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JACC STATE-OF-THE-ART REVIEW

New Concepts in Sudden Cardiac Arrest to Address an Intractable Epidemic

JACC State-of-the-Art Review

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CME/MOC/ECME Objective for This Article: Upon completion of this activity, the learner should be able to: 1) describe the changing epidemiology of sudden cardiac arrest in the U.S and contrast it with the overall burden of mortality; 2) discuss recent data on symptoms that may be experienced prior to sudden cardiac arrest by victims, and the approximate time course by which they precede the event; 3) list 3 recent technical innovations which may reduce the time to first response for victims of sudden cardiac arrest; 4) summarize current knowledge on cardiac and non-cardiac causes of sudden cardiac arrest, and some strengths and weaknesses of the types of population study that contributed this information; 5) describe the emerging concepts of molecular autopsy and noninvasive autopsy to improve the phenotyping of patients who experience sudden cardiac arrest; 6) describe risk groups for sudden cardiac death who may benefit from implantation of an implantable cardioverter defibrillator; and 7) discuss possible future strategies for prevention of sudden cardiac arrest.

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ABSTRACT

Sudden cardiac arrest (SCA) is one of the largest causes of mortality globally, with an out-of-hospital survival below 10% despite intense research. This document outlines challenges in addressing the epidemic of SCA, along the framework of respond, understand and predict, and prevent. Response could be improved by technology-assisted orchestration of community responder systems, access to automated external defibrillators, and innovations to match resuscitation resources to victims in place and time. Efforts to understand and predict SCA may be enhanced by refining taxonomy along phenotypical and pathophysiological "axes of risk," extending beyond cardiovascular pathology to identify less heterogeneous cohorts, facilitated by open-data platforms and analytics including machine learning to integrate discoveries across disciplines. Prevention of SCA must integrate these concepts, recognizing that all members of society are stakeholders. Ultimately, solutions to the public health challenge of SCA will require greater awareness, societal debate and focused public policy. (J Am Coll Cardiol 2019;73:70–88) © 2019 by the American College of Cardiology Foundation.

Sudden cardiac death (SCD) is one of the largest causes of mortality and health care utilization in the world and, for many victims, their first and last contact with the health care system. Sudden cardiac arrest (SCA) affects 150,000 to 450,000 individuals per year in the United States alone (1), most of whom would not be considered at high risk a priori (2), of whom approximately 90% experience SCD (i.e., about 10% survive SCA) (3). The causes for SCA are imprecisely defined, and evolving. Most cases still reflect ventricular arrhythmias, although increasing numbers reflect bradycardia and pulseless electrical activity (2), which have lower survival (4,5). It is unclear whether this reflects trends for reduced mortality from coronary disease (4,5), but such trends have been more modest in SCA (2) despite advances in basic, translational, and population science.

This state-of-the-art review identifies knowledge gaps in SCA, focused on unique avenues for therapy. We recognize the enormous strides made by past and current investigators but also the substantial challenges ahead. A central theme is the need for a broader taxonomy that recognizes SCA, not as a disease entity, but as the terminal event of several processes not limited to cardiovascular pathology (**Figure 1**). Current guidelines for SCA (6) identify patients mostly with cardiac phenotypes (7), yet noncardiac comorbidities worsen outcome (8), and most victims have undefined pathology (9,10). Classifying SCA by organ-system comorbidities may also foster interdisciplinary science and technology innovation. The second theme is creation of a digital infrastructure (**Central Illustration**) to translate scientific knowledge between multiple diverse specialty groups into unified management strategies for SCA. The digital network could use continuous biometric data and analytical tools including machine learning to better identify at-risk phenotypes, use these data and online platforms (11) to create actionable registries for allocating resources, then apply ubiquitous GPS devices to coordinate first response and emergency medical services (EMS) and advance resuscitation. Patient outcomes could then be used to reinforce or revise the network as appropriate. Such a framework may require substantial and novel public-private collaborations and funding initiatives.

Association (PCORI-AHA DECIDE Research Network 18SFRN34120036). Dr. Narayan has received consulting fees/honoraria from Medtronic, Abbott, and TDK; has received grant support from the National Institutes for Health; and holds intellectual property rights with the University of California Regents, Stanford University. Dr. Daubert has received consulting fees/honoraria from Medtronic, St. Jude Medical, Boston Scientific, Sorin Group, Zoll, Gilead, Iowa Approach, and VytronUS; has received research grants from Boston Scientific, Biosense Webster, Medtronic, and Gilead Sciences; and has received fellowship support from Medtronic, Boston Scientific, St. Jude Medical, and Biosense Webster. Dr. Wang has reported that he has no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

AED = automated external defibrillator

CPR = cardiopulmonary resuscitation

DM = diabetes mellitus

ECG = electrocardiogram

EF = ejection fraction

EMS = emergency medical services

HF = heart failure

ICD = implantable cardioverter-defibrillator

IoT = internet of things

LV = left ventricular

LVEF = left ventricular ejection fraction

MI = myocardial infarction

MRI = magnetic resonance imaging

NYHA = new york heart association

PEA = pulseless electrical activity

ROSC = restoration of spontaneous circulation

SCA = sudden cardiac arrest

SCD = sudden cardiac death

STEMI = ST-segment elevation myocardial infarction

VF = ventricular fibrillation

VT = ventricular tachycardia

The document is structured around 3 key concepts: respond, understand and predict, and prevent sudden cardiac arrest.

RESPOND

Despite our best efforts, <20% of victims of out-of-hospital SCA have restoration of spontaneous circulation (ROSC) and, despite recent improvements (12), under 10% survive to hospital discharge (2). Because most SCA victims are unidentified until their collapse, improved resuscitation would have enormous impact. Potential opportunities include recognizing early warnings, electronic transmittal of event and location data to improve the rapidity and efficacy (13) of first-responders and EMS networks, educational and policy initiatives, and refining the sciences of resuscitation and post-resuscitation care.

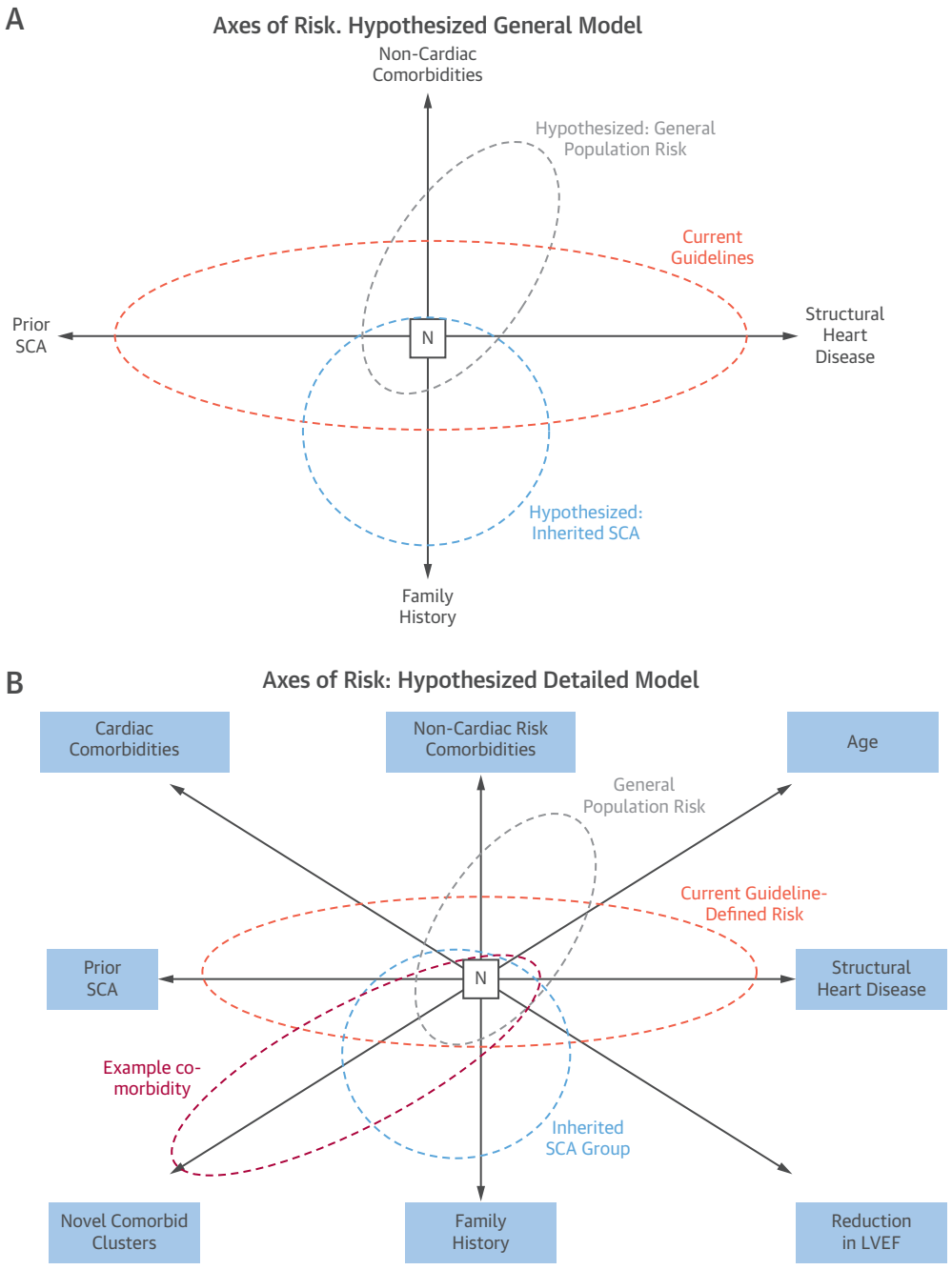
SYMPTOMS AND WARNING SIGNS. It is increasingly recognized that SCA is preceded by warning symptoms and signs, which, if promptly recognized, could greatly hasten first response. SCA is often preceded by a nonspecific physician encounter days or weeks before the event (14). However, until recently, immediately antecedent events were undefined due to difficulties in collecting data at an arrest. Müller et al. (7) dispatched physicians with SCA emergency teams in Germany to interview survivors or bystanders for antecedent events or symptoms. They concluded that SCA is "not as sudden as typically defined." Three-quarters of victims had recognizable symptoms including angina pectoris and dyspnea (**Table 1**) of which two-thirds lasted 1 h or longer (7) of median duration 50 min in patients with asystole, 20 min before pulseless electrical activity (PEA), and 30 min before ventricular fibrillation (VF) (7). In the Oregon-SUDS study (Oregon Sudden Unexpected Death Study), symptoms preceded SCA in one-half of victims, yet only 21% contacted EMS (15). Those who did were more likely to have a witnessed arrest, receive cardiopulmonary resuscitation (CPR), have a shockable rhythm, and ultimately survive (32.1% vs. 6.0%) (15). This favorable chain of survival was more likely in patients alerted to symptoms that were recognizable, such as continuous chest pain or who had a prior cardiac history. Other studies reiterate these themes (10). Symptom awareness is thus likely central to the emerging concept of "near-term prevention" of SCA (16) to bring the window for intervention forward in time.

IMPROVED RESUSCITATION ALERT SYSTEMS. Because symptoms preceding SCA are often overlooked (15), there is a need for improved early-alert systems for symptoms or potentially signs of SCA. Public education is key and should include traditional efforts, focus groups, and social media. Emerging digital technologies may be helpful. Using a smartphone software application (app) that transmits event and location data, lay responders were able to reach 58% of SCA victims, and initiate CPR before EMS arrival in 27% of cases (17). Medical or consumer wearable devices have potential to monitor biometrics for antecedent "signs" of SCA, which may be transformational because many arrests are unwitnessed. Sensors could include electrocardiogram (ECG) electrodes, photoplethysmography on limbs or the face (18) to detect pulse, or motion sensors (19) to detect lack of breathing or a sudden collapse. Sensors in smart houses (20), on smart mattresses (21), embedded in garment fabrics (22), or in other locations could network with portable devices to create an internet of things (IoT) for SCA. Although each independent data stream may be nonspecific, their combination could be very effective particularly if personalized by adaptive tools including machine learning.

A comprehensive IoT for SCA would require debates on legal and ethical issues, on privacy and security, a consensus on shared communication protocols, and considerations of funding. Nevertheless, near-term focused IoTs are feasible, and include initiatives such as extending remote management of cardiac implanted devices to include telephone callback to verify status, provide instructions, or potentially to automatically activate EMS.

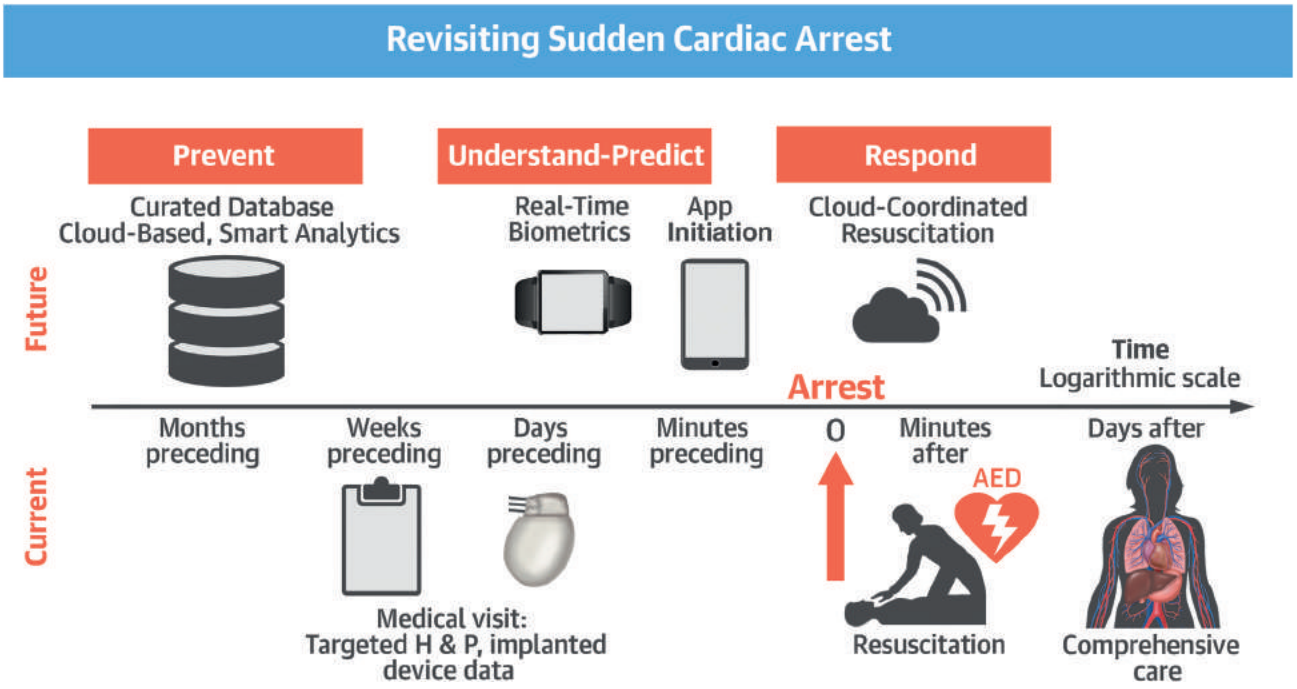
IMPROVE ACCESS TO AUTOMATED EXTERNAL DEFIBRILLATORS. The availability of automated external defibrillators (AEDs) significantly determines local outcome from SCA. Increasing AED numbers is important, but existing resources should also be optimally deployed. In a real-world study of AED availability in Toronto, Canada, Sun et al. (23) found that one-half of AEDs closest to the location of an SCA were located in offices inaccessible to first-responders when needed. One solution for this place-time mismatch would be to locate community AEDs in lock boxes accessed by neighborhood codes. An ongoing community initiative in Progetto, Italy, uses a volunteer network to deliver AEDs to the scene of SCA (24). Public policy could substantially improve outcomes but must be carefully designed. On one hand, AEDs could be allocated by residential or workplace density, and risk-stratified, taking precautions to cover less populous areas. Placing AEDs

FIGURE 1 **SCA: Hypothesized Axes of Risk**



Applied to populations, axes plot the severity of each comorbidity, while dashed ellipses are stylized representations of the prevalence of SCA in populations with each overlapping combination of comorbidities. Applied for personal risk-stratification, areas represent the SCA risk for an individual with those specific comorbidities. **(A)** General risk along proposed major axes of prior resuscitated SCA, cardiac comorbidity, family history, and noncardiac comorbidity. **(B)** Detailed axes further dissect cardiac comorbidities into reduced LVEF and other structural disease, add granularity on noncardiac comorbidities, and expand family history into inherited arrhythmia syndromes and less defined heritability. New at-risk phenotypes may be defined by new analytics, such as unsupervised cluster analysis and supervised machine learning in defined populations. The precise shapes of these plots remain to be defined in various populations. LVEF = left ventricular ejection fraction; SCA = sudden cardiac arrest.

CENTRAL ILLUSTRATION An Emerging Digital Network That Could Address Pathophysiological, Clinical, and Infrastructural Gaps in Sudden Cardiac Arrest



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In the current model, there is an undefined, yet often long, period between an anticipatory medical visit, typically for nonspecific complaints, and time zero of arrest **(arrow)**. Resuscitation is often the first medical contact. In a potential future model, SCA care could be improved in 3 areas backwards in time from time zero of arrest. **Response** may be coordinated by the digital infrastructure. Smartphone apps can alert first responders to event and GPS location; wearable biometric sensors can sense antecedent warnings that occur in one-half of victims; both may facilitate rapid dispatch of responders, AEDs, and EMS. **Understand and Predict** may be assisted by defining novel SCA phenotypes from next-generation registry databases, that upload data from wearable biometrics and existing devices (an internet of things for SCA) in the hours and minutes preceding time zero, and upstream and downstream clinical data. Such databases will enable analytics to improve prediction of high-risk individuals, who could be identified or treated for example at an anticipatory visit. **Prevent**. Upstream efforts at prevention guided by registry data that prospectively includes clinical data plus noninvasive autopsy, genetic profiles and real-time biometrics across organ systems. Emerging smart-analytics such as machine learning hold promise to reveal novel risk phenotypes and predictors as targets for prevention. AED = automated external defibrillator; EMS = emergency medical services; H & P = history and physical.

on police, firetruck, for-hire, or ride-share vehicles would increase availability, but again will require logistical, ethical, and legal discussions.

Rapid-response requires accurate data on AED location, yet this is often obscure. Recent apps provide comprehensive maps of AED locations, which may improve access (25,26) but have yet to be tested formally. Technology could incorporate traffic flow or weather at various times to dynamically optimize response.

Other technological innovations reported to improve AED availability include the use of drones to fly AEDs to sites of SCA (27), with remote audio and video instruction (28) to first-responders. Less exotic approaches include portable, battery-operated pocket ICD (29) or other less expensive designs to increase AED access.

IMPROVING FIRST-RESPONDER RATE. First-responder availability may be more critical than AED availability. SCA typically occurs in the presence of bystanders, yet fewer than 1 in 7 perform resuscitation (7). In the HAT trial (Home Automated Defibrillator Trial), this reflected lack of training and factors including the psychological stress of performing CPR (30). Training and education of the public is thus a top priority. Resuscitation efficacy is enhanced by AEDs that provide instructions, or that network automatically to EMS personnel. Combining public CPR (7) with improved EMS access improves survival, but is underused nationally.

It is troubling and unclear why SCA survival rates vary so dramatically even between U.S. urban areas. In Seattle and King County, Washington, survival

rates after out-of-hospital cardiac arrest are ~19.9%, whereas in Detroit, the rate is ~3% (31). Rates of bystander CPR vary with socioeconomic and racial characteristics of neighborhoods (32), which requires addressing public education, EMS resources, and organizational limitations. First-response rates can also be affected by mundane issues such as road traffic, for which city planners already fast-track EMS vehicles.

IMPROVING THE SCIENCE OF RESUSCITATION. The immediate goal of resuscitation is the ROSC via defibrillation and chest compression, which also improve coronary perfusion in animal and clinical (33) studies. Nevertheless, many patients even with ROSC (2,7) have poor survival to discharge, emphasizing the urgent need to identify additional mechanisms.

Targeted temperature management (therapeutic hypothermia) may reduce damage to the central nervous system as tracked by biomarkers (34), and also reduce metabolic demands or arrhythmias (35). Nevertheless, the role of targeted temperature management is under discussion (36) because it has been linked to events such as coronary (stent) thrombosis (37). Early coronary revascularization shows efficacy when combined with a network for rapid triage (38), but because studies question its benefits (39), this could be reserved for patients whose axes of risk include coronary disease (**Figure 1**).

Several devices have been proposed to improve resuscitation. Mechanical support devices can now be deployed by first-responders in cases of SCA due to PEA or asystole, which are increasingly common (2), or when EMS is delayed. However, chest compression devices are controversial and may cause visceral damage (40). Other emerging solutions include electrical stimulation to activate chest wall muscles (41), and simplified methods for cardiopulmonary bypass or extracorporeal circulation.

One may anticipate a spectrum of device complexity for SCA, tailored to individual risk. Consumer wearable technology and apps could be recommended to the general public, whereas "medical-grade" devices requiring Food and Drug Administration clearance could be prescribed for higher risk patients (**Central Illustration**). The existing implanted base of devices may provide useful information in this regard, because even implantable monitors or pacemakers that cannot defibrillate are Bluetooth enabled. Such devices could identify SCA in real time via dedicated closed-loop systems, or networked with other sensors in an SCA-focused IoT. This represents a new application of device-device interaction.

Acute resuscitation of the SCA victim does not end with ROSC, and a multidisciplinary team of cardiologists, neurologists, rehabilitation specialists, nurses, and others are needed to optimize outcomes (42). Further research into post-ROSC derangements in cardiac, neurological, and metabolic systems, and designing therapy to address them, may improve ultimate survival.

TABLE 1 Antecedent Symptoms for Out-of-Hospital SCA

	All Patients With Known Symptoms (N = 323)		Patients With Witnessed Arrest (n = 274)		Patients With Symptom Duration <1 h (n = 116)
		Duration, min		Duration, min	
Angina pectoris	88 (22)	120 (20–630)	69 (25)	120 (15–495)	38 (33)
Dyspnea	61 (15)	20 (10–375)	47 (17)	10 (10–180)	35 (30)
Nausea/vomiting	27 (7)	120 (20–420)	19 (7)	90 (5–240)	12 (10)
Dizziness/syncope	21 (5)	10 (5–60)	18 (7)	10 (5–60)	17 (15)
Other	23 (6)	60 (10–300)	23 (8)	60 (10–270)	14 (12)
No symptoms	103 (25)	N/A	71 (26)	N/A	N/A
Unknown	N/A	31 (11)	N/A	N/A	N/A

Values are n (%) or median (interquartile range). From Müller et al. (7).
N/A = not available; SCA = sudden cardiac arrest.

UNDERSTAND AND PREDICT

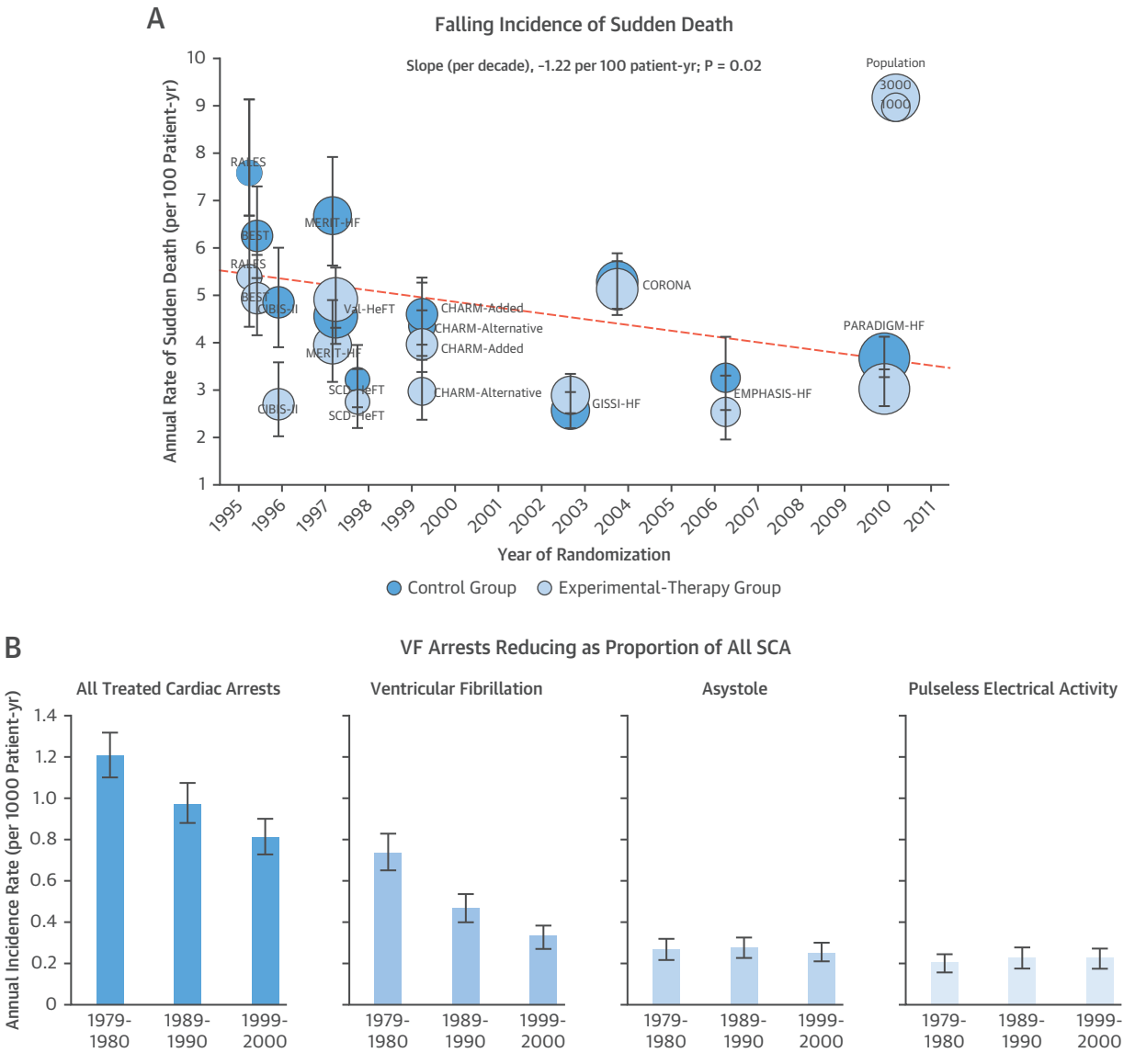
Several opportunities exist to improve understanding of SCA. These include defining novel SCA phenotypes or their determinants (comorbid risk factors), identifying cellular-phenotype interactions, leveraging technology innovations such as continuous data collection to enrich data registries, and applying novel analytics to define novel phenotypes.

EPIDEMIOLOGY. SCA affects 180,000 to 450,000 individuals per year in the United States alone (1), varying with age from 2.28 per 100,000 under 35 years of age, to ~100 at 50 years of age and ~600 at 75 years of age. Notably, its epidemiology is evolving, and from 1980 to 2000, an increasing proportion of SCA cases presented as PEA or asystole than VF (4,5,43,44) (**Figure 2**). This may reflect increasing beta-blocker use (43) or better treatment of coronary disease (4,5). This has an impact on resuscitation, because survival is lower for non-VF compared with VF arrests (4,5), risk prediction, and understanding.

Epidemiology has been our primary lens into SCA, providing key clinical, pathophysiological, and therapeutic insights including who is affected, what are their triggers and pathophysiologies, and what therapies work. However, epidemiological data on SCA have been limited in definitions, disease taxonomy, and reporting (ascertainment) that must be addressed to move the field forwards.

REFINING DEFINITION AND TAXONOMY FOR SCA. Cardiac arrest is defined as the sudden unexpected termination of cardiac activity associated with loss of

FIGURE 2 Changing Incidence and Pathophysiology of SCA In Recent Decades



(A) Falling incidence of SCA (reprinted with permission from Shen et al. [117]); **(B)** changing arrhythmia presentations of SCA (reprinted with permission from Cobb et al. [43]). BEST = Beta-Blocker Evaluation of Survival; CHARM-Alternative = the alternative trial of the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity program; CHARM-Added = the added trial of the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity program; CIBIS-II = Cardiac Insufficiency Bisoprolol Study II; CORONA = Controlled Rosuvastatin Multinational Trial in Heart Failure; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; GISSI-HF = Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca Heart Failure Trial; MERIT-HF = Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; RALES = Randomized Aldactone Evaluation Study; SCA = sudden cardiac arrest; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial; VAL-HefT= Valsartan Heart Failure Trial; VF = ventricular fibrillation.

consciousness, spontaneous breathing, and circulation occurring within 24 h after the onset of symptoms of cardiac origin. This definition is useful to target resuscitation efforts, and for public education campaigns, yet it describes a constellation of terminal symptoms rather than defining specific pathophysiology or patient phenotypes.

SCA is not a monolithic event, but rather a family of mechanisms leading to common pathways of rhythm disturbances (ventricular tachycardia [VT],

TABLE 2 Potential Clinical Taxonomy for SCA

Clinical Phenotype	Comments
Coronary artery disease	
Acute myocardial ischemia with or without prior infarct	Long duration post-MI benefits from ICD. CABG reduces SCA risk in chronic ischemic cardiomyopathy (6).
Acute coronary occlusion (no prior CAD events)	Size of ischemic zone; genetic determinants. Molecular mechanisms relatively well understood (118).
Coronary artery spasm	Diagnosis may be occult. Vasodilator therapy. ICD need unclear. Prognosis worse if atherosclerotic CAD, too.
Coronary artery dissection (119)	Female predominance. Arteritis and connective tissue disease such as fibromuscular dysplasia. Diagnosis challenging; IVUS, OCT may help.
Prior myocardial infarction, no acute ischemia	The prior infarct may be clinically evident or silent.
HFrEF (ischemic cardiomyopathy)	For EF ≤35 an ICD is indicated after 40 days (6); further risk stratification may be warranted, however. Beta-blockers, ACE inhibitors, statins, and other drugs.
HFmEF (ischemic)	Number of SCA may outnumber HFrEF though per patient risk lower; largely unstudied. Beta-Blockers, ACE inhibitors, statins, and other drugs.
HFpEF (ischemic)	Statins; most pharmacological trials have been neutral.
Dilated, idiopathic cardiomyopathy	
HFrEF (nonischemic)	For EF ≤35 an ICD is indicated after 90 days (6); further risk stratification may be warranted however. Beta-Blockers, ACE inhibitors, statins, and other drugs.
HFmEF (nonischemic)	ICD not indicated for primary prevention but SCA risk high; scar may be predictive (87).
HFpEF (nonischemic)	Statins; most pharmacological trials have been neutral.
Other cardiac	
Inherited channelopathy	Sudden arrhythmic death syndrome; drug-induced QT prolongation.
Hypertrophic cardiomyopathy	Risk factors include severe hypertrophy (3.0 cm), NSVT, abnormal blood pressure response to exercise, LVOT obstruction, LV aneurysm, syncope, suspected VT, FH of SCD, extent of LGE (120).
Inherited cardiomyopathy	Desmosomal proteins (ARVC/ALVC/AC); lamin A/C; other proteins.
Congenital heart disease	Related to VT, VF, or also AT with rapid ventricular response; bradyarrhythmias. Cyanotic lesions, Tetralogy, transposition of great vessels, univentricular hearts and Ebstein's are common causes (6).
Sarcoidosis (121)	May cause AV block, monomorphic or polymorphic VT, atrial arrhythmias, right and/or left ventricular dysfunction. MRI or PET for diagnosis.
Mitral valve prolapse	Bileaflet prolapse; need not be severe (122); outflow and fascicular or papillary muscle ectopics; localized fibrosis near mitral annulus.
Aortic disease	Aortic dissection.
Subsets at risk for non-VF arrests	
At risk for PEA	PEA more common in women, African Americans, older patients, pulmonary disease, antipsychotic drug use, prior syncope; OHT recipients. Seizure patients with SUDEP may present with PEA and without antecedent seizure. Survival higher than asystole but lower than VF. Women survive PEA > men (45).
At risk for primary asystole	Nonischemic causes of SCA; dialysis patients; OHT recipients; laryngospasm in SUDEP; pulmonary disease; some ethnicities, e.g., Asians.
Other	
OSA	Nocturnal SCA predominance; role of stretch, ischemia, autonomic changes, hypoxia.
Neuromuscular disorders	Myotonic dystrophy; Emery-Dreifuss; limb-girdle; facio-scapulo-humeral; mitochondrial; dystrophinopathies (Duchenne, Becker, other).
Schizophrenia (123)	Antipsychotic drugs, coronary risk factors, DVT/PE, other.
Neurological catastrophe (10)	Intracranial hemorrhage, Sudden unexplained death in epilepsy, aneurysm rupture, acute stroke, other neurological event (e.g., Huntington disease).
Infection (10)	Pneumonia, sepsis, other infections.
Metabolic (10)	Occult drug overdose (opiates and nonopiates), hypoglycemia, hyperglycemia, acute renal failure, acute alcohol withdrawal, hypothermia.
Gastrointestinal (10)	GI hemorrhage, incarcerated/strangulated hernia, bowel obstruction, hepatorenal failure/pancreatitis; liver failure.
Aspiration, asphyxia (10)	
Disseminated cancer (10)	
Hypercoagulable states	Pulmonary embolism.

AC = arrhythmogenic cardiomyopathy; ACE = angiotensin-converting enzyme; ALVC = arrhythmogenic left ventricular cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; AV = atrioventricular; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DVT = deep venous thrombosis; EF = ejection fraction; FH = family history; GI = gastrointestinal; ICD = implantable cardioverter-defibrillator; HFmEF = heart failure with moderately reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; IVUS = intravascular ultrasound; LGE = late gadolinium enhancement; LV = left ventricular; LVOT = left ventricular outflow tract; MI = myocardial infarction; MRI = magnetic resonance imaging; NSVT = nonsustained ventricular tachycardia; OCT = optical coherence tomography; OHT = orthotopic heart transplant; OSA = obstructive sleep apnea; PE = pulmonary embolism; PEA = pulseless electrical activity; PET = positron emission tomography; SCA = sudden cardiac arrest; SCD = sudden cardiac death; SUDEP = sudden death in epilepsy; VF = ventricular fibrillation; VT = ventricular tachycardia.

TABLE 3 Potential Mechanistic Axes for SCA

Mechanism	Comment	(Ref. #)
Electrophysiological		
Re-entry	Most common mechanism. Multiple subtypes. Myocardial re-entry related to scar; bundle branch re-entry; rotors.	(118,124)
Repolarization prolongation	Pathophysiology likely related to temporospatial dispersion. Long QT; acute ischemia; potassium channel blockade; enhanced late sodium current.	(118,125)
Repolarization dispersion	Measured as T peak to T end; phase 2 re-entry in ischemia or Brugada syndrome; T-wave area dispersion; microvolt T-wave alternans.	(76,126,127)
Triggered, early after depolarizations	Long QT syndromes; heart failure-related enhanced late inward Na current.	(128)
Triggered, delayed after depolarizations	CPVT; idiopathic OT and annular VPDs and VT.	(129)
Wave break	Transition from organized circuits, foci to fibrillation.	(89,130)
Myocardial ischemia		
Myocardium	Myocardial infarction; myocardial ischemia.	(6)
Coronary	Atherosclerosis and collaterals; coronary dissection; coronary artery spasm; myocardial-arterial bridge.	(131)
Inflammation	Coronary events; QT modulation.	(132)
Mechanical		
Stretch	LV dysfunction; mitral valve prolapse; sleep apnea; left bundle branch block.	(91,93)
Fibrosis/scar	Post infarct; NICM; HCM. Facilitates re-entry, other rhythms.	(87)
Dyssynchrony	Bundle branch may cause cardiomyopathy; predispose to SCA.	(133)
Mechanical disruption	Commotio cordis, aortic dissection.	(134)
Neurological		
Sympathetic stimulation	Stellate ganglion activity may precede ventricular arrhythmias; Takotsubo syndrome.	(135,136)
Neural sprouting	Infarction can cause sympathetic nerve sprouting and excessive regional sympathetic innervation.	(135)
Regional myocardial inhomogeneity	Regionally inhomogeneously denervated myocardium is arrhythmogenic.	(137)
Cerebral events	Known causes of sudden death.	(10,49)
Genetic	Monogenic disorders (LQTS, CPVT, Brugada, HCM, ARVC, etc.); familial pattern of death in acute MI.	(47)

CPVT = catecholaminergic polymorphic ventricular tachycardia; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome; NICM = nonischemic cardiomyopathy; OT = outflow tract; VPD = ventricular premature depolarization; other abbreviations as in Table 2.

VF, asystole) or hemodynamic failure (as in PEA), as emphasized in recent studies (10). Accordingly, it may be useful to develop structured definitions that stratify cases of SCA by other means, such as by outcome or potentially by organ system. Definitions should identify nonoverlapping categories consistently, and avoid ambiguity ("GiGo," garbage in garbage out). This section discusses some emerging taxonomies that could translate into actionable clinical phenotypes for SCA.

One nascent approach classifies SCA along axes of risk (Figure 1), attempting to unify known comorbidities (Table 2) and mechanisms (Table 3) for SCA. Although some SCA phenotypes are relatively well understood, such as VF following acute ST-segment elevation myocardial infarction (STEMI), others such as the association of PEA with a history of syncope, lung disease, black race, or female sex (2) are less understood—yet rising in prevalence (45). Conditions such as hypertension and diabetes mellitus (DM) are considered as risk factors for cardiovascular mortality, yet contribute to SCA (Table 3) and could be placed along axes of risk.

Even areas of mechanistic agreement are less clear than previously thought. Although one-half of SCA victims have cardiac disease (7) by autopsy, chart review (46), and molecular autopsy (47) (**Table 3**), this often comprises modest left ventricular (LV) dysfunction (46) or abnormalities that would not be considered critical a priori (48). Moreover, many SCA cases are unrelated to cardiac disease, but instead to gastrointestinal bleeds or cerebrovascular events (10,49). A taxonomy for SCA that recognizes the contribution of these entities (Table 2) provides a framework that may help advance the field.

IMPROVE ASCERTAINMENT: REPORTABLE DISEASE STATUS, STRUCTURED DATA RESOURCES. Reporting of SCA (ascertainment) is currently limited by variability in death certificate data (50), geographical variations in EMS reporting (2), nonuniform enrollment (e.g., age exclusions in some [51] in some studies) and other factors.

A "reportable disease" status for SCA may improve our meager understanding of its actual incidence and pathophysiology. Reporting requirements fuel funding, knowledge, and attention in a positive feedback

TABLE 4 Current Risk Scores for SCA

Risk Score	Target Population	Variables	(Ref. #)
Duke Sudden Cardiac Death risk score	Coronary artery disease (>75% stenosis)	LVEF, number of coronary vessels, HF, tobacco, DM, HTN, cerebrovascular disease.	(138)
Seattle Heart Failure Model	Mild to severe HF	Age, sex, ischemic etiology, NYHA functional class, ejection fraction, systolic blood pressure, K-sparing diuretic use, statin use, allopurinol use, hemoglobin, % lymphocyte count, uric acid, sodium, cholesterol, and diuretic dose/kg.	(139)
MUSIC (MUerte Su 'bita en Insuficiencia Cardiaca) study	Mild-moderate HF	NYHA functional class, LVEF, T-wave alternans, T-peak-to-end restitution and T-wave morphology restitution.	(140)
ESC HCM SCD Risk Calculator	Hypertrophic cardiomyopathy	Age, maximal wall thickness, LA size, LVOT gradient, family history SCA, NSVT, syncope.	(141)
ARIC (Atherosclerosis Risk in Communities) study	Community population 45–64 yrs of age	Age, sex, total cholesterol, lipid-lowering and hypertension medication use, blood pressure, smoking status, diabetes, and body mass index.	(142)
eMust study (Paris)	Prehospital STEMI	Younger age, absence of obesity, absence of diabetes mellitus, shortness of breath, and a short delay between pain onset and call to emergency medical services.	(143)
ARIC study	Community population 45–64 yrs of age	Age, male sex, black race, current smoking, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, serum potassium, serum albumin, high-density lipoprotein, estimated glomerular filtration rate, and QTc interval.	(144)
MUSTT study	Post-MI, EF ≤40	Lower LVEF (<40%), inducible VT, inpatient status, LBBB or IVCD, NSVT >10 days after CABG/no CABG, HF.	(62)
REFINE study (Prediction of Cardiac Mortality or SCA)	Post-MI, EF ≤50	Heart rate turbulence (HRT) and T-wave alternans (TWA) at >8 weeks.	(79)

DM = diabetes mellitus; HF = heart failure; HTN = hypertension; IVCD = intraventricular conduction defect; LA = left atrial; LBBB = left bundle branch block; NYHA = New York Heart Association; QTc = corrected QT interval; STEMI = ST-segment Elevation Myocardial Infarction. other abbreviations as in Tables 1 and 2.

loop (52). One immediate benefit would be to increase awareness of SCA, which is often synonymous with "heart attack" by the lay press. SCA already has reportable status in Finland, where a legal mandate exists for victims to undergo autopsy (53). In the United States, coordinated programs, such as the ROC (Resuscitation Outcomes Consortium) and CARES (Cardiac Arrest Registry to Enhance Survival), have greatly advanced our understanding (3,54), and offer a partial blueprint of specific data that ought to be collected in expanded regional or national reporting databases (11), and may ultimately enable more nuanced research and personalized care.

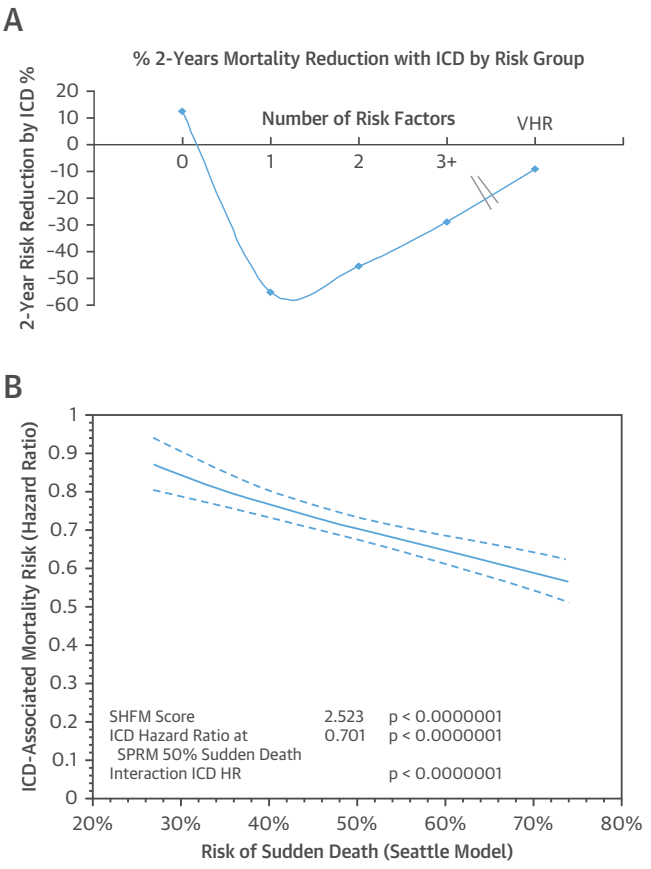
A transformational opportunity currently exists to reinvent the reporting for SCA. This may take the form of uploading granular data, potentially including continuous data from wearables recorded in the hours and minutes leading up to SCA, updating databases semiautomatically to build registries, curating data using novel analytics to identify actionable trends, then sharing databases for specific clinical or logistic goals.

REGISTRIES TO BETTER UNDERSTAND SCA. Death certificate statistics likely overestimate SCA events. Conversely, phenotyping SCA survivors, while enlightening, represents the <10% of individuals who survive and thus may or may not represent the population in general. Unfortunately, it is equally challenging to learn from those who succumb to SCD in an era of few autopsies. Large, well-organized registries are needed that include data uploaded at the time of SCA, as well as data upstream and downstream from the event.

Registries may be community based, such as the Oregon SUDS study (Sudden Unexpected Death Study) (46) or San Francisco POST SCD study (Postmortem Systematic Investigation of Sudden Cardiac Death Study) (10), or enriched for specific populations such as prior myocardial infarction (MI) and preserved ejection fraction (EF), DM, less understood populations such as African Americans with a higher risk of SCA (32) or women without structural disease (46). Registries should be prospective, include in-depth postmortem and genetic material, and should be stratified by cardiopulmonary and neurological outcome to guide actionable analyses.

Arrest-related data elements should include rhythm, antecedent symptoms, witness status, location type (home, public area), bystander CPR or AED usage and could be uploaded automatically. Downstream data should focus on STEMI/non-STEMI diagnosis, genetic panels, evolution of the ECG and biomarkers over time, coronary angiography, imaging, and cardiac or noncardiac diagnosis. Upstream elements should include antecedent symptoms (7), increasingly available antecedent biometrics from wearable devices, prior cardiac imaging or stress testing, and medications such as beta-blockers that may contribute to PEA (43). Upstream data are particularly relevant for SCA from asystole, which in

FIGURE 3 Competing Risk Factors for Mortality



(A) Relative benefit of the ICD over conventional medical therapy based on number of risk factors: higher New York Heart Association functional class, end-stage renal disease, atrial fibrillation, QRS widening, and diabetes mellitus, confer a J-shaped benefit for the ICD. From the MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) (reprinted with permission from Goldenberg et al. [8]). **(B)** Cox proportional hazards model of the ICD against Seattle Heart Failure Model (SHFM) predicted risk of SCA (as a continuous variable) using the Seattle Proportional Risk Model (SPRM). As SHFM predicted risk increases, the ICD hazard ratio (HR) for death becomes more favorable (reprinted with permission from Bilchick et al. [65]). ICD = implantable cardioverter-defibrillator; SCA = sudden cardiac arrest; VHR = very high risk.

an unknown number, but possibly a majority, of instances may have started with VF.

In SCD victims, magnetic resonance imaging (MRI) or computed tomography imaging can extend the traditional autopsy via the concept of postmortem imaging ("noninvasive autopsy") to detect coronary or structural heart disease, subtle infarction (55), mechanical complications (cardiac rupture), and noncardiac causes of arrest such as cerebral hemorrhage (10).

The challenges of organizing and populating such data platforms, then making such data secure and readily accessible, are formidable. Registries should leverage technology trends to address this challenge, using novel predictive algorithms to rapidly and efficiently curate data using "big data" methods. Nevertheless, due to the importance and complexity of the data, these authors believe in the continued need for expert data adjudication and validation.

Professional societies, academic institutions, and other stakeholders may accelerate efforts at creating digital databases for SCA (56). The American Heart Association recently launched an open digital platform to enable precision medicine for cardiovascular disease (11).

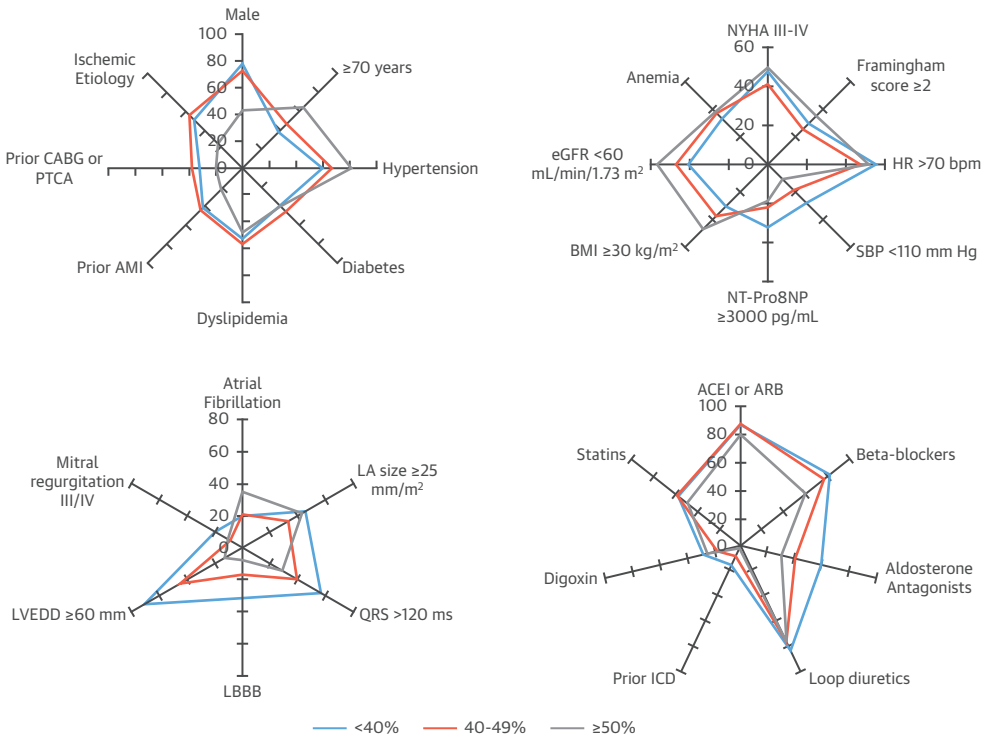
KNOWN CARDIOVASCULAR RISK PHENOTYPES IN SCA. Several systems have been proposed to score risk for SCA and other causes of mortality (**Table 4**). All systems recognize the risk continuum of Myerburg et al. (57) that individuals at highest risk are the sickest and easiest to identify, yet contribute fewer overall cases than individuals at lower risk who are more prevalent.

The highest-risk group comprises SCA survivors, in whom the case for an implantable cardioverter-defibrillator (ICD) is strong barring specific limited reversible causes (58). Even with modern shock deferring therapy, their 1-year VT/VF event rate is near 20% (59), and even those with a "reversible cause" face a mortality rate of 18% at 2 years (60).

The next highest risk group comprises those with reduced LVEF without prior SCA. Such patients qualify for primary prevention ICDs, yet their rate of appropriate therapy at 1 year is <5% to 10% (61) with modern programming. Further risk stratification of this group has proven elusive. Electrophysiological study moderately predicts events in patients with ICDs implanted for nonsustained VT, prior MI, and an LVEF ≤40% (62), but is less predictive in those with lower LVEF (≤30%) (63). Several noninvasive risk factors have been studied (**Table 4**), but few are predictive enough to guide therapy. Comorbidities such as higher New York Heart Association (NYHA) functional class, lower LVEF, atrial fibrillation, and nonsustained VT certainly confer higher risk for arrhythmias (64), yet also increase the proportion of deaths due to causes other than to arrhythmias (8) (**Figure 3**). These and other competing mortality risks limit the effectiveness of ICDs. ICD effectiveness could be improved through the use of risk scores allowing targeted ICD use for patients with the highest proportionate risk of arrhythmic death and the greatest potential mortality benefit (65) (**Figure 3**).

The next risk group, individuals with preserved LVEF, contributes more SCA events, yet their low incidence makes it difficult to devise actionable

FIGURE 4 **Disease Contributions for Forms of HF, Along Observed Phenotypic Axes of Risk**



Specific axes code for cardiac, noncardiac pathology and demographics. The shape of the clinical area profiles in these plots represents individual patient phenotypes (with permission from (69)). ACEI = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; HF = heart failure; LA = left atrium; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic dimension; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angiography; SBP = systolic blood pressure; other abbreviations as in **Figure 3**.

strategies (44,66). In a meta-analysis of 48,286 patients (67) with preserved LVEF enriched by prior non-STEMI, SCA contributed one-third of cardiovascular deaths, yet its rate was only 2.37% over 30 months. Revascularization reduced risk by 25%, suggesting an ischemic role, yet none of the comorbidities associated with SCA had sufficient hazard ratios to guide therapy a priori. SCA accounted for one-fifth of deaths in 1,767 patients with heart failure (HF) with preserved EF (LVEF >45%) in the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) trial, with modest additional risk conferred by male sex and presence of insulin-treated DM (68).

An emerging risk stratification strategy for SCA (66) is to quantify risk along concurrent "axes of comorbidity" such as age, coronary ischemia, and DM, for a population or individual. **Figure 1** shows a hypothesized schematic approach. Applied to a population, axes represent worsening of each comorbidity, and areas represent numbers of individuals with each combination of comorbidities at risk. Applied to an individual, the area represents the likelihood for SCA given his or her combination of comorbidities.

Figure 4 shows such comorbidity plots for HF with reduced EF (LVEF <40%), preserved EF (LVEF ≥50%), and moderately reduced (or "mid-range") EF (LVEF 40% to 50%) (69). HF with moderately reduced EF includes individuals with or without coronary disease, potentially transitioning from preserved to reduced LVEF (70). Such novel analyses extend risk stratification by LVEF alone, and resulting phenotypes may form populations for novel clinical trials.

Table 2 summarizes other defined SCA populations. Athletes may have increased risk for SCA; it must be reconciled why short-term exercise is associated with SCA risk, whereas long-term exercise reduces risk.

SCA in competitive athletes is highly publicized yet uncommon, of incidence 0.11 to 33.3 per 100,000 (71). Arrhythmogenic ventricular cardiomyopathy is a unique entity where exercise may be pathogenic and acutely trigger an arrhythmia (72). Other notable at-risk populations include recreational users of drugs (73,74), from cocaine to agents such as the antidiarrheal loperamide (75). Mechanisms for SCA from drugs include overdose, QT prolongation, and torsades de pointes, coronary vasospasm and dissection, accelerated atherosclerotic coronary disease, myocardial infarction, myocarditis, and seizures.

Mechanistically, current models have had modest success in explaining SCA (**Table 3**). ECG-based fluctuations in repolarization (microvolt T-wave alternans) (76), slow ventricular conduction (77), and autonomic imbalance measured by heart rate variability, baroreflex sensitivity, or heart rate turbulence are predictive in some populations (78), yet may confer only modest value beyond clinical judgment. Initiatives suggest combining (79) or improving (78) such metrics, but alternative paradigms may be needed for major advances.

NOVEL CARDIOVASCULAR AND NONCARDIOVASCULAR PHENOTYPES FOR SCA. Possible mechanisms for SCA in **Table 3** include inflammation, mechanical factors, neurological and metabolic comorbidities, and genetic factors, as well as better-studied indices of arrhythmic mechanisms of abnormal ventricular repolarization, conduction, or autonomic innervation.

Inflammation is increasingly associated with SCA and its comorbidities. This may be mediated by coronary inflammation or modulation of potassium currents (despite only subtle ECG QT prolongation), or autonomic perturbations (80). Statins have anti-inflammatory effects yet were not associated with reduced SCA in a randomized trial of at-risk patients with HF (81).

Comorbidities for SCA are increasingly described. DM is an important risk through protean mechanisms including fibrosis, inflammation (82), ventricular hypertrophy, dysautonomia, or modulation of the renin-angiotensin system (83). Sleep apnea is associated with SCA (84) through potential mechanisms of autonomic modulation, hypoxia, hypercapnia, and cardiac stretch from intrathoracic pressure swings (85).

Mechanical factors may explain some cases of SCA, via ventricular hypertrophy—particularly if eccentric (86)—fibrosis, and scar (87). Cardiac MRI abnormalities better predict monomorphic VT than VF (88), which may reflect the current inability of clinical MRI to detect microfibrosis related to VF (89). Stretch (mechanoelectric feedback) is a plausible arrhythmic mechanism in patients with LV dysfunction (90), may induce hypertrophy, and may explain extrasystoles from acute volume loading (91) and arrhythmic risk with chronic HF exacerbation. Mitral valve prolapse, long associated with SCA (92), may reflect inferobasal stretch and fibrosis. Left bundle branch block, a risk factor for SCA (78), reflects slow conduction, which induces regional stretch on the LV (93).

Premature ventricular beats and/or nonsustained VT are associated with SCA in ischemic and nonischemic cardiomyopathy (78). Suppression with antiarrhythmic drugs may cause drug-related proarrhythmia (94), yet it is unclear whether ablation to reduce electrical or mechanical ventricular heterogeneity or autonomic modulation will prolong survival.

GENETIC CONTRIBUTIONS TO SCA RISK. Younger victims of SCA (under 35 years of age) may have structural cardiac disease, yet one-third who remain elusive despite detailed histopathological and toxicological studies (95) are said to have sudden arrhythmic death syndrome (95). Sudden arrhythmic death syndrome may reflect inherited arrhythmias such as long QT syndrome, catecholaminergic polymorphic VT, and Brugada syndrome. Although exome studies have demonstrated genetic abnormalities (96), recent studies combining chart review with molecular autopsy of patients and surviving relatives found genetic etiologies in only one-half of cases (47). These studies re-emphasize the need to explore genetic, nongenetic, cardiac, and noncardiac etiologies for SCA at all ages (**Figure 1**).

Genetics also contributes to SCA in older individuals, in a more complex fashion (97). In a case control study post-STEMI (98), the only factors associated with acute VF were a family history of SCA (odds ratio: 2.72; 95% CI: 1.84 to 4.03) and ECG markers of infarct size. Genes may explain VF risk after acute MI (99), although such studies are limited in that VF survivors may not represent the wider population. Indeed, attempts to use common genetic variations as SCA risk scores have been disappointing, although they used genome-wide association studies and specific single nucleotide polymorphisms that could ultimately be improved by next-generation whole-genome sequencing (100).

IMPACT OF RACE, ETHNICITY, AND SEX. Novel SCA taxonomies should be able to explain differences in SCA based on racial and demographic factors, and hence reduce disparities in care. SCA is less likely in

women than men (42% vs. 58% of victims) (2), and female victims exhibit less structural heart disease than men (101). The risk for SCA in African Americans is nearly double (32) that in Caucasians, and occurs at a younger age (102), only partly explained by known factors such as socioeconomic status (32) or poorer residential area and lower bystander CPR rates (103). Disparities may be partly mitigated by novel methods such as patient-centric video instruction (104).

PREVENT

Prevention of SCA is our highest goal, yet poses challenges for pathophysiological understanding, clinical guidelines, and technology development, each impacted by societal priorities and funding. This section focuses on research methodologies and tools, Epidemiological and Health Services Research and Public Policy Research to improve SCA prevention.

SCIENTIFIC PATHWAYS AND TOOLS. Prevention should identify populations and individuals at risk for SCA then, using increasingly granular information on where such individuals live and work, and what their likely environmental and personal triggers may be, orchestrate delivery of resuscitation resources to them. Novel discoveries and prevention pathways for SCA will require attracting truly interdisciplinary researchers to the field.

Digital approaches to collecting registry data for prevention, as discussed in the section Understand and Predict, could facilitate research innovations such as consent via mobile devices (56), automatic updates, and curation of data for analysis. Challenges to such approaches include ensuring data quality, integrity, and security.

Analytical approaches to SCA must be developed in parallel with other technological innovations. Properly implemented, databases will contain oceans of data yet much may not inform clinical judgment. Data must be analyzed with a view to change the course of clinical endpoints including incident SCA, presentation with shockable rhythm, survival to hospital discharge, or full functional recovery. Analytics must enable actionable clinical pathways or at least risk scores (**Tables 3 and 4**). Population studies to date have used methods such as stepwise multivariate regression to identify variables associated with each endpoint, then tested in trials. This may need to be revised. First, this approach has provided limited insights thus far, albeit on less granular data. Second, traditional biostatistics have limitations when applied to large volumes of data. Third, our limited current level of understanding limits the hypotheses that can be posed a priori.

Machine learning is an emerging science that can adaptively learn, classify, and predict patterns in complex multidimensional data by combining computer science, domain-specific pattern recognition, and statistics (105). Machine learning has had great success in many fields, including voice recognition and image processing, yet its applications in cardiology and for SCA are at an early stage (106). Studies should test whether adaptive learning applied to granular data can separate individuals with and without SCA, type of presenting rhythm, or other clinical endpoints. This could be attempted using networks trained on specific data inputs (supervised learning), or via systems that identify novel data clusters (unsupervised analysis) for future testing and validation.

Ramirez et al. (107) used support vector machines to analyze ECG dispersion of repolarization restitution (Deltaalpha), which quantifies T-wave alternans and heart rate turbulence, to identify patients who may have SCA versus death from HF. Lee et al. (108) recently trained artificial neural networks on traditional ECG parameters to predict onset of sustained VT with sensitivity 88%, specificity 82%, and c-statistic 93%. Aro et al. (109) reported on 14 ECG parameters to better predict SCA in large cohorts.

Limitations of this approach include our current inability to explain results from machine learning, the fact that identified parameters are often known with previously modest results, and the fact that most machine learning is validated against experts who are limited. Nonetheless, there are high expectations that machine learning results will eventually be interpretable, and reveal clinical associations which are currently unanticipated, yet these challenges for AI remain.

A separate challenge is the need to move potentially useful tools rapidly to clinical trials (56). This has been a major obstacle. For instance, the first randomized trial testing signal-averaged ECG to predict SCA was a MUSTT (Multicenter Unsustained Tachycardia Trial) substudy (77) that confirmed its value 1 to 2 decades after its introduction. From a systems perspective, approaches to accelerate studies would be very useful, and may be facilitated by open-source resources. In this regard, the American Heart Association recently set up an open-source forum for hosting precision medicine-based data, code, and other resources on Amazon Web Services (11). From a trialist perspective, novel clinical study and statistical design methods are needed to demonstrate clinical effectiveness of interventions in large clinical studies at a sufficiently low cost to be feasible.

Prevention will ultimately require steps to alter the natural history of disease phenotypes. However, this is not always intuitive. Reverse remodeling in cardiomyopathy that normalizes LVEF may decrease overall mortality while not reducing arrhythmic risk or ICD firing rates (110). Other steps to reduce arrhythmic substrate such as reducing fibrosis may have more success. Future therapies may include systemic oral agents or small molecules that reduce myocardial fibrosis, although their cardiac selectivity may be difficult to achieve. Techniques such as treating abnormalities in the Purkinje network, which may be important in VF genesis, may reduce SCA risk in selected individuals. Development of noninvasive computational techniques to map sites that might promote ventricular arrhythmias, then ablating these regions noninvasively by external beam irradiation (111) might someday permit a non-invasive solution in high-risk individuals. Gene and stem cell therapies may in the future have a role in reversing genetic causes of arrhythmias leading to SCA.

EPIDEMIOLOGICAL AND HEALTH SERVICES RESEARCH. Epidemiological and health services research must focus on closing gaps in treatment by ensuring guideline adherence, and help develop new guidelines. Many accepted Level I guidelines have poor adherence or are implemented ad hoc.

Current SCA screening, for instance, lacks an accepted and systematic approach to identify candidate patients for guideline-based ICD therapy. Notwithstanding the limitations of current guidelines based largely on LVEF, society-based screening systems have not developed to identify asymptomatic individuals meeting this criterion. One approach is to use improve organizational quality to close identified specific gaps. Another is to develop systems across health care systems, which in some cases are countrywide, that are scalable and able to evolve with guidelines. Another approach is use systems to identify gaps in which to pursue innovations. For instance, because current imaging technology can accurately identify reduced LVEF, one system-based solution is to develop a low-cost screening tool with a low false-positive rate. Similarly, current technologies can identify coronary artery disease and with computer modeling predict coronary events, but simpler, more cost-effective tools are needed for widespread screening.

PUBLIC POLICY RESEARCH. Public policy research is critical to define better ways to prioritize SCA in the sea of demands within society, and can shape health care prioritization. Improving outcomes from SCA is one of the most pressing contemporary public health concerns, yet education of many stakeholders will still be necessary for them to recognize its importance.

One of our greatest challenges in SCA is the difficulty making financial and policy decisions related to screening for SCA. Societies may, on one hand, institute regulations requiring dissemination of AEDs, yet in parallel, find it difficult to reach consensus on requiring an ECG for sports-related screening (112). Funding such initiatives will inevitably prove costly, and neither industry nor governmental funding alone may be sufficient for this purpose. Reducing regulatory and reimbursement barriers may promote development of new avenues for intervention. Notably, studies in the United States have shown that the public may be open to novel concepts such as crowdsourcing of resuscitation for out-of-hospital SCA (113), and public policy can successfully enable risk screening and prevention of SCA (114).

Such studies demonstrate that paradigms outlined in this document are potentially feasible. We must avoid the real prospect that even the creation of cost-effective technologies that could plausibly save lives might be difficult to fund or implement. Educational efforts and societal commitment to these strategies for SCA are critical to their success. A call to action by major public and lay organizations will have a major impact on developing both governmental and societal priorities for both implementing strategies to reduce SCA as well as supporting necessary scientific investigation.

FUNDING DIRECTIONS. Research in SCA has long been funded by traditional agencies and/or industry. Research in SCA spans clinical, bioengineering, and cellular scales, which are likely to converge with industry. Novel funding opportunities that span these stakeholders are thus needed. Public support is critically important to create a mandate for the increases in government supported research necessary to advance SCA outcomes. Compared with the resources and breadth of investigations for all cancers, for example, National Institutes of Health funding for SCA research is modest. Foundations and large funding agencies such as the American Heart Association have a large role to play in funding seed grants to open innovative approaches to research for which traditional funding may be less suitable.

One major goal must be to fund studies that move the first point of contact from the time of SCA to tens of minutes or hours earlier. Promising approaches have been discussed and include developing a digital infrastructure to optimize resource allocation to at-risk individuals, wearable devices transmitting data

to detect "early warnings," alerting first responders and EMS networks. Although machine learning currently provides only modest accuracy, for instance in detecting arrhythmia from ambulatory ECGs (115), such studies show at least that it is feasible to automatically and continuously analyze biometric data to inform clinical decisions. A glimpse into the wealth of biometric sensors that could provide continuous data is provided by reports using fluctuations in facial skin reflectance (18) or in weight (116) to indicate heart rate.

Legal and ethical concerns on the application of technologies to acquire and analyze personal, medical, genetic, and other data must be addressed but are likely surmountable. Concerns may be mitigated if appropriate security measures are introduced by thoughtful design involving professional organizations, academia, patients, regulatory bodies, and industry, with appropriate guidelines (56). These discussions continue to encroach new territory.

CONCLUSIONS

Improvements in managing SCA will require a concerted effort across scientific disciplines, clinician groups and industry to combine technological innovation and rigorous scientific studies, and focused public policy initiatives. Advances can be considered in the categories of improving first response, improving our pathophysiological understanding, and using insights to prevent SCA in at-risk populations and individuals. These initiatives are diverse, and some are more well defined than others. Nevertheless, the enormity of the problem mandates urgent action at scientific, professional and society-wide levels.

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