PLACE 2026
PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

CONGRESSO
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Indicazione dell'ICD per la prevenzione primaria nella disfunzione ventricolare sinistra non ischemica

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DISCLOSURES

Bayer

Novonordisk

The speaker declares speaker fees / advisory board participation with the above companies. No conflict of interest relevant to the content of this presentation.

DEFINING THE TARGET POPULATION

Definition & Aetiologies

Non-ischemic LV dysfunction: absence of CAD sufficient to explain dysfunction — not synonymous with benign

Aetiologies: idiopathic/familial DCM, evolved myocarditis, cardiotoxicity, tachycardiomyopathy, sarcoidosis, genetic cardiomyopathies

Typical Profile

LVEF ≤35%

NYHA II–III

Optimised therapy

No prior sustained arrhythmic events (primary prevention)

Aetiology and reversibility directly condition the timing of ICD evaluation

Arbelo et al. Eur Heart J 2023; Zeppenfeld et al. Eur Heart J 2022

WHY IS THIS A DIFFICULT DECISION?

Potential Benefit

ICD prevents sudden arrhythmic death in HFrEF

Contemporary Uncertainty

Modern GDMT reduces SCD risk

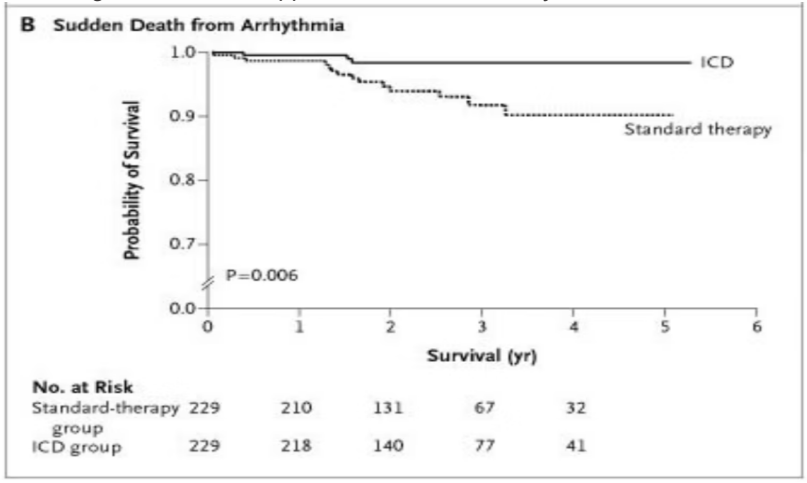
Possible Harm

Complications, shocks, infections, psychological burden

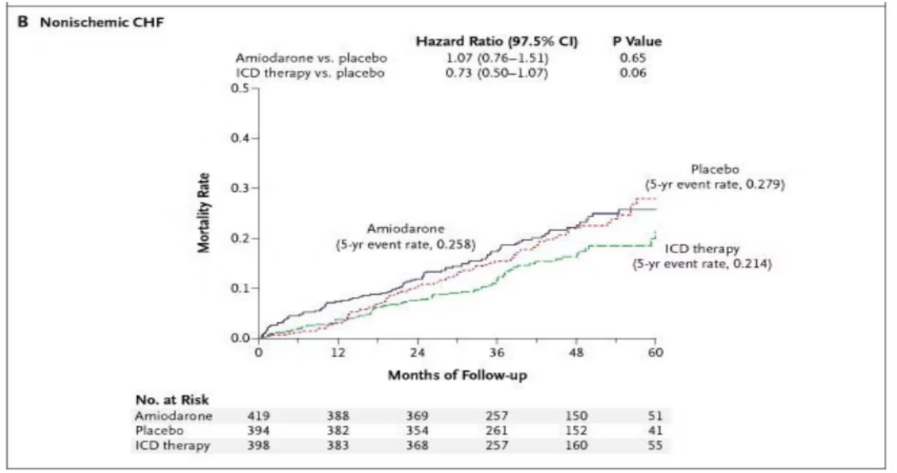
The Key Question

Does ICD meaningfully change prognosis of THIS patient?

McDonagh et al. 2021; Zeppenfeld et al. 2022; Yehya et al. 2025

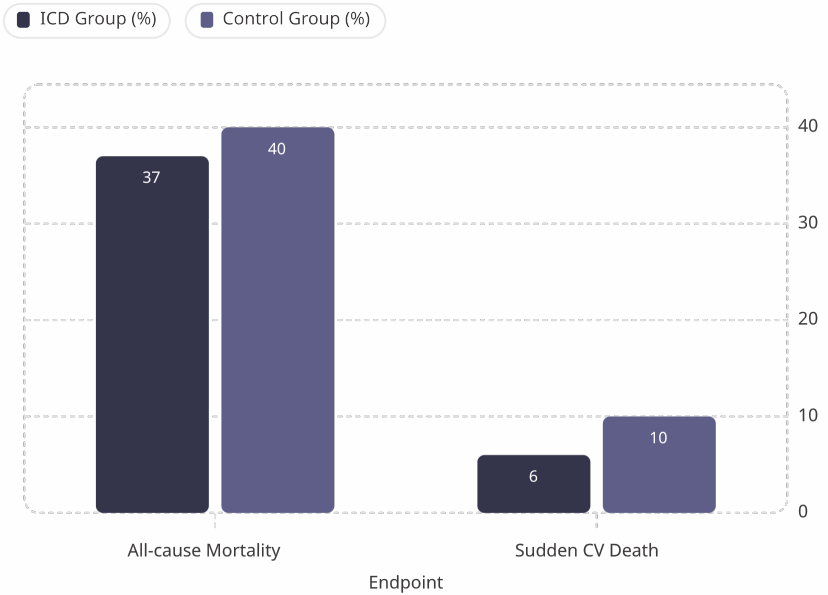


DEFINITE Trial (panel B) — Kadish et al. NEJM 2004



SCD-HeFT (Non-ischemic CHF) — Bardy et al. NEJM 2005

WHAT THE DANISH TRIAL TEACHES US



Key Lessons from DANISH (9.5 yrs)

- **All-cause mortality:** 37% (ICD) vs 40% (control) — *not statistically significant*
- **Sudden cardiovascular death:** 6% vs 10% — *significant reduction*
- ICD reduces sudden death but does not always translate into total survival benefit — competitive non-arrhythmic mortality dilutes the effect
- **2025 JACC update (13.2 yrs):** confirms no significant reduction in all-cause mortality; SCD reduction persists; benefit more evident in younger patients

Yafasova et al. Circulation 2022; Butt et al. J Am Coll Cardiol 2025

THREE ESC FRAMEWORKS TO INTEGRATE

ESC HF 2021/2023

Defines timing relative to optimised medical therapy: LVEF ≤35% after ≥3 months GDMT, NYHA II–III, expected survival >1 year.

ESC VA/SCD 2022

Guides arrhythmic risk stratification — introduces multi-marker approach beyond LVEF alone.

ESC Cardiomyopathies 2023

Phenotype–genotype framework: specific aetiologies, CMR, genetics, family history.

These guidelines are **complementary, not conflicting**: each answers a different clinical question.

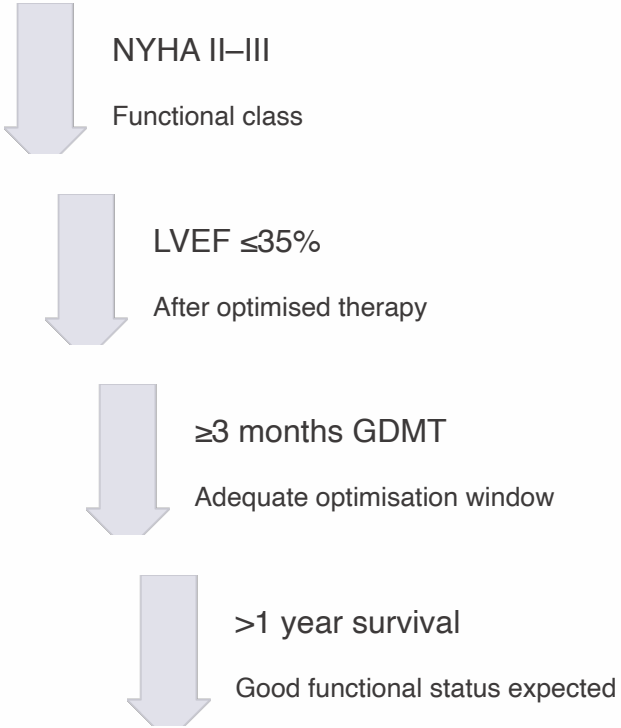
McDonagh et al. Eur Heart J 2021/2023; Zeppenfeld et al. Eur Heart J 2022; Arbelo et al. Eur Heart J 2023

ESC HF GUIDELINES: THE CLASSIC THRESHOLD

CLASS IIA, LEVEL A

- **Criteria:** NYHA II–III, LVEF ≤35%, ≥3 months optimised GDMT, expected survival >1 year with good functional status
- **Class IIa, Level A in non-ischemic DCM:** "should be considered" — strong evidence, but *not automatic*
- **Why IIa and not I?** More heterogeneous evidence, less consistent benefit on all-cause mortality, greater weight of non-arrhythmic risk vs ischaemic aetiology
- Individual risk assessment, shared decision-making and competitive risk evaluation are mandatory

McDonagh et al. Eur Heart J 2021; McDonagh et al. Eur Heart J 2023



ESC VA/SCD 2022: BEYOND LVEF — A MULTI-MARKER APPROACH

ICD may be considered in DCM/NDLVC with LVEF <50% when ≥2 risk markers are present:

- Unexplained syncope
- LGE on CMR
- Inducible VT at electrophysiological study
- High-risk genotype (LMNA, PLN, FLNC, RBM20)

LVEF alone is NOT the arrhythmic substrate — it is only a proxy. The substrate is defined by fibrosis, genetics, and electrical instability.

The Substrate Concept

Fibrosis (LGE)

Mid-wall fibrosis: arrhythmic trigger independent of LVEF

Genetics

LMNA, FLNC, RBM20, PLN: substrate before LVEF falls

Electrical Instability

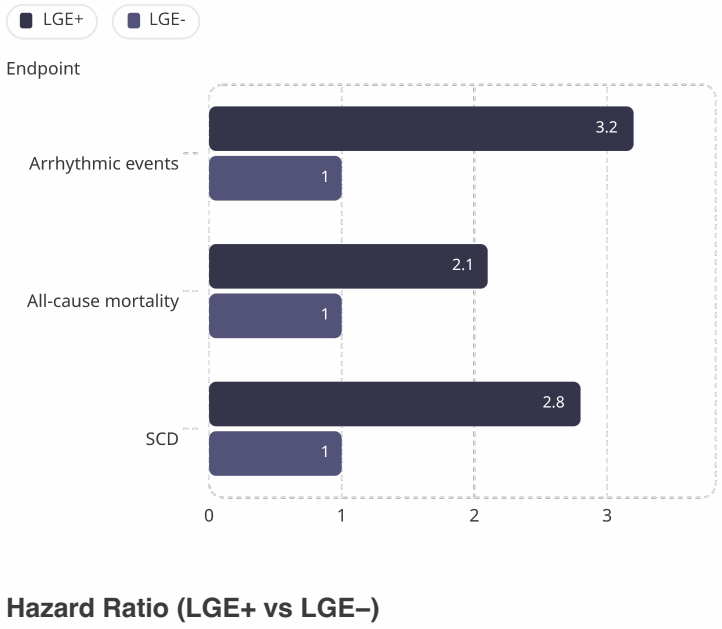
NSVT, syncope, inducible VT = substrate active

Zeppenfeld et al. Eur Heart J 2022

CMR AND LGE: SUBSTRATE MATTERS MORE THAN LVEF ALONE

- **JAMA 2024 meta-analysis** (103 studies, 29,687 NIDCM patients): LGE presence and extent consistently associated with arrhythmic events, non-arrhythmic events and mortality
- **LVEF alone** was not significantly associated with arrhythmic endpoints or mortality in this analysis
- **Mid-wall fibrosis pattern** is the most arrhythmogenic LGE pattern in DCM
- LVEF 32% with no LGE ≠ LVEF 42% with extensive mid-wall LGE — same threshold, very different substrate

Eichhorn et al. JAMA 2024;332(18):1535–1550

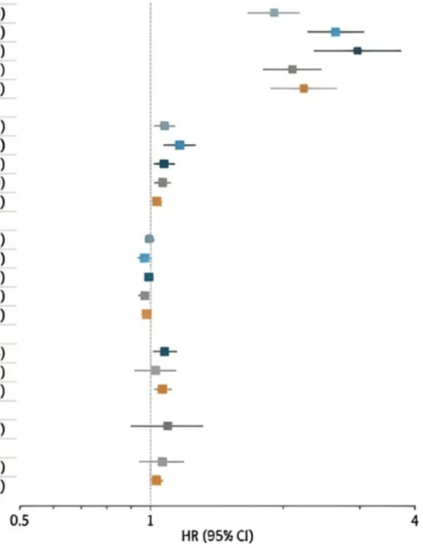


CMR AND LGE: JAMA 2024 META-ANALYSIS — FOREST PLOT

JAMA Network™

From: **Risk Stratification in Nonischemic Dilated Cardiomyopathy Using CMR Imaging: A Systematic Aystematic Review and Meta-Analysis**

Parameter	Studies/patients, n	HR (95% CI)
Late gadolinium enhancement presence (yes/no)		
All-cause mortality	23/9758	1.81 (1.60-2.00)
Cardiovascular mortality	3899236	2.43 (2.13-2.78)
Arrhythmia	49/11791	2.69 (2.09-3.30)
Heart failure	32/9464	1.98 (1.75-2.27)
MACE	54/12040	2.09 (1.75-2.44)
Late gadolinium enhancement extent (per 1%)		
All-cause mortality	4/1852	1.07 (1.62-1.12)
Cardiovascular mortality	3/1323	1.15 (1.07-1.24)
Arrhythmia	995085	1.07 (1.03-1.12)
Heart failure	6/1696	1.06 (1.01-1.10)
MACE	1333004	1.05 (1.02-1.04)
Left ventricular ejection fraction (per 1%)		
All-cause mortality	573320	0.89 (0.57-1.02)
Cardiovascular mortality	723627	0.97 (0.54-1.00)
Arrhythmia	1235055	0.99 (0.97-1.03)
Heart failure	1084576	0.97 (0.55-0.96)
MACE	24/4446	0.98 (0.56-0.99)
T1 reflection time (per 10 ms)		
Arrihythma	5/1778	1.07 (1.01-1.14)
Heart Hitbre	1/1198	1.01 (0.53-1.13)
MACE	3/963	1.06 (0.51-1.11)
Extracellular volume (per 1%)		
Heart failure	3/1772	1.07 (0.51-1.11)
Global longitudinal strain (per 1%)		
Heart failure	3/1001	1.06 (0.55-1.58)
MACE	7/1397	1.03 (0.54-1.16)



CLINICAL AND ELECTRICAL MARKERS: BEYOND THE ECHOCARDIOGRAM

Arrhythmic Markers

- Unexplained syncope
- NSVT on Holter, high PVC burden
- Inducible VT at EPS

Electrical Markers

- LBBB / QRS prolongation (CRT indication)
- AV conduction disorders
- RV involvement

Biomarkers

- NT-proBNP trajectory
- Frailty scores

No single marker is sufficient — their combination allows weighting of arrhythmic vs competitive risk. ECG + Holter + CMR + genetics describe different dimensions of the same risk.

Zeppenfeld et al. Eur Heart J 2022; Arbelo et al. Eur Heart J 2023

ESC CARDIOMYOPATHIES 2023: FROM SINGLE CRITERION TO INDIVIDUAL PROFILE

Phenotype-Specific Decision

Moves from "LV dysfunction" to specific phenotype: DCM, NDLVC, arrhythmogenic forms, evolved myocarditis, sarcoidosis, cardiotoxicity.

Integrated Assessment

Decision-making integrates CMR pattern, genotype, clinical trajectory, and family history.

Risk Beyond LVEF

Some phenotypes carry arrhythmic risk disproportionate to LVEF — e.g. LMNA-DCM, PLN-DCM, cardiac sarcoidosis.

Knowing Which Disease

Appropriateness increases when we know *which disease* we are treating — not just the LVEF value.

Arbelo et al. Eur Heart J 2023; Polovina et al. Eur J Heart Fail 2023

GENETICS: WHEN TO SUSPECT AND HOW TO ACT

When to Suspect Genetic Aetiology

- Family history of DCM or SCD
- Young age at presentation
- Conduction disorders, NSVT, suggestive CMR pattern
- Extracardiac features

Genetic testing is recommended in all DCM patients with a first-degree relative with DCM or unexplained SCD. Genetics can change the ICD decision threshold, urgency of follow-up, and family counselling.

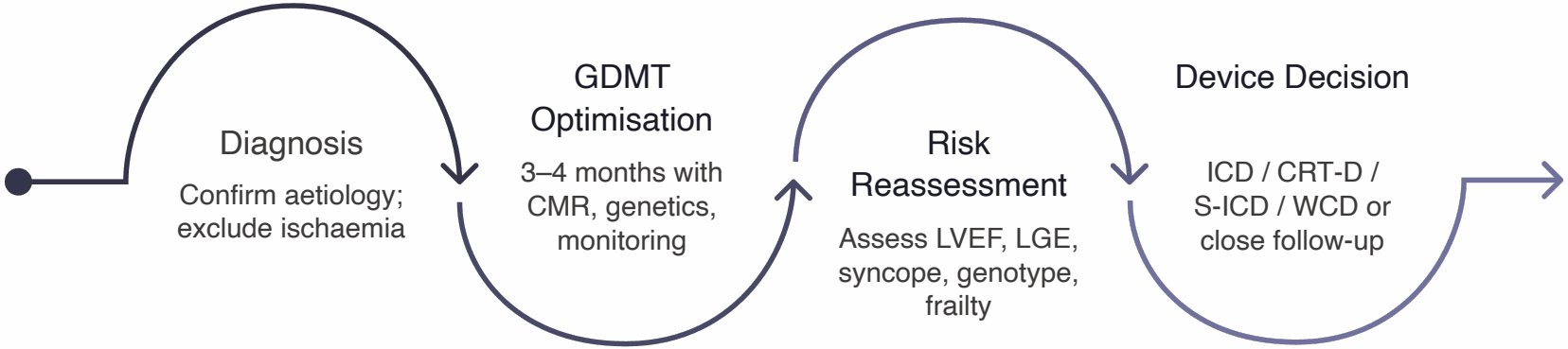
Arbelo et al. Eur Heart J 2023; Zeppenfeld et al. Eur Heart J 2022; Polovina et al. Eur J Heart Fail 2023

GENETICS: ARRHYTHMIC RISK MAY PRECEDE LVEF DECLINE

Gene	Protein	Main Risk	Clinical Feature	ICD Threshold
LMNA	Lamin A/C	High arrhythmic risk	Early AV block, NSVT	LVEF <45%
FLNC	Filamin C (truncating)	SCD even with preserved EF	RV involvement, fibrosis	Consider early
RBM20	RNA-binding protein	Aggressive DCM, VT storm	Young onset, rapid progression	Low threshold
PLN / DSP	Phospholamban / Desmoplakin	Fibrosis-driven arrhythmia	Inferolateral LGE	Consider early

Arbelo et al. Eur Heart J 2023; Zeppenfeld et al. Eur Heart J 2022; Polovina et al. Eur J Heart Fail 2023

TIMING: OPTIMISE FIRST — BUT DO NOT LEAVE HIGH-RISK PATIENTS UNPROTECTED



The waiting window is not passive: optimise therapy, identify reversible causes, perform CMR, monitor arrhythmias, assess genetics. In some genetic forms, arrhythmic risk may precede the LVEF ≤35% threshold.

McDonagh et al. Eur Heart J 2021; Casolo et al. Eur Heart J Suppl 2023; Duncker et al. Europace 2025

PRACTICAL ALGORITHM: 4-STEP DECISION PATHWAY

Step 1 — Confirm Diagnosis & Aetiology

Exclude significant ischaemia, identify reversible causes, define the specific cardiomyopathy phenotype.

Step 2 — Optimise Therapy

Achieve GDMT targets, correct reversible causes, evaluate CRT indication.

Step 3 — Stratify Arrhythmic & Competitive Risk

LVEF + LGE + syncope + NSVT + genotype + EPS + frailty / comorbidities.

Step 4 — Decide & Reassess

ICD / CRT-D / S-ICD / WCD / close follow-up — shared decision with patient; document rationale.

This algorithm reduces variability, overuse and underuse, and provides a defensible clinical record.

McDonagh et al. Eur Heart J 2021/2023; Zeppenfeld et al. Eur Heart J 2022; Arbelo et al. Eur Heart J 2023

THREE CLINICAL PROFILES: HOW DECISIONS DIFFER

Feature	Profile A	Profile B	Profile C
Age	58 yrs	69 yrs	78 yrs
LVEF	38%	32%	30%
GDMT	Complete	Incomplete	Complete
CMR/LGE	Mid-wall LGE +	No LGE	No LGE
NSVT/Syncope	NSVT +	None	None
Genotype	High-risk variant	Not tested	N/A
Comorbidities	Low	Moderate	CKD, frailty, NYHA IV
ICD Decision	**Strongly indicated**	**Reassess after GDMT**	**Net benefit doubtful**

Zeppenfeld et al. Eur Heart J 2022; Arbelo et al. Eur Heart J 2023; Yehya et al. JACC Heart Fail 2025

WHICH DEVICE? ICD, CRT-D OR S-ICD?

CRT-D

First choice when resynchronisation is indicated (LBBB, QRS ≥150 ms, LVEF ≤35%). Combines defibrillation with haemodynamic benefit.

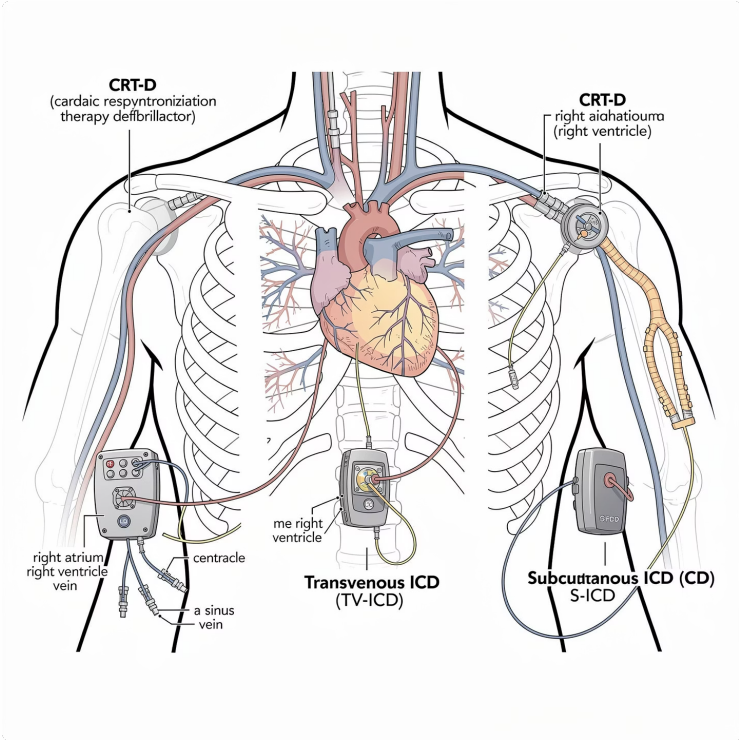
Transvenous ICD (TV-ICD)

When pacing, ATP for monomorphic VT or CRT is needed without full resynchronisation criteria.

Subcutaneous ICD (S-ICD)

Preferred when no pacing needed — especially younger patients or those with long device exposure. PRAETORIAN-XL 2025 confirms comparable long-term safety vs TV-ICD.

Device choice must anticipate the patient's **future needs** — not all ICDs are interchangeable.



Olde Nordkamp et al. Circulation 2025; Healey et al. Ann Intern Med 2022; Zeppenfeld et al. Eur Heart J 2022

SHARED DECISION-MAKING: WHAT MUST BE DISCUSSED WITH THE PATIENT

- **What ICD does**: terminates potentially fatal VT/VF — does not cure the cardiomyopathy, does not improve LVEF, symptoms or HF hospitalisations
- **What ICD does not do**: does not prevent HF progression or non-arrhythmic death
- **Risks to discuss**: procedural complications, inappropriate shocks, infections, lead failure, replacements, psychological impact
- **The question**: **"If ICD prevents an arrhythmic death, does the rest of the prognosis make this intervention proportionate to this patient's goals?"**

McDonagh et al. Eur Heart J 2021; Zeppenfeld et al. Eur Heart J 2022

BENEFIT DEPENDS ON THE RISK PROFILE

✅ High Probability of Benefit

- Younger age, LGE on CMR, high-risk genotype
- NSVT or syncope, sufficient life expectancy
- Low comorbidity burden

⚠️ Grey Zone — Reassess after GDMT

- Incomplete optimisation, no LGE, no arrhythmic markers
- Borderline LVEF
- Re-evaluate after 3–4 months

❌ Low Net Benefit

- Frailty, advanced CKD, NYHA IV
- Recurrent HF hospitalisations
- Predominant non-arrhythmic mortality risk

The NNT worsens as non-arrhythmic mortality risk increases — patient selection is critical.

Yehya et al. JACC Heart Fail 2025; Luria et al. Front Cardiovasc Med 2023

TAKE HOME MESSAGES

LVEF ≤35% is necessary but not sufficient

In non-ischemic LV dysfunction, ICD indication is Class IIa — "should be considered", not automatic.

CMR/LGE and genotype are decisive

Substrate (mid-wall fibrosis, high-risk mutations) outweighs LVEF as an arrhythmic risk marker.

Competitive risk is the key variable

ICD benefit is greatest when arrhythmic mortality risk exceeds non-arrhythmic mortality risk.

Platform matters

CRT-D if resynchronisation indicated; S-ICD if no pacing needed (especially young patients); TV-ICD if pacing or ATP required.

Appropriateness means implanting ICD in the right patient

Not reducing ICD use overall — optimise GDMT first, but protect high-risk patients during the waiting window.

McDonagh et al. 2021/2023; Zeppenfeld et al. 2022; Arbelo et al. 2023; Eichhorn et al. JAMA 2024; Butt et al. JACC 2025

THANK YOU