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Editorial

Implantable cardioverter-defibrillator therapy in primary versus secondary prevention: Reliable prediction of appropriate therapies and mortality is still an unmet need

The implantable cardioverter-defibrillator (ICD) is a well-established therapeutic modality in survivors of life-threatening ventricular tachyarrhythmias, such as ventricular tachycardia or ventricular fibrillation (secondary prevention) and in patients with advanced left ventricular (LV) dysfunction at risk of ventricular tachyarrhythmia (primary prevention). The results of major ICD trials conducted a decade ago show that patients in primary prevention have more advanced heart diseases and co-morbidities and obtained less frequent appropriate therapy than those in secondary prevention. However, follow-up studies using populations receiving the device treatment that directly compare baseline characteristics and rates of ICD therapy and mortality in primary versus secondary prevention are rather limited. The article by Kotake et al. [1] published in this issue of *Int J Cardiol Heart Vasc* reports results of the Nippon Storm Study, an observational study cohort in which 1570 ICD-patients were enrolled from 48 cardiovascular centers in Japan. Patients in primary prevention had a higher New York Heart Association (NYHA) functional class, a lower LV ejection fraction (LVEF), a higher prevalence of non-ischemic heart disease and obtained more often cardiac resynchronization therapy with a defibrillator (CRT-D) device than patients in secondary prevention. The cumulative probability for a first appropriate ICD therapy was lower in patients in primary than in secondary prevention. Of note patients in primary prevention who received a first appropriate ICD therapy had a higher chance to subsequently obtain an appropriate therapy, just like patients in secondary prevention, suggesting that this subgroup in primary prevention may have electrophysiological features and outcomes that differ from the rest population of the primary prevention group. The authors conclude that once patients in primary prevention experience a first appropriate ICD therapy subsequent therapy appears justified and should be considered. It would be of importance to develop, test and validate risk stratification markers to detect the subgroups with arrhythmogenic substrate as well as to improve patient selection for primary prophylactic ICD implantation, as suggested by Disertori et al. [2].

Potential differences between patients obtaining an ICD therapy for primary and secondary prevention were recently assessed in 2134 individuals in the Leiden University Medical Center [3] and in 2349 patients from the Israeli ICD Registry [4]. In both studies the primary prevention group had a higher NYHA functional class and a lower LVEF than the secondary prevention group and ischemic heart disease was predominant etiology in both groups. The cumulative probability for a first appropriate therapy was lower in the primary than the secondary prevention group (9 and 21% at 30 months in the Israeli Registry, 37 and 51% at 5-year follow-up in the Leiden Study, respectively). The incidence of all-cause mortality was comparable between the primary and the secondary prevention groups (14 and 15% at 30 months in the Israeli Registry, 25 and 23% at 5-year follow-up in the Leiden Study, respectively). The data from the Nippon Storm Study match the results of the two studies above: 13 and 21% at 1 year, 27 and 36% at 3 years for a first appropriate therapy, 14 and 12% at 3 years for mortality, respectively [1].

The Leiden Study [3] showed that patients in primary prevention have a 2-fold higher chance for a subsequent appropriate shock when compared with a first appropriate shock in the secondary prevention group, although this issue was not specifically discussed by the authors. The Nippon Storm Study [1] also reported a higher chance to subsequently obtain an appropriate therapy in the primary prevention group but was unable to identify any single factor that predicts a subsequent appropriate therapy, likely because the sample size was too small to uncover the potential predictive values of gender, age, LVEF, device, heart disease etiology or additional therapy. A systemic review by Germano et al. [5] demonstrated that the incidence of appropriate therapies is related to factors which can be grouped into 4 categories: basal clinical characteristics, medical therapy, device features including programming and device-related proarrhythmia. Heart failure (HF) severity appears an important predictor and determinant for appropriate therapies. Patients with NYHA class III HF have a 2-fold higher chance to experience appropriate ICD shocks as patients with class I or II HF [6,7]. Moreover, a sub-analysis of MIRACLE ICD, a multicenter InSync ICD randomized clinical evaluation trial, showed that patients in primary prevention had a significant lower frequency of appropriate episodes at significantly faster cycle lengths and that these episodes were more likely to be classified as ventricular fibrillation by the device and thus received shock therapy (42% in the primary versus 19% in the secondary prevention group) [8]. Thus, differences in arrhythmia detection and device programming and therapy might contribute to the different chance to subsequently provide an appropriate therapy in the primary versus secondary prevention groups.

The present study [1] provided some data that give some hint about the potential cause of death. Of 985 patients, 124 (13%) (72 in primary and 52 in secondary prevention) died during the follow-up of 3 years, with 112 (90%) being ascribed to non-sudden cardiac death. In the Israeli Registry [4], mortality rate was 11%

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and only 35% of these deaths were considered of cardiac causes. The different rate of deaths due to cardiac causes likely reflect the higher number of patients with non-ischemic heart disease in the Nippon Storm Study versus the Israeli Registry, with non-sudden deaths as a consequence of HF worsening being more likely in the Nippon Storm Study.

Adjuvant medication with proven beneficial effects on mortality in HF patients including β-blockers, angiotensin-converting-enzyme inhibitors or angiotensin-II-receptor blockers and miner-alocorticoid-receptor antagonists is widely used in ICD patients. Certainly, some classes of medical therapy and amiodarone reduce appropriate therapies but are not necessarily connected to a reduction in mortality [5,9]. A recent meta-analysis of 8 RCTs of drug therapy for HF, including 31,701 HF patients of whom 11.5% (3645 patients) had an ICD, demonstrated that there were no significant differences in all-cause death and sudden cardiac death in studies published either before or after 2008, and that the use of ICD was consistently associated with a reduced risk of all-cause death and sudden cardiac death, indicating that the impact of ICD on preventing sudden death was not affected by contemporary optimized medical therapy [10]. In addition, the high prevalence of HF medication in patients with electrical storm does not alter the poor outcomes [11]. Thus, development of novel drugs to attenuate HF progression is an unmet need which is expected to improve prognosis. Based on current understanding of HF pathophysiology, mitochondrial dysregulation, abnormal Ca^{2+}-handling characterized by sarcoplasmic reticulum ryanodine receptor dysfunction and overactivity of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), an established cardiomyopathic and proarrhythmic signaling molecule, appear as promising targets [12–16]. Dynamic phosphorylation-dependent regulation of key cardiac proteins by phosphatases also importantly contributes to HF pathophysiology [17]. A mitochondria-targeted antioxidant (MitoTEMPO) reverses proteome remodeling by mitochondrial ROS scavenging in a guinea pig model of non-ischemic HF [18]. A novel ATP-competitive selective CaMKII inhibitor (AS105) improve contractility in human failing hearts and sarcoplasmic reticulum dysfunction in murine failing cardiomyocytes [19]. Future clinical trials assessing the efficacy of such novel treatment approaches are expected to foster the development of innovative treatment strategies to prevent death in ICD patients with structural heart diseases and reduced LVEF.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Y. Tsuji has nothing to disclose. D. Dobrev is a member of the scientific advisory boards of OMEICOS Therapeutics GmbH and Acesion Pharma.

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