DoloMeeting Arrhythmias
international workshop

Primary prophylactic ICD implantation in nonischaemic cardiomyopathy:

for almost everyone or only for highly selected patients ?

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No change from ESC-HF GL 2012

Implantable cardioverter-defibrillator in patients with heart failure

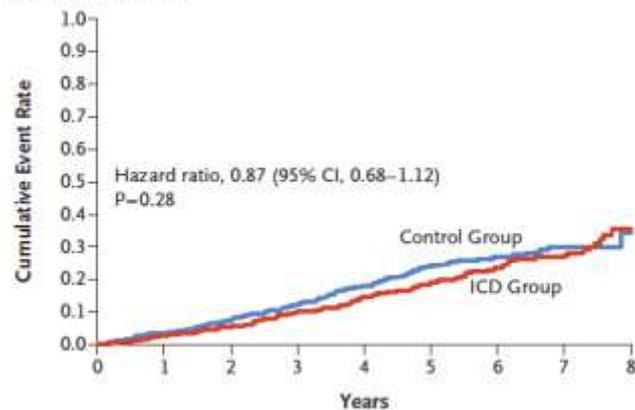| Recommendations	Class	Level
Secondary prevention An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status.	I	A
Primary prevention An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II–III), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than one year with good functional status, and they have:		
· IHD (unless they have had an MI in the prior 40 days – see below).	I	A
· DCM.	I	B
ICD implantation is not recommended within 40 days of an MI as implantation at this time does not improve prognosis.	III	A
ICD therapy is not recommended in patients in NYHA Class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for CRT, a ventricular assist device, or cardiac transplantation.	III	C
Patients should be carefully evaluated by an experienced cardiologist before generator replacement, because management goals and the patient's needs and clinical status may have changed.	IIa	B
A wearable ICD may be considered for patients with HF who are at risk of sudden cardiac death for a limited period or as a bridge to an implanted device.	IIb	C

The "DANISH study"

Trial oversight

- 1.116 pts with HFrEF, NICM and increased level of NT-proBNP randomly assigned to ICD or control group

- NYHA Class II-III : 99%.

- Mean LVEF: 25 %

- In both groups 58% received CRT

- Median FU 67,6 months

- Primary outcome: death from any cause

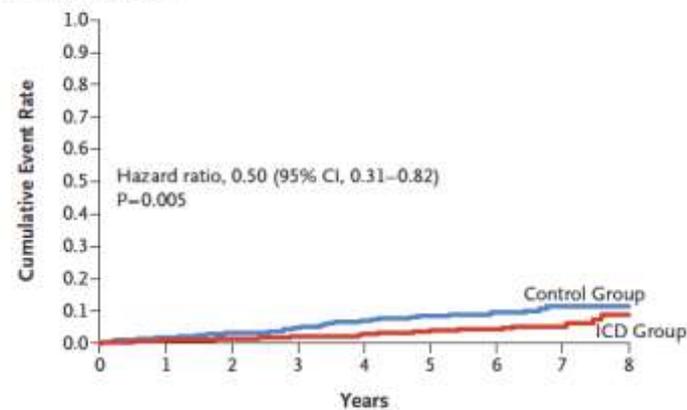- Secondary outcomes: sudden death, cardiovascular death

A. Death from Any Cause

Hazard ratio, 0.87 (95% CI, 0.68–1.12)
P=0.28

C. Sudden Cardiac Death

Hazard ratio, 0.50 (95% CI, 0.31–0.82)
P=0.005

No. at Risk									
Control Group	560	540	517	438	344	248	169	88	12
ICD Group	556	540	526	451	358	272	186	107	17

Lars Køber, M.D., D.M.Sc., Jens J. Thune, M.D., Ph.D., Jens C. Nielsen, M.D., D.M.Sc., Jens Haarbo, M.D., D.M.Sc.,
Lars Videbæk, M.D., Ph.D., Eva Korup, M.D., Ph.D., Gunnar Jensen, M.D., Ph.D., Per Hildebrandt, M.D., D.M.Sc.,
Flemming H. Steffensen, M.D., Niels E. Bruun, M.D., D.M.Sc., Hans Eiskjær, M.D., D.M.Sc., Axel Brandes, M.D.,
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Regitze Videbæk, M.D., Christian Hassager, M.D., D.M.Sc., Jesper H. Svendsen, M.D., D.M.Sc.,
Dan E. Høfsten, M.D., Ph.D., Christian Torp-Pedersen, M.D., D.M.Sc.,
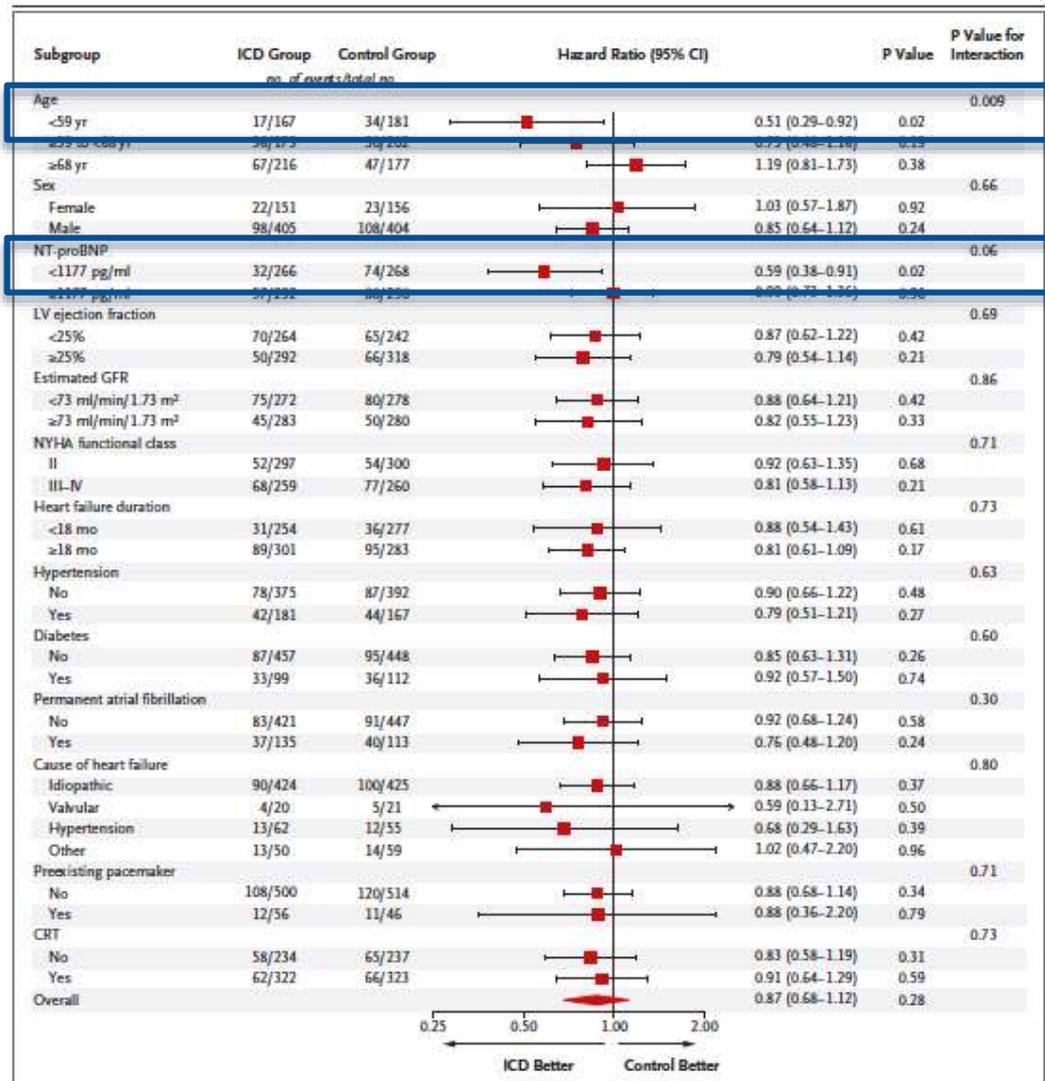and Steen Pehrson, M.D., D.M.Sc., for the DANISH Investigators*

Figure 3. Rate of Death from Any Cause (Primary Outcome) in Prespecified Subgroups.

The "DANISH study"

Outcomes

- Prophylactic ICD in pts with HFrEF, NICM and increased level of NT-proBNP did not provide a survival benefit

- The risk of SCD is halved with an ICD

- The results were independent of whether the pt receive a CRT device

- Younger pts may have a survival benefit in association with ICD implantation

The impact of the DANISH study on the "GL"
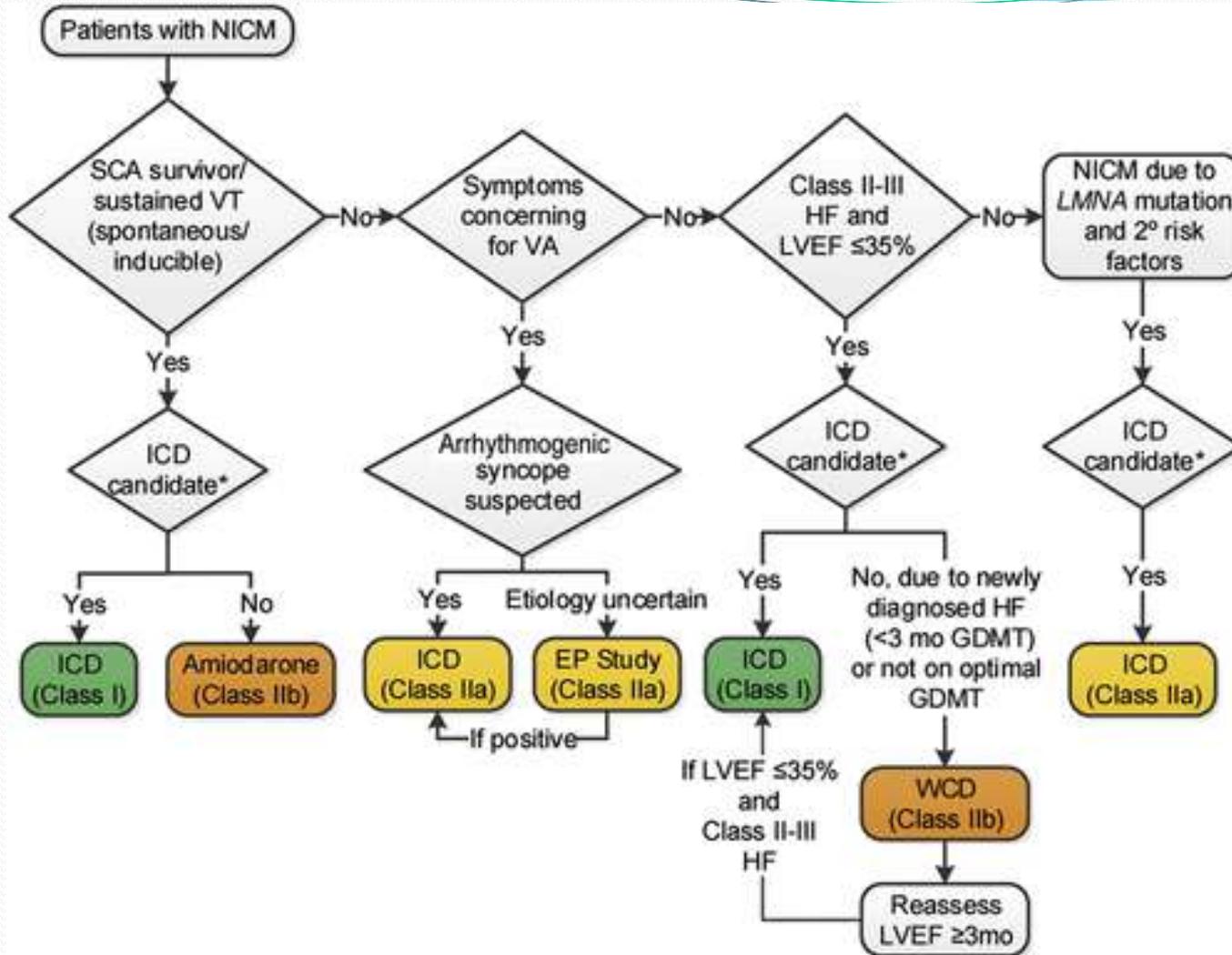
Kristina H. Haugaa[1,2*], Roland Tilz[3], Serge Boveda[4], Dan Dobreanu[5],
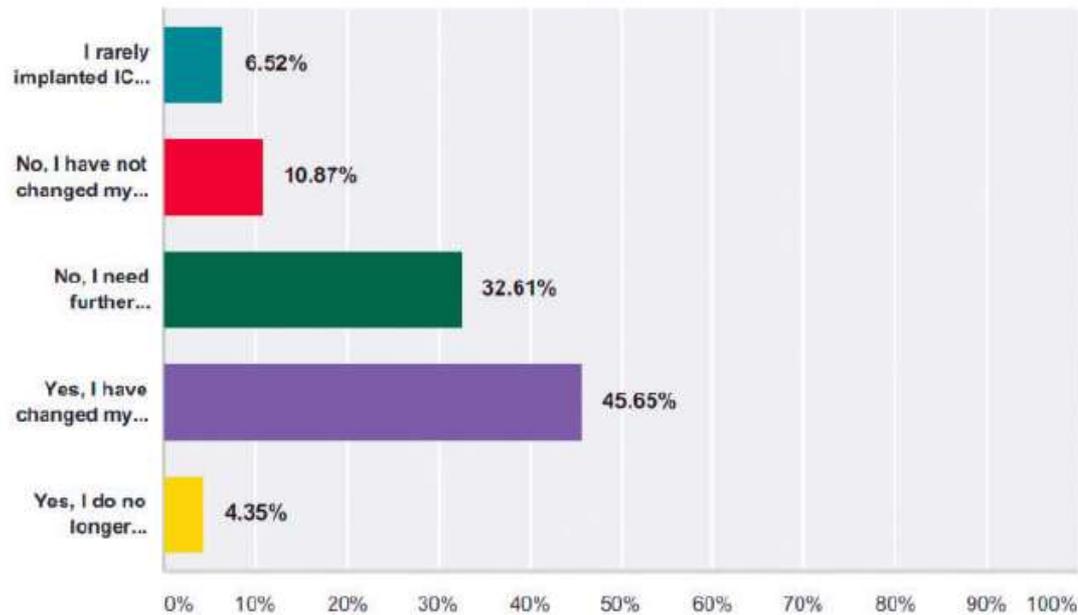Elena Sciaraffia[6], Jacques Mansourati[7], Giorgi Papiashvili[8], and Nikolaos Dagres[9]

The impact of the DANISH study on the "real world"

Figure 1 Results for non-ischaemic cardiomyopathy. Has the DANISH study changed your approach to ICD implantations for primary prevention in patients with non-ischaemic cardiomyopathy? (i) I rarely implanted ICD for primary prevention even before the DANISH trial. (ii) No, I have not changed my indications. (iii) No, I need further evidence and/or I will wait until the guidelines change before I modify my clinical practice. (iv) Yes, I have changed my practice. I am more selective and have implanted less ICDs on primary prevention for non-ischaemic cardiomyopathy after the study. (v) Yes, I do no longer systematically implant ICD for primary prevention in patients with non-ischemic cardiomyopathy.

GLs are supported by meta-analysis

Study	log Hazard Ratio (±SE)	Weight %	Hazard Ratio (95% CI)	
CAT	−0.19±0.31	7.8		0.83 (0.45–1.53)
AMIOVIRT	−0.14±0.52	2.8		0.87 (0.31–2.42)
DEFINITE	−0.43±0.25	12.4		0.65 (0.40–1.06)
SCD–HeFT	−0.32±0.19	20.3		0.73 (0.50–1.06)
COMPANION	−0.69±0.28	9.4		0.50 (0.29–0.88)
Total		100.0		0.77 (0.65–0.91)

Chi-square test for heterogeneity with 5 degrees of freedom, 3.82; P=0.58; I^2=0%

Test for overall effect: z=3.06 (P=0.002)

0.01   0.1   1   10   100

ICD Implantation Better   **Medical Therapy Better**

Figure 1. All-Cause Mortality among Patients with Nonischemic Cardiomyopathy Randomly Assigned to ICD Implantation or Medical Therapy for Primary Prevention.

The size of the boxes is proportional to the weight of the trial. Hazard ratios with 95% confidence intervals were determined with the use of an inverse-variance–weighted fixed-effects model. AMIOVIRT denotes Amiodarone versus Implantable Defibrillator; CAT Cardiomyopathy Trial; COMPANION Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; DEFINITE Defibrillators in Non-Ischemic Cardiomyopathy, Treatment Evaluation; and SCD-HeFT Sudden Cardiac Death in Heart Failure Trial.

Desai AS et Al
Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials.
JAMA 2004; 292: 2874-9.

Buof

Table 2 Meta-analyses of the RCTs conducted on primary prevention ICDs in NICM
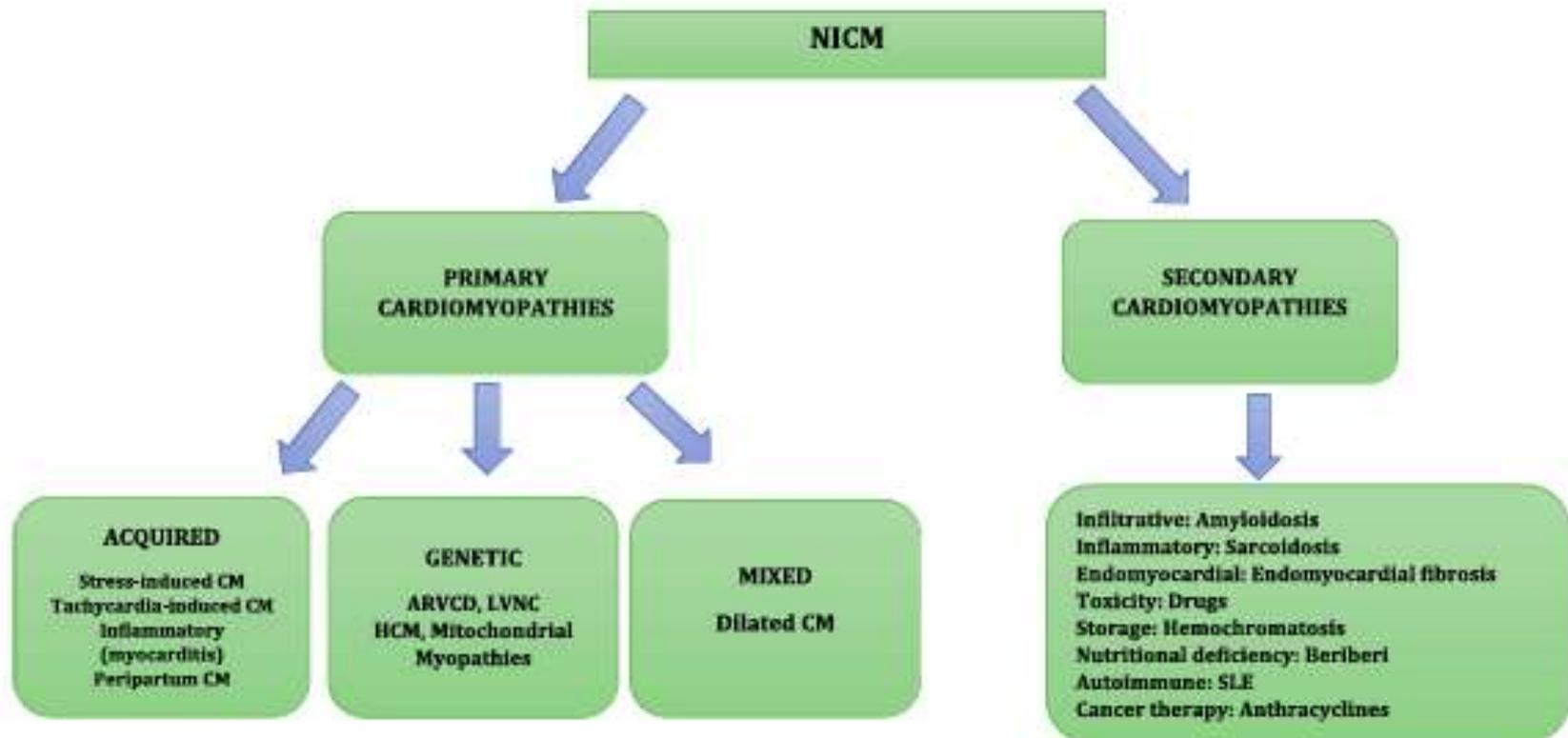
Study year	No. of trials	Total no. of patients (ICD/MT)	Primary end-point All-cause mortality (in favor of ICD arm)	Sudden death	Summary
Al-Khatib et al. 2017 [16•]	4 (CAT, DEFINITE, SCD-HeFT, DANISH)	1874 (937/937)	HR, 0.75 95% CI 0.61–0.93 P = 0.008	NA	Primary prevention ICDs are efficacious in reducing all-cause mortality in NICM
Narayanan et al. 2017 [17]	6 (CAT, AMIOVIRT, DEFINITE, SCD-HeFT, COMPANION, DANISH)	2347 (962/1385)	RR, 0.76 95% CI 0.63–0.91 P = 0.003	RR, 0.27 95% CI 0.15–0.50 P < 0.001	ICDs associated with 24% reduction in all-cause mortality and 73% reduction in SCD in non-CRT patients
Golwala et al. 2017 [18]	6 (CAT, AMIOVIRT, DEFINITE, SCD-HeFT, COMPANION, DANISH)	2970	HR, 0.77 95% CI 0.64–91	NA	Meta-analysis of all published RCTs to date shows significant clinical benefit on primary prevention ICDs on all-cause mortality in patients with NICM
Kolodziejczak et al. 2017 [19]	5 (CAT, AMIOVIRT, DEFINITE, SCD-HeFT, DANISH)	2992 (1284/1708)	HR, 0.81 95% CI, 0.72–0.91 P = 0.006	HR, 0.44 95% CI, 0.17–1.12 P = 0.001	ICD therapy associated with statistically significant reduction in all-cause mortality along with numerical trend in the same direction in case of sudden death
Barakat et al. 2017 [20]	5 (CAT, AMIOVIRT, DEFINITE, SCD-HeFT, DANISH)	2573 (1284/1289)	HR, 0.79 95% CI, 0.64–0.93 P < 0.001	RR, 0.47% 95% CI, 0.30–0.73 P = 0.001	Primary prevention ICD is associated with significant reduction in all-cause mortality in NICM patients
Stavrakis et al. 2017 [21]	6 (CAT, AMIOVIRT, DEFINITE, SCD-HeFT, COMPANION, DANISH)	2967 (1553/1414)	HR, 0.78 95% CI, 0.66–0.92 P = 0.003	NA	Primary prevention ICD is associated with 22% significant reduction in all-cause mortality in NICM patients
Romero et al. 2017 [22]	5 (CAT, AMIOVIRT, DEFINITE, SCD-HeFT, DANISH)	2573	RR, 0.84 95% CI, 0.71–0.99 P = 0.03	RR, 0.47 95% CI, 0.30–0.73 P < 0.001	Primary prevention ICD significantly reduced all-cause mortality and SCD in patients with NICM
Akel et al. 2017 [23]	5 (CAT, AMIOVIRT, DEFINITE, SCD-HeFT, DANISH)	2573	HR, 0.80 95% CI, 0.67–0.96 P = 0.02	HR, 0.51 95% CI, 0.34–0.76 P = 0.001	ICD therapy beneficial in terms of all-cause mortality in certain subgroups of patients with NICM
Masri et al. 2017 [24]	5 (CAT, DEFINITE, SCD-HeFT, COMPANION, DANISH)	2867 (1503/1364)	RR, 0.76 95% CI, 0.64–0.91 P = 0.002	RR, 0.40 95% CI, 0.18–0.90	ICD therapy reduces all-cause mortality and SCD in patients with NICM

- Analysis performed on data generated from a large remotely monitored contemporary real-world cohort of patients (1.946) receiving an ICD for primary prevention of SCD (Home Monitoring Expert Alliance network)

- Incidence of sustained VAs and appropriate device therapy was similar between ICM and NICM patients, receiving either an ICD (HR for sustained VAs in ICM vs NICM group was 0.96, p = 0.77) or a CRT-D (HR for sustained VAs ICM vs NICN was 0.85, p 0 .34)

- Sustained VAs occurred in more than 40% of ICD and CRT-D patients within a follow-up period of 5-year follow-up period
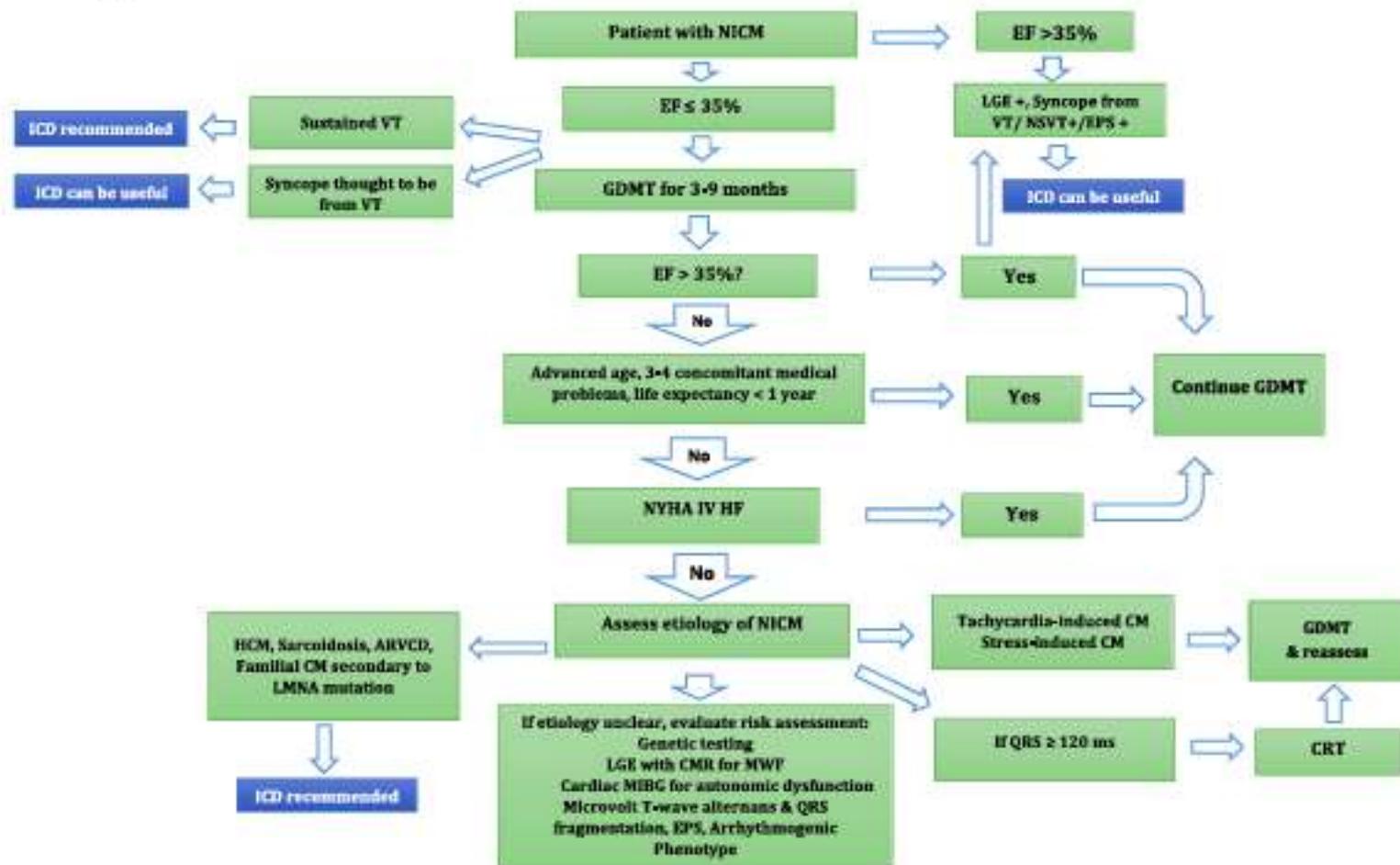
NICM is a heterogeneous disease

Risk stratification algorithm for NICM

Andreas Goette[1,2,a], Angelo Auricchio[3], Giuseppe Bariani[4], Frieder Braunschweig[5], Josep Brugada Terradellas[6], Haran Burri[7], A. John Camm[8], Harry Crijns[9], Nikolaos Dagres[10], Jean-Claude Deharo[11], Dobromir Dobrev[12], Robert Hatala[13], Gerhard Hindricks[10], Stefan H. Hohnloser[14], Christophe Leclercq[15], Thorsten Lewalter[16,17], Gregory Y.H. Lip[18,19], Jose Luis Merino[20], Lluís Mont[6], Fritz Prinzen[21], Alessandro Proclemer[22], Helmut Pürerfellner[23], Irina Savelieva[8], Richard Schilling[24], Jan Steffel[25], Isabelle C. van Gelder[26], Katja Zeppenfeld[27], Igor Zupan[28], and Hein Heidbuchel[29]

Table 7 Knowledge gaps in risk prediction of ventricular arrhythmias and SCD

Knowledge gaps	Available evidence	Feasibility of study	Ongoing trials
Personalized risk prediction	The selection of best candidates to ICD therapy is usually based on the inclusion criteria of main primary prevention trials	Intermediate	None
Temporal changes of the individual risk for SCD	Not definite role for evolution of heart disease, type of therapy, electrical and anatomical remodelling	High	Long-term follow-up in previous published trials (MADIT-II, SCD-HeFT, etc.)
Use of cardiac MRI in risk stratification	Role of LGE for SCD risk	High	Several observational studies
Information on large population	Data on several ICD registries	High	Several observational studies
Electrical storm management	Information obtained from single-centre registry	High	None

ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; MRI, magnetic resonance imaging; SCD, sudden cardiac death.

**Table 9** Knowledge gaps in device therapies for VT/SCD

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited knowledge (small trials or registries, but no RCT)	Resolution of gap (in principle) feasible	Upcoming trials in the field (Clinical Trial.gov)
Impact of modern medical treatment on the utility of ICD therapy			One RCT (DANISH trial)	Conduction of large RCT feasible but with significant difficulties	EU-CERT-ICD (NCT02064192, prospective observational)
Device therapies for protection of patients with LVEF >35% but high individual risk for SCD			None	Personalized risk prediction needed, but in principle feasible	PRESERVE-EF (NCT02124018) SMART-MI (NCT02594488)
Role of subcutaneous ICD compared with the transvenous systems			Registries (EFFORTLESS and others)	RCT already being conducted	PRAETORIAN (NCT01296022)

ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; RCT, randomized controlled trial; SCD, sudden cardiac death; VT, ventricular tachycardia.
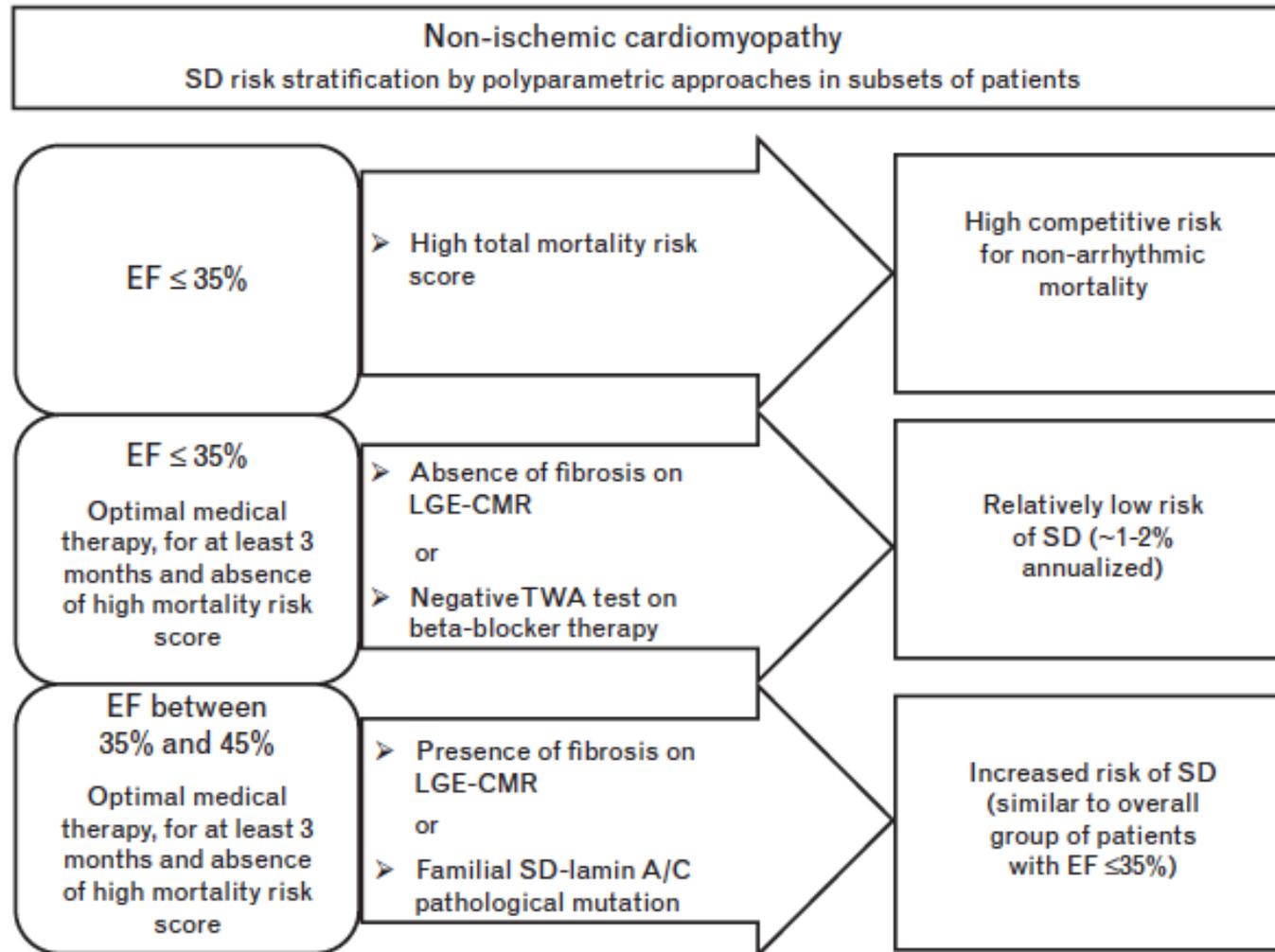
- In a prospective observational sub-study of the Danish Study to Assess the Efficacy of ICDs in Patients with Nonischemic Systolic Heart Failure on Mortality (DANISH) 252 patients underwent CMR

- The primary endpoint was all-cause mortality

- The presence of LGE was an independent predictor of all-cause mortality (HR 1.82; 95% CI 1.002-3.29; P = .049)

- ICD implantation did not impact all-cause mortality, for either patients with LGE (HR 1.18; 95% CI 0.59-2.38; P = .63), or for patients without LGE (HR 1.00; 95% CI 0.39-2.53; P=.99), (P for interaction = 0.79)

Conclusions

- GDMT initiation in NICM leads to reversal of myocardial remodeling in up to 30% of patients pressing the importance of postponing ICD implantation

- When considering ICD implantation for SD prophylaxis in NICM competing risks of death (progressive pump failure) should be taken into consideration

- An individualized approach to risk stratification, encompassing a comprehensive clinical assessment (older and frail pts should not be considered for an ICD), is needed and validated. In the meantime ICD, for medico-legal issues too, will continue to be the cornerstone of management of SD risk in NICM