

EDITORIAL VIEWPOINT

Primary Prevention of Sudden Cardiac Death in Asia*



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Sudden cardiac death (SCD) is a worldwide problem; however, the incidence differs widely among Asia, Europe, and the United States, as well as among different Asian countries.¹ For example, the SCD rates in the United States/Europe, China, Japan, and South Korea were reported to be 50 to 100, 40 to 45, 30 to 35, and 30 per 100,000 person-years, respectively. There are several reasons for the differences. The definition of SCD, and the frequency of autopsies including genetic assessment, affect the number of deaths labeled as sudden in a population. As most cases of SCD are due to underlying coronary artery disease, the lower incidence of coronary artery disease in Asian individuals contributes to a lower SCD rate. Racial differences in SCD risks with similar disease are significant. Implantable cardioverter-defibrillators (ICDs) are proven to be useful for primary prevention of SCD; however, the frequency of ICD use also differs between countries in Asia and North America/Europe and cannot be solely explained by difference in SCD rate. For instance, in the PARADIGM-HF (Prospective Comparison of ARNI with an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial,² ICDs were used in 54% of patients in North America but in only 1.7% of Asia-Pacific patients.² Guidelines for ICD prescription are based on the left ventricular ejection fraction (LVEF), which may not fully reflect the risk of SCD

in a patient. Competing causes of death that are non-sudden in an aging population are important issues. Furthermore, although the risk of SCD is lower in those subjects with normal LVEF, because of their much larger number, they contribute to the majority of SCDs. Finally, SCD risk in a patient should not be a one-time assessment. Rather, ongoing changes in risk profile, such as development of comorbidities, advancing age, and improved medical therapy should be considered.

Nowhere in the world are these issues more relevant than in Asia. There is a wide diversity of races, health care systems, and social and economic conditions. There is also a scarcity of data on the incidence of SCD in Asia, particularly in emerging countries.

Two important reviews in this issue of *JACC: Asia* provide insights on this important topic. Younis and Wilkoff³ and Ueda et al⁴ reviewed the U.S.⁵ and European guidelines⁶ for ICD use in primary prevention of SCD in ischemic cardiomyopathy (ICM). ICDs have been shown to be life-saving in major randomized controlled trials and also in meta-analyses,⁷ based on randomized trials performed between 1996 and 2005.⁸⁻¹² After 40 days of index myocardial infarction on top of the optimal medical therapy (OMT), ICD therapy reduced all-cause mortality by 23% to 54% over a period of 20 to 46 months. Thus, there is uniform agreement in both the U.S. and European guidelines to recommend ICD therapy in patients with NYHA functional class II-III symptoms due to ICM and an LVEF $\leq 35\%$ despite OMT to receive ICD as a Class Ia indication. In those patients with LVEF $\leq 30\%$ in NYHA functional class I symptoms as a 1B and 1A indication, respectively. Indeed, we have also shown that in medically stabilized patients fitting MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) criteria,¹³ Chinese patients have a similar outcome in SCD as Caucasian patients, suggesting applicability of ICD in an Asian population.

The authors³ also reviewed ICD therapy in non-ischemic cardiomyopathy (NICM), including the more recent mortality neutral results of the DANISH

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(Defibrillator Implantation in Patients with Non Ischemic Systolic Heart Failure) trial.¹⁴ Again, the overall meta-analysis¹⁵ documents the benefit of mortality reduction in primary prevention using ICDs over OMT. The DANISH trial, which used cardiac resynchronization therapy in a large proportion of patients, still showed reduction in SCD as a secondary endpoint. In those who are younger than 70 years, or in those without diabetes, ICD would show mortality benefit.¹⁶ An overall mortality and SCD rate reduction by 23% and SCD of 57% were documented in a recent meta-analysis.¹⁵ Because of the DANISH trial, the European Society of Cardiology (ESC) guideline downgraded the ICD indication for NICM as a Class IIa indication. The authors also highlighted the “dark side” of ICD therapy, including the risk of implantation, long-term issues of the defibrillator leads, such as fracture and infection, and the risk of inappropriate therapy. New medical therapy, such as sodium-glucose cotransporter-2 inhibitor and neprilysin inhibitors, have been shown to improve overall survival of patients with heart failure, and thus reduce the overall efficacy of ICDs. This is particularly relevant in Asia, as the incidence of ICD use is lower, as well as the perceived or reported lower SCD rate. Thus, additional risk stratification, such as the assessment of myocardial scar for primary prevention, will be useful.

Uede et al⁴ presented more granular data on the unsolved issues of ICD underutilization in Asia. They discussed population differences in underlying heart disease for heart failure and the rate of appropriate ICD therapy compared with Western countries. They highlighted the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry,¹⁷ which showed great disparity in ICD use: 52.5% in Japan, 17.9% in China, and 8.1% in South Korea. In the Improve SCA (Improve Sudden Cardiac Arrest) study,¹⁸ which had included many countries in Asia, the reasons for patient refusal of ICDs included inability to pay for the device (53.8%) and not believing in ICD benefits (19.4%). Out-of-pocket payment is more prevalent in the lower income regions, such as Indonesia (46.9%), Philippines (53.7%), and India (62.4%), further limiting patient access to ICD therapy.^{19,20} Knowledge and acceptability of ICDs apply not only to patients but also at the physician level. The authors also give insight into the ethnic issue on SCD rate. They discussed that the outcome of out-of-hospital cardiac arrest rate is much lower in Asian than Western countries, reflecting in part ethnic and probably efficacy of the resuscitation system in different regions.²¹ In relation to ICD therapy, several studies in Japan showed an equal rate of ICD therapy (shock and

antitachycardia pacing) in secondary prevention compared with Western countries, and a similarly reduced therapy rate for primary prevention, suggesting ICD is as effective when implanted. The prevalence of ICD use is likely to increase in Asia,^{22,23} due to increasing prevalence of coronary artery disease and an aging population.

Both reviews also highlighted the temporal reduction of SCD rate of hypertrophic cardiomyopathy, and major difference in the use of primary prevention ICD, not only between North America and Europe, but between European and Asian countries.^{24,25} There appears to be a much lower rate of ICD implantation in Asia (2% vs 19%), but a higher mortality and device therapy rate. Cardiac sarcoidosis appears to be increasingly recognized in Asia, with ICD prescription generally recommended for those with the need of permanent pacing.

These 2 scholarly reviews are limited by the paucity of accurate data on incidence of SCD in many countries in Asia. Most of the trials cited for efficacy of ICD in primary prevention are more than 10 years old, with few Asian individuals included in the studies. Improvements in medical therapies for heart failure will decrease the impact of ICD on total mortality.

How should we proceed in primary prevention of SCD in Asia? It is unlikely that a large-scale randomized controlled trial of ICDs vs modern medical therapy will be performed. However, we can learn a lot more from large cohort studies in Asia, particularly if including most countries, on the outcome of both ICD-treated and non-treated patients, not only in survival, but the rate of ICD therapy, and complications from inappropriate shocks and implantation. Randomized controlled trials of ICD application in focus diseases such as in the selection of patients for ICDs in hypertrophic cardiomyopathy and sarcoidosis in Asia will further improve our understanding. In the meantime, the bulk of data do suggest that ICDs remain an effective therapy to reduce SCD and mortality in primary prevention, both in ICM and NICM. Education for both patients and physicians, and accessibility to ICDs in Asia, remain major barriers.

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