UPDATE SCD 2025

profid-project.eu

Risk stratification for sudden cardiac death after myocardial infarction: Where to go after PROFID?
We must continue, but employing new approaches

Valentina Kutyifa, MD, PhD, FACC, FHRS, FESC

University of Rochester Medical Center, Rochester, NY and Semmelweis University, Hungary

Update on Sudden Cardiac Death Symposium 2025, November 28, 2025, Berlin, Germany

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 847999

Disclosures

Valentina Kutyifa MD, PhD, FHRS, FACC, FESC

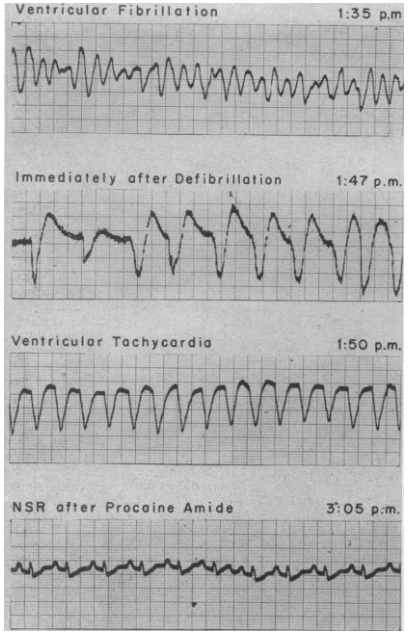
Company	Relationship
Boston Scientific, ZOLL, Biotronik, Spire Inc., NIH	Research Grant
ZOLL, Biotronik, Medtronic, Abbott	Consultant fees

Serves on the Steering Committee of PROFID EHRA and CONTEMP-ICD.

PROFD EHRA is publicly funded under Horizon 2020 program, no. 847999.

Closed-Chest Cardiac Massage in the Treatment of Ventricular Fibrillation Complicating Acute Myocardial Infarction — Report of Three Cases with Survival

- Dr. Moss's first VF case as an assistant resident at MGH
- 62-year-old housewife, diabetes, prior MI, presents with chest pain, prescribed strict bedrest and nitrates
- Develops fainting spells during observation
- Combination of external cardiac massage and external cardiac defibrillation was successfully employed for ventricular fibrillation after acute myocardial infarction



Moss et al, NEJM, 1962

Risk Stratification for Sudden Cardiac Death

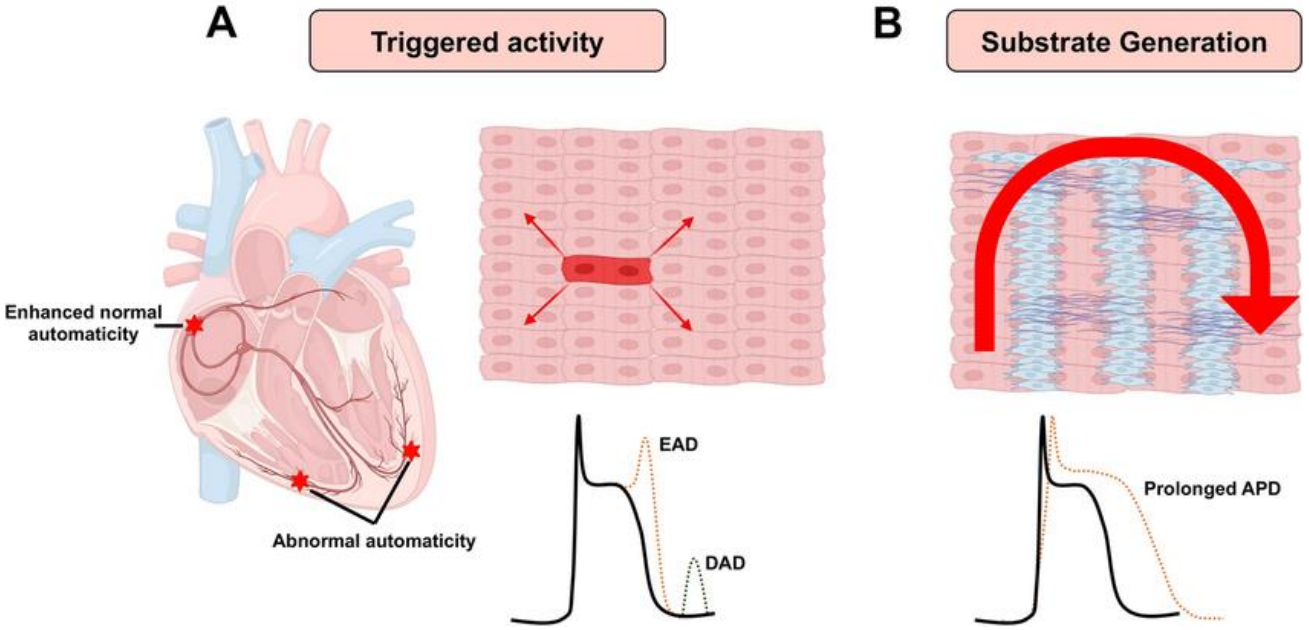
Am J Cardiol 1983 Oct 1;52(7):667-9. doi: 10.1016/0002-9149(83)90394-6.
Prognosis after myocardial infarction, A.J. Moss

✓A substantial number of patients die in the first year after myocardial infarction.

✓The major determinants of risk during this period appear to be the **extent of either damaged or potentially ischemic myocardium** and the **degree of electrical instability.**

✓Anterior infarction, early left ventricular failure, late significant arrhythmias, and **markedly reduced radionuclide left ventricular ejection fraction** are the major clinical markers of risk.

Ventricular Arrhythmia Mechanisms

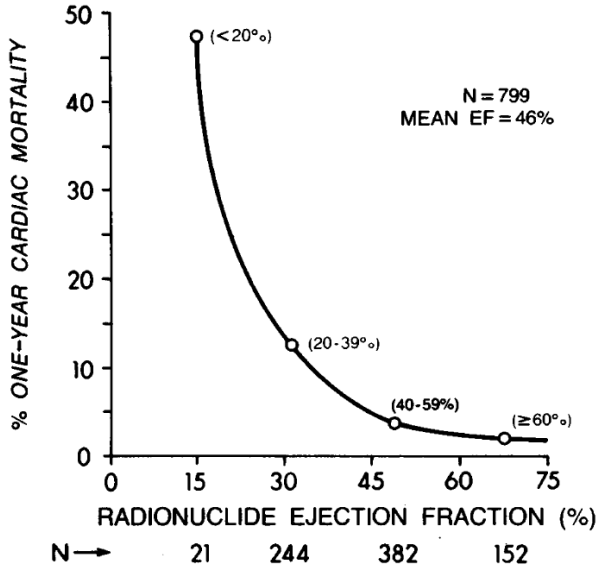


TRIAD:

- abnormal automaticity
- triggered activity
- reentry

RISK STRATIFICATION AND SURVIVAL AFTER MYOCARDIAL INFARCTION

THE MULTICENTER POSTINFARCTION RESEARCH GROUP



ejection fraction below 0.40, ventricular ectopy of 10 or more depolarizations per hour, advanced New York Heart Association functional class before infarction, and rales

Moss et al., NEJM, 1983

RISK STRATIFICATION AND SURVIVAL AFTER MYOCARDIAL INFARCTION

THE MULTICENTER POSTINFARCTION RESEARCH GROUP

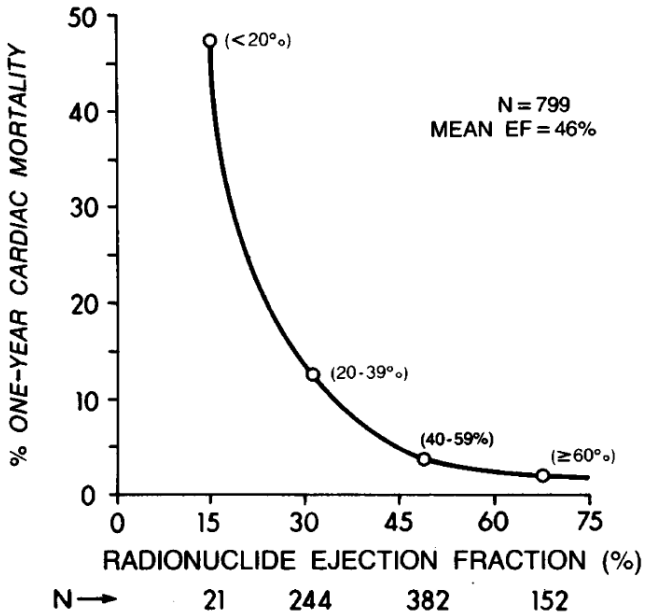


Table 2. Contribution of the Preselected Factors to the Final Survival Model.

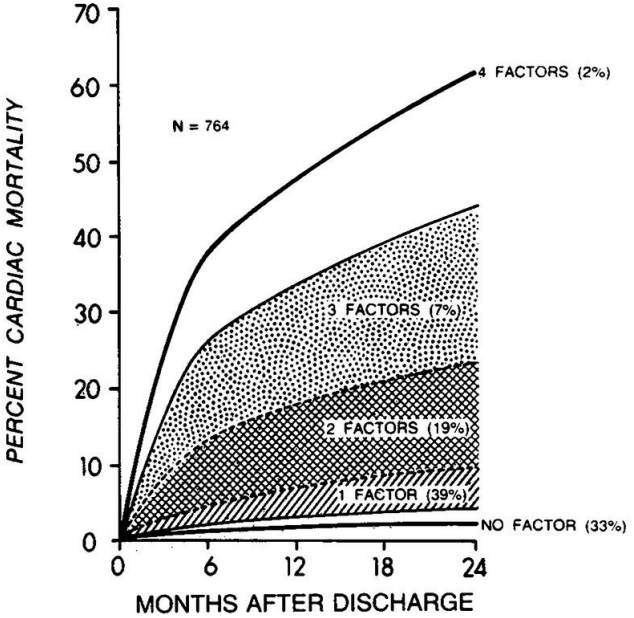
FACTOR	RELATIVE RISK *	CHI-SQUARE	P VALUE
Ejection fraction <0.40	2.4 (1.5,3.7)	12.3	<0.001
VED ≥10/hr †	1.6 (1.0,2.6)	3.8	<0.05
Rales > bibasilar	3.3 (2.1,5.2)	20.5	<0.001
NYHA class II–IV ‡	1.9 (1.2,3.0)	8.1	<0.01
Time after hospitalization			
0–3 mo	4.0 (2.2,7.2)	33.5	<0.001
3–6 mo	2.8 (1.6,5.1)		
6–12 mo	1.3 (0.8,2.4)		

*Ratio of the risk of dying per unit of time (hazard rate) for patients with factor present, to risk for patients with factor absent. For the time factors, the risks are relative to the probability of dying 12 to 36 months after discharge.

The relative risk ratios were derived from the survival analyses. The parentheses contain the 95 per cent confidence intervals.

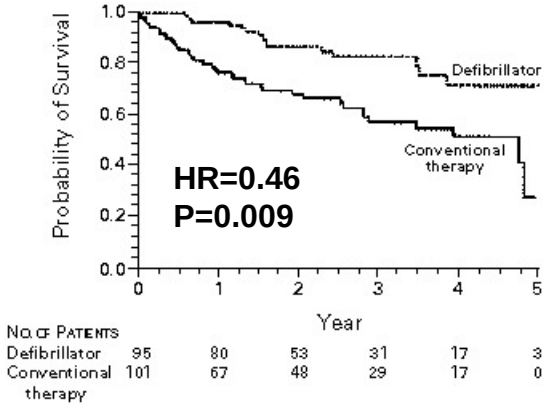
†VED denotes ventricular ectopic depolarization.

‡New York Heart Association functional classification one month before entry.



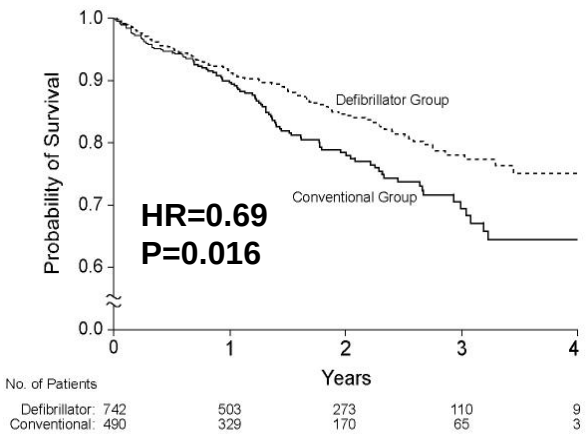
Moss et al., NEJM, 1983

MADIT-I, MADIT-II, and SCD-HEFT



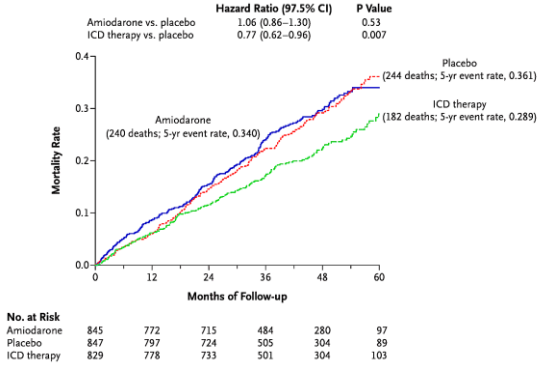
Elig: Hx MI, EF≤0.35, NSVT, +EP study, N=196
32 enrolling sites, 5 year-enrollment
(1990-1995) 1993: TV leads

Moss AJ, et al. NEJM 1996



Elig: Hx MI, EF≤0.30, HF, N=1200
32 enrolling sites, 5 year-enrollment
(1997-2001)

Moss AJ, et al. NEJM 2002



Elig: ICM, NICM, EF≤0.35, HF, N=2531

Early 2000's

Bardy G et al, N Engl J Med. 2005

Current ICD Guidelines

ICD therapy is recommended in patients with CAD, symptomatic heart failure (NYHA class II–III), and LVEF ≤35% despite ≥3 months of OMT.[354,356]	I	A
ICD therapy should be considered in patients with CAD, NYHA class I, and LVEF ≤30% despite ≥3 months of OMT.[354]	IIa	B
ICD implantation should be considered in patients with CAD, LVEF ≤40% despite ≥3 months of OMT, and NSVT, if they are inducible for SMVT by PES.[355]	IIa	B

Current ICD Guidelines

ESC European Society of Cardiology
European Heart Journal (2022) 43, 3997–4126
https://doi.org/10.1093/eurheartj/ehac262
ESC GUIDELINES

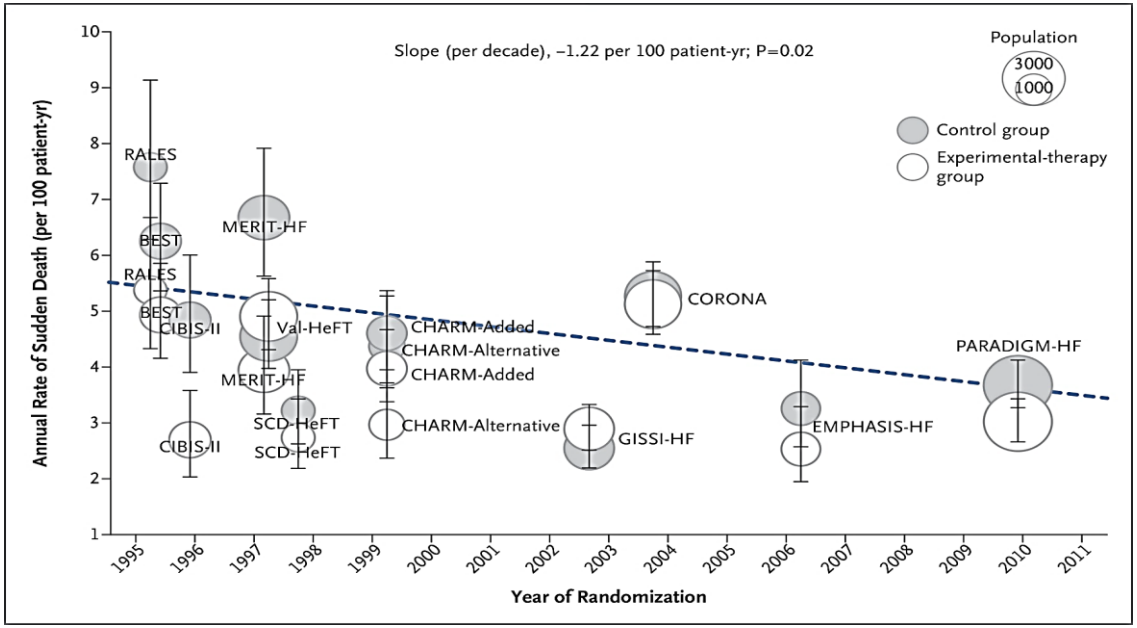
2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

No utility of additional risk stratification beyond the clinical variables has been consistently demonstrated, including:

- ECG metrics, autonomic variables
- Echo, CT, MRI-assessment of scar
- or any other newer method

ICD therapy is recommended in patients with CAD, symptomatic heart failure (NYHA class II–III), and LVEF ≤35% despite ≥3 months of OMT.[354,356]	I	A
ICD therapy should be considered in patients with CAD, NYHA class I, and LVEF ≤30% despite ≥3 months of OMT.[354]	IIa	B
ICD implantation should be considered in patients with CAD, LVEF ≤40% despite ≥3 months of OMT, and NSVT, if they are inducible for SMVT by PES.[355]	IIa	B

Why do we need a new approach?
1. Decline in the Risk of SCD Over Time



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

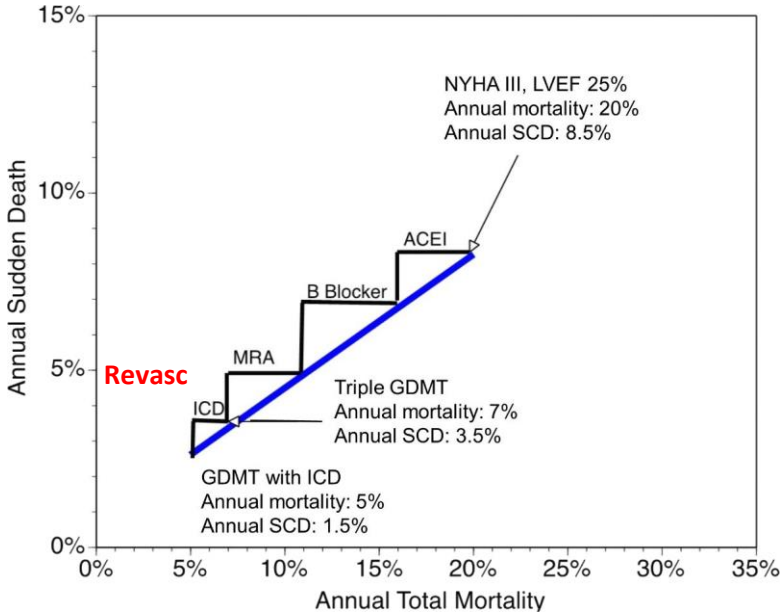
Why do we need a new approach?
Changing Landscape of SCD due to improved treatment

Changes in treatment in the last 40 years

Early, complete revascularization after MI
Beta blockers
Mineralocorticoid antagonists
ARNI
SGLT2 inhibitors
Statins
Cardiac resynchronization therapy
…

Most of these reduce not only mortality

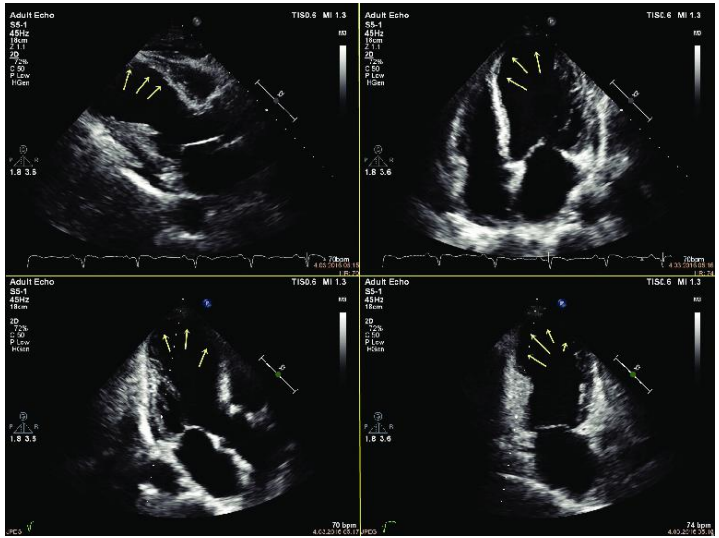
but *specifically sudden cardiac death*



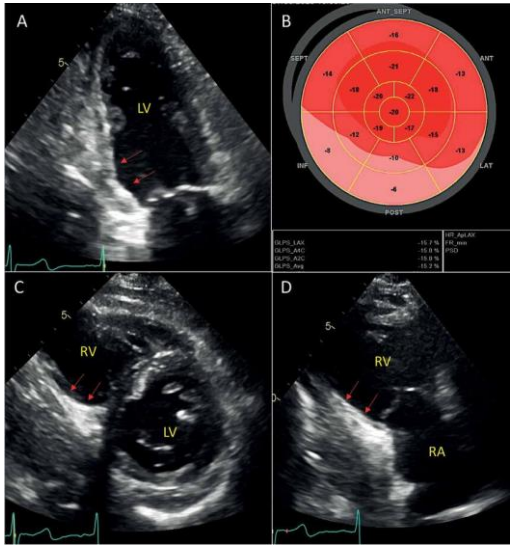
Merchant FM, Levy WC, Kramer DB.
J Am Heart Assoc. **2020**; 9:e015139.

Why do we need a new approach?
2. Substrate is different in the current era vs. old era

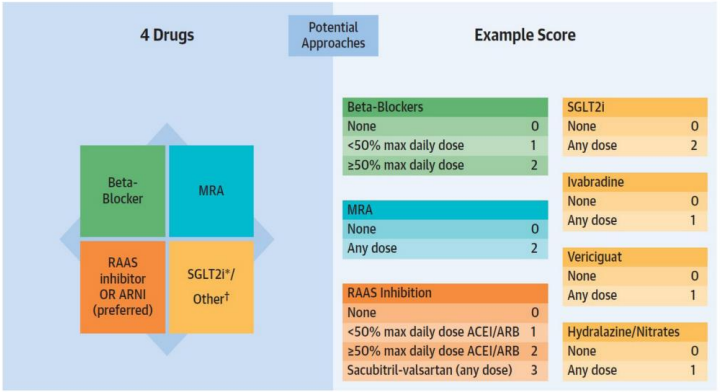
Large anterior MI, very low LVEF, partial revasc.

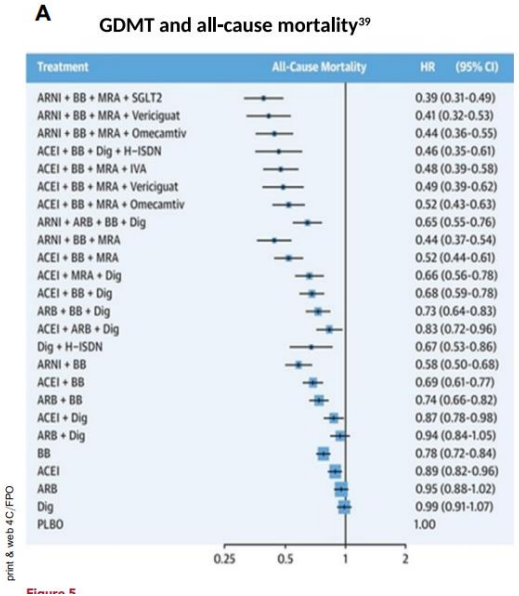


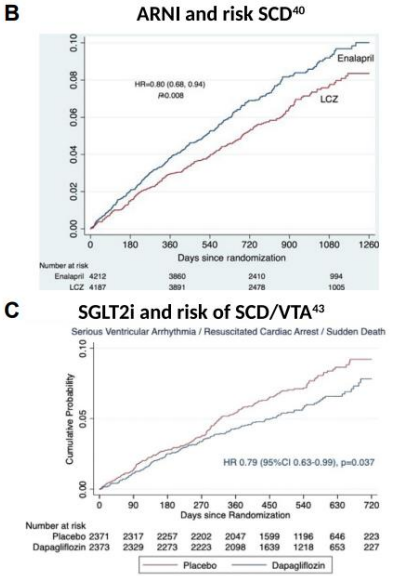
Smaller MI, quick, full revasc.
often higher LVEF



Why do we need a new approach?
3. Current GDMT is Highly Effective and Reduces SCD



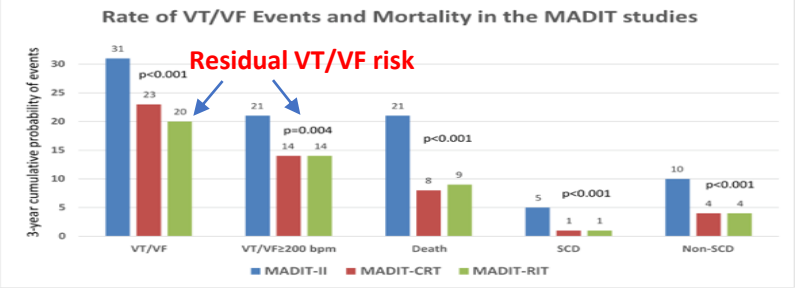




Vaduganathan, JACC, HF, 2020
Goldenberg, Heart Rhythm 2025

Why do we need a new approach?
4. Decline in the Risk of ICD Shock Rates and Mortality

Trial	MADIT-II	MADIT-CRT	MADIT-RIT
N	746	1820	1500
Enrollment years	1997-2001	2004-2008	2009-2011
Investigated device	ICD	CRT-D vs. ICD	CRT-D + ICD
Inclusion criteria	LVEF ≤ 30% Prior MI	LVEF ≤ 30% ICM + NICM NYHA I-II	LVEF ≤ 35% ICM + NICM ICD or CRT-D indication



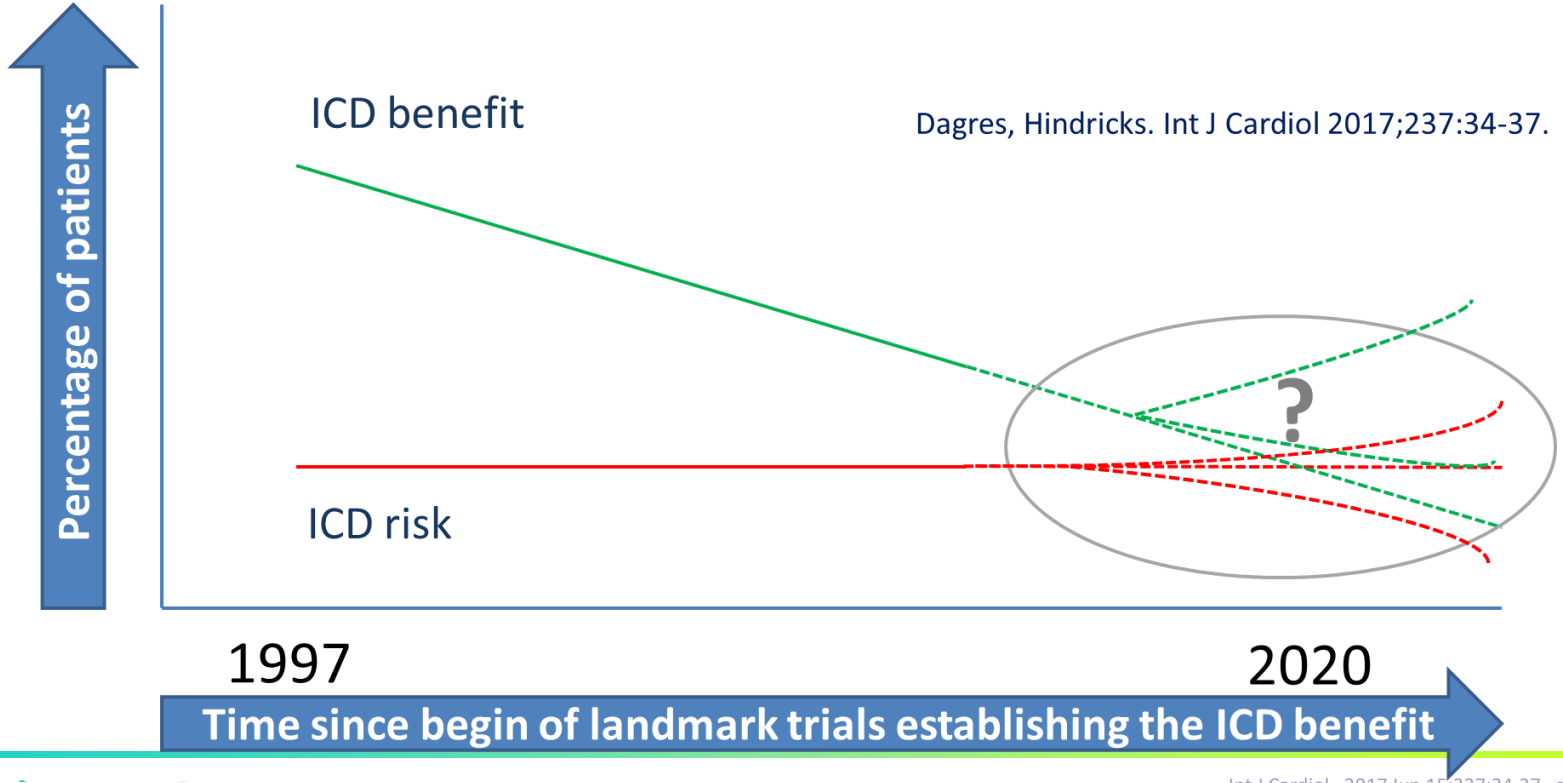
VT/VF: 30% decrease **Mortality: >50% increase**

Kutyifa V, et al. Heart Rhythm. 2019

Trial	Year	Average duration (mo)	Average annual rate of appropriate shock, %
MADIT II	2002	24	17
SCD-HeFT	2005	45.5	5
PREPARE	2008	12	5.4
MADIT-RIT	2012	16	3
ICD Registry	2014	20	1

Sabbag A et al. Heart Rhythm **2015**;12:2426–33

Why do we need a new approach?
5. Projection of the ICD benefit-risk ratio



Dagres, Hindricks. Int J Cardiol 2017;237:34-37.

Int J Cardiol, 2017 Jun 15:237:34-37., doi: 10.1016/j.ijcard.2017.03.053

Objective of the PROFID EHRA study

Improved strategy for primary prevention defibrillator implantation based on accurate prediction of the personal risk of SCD.

First part:

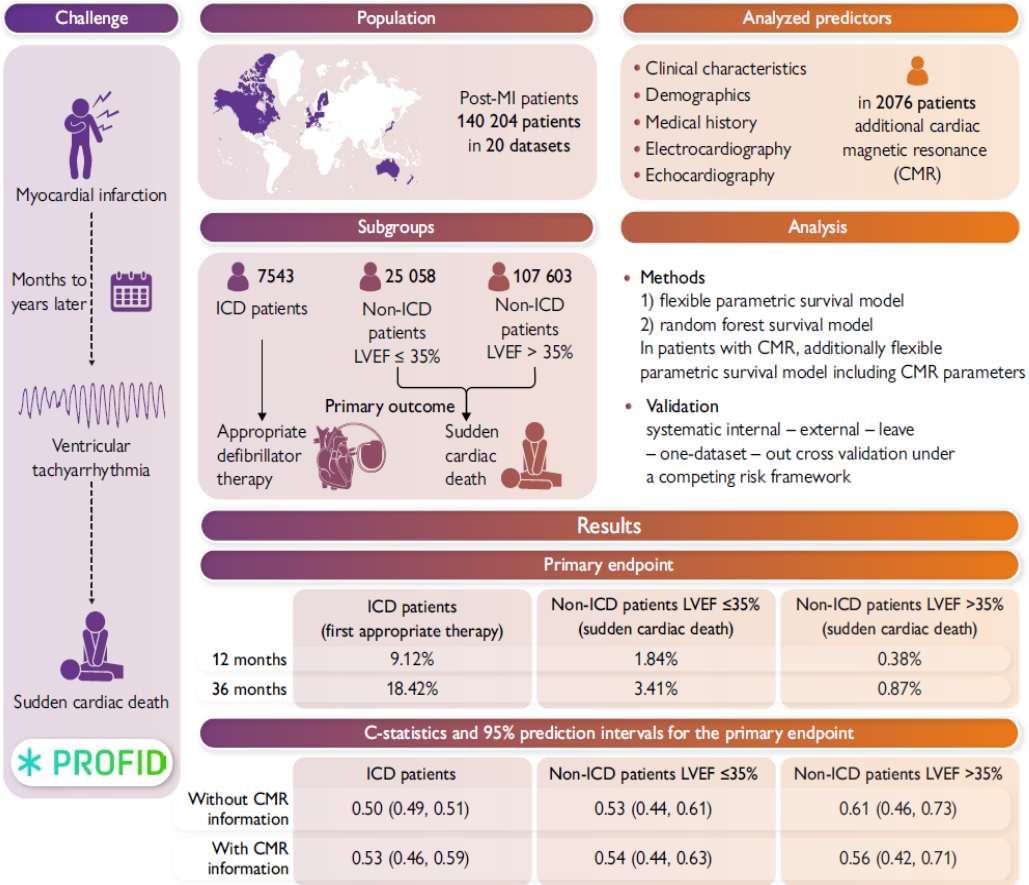
- Identification of low-risk patients with reduced LVEF without the need for defibrillator protection
- Identification of high-risk patients with moderately reduced or preserved LVEF who might benefit from defibrillator protection

Second part:

Develop a novel approach for defibrillator protection and test it in a randomized clinical trial

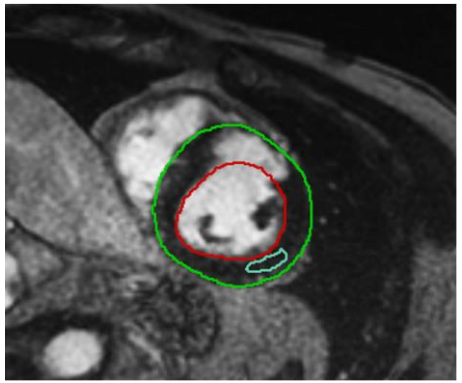
Eur Heart J. 2024 Nov 14;45(43):4616-4626. doi: 10.1093/eurheartj/ehae326

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 847999.



None deemed to be reliable predictors including:

- ✓ demographics,
- ✓ medical history,
- ✓ clinical characteristics, biomarkers,
- ✓ electrocardiography,
- ✓ echocardiography,
- ✓ cardiac MRI.



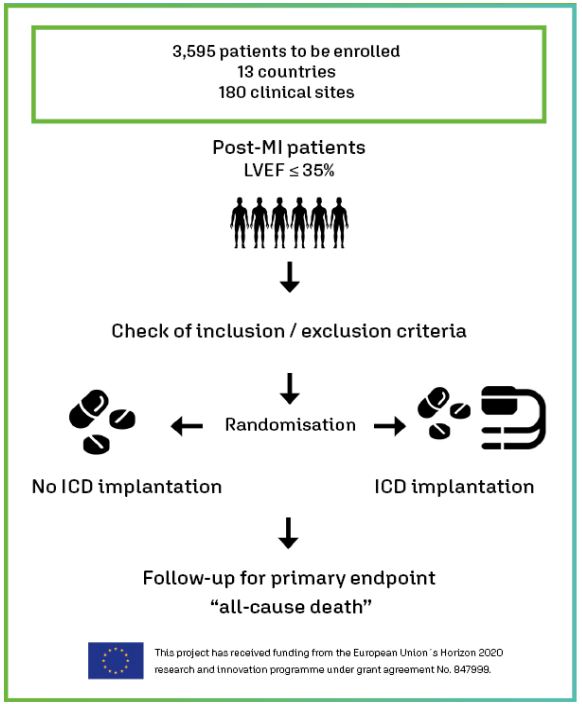
Eur Heart J. 2024 Nov 14;45(43):4616-4626. doi: 10.1093/eurheartj/ehae326

PROFID EHRA TRIAL: OBJECTIVES

Study population: **3,595 post-MI patients with symptomatic heart failure and reduced LVEF ≤35%,** all receive optimal medical therapy (OMT) for this condition

>> Demonstrate that **OMT without ICD implantation** (index group) is **not inferior to OMT with ICD implantation** (control group) with respect to **all-cause mortality** within about 2.5 years of observation.

>> Designed to be as close to routine clinical care as possible

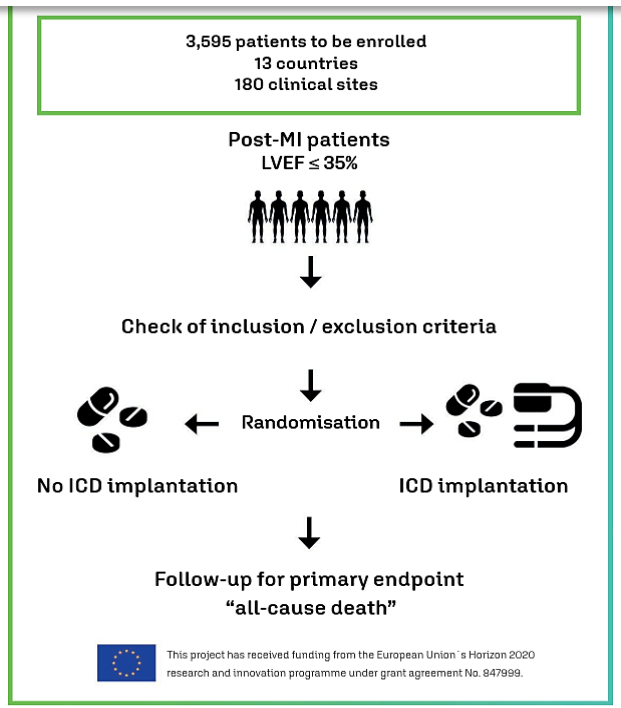


Publicly funded under Horizon 2020 program, no. 847999

PROFID EHRA TRIAL: KEY FACTS

Reassess the role of routine prophylactic ICD implantation for primary prevention of SCD and change medical guidelines

Study design	Proof of strategy, event-driven, randomised, non-inferiority trial
Random groups	Index: OMT; Control: OMT+ICD
Objectives	Demonstrate that OMT is not inferior to OMT+ICD within 2.5yrs of observation reg. all-cause mortality
Prim. Endpoint	(1) All-cause death (n=374)
Sec. Endpoints	(2) Death from cardiovasc. causes (3) First hospital readmissions for cardiovascular causes after randomisation. (4) Average length of stay in hospital during the study period. (5) QoL (EQ-5D-5L) trajectories over time at BL and 12-month intervals thereafter.
Duration	30 months enrolment, total study duration~49 months
Current Enrollment	271 patients, enrolled at 85 sites in Europe (well over feasibility phase at this time)

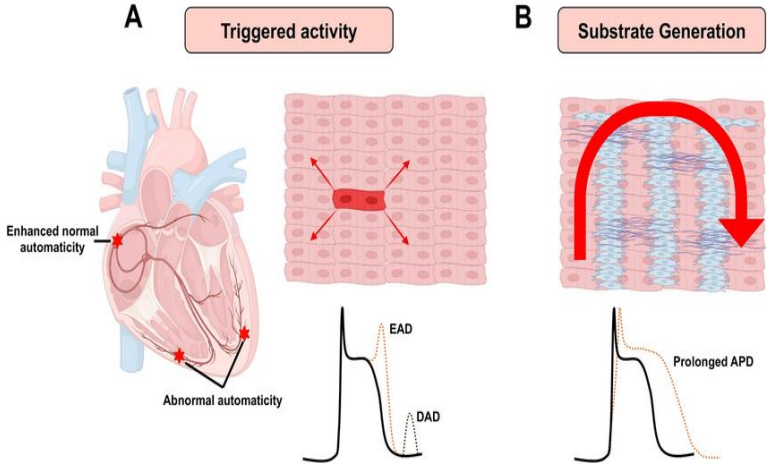


Publicly funded under Horizon 2020 program, no. 847999

Why do we need a new approach?
6. Prior predictor models only work in cohorts when the predominant mode of death is cardiac, and arrhythmic…

Prognosis after myocardial infarction, A.J. Moss

- A substantial number of patients die in the first year after myocardial infarction.
- The major determinants of risk during this period appear to be the extent of either damaged or potentially ischemic myocardium and the degree of electrical instability.



Am J Cardiol 1983 Oct 1;52(7):667-9. doi: 10.1016/0002-9149(83)90394-6.

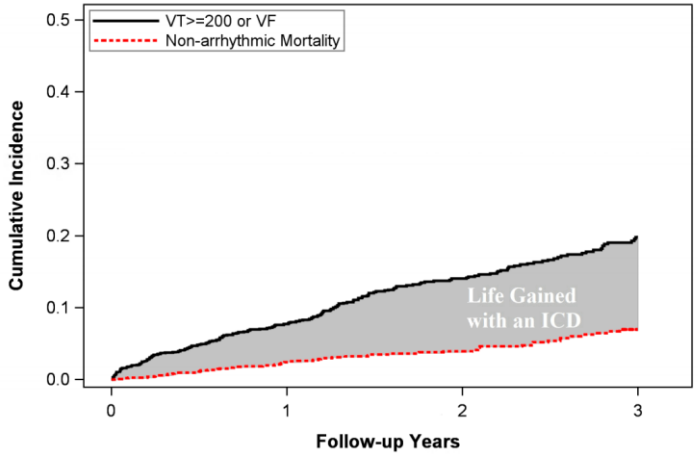
What could be a new approach?
Important to consider: life gained with an ICD
Competing risk of non-arrhythmic mortality

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 1676–1684
doi:10.1093/eurheartj/ehaa1057

CLINICAL RESEARCH
Arrhythmias

Predicted benefit of an implantable cardioverter-defibrillator: the MADIT-ICD benefit score

Arwa Younis [1], Jeffrey J. Goldberger[2], Valentina Kutyifa [1], Wojciech Zareba[1], Bronislava Polonsky[1], Helmut Klein [1], Mehmet K. Aktas[1], David Huang[1], James Daubert [3], Mark Estes[4], David Cannom[5], Scott McNitt[1], Kenneth Stein[6], and Ilan Goldenberg[1]*



Graphical Abstract

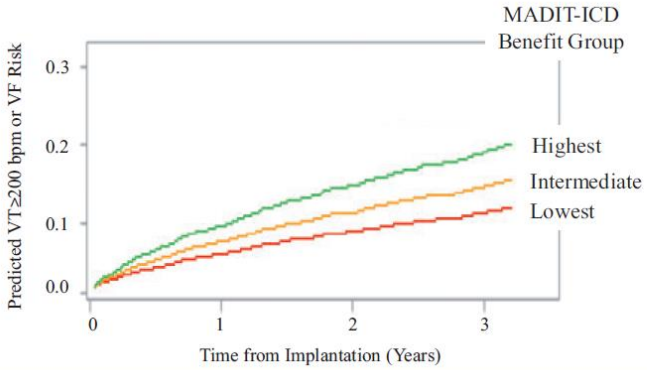
MADIT-ICD Benefit Group and corresponding personalized ICD-Benefit Score

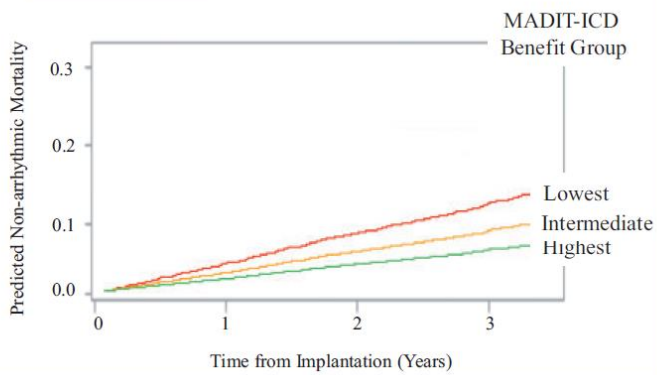
MADIT-ICD Benefit Group	Lowest	Intermediate		Highest
VT/VF Score	Low (<7)	Low (<7)	High (≥7)	High (≥7)
Non-arrhythmic Mortality Score	High (≥3)	Low (<3)	High (≥3)	Low (<3)

ICD-Benefit Score 0 13 25 38 50 63 75 88 100

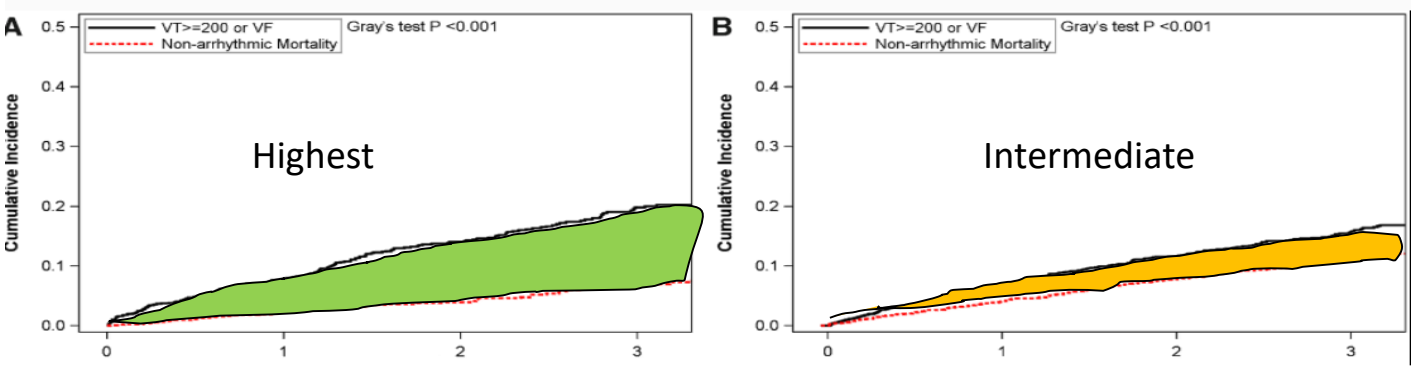
VT/VF Score	
Variable	Points
LVEF <=25%	+1
Atrial arrhythmia	
Heart Rate > 75 bpm	
SBP <140 mmHg	+2
Myocardial Infarction	
Age < 75 yrs	
Male	
Prior NSVT	

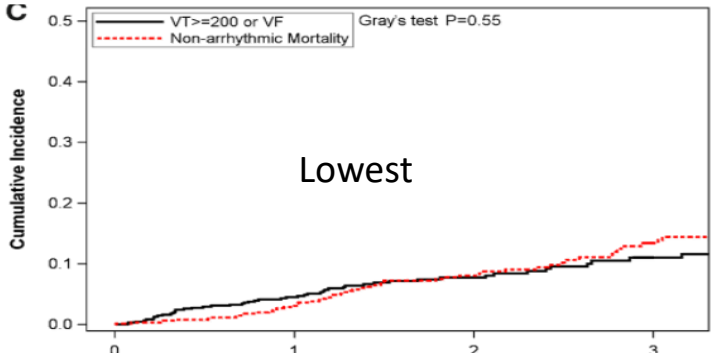
Non-arrhythmic Mortality Score	
Variable	Points
CRT-D	-1
NYHA ≥II	+1
Diabetes	
BMI <23 kg/m^2	+2
Atrial arrhythmia	
LVEF <=25%	
Age ≥ 75 years	





Currently tested in the CONTEMP-ICD trial in a low-risk cohort





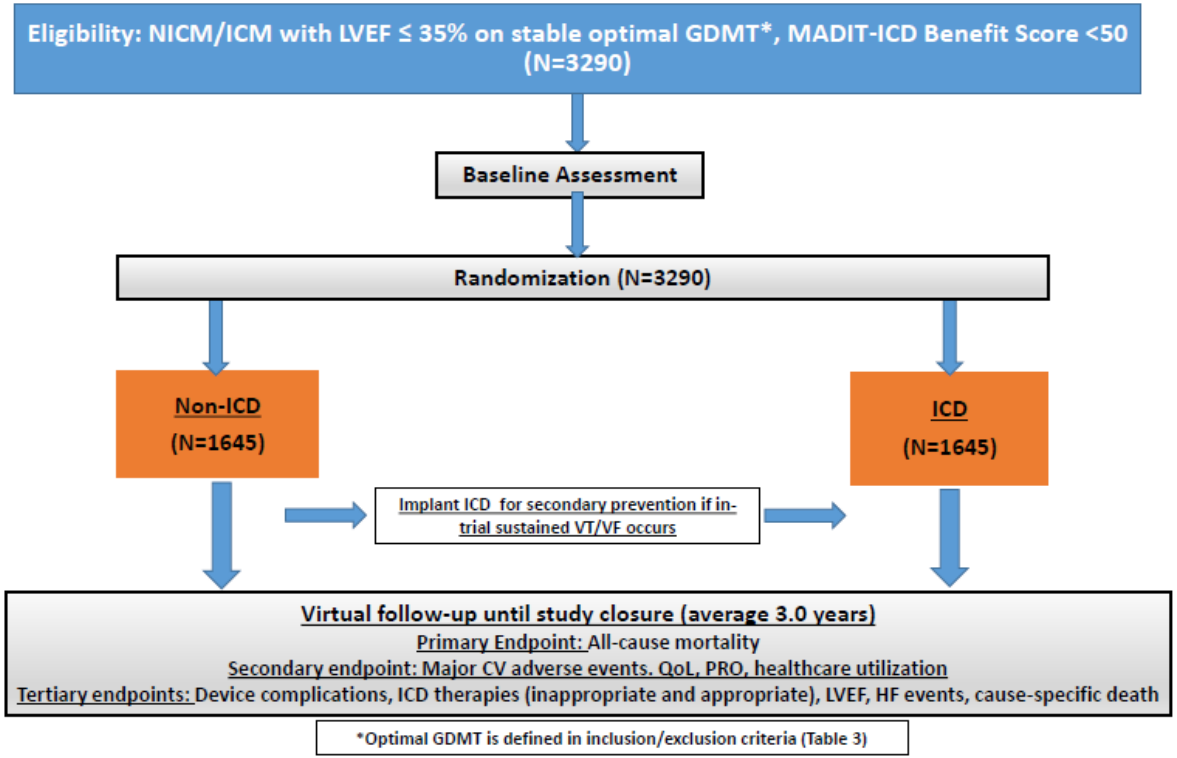
Limitations:

- Trial cohort had pre-selected clinical characteristics

Strength:

- The model was externally validated in the RAID trial

CONTEMP-ICD: 21 of 100 patients enrolled in feasibility phase



What would be the futuristic/AI approach?

ChatGPT: “What could be paradigm changing about risk stratification for sudden cardiac death after myocardial infarction based on current knowledge?”

Thought for 4 seconds…

If we take “paradigm changing” seriously for post-MI SCD risk, it probably means moving away from “EF + waiting period → yes/no ICD” toward a truly individualized, dynamic model of arrhythmic vs non-arrhythmic risk.

What would be the futuristic/AI approach?

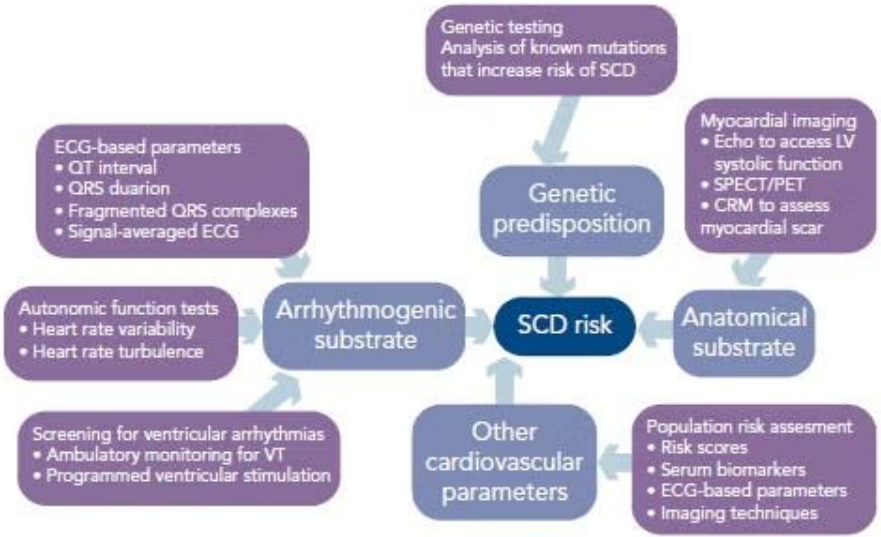
The AI “solution”

- ✓Risk assessment as a longitudinal process, embedded in routine care, with EHR-integrated decision support.
- ✓ICDs (or alternatives) deployed on the basis of personalized, model-estimated benefit, not just EF and guidelines.
- ✓Trials and registries co-designed with implementation scientists and payers to ensure that any new paradigm can be scaled.

Major Challenges Remain

Challenges:

- SCD definition, adjudication
- Reproducibility, and external validity
- Actionable, that can be confirmed in a randomized clinical trial
- Overall low risk of SCD in selected cohorts (not in registries) with GDMT
- Competing risk of non-arrhythmic mortality
- Two trials ongoing to assess the ICD in all pts (PROFID EHRA), vs. in those in low risk (CONTEMP-ICD) are ongoing



CMR = cardiac magnetic resonance imaging, LV = left ventricle, PET= positron emission tomography, SCD = sudden cardiac death, SPECT= single photo emission computed tomography, VT = ventricular tachycardia

THANK YOU

Valentina Kutyifa, MD, PhD, FACC, FHRS, FESC

Professor of Medicine with Tenure

University of Rochester Medical Center, Rochester, NY

Adjunct Lecturer, Semmelweis University, Budapest, Hungary

Vice Chair for Clinical Research, Department of Medicine

Director of the Clinical Trial Enrollment Unit, Cardiology Division

E-mail: Valentina_Kutyifa@URMC.Rochester.edu