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Letters

RESEARCH LETTER

Effect of Defibrillator on All-Cause Mortality in Patients With Cardiac Amyloidosis

CA is a restrictive cardiomyopathy caused by extracellular deposition of abnormally folded protein fibrils in the myocardium that manifests as clinical heart failure. In addition to heart failure, a large proportion of patients with CA present with ventricular arrhythmias (VAs) and conduction system disease.[1] The incidence of sudden cardiac death (SCD) has been reported to be as high as 50% in patients with CA and is thought to be related to electromechanical dissociation (EMD) and VAs.[2]

Given the increased risk for SCD, current society guidelines for CA recommend ICD placement if life expectancy is >1 year.[1] However, this recommendation is based on limited evidence and studies have shown mixed results regarding ICD therapy in CA.[1] We performed a systematic review and meta-analysis to determine the effect of ICD implantation on all-cause mortality in patients with CA, and to compare mortality among patients with ICD with CA and other etiologies of nonischemic cardiomyopathy (NICM).

The protocol for the systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[3] Ovid MEDLINE, EMBASE, Scopus, Web of Science, Google Scholar, and EBSCO CINAHL were searched from database inception for studies reporting the effect of ICDs on all-cause mortality in patients with CA were performed in November 2022. A second database search was conducted for studies reporting the effect of ICDs on all-cause mortality in patients with CA as well as for NICM other than CA. The prespecified inclusion criteria were studies with at least 1 year of follow-up and the outcome of all-cause mortality. Review articles, abstracts, or publications in non-English languages were excluded. Study titles and abstracts were screened, and data were extracted independently by 2 investigators (M.H. and M.T.). The year of publication, numbers of participants, baseline characteristics (age, sex, left ventricular ejection fraction, amyloidosis subtype: transthyretin [ATTR] or immunoglobulin light-chain amyloidosis [AL]) were collected. The primary end point was all-cause mortality. Data analysis was performed using ORs.

What is the clinical question being addressed?
Does ICD implantation decrease all-cause mortality in patients with CA?

What is the main finding?
ICD implantation was not associated with decreased mortality in patients with CA.

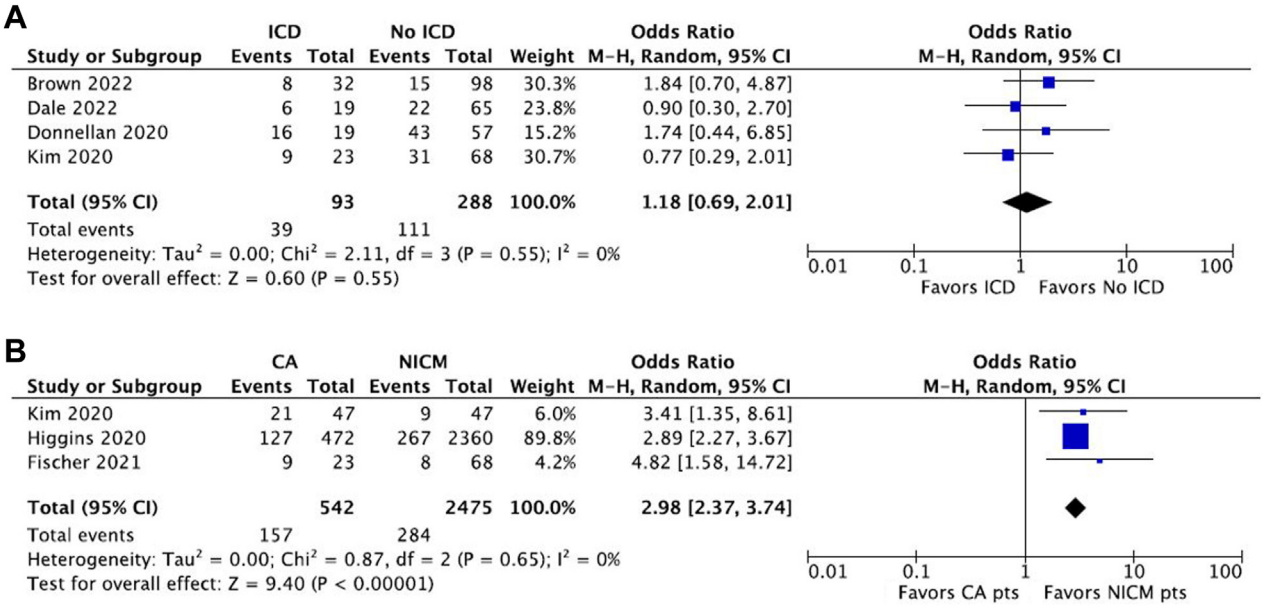
Meta-analysis was performed in Review Manager version 5.4.1 (Cochrane Collaboration). A random effects model was used to estimate the association between all-cause mortality and ICD implantation. The outcomes were reported as ORs with a 95% CI. The extent of heterogeneity was determined by inconsistency values (I^2), ranging from 0% to 100%. A P value <0.05 was considered statistically significant. We used ROBINS-I (Risk Of Bias In Non-Randomized Studies-of Interventions) for bias assessment.

The initial literature search identified 153 candidate studies. A total of 6 were included for meta-analysis. The CA population included 575 patients with mean age 73.2 ± 3.5 years, 84% ± 8% are males and mean left ventricular ejection fraction 36.2% ± 7.4%. ATTR CA was present in 83.3% of subjects and AL CA in the remainder. The mean follow-up was 30.6 ± 11.8 months. ICD indication was primary prevention in 77.9% of patients with CA. ICD implantation was not associated with a mortality benefit in patients with CA (OR: 1.18; 95% CI: 0.69-2.01; $P = 0.55$) (Figure 1A). CA was associated with higher mortality as compared to other NICM etiologies (OR: 2.98; 95% CI: 2.37-3.74; $P < 0.0$) (Figure 1B). Heterogeneity was low with I^2 of 0%. We concluded low to moderate risk of bias.

Our systematic review and meta-analysis evaluating the effect of ICD implantation on mortality in 575 patients with CA suggests 2 important findings based on a limited number of patients. First, ICD implantation was not associated with a mortality benefit in patients with CA. Second, CA was associated with higher mortality as compared to other NICM etiologies among patients with ICDs.

CA is a heterogeneous disease process due to different proteins deposited in variable locations of

FIGURE 1 Forest Plots Showing the Relationship Between Cardiac Amyloidosis and Outcomes



(A) Forest plot showing no significant difference in mortality in cardiac amyloidosis with or without implantable cardioverter-defibrillator. **(B)** Forest plot showing significantly higher mortality in cardiac amyloidosis and implantable cardioverter-defibrillator compared to nonischemic cardiomyopathy and implantable cardioverter-defibrillator. **Blue squares** = point estimate of the study result which gives a representation of the size of the study. The bigger the box, the more participants in the study. **Black diamonds** = point estimate and confidence intervals when you combine and average all the individual studies together. CA = cardiac amyloidosis; ICD = implantable cardioverter-defibrillator; M-H = Mantel-Haenszel method; NICM = nonischemic cardiomyopathy.

the myocardium. This is highlighted by significant differences in prognosis between the 2 most common forms of CA—AL and ATTR—the former carrying a mean survival of <1 year, while the latter ranges from 2.6 to 5.8 years depending upon transthyretin variant.[4] SCD in patients with CA may more commonly result from EMD leading to pulseless electrical activity arrest rather than from VA.[4] In this scenario, the presence of an ICD would not be likely to improve survival. Differences in the mode of death (EMD vs VA) may also explain why CA was associated with significantly higher mortality than other NICM etiologies among patients with ICD. Additionally, CA infiltration into the myocardium has been shown to increase defibrillation thresholds in small series of patients, and therefore, may not effectively protect patients from VA.[5]

Ongoing advances in ATTR CA treatment may continue to improve mortality from nonarrhythmic causes, and ultimately confer an ICD benefit for some patients. As our understanding of the complexity of CA progresses, it is important that we integrate a multidisciplinary team of CA specialists, electrophysiologists, and hematologists to collaborate on the development of a shared decision-making process for ICD implantation in patients with CA.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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