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Title	Clarification of the Australian heart failure guideline recommendation for primary prevention defibrillator implantation in non-ischaeamic cardiomyopathy
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Clarification of the Australian heart failure guideline recommendation for primary prevention defibrillator implantation in non-ischaemic cardiomyopathy

The use of defibrillators for ventricular arrhythmias may significantly reduce mortality when sudden cardiac death is the major contributor

The 2018 guidelines from the National Heart Foundation and the Cardiac Society of Australia and New Zealand provide evidence-based direction for the management of heart failure in Australia.¹ A Perspective article published in the Journal in 2019² challenged the weak recommendation for the implantation of a defibrillator in the primary prevention of mortality in dilated cardiomyopathy (DCM) with a left ventricular ejection fraction (LVEF) of 35% or below.¹ The authors of the *MJA* article² questioned the differences between this recommendation¹ and recent Canadian and American guidelines.^{3,4} We welcome this opportunity to clarify the basis for the Australian guidelines recommendation.

To understand the heart failure disease process, it is fundamental to recognise the differences in mechanisms of death and prognosis in ischaemic cardiomyopathy (ICM) versus DCM. Sudden cardiac death is more frequently responsible for mortality in ICM compared with pump failure and death from non-cardiac causes in DCM. As such, defibrillators that provide shocks for ventricular arrhythmias are expected to significantly reduce mortality when sudden cardiac death is the major contributor. Combined with recent clinical trial data, this is the foundation for the current guidelines in primary prevention, making a strong recommendation for a defibrillator in reducing mortality in ICM compared with a weak recommendation for DCM.¹ The GRADE methodology (www.gradeworkinggroup.org) used in these guidelines ensures that the strength of a recommendation not only takes into account the quality of evidence but also the benefits and harms of an intervention, improvements in quality of life, longevity, patient preferences, and resource considerations.

The contrasting prognoses of the two major underlying causes for systolic heart failure is demonstrated in the outcomes of clinical trials exploring the role of primary prevention defibrillators. The MADIT-II trial found a significant reduction in mortality in ICM with an ejection fraction of 30% or below ($P = 0.016$).⁵ In contrast, there have been no randomised controlled trials demonstrating a significant reduction in total mortality with implantable cardioverter defibrillators (ICDs) in DCM. On the basis of the SCD-HeFT trial,⁶ ICDs were recommended in patients with heart failure with reduced ejection fraction with an LVEF below 35% regardless of underlying coronary artery disease, despite the absence of statistical significance in DCM. The 2016 DANISH study randomly allocated 1116 patients with DCM and a LVEF below 35% to ICDs versus medical therapy, with no significant difference in total mortality.⁷ Importantly, there were higher rates of optimised medical therapy compared with earlier randomised ICD studies, and cardiac resynchronisation therapy was included in 58% of patients. The limitations of the DANISH trials suggested in the *MJA* article,² such as the optimised medical treatment and low mortality, are strengths and more accurately reflect the expected outcomes in a contemporary DCM population who receive guideline-directed medical therapy.

Nonetheless, despite the absence of positive randomised controlled trials, recent meta-analyses, with the inclusion of DANISH, continue to demonstrate a significant mortality reduction for primary prevention defibrillators in DCM.⁸ While meta-analyses provide an analytical technique to pool results and inflate sample sizes to improve statistical power, there are important limitations. Biases related to study selection, publication bias, heterogeneity of study populations in relation to treatment, follow-up, and study time points have an impact on the findings of meta-analyses, despite attempts at statistical corrections. Early primary prevention ICD studies were stopped prematurely due to futility and, as such, contribute little to meta-analyses.⁹ The inclusion of older studies in undertreated medical patients with the variable inclusion of cardiac resynchronisation therapy is an important limitation in the interpretation of meta-analyses investigating primary prevention ICDs in DCM.

Implanting physicians are cognisant of potential harm, with Australian data reporting ICD-related complications requiring rehospitalisation or re-operation in 10% of patients.¹⁰ Battery longevity and defibrillator lead durability are additional considerations.

Careful patient selection is required to identify patients with DCM likely to benefit from ICD therapy. The 2018 Australian guidelines draw attention to the increased efficacy of ICD therapy in patients younger than 70 years identified as a pre-specified endpoint in the DANISH study.¹¹ Although the incidence of sudden cardiac death did not differ between age groups, the incidence of non-sudden cardiac death becomes significantly higher in the older population. Our recommendation is supported by a recent clinical practice update from the Heart Failure Association of the European Society of Cardiology. Providing specific recommendations regarding subpopulations, such as patients with infiltrative or hypertrophic cardiomyopathy, was beyond the scope of the 2018 national guidelines.

As we await better tools for risk stratification of patients with DCM, supportive data from randomised controlled trials and improvements in pharmacological and device-based heart failure therapy, the weak recommendation for ICDs for the primary prevention of mortality¹ provides the support for a considered decision between patient and physician, balancing the absence of randomised controlled trial data with the morbidity of an ICD implant. “It is precisely where evidence is lacking or is controversial that clinicians need the most guidance.”¹²

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References

- 1 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.
- 2 Lau DH, JM Kalman, Sanders P. Primary prevention implantable cardioverter defibrillators in non-ischaemic cardiomyopathy: challenging the Australian heart failure guidelines. *Med J Aust* 2019; 211: 154-155. <https://www.mja.com.au/journal/2019/211/4/primary-prevention-implantable-cardioverter-defibrillators-non-ischaemic>
- 3 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.
- 4 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.
- 5 Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; 346: 877-883.
- 6 Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; 352: 225-237.
- 7 Køber L, Thune JJ, Nielsen JC, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016; 375: 1221-1230.
- 8 Stavrakis S, Asad Z, Reynolds D. Implantable cardioverter defibrillators for primary prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. *J Cardiovasc Electrophysiol* 2017; 28: 659-665.
- 9 Strickberger SA, Hummel JD, Bartlett TG, et al. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia — AMIOVIRT. *J Am Coll Cardiol* 2003; 41: 1707-1712.

- 10 Ranasinghe I, Labrosciano C, Horton D, et al. Institutional variation in quality of cardiovascular implantable electronic device implantation: a cohort study. *Ann Intern Med* 2019; 171: 309-317.
- 11 Elming MB, Nielsen JC, Haarbo J, et al. Age and outcomes of primary prevention implantable cardioverter-defibrillators in patients with nonischemic systolic heart failure. *Circulation* 2017; 136: 1772-1780.
- 12 Jacobs AK, Anderson JL, Halperin JL, et al. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 64: 1373-1384.

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