*UPDATE SCD 2025

profid-project.eu

CONTEMP-ICD

Elijah R Behr

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

Risk of SCD: Primary prevention

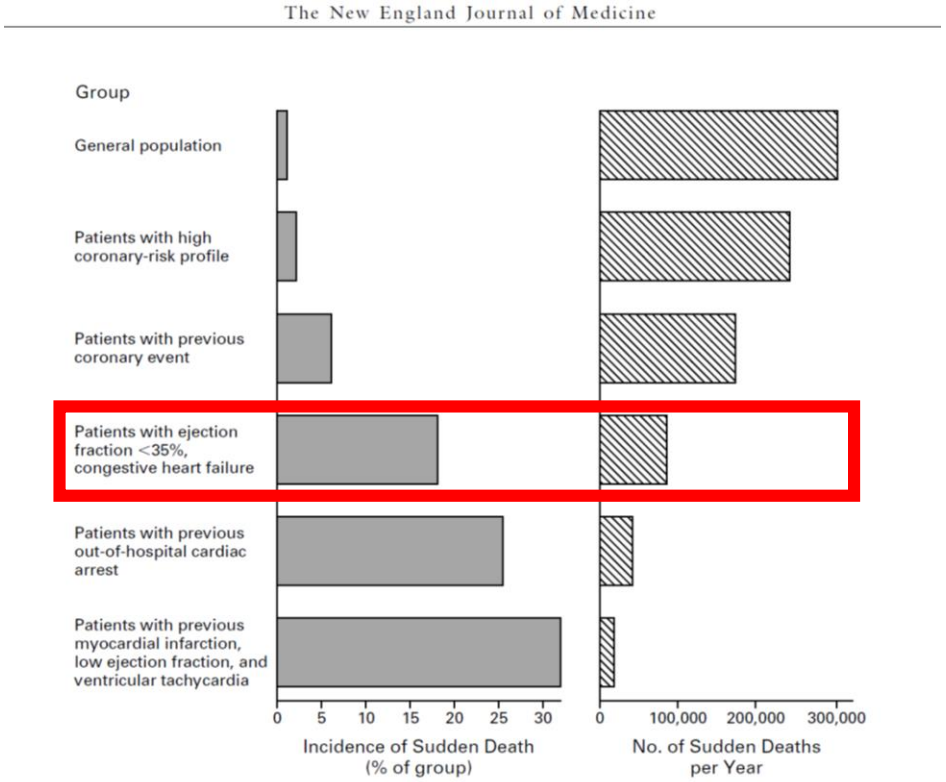
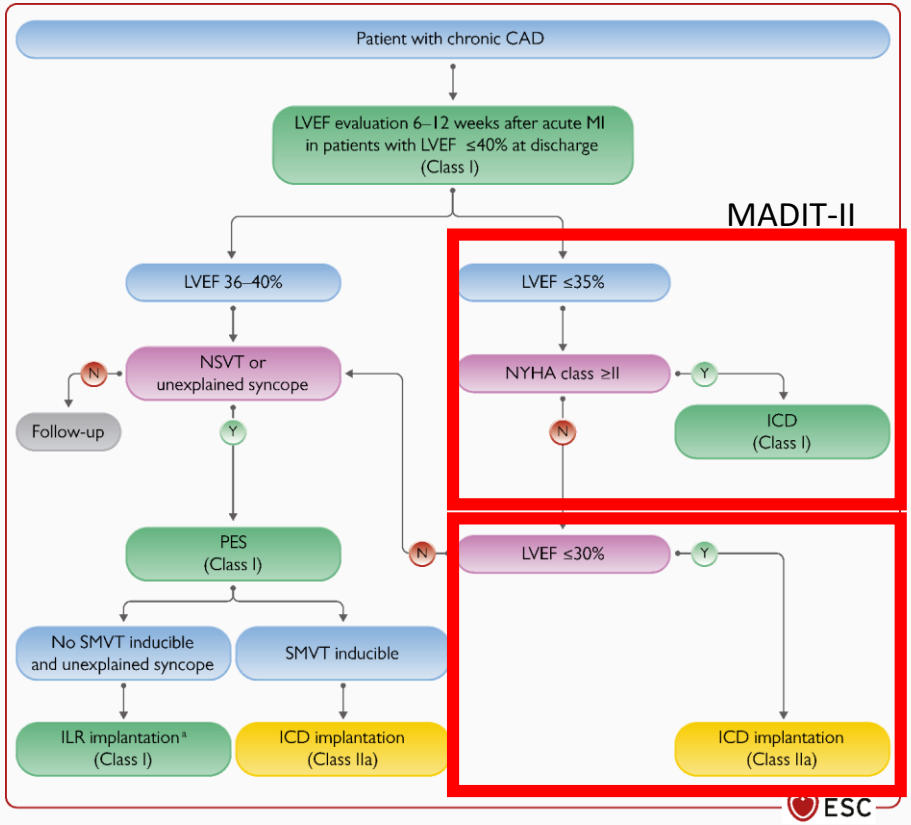


Figure 1. The Incidence of Sudden Death in Specific Populations and the Annual Numbers of Sudden Deaths in Those Populations.. Most of the deaths occur in the larger, lower-risk subgroups. Modified from Myerburg et al.[10] with the permission of the publisher..

Risk stratification and primary prevention of SCD in chronic CAD



	Class	Level
ICD therapy should be considered in patients with CAD, NYHA class I, and LVEF ≤30% despite ≥3 months of OMT.	IIa	B

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (European Heart Journal; 2022 – doi: 10.1093/eurheartj/ehac262)

ICD implantation for Primary Prevention of SCD

Most have LVEF ≤ 35% and HF symptoms

However, current recommendations in patients with both ischaemic and non-ischaemic cardiomyopathy originate from clinical trials carried out approximately two decades ago

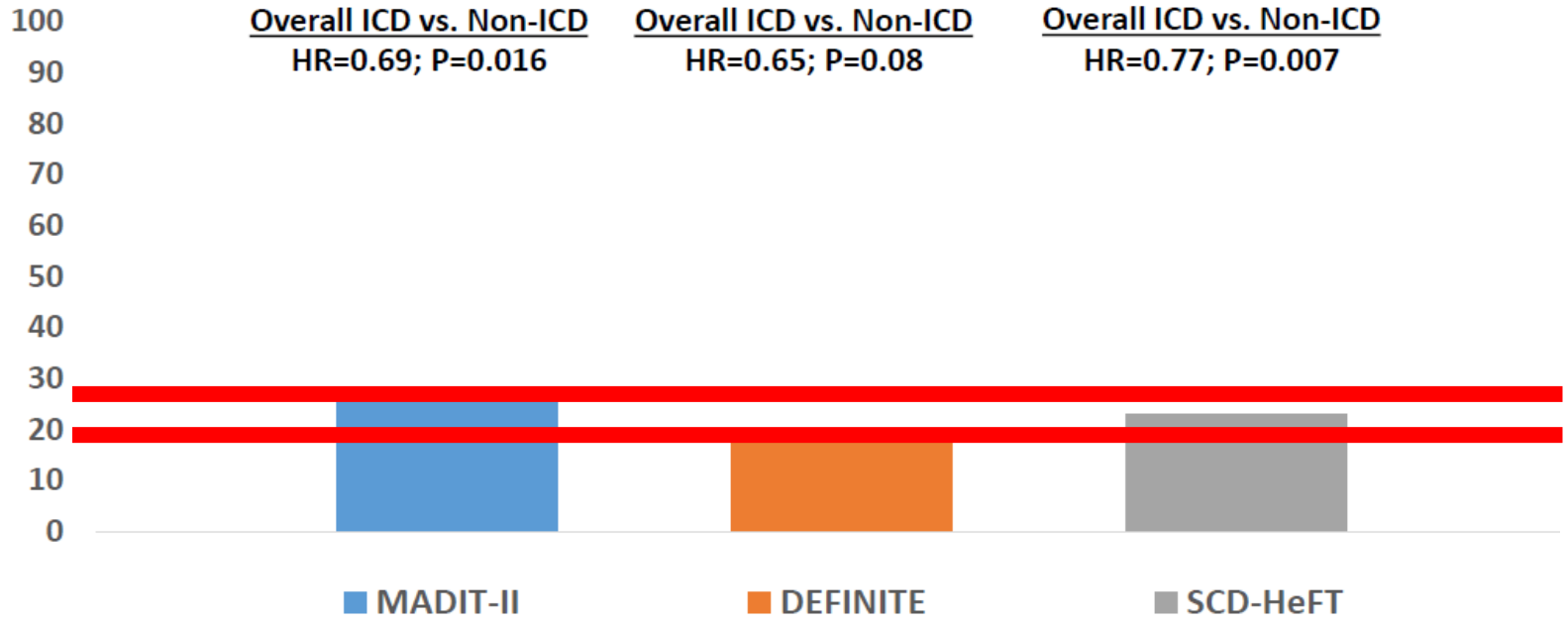
Are they still applicable in the current era of contemporary HF management?

CAVEAT: Cardiac Resynchronisation Therapy

Recommendations	Class[a]	Level[b]
When an ICD is indicated, it is recommended to evaluate whether the patient could benefit from CRT-defibrillator.[367]	I	C

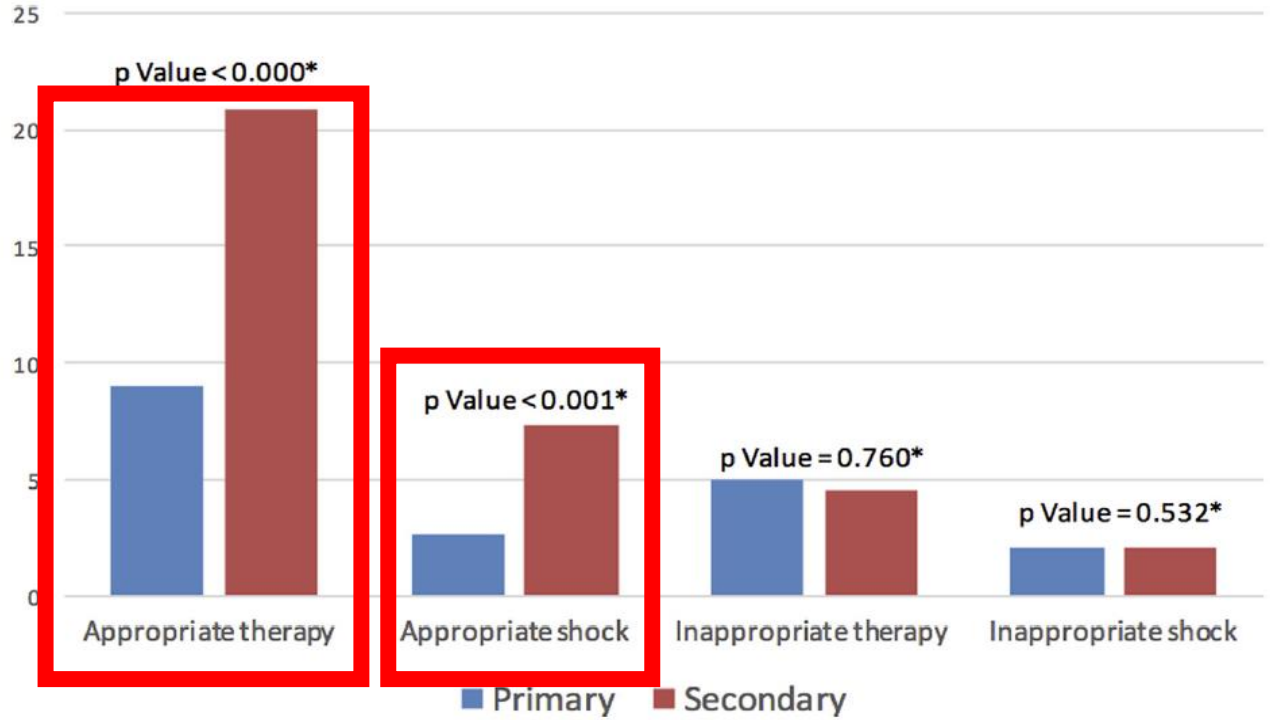
2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death
(European Heart Journal; 2022 – doi: 10.1093/eurheartj/ehac262)

Rate of Appropriate ICD Therapy in Landmark Primary Prevention Trials



Background of standard GDMT

Real world rates of ICD therapy: 30 month F-U



Background of standard GDMT

Heart Rhythm: Volume 12, Issue 12, December 2015, Pages 2426-2433

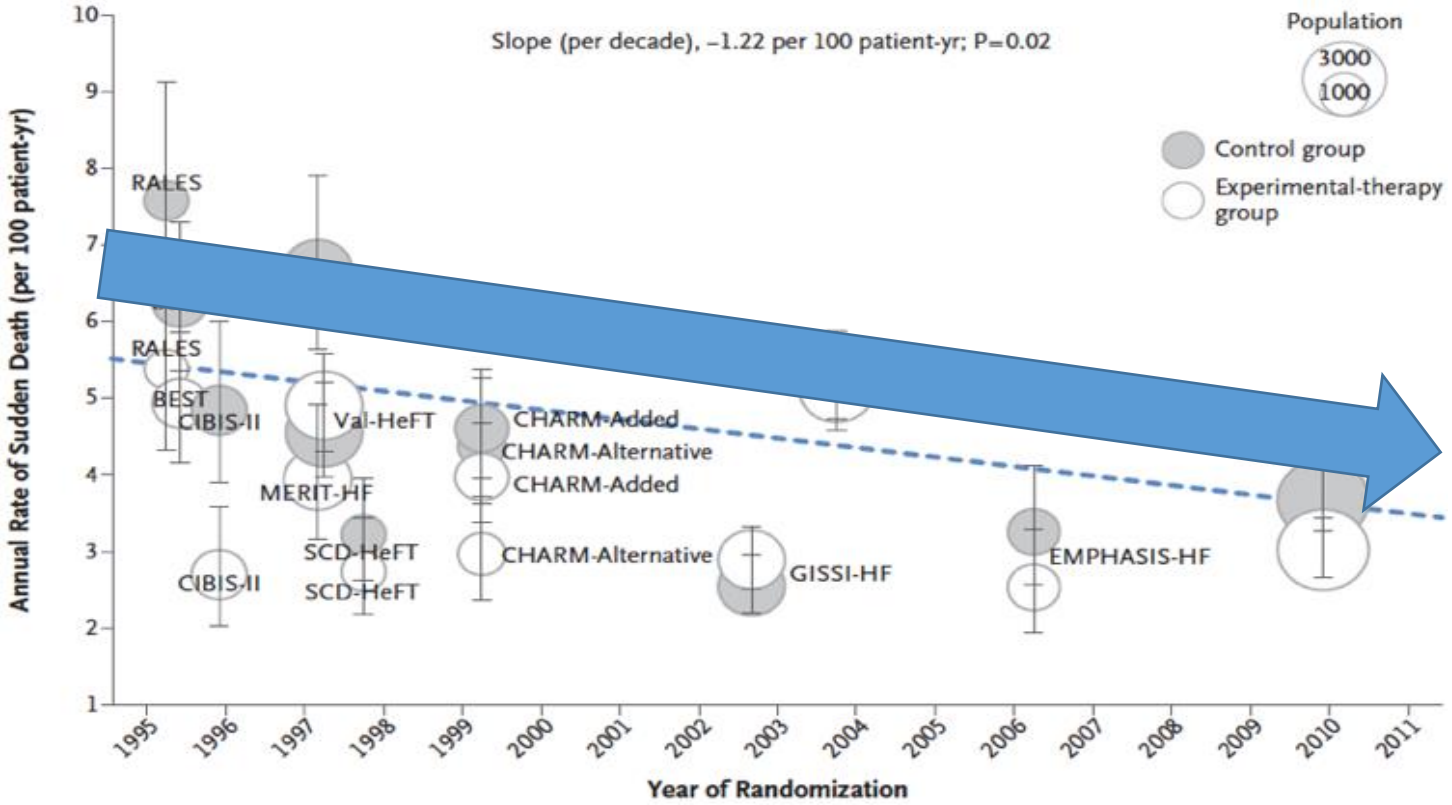
Rates of ICD therapy: Real world vs Historical studies

Trial	Year	Average duration (mo)	Average annual rate of appropriate shock, %	1-Year all-cause mortality, %	2-Year all-cause mortality, %
MADIT II	2002	24	17	9	16
SCD-HeFT	2005	45.5	5	6	11.6
PREPARE	2008	12	5.4	4.9	NA
MADIT-RIT	2012	16	3	3	10
ICD Registry	2014	20	1	6	11

Background of standard GDMT

Heart Rhythm: Volume 12, Issue 12, December 2015, Pages 2426-2433

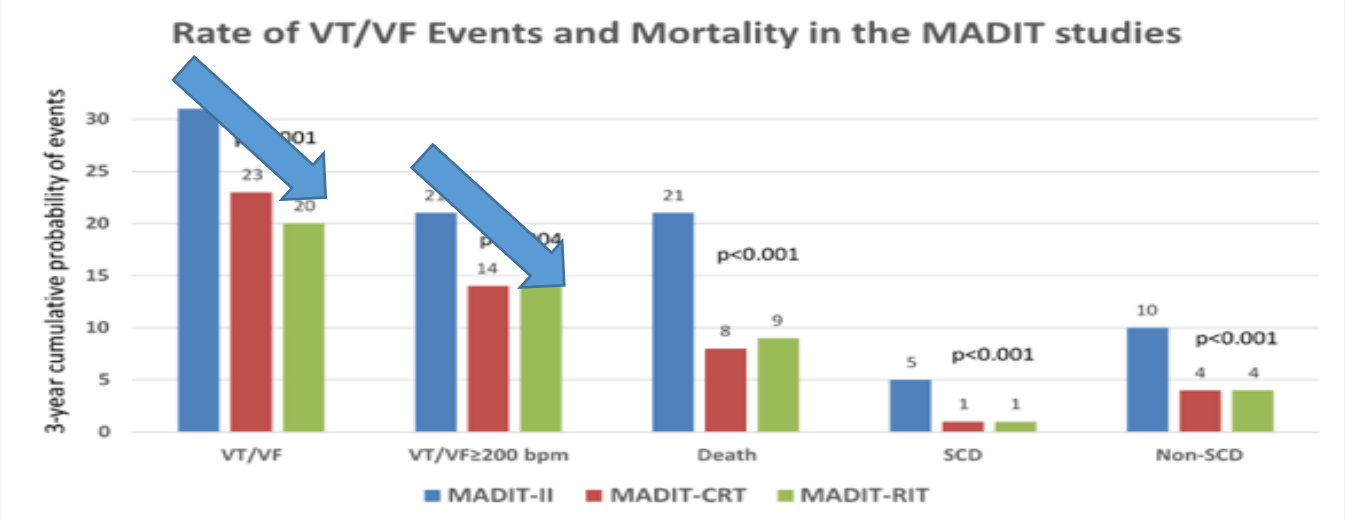
Background: Declining rate of SCD



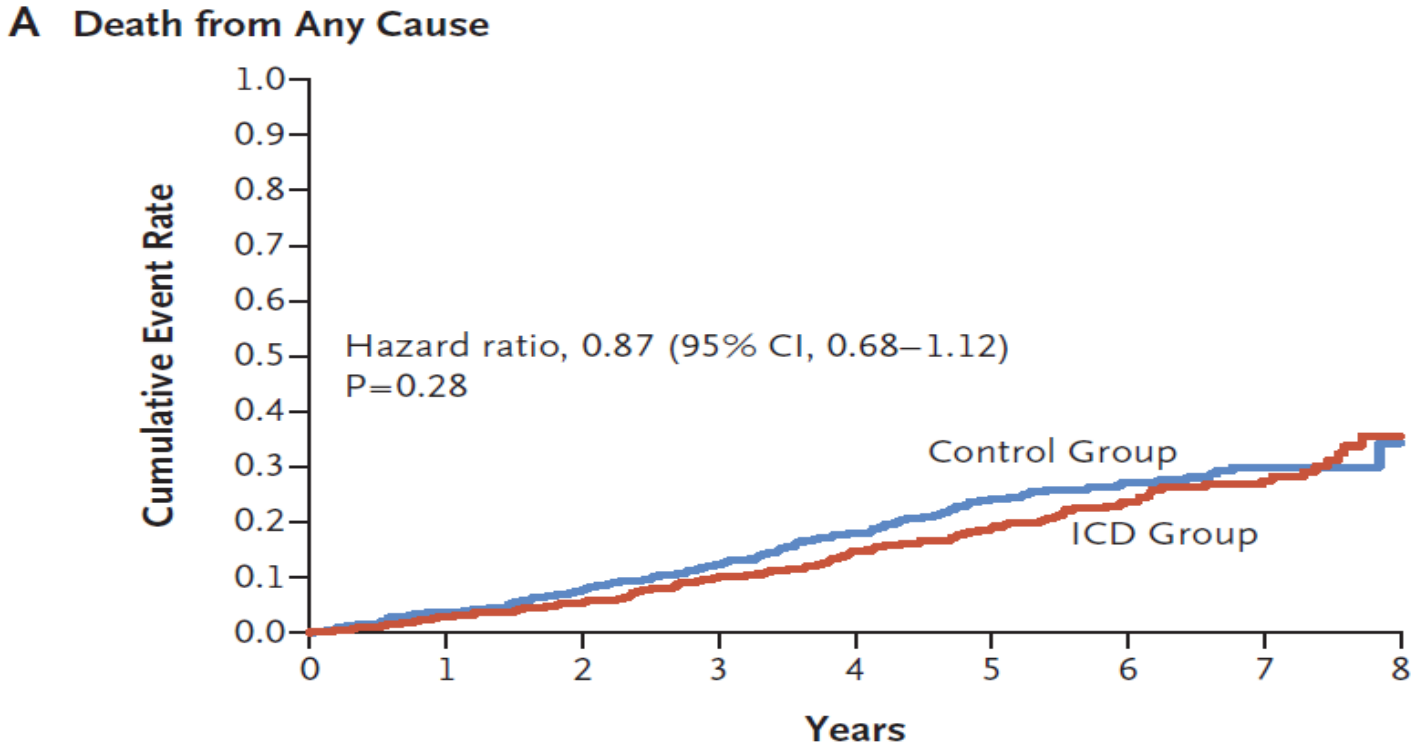
N Engl J Med 2017; 377:41-51 DOI: 10.1056/NEJMoa1609758

Declining rate of VT/VF in the MADIT-Trials

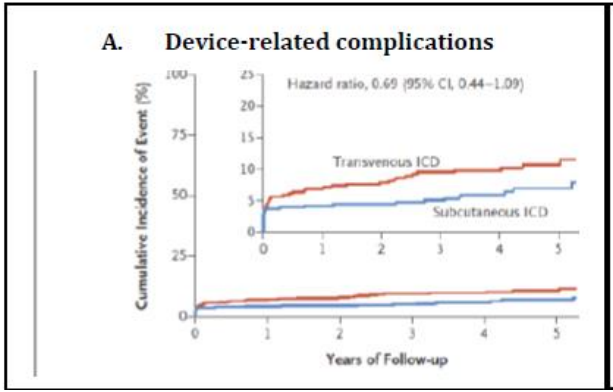
Trial	MADIT-II	MADIT-CRT	MADIT-RIT
N	746	1820	1500
Enrollment years	1997-2001	2004-2008	2009-2011
Investigated device	ICD	CRT-D vs. ICD	CRT-D + ICD
Inclusion criteria	LVEF ≤ 30% Prior MI	LVEF ≤ 30% ICM + NICM NYHA I-II	LVEF ≤ 35% ICM + NICM ICD or CRT-D indication

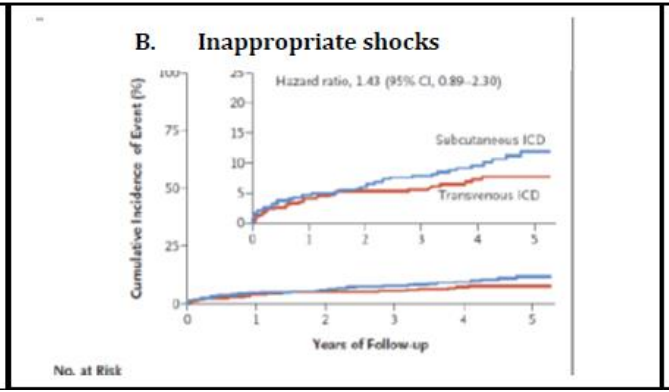


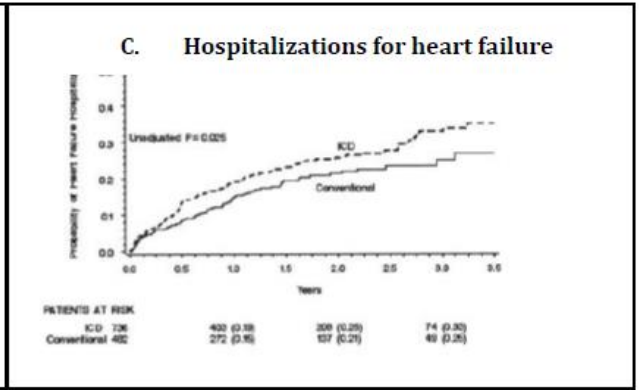
DANISH TRIAL



ICD-Related CV major adverse events



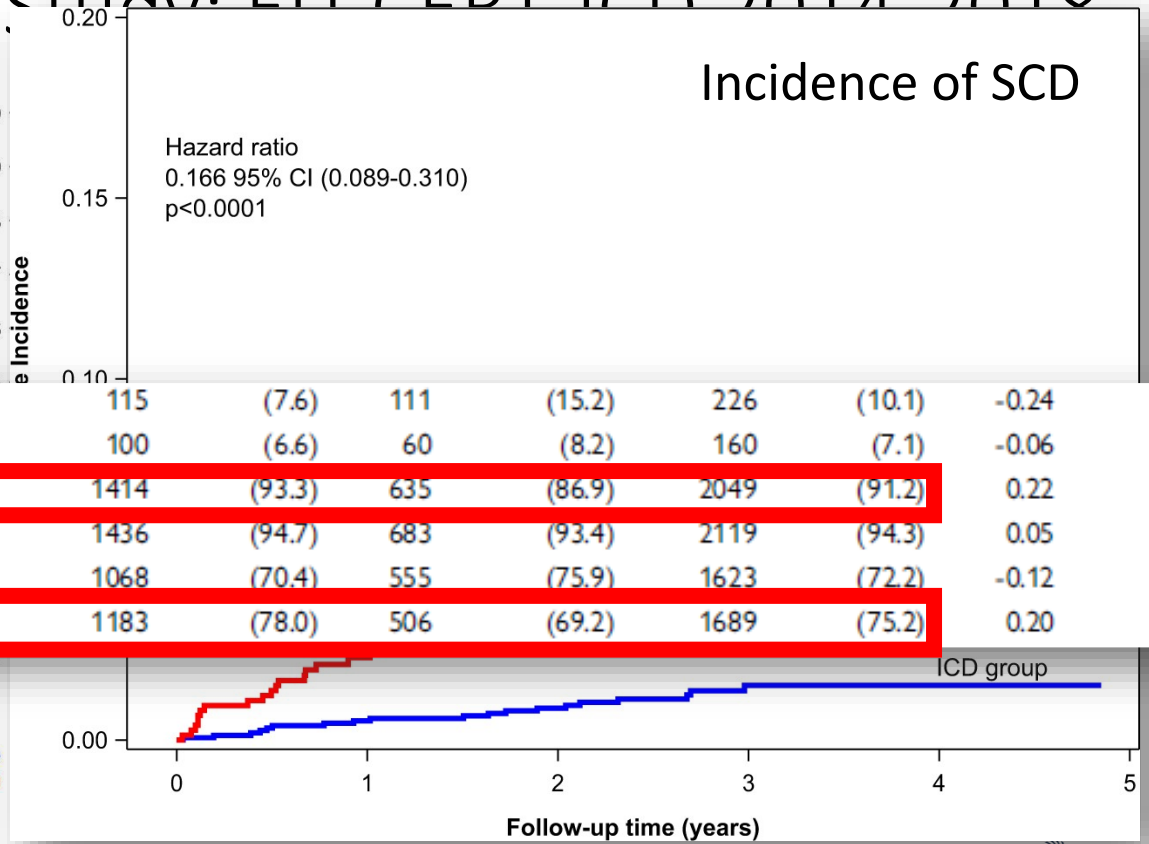




PRAETORIAN Study: 3 year rates for TV-ICD:
A: 10% Device related complications B: 8% Inappropriate shock rates

MADIT II:
C: 39% increased risk for HF admission

Registry Study: EU CERT ICD 2014-2018



Amiodarone	115	(7.6)	111	(15.2)	226	(10.1)	-0.24	<0.0001
Digitalis glycosides	100	(6.6)	60	(8.2)	160	(7.1)	-0.06	0.1640
ACE or AT1 antagonist	1414	(93.3)	635	(86.9)	2049	(91.2)	0.22	<0.0001
Beta-blocker	1436	(94.7)	683	(93.4)	2119	(94.3)	0.05	0.2167
Loop diuretic	1068	(70.4)	555	(75.9)	1623	(72.2)	-0.12	0.0066
MRA	1183	(78.0)	506	(69.2)	1689	(75.2)	0.20	<0.0001

Eur Heart J, Volume 41, Issue 36, 21 September 2020, Pages 3437–3447,
https://doi.org/10.1093/eurheartj/ehaa226

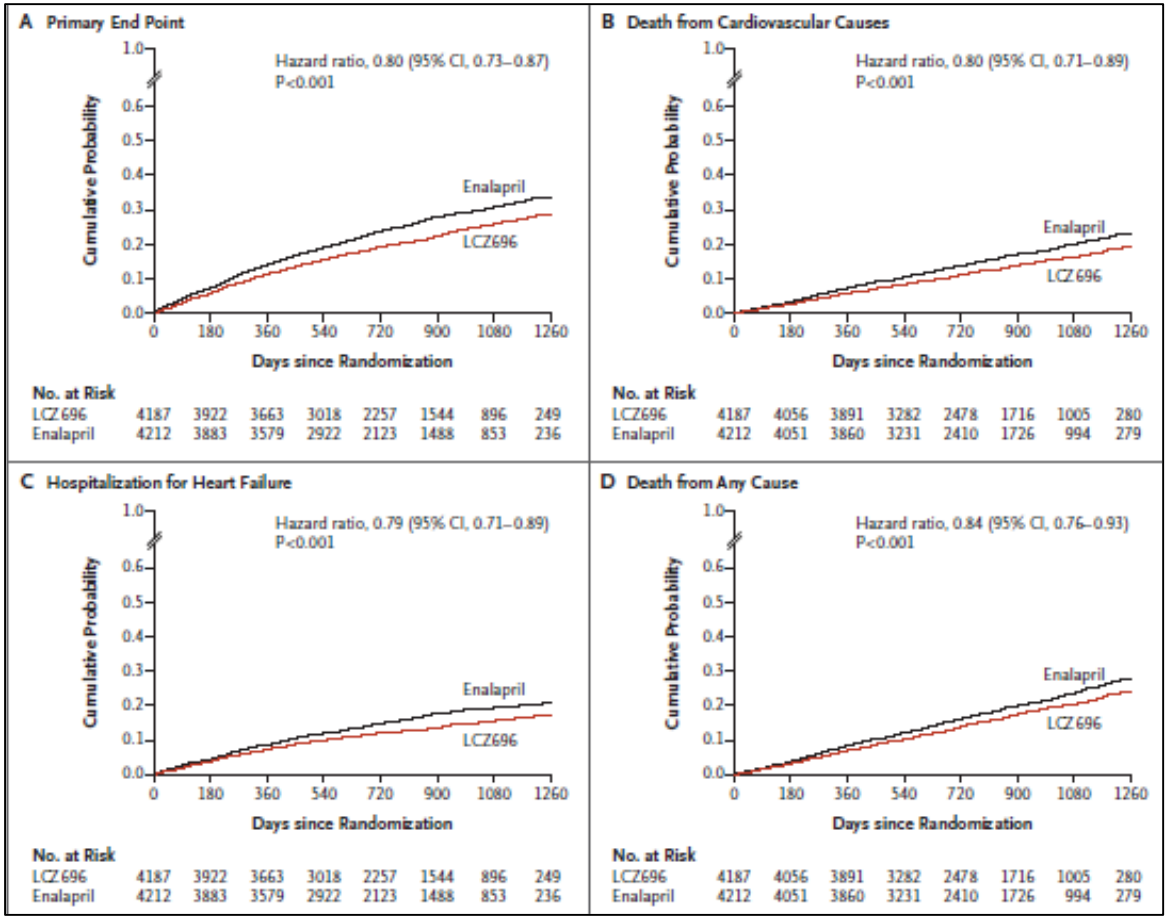
Contemporary Management in HFrEF

Angiotensin receptor/Neprilysin inhibitor - ARNi

SGLT2-Inhibitors

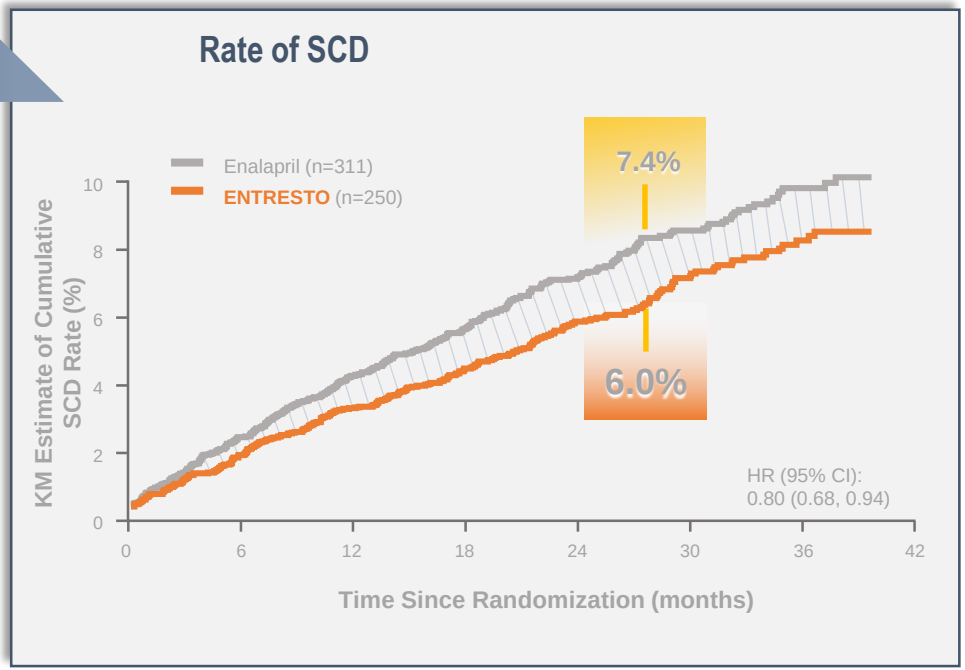
Optimization of GDMT doses

ARNi for HFrEF: PARADIGM-HF



ENTRESTO reduced risk of SCD* by 20% compared to enalapril *(post-hoc analysis)*

PARADIGM-HF



20%
RELATIVE RISK REDUCTION VS ENALAPRIL

(1.4% ARR)
over a median duration of 27 months[2]

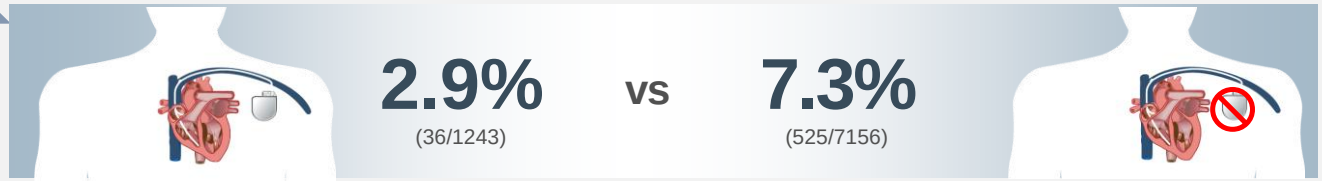
*Risk reduction of SCD as a cause of death was not a prespecified analysis of PARADIGM-HF and patients were not randomized by ICD status.

Desai AS, et al. *Eur Heart J*. 2015;36(30):1990-1997.

Risk of SCD in absence or presence of ICDs[1,*]

(post-hoc analysis)

PARADIGM-HF



Patients **WITH** an ICD treated with **ENTRESTO** had a lower risk of SCD vs ICD patients treated with enalapril[1-3]

	SCD, n (%)	HR, ENTRESTO vs Enalapril (95% CI)
ENTRESTO	12/623 (1.9%)	0.49 (0.25 – 0.98)
Enalapril	24/620 (3.9%)	

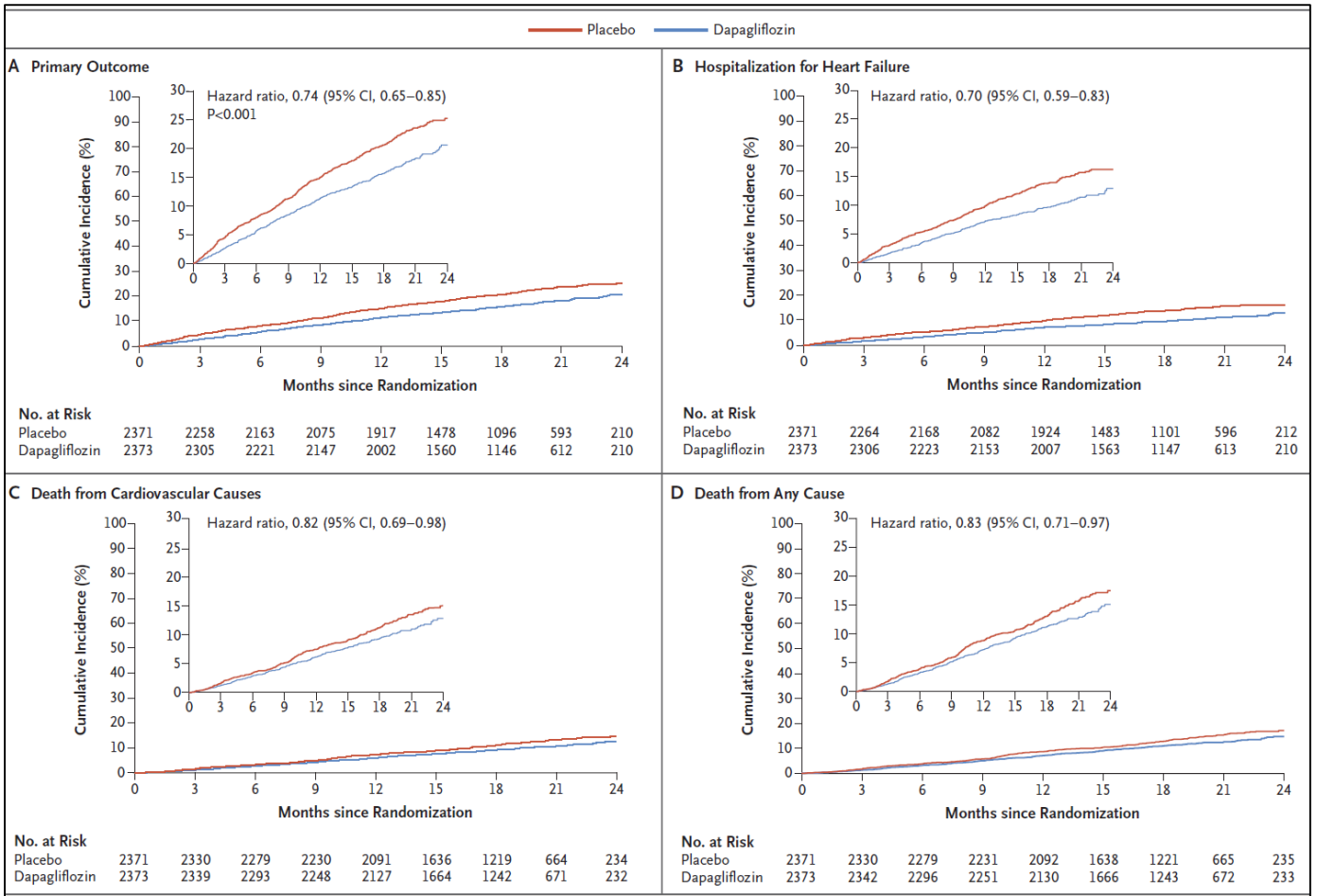
Patients **WITHOUT** an ICD treated with **ENTRESTO** had a lower risk of SCD vs non-ICD patients treated with enalapril[1-3]

	SCD, n (%)	HR, ENTRESTO vs Enalapril (95% CI)
ENTRESTO	238/3564 (6.7%)	0.82 (0.69 – 0.98)
Enalapril	287/3592 (8.0%)	

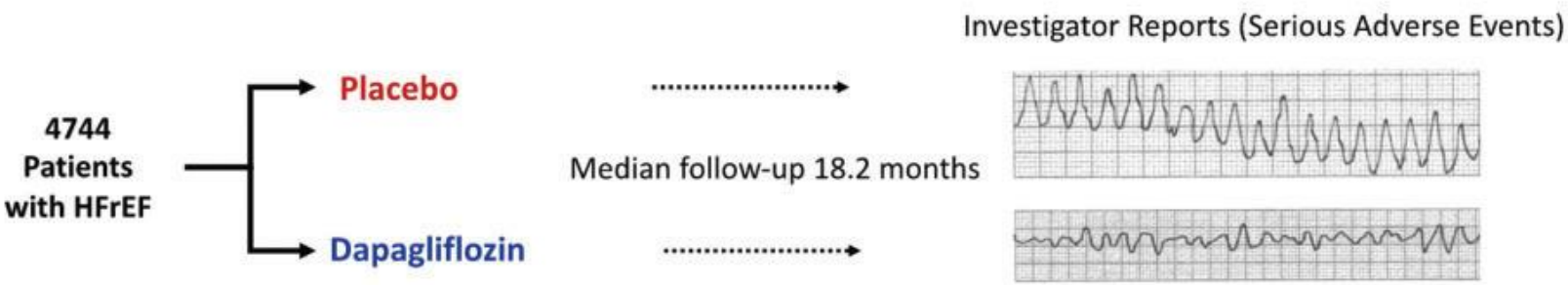
*Risk reduction of SCD as a cause of death was not a prespecified analysis of PARADIGM-HF and patients were not randomized by ICD status.

1. Desai AS, et al. *Eur Heart J*. 2015;36(30):1990-1997.
2. Data on File. CLCZ696B2314. SCD by ICD use and treatment group, Novartis Pharmaceutical Corp; April, 2018.
3. McMurray JJ, et al. *N Engl J Med.* 2014;371(11):993-1004.

SGLT2 Inhibitors for HFrEF: DAPA-HF



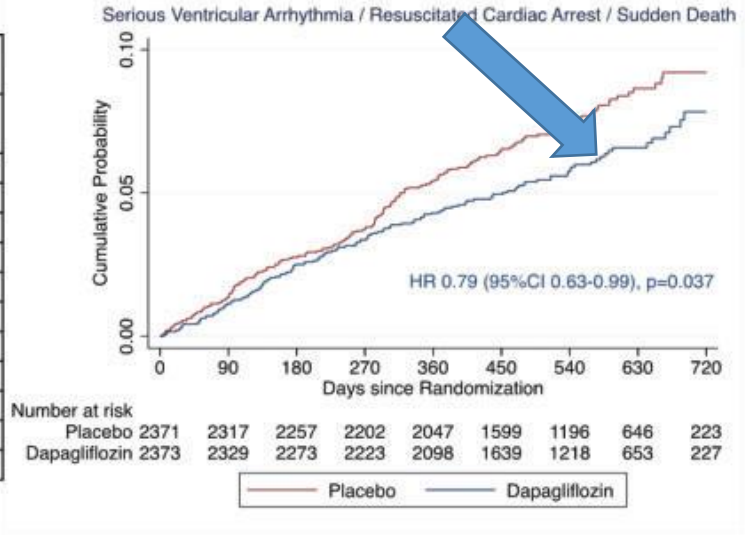
Effect of SGLT2 Inhibitors on the risk of SCD: DAPA-HF



Backward stepwise logistic regression multivariable model to predict any serious ventricular arrhythmia, resuscitated cardiac arrest or sudden death

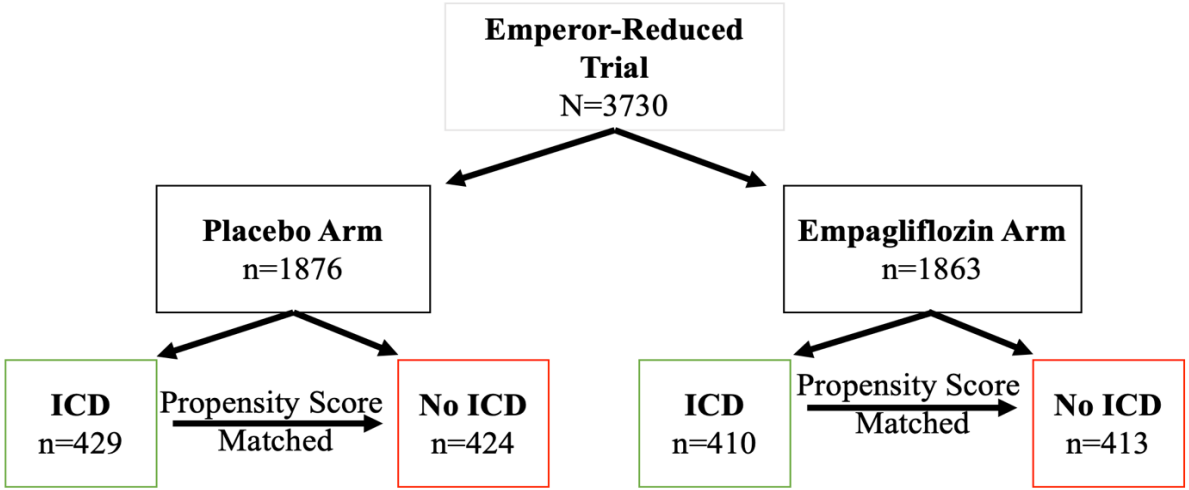
Predictor Variable*	Odds Ratio (95% CI)	p Value**	χ2
Log-transformed NT-proBNP (per 1 unit increase)	1.54 (1.34 – 1.77)	<0.001	36.0
Previous Ventricular Arrhythmia	1.93 (1.41 – 2.64)	<0.001	16.8
LVEF (per 5% increase)	0.86 (0.78 – 0.94)	0.001	11.9
Systolic BP (per 10mmHg)	0.88 (0.81 – 0.96)	0.004	8.1
Previous MI	1.42 (1.11– 1.82)	0.005	7.8
Sex- male	1.53 (1.10 – 2.12)	0.012	6.3
BMI (per 1 kg/m^2 increase)	1.03 (1.00 – 1.05)	0.020	5.4
Sodium (per 1 mmol/L increase)	0.96 (0.92 – 0.99)	0.039	4.3
Non-white race	0.85 (0.72 – 0.99)	0.038	4.3
Dapagliflozin	0.80 (0.63 – 1.02)	0.067	3.4
Cardiac Resynchronization Therapy	0.64 (0.39 – 1.04)	0.070	3.3
Previous HF hospitalization	0.99 (0.78 – 1.27)	0.985	0.0

*Randomized treatment and history of heart failure hospitalization were fixed factors in the model. **The p-value threshold was set at p<0.1



European Heart Journal (2021) 42, 3727–3738 doi:10.1093/eurheartj/ehab560

ICD Benefit in EMPEROR Reduced

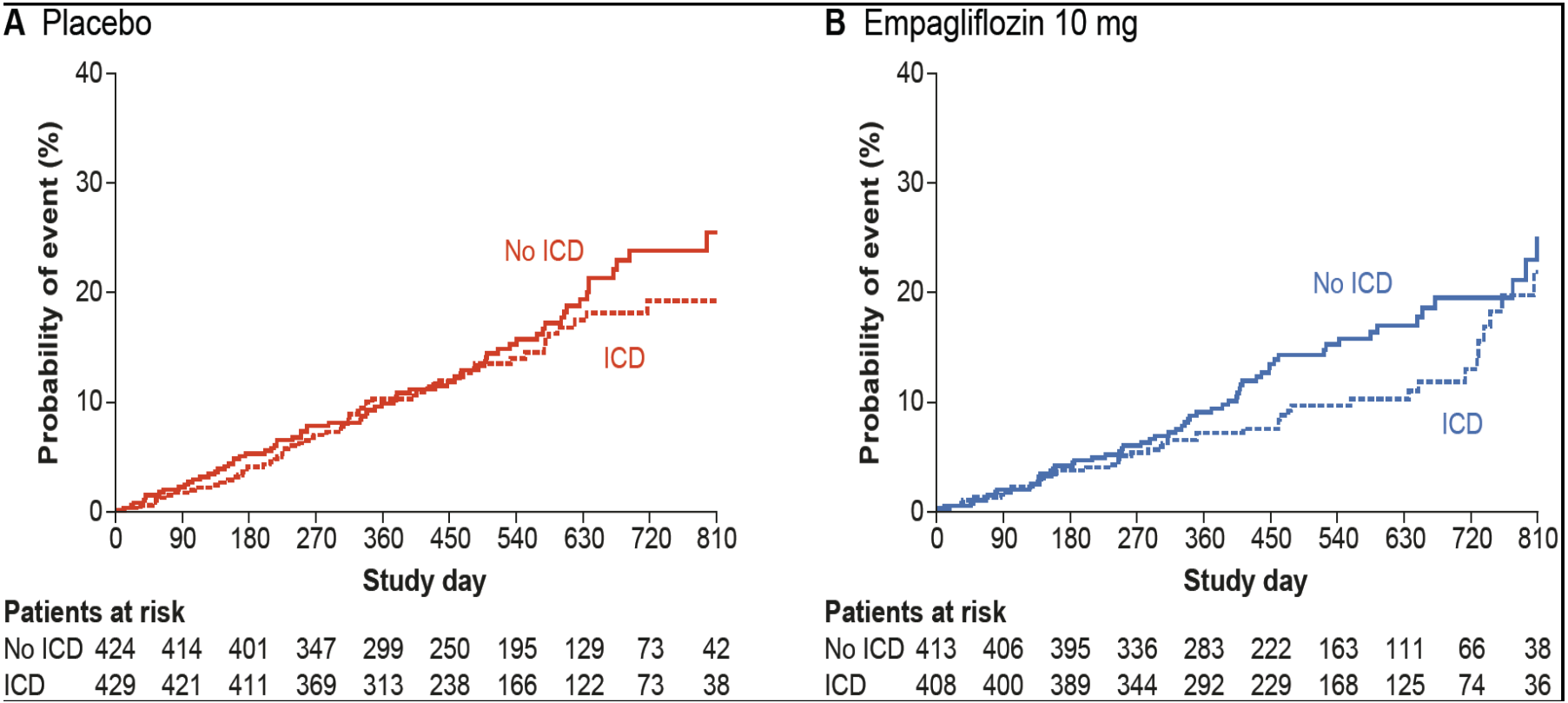


Variables Used for Propensity Matching

Age, sex, New York Heart Association functional class, cause of cardiomyopathy (ischemic/non-ischemic), left ventricular ejection fraction, estimated glomerular filtration rate, geographic region, mineralocorticoid receptor antagonist use

Personal communication – Ilan Goldenberg

ICD Benefit in EMPEROR Reduced



Personal communication – Ilan Goldenberg

CONTEMP-ICD
Study Design and Hypothesis

Prospective, multicentre, open-label, randomized-controlled trial

Eligible for a primary prevention ICD (exclude CRT) but have a higher predicted risk of non-arrhythmic mortality vs. SCD.

Non-ICD vs. ICD treatment arms

Ethical issues associated with randomization to Non-ICD in clinical trials

Consistent GDMT optimization:

GDMT Score

Exclusion of patients who are at a high risk for the development of arrhythmic events:

MADIT-ICD Benefit Score

MADIT-ICD BENEFIT SCORE

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	

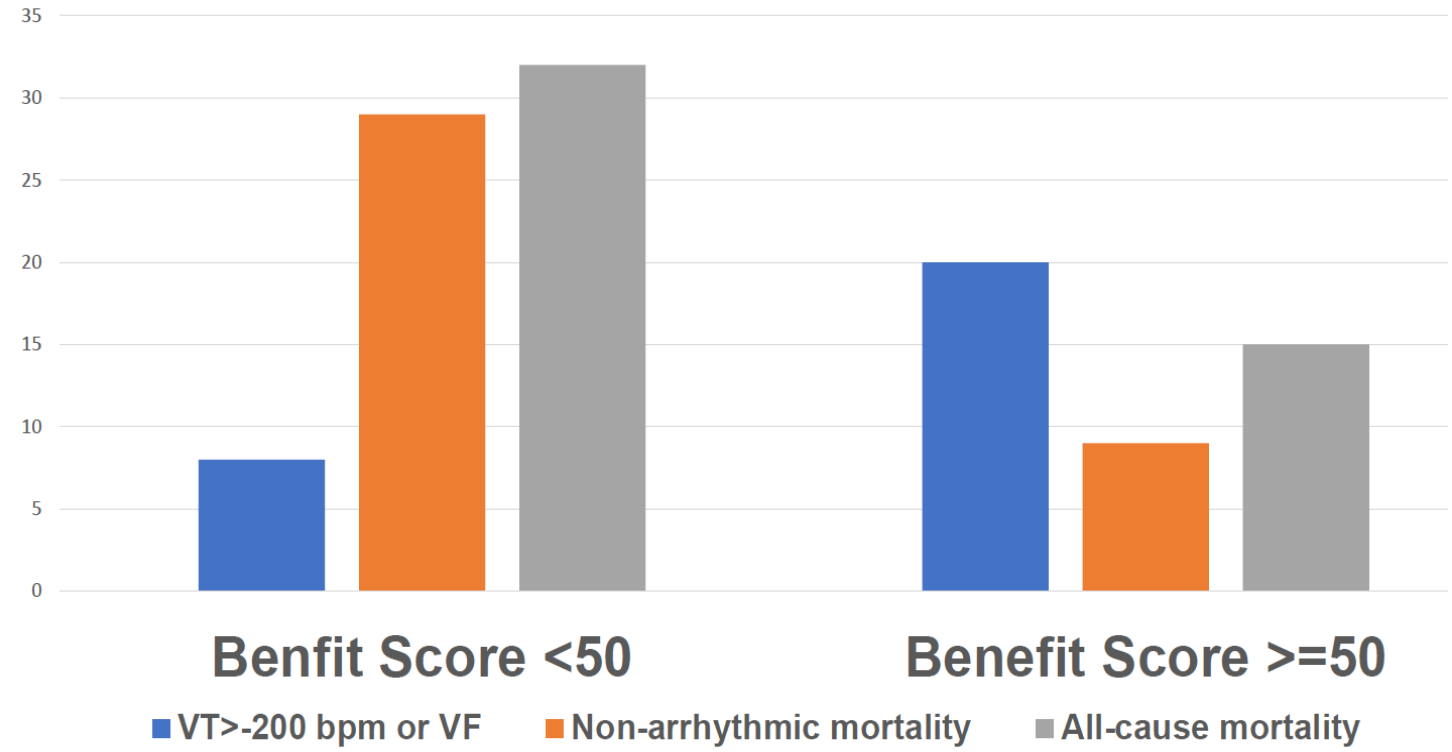
Non-arrhythmic Mortality Score

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

https://is.gd/madit

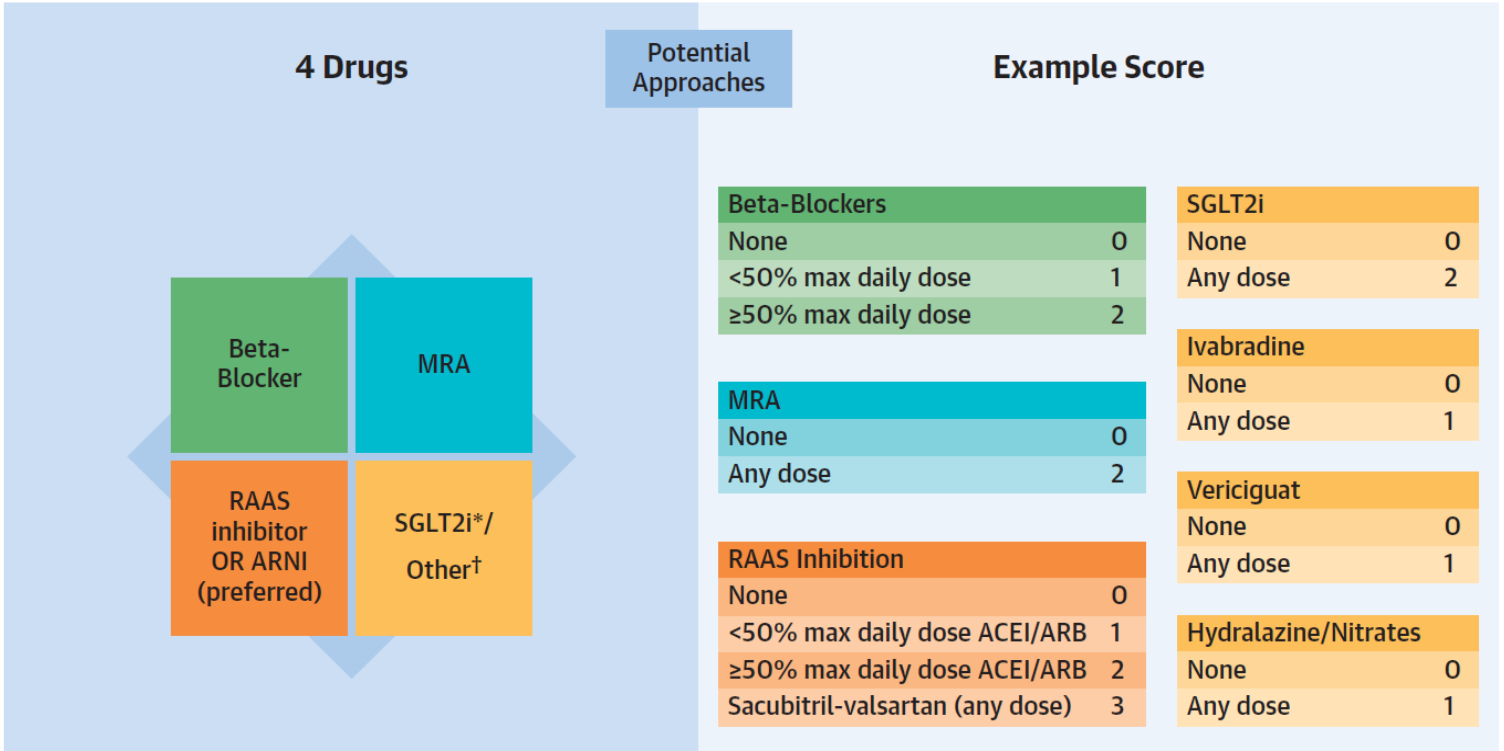
European Heart Journal, Volume 42, Issue 17, 1 May 2021, Pages 1676–1684,

Figure 5: Three-year rates of VTA, non-arrhythmic death, and all-cause mortality by the MADIT-ICD Benefit Score (excluding CRT)



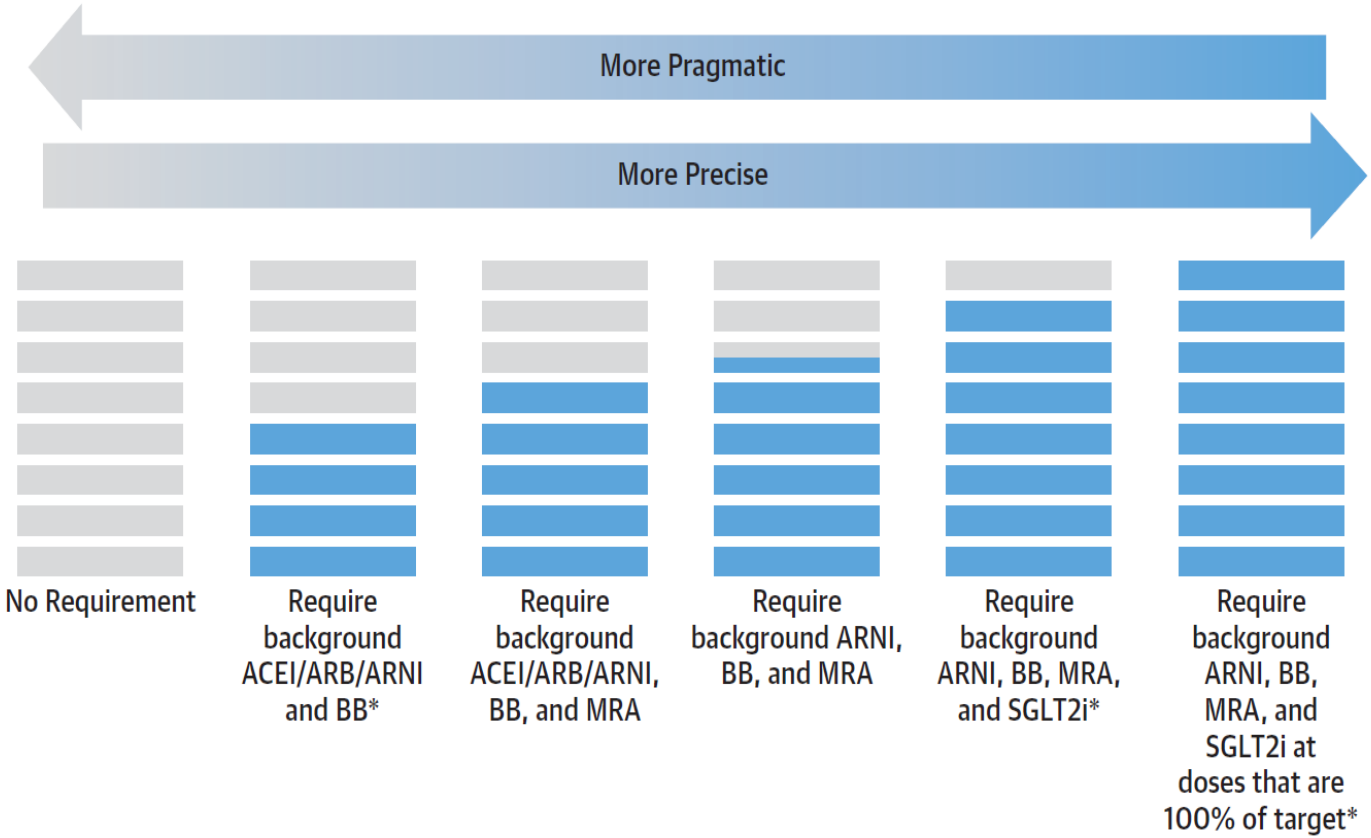
GDMT SCORE

CENTRAL ILLUSTRATION Potential Approaches to Background Drug Therapy for Heart Failure Patients



Fiuzat, M. et al. J Am Coll Cardiol. 2022;79(5):504-510.

GDMT SCORE


More Pragmatic
More Precise
No Requirement
Require background ACEI/ARB/ARNI and BB*
Require background ACEI/ARB/ARNI, BB, and MRA
Require background ARNI, BB, and MRA
Require background ARNI, BB, MRA, and SGLT2i*
Require background ARNI, BB, MRA, and SGLT2i at doses that are 100% of target*

Primary Specific Aim

Compare the risk of all-cause mortality of Non-ICD vs. ICD management in HFrEF patients who have a non-arrhythmic mortality risk that exceeds the risk of VTA per the MADIT-ICD Benefit Score

We hypothesize that in HFrEF patients at a lower arrhythmic risk medical management without an ICD is non-inferior to prophylactic ICD placement for the primary endpoint of all-cause mortality.

Secondary Aims

<u>Specific Aim 2:</u> Evaluate whether Non-ICD vs. ICD is associated with improved survival free of major CV events in patients with HFrEF who are at a lower arrhythmic risk

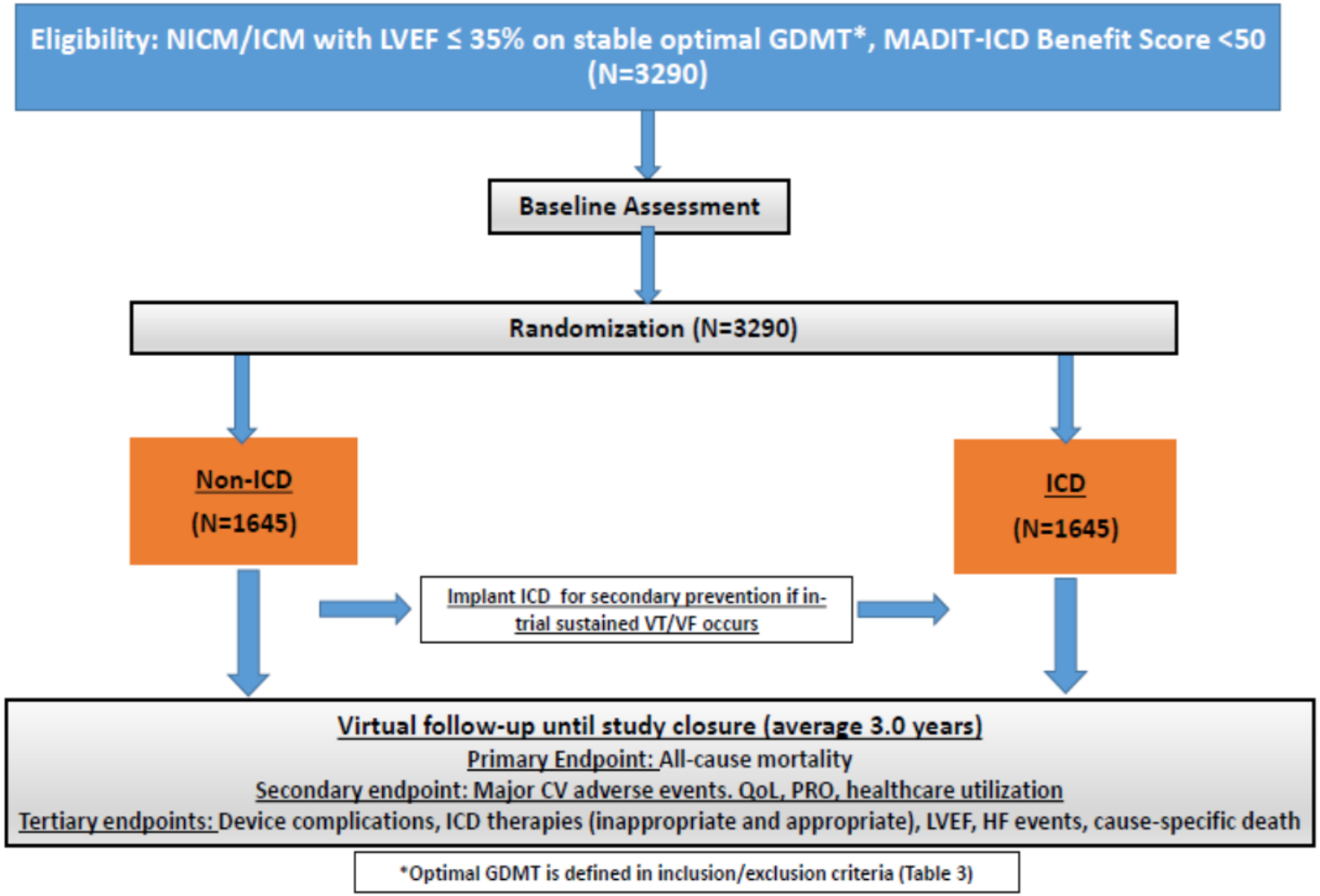
We hypothesize that Non-ICD management is associated with improved survival free of major CV events requiring hospitalization compared with prophylactic ICD implant.

<u>Specific Aim 3:</u> Assess the healthcare utilization (HCU) and quality of life (QoL) implications of Non-ICD vs. ICD management approaches in HFrEF patients with a lower predicted arrhythmic risk

We hypothesize that the reduction in major CV events associated with Non-ICD management approach will translate into lower HCU (defined in section C.1.2.) and improved QoL (assessed through the Kansas City Cardiomyopathy Questionnaire [KCCQ], EuroQol-5 Dimension (EQ-5D), Patient-reported Outcomes [PRO]).

<u>Specific Aim 4:</u> Determine the effect of Non-ICD vs. ICD management on all-cause mortality in prespecified subgroups

We hypothesize that, in HFrEF patients who are at a lower arrhythmic risk, Non-ICD vs. ICD is consistently non-inferior with respect to the primary endpoint of all-cause mortality in prespecified subgroups (including age, sex, race/ethnicity, ICM/NICM status, Charlson comorbidity index, and the use of novel GDMT treatment).


Eligibility: NICM/ICM with LVEF ≤ 35% on stable optimal GDMT*, MADIT-ICD Benefit Score <50 (N=3290)
Baseline Assessment
Randomization (N=3290)
Non-ICD (N=1645)
ICD (N=1645)
Implant ICD for secondary prevention if in-trial sustained VT/VF occurs
Virtual follow-up until study closure (average 3.0 years)
Primary Endpoint: All-cause mortality
Secondary endpoint: Major CV adverse events. QoL, PRO, healthcare utilization
Tertiary endpoints: Device complications, ICD therapies (inappropriate and appropriate), LVEF, HF events, cause-specific death
*Optimal GDMT is defined in inclusion/exclusion criteria (Table 3)

Eligibility Criteria

Inclusion criteria:	***Exclusion criteria:***
Age ≥ 18 years (no upper limit)	Existing ICD/CRT-D
Class I or IIa indication for a primary prevention ICD[15]: Ischemic or non-ischemic cardiomyopathy and NYHA Class ≥ II if most recent LVEF is ≤ 35% OR ischemic cardiomyopathy with NYHA Class I if most recent LVEF is ≤ 30%	Planned CRT-P or CRT-D implant for any indications including Class I or IIa indication for CRT including: Presence of left bundle branch block (LBBB) with QRS ≥ 120 msec OR QRS duration ≥ 150 msec regardless of QRS morphology OR decision for CRT implant by EP provider for other indications
Most recent LVEF (%) per cardiac imaging* obtained at any time prior to enrollment after being stable on optimal GDMT** for at least one month	Acute MI within the past 3 calendar months
Optimal GDMT for at least one calendar month prior to last LVEF imaging is prespecified as one of the following: ➢ Receiving all 4 therapies (beta-blockers, ARNI/ARB/ACE, MRA, and SGLT2i) Or ➢ GDMT Score ≥ 6 (per Figure 7)	Chronic renal failure requiring hemodialysis
MADIT-ICD Benefit Score < 50 (per Figure 4)	Coronary revascularization within the past 3 calendar months
	History of sustained VT or VF
	Known genetic cause of cardiomyopathy
	Life expectancy < 1 year
	Unable or unwilling to follow study protocol
	Inability to consent
*Echocardiogram, MRI or nuclear, performed as a standard of care procedure; **As defined in inclusion criterion #4 below.	

Outcome measures

Primary or Secondary	Name of Outcome	Specific measure to be used	Timepoints	Estimated power
Primary	All-cause mortality	All-cause mortality	End of follow-up (average 3.0-years)	90% (Cox model) (NI margin = 1.20)*
Secondary	Major adverse CV events requiring hospitalization*	First occurrence of HF hospitalizations, stroke, MI, device-related major complications or inappropriate ICD shocks requiring admission**	End of follow-up (average 3.0-years)	>99% (Cox model)‡
Secondary	Healthcare utilization	All-cause hospital admissions, ED visits, planned and unplanned clinic visits	End of follow-up (average 3.0-years)	>99% (Fisher exact test)***
Secondary	Quality of life	Kansas City Cardiomyopathy Questionnaire [KCCQ], Patient-reported Outcomes [PRO],¶ EuroQol-5 Dimension (EQ-5D)	One-year	>99.9% (Fisher's exact test) ⁺

STATISTICAL DESIGN AND POWER

Noninferiority two-arm design for primary endpoint of all-cause mortality, comparing ICD+CRT-D & no-ICD+CRT-D

Letting HR = Hazard ratio [No-ICD+CRT-D / ICD+CRT-D], study is powered for the following null and alternative hypotheses:

H_0:HR $\geq$ 1.20 vs H_a:HR < 1.20

(i.e., No-ICD+CRT-D is inferior to ICD+CRT-D, vs. not)

Margin (i.e., 1.20 on HR scale) selected based on previous trial data: all ICD trials show a mortality reduction of >25% for prophylactic ICD implantation vs. Non-ICD therapy

<u>Proposed trial sample size:</u> 3290 patients from ~115 sites

Study Team and Partners

Funding support: Patient-Centered Outcome Research Institute (PCORI)
Sponsor: University of Rochester
Steering Committee:
Leading HF and EP specialists
Engagement Committee:
Patient partners and stakeholders
Pharmacologic counseling: Dr. Kathrine DiPalo
Endorsement from:

Heart Rhythm Society
European Heart Rhythm Association
Heart Failure Society of America
European Heart Failure Society
American Heart Association
American College of Cardiology
Canadian Heart Failure and Heart Rhythm Societies

HeartRhythm
The Official Journal of the Heart Rhythm Society, The Cardiac Electrophysiology Society, and The Pediatric & Congenital Electrophysiology Society
Heart Rhythm Society SM

Contemporary Review

Reassessing the need for primary prevention implantable cardioverter-defibrillators in contemporary patients with heart failure

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Trial Designs

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Review Articles

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Rationale and design of the comparative effectiveness of ICD vs non-ICD therapy in contemporary heart failure patients at a low risk for arrhythmic death (CONTEMP-ICD) trial

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Clinical Implications

Findings from the proposed study will result in a paradigm change in HFrEF management, shifting healthcare resources from unnecessary routine prophylactic ICD placement to more appropriate HF management that actively incorporates pharmacologic and non-pharmacologic management with personalized selection for primary device therapy.

If the trial confirms the hypothesis, it is expected that approximately one half of HFrEF patients who are currently referred for prophylactic ICD placement will no longer be indicated for a device.