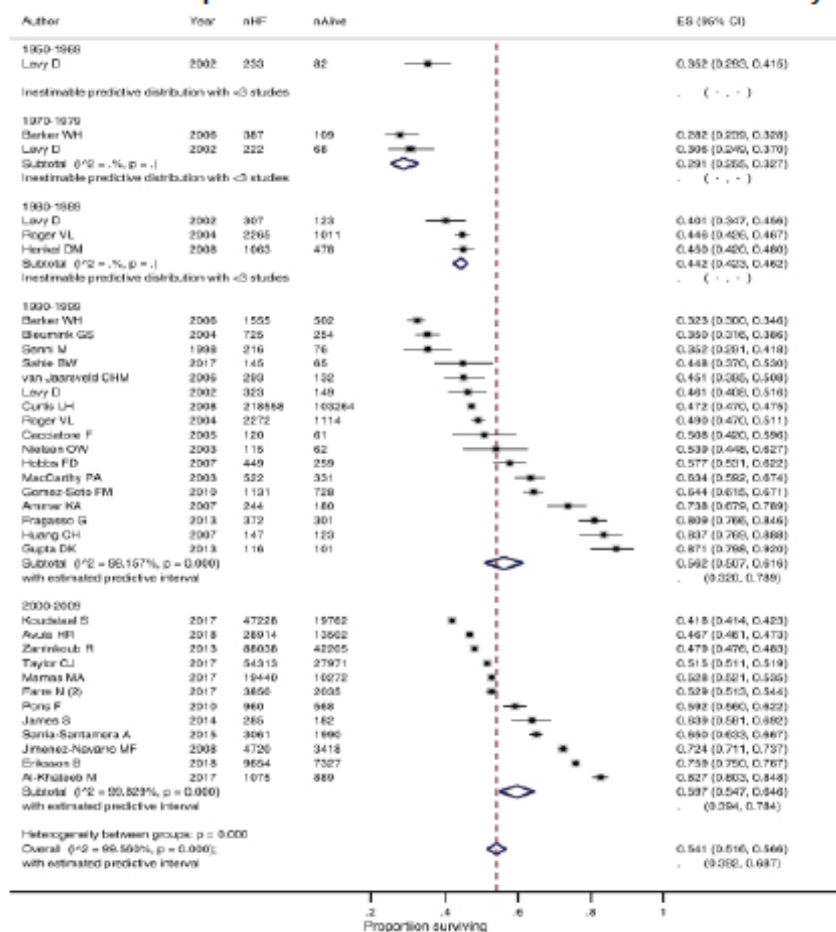
**CENTRAL ILLUSTRATION: Use and Dosing of Guideline-Directed Medical Therapy Among Patients With Chronic HFrEF in Contemporary U.S. Outpatient Practice**



# Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis

60 studies, n = 1.5 million

Survival of patients with chronic heart failure in the community



Jones, NR et al. Eur J Heart Fail 2019;21:1306-1325

**Miglioramento della FE a valori  
 $\geq 35\%$ =non c'è più bisogno  
dell'ICD?**

# Effect of SACubitril/Valsartan on left vEntricular ejection fraction and on the potential indication for Implantable Cardioverter Defibrillator in primary prevention: the SAVE-ICD study

Multicentre, observational, prospective study  
N=230  
HFrEF (LVEF $\leq$ 35%)  
Primary prevention ICDs  
6 month treatment with sacubitril/valsartan

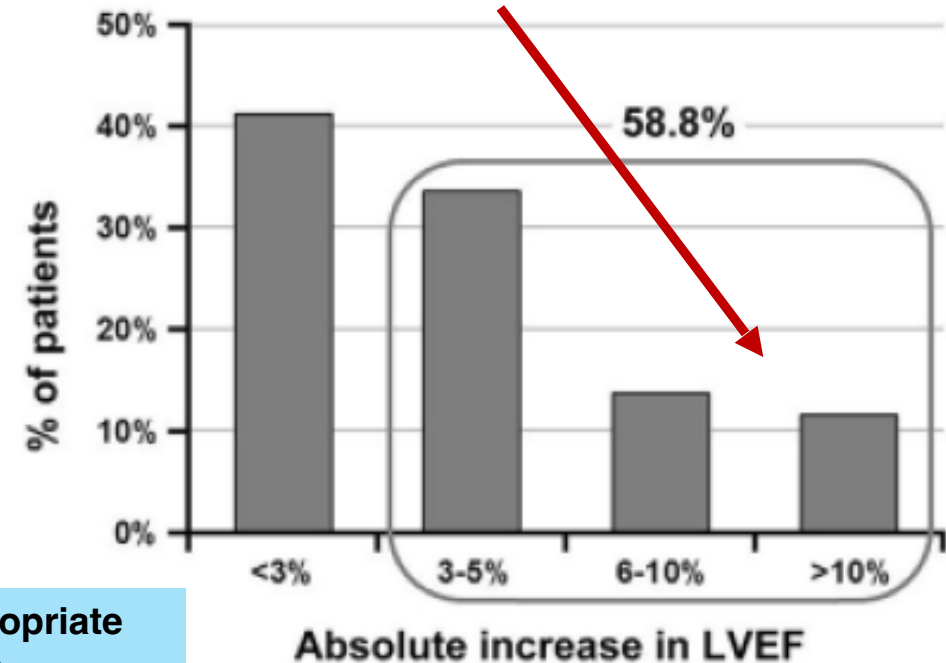
## PRIMARY ENDPOINT

Number of patients no longer meeting LVEF criteria for a primary prevention ICD

Analisi retrospettiva su pazienti con ICD: terapie appropriate comunque, anche nei pazienti con dosaggio massimo

**Non-responder rate to ARNI: 41%**  
( $< 3\%$  increase in LVEF)

**Circa il 25% potrebbe non necessitare più di un ICD**



**5.3% of patients had an arrhythmic event in the first 6 months**

## ICD shocks in recovered LVEF

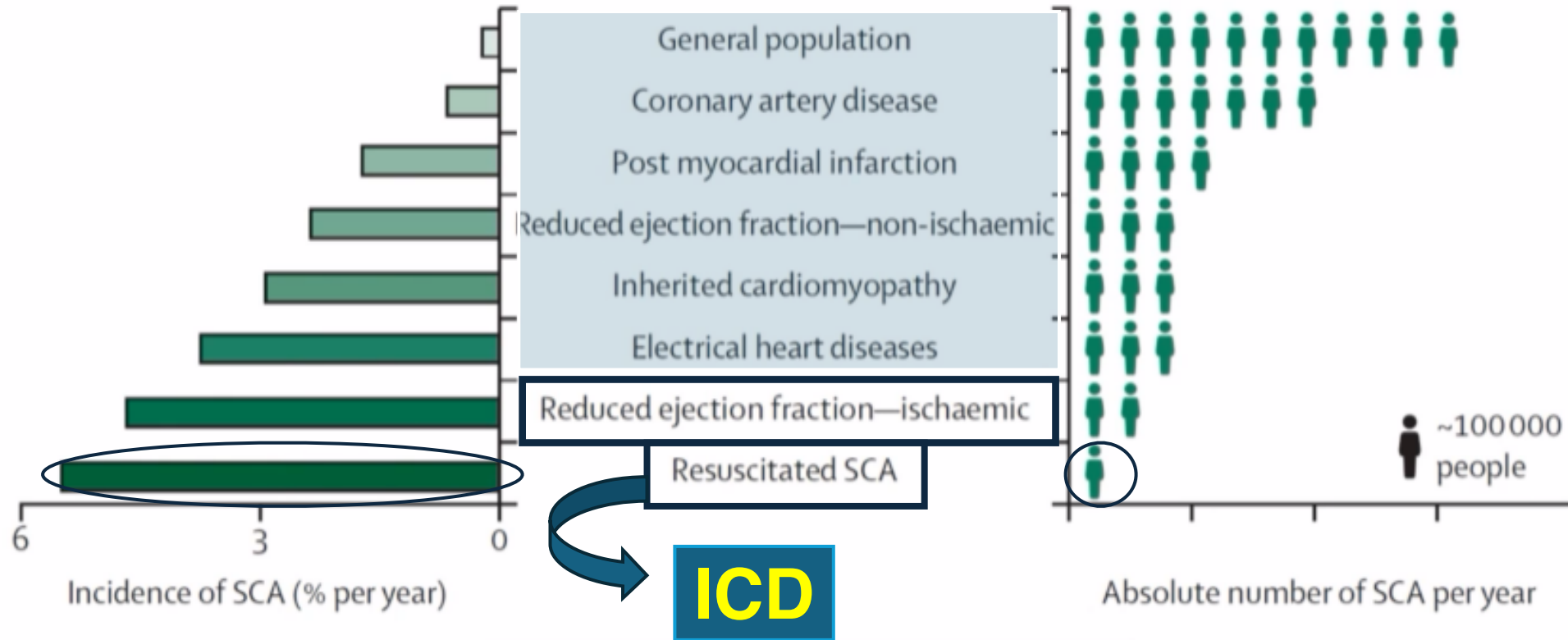
N=26, 355 patients undergoing replacement  
17.4% had partially recovered EF (>35% and ≤50%)  
7.3% had recovered EF (>50%).

Coorte a lungo termine, **fino al 20% dei pazienti con LVEF >35%** ha ricevuto **terapie ICD appropriate** durante il follow-up

### Appropriate ICD shocks after generator change (LVEF>35%)

| Source                                              | Year | Generator exchange, n | ICD shocks following generator exchange and recovered LVEF, n (%) | Years to follow-up |
|-----------------------------------------------------|------|-----------------------|-------------------------------------------------------------------|--------------------|
| Naksuk <i>et al.</i> <sup>6</sup>                   | 2016 | 25                    | 5 (20)                                                            | 6.2 ± 2.2          |
| <sup>a</sup> Madhavan <i>et al.</i> <sup>7</sup>    | 2014 | 71                    | 24 (14)                                                           | 3                  |
| Kini <i>et al.</i> <sup>31</sup>                    | 2016 | 59                    | 5 (8.5)                                                           | 3.5 ± 2.0          |
| <sup>b</sup> Schliamser <i>et al.</i> <sup>33</sup> | 2017 | 70                    | 4 (5.7)                                                           | 2                  |

# Paradosso epidemiologico nella SCD: rischio vs numero assoluto di eventi



Marijon E et al. Lancet 2023;402:883-936

# Oltre alla FE, “*the magic number*”, sappiamo davvero stratificare il rischio?

## PROFID TRIAL

19 datasets from Europe, US and Israel - 224,898 patients

Phase 1, clinical variables.  
Prediction of SCD. ICD patients, LVEF  $\leq 35\%$ .

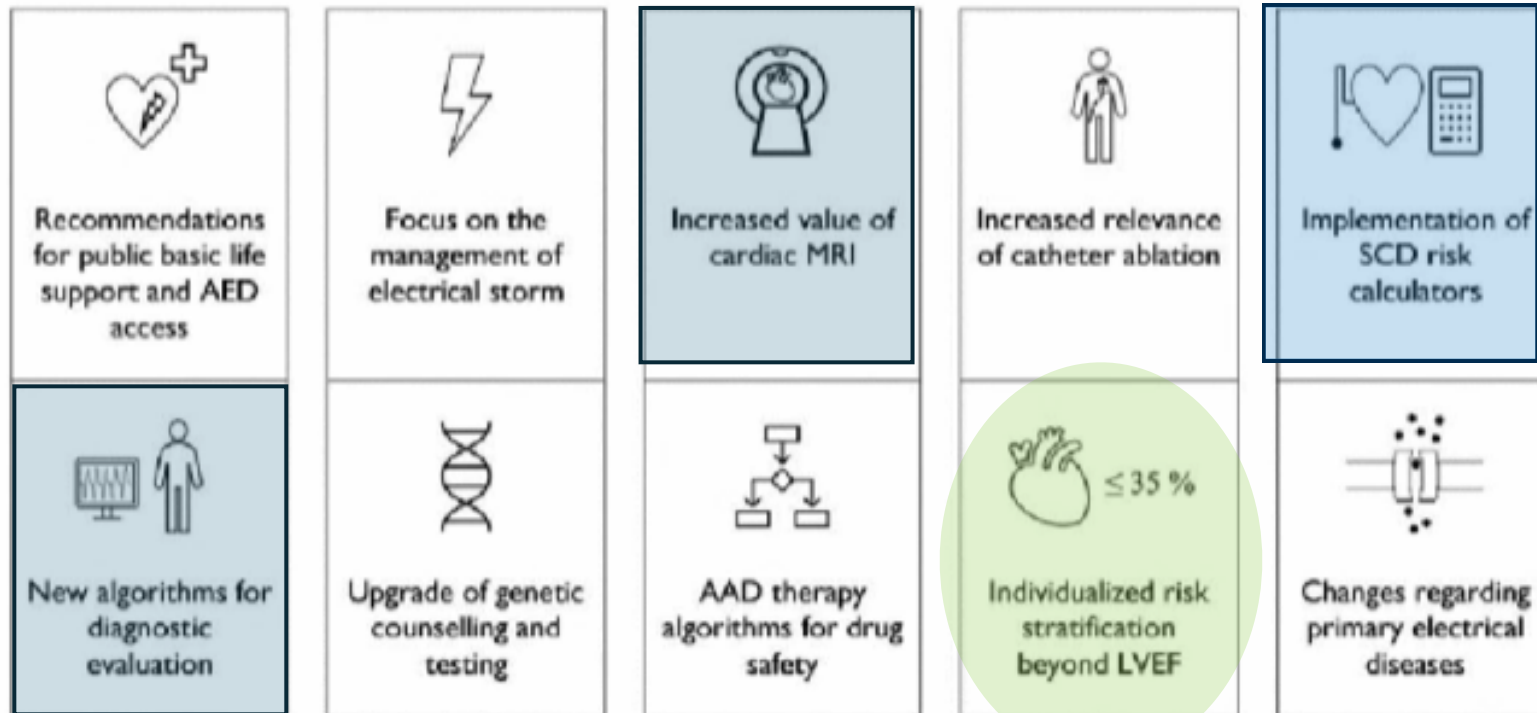
|                          | Method                       | AUC at 12 months<br>(95% CI) | O:E ratio at 12 months<br>(95% CI) |
|--------------------------|------------------------------|------------------------------|------------------------------------|
|                          | LVEF alone                   | 0.523 (0.480, 0.565)         | 0.941 (0.209, 4.241)               |
| statistical<br>modelling | Weibull model                | 0.521 (0.470, 0.572)         | 0.262 (0.049, 1.401)               |
|                          | Flexible parametric<br>model | 0.521 (0.469, 0.572)         | 0.249 (0.047, 1.322)               |
| machine<br>learning      | Random forest                | 0.525 (0.486, 0.563)         | 1.025 (0.221, 4.746)               |
|                          | Deep neural network          | 0.517 (0.419, 0.615)         | 2.114 (0.337, 13.248)              |

Prevention of Sudden Cardiac Death in Heart Failure Patients



# Spotlight on the 2022 ESC Guidelines

## 10 novel key aspects for the prevention of SCD



Könnemann H et al. Europace 2023;25:1-12

## 2023 ESC Guidelines for the management of cardiomyopathies

Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC)

1. Sincope.
2. LGE alla risonanza magnetica
3. Genotipo ad alto rischio
  - LMNA (%SCD anno 5-10%)
  - FLNC var. tron. (5-10%)
  - TMEM43 (5-10%)
  - PLN (3-5%)
  - DSP e RBM20 (3-5%)
4. FE < 45%.
5. TVNS
6. Elevato burden di BEV
7. Sesso maschile

| Primary prevention                                                                                                                                                                                                 | DCM |   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|---|
| An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with DCM, symptomatic heart failure, and LVEF $\leq 35\%$ despite >3 months of OMT. <sup>861,885</sup>          | IIa | A |
| The patient's genotype should be considered in the estimation of SCD risk in DCM. <sup>185,186,869,886</sup>                                                                                                       | IIa | B |
| An ICD should be considered in patients with DCM with a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors (see Table 21). <sup>541,542,867,869,873,878,881,886</sup> | IIa | C |
| An ICD may be considered in selected patients with DCM with a genotype associated with high SCD risk and LVEF >35% without additional risk factors (see Table 21). <sup>869,873,881,886</sup>                      | IIb | C |
| An ICD may be considered in patients with DCM without a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors. <sup>c138,873,874</sup>                                   | IIb | C |

2023 guidelines on CM

LVEF  $\leq 35\%$  (large RCTs)

use genotype

LVEF > 35% + high risk genotype + risk factors

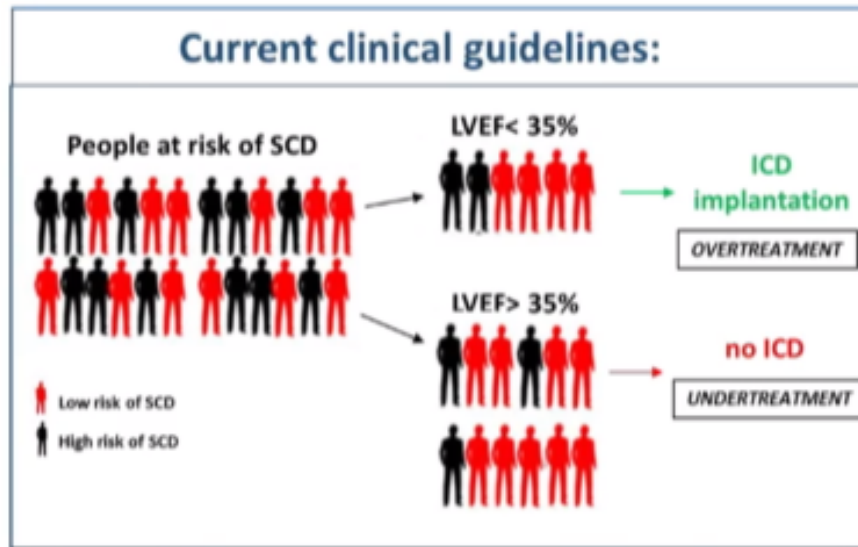
LVEF > 35% + high risk genotype (w/o risk factors)

LVEF > 35%, no genotype but +risk factors

# Conclusioni...

So where are we with SCD prevention?

This is where we are:



This is our ambition



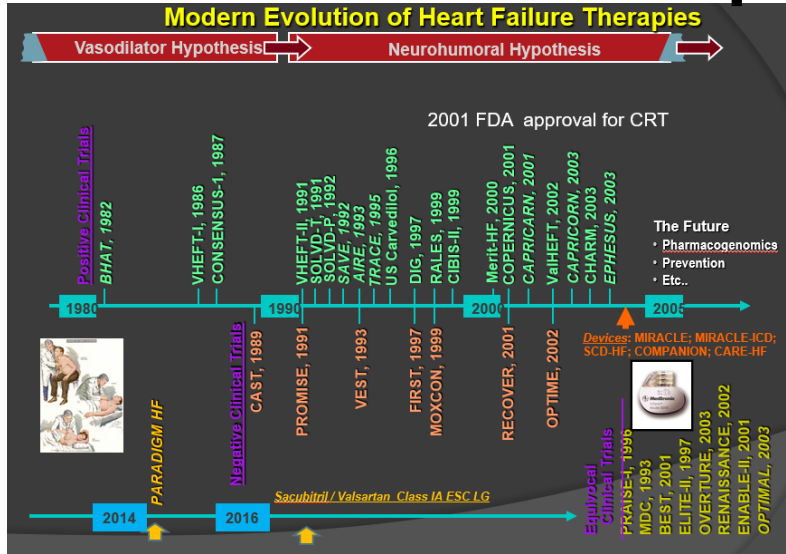
Hindricks et al

# Il Futuro della Stratificazione del Rischio

Il passaggio dal fenotipo geometrico (LVEF) alla stratificazione tissutale e biologica.



# Conclusioni per la pratica clinica



## 1. Il Rischio Assoluto Domina

I farmaci da soli non bastano. Il rischio residuo nello scompenso in GDMT resta più del doppio della soglia critica (2.70% vs 1.2%). La morte improvvisa colpisce inesorabilmente il 22% dei pazienti nel mondo reale.

## 2. L'Illusione Ecocardiografica

Il reverse remodeling (LVEF >35%) rappresenta una guarigione emodinamica, NON elettrica. Le cicatrici fibrose restano attive e fino al 20% I 20% dei pazienti 'recuperati' necessita ancora di shock salvavita.

## 3. Sinergia come Standard of Care

Mai ritardare la protezione. GDMT e ICD sono alleati inseparabili, garantendo una riduzione del 56% della SCD in combinazione. Integrazione immediata per azzerare il rischio della finestra d'attesa.

Evidenze consolidate dal Programma internazionale peer-to-peer DIRECT HF.



**GRAZIE PER L'ATTENZIONE**



**CONGRESSO**  
ROMA, 25 - 27 Giugno 2026