JAMA | Review

Out-of-Hospital Cardiac Arrest in Apparently Healthy, Young Adults

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IMPORTANCE Out-of-hospital cardiac arrest incidence in apparently healthy adults younger than 40 years ranges from 4 to 14 per 100 000 person-years worldwide. Of an estimated 350 000 to 450 000 total annual out-of-hospital cardiac arrests in the US, approximately 10% survive.

OBSERVATIONS Among young adults who have had cardiac arrest outside of a hospital, approximately 60% die before reaching a hospital (presumed sudden cardiac death), approximately 40% survive to hospitalization (resuscitated sudden cardiac arrest), and 9% to 16% survive to hospital discharge (sudden cardiac arrest survivor), of whom approximately 90% have a good neurological status (Cerebral Performance Category 1 or 2). Autopsy-based studies demonstrate that 55% to 69% of young adults with presumed sudden cardiac death have underlying cardiac causes, including sudden arrhythmic death syndrome (normal heart by autopsy, most common in athletes) and structural heart disease such as coronary artery disease. Among young adults, noncardiac causes of cardiac arrest outside of a hospital may include drug overdose, pulmonary embolism, subarachnoid hemorrhage, seizure, anaphylaxis, and infection. More than half of young adults with presumed sudden cardiac death had identifiable cardiovascular risk factors such as hypertension and diabetes. Genetic cardiac disease such as long QT syndrome or dilated cardiomyopathy may be found in 2% to 22% of young adult survivors of cardiac arrest outside of the hospital, which is a lower yield than for nonsurvivors (13%-34%) with autopsy-confirmed sudden cardiac death. Persons resuscitated from sudden cardiac arrest should undergo evaluation with a basic metabolic profile and serum troponin; urine toxicology test; electrocardiogram; chest x-ray; head-to-pelvis computed tomography; and bedside ultrasound to assess for pericardial tamponade, aortic dissection, or hemorrhage. Underlying reversible causes, such as ST elevation myocardial infarction, coronary anomaly, and illicit drug or medication overdose (including QT-prolonging medicines) should be treated. If an initial evaluation does not reveal the cause of an out-of-hospital cardiac arrest, transthoracic echocardiography should be performed to screen for structural heart disease (eg, unsuspected cardiomyopathy) or valvular disease (eg, mitral valve prolapse) that can precipitate sudden cardiac death. Defibrillator implant is indicated for young adult sudden cardiac arrest survivors with nonreversible cardiac causes including structural heart disease and arrhythmia syndromes.

CONCLUSIONS AND RELEVANCE Cardiac arrest in apparently healthy adults younger than 40 years may be due to inherited or acquired cardiac disease or noncardiac causes. Among young adults who have had cardiac arrest outside of a hospital, only 9% to 16% survive to hospital discharge. Sudden cardiac arrest survivors require comprehensive evaluation for underlying causes of cardiac arrest and cardiac defibrillator should be implanted in those with nonreversible cardiac causes of out-of-hospital cardiac arrest.

Multimedia

Supplemental content

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Sudden cardiac arrest and sudden cardiac death in apparently healthy young adults (aged 18-40 years) are catastrophic life events that have substantial negative effects on patients and their family members. In the US, recent data estimate between 350 000 and 450 000 annual total adult out-of-hospital cardiac arrests, approximately 90% of which are fatal.[1] The causes of sudden cardiac arrest in young adults are heterogeneous and may include genetic and acquired factors, such as hypertension, dyslipidemia, and physical inactivity. The 3 outcomes following out-of-hospital cardiac arrest in previously healthy young adults are (1) death out of the hospital, (2) resuscitation with subsequent in-hospital death, or (3) survival to discharge (including long-term survival). In this review, we summarize the epidemiology and pathophysiology of out-of-hospital cardiac arrest and sudden cardiac death, and the clinical assessment and treatment of apparently healthy young adults with no known structural heart or coronary artery disease (CAD), who are resuscitated from sudden cardiac arrest (see **Box**).

Box. Frequently Asked Questions About Out-of-Hospital Cardiac Arrest in Apparently Healthy, Young Adults

What is the survival rate after out-of-hospital cardiac arrest in young adults?
Approximately 60% of young adults aged 18 through 39 years who experience cardiac arrest outside a hospital die before reaching the hospital. Overall, 9% to 16% survive, of whom 90% have favorable neurological outcomes.

How can clinicians decrease the risk of recurrent sudden cardiac arrest?
If a noncardiac (eg, overdose) or reversible cardiac cause (eg, ST elevation myocardial infarction or coronary anomaly) for sudden cardiac arrest is identified, treatment of the underlying cause can reduce the risk of recurrent episode. If noncardiac or reversible cardiac causes are ruled out, an implantable cardioverter-defibrillator (ICD) is recommended because these survivors remain at high risk of recurrent lethal ventricular arrhythmias. After an ICD is implanted, adjunctive therapy (eg, amiodarone, catheter ablation) and lifestyle modifications for certain genetic arrhythmia syndromes may reduce ventricular arrhythmia recurrence.

What are the benefits and yields of genetic testing after out-of-hospital cardiac arrest?
Genetic testing of young adults who experienced a sudden cardiac arrest may be useful for diagnosis and treatment of cardiomyopathies and primary arrhythmia syndromes. Genetic testing of first-degree family members may help identify asymptomatically affected relatives. The reported diagnostic yield of genetic testing among individuals with sudden arrhythmic death syndrome (normal heart at autopsy with no cause of death identified) is 13% to 34%, whereas the yield of genetic testing of survivors of sudden cardiac arrest resuscitated from idiopathic ventricular arrhythmias is 2% to 22%.

Methods

We conducted a PubMed literature search for English-language articles using the keywords *sudden cardiac death*, *out of hospital cardiac arrest*, and *young* published between January 1, 2000, to December 13, 2024. Among 4340 records identified, we excluded studies involving patients with known underlying disease, infants and children, and case reports. We reviewed a total of 1035 articles and included studies that addressed the epidemiology, pathophysiology, clinical practice, or prognosis of out-of-hospital cardiac arrest in young adults. Of the 125 studies included in this review; 11 were randomized clinical trials; 4 meta-analyses; 22 longitudinal, prospective observational studies; 64 retrospective observational studies; 3 guidelines documents; 6 consensus statements; 11 reviews; 1 basic research study; an editorial; a Centers for Disease Control and Prevention (CDC) brief report; and a CDC web page reference. This review primarily summarizes evidence published for young adults aged 18 to 40 years, but was extended to 50 years when certain data were limited in this age range.

Overview of Definitions and Classification Scheme

Out-of-hospital cardiac arrests are "events that occur out of the hospital in which an emergency medical services (EMS) rescuer detects no signs of circulation or mechanical cardiac activity."[2-4] This definition does not specify "suddenness" of cardiac arrest (ie, duration of symptoms prior to event), or "unexpectedness." The case definitions of *sudden cardiac death* in clinical registries or epidemiological research vary based on the use of death certificates,[5-7] reviews of EMS[8] or hospital records[6,9-12] or whether the cases met the criteria of epidemiological definitions (eg, World Health Organization),[13] society definitions (eg, Cardiac Arrest Registry to Enhance Survival [CARES]),[3,4] outcomes of clinical trials,[14-17] or the definition required in pathology-based studies.[18-27] Because most individuals who died from sudden cardiac death do not have autopsies to confirm the underlying cause, sudden cardiac death is typically presumed to be of cardiac etiology.[28] A person resuscitated from an out-of-hospital cardiac arrest to hospitalization is classified as having *resuscitated out-of-hospital cardiac arrest*, regardless of subsequent in-hospital death or survival to discharge, the latter of whom are *sudden cardiac arrest survivors*. A summary of these definitions is shown in **Figure 1**.

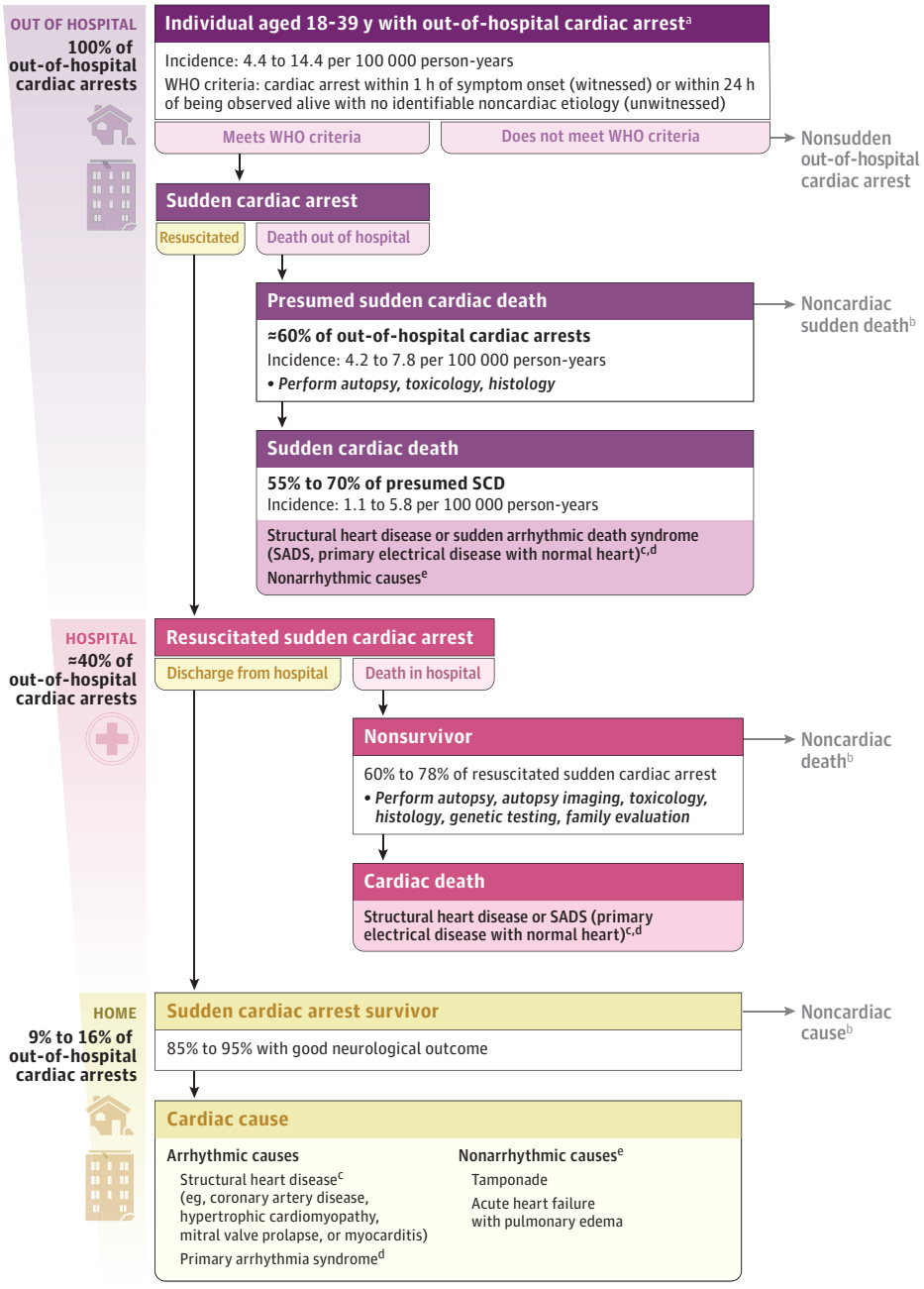
Out-of-Hospital Cardiac Arrest

The reported worldwide incidence of out-of-hospital cardiac arrest among adults younger than 40 years is 4.4 to 14.4 per 100 000 person-years (**Table 1**).[8,11,29,30] Few worldwide data exist on outcomes following an event specifically in young adults. However, among 206 individuals aged 18 to 44 years who had arrested outside the hospital in Taiwan from 2017 to 2021, approximately 60% had sudden death (ie, presumed sudden cardiac death) and approximately 40% were resuscitated to hospitalization, thus classified as having resuscitated sudden cardiac arrest.[37]

Pathophysiology of Cardiac Arrest

Arrhythmias that cause cessation of cardiac mechanical activity[2,4,9] include tachyarrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF), and bradyarrhythmias. VT, VF, and bradyarrhythmias are acutely reversible with defibrillation or pacing and may be caused by myocardial injury via acquired cardiac disease (eg, ischemia, inflammation, pressure overload), inherited cardiac disease (eg, arrhythmia syndromes), acute electrolyte imbalance (eg, hyperkalemia due to kidney failure), or autonomic dysregulation. Approximately 10% of persons who have had cardiac

Figure 1. Worldwide Incidence of Out-of-Hospital Cardiac Arrest, Presumed Sudden Cardiac Death, and Sudden Cardiac Death in Young Adults



[a]Meeting Cardiac Arrest Registry to Enhance Survival (CARES) criteria emergency medical service primary impression "cardiac arrest."

[b]Includes pulmonary embolism, overdose, hemorrhage, neurological, diabetic ketoacidosis, sepsis, gastrointestinal disorders, aortic aneurysm, aortic dissection.

[c]Structural heart disease includes coronary artery disease, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, dilated cardiomyopathy, valvular heart disease (mitral valve prolapse, aortic stenosis), left ventricular hypertrophy, myocarditis.

[d]Sudden arrhythmic death syndrome, also referred to as primary electrical disease with normal heart or unexplained sudden cardiac death in nonsurvivors. This condition is termed *primary arrhythmia syndrome* in survivors.

[e]Tamponade, myocardial infarction with wall rupture, acute heart failure with pulmonary edema.

WHO indicates World Health Organization.

arrests out of the hospital have pulseless electrical activity,[8] characterized by the absence of a palpable pulse in an unconscious person with organized electrical activity other than VT or VF on electrocardiogram (ECG).[38] Underlying conditions responsible for pulseless electrical activity include acute heart failure, cardiac tamponade, acidosis, hemorrhage, hypoxia, or tension pneumothorax. Asystole is defined as a complete absence of electrical and mechanical cardiac activity.

These terminal rhythms can be due to unrecognized underlying structural heart disease such as CAD or cardiomyopathy, arrhythmia syndromes such as long QT syndrome (LQTS) or Brugada syndrome, and conditions that predispose to arrhythmias such as muscular dystrophies[39] but may also be caused by noncardiac conditions such as neurocardiogenic VF due to intracranial hemorrhage,[40] bradyarrhythmias secondary to opioid overdose,[18] and serum electrolyte disorders.[41] Opioids, stimulants (eg, cocaine), or supplements (eg, herbal medications, energy drinks)[42,43] can also cause sudden cardiac arrest via QT prolongation,[44] predisposing to polymorphic VT, also called torsades de pointes. Congenital conditions such as anomalous coronary artery origin with a course between the aorta and pulmonary artery can predispose to cardiac arrest via myocardial ischemia.[45]

Table 1. Studies of Sudden Cardiac Death in Young Adults

Source	Setting	Study years	Study type	Age range, y	Data source	No. of individuals	Autopsy rate, %	Toxicology	Incidence/100 000 patient-years	Cardiac cause, %	SADS or SUD, %	Witnessed, %	During sleep, %	During exercise, %
Out-of-hospital cardiac arrest														
Kitamura et al,[8] 2010	Japan (Osaka)	1998-2007	Prospective	13-49	EMS records	2220	0		3.8			22-32.1		
Meyer et al,[11] 2012	US (King County)	1980-2009	Retrospective	25-35	EMS and medical records, death certificates, autopsy reports	361	72.9	Overdoses excluded	4.4		19.4	66.7		24.5
Paratz et al,[29] 2022	Australia (Victoria)	2019-2021	Prospective	36-49	Medical records, autopsy reports	754	67.5	Yes, positive in 17.1% (for ages 1-50 y)	30.2	55	10.9	28	41.2	9
Empana et al,[30] 2022	Europe	2012-2017	Retrospective	18-39	Registry data		0		14.4 (Men), 9.5 (women)					
Range									3.8-30.2	55	10.9-19.4	28-66.7	41.2	9-24.5
Presumed sudden cardiac death														
Hua et al,[31] 2009	China (4 regions)	2005-2006	Retrospective	25-34	National data, medical records, death certificates, autopsy reports	284	Rare		7.8					
Hendrix et al,[32] 2010	The Netherlands (12 provinces)	1996-2006	Retrospective	30-39	Death certificates, forensic database	1458	0		5.5 (Men), 2.4 (Women)					
Margey et al,[33] 2011	Ireland	2005-2007	Retrospective	15-35	National data, autopsy reports	292	70.5	Yes, positive in 21.1%	2.9	64	26.7			7.8
van der Werf et al,[34] 2016	The Netherlands (4 regions)	2008-2011	Retrospective	1-44; Median, 38 (IQR, 29-42)	EMS records, autopsy reports, general practitioners	390	43	Rarely, at coroner's discretion	4.6	70	13.6		33	8
Bonny et al,[10] 2017	Cameroon (Douala)	2013	Retrospective	18-39	EMS and medical records		Rare		11.9 (Age range,18-29 y) 42 (Age range, 30-39 y)					
Tseng et al,[18] 2018	US (San Francisco)	2011-2014	Prospective	18-39	EMS and medical records, forensic and autopsy reports	32	97	Yes, positive in 18.8%	4.2	59	9	22	50	6
Zhang et al,[12] 2019	China (Xinjiang)	2015	Retrospective	18-35	Medical records, patient interview		Rare		4.2					
Empana et al,[30] 2022	Europe	2012-2017	Retrospective	18-39	Registry data		0		6.7 (Men) 4.3 (Women)					
Carrington et al,[24] 2023	Portugal (9 districts)	2012-2016	Retrospective	1-40 Mean (SD): 32 (7)	Medical records, forensic database	159	100	Yes, none positive	2.4	58	32.1		17.5	15
Range (except Bonny et al[10])									2.4-7.8	40.7-67	9-32.1	22	17.5-50	6-15

(continued)

Table 1. Studies of Sudden Cardiac Death in Young Adults (continued)

Source	Setting	Study years	Study type	Age range, y	Data source	No. of individuals	Autopsy rate, %	Toxicology	Incidence/100 000 patient-years	Cardiac cause, %	SADS or SUD, %	Witnessed, %	During sleep, %	During exercise, %
Sudden cardiac death														
Winkel et al,[35] 2011	Denmark	2000-2006	Retrospective	1-35 Median (IQR), 28 (21-33)	EMS and medical records, death certificates, autopsy reports, police reports	469	75	Done in 23.9% of SUDs, none positive	1.9		29	45	34	11
Bagnall et al,[20] 2016	Australia and New Zealand	2010-2012	Prospective	21-35	Medical records, death certificates, autopsy reports	490	100	Yes	1.1-3.2		40		38	15
Wisten et al,[21] 2017	Sweden	2000-2010	Retrospective	18-35	National data, medical records, death certificate	552	95	Positive toxicology cases excluded	1.2-5.8 (Men), 0.5-2.2 (women)		31	40	38	14
Tseng et al,[18] 2018	US (San Francisco County)	2011-2014	Prospective	18-39	EMS and medical records, forensic and autopsy reports	19	97	Yes, none positive	2.4		18	37	39	21
Ha et al,[22] 2020	Australia	2000-2016	Retrospective	1-35 Mean (SD): 28 (7)	Registry data, medical records, autopsy reports	2006	95	Done in 97%, positive toxicology cases excluded	0.9-1.5		14		38	7
Rücklová et al,[23] 2022	Czech Republic (5 regions)	2014-2019	Retrospective	21-40	Medical records, autopsy and police reports	232	93	Done in 51%	3.4		11.8	27	38	7
Lynge et al,[36] 2023	Denmark	2002-2009	Retrospective	21-40	Registry data, medical records, death certificates, autopsy reports	620	55		2.7 (Age, 21-25 y) 4.4 (Age, 26-30 y) 6.5 (Age, 31-35 y) 10.7 (Age, 36-40 y)			42	32	9
Range									0.5-10.7		11.8-40	27-45	32-39	7-21

Abbreviations: EMS, emergency medical services; empty cells, not applicable; SADS, sudden arrhythmic death syndrome; SUD, sudden unexplained death.

Etiology

The most common etiologies of out-of-hospital cardiac arrest in US adults aged 25 to 35 years are CAD (43%), followed by sudden unexplained death (14%).[11] In a Canadian study, the most common etiologies of cardiac arrest among 131 individuals aged 25 through 34 years were structural heart disease (including cardiomyopathy and myocarditis) and sudden unexplained death, each accounting for 28%.[46] Among hospitalizations in the US for overdoses, opioid-associated out-of-hospital cardiac arrest increased from 1% of hospitalizations in 2000 to 2% in 2013,[47,48] although recent CDC data show a decrease in opioid overdose deaths from 84 181 in 2022 to 81 083 in 2023.[49] Positive drug toxicology was reported in 17.1% of out-of-hospital cardiac arrests among persons aged 1 to 50 years (median, 42.4 years) in an Australian study from April 2019 to April 2021.[29]

Outcomes

A retrospective observational cohort study from the CARES registry reported 101 968 out-of-hospital cardiac arrests in the US from 2006 through 2013, of which approximately 6% occurred among individuals aged 20 through 39 years; survival rate to hospital discharge ranged from 11% (30-39 years) to 16% (20-24 years).[50] Approximately 85% to 95% of out-of-hospital cardiac arrest survivors aged 20 through 49 years were discharged with good neurological outcome, as defined by a Cerebral Performance Categories scale of 1 or 2.[2,50,51] In an Australian registry conducted from 2000 through 2009 involving 3912 patients aged 16 though 39 years with out-of-hospital cardiac arrest, the survival rate was 8.8%.[52] The overall survival rate of young adults experiencing out-of-hospital cardiac arrest was 9% in a prospective US study from 2005 through 2007 involving 665 persons aged 20 through 39 years, and increased to 34.8% for those with bystander-witnessed VT or VF who were more likely to receive prompt initial cardiopulmonary resuscitation (CPR) or automated external defibrillator use[53] (Figure 1).

Sudden Cardiac Death

Epidemiology

The worldwide incidence of presumed sudden cardiac death is 4.2 to 7.8 per 100 000 person-years in adults younger than 40 years and 23 to 34 per 100 000 person-years in adults aged 40 through 49 years (Table 1).[12,18,30-32] In a US study from 1999 through 2015 (n = 31 492) with race determined by examination of death certificates, Black individuals younger than 34 years had a higher incidence of presumed sudden cardiac deaths (1.88 per 100 000 person-years in 2015) than Hispanic individuals (0.66 per 100 000 person-years), and White individuals (1.17 per 100 000 person-years),[54] which may be due to inequitable access to care[55] and racial disparities among out-of-hospital resuscitation attempts. Several US studies have found that White individuals were more likely to receive bystander CPR after a witnessed cardiac arrest and postresuscitation care than were Black and Hispanic persons.[56,57] Incidence of presumed sudden cardiac death among adults younger than 40 years in Cameroon was higher at 12 to 42 per 100 000 person-years (Table 1).[10]

Over a 3-year study period (2011-2014), autopsies of 32 persons aged 18 through 39 years with presumed sudden cardiac deaths in San Francisco demonstrated that 40% had a noncardiac cause.[18] Even when a lethal rhythm is documented at the time of sudden death, including VT or VF[40] or complete heart block,[18] death may be due to underlying noncardiac causes, such as intracranial hemorrhage or drug overdose. Autopsy rates to confirm the cause of presumed sudden cardiac death after an out-of-hospital cardiac arrest vary widely depending on sex, country, region, and study.[58] Combined data from 4 autopsy-based studies worldwide that include 529 presumed sudden cardiac deaths among those aged 14 through 44 years, with autopsy rates ranging from 43% to 100%, demonstrated that cardiac causes accounted for 64% of sudden deaths. The most frequent cardiac causes were coronary artery disease (22% of all presumed sudden cardiac deaths), sudden arrhythmic death syndrome (16%), hypertrophic cardiomyopathy (12%), and cardiomyopathy (11%). The most frequent noncardiac causes were neurological (9.3%), pulmonary (8.1%), overdose (4.7%), and infection (4.7%).[18,24,33,34]

The incidence of sudden cardiac death defined by autopsy for individuals younger than 40 years is 1.1 to 5.8 per 100 000 person-years (Table 1).[20-23,35,36] The distribution of underlying causes of sudden cardiac arrest in resuscitated patients differs from those who were not resuscitated (ie, sudden cardiac death) with significantly more noncardiac causes in the latter.[59] Among autopsy studies of persons younger than age 30 years who had sudden cardiac death, the most common cause was sudden arrhythmic death syndrome with normal heart on postmortem examination (36%-49%).[20,21] The proportion of cases attributable to CAD increased with age, from 6% to 14% in persons younger than 30 years and to 19% to 46% in persons aged 30 years or older.[20,21,35,36] Unexpected myocarditis is another relatively common underlying cause of sudden cardiac death in young adults.[20,21,35] Autopsy-confirmed dilated cardiomyopathy was more frequently identified among individuals who were older than 30 years (10%) than individuals who were younger than 30 years (5%).[20,21] In 1 study of sudden cardiac death in young adults (n = 2006, median age, 28 years), CAD was more common in males (44%) than in females (27%), whereas unspecified cardiomyopathy (5% males vs 7% females, $P = .04$), myocarditis (9% males vs 14% females, $P < .001$), and valvular heart disease (2% males vs 7% females, $P < .001$) were more common in young females.[22]

Autopsy-based studies of individuals with sudden cardiac death aged 18 to 50 years reported that 65% to 78% had at least 1 known cardiovascular disease (CVD) risk factor (ie, hypertension, diabetes, dyslipidemia, obesity, smoking) before death.[18,60] In these studies, compared with the reported prevalence of individual risk factors in the general US population among those aged 20 through 44 years,[61] the reported prevalence of hypertension and diabetes was higher among those with sudden cardiac death (22%-24% vs 12% and 12%-19% vs 4%, respectively).

Clinical Presentation of Sudden Cardiac Death

In young adults, sudden cardiac arrest occurs more frequently at rest and during sleep than during exercise. In a study in which 153 persons aged 19 to 34 years, only 8 (5.2%) occurred during sports-related activity.[62] Other studies have found that among young adults, the sudden cardiac death occurred during exercise in 7% to 15%, whereas 30% to 40% died during sleep.[20-23,35,36]

Sudden cardiac death during sexual intercourse is rare. An autopsy-based study involving 6847 persons with sudden cardiac death in the UK reported that 17 (0.2%) occurred during or within an hour of sexual intercourse. The mean age of the 17 who died suddenly was 38 years, 11 (65%) of whom were men. The autopsy results showed

that 9 cases (53%) had a structurally normal heart consistent with sudden arrhythmic death syndrome.[63]

Resuscitated Sudden Cardiac Arrest

Approximately 40% of young adults who have had cardiac arrest outside of a hospital survive to hospitalization and are thus classified has having resuscitated sudden cardiac arrest (Figure 1).

Evaluation and Management of Young Adults Resuscitated From Sudden Cardiac Arrest

Figure 2 shows an overview of the evaluation of young adults who had been resuscitated from sudden cardiac arrest. Emergency workup includes a 12-lead electrocardiogram (ECG) after return of spontaneous circulation, toxicology testing, a bedside neurological assessment, and neuroimaging (eg, head computed tomography [CT]) after the patient has stabilized. If ECG shows STEMI or unstable arrhythmia, the patient should be referred for emergency coronary angiography. Complete coronary revascularization should be performed for acute ischemia causes, including surgery if coronary anomaly is found. **Figure 3** shows representative ECGs of high-risk arrhythmia conditions: LQTS (present in 13% of young adults resuscitated from sudden cardiac arrest),[64] Wolff-Parkinson-White syndrome (5%-12%),[64,65] arrhythmogenic right ventricular cardiomyopathy (10%),[64] and Brugada syndrome (<1%).[66] Repeating 12-lead ECGs are important during evaluation because ECG waveforms, particularly type 1 waveform in Brugada syndrome[67] and the QT interval, may show day-to-day and circadian variation[68] and variation after the initial resuscitation due to ischemia, autonomic fluctuations, and electrolyte derangements (eg, hypokalemia, hypomagnesemia) after sudden cardiac arrest.[69]

If the corrected QT interval remains at 460 milliseconds or longer for females or 450 milliseconds or longer for males[70] beyond 6 days after resuscitation,[71] patients should be evaluated for LQTS, the most common arrhythmia syndrome causing sudden cardiac arrest.[64] In patients with LQTS, a prolonged QT interval results in the end of the T wave often exceeding half of the RR interval, along with broad, biphasic, or notched T waves with beat-to-beat alternans (Figure 3A).[72] In a study of 647 untreated patients older than 28 years with LQTS, 13% experienced out-of-hospital cardiac arrest or sudden death before age 40 years.[73] LQTS can be either congenital or acquired, most commonly due to drugs such as antiarrhythmics, antipsychotics, antidepressants, or antibiotics (a continuously updated list can be found at https://crediblemeds.org/). However, some acquired LQTS cases may have underlying congenital LQTS unmasked by drugs or other predisposing factors such as electrolyte abnormalities (hypokalemia, hypomagnesemia, and hypocalcemia) or bradyarrhythmias. Evaluation for acquired LQTS should be reassessed after resolution of these factors.[74]

In Brugada syndrome, type 1 pattern (ie, coved shape of ST segment) in leads V1 and V2 can sometimes be recorded when these leads are moved to the second or third intercostal spaces instead of the typical fourth intercostal space (Figure 3B).[74] In preexcitation syndromes (ie, Wolff-Parkinson-White), the observed delta waves are a marker for potential atrioventricular reentrant tachycardia or VF via preexcited atrial fibrillation (Figure 3C).[75] In some cases of arrhythmogenic right ventricular cardiomyopathy, epsilon waves that represent delayed right ventricular conduction can be observed in the ST segment in the right precordial leads (Figure 3D).[76]

Clinicians evaluating persons hospitalized after resuscitation from out-of-hospital cardiac arrest should review documented cardiac rhythm from EMS records and the circumstances of arrest, including witness accounts. They should obtain a family history of heart disease for at least 3 generations, syncope, sudden cardiac arrest, or sudden cardiac death and should evaluate for use of QT-prolonging medications, substance use (eg, cocaine, methamphetamine, or ketamine), and supplements (eg, kratom, tianeptine).[43,77,78] If the cause is not determined with initial laboratory tests (eg, serum electrolytes or troponin), coronary angiography, or imaging examinations (eg, chest x-ray for pneumothorax, bedside ultrasound for pericardial tamponade, aortic dissection, or hemorrhage, and head-to-pelvis CT scan for intracranial or chest or pelvis emergencies), transthoracic echocardiography should be performed to screen for structural heart disease such as unsuspected cardiomyopathy or valvular disease such as mitral valve prolapse, a condition in young persons (especially females) that can precipitate sudden cardiac death due to VF or sustained VT.[79]

If transthoracic echocardiography reveals a normal structural heart and ECG shows no findings consistent with an arrhythmia syndrome, further evaluation with electrophysiological study (EPS), sodium channel blocker challenge, or stress ECG testing may be performed (Figure 3). Because delta waves in Wolff-Parkinson-White syndrome and Brugada pattern may not be apparent on initial ECGs after resuscitation, an EPS can identify and treat accessory pathways responsible for cardiac arrest.[80] A sodium channel blocker challenge during EPS involves administration of drugs such as flecainide, ajmaline, and pilsicainide to unmask a type 1 Brugada ECG pattern.[74] Stress ECG testing can identify catecholaminergic polymorphic VT (CPVT) if bidirectional VT is observed during exercise, or LQTS if the QT interval does not shorten with exercise or remains prolonged during the recovery phase.[74,81]

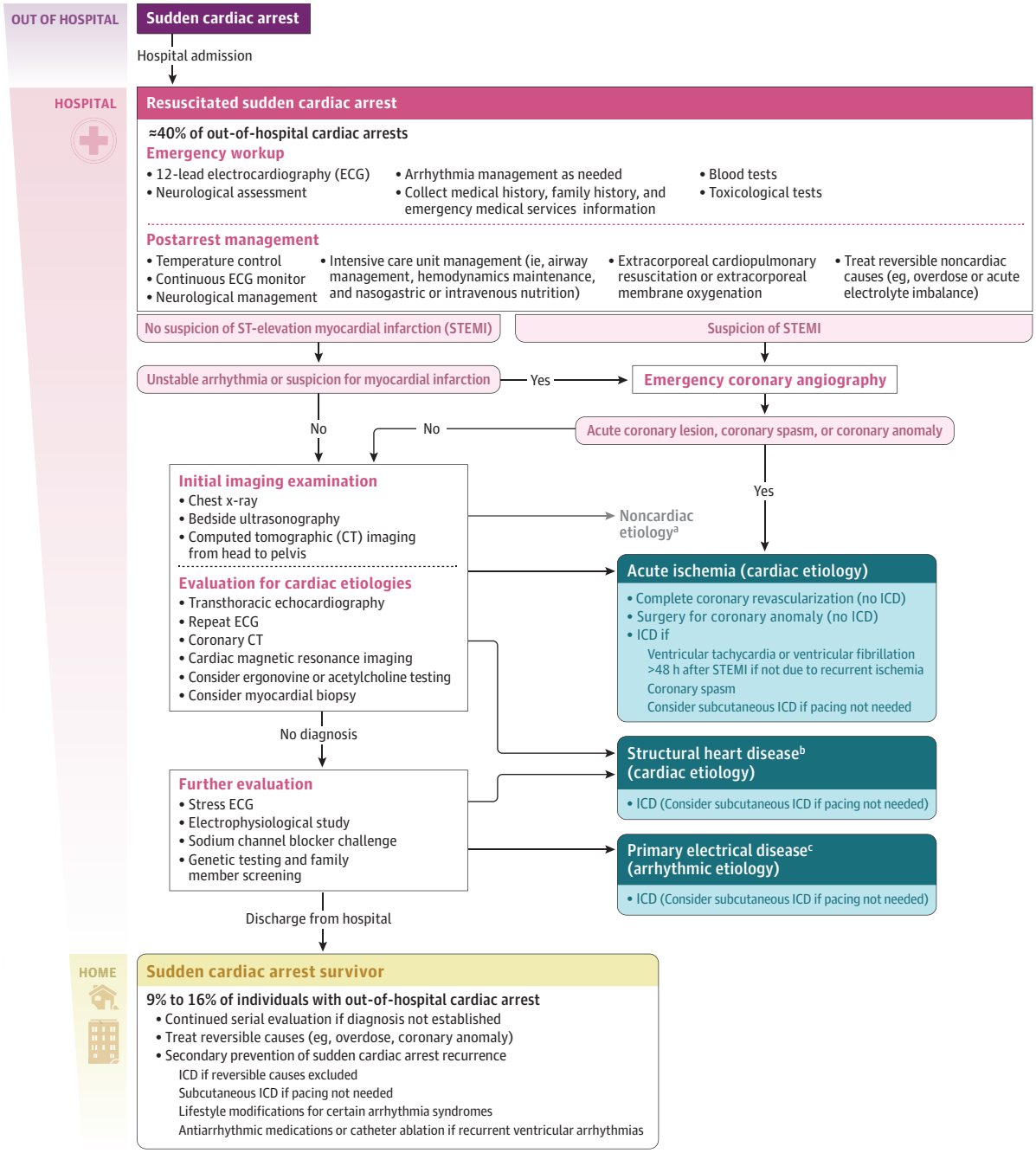
Outcomes After Resuscitation

An estimated 60% to 78% of young adults hospitalized after resuscitation from sudden cardiac arrest do not survive to hospital discharge (Figure 1).[52,53,82] This in-hospital mortality rate is similar to that of older adults who were resuscitated to hospitalization (≈ 65%).[59]

Secondary Prevention of Recurrent Sudden Cardiac Arrest

For certain noncardiac causes of out-of-hospital cardiac arrest (eg, hemorrhage, infection, hypoxia) or reversible cardiac causes (eg, acute ischemia due to ST-segment elevation MI or coronary anomaly), treatment of the underlying condition reduces risk of recurrent sudden cardiac arrest. For patients who survived an out-of-hospital cardiac arrest that involved stimulants or supplements, avoidance of these substances can prevent recurrence. For patients with an event caused by an opioid overdose, counseling, education, and medications to treat opioid use disorder (eg, buprenorphine, methadone, and naltrexone) are recommended to decrease the risk of recurrence.[48] Survivors with a previously undiagnosed seizure disorder should be treated and closely followed up given a more than 20-fold higher risk of sudden unexplained death in persons with epilepsy compared with the general population.[83] For survivors with coronary anomalies such as congenital atresia of the left main artery and anomalous aortic origin of a coronary artery, surgical intervention is recommended to prevent

Figure 2. Evaluation of the Resuscitated Young Adult Sudden Cardiac Arrest Patient



[a]Includes aortic dissection, gastrointestinal bleeding, diabetic ketoacidosis, infection, neurologic causes, overdose, pulmonary embolism, renal failure, respiratory causes.

[b]Includes chronic coronary artery disease, cardiomyopathy (eg, arrhythmogenic right ventricular cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy, left ventricular noncompaction), hypertrophy, myocarditis, sarcoidosis, valvular heart diseases (eg, mitral valve prolapse).

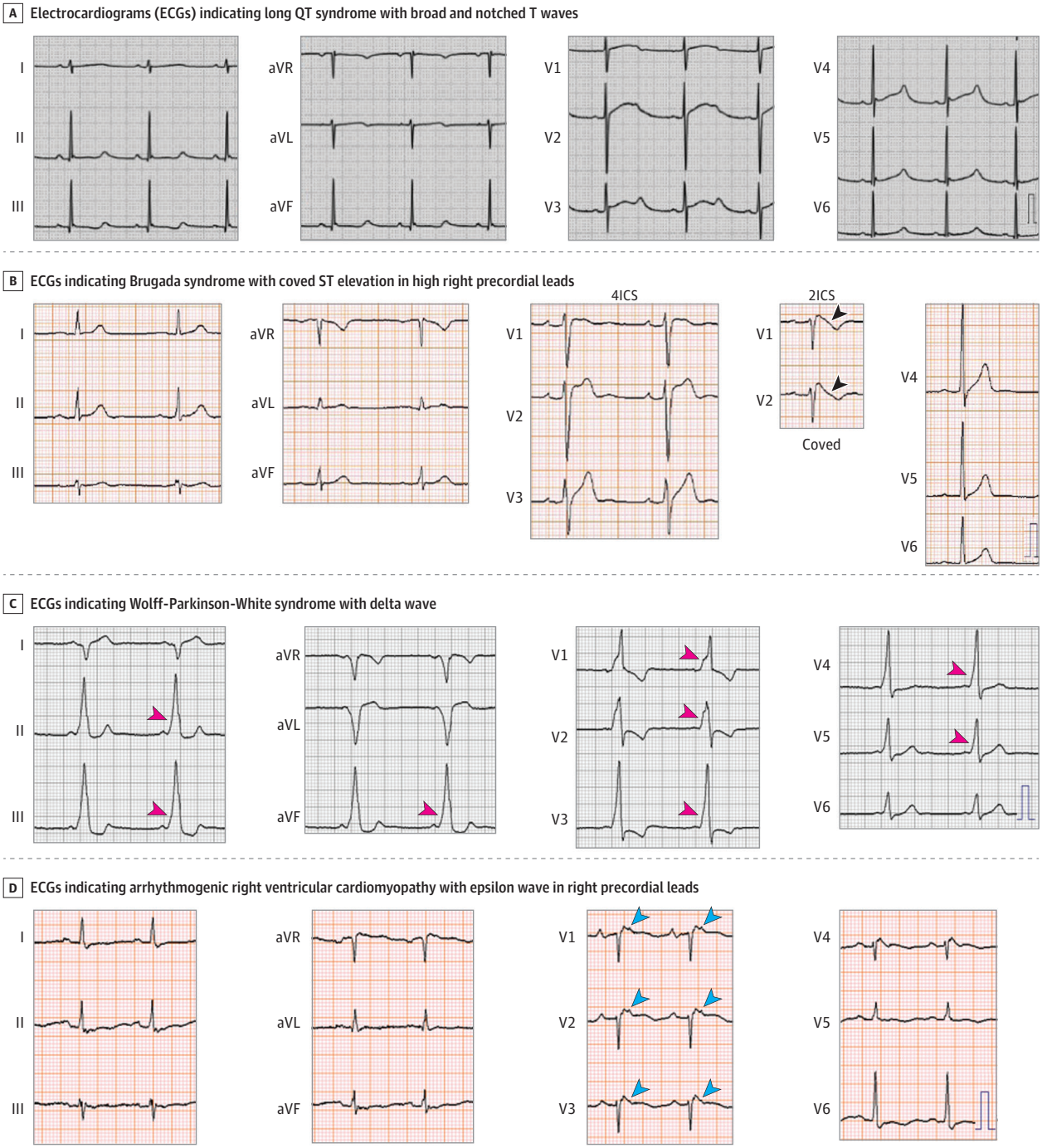
[c]Includes long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, idiopathic ventricular fibrillation, bradyarrhythmias.

ICD indicates implantable cardioverter-defibrillator.

recurrent sudden cardiac arrest.[74,80,84] Among persons presenting with VF due to acute MI with coronary plaque rupture and/or thrombus (typically <48 hours), risk of a recurrent event is reduced after early revascularization such as percutaneous coronary intervention. Implantable cardioverter-defibrillator (ICD) is not indicated for secondary prevention.[74,85]

Sudden cardiac arrest survivors in whom noncardiac or reversible causes are excluded remain at high risk of recurrent ventricular

Figure 3. Representative Electrocardiographs of High-Risk Arrhythmia Conditions



B, The black arrowhead points to the coved ST elevation. C, The pink arrowheads point to the delta wave. D, The blue arrowheads point to the epsilon wave.

arrhythmias.[86] Based on landmark trials in the 1990s and 2000s, ICD implants as secondary prevention is indicated for these patients,[87-89] particularly for those diagnosed with structural heart disease, such as dilated cardiomyopathy, or arrhythmia syndromes, such as LQTS, Brugada syndrome, and CPVT (Figure 2, **Table 2**). An alternative to conventional ICD with transvenous leads is a subcutaneous ICD in which the lead is tunneled subcutaneously instead of passing through the blood vessels. Subcutaneous ICDs have fewer long-term lead-related complications than conventional ICDs, so they may be reasonable for younger patients with primary arrhythmia syndromes. However, according to recent European Society of Cardiology guidelines (class IIa, level B), conventional transvenous ICDs are recommended for patients who require pacing for bradyarrhythmias or LQTS, cardiac resynchronization therapy with

Table 2. Secondary Prevention in Young Adult Survivors of Sudden Cardiac Arrest[24]

Strength of recommendation[a]	General SCA	Idiopathic VF	Long QT syndrome	Brugada syndrome	Catecholaminergic polymorphic VT	Coronary anomalies	Vasospastic angina	Chronic CAD	Dilated or hypokinetic nondilated cardiomyopathy	Arrhythmogenic right ventricular cardiomyopathy	Hypertrophic cardiomyopathy	Myocarditis	Cardiac sarcoidosis
I	ICD	ICD	ICD with β-blocker[b]; LCSD[c]; Avoid QT-prolonging drugs, genotype-specific triggers for arrhythmias; Electrolytes correction	ICD; avoid cocaine, excessive alcohol intake, or drugs that may induce ST elevation in right precordial leads; fever control	ICD with β-blocker and flecainide; avoid precipitants such as competitive sports, strenuous exercise, and stressful environments	Surgery		ICD[d]	ICD	ICD with β-blocker	ICD	ICD in chronic phase	ICD
IIa			ICD or LCSD[e]		LCSD[f]		ICD					Antiarrhythmics in acute phase[g]	
IIb	Amiodarone; ablation (otherwise see specific etiologies)[c]							Ablation with ICD					
III			Invasive EPS[h]					Antiarrhythmics	High-intensity exercise[i]				

Abbreviations: CAD, coronary artery disease; EPS, electrophysiological study; ICD, implantable cardioverter-defibrillator; LCSD, left cardiac sympathetic denervation; LQTS, long QT syndrome; SCA, sudden cardiac arrest; VF, ventricular fibrillation; VT, ventricular tachycardia.

[a] Class I indicates strong evidence or consensus that a procedure or treatment is beneficial ("recommended" or "indicated"); class IIa, weight of evidence in favor of its efficacy ("should be considered"); class IIb, the efficacy is less well established by evidence or consensus ("may be considered"); and class III, evidence or consensus shows the procedure or treatment is ineffective or potentially harmful ("not recommended").

[b] Mexiletine for long QT type 3 instead of β-blocker.

[c] When ICD therapy is unavailable, contraindicated, or declined treat with amiodarone or ablation.

[d] More than 48 hours after myocardial infarction.

[e] When β-blocker or genotype-specific therapies are not tolerated or contraindicated at the therapeutic dose.

[f] When β-blocker and flecainide are either not effective, not tolerated, or contraindicated.

[g] Amiodarone and β-blocker.

[h] To evaluate for ventricular arrhythmias and arrhythmia syndromes such as Wolff-Parkinson-White syndrome or Brugada syndrome that can precipitate sudden cardiac arrest.

[i] In cases of *LMNA* variants.

coronary sinus lead, or antitachycardia pacing for VT.[74,90] Despite ICD implants, survivors remain at risk of spontaneous VT or VF, with a reported recurrence rate of 37% during a 2-year follow-up among Australian adults.[91] Thus, adjunctive pharmacotherapy, especially amiodarone,[92,93] or catheter ablation[92,94,95] may be used in combination with ICD.

A summary of recent European recommendations for secondary prevention of recurrence in survivors of sudden cardiac arrest is shown in Table 2.[74] Certain medications and lifestyle habits such as exercise should be avoided in patients with specific primary arrhythmia syndromes. For patients with LQTS, QT-prolonging medications (eg, ciprofloxacin and odansetron) and genotype-specific triggers that increase ventricular arrhythmia risk (strenuous exercise in LQT type 1 [LQT1]; emotions such as extreme stress or fear, and sudden loud noise in LQT2) should be avoided. Individuals with Brugada syndrome should avoid excessive alcohol use and certain drugs (eg, tricyclic antidepressants, class 1A or class 1C antiarrhythmics such as procainamide or flecainide, cocaine, and other drugs; see https://www.brugadadrugs.org/drug-lists/). Fever (temperature >38.0 °C) can increase risk of VF in patients with Brugada syndrome so should be promptly reduced with antipyretics.[74,96] For patients with CPVT, strenuous exercise and high psychological stress may increase adrenergic activity and should be avoided.

Prognosis in Sudden Cardiac Arrest Survivors

The 10-year survival rate of sudden cardiac arrest survivors aged 40 years or younger was 90% in an Australian registry.[97] The rate of recurrent arrest (both out of and in the hospital) or death in survivors aged 18 to 39 years in a Swedish registry was approximately 15% a year after the out-of-hospital cardiac arrest.[98] One-year overall mortality of subcutaneous ICD recipients aged 15 to 34 years was 4.3% in one cohort,[90] whereas the VT or VF recurrence rate estimated by subcutaneous ICD recording in secondary prevention recipients (age not reported) in a separate study was 9.9% at 1 year and 15.8% at 3 years.[99]

Genetic Testing

Postmortem Genetic Investigation

Postmortem genetic testing to investigate the association between gene variants (genotype) and etiology assessments by autopsy (phenotype) has increased recently for research purposes and to inform family members about potentially inherited disease. Genetic studies of sudden deaths in young adults demonstrate that the genetic yield for pathogenic or likely pathogenic variants in autopsy-confirmed sudden cardiac deaths ranged from 13% to 34% (see eTable 1 in the Supplement).[20,100-103] These yields are obtained after careful etiologic assessment by comprehensive postmortem investigation (including toxicology) for accurate genotype-phenotype correlation.

Sudden arrhythmic death without an apparent cause identified by autopsy is often attributed to arrhythmia syndromes. Of 490 prospectively ascertained sudden cardiac deaths by autopsy in persons aged 1 to 35 years in Australia,[20] 113 were adjudicated as sudden arrhythmic death syndrome (ie, normal structural heart) and underwent genetic testing. Clinically relevant pathogenic or likely pathogenic variants in cardiac genes were found in 27%; major associated disorders included LQTS, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and CPVT. Another study of 103 sudden cardiac deaths defined by autopsy in persons aged 1 to 44 years without known CVD referred from 24 US medical examiners' offices identified pathogenic or likely pathogenic variants associated with dilated cardiomyopathy, hypertrophic cardiomyopathy, LQTS, and arrhythmogenic right ventricular cardiomyopathy in 13%.[103] However, the total number of eligible sudden deaths was not reported, so it is unclear how this applies to all young adults with sudden cardiac death. A single center prospective study in the UK revealed that among 303 referred family members of individuals who had sudden arrhythmic death syndrome, 128 (42%) were diagnosed with inherited cardiac diseases including Brugada syndrome, LQTS, and dilated cardiomyopathy.[104]

Genetic Testing of Sudden Cardiac Arrest Survivors

Genetic testing of sudden cardiac arrest survivors and additional cardiac screening of family members may detect previously unknown cardiomyopathy, such as dilated cardiomyopathy, hypertrophic cardiomyopathy, or primary arrhythmia syndrome.[64,101,103] In the 2020 Asian Pacific Heart Rhythm Society and Heart Rhythm Society expert consensus statement, genetic testing of survivors is recommended if the results are likely to aid diagnosis, management, or family screening (class I, level B).[105] However, the yield of genetic testing from studies of survivors with clinically unexplained VT/VF targeting arrhythmia and cardiomyopathy genes ranged from 2% to 22%, which is lower than the percentage of pathogenic or likely pathogenic variants in cardiac genes among those who had sudden cardiac death (ie, nonsurvivors).[106-109]

Cardiac Screening of Family Members of Resuscitated Patients

In a Canadian study of 63 patients with unexplained cardiac arrest due to VT or VF (although toxicology was not performed), genetic testing of family members (mean age, 30 years) identified causative genetic variants for LQTS, Brugada syndrome, and CPVT in 24%.[64] If the phenotype in a patient resuscitated after sudden cardiac arrest is established, a recent expert consensus statement[105] recommends genetic testing focused on potential candidate genes and clinical evaluation of family members to identify relatives who have or are at risk of developing the same condition. If the cause of sudden cardiac arrest is not determined, first-degree relatives may undergo clinical evaluation, including ECG, cardiac imaging, ambulatory monitoring, and provocative testing. In addition, psychological evaluation and treatment of grief and posttraumatic stress in survivors and their immediate family members by trained mental health professionals is recommended.[105]

Sudden Cardiac Arrest in Young Athletes

Athletes are generally considered healthier than young adults in the general population. In studies of children and young adults, incidence of sudden death in athletes was reported to be low at approximately 1 per 100 000 person-years.[110,111] However in a prospective study of 11 168 adolescent soccer players (mean age, 16.4 years, 95% male) in the English Football Association cardiac screening program from 1996 through 2016, the incidence of sudden death was 6.8 per 100 000 person-years.[112] The most common causes of sudden death in young athletes are sudden arrhythmic death syndrome, coronary anomalies, myocarditis, and valvular disease.[110,113] A meta-analysis evaluating sudden cardiac death etiology in individuals younger than 35 years from 2010

through 2020 demonstrated that the following cardiac conditions were more common among athletes than nonathletes: hypertrophic cardiomyopathy (11.9% vs 3.9%; *P* = .002), dilated cardiomyopathy (3.6% vs 0.8%; *P* = .047), and anomalous coronary arteries (7.2% vs 1.9%; *P* = .009).[114]

In the last 2 decades, preparticipation screening for early identification of young competitive athletes at risk of sudden cardiac arrest in high school, college, and professional settings has been investigated. A study of competitive athletes in the Veneto region of Italy, where ECG is routinely employed as part of preparticipation screening, and those in the US (Minnesota), where preparticipation prescreening is limited to history and physical examination, found a comparable incidence of cardiovascular deaths (0.87 vs 0.93 per 100 000 person-years, respectively) between 1993 and 2004.[115] The American Heart Association–American College of Cardiology consensus statement[116] on preparticipation screening recommends the American Heart Association 14-point screening guide,[110] including a comprehensive history taking and a physical examination for young athletes (class I recommendation), but does not recommend routine ECG screening of young adults (athletes and nonathletes) in the general population (class III), due to concerns about diagnostic accuracy, cost-effectiveness, and availability of physicians and equipment needed for screening. ECG or transthoracic echocardiography should only be performed in select individuals in whom genetic, congenital, or other cardiovascular abnormalities are suspected or identified (class IIb).[116] This recommendation differs from recent ESC guideline recommendations that preparticipation screening should include a 12-lead ECG for all competitive athletes younger than 35 years (class IIa).[74] This recommendation was supported by outcome data from the Veneto region, which showed declining incidence of sudden death in young competitive athletes after introduction of a nationwide prescreening program using ECG.[117] Some data suggest that compared with history and physical examination, ECG may provide superior accuracy to identify athletes at potential risk of sudden death, primarily due to detection of preexcitation syndromes (sensitivity 88% vs 19%, specificity 98% vs 75%).[118,119]

Commotio cordis is cardiac arrest precipitated by blunt force to the chest sufficient to trigger VF, as has been witnessed during televised sporting events recently.[120,121] Although the incidence of commotio cordis is unknown, in the US more than 90% of cases occur among individuals younger than 25 years.[122] Commotio cordis occurs most commonly in baseball, softball, and football in the US, whereas soccer, cricket, and hockey were the sports most commonly associated with it in non-US populations.[122] The US Commotio Cordis Registry reported a survival rate of 58% in 216 persons with sudden cardiac arrest due to commotio cordis (age range, 0.2-51 years; mean, 15 years, 95% male) from 2006 through 2012.[123] Higher survival rates were associated with more prompt resuscitation and participation in organized competitive sports. Multivariate analysis identified participation in recreational sports with lower survival (odds ratio [OR] compared with organized competitive sports, 0.33; 95% CI, 0.16-0.67) and onsite automated external defibrillator with higher survival (OR, 4.61; 95% CI, 1.43-14.88).[123]

A prospective cohort study from 2012 through 2019 of individuals aged 18 to 35 years with sports-related sudden cardiac arrest in Germany and France demonstrated that public automated external defibrillator use prior to EMS arrival was associated with improved survival to hospital discharge (OR, 6.25; 95% CI, 1.48-43.20); individuals with sudden cardiac arrest who received both immediate bystander CPR and automated external defibrillator had 91% survival.[124] A recent meta-analysis demonstrated that in sports-related sudden cardiac arrest, bystander presence (OR, 2.55; 95% CI, 1.48-4.37), bystander CPR (OR, 3.84; 95% CI, 2.36-6.25), and bystander automated external defibrillator use (OR, 5.25; 95% CI, 3.58-7.70) were associated with improved survival.[125]

Limitations

This review has several limitations. First, literature on cardiac arrest in young adults was limited and many epidemiological studies of young adults often also include children and adolescents. Therefore, we included some articles with a wider age range (1-50 years) in this review. Second, the quality of included studies was not formally assessed. Third, some relevant articles may have been missed. Fourth, data from autopsy-based studies are limited by regional variations in autopsy rates and associated bias of cases selected for autopsy.

Conclusions

Cardiac arrest in apparently healthy adults younger than 40 years may be due to inherited or acquired cardiac disease or noncardiac causes. Among young adults with out-of-hospital cardiac arrest, only 9% to 16% survive to hospital discharge. Sudden cardiac arrest survivors require comprehensive evaluation for underlying causes of cardiac arrest, and cardiac defibrillator should be implanted in those with nonreversible cardiac causes.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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