# Risk stratification in ICD patients based on cardiac magnetic resonance imaging – The CMR-Guide Study

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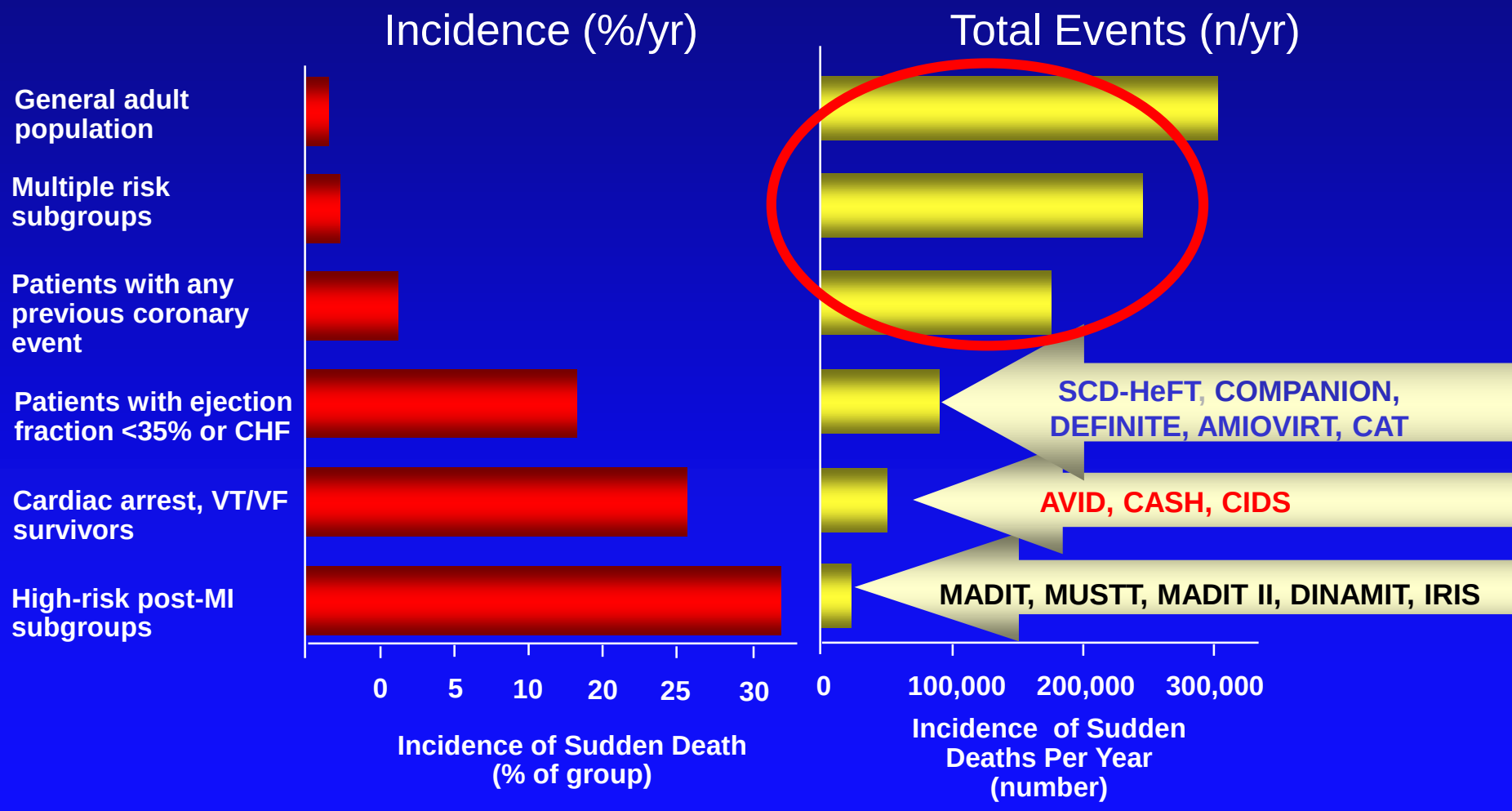
# Disclosure

- Speakers fee and/or Advisory Board
- Biotronik
- Boston Scientific
- Medtronic
- Abbott
- Zoll

# Background

- Current guidelines for use of ICDs to prevent SCD are based primarily on the measurement of LVEF.
- Although reduced LVEF is associated with increased total cardiac mortality after MI, the focus of current guidelines on LVEF **omits~50%** of patients who die suddenly.
- Thus, LVEF is neither sensitive nor specific as a tool for post-MI risk stratification.

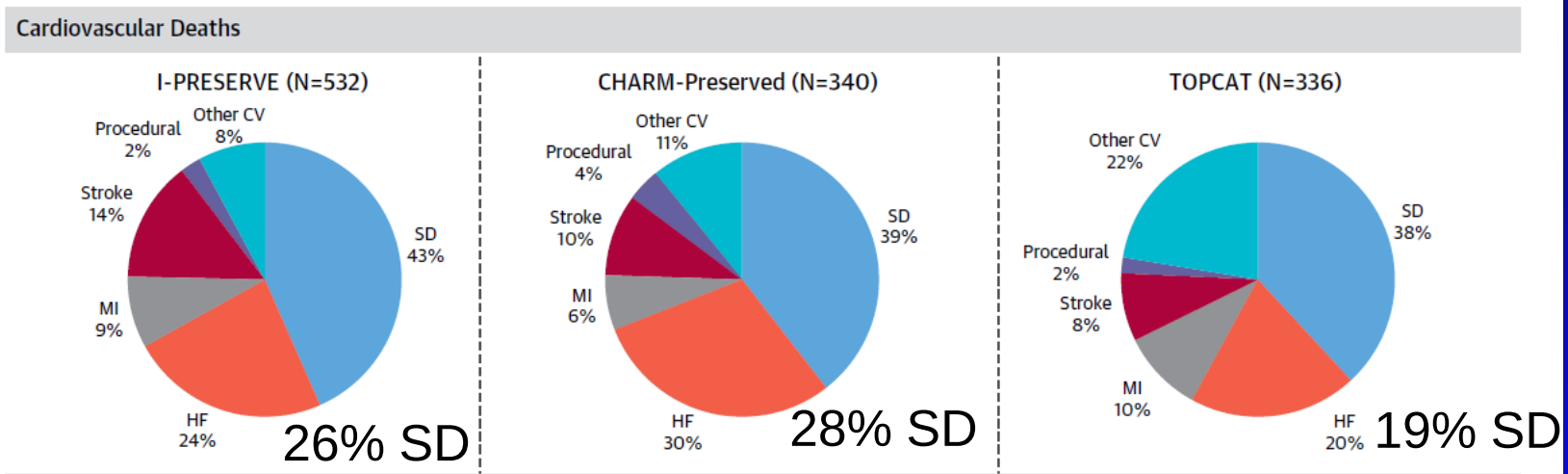
# Incidences and absolute numbers of sudden cardiac deaths among six defined populations




Myerburg et al. Circulation 1998;97:1514-1521

Adapted from Myerburg JCE 2001

# Cause-Specific Mortality in RCTs of HFpEF




**SCD** is the most common single mode of death in HFpEF constituting 40% of cardiovascular deaths and 25% of all deaths

Vaduganathan et al. J Am Coll Cardiol 2017;69:556–69

# Risk Stratification for SCD

- LVEF ≤ 35%

- QRS duration
- QT dispersion
- Mircro T wave alternans
- Ventricular ectopy
- Signal averaged ECG

- Heart rate variability
- Heart rate turbulence
- Barorefelx sensitivity

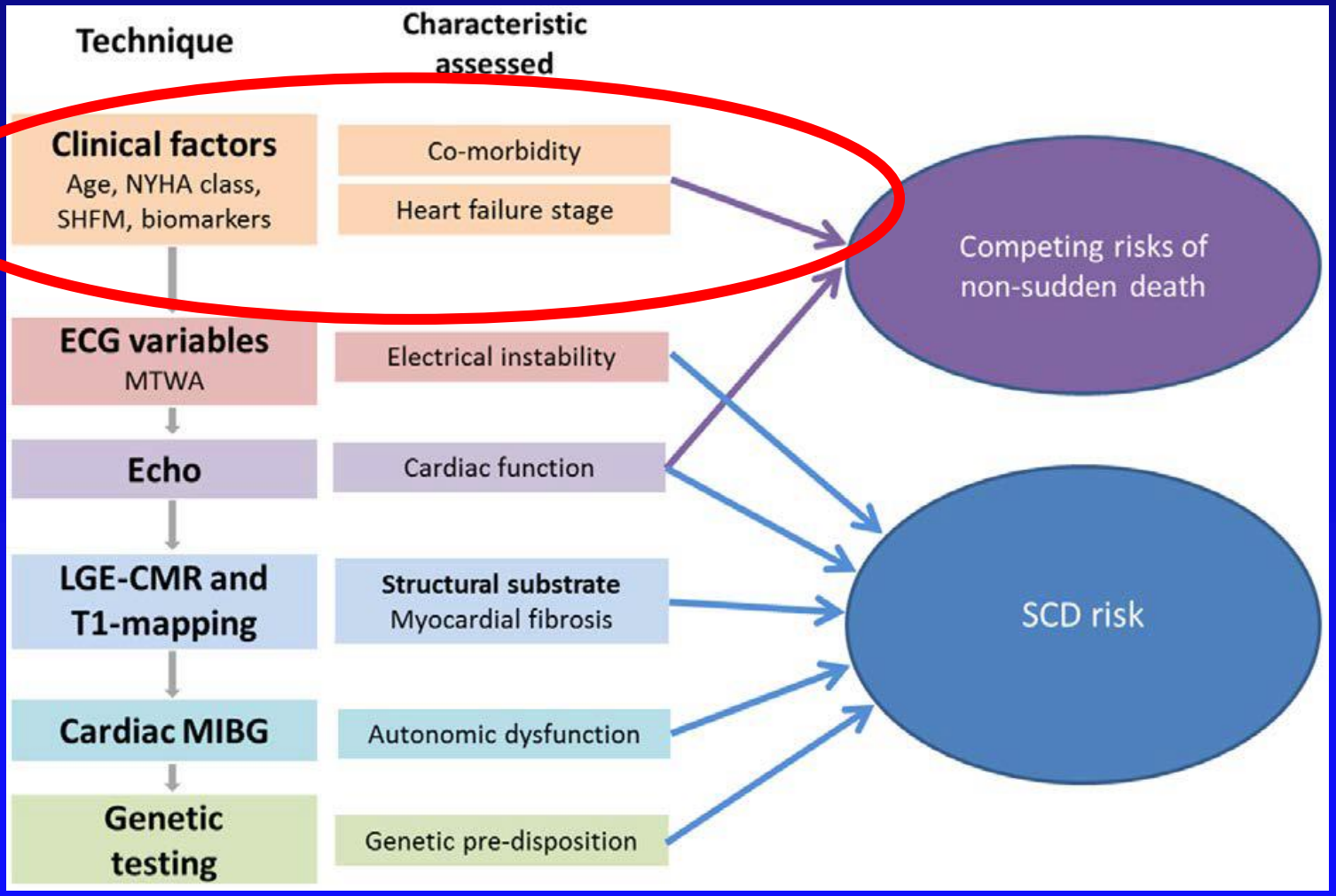
- Programmed ventricular stimulation

**Importance of Risk Stratification**

Given the relatively poor performance of current risk stratification approaches for SCD and the aforementioned various challenges and limitations, it is reasonable to query whether further efforts should be devoted to this area. From a therapeutic perspective, **there is great need for risk stratification for SCD**.

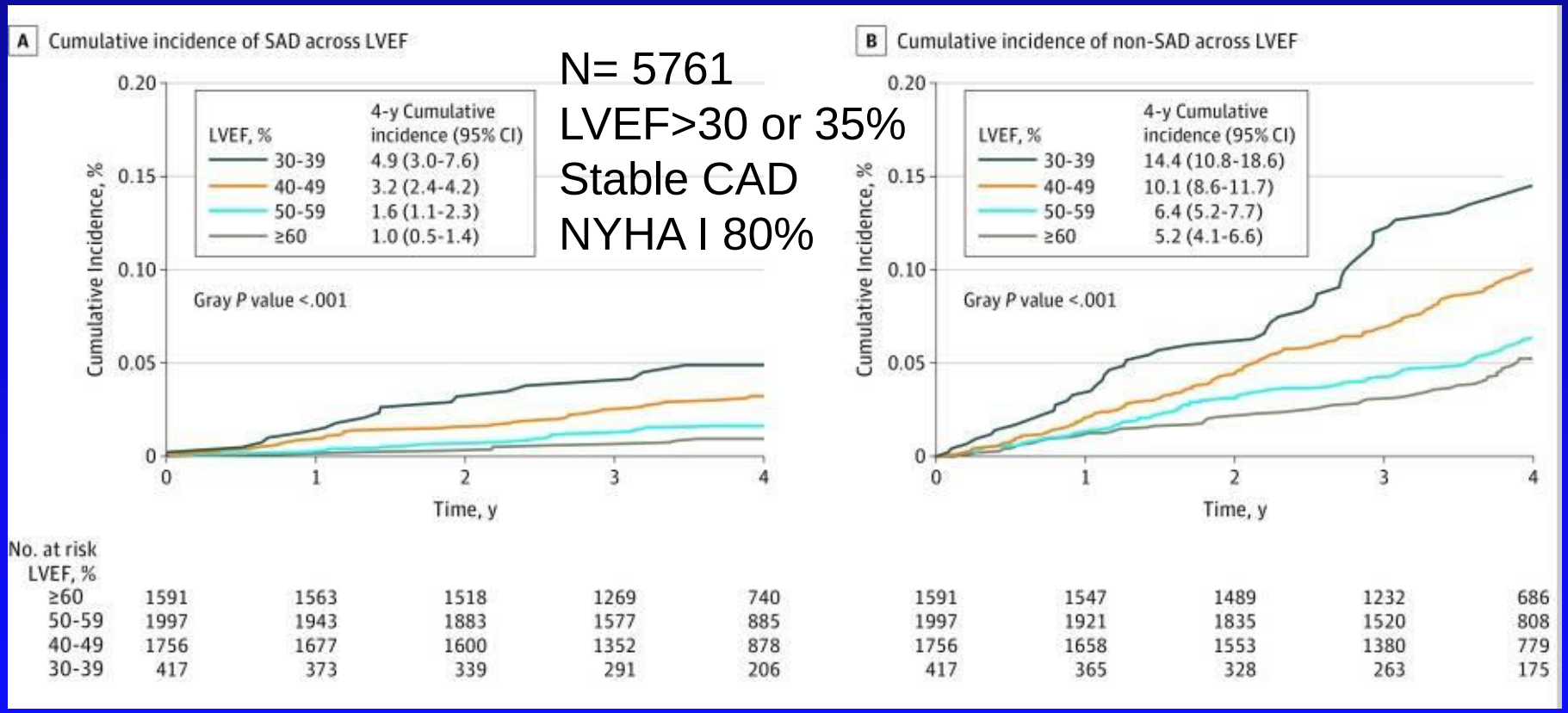
Goldenberger et al. Circulation. 2011;123:2423-2430

# Flowchart of the potential techniques that may be used to improve risk stratification




Halliday et a. Circulation. 2017;136:215–231. DOI: 10.1161/CIRCULATIONAHA.116.027134

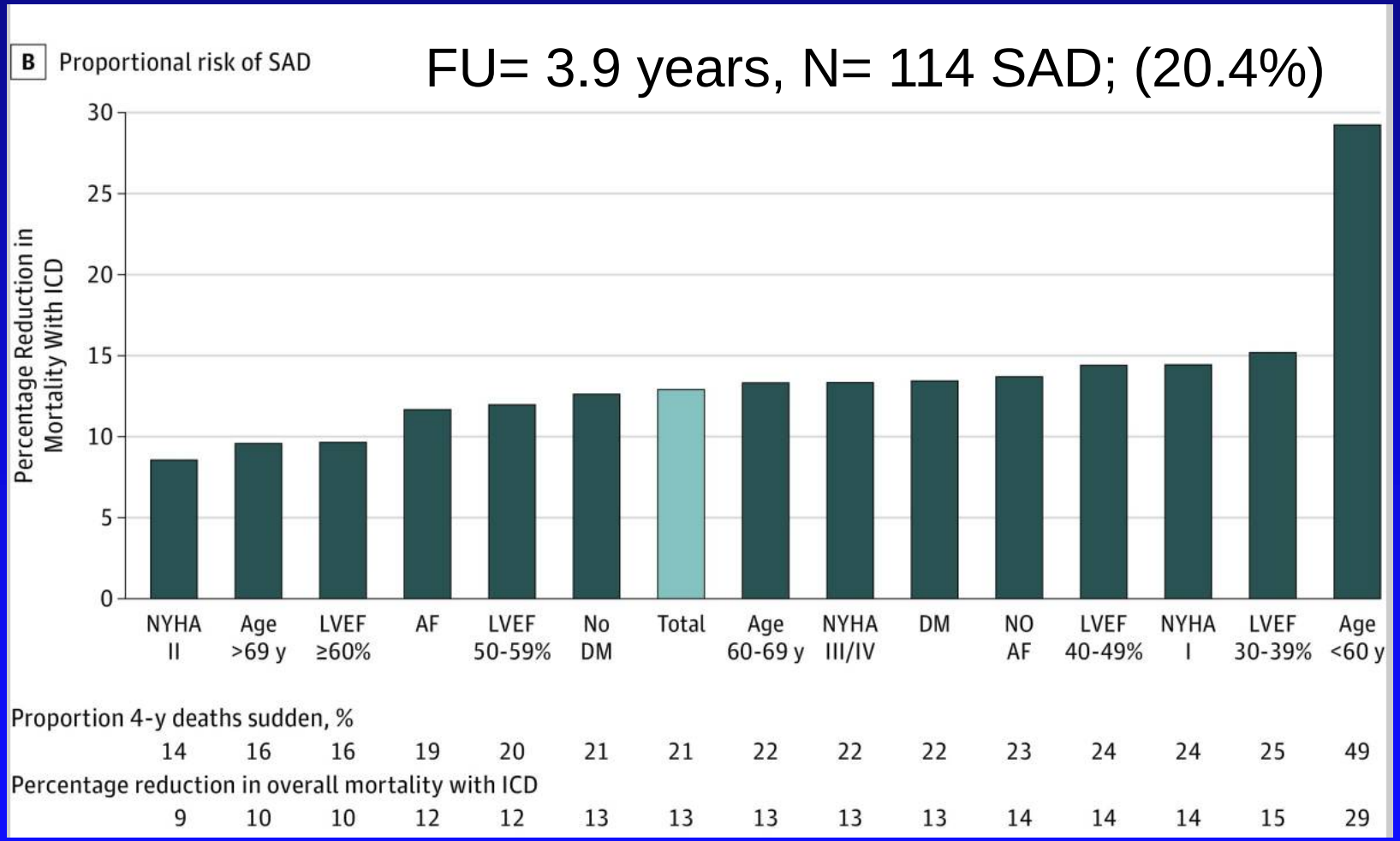
# **PRE-DETERMINE Study**:
# prospective observational cohort study
# 4 year cumulative incidence of each mode of death stratified by LVEF




N= 5761
LVEF>30 or 35%
Stable CAD
NYHA I 80%

Chatterjee et al., JAMA Cardiol 2018;3:591-600

# Proportional risk of sudden/arrhythmic death (SAD)




Chatterjee et al., JAMA Cardiol 2018;3:591-600

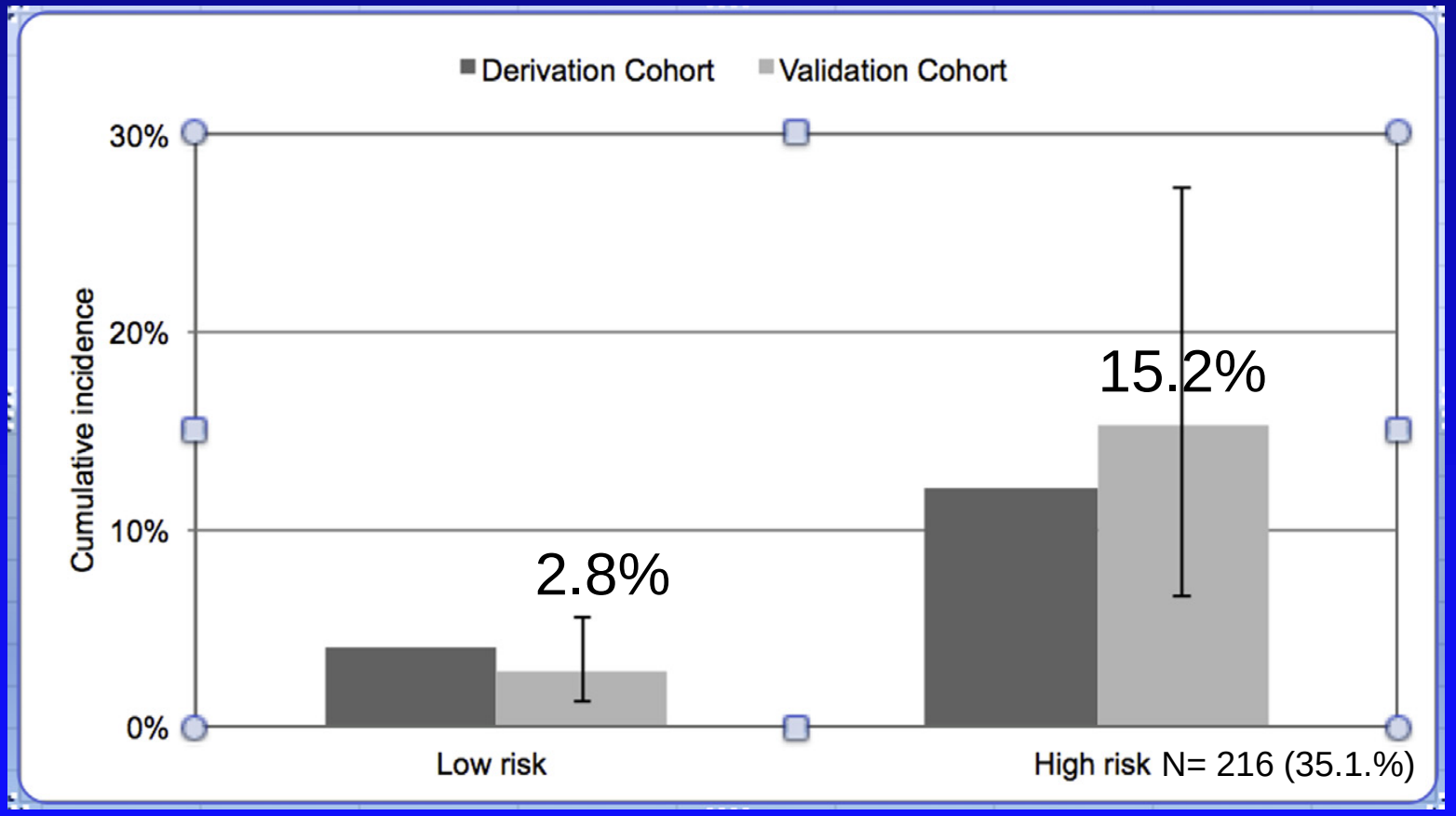
# SCD Risk Score in HFpEF: Baseline characteristics of the validation and derivation cohorts

| Variable | TOPCAT validation sample (n = 615) | I-PRESERVE trial derivation sample (n = 4128) |
|---|---|---|
| Age (y) | 70.1 ± 9.5 | 72 ± 6.9 |
| Male sex | 49.3 | 40 |
| Diabetes mellitus | 30.9 | 28 |
| Myocardial infarction | 31.1 | 24 |
| Bundle branch block | 18.7 | 8.3 |
| NT-proBNP level (pg/mL) | 839 (461–1710) | 340 (135–971) |
| Sudden death risk score | 5.3 ± 0.76 | 4.80 ± 0.83 |
| High risk | 35.1 | 24 |

- The SCD risk score was calculated from the estimated regression coefficients in the Fine-Gray competing risk model.
- A SCD risk score ≥ 5.3% had a ≥ 10% individual predicted risk of SCD over 5 years FU

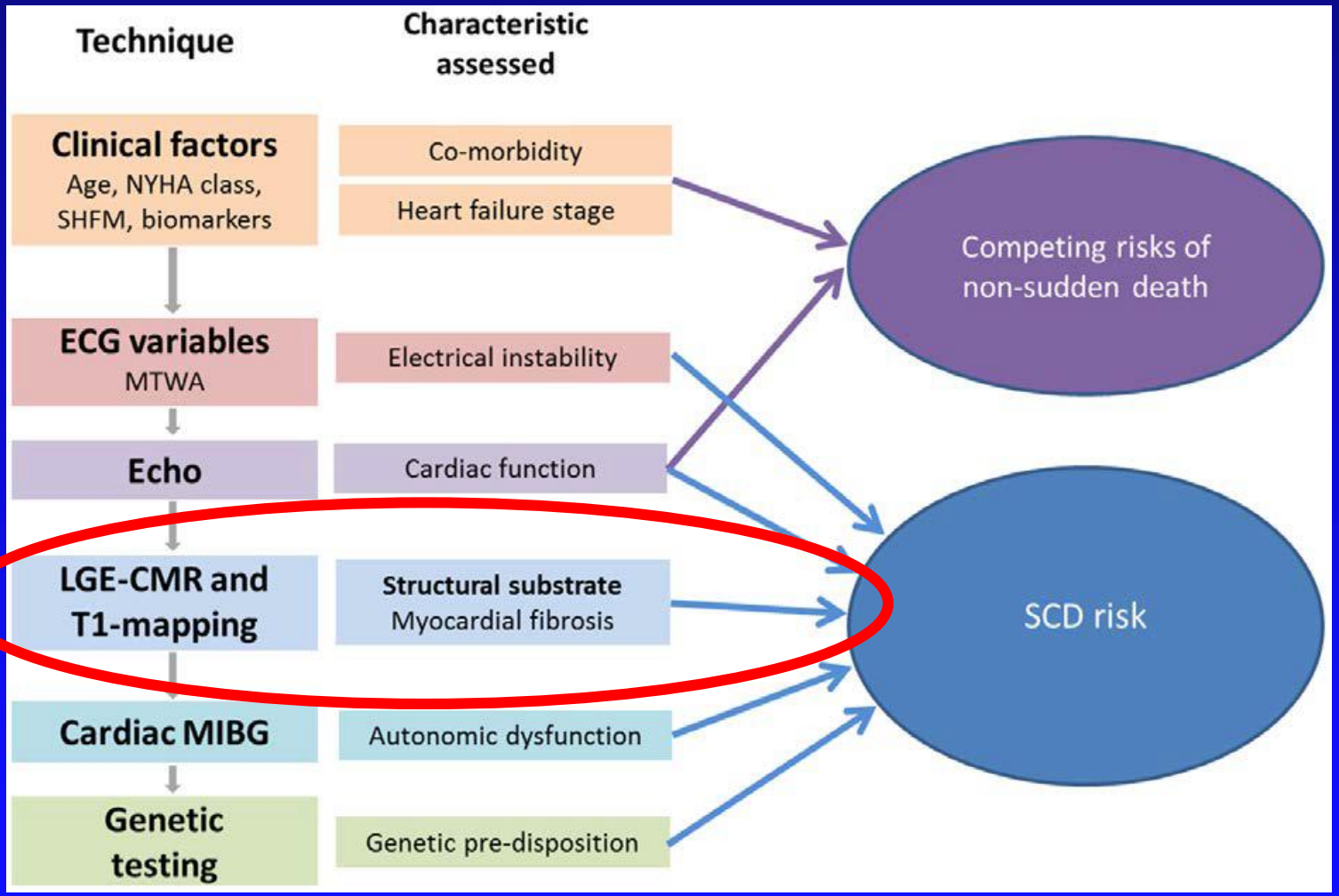
Adabag et al. Heart Rhythm 3 January 2020 in press

# Comparison of the estimated 5-year cumulative incidence of SCD in patients with high vs low predicted risk in the derivation and validation cohorts




Adabag et al. Heart Rhythm 3 January 2020 in press

# Flowchart of the potential techniques that may be used to improve risk stratification



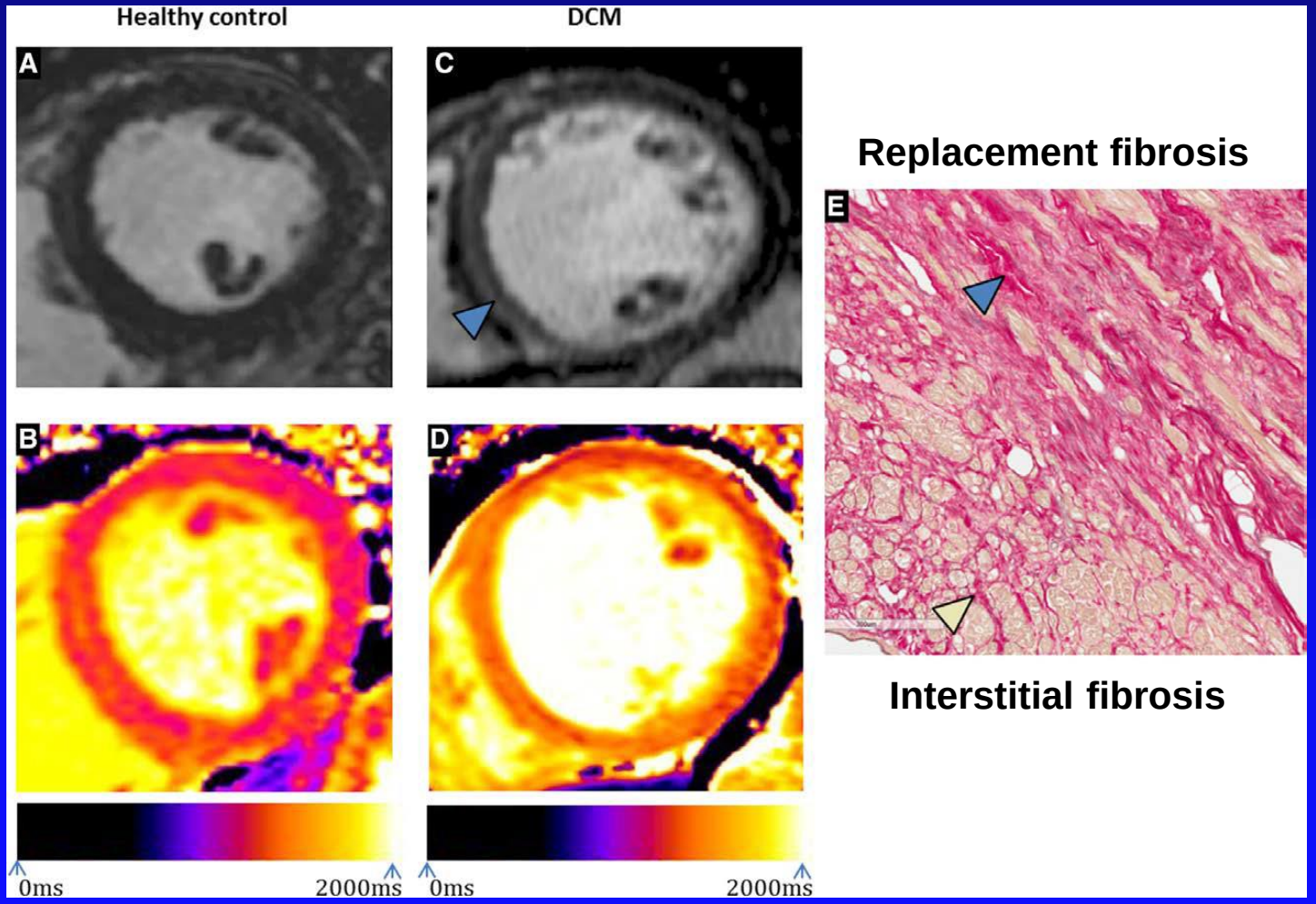

Halliday et a. Circulation. 2017;136:215–231. DOI: 10.1161/CIRCULATIONAHA.116.027134

# The emerging risk stratification method in idiopathic dilated cardiomyopathy: **Late gadolinium enhancement**

- Histological studies have demonstrated two forms of fibrosis:
  - **Replacement fibrosis** (describe discrete areas of myocyte cell death) -> **LGE**
  - **Interstitial fibrosis** (expansion of the interstitium with accumulation of collagen in the absence of cell death) -> **T1 Mapping**

Brown PF, et al. Heart 2019;**105**:270–275. doi:10.1136/heartjnl-2018-313767

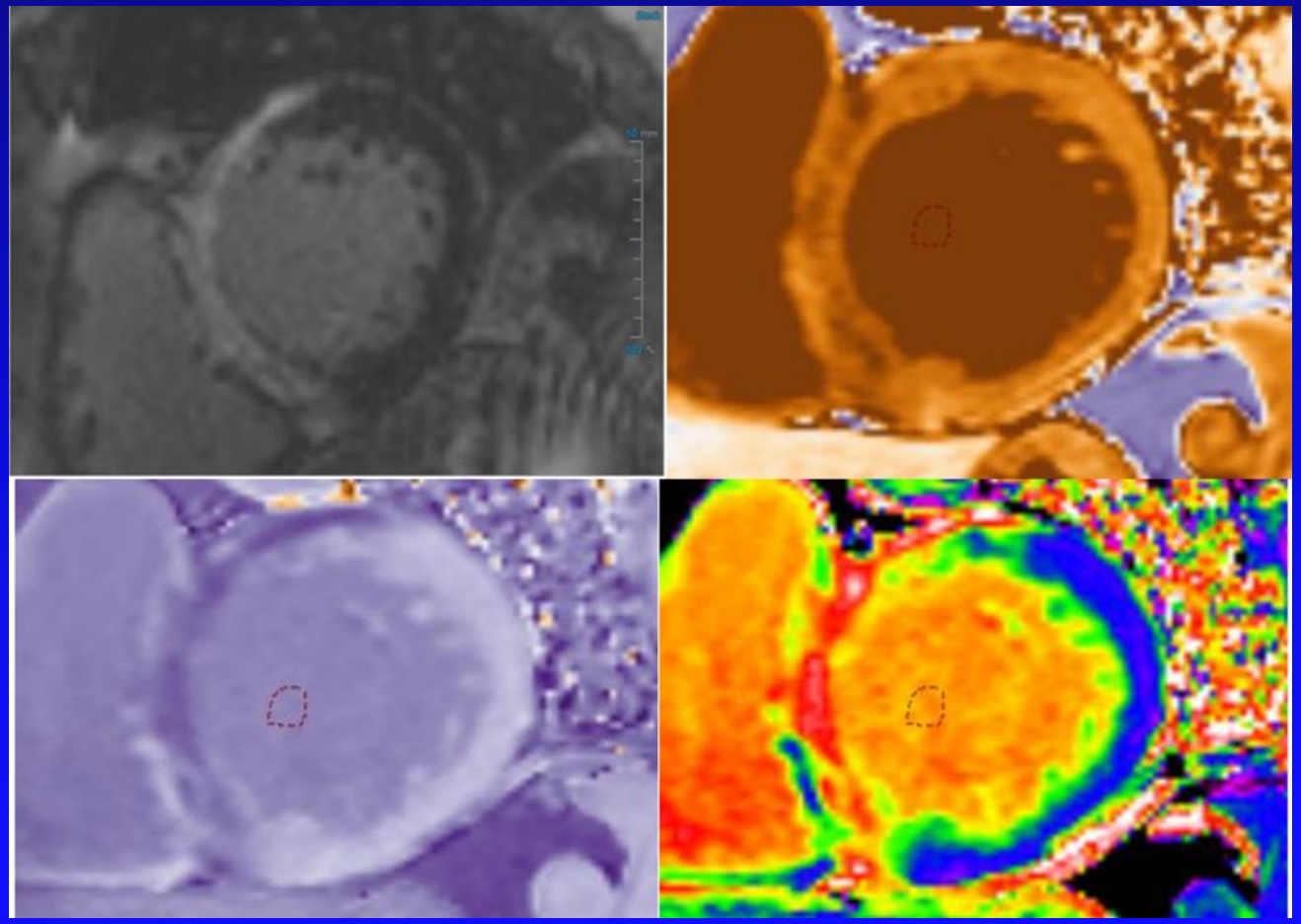
# Detecting myocardial fibrosis using cardiovascular magnetic resonance




Halliday et a. Circulation. 2017;136:215–231. DOI: 10.1161/CIRCULATIONAHA.116.027134

# Mid-wall fibrosis (MWF) in a clockwise direction from upper left corner on late gadolinium enhancement (LGE) imaging, native T1, postcontrast T1 and extracellular volume (ECV) maps

LGE



T1 native mapping

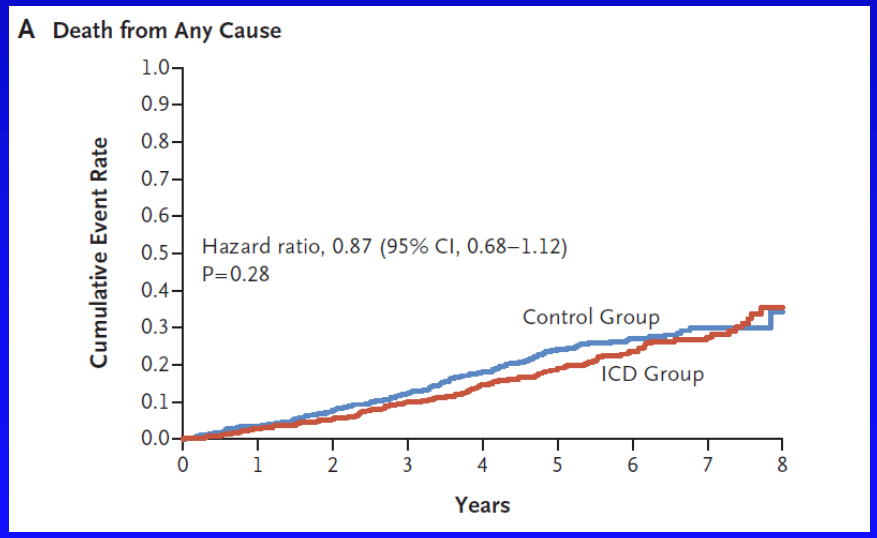
T1 post-contrast

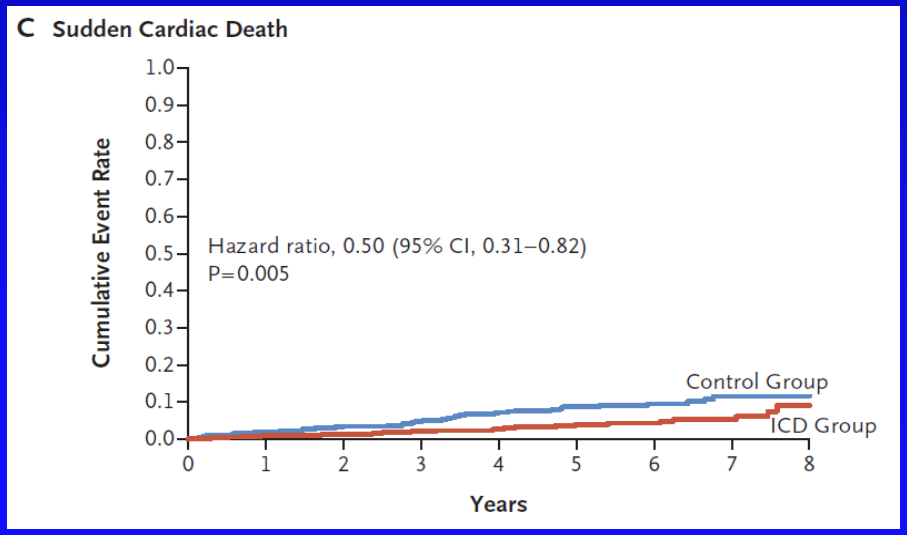
ECV map

Brown PF, et al. Heart 2019;**105**:270–275. doi:10.1136/heartjnl-2018-313767

# DANISH: ICD in Non-Ischemic HF

- 1,116 non-ischemic HF pts. with **EF ≤35**% and NT-proBNP >200pg/ml randomized to ICD or control
- Age 64 y, 58% got CRT, FU 67.6 months
- **No difference in mortality**, 50% reduction of SCD in ICD group, mortality benefit in pts. <68 y
- Selection of ICD candidates: long life expectancy, age <68



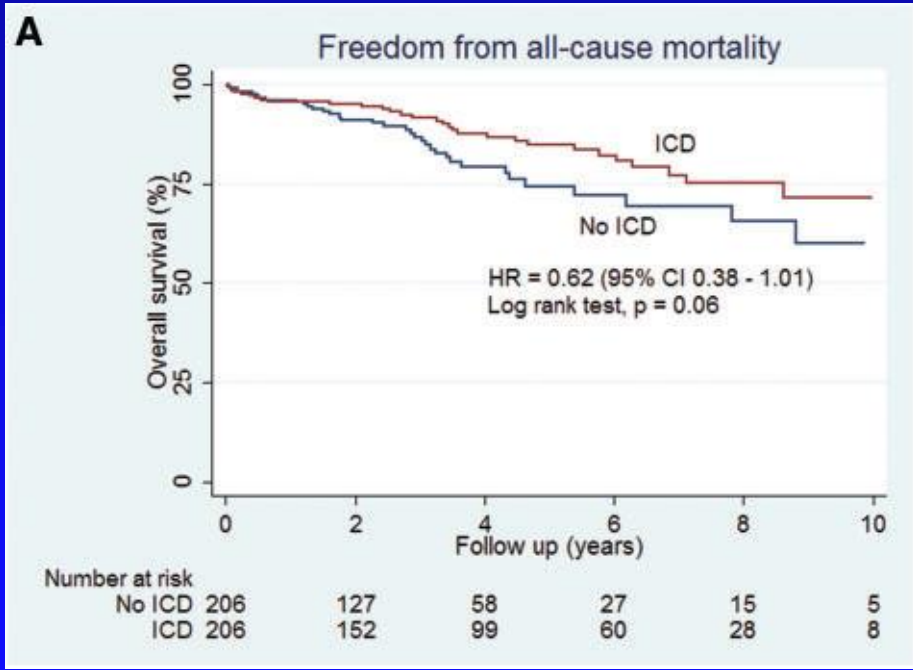



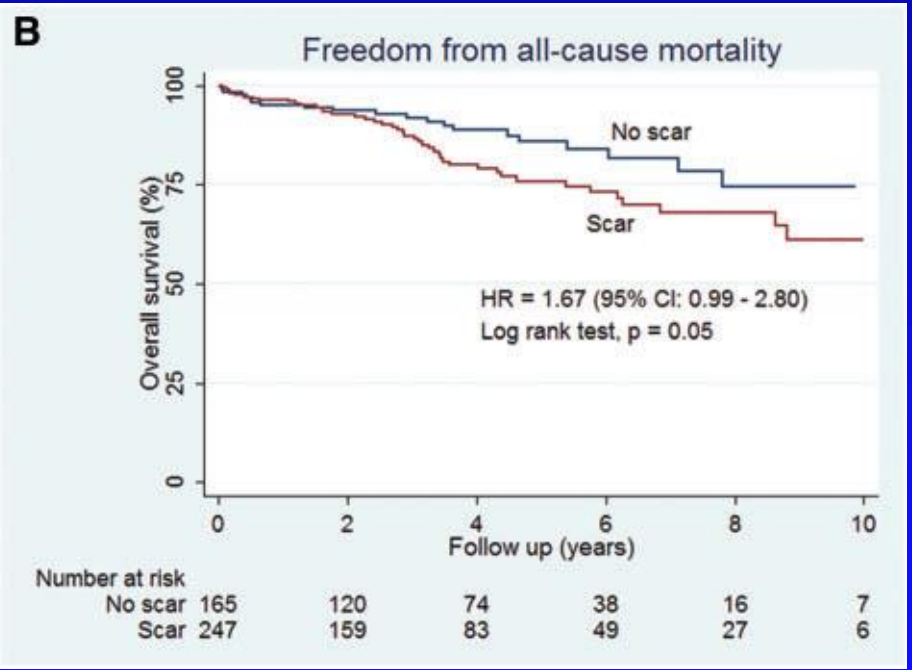

Kober L. *N Engl J Med* 2016; 375(13): 1221-30

# Propensity-matched cohort— all-cause mortality in total cohort

N= 452 patients, **LVEF ≤ 35%,** NYHA II/III, **NICM**, FU= 38 months

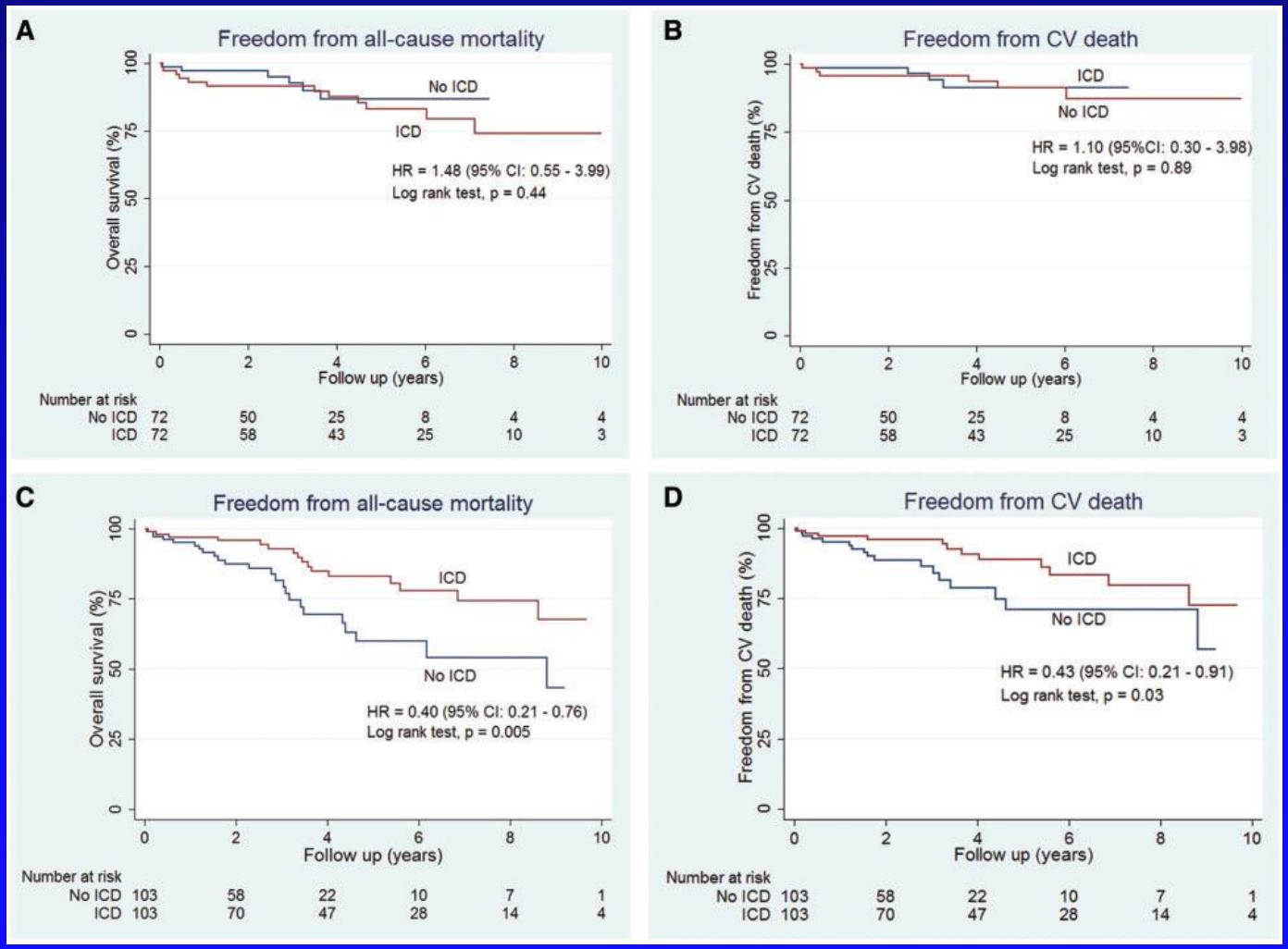
**ICD** **Scar**




Gutman et al. European Heart Journal (2019) 40, 542–550

# Propensity-matched cohort—effect of ICD on survival

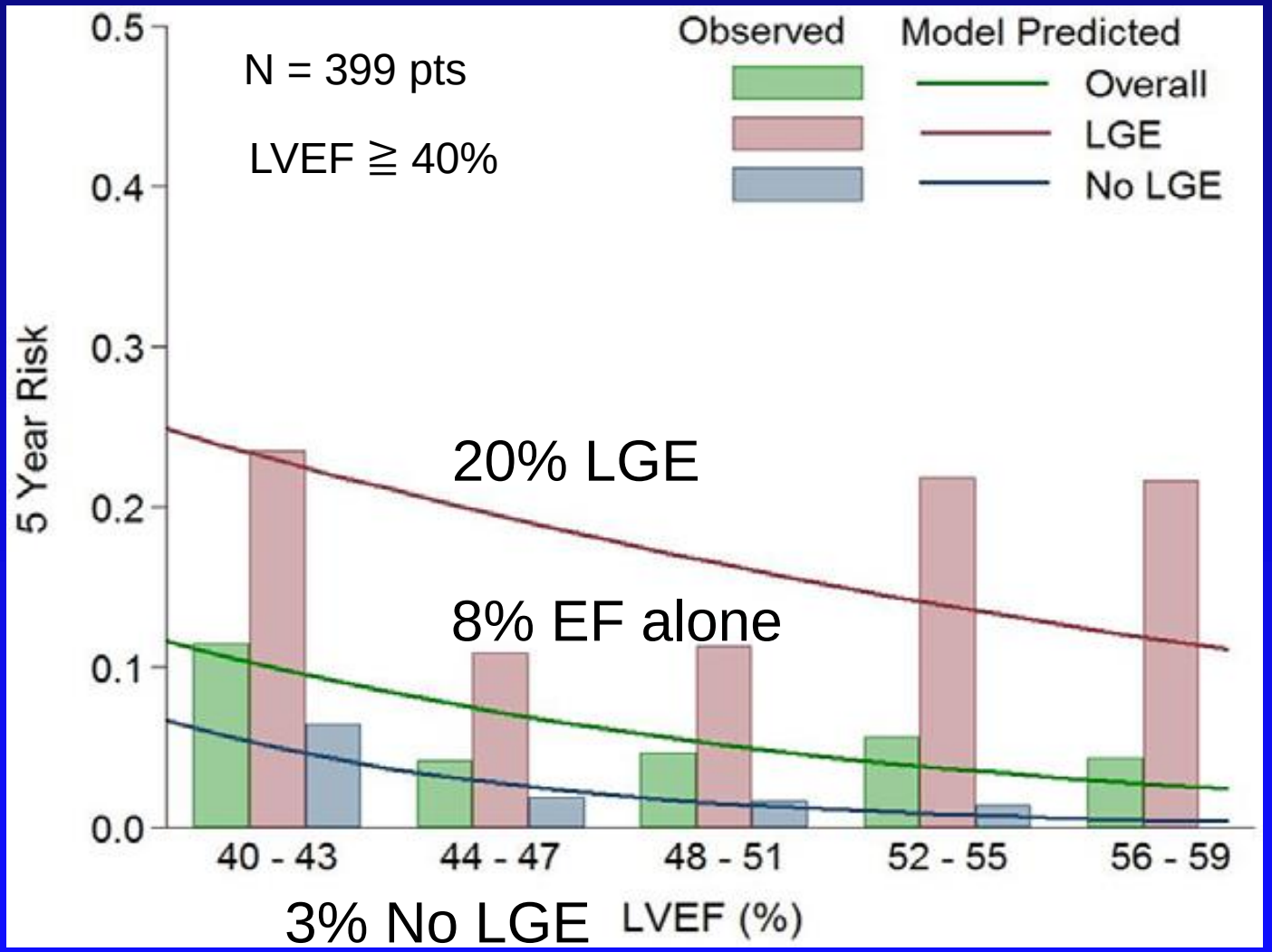



**scar negative** patients (A and B)

**scar positive** patients (C and D)

Gutman et al. European Heart Journal (2019) 40, 542–550

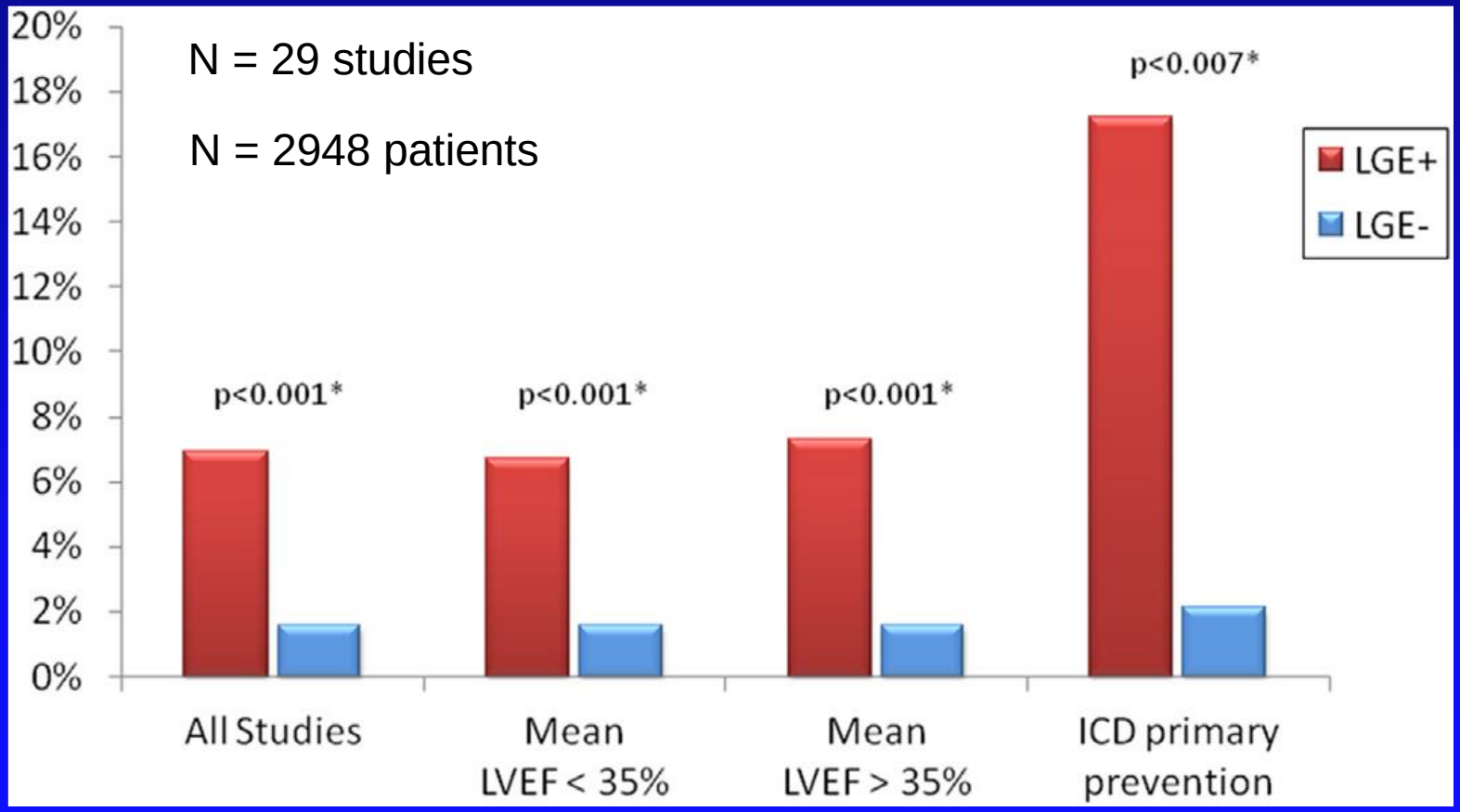
# Five-year risk estimates of the primary end point




LVEF

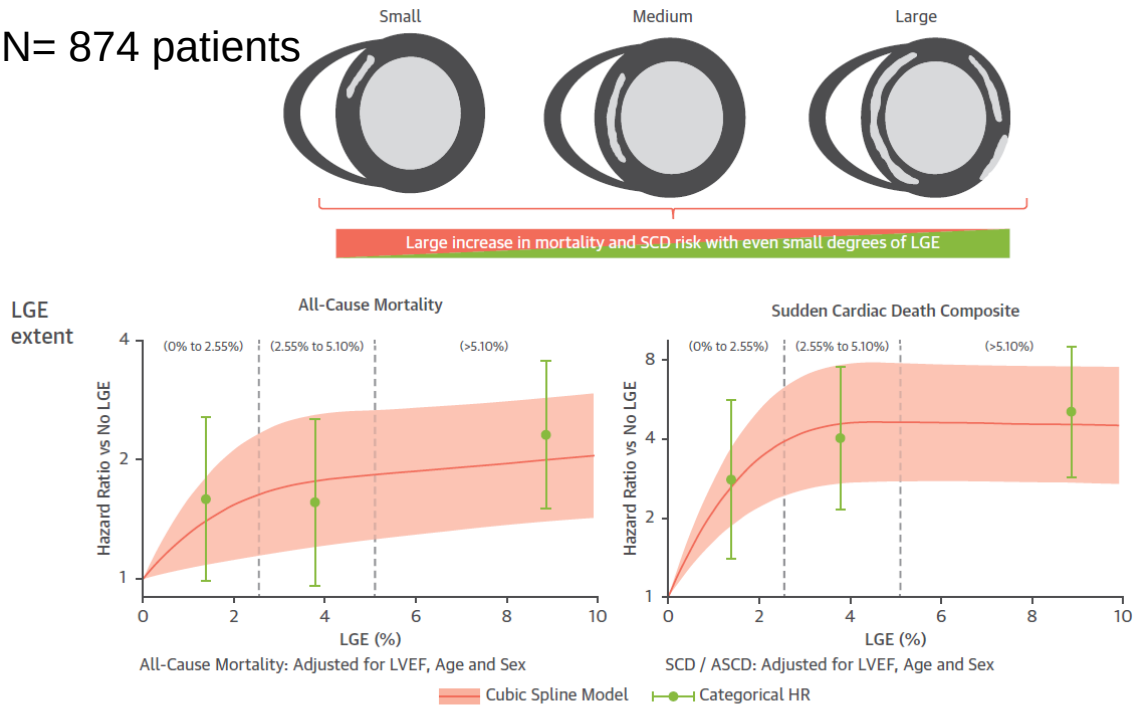
Halliday et al. Circulation. 2017;135:2106–2115. DOI: 10.1161/CIRCULATIONAHA.116.026910

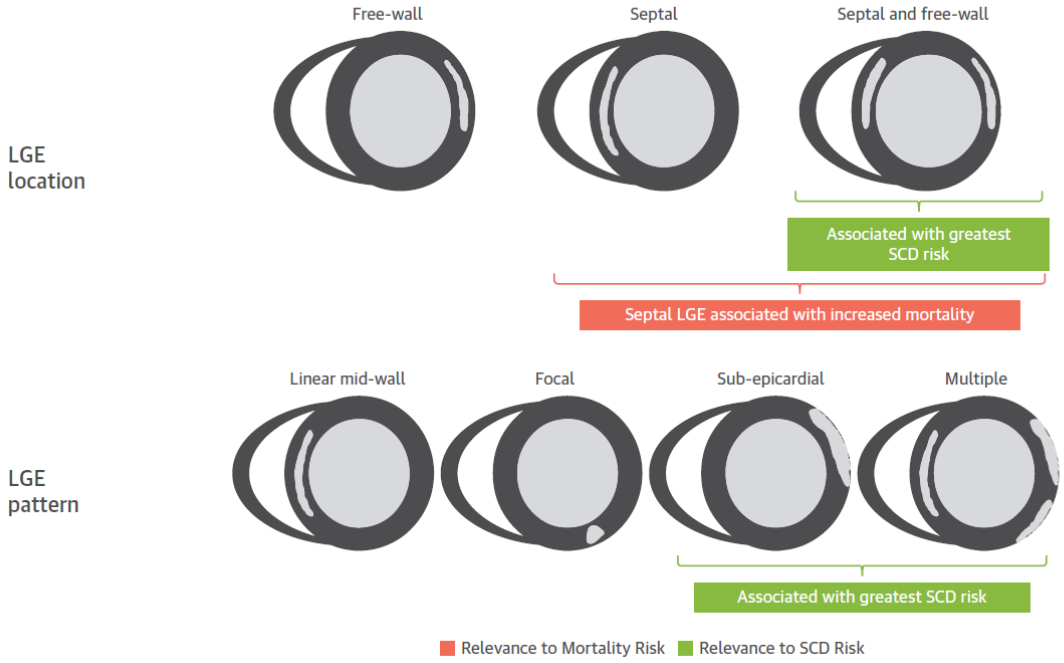
# Metaanalysis: Annual Rate of the Arrhythmic Endpoint According to Late Gadolinium Enhancement Status




Di Marco et al. JACC : Heart Failure 2017

N= 874 patients




**LGE extent** -> even small degrees

LGE and Outcome in DCM

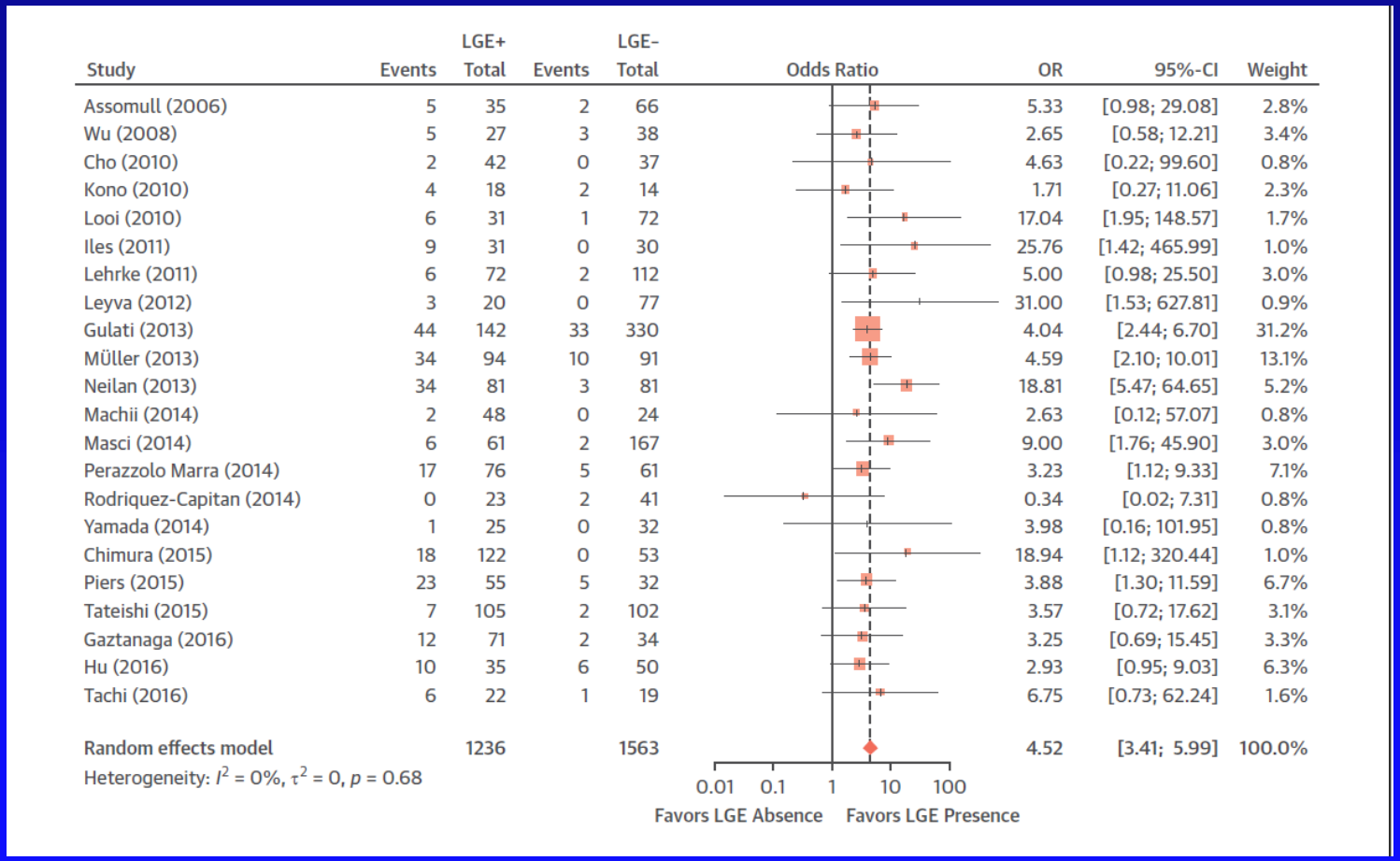
**LGE location** -> septal

**LGE pattern** -> sub-epicardial

Halliday et al. J A C C : CARDI O V A SC U LAR IMAGI NG 2018

# Metaanalysis: Combined Endpoint of Ventricular Tachyarrhythmic Events in ICM/NICM Patients

4,554 patients, n= 34 studies



| Study | LGE+ Events | LGE+ Total | LGE− Events | LGE− Total | OR | 95%-CI | Weight |
|---|---|---|---|---|---|---|---|
| Assomull (2006) | 5 | 35 | 2 | 66 | 5.33 | [0.98; 29.08] | 2.8% |
| Wu (2008) | 5 | 27 | 3 | 38 | 2.65 | [0.58; 12.21] | 3.4% |
| Cho (2010) | 2 | 42 | 0 | 37 | 4.63 | [0.22; 99.60] | 0.8% |
| Kono (2010) | 4 | 18 | 2 | 14 | 1.71 | [0.27; 11.06] | 2.3% |
| Looi (2010) | 6 | 31 | 1 | 72 | 17.04 | [1.95; 148.57] | 1.7% |
| Iles (2011) | 9 | 31 | 0 | 30 | 25.76 | [1.42; 465.99] | 1.0% |
| Lehrke (2011) | 6 | 72 | 2 | 112 | 5.00 | [0.98; 25.50] | 3.0% |
| Leyva (2012) | 3 | 20 | 0 | 77 | 31.00 | [1.53; 627.81] | 0.9% |
| Gulati (2013) | 44 | 142 | 33 | 330 | 4.04 | [2.44; 6.70] | 31.2% |
| Müller (2013) | 34 | 94 | 10 | 91 | 4.59 | [2.10; 10.01] | 13.1% |
| Neilan (2013) | 34 | 81 | 3 | 81 | 18.81 | [5.47; 64.65] | 5.2% |
| Machii (2014) | 2 | 48 | 0 | 24 | 2.63 | [0.12; 57.07] | 0.8% |
| Masci (2014) | 6 | 61 | 2 | 167 | 9.00 | [1.76; 45.90] | 3.0% |
| Perazzolo Marra (2014) | 17 | 76 | 5 | 61 | 3.23 | [1.12; 9.33] | 7.1% |
| Rodriquez-Capitan (2014) | 0 | 23 | 2 | 41 | 0.34 | [0.02; 7.31] | 0.8% |
| Yamada (2014) | 1 | 25 | 0 | 32 | 3.98 | [0.16; 101.95] | 0.8% |
| Chimura (2015) | 18 | 122 | 0 | 53 | 18.94 | [1.12; 320.44] | 1.0% |
| Piers (2015) | 23 | 55 | 5 | 32 | 3.88 | [1.30; 11.59] | 6.7% |
| Tateishi (2015) | 7 | 105 | 2 | 102 | 3.57 | [0.72; 17.62] | 3.1% |
| Gaztanaga (2016) | 12 | 71 | 2 | 34 | 3.25 | [0.69; 15.45] | 3.3% |
| Hu (2016) | 10 | 35 | 6 | 50 | 2.93 | [0.95; 9.03] | 6.3% |
| Tachi (2016) | 6 | 22 | 1 | 19 | 6.75 | [0.73; 62.24] | 1.6% |
| Random effects model | | 1236 | | 1563 | 4.52 | [3.41; 5.99] | 100.0% |

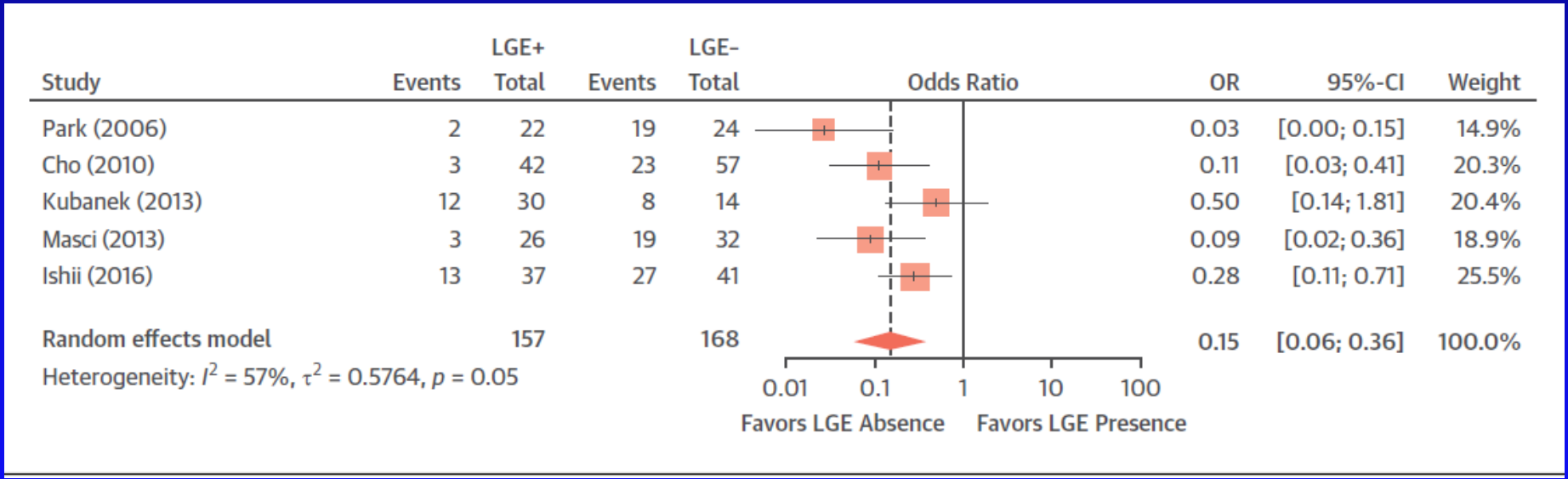
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.68$



Becker et al. J Am Coll Cardiol Img 2018;11:1274–84

# Left Ventricular Reverse Remodeling

4,554 patients, n= 34 studies




Becker et al. J Am Coll Cardiol Img 2018;11:1274–84

# Cardiovascular magnetic resonance-GUIDEd management of mild to moderate left ventricular systolic dysfunction (CMR GUIDE): Study protocol for a randomized controlled trial

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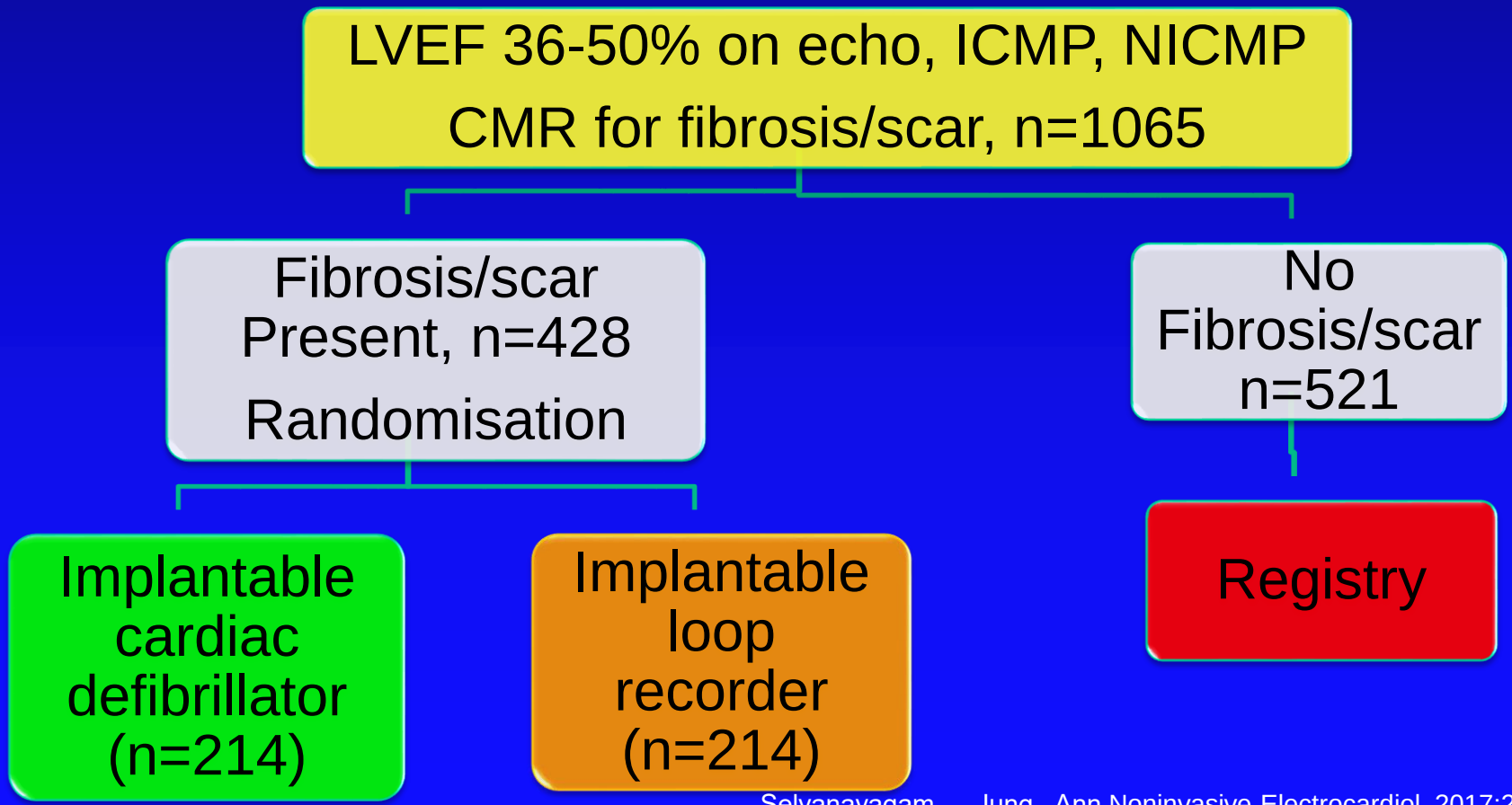


Selvanayagam…..Jung.. Ann Noninvasive Electrocardiol. 2017;22:e12420

# Primary endpoint

- The primary endpoint is a composite of:

- **1.** Sudden cardiac death (SCD) *or*
- **2.** Hemodynamically significant ventricular arrhythmia producing syncope (defined by a loss of consciousness) or associated with hypotension (systolic blood pressure < 90 mmHg)

Selvanayagam…..Jung.. Ann Noninvasive Electrocardiol. 2017;22:e12420

# Conclusions

- Current research demonstrates the inadequacy of a risk-stratification algorithm based on LVEF alone and illustrates the importance of developing a more sensitive, specific, and cost-effective approach.

- The presence of LGE on CMR imaging is associated with a significant and relevant increase in the risk for VAs or SCD in patients with ICM/DCM.

- Randomized controlled trials are in need to demonstrate whether patients with DCM and LGE could benefit from a primary prevention ICD regardless of LVEF.

# Conclusions

- Multicenter, prospective registries and RCTs incorporating CMR imaging, genetic, biomarker, and autonomic dysfunction in unselected DCM/ICM cohorts should be the next step in the pursuit of improved risk stratification, with the aim of creating a multivariable risk score that can accurately discriminate between the risk of SCD and non- sudden death.