Declining Sudden Death in Heart Failure Questions ICD Patient Selection

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BOSTON, MA — The rate of sudden death in patients with heart failure with reduced ejection fraction (HFrEF) fell by 44% across 12 large trials conducted over the past two decades, encompassing >40,000 patients[1]. The rate was only about 1% at 90 days in the most recent of the trials.

The findings come from a period of growing use of meds that inhibit the neurohormonal underpinnings of heart failure and have been shown to cut the risk of sudden death, observe the authors of the analysis, published July 5, 2017 in the *New England Journal of Medicine*, led by Dr Li Shen (University of Glasgow, Scotland).

The analysis of patient-level data, which excluded patients with LVEF >40% and those who entered the trials with an implantable cardioverter defibrillator (ICD), suggest "that it may be difficult to show a significant benefit of ICD implantation for primary prevention in most patients with heart failure with reduced ejection fraction in the current era," the authors write.

"Most people who have an implant never use it, and as sudden death rates decline, the potential to reduce the risk further also decreases," senior author Dr John JV McMurray (University of Glasgow) told **theheart.org**|Medscape Cardiology.

"Our study, in conjunction with the DANISH trial, argues for physicians to take time to get medical therapy right and only put an ICD in if the patient's LVEF remains persistently low despite this treatment," he said.

DANISH concluded that with contemporary evidence-based medical therapy, ICDs were of limited benefit in patients with nonischemic heart disease.

"Many patients will have an improvement in LVEF above 35% and not need an ICD. There is no need to rush. Early implantation may mean use of an expensive and unnecessary device with only the harms and without the benefit," he said.

Patients in the trials, most of whom had coronary disease, McMurray pointed out, likely received more evidence-based medical therapy than is typical in practice, and often they are younger with fewer comorbidities, so the observed decline in sudden death doesn't necessarily parallel what would be seen outside trials.

But the findings are indeed plausible and consistent with "published data on trends in ischemic heart disease in the United States in the past 20 years," Dr Veronique L Roger (Mayo Clinic, Rochester, MN), who was not involved with this report, said in an interview.

"If we accept that coronary disease is declining, at least as measured by myocardial infarction and unstable angina, then we can potentially hypothesize that some of the cases included in these trials are less likely, over time, to be reflecting ischemic etiology. And therefore, overall the risk of sudden death might go down," she said.

The "signal" of reduced sudden death risk over time in the analysis "is still is subject to residual confounding" despite adjustments even for baseline ICD therapy, Roger said. So the finding "deserves confirmation in other data sets."

The analysis looked only at trials with adjudicated mortality end points, the group reported, and HFrEF was defined by an LVEF cutoff of 40%.

The randomized treatments included statins, beta-blockers, angiotensin-receptor blockers, mineralocorticoid-receptor antagonists, or ICD vs placebo, and in one case, an angiotensin–neprilysin inhibitor vs an ACE inhibitor.

Of the combined 40,195 patients with HFrEF, 3583 (8.9%) experienced sudden death during the follow-up, but the rates in individual trials declined sharply across the decades. The hazard ratio for sudden death at the start of the period compared with the end, adjusted for randomization group (active therapy vs control) and other possible confounders, was 0.56 (95% CI 0.33–0.93, P=0.03).

The cumulative 90-day rate of sudden death ranged from 2.4% in the earliest trial, RALES, down to 1.0% in the trial completed most recently, PARADIGM-HF. The corresponding cumulative mortality at 1 year ranged from 6.7% to 3.7%, respectively. Mortality at 3 years went from 13.4% to 8.8% respectively.

The observed annual rate of sudden death fell from 6.5% in RALES to 3.3% in PARADIGM-HF (*P*=0.02 for trend).

The findings highlight a current challenge with ICD therapy: how to provide it to patients mostly likely to benefit, rather than the much broader population based on its current LVEF-dominated indications, according to both McMurray and Roger.

"If sudden death rates are low and hard to reduce much further in absolute terms, at what point does the benefit of an ICD no longer outweigh the harm?" posed McMurray. "We need to figure out who really needs an ICD."

Almost a fifth of ICD recipients have reported inappropriate delivery of device therapy, he said. "These constitute up to half of all shocks, despite advances in device programming, and are associated with an increase in mortality."

Other complications of ICD implantation, he noted, include "lead fracture, device failure, and infection necessitating system extraction. The potential benefits of ICDs must always be weighed against these risks."

That is especially true in older patients, who are probably at increased risk of complications from receiving an ICD, he said. "These are also the patients less likely to benefit from an ICD."

Sudden death is rare enough so that many trials may have been underpowered for determining its risk, Roger noted. "One of the implications is that it would be desirable to improve risk prediction of sudden death among patients with heart failure," she agreed.

Roger pointed to several independent, possible predictors of sudden death in the meta-analysis, which included advanced age, being male, lower LVEF, lower systolic BP, ischemic etiology, and a history of renal dysfunction, MI, or diabetes.

"I'm not sure they're very actionable for us as practitioners," she said, but "this should be a call for more personalized risk prediction in this patient population."

Shen had no relevant financial relationships. McMurray discloses receiving fees or travel support or serving as principal or coprincipal investigator or in other leadership positions for numerous clinical trials both inside and outside the scope of the current report. Disclosures for the coauthors are listed in the paper. Roger had no relevant financial relationships.

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References

1. Shen L, Jhund PS, Petrie MC, et al. Declining risk of sudden death in heart failure. *N Engl J Med* 2017; 377:41-51. Abstract

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