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Primary prevention implantable cardioverter defibrillator in non-ischaemic cardiomyopathy: challenging the Australian heart failure guidelines

The 2018 Australian guidelines' recommendations require further clarifications to ensure eligible patients will receive appropriate ICD therapy

The implantable cardioverter defibrillator (ICD) has been shown to be a cost-effective option for primary prevention of sudden cardiac death (SCD) in patients with heart failure with reduced ejection fraction (HFrEF). However, in the recently published 2018 guidelines for the prevention, detection and management of heart failure in Australia, the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Heart Failure Guidelines Working Group downgraded the recommendation for primary prevention ICD to decrease mortality in patients with HFrEF and left ventricular ejection fraction (LVEF) 35% or below associated with non-ischaemic cardiomyopathy (NICM).[1,2] In particular, the level of recommendation and quality of evidence for primary prevention ICD was deemed weak and low for NICM versus strong and moderate for ischaemic cardiomyopathy, respectively. The document cited the lack of single randomised controlled trials demonstrating mortality benefits with primary prevention ICD in patients with NICM. It also highlighted recent prospective randomised controlled data of 1116 patients with HFrEF and LVEF 35% or below associated with non-ischaemic causes from the DANISH trial — a Danish study to assess the efficacy of ICD in patients with non-ischaemic systolic heart failure on mortality — whereby primary prevention ICD did not reduce mortality compared with usual clinical care over a median follow-up duration of 67.6 months (interquartile range, 49–85 months).[3]

However, two other international cardiovascular societies' guidelines have not downgraded their recommendations for primary prevention ICD in patients with NICM despite taking into consideration the DANISH study data.[4,5] Of note, the 2016 Canadian guidelines have not differentiated its recommendations between patients with HFrEF due to ischaemic or non-ischaemic causes. Its recommendations for primary prevention ICD in both ischaemic cardiomyopathy and NICM were based on LVEF, with strong recommendation and high quality evidence in patients with LVEF 30% or below, and weak recommendation and moderate quality evidence in those with LVEF 31–35%.[4] The 2017 American Heart Association/American College of Cardiology/Heart Rhythm Society Guidelines have maintained class I (strong) recommendations with level A (high quality) evidence for primary prevention ICD in patients with NICM with New York Heart Association Class II–III symptoms and LVEF 35% or below, despite optimised medical therapy and expected meaningful survival of greater than one year.[5] At the same time, a recent survey conducted by the European Heart Rhythm Association from 48 centres (17 different countries) showed that up to 50% of centres have become more selective and implanted fewer primary prevention ICD in patients with NICM in light of the DANISH trial results.[6] The changing practice pattern raises concerns whether the most appropriate therapy is being offered to the individual patient with NICM. Here, we wish to highlight several important considerations relating to the DANISH study data that challenge the downgrade of recommendation in the recent 2018 Australian guidelines.

First, the powering of the DANISH study may not be adequate in an extremely well treated cohort of patients with

HFrEF due to NICM, in which the rate of all-cause mortality was low at less than five per 100 person-years. This was compounded by the high rate of non-cardiac deaths in the study. Second, in the log-rank survival analysis, the proportional hazard assumption was found to be violated in the DANISH study, with crossover seen in the Kaplan–Meier graph after lower death rate in the ICD group in the first 7 years. The mortality benefit of ICD appears to be time-dependent, perhaps owing to a decline in SCD as a cause of death over time. Third, recent inclusion of the DANISH study data in several updated meta-analyses did not affect the overall all-cause mortality benefit of primary prevention ICD over optimised medical therapy in patients with HFrEF due to NICM (Box).[7-10] Notably, the magnitude of reduction in all-cause mortality with ICD appears identical in patients with HFrEF due to ischaemic and non-ischaemic causes, with hazard ratios (HRs) of 0.76.[10] Fourth, ICD conferred a significant 50% reduction in SCD despite the low rates of SCD in the DANISH study at 1–2% per year.[3] To this end, a recent meta-analysis confirmed that the magnitude of reduction in SCD appears similar between patients with HFrEF due to ischaemic and non-ischaemic causes with HRs of 0.38 and 0.40, respectively.[10] Last, NICM encompasses a diverse range of aetiologies, including dilated cardiomyopathy, infiltrative, inflammatory, neuromuscular, alcohol and drug toxicities whereby the prognosis differs widely as do management strategies.[12] For example, HFrEF due to sarcoidosis and giant cell myocarditis are known to confer poor prognosis due to their progressive and non-reversible nature, while HFrEF due to tachycardia-mediated or excessive alcohol use can be reversible following adequate heart rate control or abstinence from alcohol in conjunction with optimised medical therapy.

Notwithstanding, the DANISH study highlights the importance of optimised medical therapy and cardiac resynchronisation therapy in patients with HFrEF that would have contributed to the overall low rates of all-cause mortality and SCD. Specifically, more than 90% of the DANISH cohort were taking β-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, while 58% of the cohort were taking a mineralcorticoid receptor antagonist or had received biventricular pacing therapy. In addition, in a pre-specified subgroup analysis of the DANISH study, there was a significant association between reduced all-cause mortality (HR, 0.70; $P = 0.03$) and primary prevention ICD in patients aged 70 years or less with HFrEF and LVEF 35% or below associated with non-ischaemic causes, which was not present in patients aged over 70 years (HR, 1.05; $P = 0.84$).[13] As an ICD is used to prevent SCD, the lack of mortality benefit in patients aged over 70 years was accounted for by the twofold higher risk of death due to causes other than SCD compared with patients aged 70 years or less.

Is the 2018 Australian heart failure guidelines' downgrading of the level of recommendations for primary prevention ICD for NICM imprudent? What are the potential implications? Taking into consideration the nuances of the DANISH study, we contend that the 2018 Australian recommendations for primary prevention ICD for NICM may mislead clinicians managing such patients, with the potential outcome that eligible patients may miss out on life-saving therapy. This may also exacerbate the well documented underuse of device therapy in patients with HFrEF in Australia.[14] While we await an updated cost-effectiveness analysis of ICD therapy in NICM in the post-DANISH era, the improved longevity of ICDs will likely beget favourable cost–benefit ratios and reduced morbidities associated with device replacements, particularly in younger patients.[15] Meanwhile, improved risk stratification beyond LVEF is urgently needed to guide more targeted intervention, including ICD implantation. This may entail improved electrophysiological substrate characterisation, scar characterisation with late gadolinium enhancement on magnetic resonance imaging, cardiac autonomic assessment with nuclear imaging, and novel genetic markers.[16]

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[Insert Box]

Updated meta-analyses of randomised controlled trials (RCTs) on all-cause mortality with primary prevention implantable cardioverter defibrillator (ICD) in non-ischaemic cardiomyopathy versus optimised medical therapy (including data from the DANISH study)

Meta-analyses of RCTs on all-cause mortality	Patients (*n*)	Hazard/odds ratio	95% CI	Comments
Al-Khatib et al[7]	1874	0.75*	0.61–0.93	ICD patients only
Golwala et al[8]	2970	0.77*	0.64–0.91	Including CRT-D patients†
		0.76*	0.62–0.94	ICD patients only
		0.70	0.39–1.26	CRT-D patients only
Luni et al[9]	3255	0.76*	0.64–0.91	Including CRT-D patients†
		0.80*	0.66–0.96	ICD patients only
		0.79*	0.63–0.99	CRT-D patients only
Shun-Shin et al[10]	3128	0.76*	0.64–0.90	Including CRT-D patients†

CRT-D = cardiac resynchronisation therapy defibrillator. * Denotes $P < 0.05$. † These analyses included the COMPANION study,[11] whereby comparison was made between CRT-D versus optimised medical therapy-only groups rather than CRT-D versus CRT-P (cardiac resynchronisation therapy pacemaker) plus optimised medical therapy.