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Editorial

Sudden cardiac arrest

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Sudden cardiac arrest continues to be a major public health challenge. Nearly 20% of all mortality in industrialized countries is due to sudden cardiac arrest. This is of epidemic proportion and remains a daunting problem. The actual incidence of sudden cardiac death is highly variable but recent prospective studies using multiple sources in the United States, Europe, and China have estimated sudden death rates ranging from 50 to 100 per one hundred thousand people in the general population. Despite the reduction in overall coronary heart disease mortality in the past thirty years, sudden cardiac death has not declined to a similar extent suggesting the percentage of deaths that are due to sudden cardiac arrest has remained fixed or actually increased as a percent of the total mortality. More than 50% of all coronary heart disease deaths are caused by sudden cardiac arrest. The exact nature of that sudden cardiac death has changed somewhat over the past two decades. While a vast majority of sudden cardiac arrest victims were felt to be due to ventricular tachycardia or fibrillation two decades ago, recent data suggests the percentage of people dying of ventricular tachycardia/fibrillation has decreased and incidence of sudden death associated with bradyarrhythmias has increased. This is probably an expression of an aging population within an increasing incidence of heart failure which demonstrates an inverse relationship to the degree of heart failure with the incidence of sudden cardiac death. Obviously death associated with end-stage heart failure is not going to be mitigated by wide spread implantation of an implantable defibrillator.

The underlying cause of sudden cardiac death is very complex. Sudden cardiac arrest increases with age, but at any age the incidence is higher in men than women, until the eighth decade where the incidences approach one another. Since women are living longer it suggests that the incidence of sudden cardiac arrest has not really increased over time, just the patients who are susceptible. Moreover, the incidence of sudden death in older women does not appear to be related to prior infarction, so the underlying substrate may be very different. Despite the fact that coronary artery disease is present in nearly three quarters of the patients with cardiac arrest it is much lower in women of older age and thus the mechanisms may be different. As such nearly two-thirds of women who present with cardiac arrest have that event as the first episode which is not the case in men where only about 40–50% present with sudden cardiac arrest as the first episode of heart disease. This again suggests a different substrate. We know that there are racial differences in the incidence of sudden cardiac death. Hispanic Americans have a lower incidence of sudden cardiac arrest than non-Hispanic in the United States. African Americans have a higher incidence of sudden cardiac death than white Americans. Survival rates are lower for African American than non-African American populations. Most sudden cardiac deaths occur in individuals without a history of heart disease and importantly, with relatively normal function and ejection fractions greater than 40%. Prediction of those patients at risk remains elusive. Most of the efforts over the last 25 years have been focused on patients with abnormal ventricular function and congestive heart failure, who are a minority of those who die suddenly. There are many biological markers that have been looked at, including incidence of coronary disease, coagulation factors, renal function or hormonal status, family history, etc - none of which are of specific value in individual patients. There are known genetic risk factors for monogenetic primary arrhythmic diseases, which make up a small percent of those

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who die suddenly, but are particularly important in the under twenty population. The role of ion channel abnormalities in the general population as a part of a complex underlying substrate is yet to be determined. Clearly genome (GWAS) studies have determined a number of potassium channel defects that seem to be a high risk for certain populations, as well as sodium channel defects. The markers which regulate the nitrous oxide synthetase system (NOS1AP) have been highly associated with sudden death. None of these genetic markers in and of themselves can be a sole explanation for such a complex disease. Numerous biological markers including fatty acids, cytokines, CRP, BNP have all been related to sudden cardiac death. A number of risk stratifiers have been looked at, including autonomic dysfunction as measured by heart rate turbulence, heart rate variability, and baroreceptor responsiveness. Still other markers to assess alterations of repolarization such as T-Wave alternans have been used. Simple surrogate measures on an ECG including QRS width, QRS notching, QT interval all have some small impact in our understanding of the complex interrelationship of various factors that culminate in sudden cardiac death. None of these is currently useful in predicting outcome in any individual. Obviously the QT interval used as a surrogate for potassium channel defects as well as the NOS1APgene, which is highly related to modulation of long QT syndrome. Half of the genetic variants noted in the GWAS studies have not been implicated in potassium channel abnormalities or factors regulating repolarization. Probably only a small portion of the QT variation is explained by the findings of GWAS studies. The QRS abnormalities, which are another risk factor, also seem to be associated with genetic abnormalities, but these are more related sodium channel defects. It is likely that many polymorphisms in addition to previously unrecognized mutations are responsible for defining the complex substrate causing sudden death. As such we need better risk factors that have a greater sensitivity and specificity to identify those patients with near normal heart function who represent the major group of people who die suddenly. Since the incidence of sudden death is so low in these patients, the chance of false positives is extremely high; thus intervening based on such risk factors may be fraught with poor cost effective delivery of care and complication related to the delivery of that care. This is particularly true if ICDs are the therapy chosen. Beta blockers seem to be the only drugs that are efficacious in the prevention of sudden death in virtually all populations. The management of heart failure symptoms with ACE inhibitors, beta blockers and aldosterone antagonists seems to improve sudden death as it improves the survival of heart failure, but not specifically sudden death. The initial studies suggesting that eplerenone is useful in preventing sudden death were limited by the fact that the drug worked to prevent sudden cardiac death in a population that may have a high incidence of hypokalemia which itself may have been responsible for the sudden death.

As such the prevention of sudden cardiac death remains a daunting challenge, which appears insurmountable because of our inability to identify patients at risk. It is likely over the next decade the use of genomics, proteomics, and metabolomics may help identify patients at risk when added to non-invasive tests which can demonstrate small abnormalities of an intramyocardial conduction and repolarization and abnormalities of autonomic tone. It is likely that the abnormalities of autonomic tone may be more dealing with the triggers of an event while other factors, such as conduction or underlying substrate problems, have to do with the latent ability of that individual's heart to wind up in fibrillation in response to a trigger. This supplement will address many of these problems. While no definitive solution of sudden cardiac death will evolve from this symposium, organization of the issues is the first step in our understanding of the problem and the methods by which identification of those at risk can be undertaken. The purpose of this special supplement is really to give the readers an overview on what the definitions, epidemiology, and incidence of sudden cardiac death is and the methods identifying those patients at risk. The role of ICDs and non-ICD interventions will be discussed as well as the guidelines for ICD implantation in clinical practice. The role of pharmacology will be addressed as well. This symposium is just the beginning. The next decade or more will hopefully yield better information to select those patients in whom more cost effective therapy can be easily applied.