Alternative Research Funding to Improve Clinical Outcomes
Model of Prediction and Prevention of Sudden Cardiac Death

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Abstract—Although identification and management of cardiovascular risk markers have provided important population risk insights and public health benefits, individual risk prediction remains challenging. Using sudden cardiac death risk as a base case, the complex epidemiology of sudden cardiac death risk and the substantial new funding required to study individual risk are explored. Complex epidemiology derives from the multiple subgroups having different denominators and risk profiles, while funding limitations emerge from saturation of conventional sources of research funding without foreseeable opportunities for increases. A resolution to this problem would have to emerge from new sources of funding targeted to individual risk prediction. In this analysis, we explore the possibility of a research funding strategy that would offer business incentives to the insurance industries, while providing support for unresolved research goals. The model is developed for the case of sudden cardiac death risk, but the concept is applicable to other areas of the medical enterprise. (Circ Arrhythm Electrophysiol. 2015;8:492-498. DOI: 10.1161/CIRCEP.114.002580.)

Key Words: cardiac arrest ■ cost-benefit analysis ■ death, sudden, cardiac ■ research design

Despite major advances in the prediction, detection, and management of cardiovascular disorders during the past 40 years, cardiac arrest and sudden cardiac death (SCD) remain a major worldwide public health problem.1 The 40% reduction in age-adjusted cardiovascular mortality between 1990 and 20082 does not seem to have had the same impact on cumulative numbers and proportional contributions of cardiac arrest and SCD.3 Current estimates of the SCD burden remain in the range of 45% to 50% of all cardiovascular deaths,4 accounting for 424,000 nontraumatic out-of-hospital cardiac arrests (OHCA) responded to by emergency rescue systems annually, with a mortality rate of ≈90%.5 This accounts for the estimated 300,000 to 382,000 SCD’s per year in the United States.4 This is 10x the annual mortality rate for breast cancer, and equivalent to the annual mortality rates for Alzheimer’s disease, breast cancer, cervical cancer, colorectal cancer, diabetes mellitus, HIV/AIDS, prostate cancer, as well as death from guns, residential fires, car accidents, and suicide combined.246 Moreover, individual risk prediction continues as an unresolved challenge that is the rate-limiting step for progress in clinical practice.

It is unlikely that major impact on individual risk prediction will emerge from anything short of large-scale research efforts to identify small subgroups at high risk that are currently concealed within larger general population subsets at low cumulative risk. This analysis is designed to summarize the epidemiological and clinical factors that limit prediction and prevention of SCD, develop the rationale for a new approach to research funding, and propose a different resource for such funding.

Analysis of the Problem
The first principle for defining the SCD challenge derives from its complex epidemiology. The total population at risk consists of several distinct subgroups, each having specific epidemiological and clinical characteristics.67 The 5 general categories into which SCD risk can be separated have different risk densities, with identifiable overlap among them. Historically, the categories have been classified as follows: (1) the general population, (2) a subgroup with known risk factors in the absence of identified cardiovascular disease, (3) those with cardiovascular disease and preserved cardiac function, (4) the class of patients with known heart disease and poor heart function, and (5) a category associated with confirmed or suspected genetic abnormalities associated with a cause or risk of SCD.7

The category referred to as the general population literally represents the total population, but by usage has become conceptualized as a large population, excluding the other 4 subsets identified by their specific risk characteristics. Available statistics suggest that the cumulative number of SCDs emerging from the 4 specific categories is a small fraction of those occurring in the general population, the latter being dominated by subjects without identified cardiovascular disease or high impact risk markers. Therefore, for the purpose of research, planning, and development of preventive strategies, it is logical...
to consider the general population category as those individuals at unrecognized risk for cardiac arrest, often expressing as the first clinical manifestation of previously undiagnosed or unsuspected heart disease.

In the second category, characterized by the presence of risk factors for development of disease, SCD risk is considerably higher than the segment of the population without risk markers, but still low enough to create a challenge for accurately predicting and preventing SCD in the individual subject. The risk factors in this category are used in various scoring systems and other clinical risk profiling strategies. The major risk factors, including diabetes mellitus, cigarette smoking, obesity, hypertension, obesity, diet, and sedentary lifestyle, associate with increased risk in this population subset based on the number of risk factors, and risk factor interventions offer benefit from a population perspective. However, individual effect size and prediction remain a challenge that should be a target of future research. The importance of identification within this subgroup is further highlighted by a recent observation that OHCA victims who are admitted to a hospital alive are increasingly likely to have only risk factors, as opposed to manifest disease. The complexity within both of these first two-categories is that the number and power of the specific risk factors available for either groups or individuals establish gradients of risk, based on the sizes of the denominators and event rates (Figure 1).

The third and fourth categories are those recognized in clinical practice, in which risk profiling has become dependent on imperfect sets of clinical markers that have evolved over the years. The final category, genetic determinants of risk, include both rare arrhythmia syndromes and the recognized familial risk of cardiac arrest as the initial manifestation of heart disease in the general population. Rare inherited arrhythmias constitute a category that stands alone as a specific component, whereas familial clustering of SCD risk offers the potential to contribute to risk profiling in the general population and categories of common causes of SCD.

Each of the defined categories of risk has unique epidemiological characteristics and clinical challenges, requiring different approaches to the translation of population risk to individual risk and interventional strategies. The relevant epidemiological targets are subclassified into conventional epidemiology, transient risk prediction, interventional epidemiology, and genetic/personalized risk prediction. Conventional epidemiology is best applied to the general population at risk for SCD as a first cardiac event in the absence of recognized structural heart disease. The concept of the epidemiology of transient risk refers to a strategy for predicting triggering events in a timeframe that is useful for preventive actions. This highly desirable strategic target has been elusive, but is beginning to emerge with new screening technologies and biomarker profiling. Interventional epidemiology embodies analyses of the elements of clinical trial design and interpretation to maximize benefit of defined therapies and expand their application in new subsets of patients. Clues to future research opportunities for prediction commonly emerge unexpectedly from secondary analyses of clinical trial data. Genetic epidemiology refers to personalized risk identified at a molecular level.

The various categories of population risk require further analysis in the context of the pathophysiology of cardiac arrest itself. These include substrate-based risk derived from underlying structural disease analysis, and expression-based risk derived from factors that have the potential to convert a stable substrate into an active arrhythmogenic substrate. Substrate and expression risks intersect within the various epidemiological strategies discussed above. Expression factors include neurohumoral contributions to electrophysiological instability, hemodynamic variants contributing to cardiac arrest risk, markers of electrophysiological instability, and the role of genetic variants in each of these pathophysiological subsets.

**Rationale for Seeking a New Approach to Funding**

It is evident from the foregoing that the challenge of SCD prediction and prevention is considerable, but the potential rewards are large. Although the cumulative SCD numbers have not changed substantially in recent years, there seems to have been a shift in the distribution of the population at risk among the various categories over time. The size of the population falling into more easily identifiable high risk subgroups has decreased, putatively as a result of medical and interventional progress. The improved outcomes after myocardial infarction in the era of acute interventions are exemplary. This has resulted in a shift in focus to the numerically larger cluster of events that are diluted in much larger population denominators, creating lower population risk, but large cumulative numbers. Identification of small pockets of high-risk density within large population subsets offers the best opportunity for the reduction of the SCD burden, but constitutes the greatest challenge (Figure 1).

The research models will differ for the first event subgroup, those with risk factors in the absence of defined disease, and
those with defined disease with preserved cardiac function. In part, these are currently addressed as general preventive strategies in an attempt to achieve a population effect that is desirable and necessary, but not sufficient to have a major impact alone. Additional studies are needed to identify pathways of investigative efforts that will yield high-resolution risk profiling to identify targets of opportunity for individual risk prediction. Such studies will be complex and expensive.\textsuperscript{8,11} They will also require designs that are much longer than conventional studies to yield meaningful outcome data. However, when dealing with a condition that accounts for one-half of all cardiovascular deaths, with half of those emerging as the first manifestation of previously unrecognized disease, often during the productive years of life, the justification of such an investment seems appropriate. More than 10 years ago, the US Department of Health and Human Services’ Agency for Healthcare Research and Quality highlighted: “Patients at high risk of sudden cardiac death are hard to identify... accurate targeting is necessary for cost effective treatment.”\textsuperscript{12}

The realistic dilemma, however, is sources of funding.\textsuperscript{13} Traditional sources of research funding from the federal government and professional societies are not positioned to make new investments of this magnitude (Figure 2). Private philanthropy and foundations can help, but are usually limited to specific areas of focus and resources as well. The other major component of the research pool, the pharmaceutical, biotechnology and device industries, have contributed substantially to the nationwide research commitment, accounting for >50% of the $110 billion US biomedical research budget,\textsuperscript{14} while the NIH budget has recently remained constant in the range of $30 billion. However, in contrast to the past, the vast majority of industry support is currently allocated for product development and testing, and meeting regulatory requirements. Little goes to the type of preclinical research that would improve pathophysiological pathway identification and population science for improved risk prediction, endeavors where the promises for future efficiencies are hidden.

On the surface, hope for substantial increases in the type of support proposed seems dismal. But perhaps we have remained too focused on the notion that funding of biomedical research should be restricted to public and private sources with a primary research mission. If society has so much to gain, and conventional sources of funding have blunted, other elements should be considered in the funding mix.

**Potential Impact of Research Investment by the Insurance Industry**

Prior suggestions for expanding the research funding base have included establishment of tax-advantaged biomedical innovation trusts, preferential funding for new research institutes, creation of a new class of bonds dedicated to support discovery, and deferring patent protection to later in the discovery chain in return for funding.\textsuperscript{15} Another example, given only limited consideration, are the insurance industries (health, disability, and life), which might have much to gain from improvements in prediction, prevention, and therapeutic efficiencies. The issues and opportunities can be considered separately for each component.

**Health Insurance**

The health insurance industry has multiple levels of exposure directly associated with cardiac arrest and SCD. Costs are generated for both OHCA and in-hospital cardiac arrest (IHCA) survivors. First is the cost of immediate short-term care of hospitalized OHCA survivors and subsequent short-term rehabilitation. Among those who survive to hospital discharge, additional costs are generated for longer-term rehabilitation and chronic care facility costs where needed. Finally, insurers bear the cost of long-term strategies for prevention of SCD, primarily ICDs, in population subsets at high risk for cardiac arrest. The latter include both SCD preventive therapy targeted to survivors of cardiac arrest (secondary prevention) and prevention of SCD within high-risk subgroups, based on risk profiling (primary prevention).\textsuperscript{16}

Hospital costs for OHCA victims who are resuscitated and arrive at the hospital alive are substantial. A recent meta-analysis of 140,000 individuals who experienced OHCA, found that the survival rate of hospital admission was 23.8% and the survival rate to hospital discharge was 7.8%.\textsuperscript{17} Applying these rates to the estimated numbers of Emergency Rescue cardiac arrest runs annually,\textsuperscript{6} yields an estimated 100,912 hospital admissions per year, with 33,072 patients discharged alive and 67,840 dying in-hospital. In another study, the direct incident-related cost of providing care to a patient experiencing an
OHCA was estimated to be $102,017, including acute care and early rehabilitation. Allocating proportional costs of the meta-analysis data to differences between survivors to discharge and those who died during hospitalization generates an annualized cost of $2.8 billion, based on the estimate of post-OHCA hospitalizations. An additional $3.01 billion is allocated to care in long-term facilities and $800 million is expended for initial ICD implants in OHCA survivors, assuming 80% of survivors receive devices. These figures are not inclusive of other postcardiac arrest, long-term therapies, such as pharmaceuticals (ranging from $214 to $470 per month) and related surgical procedures (ranging from $30,000 to $200,000). An estimated additional 200,000 cardiac arrests occur in-hospital (IHCA) annually, with a 2009 survival estimate of 22.1%. The incremental costs are difficult to define because a large proportion of IHCA’s are deaths associated with end-stage diseases or transient triggers for cardiac arrest.

The other major cost center for insurers is that related to implantable device therapy for patients determined to be at high risk for a primary cardiac arrest, with or without heart failure, based on the major ICD and cardiac resynchronization therapy clinical trials. Data from the National Cardiovascular Disease ICD Registry (NCDR-ICD) indicate that 110,000 devices were implanted in 2011, including both initial implants and replacements, at a conservative estimated cost of $3.3 billion for devices alone; this is not inclusive of long-term follow-up and monitoring costs for device recipients. An additional $2.5 billion is estimated for lifetime expenditures related to ICD therapy prescribed for primary prevention indications, based on lifetime cost profiles attributed to secondary prevention ICD recipients. Cumulative acute and long-term costs for cardiac arrest survivors and primary prevention ICD recipients, therefore, far exceed $10 billion per year.

The foregoing direct costs for postcardiac arrest management is a major part, but not the total, of the aggregate cost of cardiac arrests in the United States, placed by one estimated at $33 billion annually for OHCA. To put this in perspective, the entire cost of implementation of the Affordable Care Act, is estimated at $1.36 trillion from 2011 to 2023, or an average of $105 billion annually. So research that would potentially bring about a reduction of the costs of OHCA by 20% to 50% could offset a significant portion of the costs conceivably in the range of 10% to 15% of the Affordable Care Act costs.

Private insurance providers serving in commercial markets would be major beneficiaries of a reduction in healthcare costs allocated to short- and long-term OHCA and IHCA survivors, and of better efficiencies in primary prevention strategies, helping the industry to remain viable in a market place that has become increasingly stressed over the last few years. Furthermore, there is a significant expansion of private insurance provision into the Medicare Advantage private market place and the State Medicaid programs as these government programs increasingly move toward contracting with private health insurance companies. Private health insurance companies currently cover just under 70% of the US population, or 220 million individual lives. All have an interest in cost savings. The return on investment from a reduction in the incidence of cardiac arrest and its consequences would be significant.

When analyzing cost figures, especially for expensive long-term interventions, it is important to recognize that the healthcare insurers inherit the limitations of our ability as investigators and physicians to identify individuals or small subgroups at high risk, and to prescribe expensive therapies efficiently. These limitations result from marginal research funding patterns for past pivotal clinical trials that were usually sufficient to adequately define acceptable levels of efficacy, but not optimal. Most were underpowered for stratification of individual risk efficiently. The latter is generally viewed as a metric of the proportion of a treated population that will achieve the targeted benefit absolute risk reduction usually a small number or the number needed to treat to prevent one event (often a relatively large number). Accordingly, one could make an argument that healthcare insurers, including both private carriers and CMS, should have an incentive to contribute to such research efforts. The rationale, although inclusive of good will and general welfare, can be based on business modeling alone. To the extent that investment in a higher level of individual risk prediction would lead to greater efficiencies in the expenditures of healthcare funds, the insurance system would achieve improvements in its business model. An example is reduced ICD expenditures based on improved individual risk prediction. In this example, our limitation in the ability to risk profile individual ICD candidates results in clinical Guidelines that lead to only 20% to 30% of recipients ever receiving appropriate delivered therapy. If we could improve delivered therapy from implanted ICDs to 50% to 60%, based on more precise identification of higher-risk candidates, healthcare savings would emerge from an appropriately reduced denominator of recipients. In addition, the research expense for any one project is time-limited, while savings accumulate year-to-year. Nonetheless, the cost for scientifically valid and clinical research addressing low incidence, high absolute number events is a major reason why healthcare insurance companies are investing in big data. The intent is to determine a pattern of use and to reduce risk and healthcare cost over time, but there are concerns about its limitations for accurately identifying efficacy. Valid clinical efficacy measures are more likely to emerge from big science. In large part, big data is an accommodation to the status quo of conventional research funding.

With annual healthcare expenditures in the range of $2.7 trillion in the United States, and a federal research funding budget of ≈$30 billion, a 1% set-aside for research targeted to generate better efficiencies would provide an additional funding pool equivalent to the current NIH budget. The magnitude of this set-aside example is far in excess of what is needed or justified for the model case of cardiac arrest and SCD, which was chosen as a demonstrative of what could be done from the perspective of a personal interest in SCD. It is self-evident that other disease states, not limited to the cardiovascular enterprise, with similar prediction and prevention dilemmas should share in such a funding pool.

Health insurance industry contributions for this type of research are uncommon, although there are examples of support for research targeted for compliance and secondary outcomes. The strategies proposed for the Patient-Centered Outcomes Research Institute for implementation...
of comparative effectiveness research, funded by an ACA-mandated fee on covered lives, is another form of industry involvement. Although patient-centered research goals address efficiencies, they do so from a perspective that derives in large part from existing data and guidelines, with their inherent limitations. This proposal focuses more exclusively on generation of new knowledge that would cycle back through patient-centered analysis. Substantial support is envisioned for new, in-depth studies focused on high-resolution individual risk stratification for the purpose of achieving therapeutic and preventive efficiencies that are currently beyond our capabilities.

**Disability Insurance**

To the extent that currently available responses to OHCA are successful, a population of survivors is created, a significant proportion of whom have long-term neurological disabilities. Less than 10% of survivors are able to return to full normal functional status. It has been estimated that ≈26% of survivors have severe neurological impairment (CPC scores, 3–4), most of whom die within 6 to 12 months. Among those with CPC scores 1 to 2, long term survival is considerably better, but return to normal function is still limited, primarily for those remaining in CPC category 2. Disability costs accumulate primarily for those in CPC 2 to 4. At a cost of ≈$130,000 for 30 days of rehabilitation and 365 days of long-term facility care, this extrapolates to $1.23 billion nationwide per year. Assuming a 1-year mean survival of those with severe disabilities, costs for those with moderate disabilities are not included, nor are those on long-term respirator or feeding support.

For IHCA, a survival estimate of 22.1% in 2009 was associated with 28.1% of the survivors discharged with significant neurological deficits (CPC>1), or 6.3% of the total cardiac arrests. Extrapolation from the participating hospitals to an estimated US total of 200,000 IHCA per year adds 12,533 subjects to the significant disability population pool annually, at an estimated annual cost of $1.63 billion. Research contributions to improve response systems and postresuscitation care would offer the opportunity to reduce the payout burden on disability insurance providers. Although the total $2.86 billion is smaller than the cost accumulated in the healthcare insurance model, disability insurance is a less complex model than health and life insurance, requiring fewer variables in the analysis of the relationship between premiums, research contributions, and financial benefits.

There is an added component to the disability model that affects employees, as well as the costs of disability that are passed on to the employer. It is estimated that an employer incurs a cost 1.75 times the earnings of the affected worker, related to the cost of replacing the individual. There are an estimated 39,000 to 48,750 individuals who die in the workplace from cardiac arrest. The psychic affect survivors in the workplace and the net impact on surviving workers performance is significant.

**Life Insurance**

There would seem to be a business advantage for delaying deaths for life insurance policy holders, allowing companies to earn off of retained funds for longer periods of time. Although the same advantage might not hold for their expanding annuity businesses, it is notable that the life insurance industry did create a Life Insurance Medical Research Fund in 1945. The fund provided support primarily for the generic type of science envisioned here, plus training grants, and structured the program as a foundation, which was led independently by prominent clinical scientists. The research fund seems to have ceased functioning in the early 1990s. So the concept is not new, but is worthy of re-exploration in light of current funding dilemmas.

It might be argued that successful risk profiling for first-event SCDs would be a disincentive to insurers to issue policies to individuals populating the newly identified high-risk subgroups. Whereas an individual cannot be denied healthcare insurance under the ACA, nor can they be charged a higher premium for higher risk, there is no such requirement placed on life insurance companies. This disincentive argument is countered, however, by the parallel goal of early interventions for preventing premature deaths once such subgroups are identified, providing a net benefit to the insurer and the general population. Reducing first-event SCDs from 50% to 20% by effective routine risk profiling earlier in life could provide a broad-based societal benefit, encompassing the realms of healthcare cost efficiency, disability payments to cardiac arrest survivors with neurological deficits, and premature life insurance payouts, in addition to preventing the annual unanticipated premature loss of some proportion of up to 150,000 people, many still in their productive years.

**Revisiting the Pharmaceutical, Biotechnology, and Medical Device Industries**

In addition to the insurance industries, the pharmaceutical, biotechnology, and medical device industries may also gain from returning to contributions for research beyond the scope of direct product development. Extending the example of ICDs cited earlier, implants seem to be decreasing based on effective interventions for acute coronary syndromes and other therapies. If they were to decrease further for the common guidelines-based indications as a result of better risk profiling, the device business would be further reduced – an apparent disincentive. However, this loss might be offset by new indications emerging in parallel with developing insights into the pockets of high risk in the general population that currently contribute such large numbers to first-event SCDs. The dilemma of a low incidence concealed in a large denominator translates to the large numbers that may be identified within subgroups of high-risk density (Figure 1). The net effect over time can be positive for both the corporations and the public.

**Interface Between Business Interests, Cost Effectiveness, and Clinical Benefits**

The interface requires a model that would be acceptable to the various segments of the insurance industries, investigators and universities, hospitals and physicians, government, and the public. The previously suggested creation of research trusts is a good starting point, but does not mention sources of funding, independent of tax benefits. The term set-asides, mentioned previously in this statement cannot take the form of...
a federal tax on industry in support of expanding research; that does not seem feasible in this era. In contrast, if the industries see business merit to the concept, a direct infusion into carefully structured, tax-advantaged independent entities, dedicated to prediction and prevention research, would likely be the most palatable funding and management mechanism.

To preserve credibility and be compliant with the law, such entities would have to be carefully structured for independence, oversight, and transparency, as discussed elsewhere. For example, in addition to a charter defining intent and organization, the trusts might consider creating institutes, having an Executive Committee for policy oversight and adherence, and one or more Research Evaluation Committees (study sections), with final decisions recommended by an Awards Committee.

In contrast to a recent study supporting the long-held view that public research funding contributes to the general economy beyond the confines of academic research institutions, the arguments provided here are largely developed from the perspective of a combination of private and public business considerations and the potential for public health benefits. Given that the costs of cardiac arrest to the insurance industry are so large, and significantly outstrip the death rate and associated costs of so many other health and insured events, it is curious that research is not supported significantly in the health insurance sector. In other sectors of the insurance industry, consortia of individual insurance companies do support research to save life and limb, and resultant costs. For example, the Property Insurance Research Group is part of the Fire Protection Research Foundation, whose mission is to recommend research projects, and is funded by property insurance company contributors. For research into the prevention of auto accidents, the Insurance Institute for Highway Safety and the Highway Loss Data Institute focus on human loss and economic loss, and undertake research funded by more than 100 auto insurance companies and insurance foundations. Feasibility would require reorientation of some existing business practices. The tendency to focus growth and performance in terms of quarter-to-quarter or year-to-year would have to adjust to multiple years or even a decade or more to complete appropriate studies, implement the results and realize health and business gains. In addition, an industry-wide pooling strategy, similar to the model developed by the life insurance industry in the 1940s, would be required. It is unrealistic to expect the contributions of a few corporations to fund the development of a product that by its nature would trickle into the public domain and benefit all, even if it were tax-advantaged. Contributions proportionate to corporate size or market share might be principles for compromise. But, as stated above, there is a strong precedent for insurance company consortiums to support research in other sectors of the economy. Finally, setting the business element aside, and thinking of the parallel public health and medical practice gains, the initiatives proposed offer the hope of doing better for our patients and their families, and addressing, at least in part, the recent emphasis on the needs and directions of relevant clinical research going forward.

Conclusions

The aim of this discussion is to initiate a conversation on a proposal for new methods of funding critically important research that may impact at both population and individual patient levels. Feasibility, considering the complexities of the healthcare system and related industries, requires in-depth collaborative analyses by the various interested stakeholders who have access to relevant data and system designs. The creation of an ad hoc national commission to evaluate and model such systems, or an exploratory study by the Institute of Medicine, would be appropriate next steps. The alternative, maintaining the status quo, would leave us locked into the current funding circumstances, facing the consequences of opportunities lost.

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Disclosures

None.

References


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