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Sudden Cardiac Death in 2017: Spotlight on Prediction and Prevention

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Abstract

This commentary will provide a brief synopsis of the progress made in prediction and prevention of sudden cardiac death (SCD), the challenges that remain, and the opportunities available to make a real impact in this field. The dawning of the new millennium saw the prophylactic implantable defibrillator (ICD) firmly established as the major primary prevention modality, poised to make a major impact on the burden of SCD. More than a decade and a half later, has this expectation been realized? The modest impact of the primary prevention ICD on SCD burden is largely due to the now well-recognized inadequate performance of the left ventricular ejection fraction as a risk stratification tool. Consequently, the field has transitioned from a focus on the “high-risk ejection fraction” to the broader concept of the “high-risk patient”. There are currently no effective means of stratifying SCD risk in patients with preserved EF, who constitute the majority (at least 70%) of all patients who will suffer SCD. Can the field be disrupted and novel predictors of SCD identified? In addition to the ongoing quest for identification of the high-risk patient early in the nature history of SCD, a new paradigm for preventing SCD in the “near-term”, within several weeks of the lethal event, has been proposed. While rapid advances in technology, data warehousing and analysis will accelerate this process; regulatory, funding and clinical implementation strategies will need to keep pace if these expectations are to be realized.

INTRODUCTION

Sudden cardiac death remains a major public health problem, annually accounting for an estimated 350,000 deaths in the US, 700,000 in Europe and 4–5 million around the globe. Looking back from 2017, this commentary will provide a brief synopsis of the progress made in the field of sudden cardiac death (SCD) prediction and prevention, the challenges that remain, and the opportunities that currently exist in this sphere.

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None.

PROGRESS

The dawning of the new millennium saw the prophylactic implantable defibrillator (ICD) firmly established as the major primary prevention modality, poised to make a major impact on the burden of SCD. More than a decade and a half later, has this expectation been realized?

In patients with ICDs that eventually manifest with ventricular arrhythmias, device therapies are a lifesaving intervention. However, the overall impact of the ICD on this major public health problem has been modest.^{1, 2} Among patients with the most common forms of SCD high-risk conditions such as ischemic and non-ischemic cardiomyopathies, improved health care provider awareness and consistency in diagnosis and treatment of heart failure, may have lowered rates of ICD therapies. However, the limited effectiveness of the left ventricular ejection fraction (LVEF) as a risk stratification tool has now been identified as a major stumbling block. Based on identification of severely reduced LVEF, we continue to implant this device in significant numbers of patients, yet only a minority, in the range of 1–5 percent per year, have need for the potentially life-saving therapies the ICD is capable of delivering.³ Therefore, the “number needed to treat” with a primary prevention ICD in order to save one life, in the range of 20–99 per year depending on the population studied, is not acceptable. Secondly, the large majority, approximately seventy percent of all SCDs occur in subjects with LVEF over 35%; and at least half of all SCDs have preserved LVEF.^{4, 5} As a result, it is now well-recognized that LVEF measurement has both limited sensitivity and specificity as a tool for SCD clinical risk stratification. Overall, the recognition that the field of SCD prediction needs to extend beyond the LVEF represents progress based on objective evidence. Today, the field has transitioned from a focus on the “high-risk ejection fraction” to to the broader concept of the “high-risk patient” (Figure 1). There has been renewed interest in identification of novel SCD risk predictors, and multiple, non-LVEF SCD risk predictors have been identified, but individually, none of these are likely to represent an improvement compared to the LVEF. However, when combined with LVEF, these markers have potential to improve the risk prediction instrument.^{6, 7}

During the same time-period, there have been significant advances in device technology that are already having a beneficial impact on clinical care. We are currently implanting the second generation subcutaneous defibrillator for primary prevention in selected subgroups of patients, and ongoing developments in device size optimization, sensing and leadless pacing are likely to further increase utilization.⁸

Among patients with the less common conditions leading to high risk of SCD such as the familial primary arrhythmia syndromes, ARVC and HCM, the ongoing discovery of new mechanisms, diagnostics and therapeutics has translated into improvements in prediction and prevention for these patients.⁹ While the ICD remains the mainstay of primary prevention in patients at highest risk, there are clinical situations where drugs can be used as the first tier of prevention, such as beta blockers in LQTS and flecainide in CPVT. Surgical left cardiac sympathetic denervation, earlier limited to LQTS, may be considered in patients with refractory CPVT.¹⁰ For Brugada syndrome, there is growing evidence that supports quinidine use to treat recurrent ventricular arrhythmias in ICD-supported patients; and also

emerging evidence that epicardial catheter ablation over the anterior RVOT may prevent electrical storms.¹¹ For both common and rare forms of SCD, ongoing innovations in cardiac imaging are likely to make salient contributions to risk stratification of the future.¹²

CHALLENGES AND OPPORTUNITIES

There are several major challenges confronting the field of SCD prediction and prevention in the present day. However, the field has also evolved to a level where there are multiple opportunities to overcome these challenges. The primary prevention ICD continues to have both an “underutilization” and an “overutilization” problem. In the absence of a systematic, step-wise screening approach to identification of subjects with severely reduced LVEF, many such cardiomyopathies remain undiagnosed and untreated especially since a subgroup may be clinically asymptomatic. Novel screening approaches need to be explored. On the other hand, significant evidence has accumulated to indicate that our current approach to candidate selection for the primary prevention ICD could be somewhat simplistic. Among those implanted with primary prevention ICDs, refractory clinical heart failure or comorbidities such as chronic renal failure, peripheral vascular disease and complicated diabetes, present a competing risk of mortality that may negate the potential benefit from the ICD.^{13, 14} While it is difficult to agree on an age cut-off, there is weak evidence for benefit of the primary prevention ICD over age 75.¹⁵ There is a need for evidence-based, realistic ICD candidate selection, that will be incorporated into the clinical guidelines. Some attempts have been made to develop SCD prediction models for the general population using existing cohort studies. However, the individual risk factor components as well as the collective models also predict overall cardiovascular mortality, and are not specific for risk of SCD. There is a need to identify predictors that are specific for lethal arrhythmias leading to SCD.

Other than the screening processes employed for the inherited arrhythmia syndromes, there are currently no effective means of stratifying SCD risk in patients with preserved EF, who constitute the majority (at least 70%) of all patients who will suffer SCD. Can the field be disrupted and novel predictors of SCD identified? It is likely that the significant advances made in detailed phenotyping of larger numbers of patients with common, complex forms of SCD, coupled to growing biobanks for genomic and proteomic discovery will present significant opportunities. However, given the importance of analyzing significant numbers of patients to obtain meaningful results, such resources will need to be preserved, grown and fostered. Ongoing discovery of novel SCD prediction methodology will need to be validated and tested prospectively in randomized clinical trials or pragmatic clinical trials, for which appropriate funding will need to be allocated and utilized.¹⁶

There has been a major epidemiological shift in the type of the lethal arrhythmias manifesting during cardiac arrest, that is presenting another major challenge for SCD prevention. The first studies were reported two decades ago, and ongoing reports continue to confirm the ominous trend of a rising proportion of pulseless electrical activity/asystole and falling rates of ventricular tachycardia/VF.¹⁷ While a large proportion of the latter arrhythmias are amenable to early defibrillation, whether in the field or via the ICD; the rates of successful resuscitation for the former, non-shockable rhythms are extremely low. More recent studies report that this paradigm shift may partly be explained by an aging

population with high present-day rates of treated coronary artery disease, resulting in a larger proportion of SCD related to non-cardiac etiologies.¹⁷ There is likely to be a small yet distinct subset of patients more likely to survive PEA, and these individuals need to be identified for targeted novel therapeutics.¹⁸

Like most areas of clinical science today, the concept of harnessing “big data” is also being hotly debated in this field, particularly in the context of a broad array of measurements made by a variety of “wearable technologies”. Unfortunately, the collected data can be as variable and heterogeneous as the sources from which it is obtained, with implications for consistency and reproducibility of data as well as selection bias based on who is mostly likely to volunteer information. There is an urgent need to refine and validate the devices that measure and collect this big data from diverse and unselected populations. SCD is a dynamic, unexpected event, relatively rare in the general population. Accurate wearables have the potential to deliver previously unavailable, real-time information from large numbers of patients with major implications for SCD mechanistic discovery.¹⁹ While rapid advances in technology, data warehousing and analysis will accelerate this process; however sound epidemiological principles, appropriate study design, as well as regulatory, funding and clinical implementation strategies will need to keep pace if these expectations are to be realized.

New paradigm for near-term SCD prevention

In addition to the ongoing quest for identification of the high-risk patient early in the nature history of SCD, a new paradigm for preventing SCD in the “near-term”, within several weeks of the lethal event, has been proposed (Figure 2). While this remains a concept that needs to be prospectively evaluated, a recent paper from the Oregon Sudden Unexpected Death Study²⁰ reported that at least 50% of middle aged subjects who suffer sudden cardiac arrest have warning symptoms in the four weeks preceding the lethal event. There was a six-fold higher survival from sudden cardiac arrest in symptomatic middle-aged patients who contacted the emergency response system by calling 911 immediately after experiencing symptoms, compared to those who chose not to act following onset of symptoms. The dynamic nature of triggers and symptoms combined with complex disease substrates and pathophysiology suggests a potentially useful role for mobile, wireless and wearable technology in further prospective evaluation of SCD near-term prevention.

CONCLUSIONS

Looking back at the past decade and a half from the 2017 lens, the real-world impact of SCD prediction and prevention on the burden of this major public health problem has been modest. However, based on scientific discovery during the same time-period, several major evolutionary steps have been made that represent real progress toward an SCD risk prediction instrument that will identify candidates most likely to benefit from preventive interventions. While significant challenges remain, we are in a phase of escalating discovery, enabled by rapid developments in technology, that will expedite translation of findings to routine clinical care.

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Figure 1. Sudden cardiac death prediction and prevention has transitioned from a focus on the “high-risk ejection fraction” to the concept of the “high-risk patient”.

Figure 2.

A new paradigm for predicting and preventing SCD in the “near-term”, within several weeks of the lethal event, has been proposed but needs to be prospectively evaluated.