Cardiovascular Magnetic Resonance GUIDEd management of mild-moderate LV systolic dysfunction with an ICD: The CMR GUIDE Randomised Clinical Trial

Joseph B. Selvanayagam MBBS (Hons) DPhil

Flinders University, Flinders Medical Centre, Adelaide, Australia

On behalf of the CMR GUIDE Trial Investigators

ESC CONGRESS 2026 MUNICH

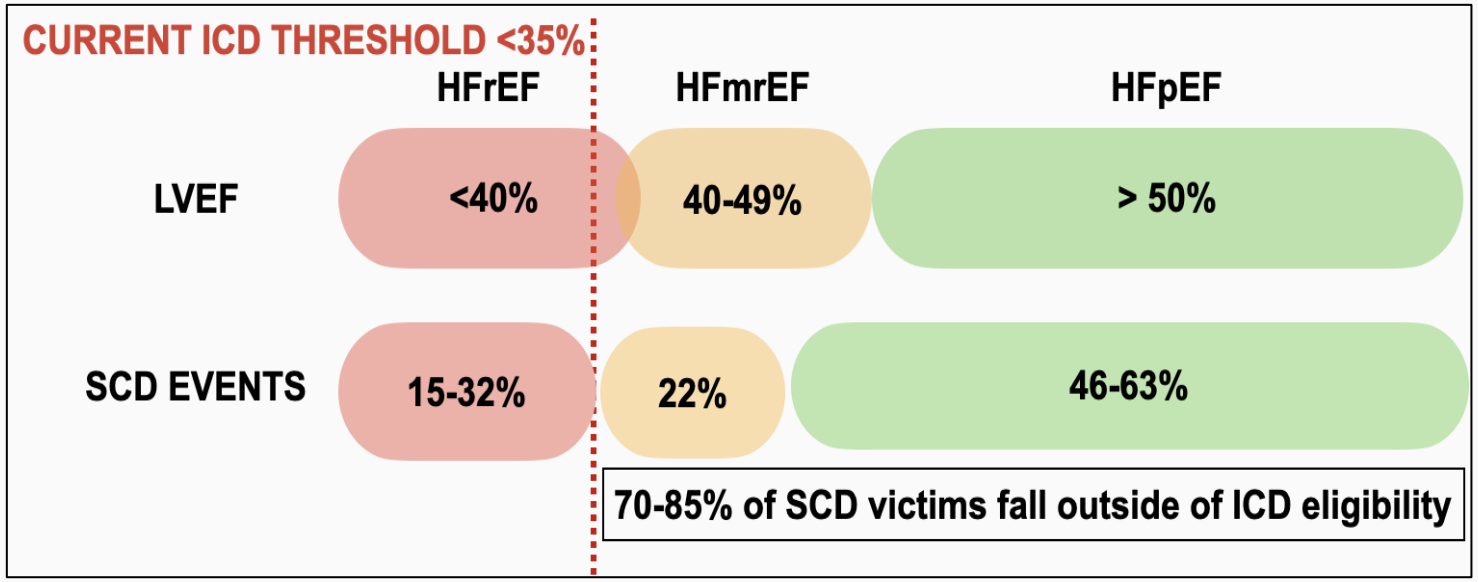
Disclosures

Research Contracts: Biotronik, National Heart Foundation Australia, NHMRC Australia, Sanofi, Pfizer, Honya

Consulting/Advisory Board: AstraZeneca, BMS, Sanofi, Pfizer, Boehringer-Ingelheim, Novartis, Bayer, Amicus, CSL

Background

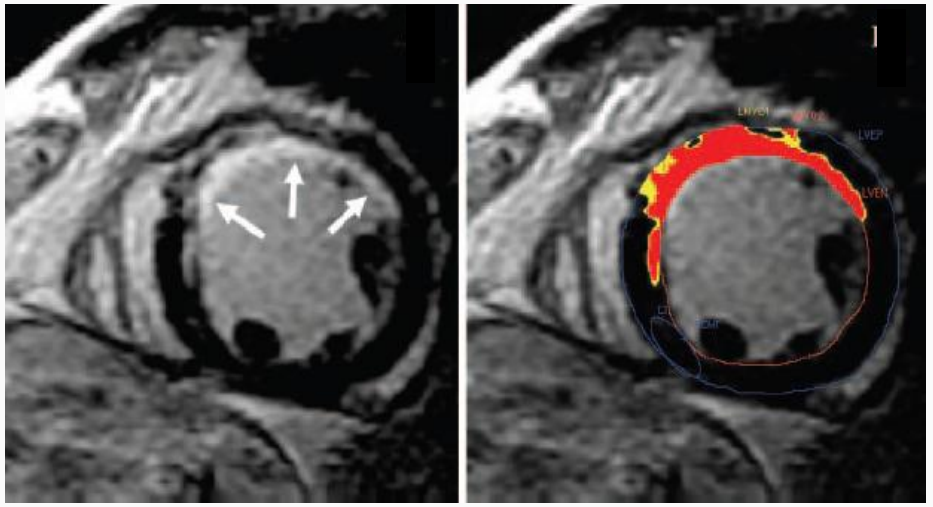
- Sudden cardiac death (SCD) is a major cause of mortality in heart failure with reduced LV systolic function
- Current guidelines recommend ICDs for primary prevention only when LVEF ≤35%, based on historical RCT evidence
- A substantial proportion of SCD events occur in patients with LVEF above this threshold
- No ICD recommendations currently exist for primary prevention when LVEF >35%



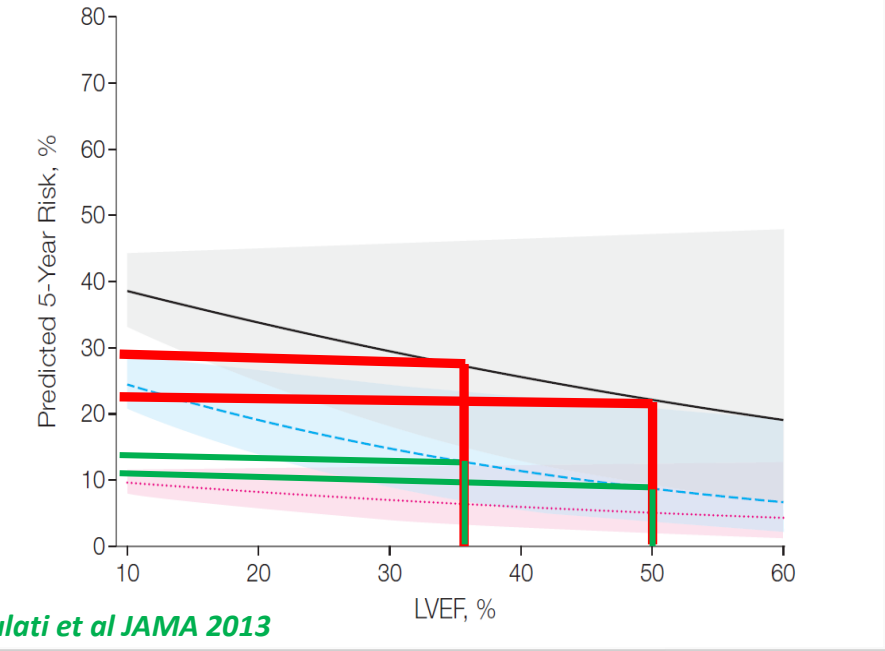
Stecker et al., JACC 2006; Narayanan et al., Circulation 2013; Junttila et al., Europace 2025

Background

- LGE-CMR directly visualises myocardial scar, the key substrate for re-entrant ventricular arrhythmias
- Presence and extent of LGE is independently associated with SCD and ventricular arrhythmia, regardless of LVEF
- No randomised trial to date has tested a scar-guided approach to ICD implantation



Yan et al Circulation 2013



Gulati et al JAMA 2013

TRIAL HYPOTHESIS

ICD implantation guided by the presence of myocardial scar on LGE CMR reduces sudden cardiac death (SCD) and/or haemodynamically significant ventricular arrhythmia (HSVA), in patients with ischaemic or non-ischaemic cardiomyopathy and LVEF 36–50%

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Primary Aim

To determine whether ICD implantation reduces sudden cardiac death (SCD) or haemodynamically significant ventricular arrhythmia (HSVA) in patients with LVEF 36–50% and CMR-defined myocardial scar

Design

Investigator-initiated, multicenter, prospective, randomized, open-label, blinded-endpoint trial

Setting

18 sites in Australia, Germany, United Kingdom

Enrolment

2015-2022; follow up May 2026

Inclusion and Exclusion Criteria

Inclusion

- **LVEF 36–50% after optimisation of guideline-directed medical therapy**
- **Ischaemic or Non-Ischaemic Cardiomyopathy**
- **CMR evidence of myocardial scar**
- **NYHA class I–III**

Exclusion

- **Established clinical indication for ICD**
- **Infiltrative or Hypertrophic Cardiomyopathy**

Patients meeting clinical/LVEF criteria but without scar on LGE-CMR were enrolled in a parallel observational registry

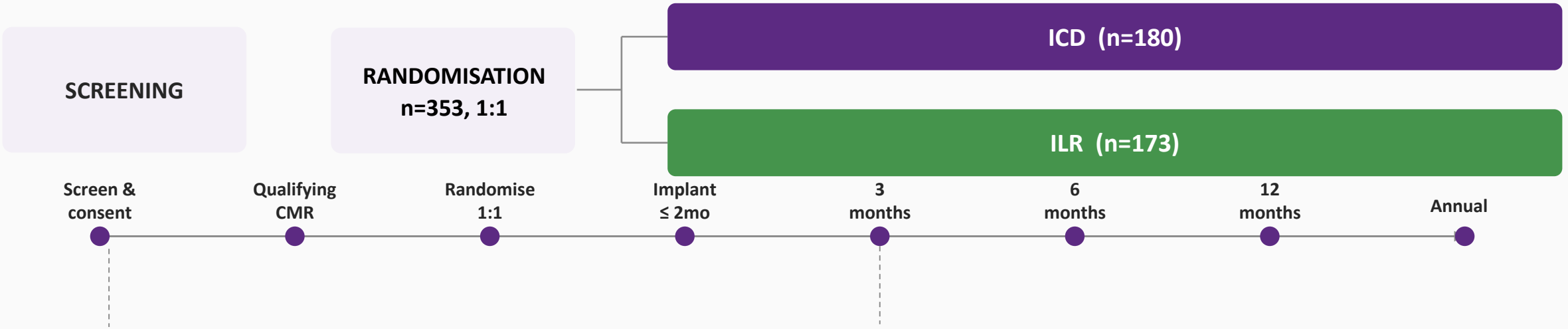
Ischaemic Cardiomyopathy

Prior MI, >50% stenosis of a major epicardial artery, or prior revascularisation (PCI/CABG)

Non-Ischaemic Cardiomyopathy

LV impairment without coronary disease sufficient to explain dysfunction (familial, prior myocarditis, or idiopathic)

CMR GUIDE: Study Design



BASELINE ASSESSMENTS

- Clinical
- Qualifying CMR
- Randomisation

FOLLOW-UP ASSESSMENTS

- Clinical: 3, 6, 12 months, annual
- **All clinical events were adjudicated by the CEC**
- Quality of life (MLHFQ)

ICD PROGRAMMING & DEVICE FOLLOW-UP

Standardised MADIT-RIT parameters; device interrogation at 3, 6, 12 months, then annually

All device downloads were adjudicated by the DDC

End Points

Primary Endpoint

Composite of:
Sudden Cardiac Death (SCD) or
Haemodynamically Significant Ventricular Arrhythmia (HSVA)
Ventricular arrhythmia producing syncope or hypotension (SBP <90mmHg)

Secondary Endpoints

- **SCD**
- **HSVA**
- **All-cause Mortality**
- **Cardiovascular Mortality**
- **Heart failure hospitalisation**
- **Quality of life (Minnesota Living with Heart Failure Questionnaire)**

Power Calculation

- **Designed with 80% power to detect a hazard ratio of 0.45 for the primary outcome between arms**
- **At least 51 primary-outcome events required**
- **Planned enrolment of approximately 428 patients, with an average follow-up of 4 years**

As the enrolment rate was lower than anticipated, both the recruitment and follow-up periods were extended. The longer follow-up was expected to yield a similar number of primary-outcome events as assumed in the original design, thereby preserving statistical power.

Statistical Analysis

- **Fine–Gray competing-risks models (subdistribution HR, 95% CI); adjusted for age, sex, aetiology, baseline LVEF**
- **Six prespecified subgroups: age, sex, LVEF, aetiology, NYHA class, QRS duration**
- **Exploratory hierarchical win ratio: SCD, HSVA, HF hospitalisation, and QoL**

Flow chart

25 additional patients with LVEF 36-50% and without sufficient myocardial scar were enrolled in a parallel observational registry (not randomised)

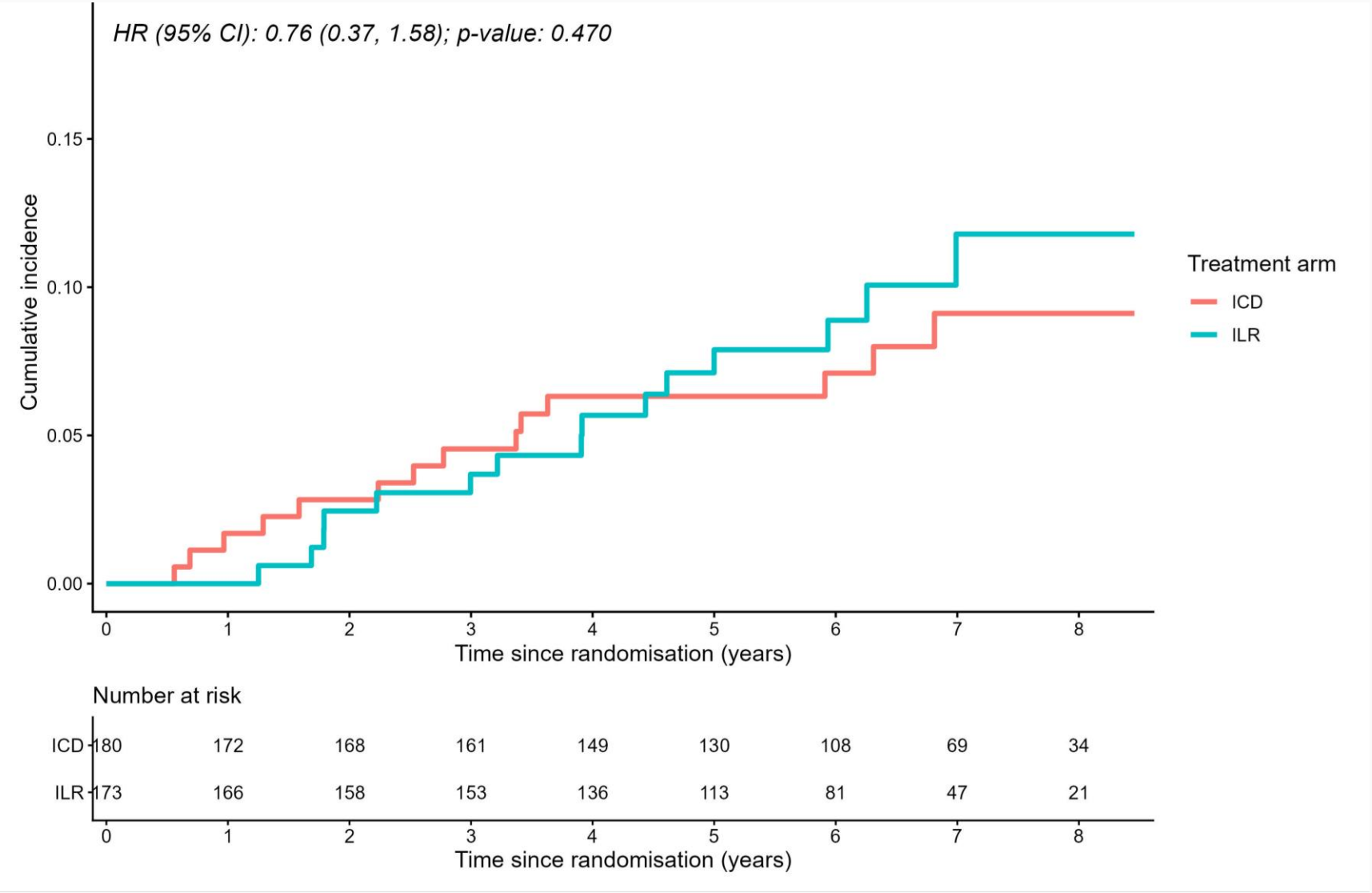
Results: Baseline Characteristics (1)

Characteristic	ICD (n=180)	ILR (n=173)
Age (IQR) – Yr	65 (57-72)	65 (57-71)
Male sex – no (%)	147 (82%)	143 (83%)
Type of Cardiomyopathy – no (%)		
Ischaemic	133 (74%)	121 (70%)
Non-Ischaemic	47 (26%)	52 (30%)
Cardiovascular History – no (%)		
Prior Myocardial Infarction	123 (68%)	117 (68%)
Current Smoker	32 (18%)	24 (14%)
Diabetes Mellitus	46 (26%)	49 (28%)
Hyperlipidemia	112 (62%)	102 (59%)
Hypertension	100 (56%)	90 (52%)
Peripheral Vascular Disease	10 (6%)	12 (7%)
Body Mass Index (IQR) – kg/m^2	29 (26-32)	29.1 (26-33)
Blood Pressure (IQR) – mmHg		
Systolic	125 (112-138)	122 (114-141)
Diastolic	74 (65-83)	75 (68-81)

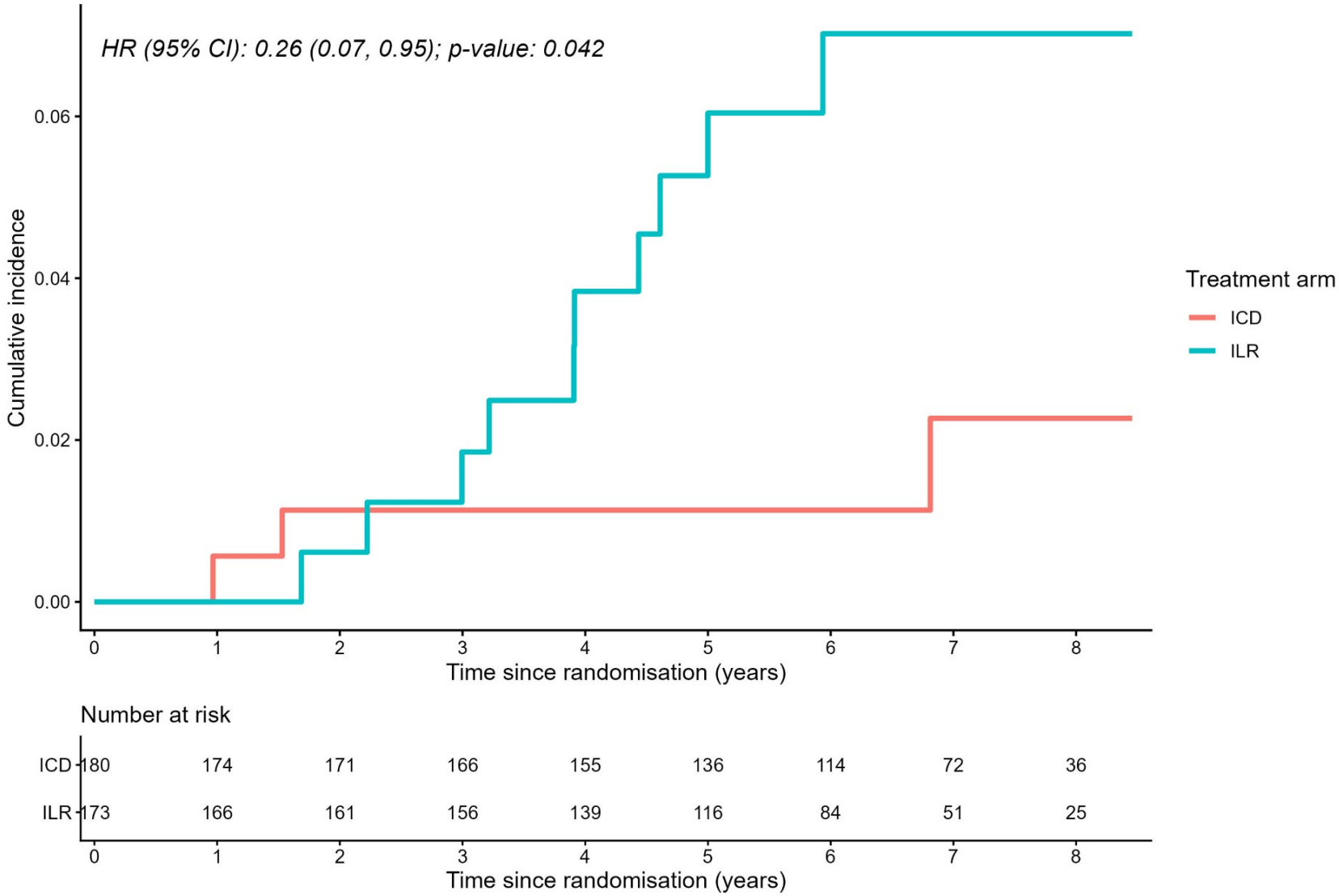
Results: Baseline Characteristics (2)

Characteristic	ICD (n=180)	ILR (n=173)
Baseline Medications – no (%)		
ACE inhibitor/ARB/ARNI	174 (97%)	162 (94%)
Beta Blockers	156 (87%)	149 (86%)
Aldosterone Receptor Antagonist	80 (44%)	67 (39%)
Baseline NYHA Functional Class[a]		
I	79 (44%)	93 (54%)
II	88 (49%)	71 (41%)
III	13 (7%)	9 (5%)
Baseline NT-proBNP (IQR) – pg/mL	420 (198-852)	412 (217-951)
QRS Duration (IQR) – ms	102 (90-120)	102 (92-112)
Baseline CMR Characteristics		
LVEF (IQR) – %	41 (39-45)	40 (38-44)
LGE Mass (IQR) – g	24 (11-34)	22 (11-31)
LGE (IQR) – %	19 (9-27)	18 (9-26)
LVESVi (IQR) – mL/kg/m²	56 (47-67)	56 (48-67)
LVEDVi (IQR) – mL/kg/m²	98 (85-112)	98 (88-114)
LV Mass Index (IQR) – g/m²	61 (54-72)	61 (53-71)

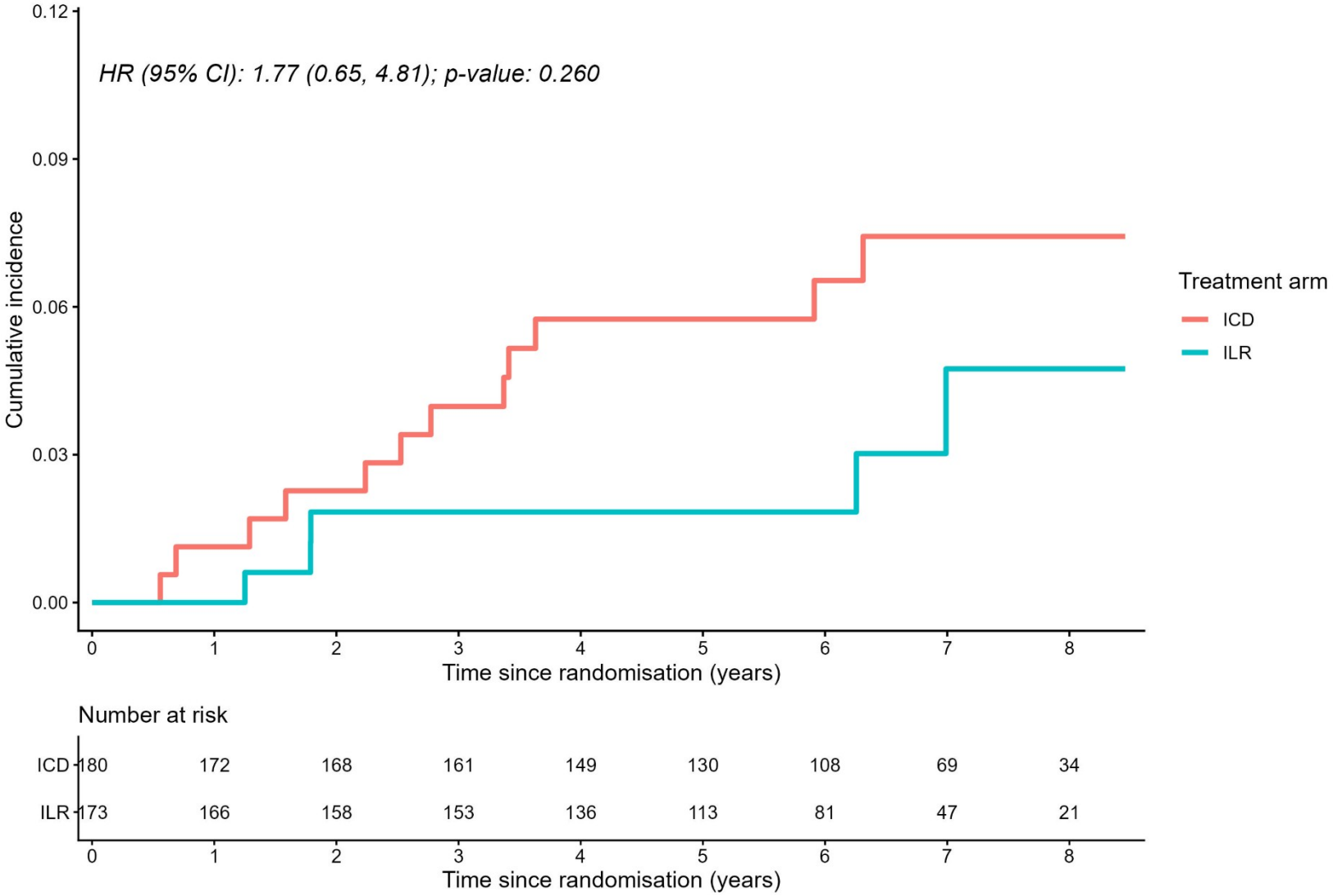
Primary Endpoint: Sudden Cardiac Death or HSVA



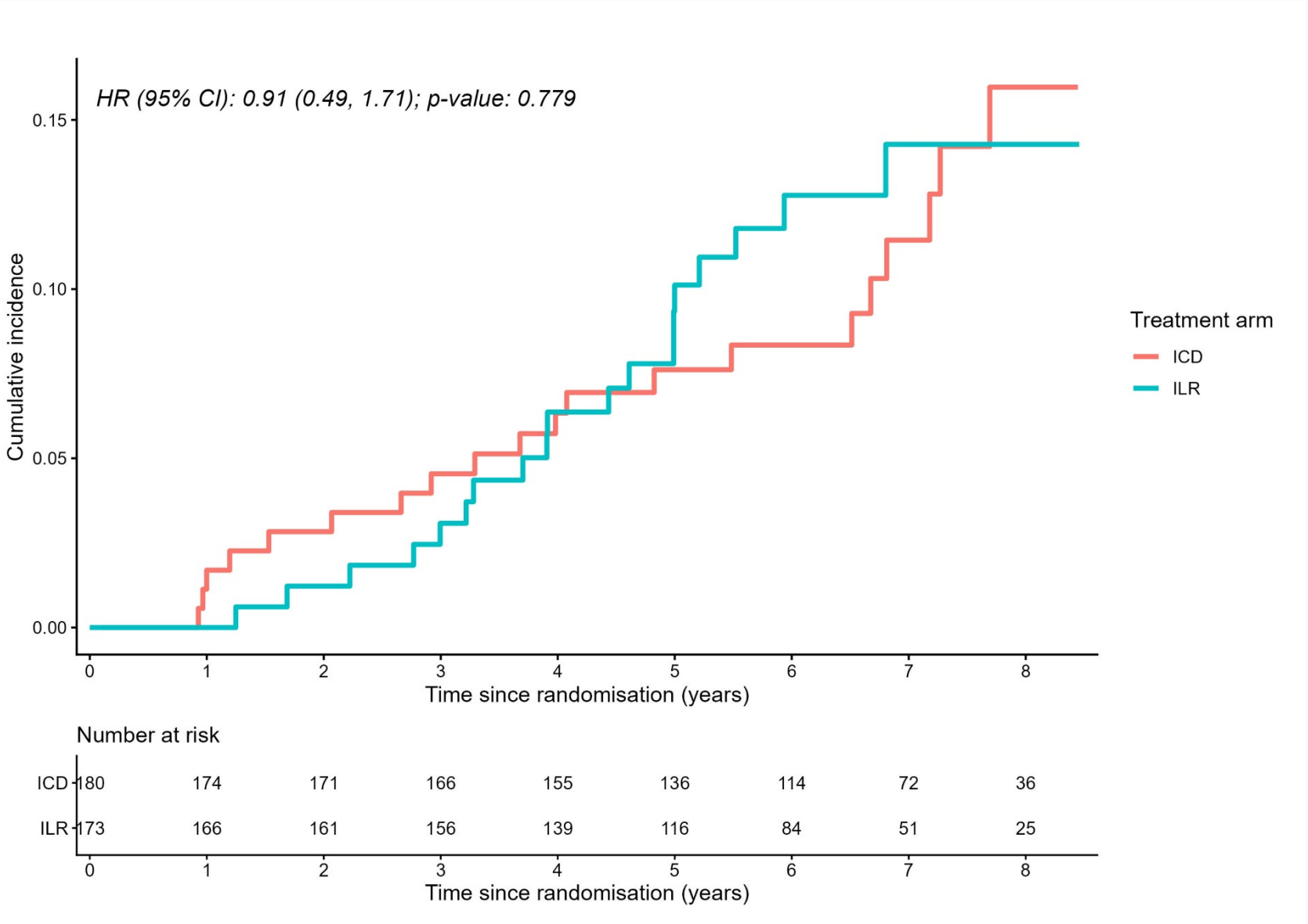
Secondary Endpoint: Sudden Cardiac Death



Secondary Endpoint: HSVA



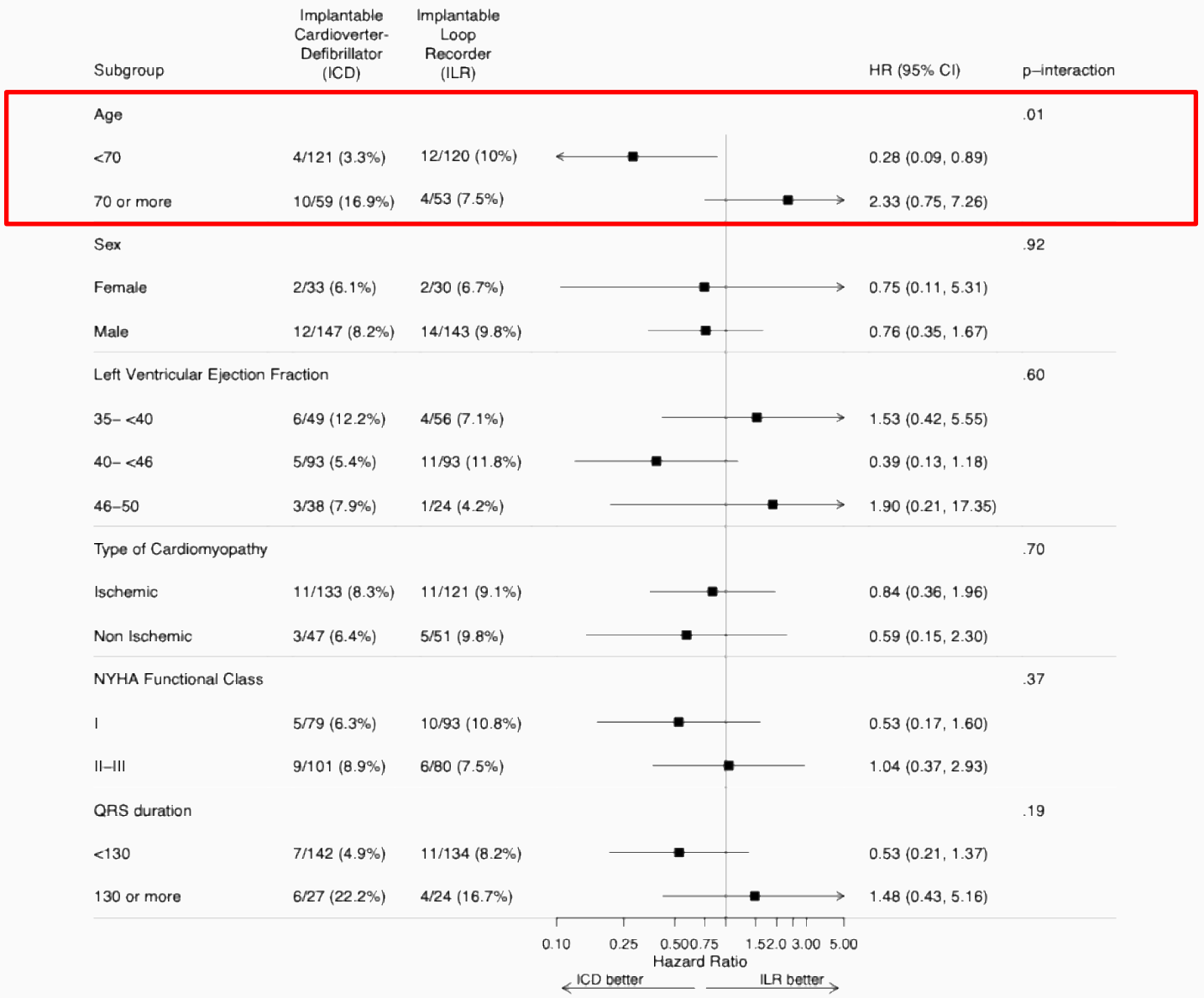
Secondary Endpoint: All Cause Mortality



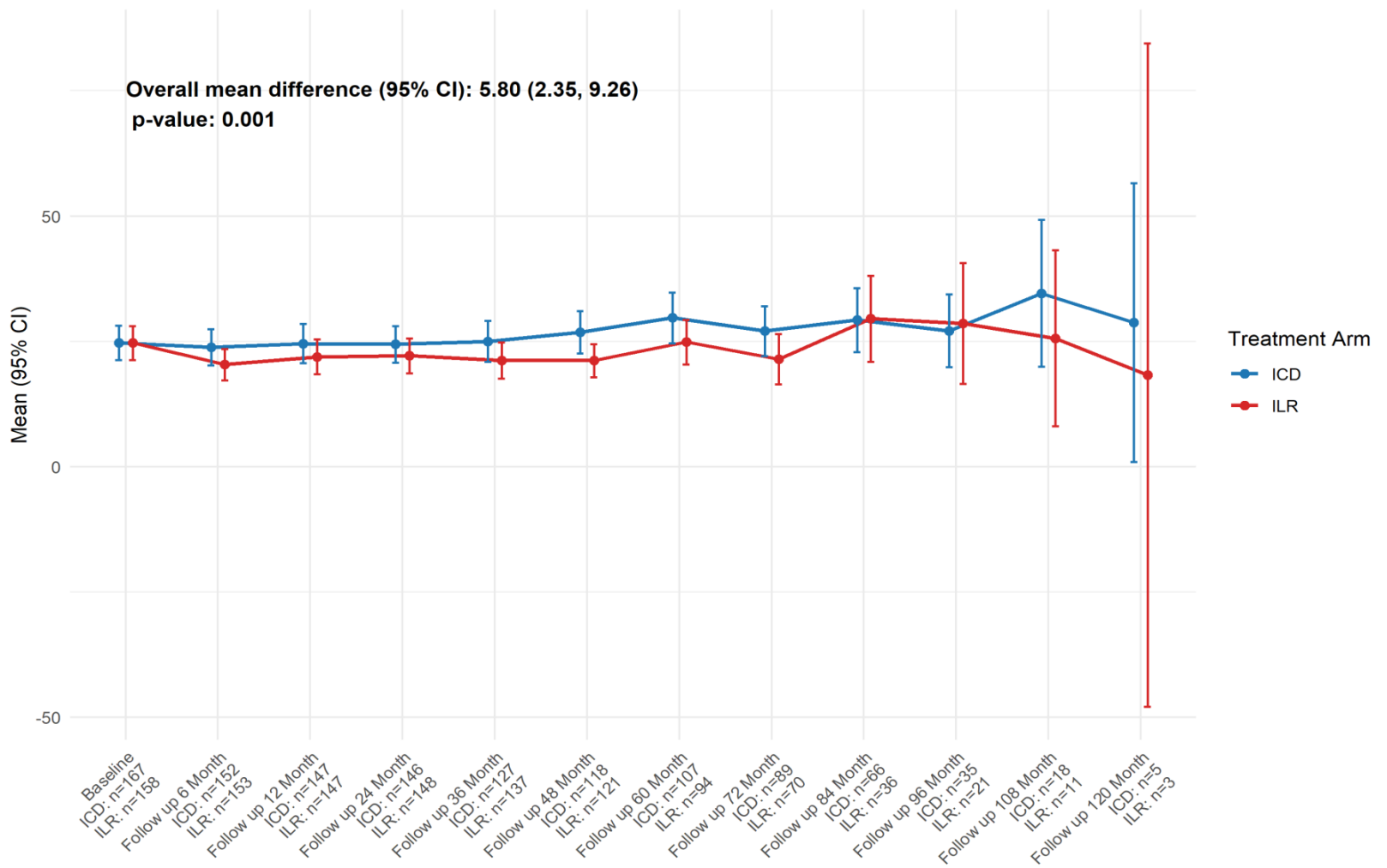
Prespecified Subgroup Analysis

Six prespecified subgroups tested:

- **Age**
- **Sex**
- **LVEF**
- **Aetiology**
- **NYHA class**
- **QRS duration**



Secondary Endpoint: MLHFQ Score



Outcome	ICD (n=180) No. (%) [rate][a]	ILR (n=173) No. (%) [rate][a]	Absolute Difference % (95% CI)	Hazard Ratio (95% CI)	P value
Quality of life (MLHFQ score)[f]	28 (1.4)	22 (1.5)	—	6 (2.4–9.3)	**P= 0.001**

Adverse Events

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	ICD (n=180)	ILR (n=173)	P value
Any device-related adverse event	**29**	**14**	**.02**
Wound complications — any	8	11	.48
Haematoma, bruising, or pain	7	5	
Wound infection	1	6	
Lead-related complications[b]			
Lead fracture	8	1[a]	
Threshold rise	3	-	
Oversensing	4	-	
Battery-related events[c] — any	**5**	**2**	**.45**
Battery depletion — generator replaced	5	0	
Battery depletion — not replaced	0	2	
Device malfunction — explanted	1	-	
Device malfunction — replaced	-	1	
Any inappropriate therapy	**2**	**1[a]**	
Anti-tachycardia pacing	1[d]	-	
Inappropriate shock	1[e]	1[a,d]	

a Cross-over patients. b 5 patients had ICD deactivated. c The ILR device used in this trial demonstrated longer-than-anticipated battery longevity, exceeding the expected 3-year lifespan. d Due to atrial fibrillation with rapid ventricular response. e Due to oversensing. f P values from two-sided Fisher's exact test, comparing patients with each adverse event category between randomised groups (ICD, n=180; ILR, n=173). n, number of patients.

Discussion

- Primary composite endpoint (SCD or HSVA) not significantly reduced by ICD implantation
- 74% reduction in SCD hazard with ICD, but numerically more HSVA
- SCD reduction with ICD was seen across the overall trial population; the composite endpoint benefit was significant only in patients <70 years consistent with the age interaction seen in prior trials
- All-cause mortality similar between groups
- Serious device complications incl inappropriate ICD therapy was rare

Conclusion

Across all age groups studied, ICD implantation did not significantly reduce primary end-point of SCD/HSVA in LVEF 36–50% with CMR-defined scar

Signal for SCD reduction

Overall SCD/HSVA reduction in younger patients (where competing risk from other causes is low) warrants further study

Thank you

On behalf of the CMR GUIDE investigators

Simultaneous publication