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Review Article

Tools for risk stratification of sudden cardiac death: A review of the literature in different patient populations

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ABSTRACT

While various modalities to determine risk of sudden cardiac death (SCD) have been reported in clinical studies, currently reduced left ventricular ejection fraction remains the cornerstone of SCD risk stratification. However, the absolute burden of SCD is greatest amongst populations without known cardiac disease. In this review, we summarize the evidence behind current guidelines for implantable cardioverter defibrillator (ICD) use for the prevention of SCD in patients with ischemic heart disease (IHD). We also evaluate the evidence for risk stratification tools beyond clinical guidelines in the general population, patients with IHD, and patients with other known or suspected medical conditions.

1. Introduction

In spite of the advances in modern technology, accurate identification of the patient who will experience sudden cardiac death (SCD) remains one of the holy grails of cardiology. The closest the clinician can come to prediction is an estimation of risk for this event which is likely to be terminal, and to determine an approximate categorization of patients into high and low risk groups. Appropriate high risk patients can be offered an implantable cardioverter defibrillator (ICD), the only currently available option for SCD prevention. However, the ICD is incompletely effective in preventing SCD since it treats only ventricular tachyarrhythmias but not electromechanical dissociation/pulseless electrical activity in the failing heart.

The overall annual incidence of SCD, based on extrapolation of data from the United States, is approximately 1 in 1000 adults over the age of 35 years.[1] While SCD occurs in a higher proportion of adults with traditional cardiac risk factors and a history of heart disease, the absolute number of SCDs which occur in the general population by far outnumber the absolute number of SCDs in the high risk groups. Thus the majority of SCD accrues from the general population, in whom there are no currently available screening tools.

Prevention of SCD can be categorized into primary prevention (i.e., in patients with no prior history of SCD), and secondary prevention (i.e., in patients with a history of resuscitated cardiac arrest, unstable ventricular tachycardia (VT), ventricular fibrillation (VF), or syncope with high risk features). The focus of this review will be primary prevention

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of SCD in adults; ICD use for secondary prevention of SCD will be discussed briefly for completeness.

We present here an enumeration and summary of prospective clinical studies evaluating SCD risk in three categories of patients: the population of patients with ischemic heart disease (IHD), populations of patients with other high-risk conditions, both cardiac and non-cardiac, and the general population. Only studies with a sample size of at least 200 patients were included in this review. The tools available for risk stratification of SCD can be broadly categorized as follows: historical factors, autonomic parameters, biomarkers, characteristics of the surface ECG, invasive electrophysiological study (EPS), left ventricular ejection fraction (LVEF), and assessment of myocardial scar burden. Populations with congenital disorders known to carry a high risk of SCD, namely long QT syndrome, short QT syndrome, Brugada syndrome, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, tetratogy of Fallot, Wolff–Parkinson–White syndrome, and idiopathic VT are excluded from this review, and addressed elsewhere in this supplement.

2. Primary prevention of SCD in patients with ischemic heart disease (IHD)

2.1. *Left ventricular ejection fraction (LVEF)*

The mainstay of current clinical guidelines in the determination of patients at high risk for SCD is the LVEF. LVEF has been recognized as a predictor of overall cardiac mortality in IHD patients since the 1980's.[2] For this reason, clinical trials evaluating the efficacy of the ICDs in primary prevention of SCD have consistently used LVEF cut-offs in the selection of patients. Large clinical trials on SCD risk stratification over the last 20 years have all proven a reduction in SCD with ICD use in patients with reduced LVEF.

In 1999, the Multicenter Unsustained Tachycardia Trial (MUSTT), showed that amongst 704 coronary artery disease patients with LVEF ≤40% asymptomatic non-sustained ventricular tachycardia (NSVT), and inducible sustained ventricular tachyarrhythmias on EPS, ICD therapy decreased the risk of SCD by 27% over a 2 year follow up period. In comparison, anti-arrhythmic drug therapy was not found to be beneficial in reducing the risk of SCD. Patients who were inducible to sustained VT (whether treated with anti-arrhythmic drugs or not) fared worse than non-inducible patients, highlighting the ability of EPS to stratify risk.[3] In 2002, the Multicenter Automatic Defibrillator Implantation Trial (MADIT II) showed that amongst 1232 patients following myocardial infarction (MI) with LVEF ≤30%, prophylactic ICD implantation decreased the rate of SCD by over 30% over a follow up period of 20 months.[4] In 2005, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), showed that amongst 2521 New York Heart Association (NYHA) class II or III heart failure patients (due to both ischemic and non-ischemic causes) with LVEF ≤35%, ICD implantation reduced overall mortality by 23% over a median follow up period of 45.5 months.[5]

Clinical trials directly evaluating the risk of SCD among various LVEF strata are comparatively fewer. In 2008, the Improved Stratification of Autonomic Regulation (ISAR-risk) study showed that amongst 2343 survivors of MI in sinus rhythm, LVEF ≤30% predicted increased all cause mortality and SCD compared with LVEF >30%.[6] The Risk Estimation Following Infarction, Noninvasive Evaluation (REFINE) trial in 2007 showed that amongst 322 post-MI patients, LVEF ≤30% as compared with LVEF >30% had an increased risk of SCD or resuscitated cardiac arrest (HR 3.30, $p = 0.005$).[7] This paucity of trials directly comparing SCD risk in different LVEF strata contributes to the discordance of LVEF cut-offs across various published clinical guidelines for primary prevention ICD implantation.[8] The most recent 2013 consensus guidelines on appropriate use of ICD for the primary prevention of SCD in IHD are summarized in Fig. 1.[9] In these latest guidelines, LVEF

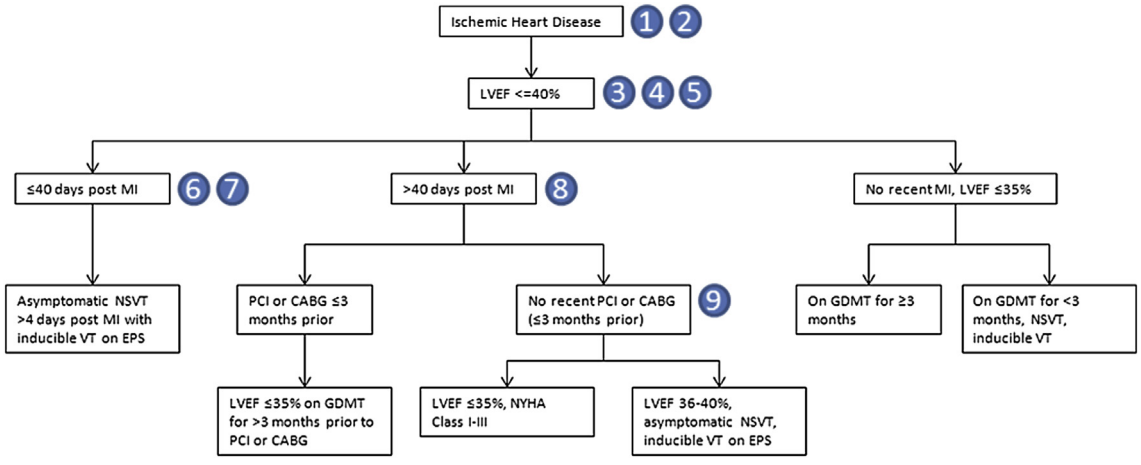

Fig. 1 – Current recommendations for appropriate use of implantable cardioverter defibrillators in ischemic heart disease patients. Numbers indicate new evidence shown in Table 1 for additional risk stratification tools in the given subsets of patients. LVEF – left ventricular ejection fraction, MI – myocardial infarction, NSVT – non-sustained ventricular tachycardia, VT – ventricular tachycardia, EPS – electrophysiology study, PCI – percutaneous coronary intervention, CABG – coronary artery bypass graft, GDMT – goal-directed medical therapy, NYHA – New York Heart Association.