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Chu-Pak Lau

Hung-Fat Tse

Chung-Wah Siu

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Editorial

Is Implantable Cardioverter Defibrillator Useful in Non-Ischaemic Cardiomyopathy Useful?

CHU-PAK LAU,[1] HUNG-FAT TSE,[1-3*] CHUNG-WAH SIU[1,2*]

From [1]Cardiology Division, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong; [2]Division of Cardiology, Department of Medicine, The University of Hong Kong Shenzhen Hospital, China; [3]Shenzhen Institutes of Research and Innovation, University of Hong Kong, China

Dilated cardiomyopathy (DCM) is defined as left ventricular dilation and enlargement not due to loading condition of the heart which cannot be explained by epicardial coronary artery disease.[1] It has a prevalence of 1/2,500 population, and an annual incidence of 7/100,000. DCM affects men more than women. The causes of cardiovascular death are due to arrhythmias or progressive heart failure. Sudden cardiac death (SCD) is more often due to ventricular tachyarrhythmias (VA), whereas bradycardia and pulseless electrical activities predominate as heart failure progress.[2]

Familial type of DCM can be due to mutations in sarcomere and desmosomal protein gene, proteins that directly affect cardiac contractile muscle. An important gene is the lamin A/C mutations, in which patients present with asymptomatic conduction disease for decades, followed by atrial arrhythmias and VA and DCM. In the setting of a familial occurrence of DCM and conduction disturbance, screening of lamin A/C mutation and SCN5A genes are recommended. A mutation specific screening is indicated in family members if a patient has documented mutation in a DCM related genes.[3]

The majority of DCM patients do not have a familial incidence. Hence predictors of future VA have relied on risk factors testing. These include (1) autonomic parameters, (2) structural/functional parameters such as left ventricular ejection fraction (LVEF) and ventricular dismission; and (3) arrhythmia indicators such as electrophysiology testing, and electrocardiographic (ECG) depolarisation and repolarisation abnormalities. In a meta-analysis of 12 conventional parameters involving 45 trials in 6,088 patients,[4] autonomic parameters were found to be unpredictive. Structural/functional and ECG parameters are helpful, but their overall specificity ranges only from 36.2 to 87.3%, with a sensitivity of 28.8-91.0%. Indeed, LVEF, the basis on which implantable cardioverter defibrillators (ICD) therapy is prescribed, has only a sensitivity and specificity of 71.7 and 50.5% and a positive predictive accuracy of 21.9%.

VA originated from trigger or reentry, often from fibrous tissues that develop in the myocardium of DCM. The use of late gadolinium enhancement (LGE) to detect LV scarring has been proposed as a marker of VA. Indeed, positive LGE in the LV increase the VA risk almost 10 folds, both in patients with LVEF below and above 35%.[5] In a recent cohort studies that include only patients with milely impaired LVEF of ≥40%, the 4 year arrhythmic risk was 17.8% vs 2.3% in those with and without LGE.[6] LGE defines the VA substrate and many emerge as a good marker to predict SCD independent of the LVEF.

What are our therapeutics means now to combat

Address for Correspondence: Dr Chu-Pak Lau
Honorary Clinical Professor, The University of Hong Kong, Suite 1303, Central Building, 1 Pedder Street, Central, Hong Kong

Email: cplau@hku.hk

*This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

SCD in patients with DCM? Obviously, optimal pharmacological therapy of heart failure is essential. Triggers for VA such as hypokalaemia, thyrotoxicosis and new onset ischaemia should be promptly diagnosed and treated. VA ablation can be performed, but due to the often patchy fibrosis that can involve multiple myocardial layers, the success rate of VA ablation is less durable than VA ablation in cardiomyopathy due to ischaemic heart disease,[7] notwithstanding the low acute success rate of 22.2%.

Implantation of ICD is the recommended therapy in those survivors of SCD and VA in DCM. For primary prevention, both the ACC/AHA[8] and ESC[1] guidelines have used LVEF and the degree of symptomatic heart failure as criteria for ICD prescription: In patients with DCM and an LVEF ≤35%, with NYHA class I - IV are for ICD implantation. These are based on the CAT,[9] AMIOVIRT,[10] DEFINITE[11] and the SCD-HeFT[12] studies which were published before 2005. These studies showed a combined 31% of reduction in total mortality in the ICD therapy vs medical therapy arms, a result mainly driven by a 56% SCD reduction.

In view of the change in medical therapy that has occurred over the last 15 years, the advent of the cardiac resynchronization therapy (CRT), the increase in patient longevity, and the frequent associated co-morbidities which increases the proportion of death for non-arrhythmic disease, the role of the ICD has now been questioned.

The COMPANION trial[13] has involved patients with both DCM and ischemic heart failure who are in Class III-IV heart failure with a wide QRS width, a group that has high baseline mortality. The use of cardiac resynchronization therapy defibrillator (CRT-D) but not CRT reduces total mortality over medical therapy, although it is not sure the effect is due to ICD or CRT alone. Indeed, the study did not show mortality difference between CRT-D vs CRT.

The recent DANISH trial[14] is a focus study on this issue. In a randomized control study of 1,116 patients with heart failure, half of them were randomized to ICD (or CRT-D) and half to medical therapy (or corresponding CRT). CRT-D or CRT were used in 58% in total. ICD/CRT-D therapy was shown not to change the risk of total mortality vs control arm over a median of over 5 years of follow up, although the SCD risk was significantly reduced from 8.3 to 4.3%. The study was powered to detect a difference of 25% total mortality. According to the authors, this difference from prior trials of ICD can be due to less VA risk in DCM than ischaemic cardiomyopathy, the beneficial impact of CRT, and the high percentage of use of angiotensin-receptor and betablockers (>90%) compared to older studies, and vigorous exclusion of coronary artery disease.

Figure 1 shows the demographics and the SCD rates in the controlled arms of the major studies of ICD in DCM. With the exception of the COMPANION trial, which is a CRT trial in sicker patients, the DANISH recruited the oldest patients, had the longest follow up and the lowest annual mortality. In addition, there was an initial separation of mortality rates between the ICD vs control arms, although the 2 curves come together with follow up, quite unlike the continued separation of ICD trial for MADIT-II[15] for ischaemic cardiomyopathy (Figure 2). This suggests that over time with progression of heart failure or development of comorbidities or both in these patients, the benefit of ICD in DCM is reduced. Several meta-analysis have since been published combining these trial data. The total mortality reduction for all trials using ICD/CRT-D and ICD only were 24 and 23% reduction, whereas CRT-D did not reduce mortality.[16] Such meta-analyse that include trials performed at disparate time are limited by major difference in the patients demographic and changes in heart failure treatment.

In conclusion, the benefit (if present) of primary prevention for mortality in DCM is now significantly reduced due to better medical care and the use of CRT. Nevertheless, the benefit on SCD prevention remains valid. Better identification of subjects with higher risk of SCD such as younger patients and those with LGE may allow a better cost-performance of ICD, although dedicated trials using these parameters will be needed.

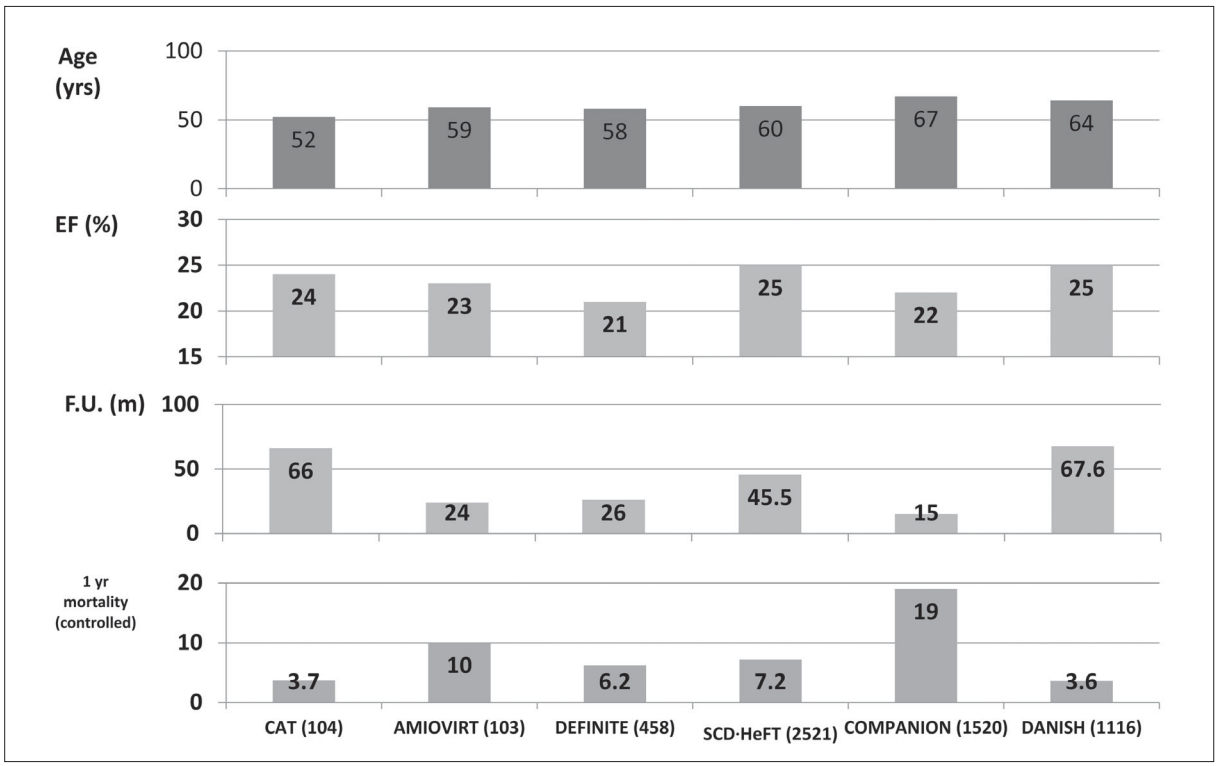

Figure 1. *Demographic and outcome of 6 randomized trials on implantable cardioverter defibrillator in non-ischaemic dilated cardiomyopathy.*[9-14]

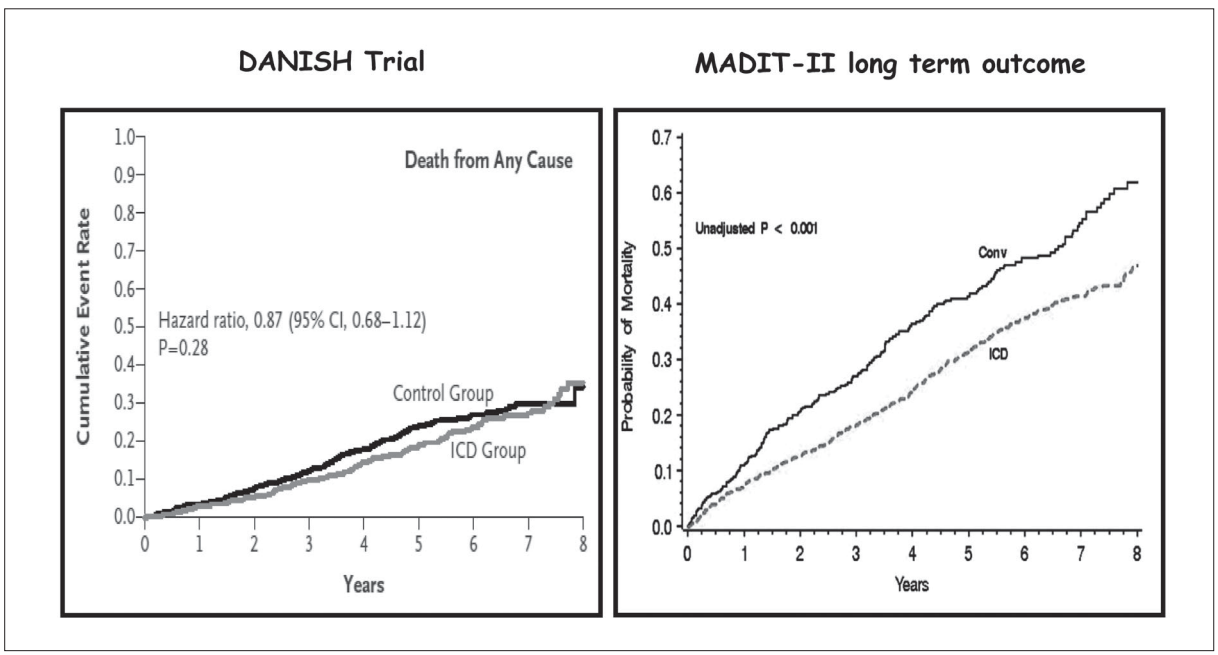

Figure 2. *Total mortality between implantable cardioverter defibrillator and control arm in dilated cardiomyopathy (DANISH trial*[14]*) and ischaemic cardiomyopathy (MADIT-II long term outcome*[15]*). The curves separate and converge overtime for dilated cardiomyopathy, but continue to separate in the ischaemic cardiomyopathy trial.*

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