

# Practice viewpoints: AICD, who and when?

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## ABSTRACT

Automatic implantable cardioverter-defibrillator (AICD) is a costly but effective treatment modality for the prevention of sudden cardiac death (SCD). Causes of SCD are age-dependent, disease-specific and affected by racial/ethnic differences. Atherosclerotic heart disease (ASHD) is the most frequent underlying disease in individuals  $\geq 35$  years old. Available information suggests that Asians have a lower rate of SCD compared with African black individuals and Caucasians. Whether it is for secondary or for primary prevention, physicians should be educated to perform a thorough diagnostic work-up and be able to identify transient and/or reversible causes of lethal ventricular tachyarrhythmias such as acute myocardial infarction, residual ischaemia, electrolyte imbalance, adverse effect of drugs, valvular heart diseases, etc before contemplating AICD implantation. Correction of these reversible causes may avoid the necessity of AICD implantation. The status of left ventricular function is not sufficiently specific for guiding AICD implantation in ASHD patients after acute myocardial infarction. The urgent need is to develop better biological or physiological markers for risk stratification so that patients who would actually benefit from AICD implantation can be readily identified. Such an approach will make the use of AICD more cost-effective. Based on molecular genetic data obtained from patients with inherited structural cardiovascular diseases and malignant arrhythmogenic disorders in which the risk of SCD appears to be gene- and/or mutant-specific, a continuous search for genetic markers for better risk stratification is warranted in patients suffering from ASHD.

Implantation of automatic implantable cardioverter-defibrillator (AICD) is a well-established therapeutic modality for the prevention of sudden cardiac death (SCD),<sup>1</sup> but its cost and follow-up care are expensive. The estimated cost per AICD implantation is about USD \$30 000 (\$10–15 000 in Asia), and the average AICD replacement time is 5 years due to its short battery life (Medtronic, The Asian representatives, personal communication). In addition, there are potential complications related to AICD implantation. These include bleeding, pericardial effusion, infection, inappropriate shocks and lead fracture causing AICD malfunction. Less appreciated adverse effect are poor psychosocial adjustment (eg, fears of shock, device malfunction, death and embarrassment)<sup>2</sup> and an increased risk of congestive heart failure (CHF) attributable to worsening of cardiac function induced by repeated shocks<sup>3</sup> and/or frequent use of right ventricular pacing with dual-chamber programming.<sup>4</sup>

Since patients who survive a cardiac arrest are often older with multiple or severe comorbidities at risk of death resulting from causes other than recurrent ventricular tachyarrhythmias, clinicians

should be aware that there are subgroups of patients who may not benefit from AICD implantation: those who may die without or prior to the first appropriate AICD therapy (eg, patients with advanced CHF) and those who would never manifest a sustained ventricular arrhythmia.<sup>5–6</sup> Most information regarding SCD has emanated from the US and Europe. A critical question to ask is that “should we, as Asians, follow the guidelines for AICD implantation set forth by American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS)?”

## SECONDARY PREVENTION OF SUDDEN CARDIAC DEATH

For the management of patients who have already experienced a serious sustained ventricular tachyarrhythmia (secondary prevention), the indication of AICD implantation is relatively clear, as AICD is highly effective in terminating ventricular tachycardia/ventricular fibrillation, thereby aborting SCD.<sup>1</sup> In this regard, AICD implantation is very likely underused in Asia. Taking Taiwan and Hong Kong as examples, with respective populations of 23 million and 7 million, the numbers of new AICD implantations are approximately 160 and 210 per year, respectively (Medtronic, The Asian representatives, personal communication). Despite its being underused for secondary SCD prevention, clinicians should be educated to meticulously exclude non-cardiac causes of abortive sudden death (eg, asthma, heat stroke, drowning, head trauma, ruptured cerebral artery, blunt chest trauma, aortic dissection, pulmonary embolism, etc) and to rule out acute myocardial infarction and all reversible causes of lethal ventricular arrhythmias such as electrolyte imbalance, drug-induced proarrhythmia and valvular heart disease (eg, severe aortic stenosis) before contemplating AICD implantation.

For practical purposes, a diagnostic workup such as exercise testing with or without thallium-201 imaging aimed at identifying the presence or absence of active myocardial ischaemia in patients with atherosclerotic heart disease (ASHD) should be included. The Coronary Artery Bypass Graft (CABG) Patch trial<sup>8</sup> has shown that implantation of AICD is not beneficial in patients who have already undergone CABG. Additionally, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial Nuclear Substudy<sup>9</sup> has revealed that the extent of residual myocardial ischaemic burden under optimal medical therapy with or without percutaneous coronary intervention positively and proportionally predicts future occurrence of cardiac events. Taken together, it appears that total revascularisation or maximal reduction in the ischaemic burden ought to be considered as an important therapeutic goal for the prevention of SCD.

## PRIMARY PREVENTION OF SUDDEN CARDIAC DEATH

For primary SCD prevention, the indication of AICD implantation remains debatable. While ASHD is the most common cause of SCD in individuals who are 35 years or older, the risk of SCD is highest during and immediately following acute myocardial infarction (AMI) and then declines thereafter.<sup>10</sup> Nevertheless, one-fourth of arrhythmic deaths still occur in the first 3 months and one-half within the first year after AMI, especially those with left ventricular dysfunction.<sup>10</sup> Accordingly, the 2008 ACC/AHA/HRS guidelines<sup>7</sup> recommend that AICD be implanted prophylactically in ASHD patients with left ventricular ejection fraction  $\leq 35\%$  at least 40 days following acute myocardial infarction. However, it was noted in one study<sup>11</sup> that only 50% of patients who had had AICD implanted for primary SCD prevention received appropriate AICD therapy for ventricular tachyarrhythmias compared with 74% of patients for secondary SCD prevention during a follow-up period of 3 years. And in another study,<sup>12</sup> appropriate AICD therapy was found to be twice as likely in patients receiving AICD for secondary prevention compared with those for primary prevention of SCD during a follow-up period of 7 years. Thus, it appears that not all patients recovering from AMI with left ventricular dysfunction would need prophylactic AICD implantation, as some of them may not manifest sustained ventricular tachyarrhythmias.

Furthermore, an important issue to ponder is that there are indeed racial/ethnic differences in the rate of SCD. Based on the 1998 USA (US) Vital Statistics data,<sup>13</sup> SCD occurred in 456 076 (63%) of 719 456 cardiac deaths aged  $\geq 35$  years, and ASHD was the most frequent underlying disease (58.9–62.9%) followed by cardiomyopathy and arrhythmia (8.8–11.6%). Notably, Asian/Pacific Islanders were found to have the lowest rate (213 per 100 000) of SCD compared with American Indian/Alaskan native (259 per 100 000), white (407 per 100 000) and African-Americans (503 per 100 000). Also of note, in the State of Hawaii, it was observed that non-Hawaiians, mainly Asian ancestry groups (eg, Filipino and Japanese), had significantly lower cardiovascular mortalities compared with Hawaiians (68.5 vs 375.9 per 100 000) despite having similar cardiovascular risk factors (eg, diabetes, hypertension, hyperlipidaemia, etc).<sup>14</sup> And in a community population-based cohort of 3602 residents (age  $\geq 35$  years, 47% male) in Taiwan, a 10-year follow-up analysis<sup>15</sup> showed an SCD rate of 73 per 100 000, which was much lower than that of the US as described above. We realise that the data of a small community may not represent the entirety of a country with a population of 23 million. Nonetheless, it does urgently call for further epidemiological studies on the incidence of SCD in many other regions in Asia.

## ROLE OF MEDICAL THERAPY IN THE PREVENTION OF SUDDEN CARDIAC DEATH WITH AND WITHOUT AICD IMPLANTATION

Antiarrhythmic drug therapy is usually applied as an adjunctive therapy in AICD patients who experience frequent shocks or less commonly as primary therapy in patients who refuse or are not candidates for AICD implantation. Under these circumstances, amiodarone is frequently the drug chosen for this clinical setting.<sup>16</sup> Another relevant aspect of medical therapy is that AICD therapy often shifts arrhythmic death to non-arrhythmic death, especially CHF in this subset group of patients. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) study<sup>12</sup> reported that prophylactic AICD implantation in patients with left ventricular dysfunction and impaired cardiac autonomic function 6–40 days after AMI did not alter the overall mortality; the AICD group had a substantially lower

rate of death due to arrhythmia than the control group (1.5% vs 3.5% per year) but had more deaths from non-arrhythmic causes, mostly CHF, compared with the control group (6.1% vs 3.5% per year). Consequently, an aggressive medical regimen against CHF should be implemented in patients who are candidates for AICD implantation. A list of pharmacological agents including beta-adrenergic blocking agents, angiotensin II-converting-enzyme inhibitor, angiotensin II-receptor blockers, statins and aldosterone antagonists have individually been shown to improve CHF and reduce rates of total mortality and SCD.<sup>17</sup> In fact, these agents should be given soon after AMI to reduce ventricular remodelling if there are no contraindications.

## ROLE OF MOLECULAR GENETICS IN THE RISK STRATIFICATION OF SUDDEN CARDIAC DEATH

In patients who are 35 years or younger, there is an increasing incidence of SCD caused by inherited structural cardiovascular diseases and malignant arrhythmogenic disorders.<sup>18</sup> In the former, most frequently encountered are hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular dysplasia/cardiomyopathy and dilated cardiomyopathy, and in the latter, congenital long QT syndrome (LQTS), Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT) and short QT syndrome. The risk of SCD in these various inherited diseases/disorders appears to be gene- and/or mutant-specific and affected by racial and ethnic differences.<sup>18</sup>

For examples, Brugada syndrome, also referred to as “sudden unexpected nocturnal death syndrome,”<sup>19</sup> is endemic in east and southeast Asia, particularly in northeastern Thailand, Philippines and Cambodia with a mortality as high as 38/100 000. Approximately 30% of patients with such a syndrome have mutations in SCN5A resulting in reduced Na<sup>+</sup> current. Interestingly, the prevalence of the Brugada-type ECG pattern in the asymptomatic South East Asian population is also higher (1–3%) compared with European (0.05%) and Japanese (0.45%) populations.<sup>18</sup> CPVT is caused by mutations in the gene encoding either the ryanodine receptor (RyR2) or calsequestrin (CASQ2).<sup>20</sup> Ventricular tachycardia usually occurs during enhanced sympathetic tone (eg, physical activity or acute emotional distress), and the mortality is as high as 30–50% by the age of 40.

In LQTS, LQT1 (KCNQ1, 30–35%), LQT2 (KCNH2, 25–30%) and LQT3 (SCN5A, 5–10%) constitute the majority of the cases.<sup>21</sup> In LQT1, A341V patients are more likely to have cardiac events compared with non-A341V patients (75% vs 24%) having a rate of SCD as high as 14%.<sup>22</sup> LQT7 and LQT8 are rare subtypes of LQTS, also known as Andersen–Tawil syndrome and Timothy syndrome, respectively.<sup>23 24</sup> LQT7 is caused by mutations in KCJN2 which encodes the cardiac and skeletal muscle inward rectifier K<sup>+</sup> channel, Kir2.1, and LQT8 is due to mutations in CACNA1C that encodes the pore-forming  $\alpha$ -subunit of the cardiac L-type Ca<sup>2+</sup> channel. LQT7 patients may live into adulthood, but in contrast, LQT8 patients seldom survive beyond 3 years of age.

In HCM, cardiac myosin binding protein C (MYBP3) and beta-myosin heavy chain (MYH7) are most frequently found, 42% and 40%, respectively.<sup>25</sup> In 22 index cases with a malignant course, MYH7 was the most prevalent gene (45%) followed by MYBPC3 (18%), cardiac troponin I (TNNI3) (14%) and myosin ventricular regulatory light chain2 (MYL2) (14%). In each protein, “hot spots” associated with malignant prognosis have been identified—for example R403, R719 and R663 in MYH7, R502, D778 in MYBP3, R162 in TNNI3 and R58 in MYL2.<sup>26</sup> Of

interest, a subset of HCM patients with mutations in the cardiac troponin T (TNNT2) gene have a high risk of SCD associated with no or mild left ventricular hypertrophy, and another subset of HCM patients with mutations in MYH7 and TNNT3 may exhibit a restrictive phenotype associated with a poor prognosis because of severe physical limitations, diastolic heart failure and high rates of atrial fibrillation/flutter and stroke.

Chinese HCM patients have certain features distinctively different from those of Caucasian patients.<sup>27</sup> Specifically, they have a high percentage of phenotypic expression of non-obstructive apical hypertrophy in the left ventricle (41% vs 3% in non-Asians and 15% in Japanese) and a high incidence of atrial fibrillation (35% vs 20%) but a relatively low annual mortality (1.6% vs 5.6% in the literature). In contrast to the experience of non-Asian patients, HCM appeared to be more severe in Chinese women, as the female sex is the only independent predictor of mortality. Genetically, MYH7 and MYBCP3 are also found to be the predominant genes similar to those reported in the Western world,<sup>27</sup> but the most common hot and malignant mutation R403Q in MYH7 identified in Caucasians has not been documented.

To date, no genetic markers of SCD can be demonstrated in patients with ASHD. Nevertheless, among various ethnicities (black, white, Asian and Hispanic), certain variants of SCN5A and distinct variants in LQTS-causing K<sup>+</sup> channel genes (KCNQ1, KCNH2, KCNE1 and KCNE2) can be found exclusively in the black cohort.<sup>28</sup> Similarly, in studies searching for genetic factors predisposing to arrhythmias associated with myocardial ischaemia/infarction, five rare missense variants in SCN5A (A572D, G615E, F2004L, A572D and A572F) can be seen in 10% (6/60) of white elderly female SCD cases (age 60.8) but in 0% (0/53) of the male counterpart (age 66.5).<sup>29</sup> All these genetic variants may alter the repolarisation properties of cardiac tissues, thereby mediating an increased susceptibility to arrhythmias in the settings of diseases or drug ingestion.

## CONCLUSION

The decision as to “who and when for AICD implantation” poses a clinical challenge. Because causes of SCD are age-dependent, disease-specific and affected by racial and ethnic differences, the decision-making should be individualised. A detailed medical history and a thorough physical examination along with functional diagnostic work-ups remain the mainstay for the decision-making process. Apart from having a different spectrum of causes of SCD, Asians seem to have a relatively lower rate of SCD compared with African black individuals and Caucasians. Current ACC/AHA/HRS guidelines<sup>7</sup> expanding indications for prophylactic AICD implantation do not appear to be readily applicable in Asians.

It is apparent that left ventricular dysfunction is not a sufficiently specific parameter for guiding AICD implantation after AMI. The urgent need is to develop better biological and/or physiological markers for risk stratification so that patients who would actually benefit from AICD implantation can be readily identified. Such an approach will make the use of AICD more cost-effective. As inferred from molecular genetic data obtained from patients with inherited diseases/disorders causing SCD, a continuous search for genetic markers for better risk stratification is warranted in patients with ASHD.

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