Article type : Perspective (2-pp)

Article begins on page three of this document.

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

Authors:

	Title	First name	Mid initials	Last name	Postnom (eg, PhD) [3 only for publication]	Position1	Address1	Position2	Address2	Tel	Email
1	Assoc. Prof.	Dennis	H	Lau	MBBS, PhD	Associate Professor	1	Cardiac Electrophysiologist	2	08 8313 9000	dennis.h.lau@adelaide.edu.au
2	Prof.	Jonathan	M	Kalman	MBBS, PhD	Professor of Medicine	3	Director of Heart Rhythm Services	4	03 934954 00	jon.kalman@mh.org.au
3	Prof.	Prashanthan		Sanders	MBBS (Hons), PhD,	Professor of Cardiology and Director of Centre for Heart Rhythm Disorders	1	Director of Cardiac Electrophysiology and Pacing	2	08 831390 00	prash.sanders@adelaide.edu.au
4											
5											

Number of corresponding author:	3
Number of alternative corresponding author:	

Addresses:

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/MJA2.50248](#)

	Institution		City	State	Post Code	
1	Centre for Heart Rhythm Disorders, University of Adelaide		Adelaide	SA	5005	
2	Royal Adelaide Hospital		Adelaide	SA	5000	
3	University of Melbourne		Melbourne	VIC	3000	
4	Royal Melbourne Hospital		Melbourne	VIC	3050	
5						

Postal address of first corresponding author (if different from the institutional address given above)	
--	--

Primary Keywords [Office use only]	Cardiovascular diseases
Secondary keywords [Office use only]	Arrhythmias, cardiac; Cardiomyopathies; Defibrillator; Heart failure; Ventricular dysfunction
Notes:	

Article details (press ctrl – 9 to enter details):

Article type	Perspective
Blurb	The 2018 Australian recommendations for primary prevention implantable cardioverter defibrillator for non-ischaemic cardiomyopathy may result in eligible patients missing out on life-saving therapy

Office use

<i>Ms. Number</i>	mja18.01219.R2
<i>Medical editor</i>	Francis Geronimo
<i>Medical editor email</i>	fgeronimo@mja.com.au
<i>Structural editor</i>	Laura Teruel
<i>Structural editor email</i>	lteruel@mja.com.au
<i>Section/Category</i>	Perspective (2-pp)
<i>Strapheading</i>	Perspective
<i>Substrap</i>	

Wiley – file data:

Filename for copyediting	lau_mja18.01219_ms.docx
Accompanying graphics	None
Stock images	lau_mja18.01219_im.jpg, lau_mja18.01219_im.tif
Appendices	None

Office use – history:

Event	Date
Original submission received	26/11/2018

Event	Date
Accept	07/03/2019

Proof sent to author	
Proof returned by author	
Published (date format xx/xx/xx)	
Issue	
Vol	
DOI	
Journal	
Original article DOI (for response)	

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

Acknowledgements: Dennis Lau is supported by the Robert J Craig Lectureship from the University of Adelaide. Jonathan Kalman and Prashanthan Sanders are supported by Practitioner Fellowships from the National Health and Medical Research Council. Prashanthan Sanders is supported by the National Heart Foundation of Australia.

Competing interests: The University of Adelaide reports receiving on behalf of Dennis Lau lecture and/or consulting fees from Abbott, Bayer, Biotronik and Pfizer. Prashanthan Sanders reports having served on the advisory board of Biosense-Webster, Medtronic, Abbott, Boston Scientific and CathRx. The University of Adelaide reports receiving on behalf of Prashanthan Sanders lecture and/or consulting fees from Biosense-Webster, Medtronic, Abbott, and

Boston Scientific. The University of Adelaide reports receiving on behalf of Prashanthan Sanders research funding from Medtronic, Abbott, Boston Scientific, Biotronik and Liva Nova.

Provenance: Not commissioned; externally peer reviewed.

Author details

Dennis H Lau^{1,2}

Jonathan M Kalman^{3,4}

Prashanthan Sanders^{1,2}

1 Centre for Heart Rhythm Disorders, University of Adelaide, Adelaide, SA.

2 Royal Adelaide Hospital, Adelaide, SA.

3 University of Melbourne, Melbourne, VIC.

4 Royal Melbourne Hospital, Melbourne, VIC.

Prash.Sanders@adelaide.edu.au

doi: 10.5694/mja18.01219

References

- 1 Atherton JJ, Sindone A, De Pasquale CG, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of heart failure 2018. *Med J Aust* 2018; 209: 363-369. <https://www.mja.com.au/journal/2018/209/8/national-heart-foundation-australia-and-cardiac-society-australia-and-new-0>
- 2 Atherton JJ, Sindone A, De Pasquale CG, et al; NHFA CSANZ Heart Failure Guidelines Working Group. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: guidelines for the prevention, detection, and management of heart failure in Australia 2018. *Heart Lung Circ* 2018; 27: 1123-1208.
- 3 Kober L, Thune JJ, Nielsen JC, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016; 375: 1221-1230.
- 4 Bennett M, Parkash R, Nery P, et al. Canadian Cardiovascular Society/Canadian Heart Rhythm Society 2016 implantable cardioverter-defibrillator guidelines. *Can J Cardiol* 2017; 33: 174-188.
- 5 Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm* 2018; 15: e73-e189.
- 6 Haugaa KH, Tilz R, Boveda S, et al. Implantable cardioverter defibrillator use for primary prevention in ischaemic and non-ischaemic heart disease: indications in the post-DANISH trial era: results of the European Heart Rhythm Association survey. *Europace* 2017; 19: 660-664.
- 7 Al-Khatib SM, Fonarow GC, Joglar JA, et al. Primary prevention implantable cardioverter defibrillators in patients with nonischemic cardiomyopathy: a meta-analysis. *JAMA Cardiol* 2017; 2: 685-688.
- 8 Golwala H, Bajaj NS, Arora G, Arora P. Implantable cardioverter-defibrillator for nonischemic cardiomyopathy: an updated meta-analysis. *Circulation* 2017; 135: 201-203.
- 9 Luni FK, Singh H, Khan AR, et al. Mortality effect of ICD in primary prevention of nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. *J Cardiovasc Electrophysiol* 2017; 28: 538-543.
- 10 Shun-Shin MJ, Zheng SL, Cole GD, et al. Implantable cardioverter defibrillators for primary prevention of death in left ventricular dysfunction with and without ischaemic heart disease: a meta-analysis of 8567 patients in the 11 trials. *Eur Heart J* 2017; 38: 1738-1746.
- 11 Bristow MR, Saxon LA, Boehmer J, et al; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; 350: 2140-2150.
- 12 Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000; 342: 1077-1084.
- 13 Elming MB, Nielsen JC, Haarbø J, et al. Age and outcomes of primary prevention implantable cardioverter-defibrillators in patients with nonischemic systolic heart failure. *Circulation* 2017; 136: 1772-1780.
- 14 Thavapalachandran S, Leong DP, Stiles MK, et al. Evidence-based management of heart failure in clinical practice: a review of device-based therapy use. *Intern Med J* 2009; 39: 669-675.
- 15 Munawar DA, Mahajan R, Linz D, et al. Predicted longevity of contemporary cardiac implantable electronic devices: a call for industry-wide "standardized" reporting. *Heart Rhythm* 2018; 15: 1756-1763.
- 16 Pathak RK, Sanders P, Deo R. Primary prevention implantable cardioverter-defibrillator and opportunities for sudden cardiac death risk assessment in non-ischaemic cardiomyopathy. *Eur Heart J* 2018; 39: 2859-2866.

[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.

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Lau, DH;Kalman, JM;Sanders, P

Title:

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

Date:

2019-08-01

Citation:

Lau, D. H., Kalman, J. M. & Sanders, P. (2019). Primary prevention implantable cardioverter defibrillators in non-ischaemic cardiomyopathy: challenging the Australian heart failure guidelines. MEDICAL JOURNAL OF AUSTRALIA, 211 (4), pp.154-+. <https://doi.org/10.5694/mja2.50248>.

Persistent Link:

<http://hdl.handle.net/11343/286015>