Circulation

AHA SCIENTIFIC STATEMENT

The Evolving Role of the Cardiac Catheterization Laboratory in the Management of Patients With Out-of-Hospital Cardiac Arrest

A Scientific Statement From the American Heart Association

ABSTRACT: Coronary artery disease is prevalent in different causes of out-of-hospital cardiac arrest (OHCA), especially in individuals presenting with shockable rhythms of ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT). The purpose of this report is to review the known prevalence and potential importance of coronary artery disease in patients with OHCA and to describe the emerging paradigm of treatment with advanced perfusion/reperfusion techniques and their potential benefits on the basis of available evidence. Although randomized clinical trials are planned or ongoing, current scientific evidence rests principally on observational case series with their potential confounding selection bias. Among patients resuscitated from VF/pVT OHCA with ST-segment elevation on their postresuscitation ECG, the prevalence of coronary artery disease has been shown to be 70% to 85%. More than 90% of these patients have had successful percutaneous coronary intervention. Conversely, among patients resuscitated from VF/pVT OHCA without ST-segment elevation on their postresuscitation ECG, the prevalence of coronary artery disease has been shown to be 25% to 50%. For these patients, early access to the cardiac catheterization laboratory is associated with a 10% to 15% absolute higher functionally favorable survival rate compared with more conservative approaches of late or no access to the cardiac catheterization laboratory. In patients with VF/pVT OHCA refractory to standard treatment, a new treatment paradigm is also emerging that uses venoarterial extracorporeal membrane oxygenation to facilitate return of normal perfusion and to support further resuscitation efforts, including coronary angiography and percutaneous coronary intervention. The burden of coronary artery disease is high in this patient population, presumably causative in most patients. The strategy of venoarterial extracorporeal membrane oxygenation, coronary angiography, and percutaneous coronary intervention has resulted in functionally favorable survival rates ranging from 9% to 45% in observational studies in this patient population. Patients with VF/pVT should be considered at the highest severity in the continuum of acute coronary syndromes. These patients have a significant burden of coronary artery disease and acute coronary thrombotic events. Evidence from randomized trials will further define optimal clinical practice.

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According to the 2015 Institute of Medicine report *Strategies to Improve Cardiac Arrest Survival: A Time to Act*, ≈395 000 people suffer an out-of-hospital cardiac arrest (OHCA) each year in the United States.[1] The survival rate is 6% to 10%, resulting in >350 000 deaths per year, making sudden cardiac arrest virtually synonymous with sudden cardiac death.[1,2]

Over the past 20 years, a significant body of evidence has emerged highlighting the importance of significant coronary artery disease (CAD; unless otherwise specified, hereafter defined as 1 narrowing of coronary luminal diameter of >70%) in patients presenting with ventricular fibrillation (VF)/pulseless ventricular tachycardia (pVT) and OHCA. The accumulated evidence for the presence of significant CAD in patients with VF/pVT cardiac arrest has introduced significant scientific questions about the role and timing of diagnostic and interventional procedures to identify and reverse this potential cause of cardiac arrest.

Furthermore, a novel notion has been forming in the international resuscitation community suggesting that early access to the cardiac catheterization laboratory (CCL) serves 3 roles in this group of patients: (1) It provides a more informed diagnosis (of CAD or its absence), which can better guide future therapy even in the absence of a percutaneous coronary intervention (PCI); (2) it allows immediate PCI, which improves hemodynamics and prognosis analogous to patients with acute coronary syndromes; and (3) it provides access to circulatory assist devices that can be used to support and stabilize patients beyond standard medical therapy. Therefore, access to the CCL has the potential to improve outcomes in these patients.

For many patients, the first presenting symptom of an acute coronary syndrome is sudden cardiac death. In a 1984 autopsy study, patients who died of ischemic heart disease within 6 hours after symptom onset were compared with control subjects who died of natural or unnatural noncardiac causes within 6 hours after symptom onset. Controls were matched to cases by age, sex, and socioeconomic status. Intraluminal thrombosis was observed in 93% of cases and 4% of controls.[3] In another 1988 case series of patients undergoing autopsy after unsuccessful field resuscitation, CAD was considered to be the cause of death in 78% of patients with a presenting rhythm of VF.[4]

Although VF/pVT constitutes only 20% to 30% of all cardiac arrests, 60% to 80% of all cardiac arrest survivors with favorable neurological function present with VF/pVT (Figure 1). In fact, compared with the other presenting rhythms (asystole and pulseless electrical activity [PEA]), VF/pVT is associated with the highest survival and predictive factor for neurologically intact survival, with odds ratios (ORs) ranging from 5 to 15 or greater.[5–8] Yet, despite having a more favorable prognosis than those with other rhythm causes of OHCA, only ≈25% to 30% of patients with OHCA caused by VF/pVT survive to hospital discharge with good neurological function. Thus, identifying more effective treatments for all rhythm causes of OHCA remains a high priority, particularly the role of acute coronary intervention. For that reason and given the potential implication of costs and resources that may be needed to provide access to the CCL for most patients with OHCA, we present the available evidence of the potential benefit of emergent CCL access and subsequent interventions in patients with OHCA on the basis of initial presentation with shockable and nonshockable rhythms and the presence of refractory cardiac arrest.

THE PRESENCE OF CAD IN PATIENTS WITH OHCA

Shockable Rhythms: The Weighted Importance of Shockable Rhythms to Survival

In most medical conditions, identification and treatment of an underlying pathogenesis are a fundamental tenant of medical practice and provide improved outcomes. For patients with VF/pVT OHCA, CAD is the most common reversible underlying cause.[7,9] Patients resuscitated from VF/pVT cardiac arrest have clinically significant coronary stenosis in 25% to 50% of cases.[3,10–16]

Fundamentally, patients who present with OHCA VF/pVT can be divided into 2 major categories: patients with return of spontaneous circulation (ROSC) and patients with refractory VF/pVT. Most survivors achieve ROSC in <15 minutes after cardiopulmonary resuscitation (CPR) and other life support interventions. After that, survival dramatically decreases.[17–19] We define refractory VF/pVT as that which remains either recurrent or incessant after >3 direct current shocks or after antiarrhythmic medications have been given. Usually, both of those interventions fall within a 15-minute window from the initiation of resuscitation after the 9-1-1 call.

Patients with ROSC can be further divided into those who have ST-segment elevation on their 12-lead ECG and those who do not. Thus, we can categorize the patients with VF/pVT into 3 major groups that also represent different severities of CAD and outcomes (Figure 2):

1. Patients with sustained ROSC and without the presence of ST-segment elevation on the initial surface ECG have been shown to have significant CAD, with prevalence varying between 25% and 50% in different published cohorts.[16,20] Acute coronary lesions were identified in 25% to 35% of cases.

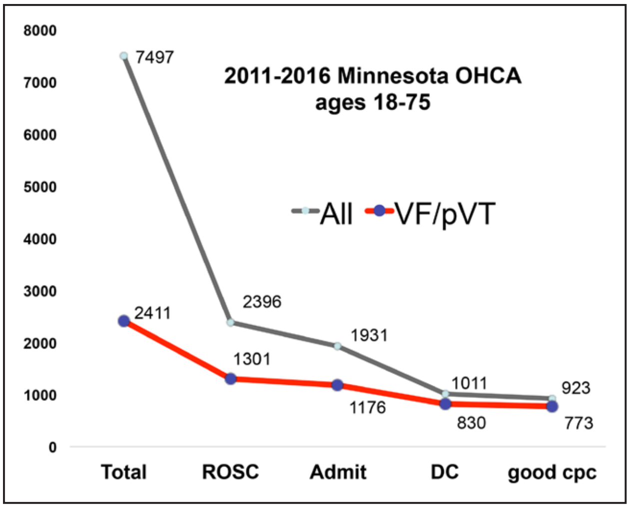

Figure 1. Contribution of ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT) to overall survival in the state of Minnesota over 5 years.

Nationally for 2016, on the basis of CARES (Cardiac Arrest Registry to Enhance Survival) data, shockable rhythms accounted for only ≈20% (12 172 of 61 523) of all out-of-hospital cardiac arrests (OHCA) and contributed to 60% of all survivors with favorable neurological function (3171 of 5245). One theme remains obvious: Most survivors present with shockable rhythms. CPC indicates Cerebral Performance Category; DC, discharge; and ROSC, return of spontaneous circulation.

2. Patients with sustained ROSC and ST-segment elevation or new left bundle-branch block on the surface ECG have been shown to have significant CAD in 70% to 95% of cases, with acute coronary lesions in 70% to 80%.[16,20]
3. Patients with refractory VF/pVT have been shown to have significantly higher rates of CAD (75%–85%), often with greater severity, and a higher prevalence of multivessel disease and chronic total coronary occlusions compared with resuscitated patients.[7,14–16,21–26] Acute coronary lesions were present in 60% to 65% of the patients who had CAD.[7,23]

The accumulated data suggest that VF/pVT as the presenting cardiac arrest rhythm is a strong predictor of acute coronary occlusion or stenosis, which may be amenable to timely PCI.

Nonshockable Rhythms

Nonshockable rhythms can be divided into asystole and PEA. The presence of CAD in this population is poorly defined. In mainly autopsy studies, these populations have shown lower rates of CAD compared with shockable rhythms, but meaningful comparisons are impossible because of inconsistent autopsy indications and permissions.[4,23,27] Furthermore, the outcomes for asystole and PEA are extremely poor, and there are no major published series of homogeneous populations that can inform a role for CAD in those rhythms, even in resuscitated patients, because access to the CCL is the exception.[23] With those limitations, the role of CAD in patients with nonshockable rhythms is unknown.

PATIENTS WITH SUSTAINED ROSC AFTER OHCA UNDERGOING CARDIAC CATHETERIZATION

Cardiac Arrest Caused by Shockable Rhythms: Patients Resuscitated From VF/pVT With and Without ST-Segment Elevation on the Initial 12-Lead ECG

No randomized clinical trial has assessed the role of early coronary angiography (CAG) after OHCA.[28] Multiple observational studies have identified an association between early CAG and survival to hospital discharge or functionally favorable survival after cardiac arrest resulting from shockable rhythms.[9,15,28–40] A review of these studies (1995–2013) was performed in 2014 by the European Association for Percutaneous Coronary Interventions/Stent for Life groups.[28] A total of 42 studies that included 3655 patients reported survival rates of 60% and functionally favorable survival (defined as a Cerebral Performance Category [CPC] 1 or 2)[41] of 52%. A meta-analysis that included 3103 patients compared the outcomes of patients with OHCA according to early CAG versus early conservative strategy.[12] Early access to CAG with timely revascularization, when significant lesions were identified, was associated with a significant increase in the OR for survival and functionally favorable survival (pooled unadjusted OR for survival of 2.78 [95% CI, 1.89–4.10]; $P<0.001$; Figure 3).[42]

It is important to recognize the potential for bias and confounding in observational studies,[28,42] particularly with respect to the selection of comatose patients after OHCA for invasive treatments. In general, patients selected for early CAG after OHCA have generally had more favorable clinical and resuscitation parameters (eg, younger age, fewer comorbidities, more often witnessed having cardiac arrest, and recipients of bystander CPR) compared with patients in whom early CAG is not pursued.[42,43] In addition, the indication or timing of early CAG was not specified in most studies, with use rates of CAG among studies that vary widely from 14% to 83%.[42]

Since 2014, several large observational studies that have been published have used statistical techniques (covariate adjustment, propensity matching) or standardized treatment algorithms (Minnesota Resuscitation Consortium) to overcome some of these limitations of early studies (Table 1).[11,16,20,43]

In a subgroup analysis of the Resuscitation Outcomes Consortium,[11] among 3981 patients who arrived at 151

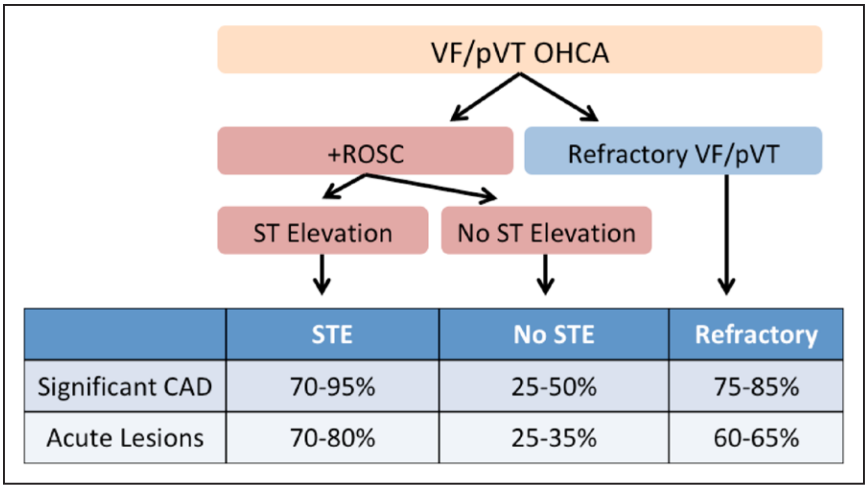

Figure 2. Breakdown of shockable rhythms based on the presence or absence of return of spontaneous circulation (ROSC) and the presence or absence of ST-segment elevation (STE) on the 12-lead ECG. Corresponding percent of coronary artery disease (CAD; >70% stenosis) and acute (thrombotic) lesions are presented. OHCA indicates out-of-hospital cardiac arrest; and VF/pVT, ventricular fibrillation/pulseless ventricular tachycardia.

hospitals with sustained pulses after OHCA, 765 (19%) underwent CAG and 705 (18%) had revascularization therapy. After adjustment for all covariates, early CAG was associated with increased survival to hospital discharge (adjusted OR, 1.69 [95% CI, 1.06–2.70]) and favorable functional survival (adjusted OR, 1.87 [95% CI, 1.15–3.04]).[11]

In 2015, Kern et al[20] reported the outcomes of 746 patients with OHCA included in INTAR (International Cardiac Arrest Cardiology Registry) according to postresuscitation ECG findings. Use of CAG was high (96%) among patients with ST-segment–elevation myocardial infarction (STEMI) in their postresuscitation ECG. In contrast, only 45% of patients without STEMI underwent CAG. Among patients without STEMI, survival to hospital discharge (66% versus 20%; *P*<0.001) and functionally favorable survival (93% versus 78%; *P*=0.003) were higher for those who underwent CAG than for those who did not.[20]

Using data from CARES (Cardiac Arrest Registry to Enhance Survival), Vyas et al[43] identified 4029 patients admitted to 374 hospitals after OHCA caused by shockable rhythms. Early CAG (within 24 hours after admission) was performed in 45% of patients, of whom 64% received coronary revascularization. A propensity score analysis of 1312 pairs of patients showed that early CAG was associated with higher odds of survival to discharge (OR, 1.52 [95% CI, 1.28–1.80]; *P*<0.001) and functionally favorable survival (OR, 1.47 [95% CI, 1.25–1.71]; *P*<0.001).[43]

In 2013, the Minnesota Resuscitation Consortium developed an organized approach for the management of patients resuscitated from OHCA caused by shockable rhythms that promoted early access (within 4 hours) to the CCL in the metro area of Minneapolis–St. Paul.[16] With a standardized protocol, 73% of patients underwent CAG within 4 hours after their OHCA. In this group, 151 (65%) had functionally favorable sur-

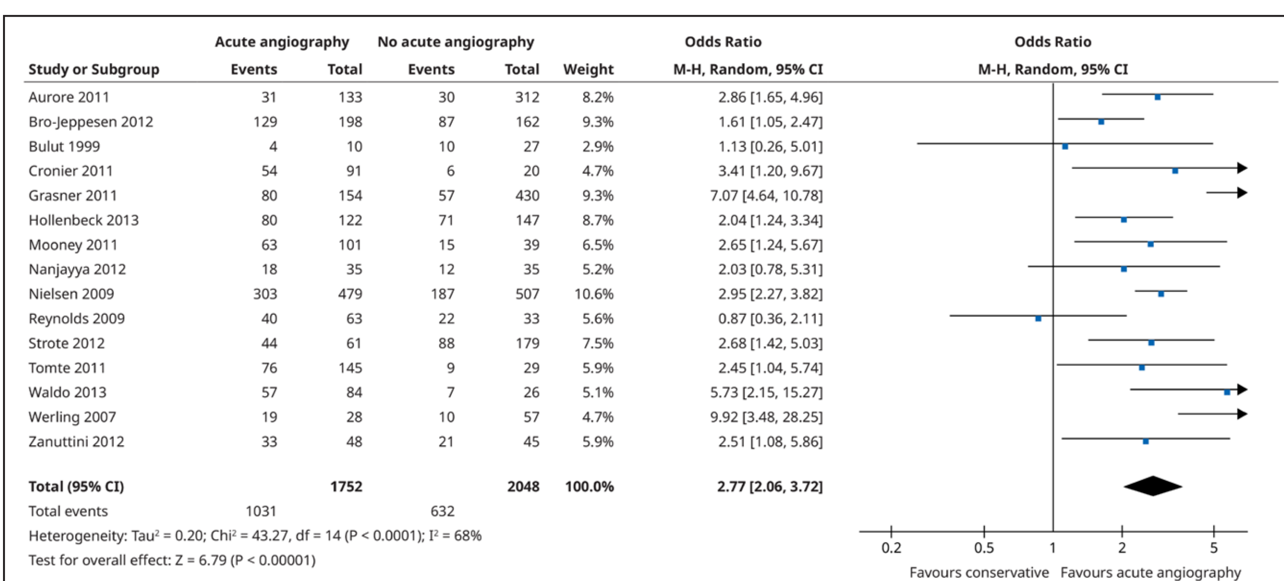

Figure 3. Meta-analysis of the effect of acute angiography after ventricular fibrillation/pulseless ventricular tachycardia cardiac arrest on survival. df indicates degrees of freedom; and M-H, Mantel-Haenszel test. Reprinted from Camuglia et al[12] with permission from Elsevier. Copyright © 2014, Elsevier.

Table 1. Summary of Contemporary (2014 or Later) Studies of Early CAG After OHCA

Study	Sample Size, n	CAG, n (%)	STEMI, n (%)	Coronary Revascularization, % of Total	Culprit Vessel (NSTEMI), %
Callaway et al[11]	3981	765 (19)	573 (17)	705 (17)	NR
Kern et al[20]	746	439 (58)	192 (27)	209 (28)	33
Vyas et al[43]	4029	1953 (49)	802 (20)	1480 (36)	NR
Garcia et al[16]	315	231 (73)	112 (35)	139 (44)	48

CAG indicates coronary angiography; NR, not reported; NSTEMI, non–ST-segment–elevation myocardial infarction; OHCA, out-of-hospital cardiac arrest; and STEMI, ST-segment–elevation myocardial infarction.

Data derived from Millin et al.[44]

vival; whereas in the group who did not follow the Minnesota Resuscitation Consortium protocol, only 46 (55%) had functionally favorable survival (adjusted OR, 1.99 [95% CI, 1.07–3.72]; *P*=0.03).[16]

Prevalence of CAD and Survival After CAG in Patients With Sustained ROSC After VF/pVT OHCA and ST-Segment Elevation on Initial 12-Lead ECG

There is substantial physician agreement on the need to provide access to the CCL for immediate CAG (especially after VF/pVT OHCA) for resuscitated patients who present with ST-segment elevation. Despite this, there are no randomized trials because equipoise is not present in the opinion of the scientific community. In all ongoing trials, such patients are excluded from randomization. Patients with sustained ROSC after VF/pVT OHCA with STEMI have been shown to have a 70% to 85% prevalence of significant CAD. Findings from Garcia et al[16] demonstrate that STEMI is associated with PCI or coronary artery bypass grafting (CABG) in 72% of patients compared with 42% of patients without STEMI (Table 2). This was corroborated by the PROCAT registry (Parisian Region Out of Hospital Cardiac Arrest).[15] Dumas et al[15] reported that at least 1 coronary artery lesion was present in 128 of 134 patients (96%) with STEMI and in 176 of 301 patients (58%) with no ST-segment elevation. That prevalence was higher than in US registries because of the definition of significant CAD used: >70% stenosis in the United States and >50% in the French registry.[15,16]

Prevalence of CAD and Survival After CAG in Patients With Sustained ROSC After VF/pVT OHCA Without ST-Segment Elevation on the Initial 12-Lead ECG

Whether access to the CCL for immediate CAG will result in improved functionally favorable survival in patients resuscitated from VF/pVT OHCA with no ST-segment elevation may depend on the prevalence of significant CAD. Kern et al[20] showed that 82 247 patients (33%) without ST-segment elevation undergoing CAG had a culprit lesion identified. Of those, 66 of 82 (81%) had successful PCI.[20] In comparison, patients in whom OHCA was accompanied by ST-segment elevation had higher rates of culprit lesions identified (154 of 192, 80%), and 93% had PCI.[20] Garcia et al[16] reported slightly different rates than Kern et al,[20] with a higher prevalence of CAD in patients with no ST-segment elevation (42% versus 33%) and lower rates in patients with STEMI (72% versus 80%; Table 2).

In a Parisian cohort of 695 patients without ST-segment elevation after OHCA, Dumas et al[14] reported that a culprit lesion was identified in 29% of the patients. Functionally favorable survival was significantly higher in patients who had CAD and were treated with PCI (43%) compared with patients with no culprit lesion (33%). In other studies encompassing 1145 patients with no ST-segment elevation and early access to CAG, the prevalence of CAD varied from 30% to 42%.[15,16,20] These cohorts of patients, representing

Table 2. Prevalence of CAD and PCI/CABG in Patients With STEMI and No STE After VF/pVT OHCA in a Large US Metropolitan Area

	Overall (n=263), n (%)	STEMI (n=104), n (%)	No STE (n=159), n (%)	*P* Value
Multivessel CAD	136 (52)	56 (54)	80 (50)	0.58
PCI	128 (49)	74 (71)	54 (34)	<.0001
CABG	16 (6)	2 (2)	14 (9)	0.03
PCI and CABG	142 (54)	75 (72)	67 (42)	<0.001
Location of stents placed				
1 Vessel	115 (44)	69 (66)	46 (29)	
2 Vessels	13 (5)	5 (5)	8 (5)	
3 Vessels	1 (0.4)	1 (1)	0 (0)	
No stents placed	133 (51)	29 (28)	104 (65)	

CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; STE, ST-segment elevation; STEMI, ST-segment–elevation myocardial infarction; and VF/pVT, ventricular fibrillation/pulseless ventricular tachycardia.

different metropolitan areas and hospitals, demonstrate that the prevalence of disease in the population without ST-segment elevation is sufficiently high that early CAG has significant opportunity to identify culprit lesions.[15,16,20]

Access to CAG and Effects on Survival in the United States

Currently, anticipated survival to hospital discharge for patients resuscitated from VF/pVT OHCA with early access to CAG is similar regardless of the presence (60%) or absence (57%) of ST-segment elevation on ECG. In 2016, Millin et al[44] showed that patients presenting with STEMI after cardiac arrest are 13 times more likely to be taken urgently to the CCL than patients without STEMI (OR, 13.8 [95% CI, 4.9–39.0]). Most important, the cumulative data show that when taken to the CCL, as many as 32% of patients without ST-segment elevation had an acute culprit lesion requiring intervention compared with 72% of patients with STEMI (OR, 0.15 [95% CI, 0.06–0.34]).

There are no randomized human studies to address whether early CAG improves functionally favorable survival from cardiac arrest. On the basis of observational studies that use large registries in the United States, early access to CAG appears to be associated with improved functionally favorable survival in patients with no ST-segment elevation. The published, absolute difference in survival between patients with no ST-segment elevation who receive early CAG and patients who do not is reported to be between 12% and 18% in the United States.[12,16] There are no data to compare similar differences in patients with STEMI, given that most patients with STEMI undergo CAG.

The Minnesota Resuscitation Consortium Experience

In Minneapolis–St. Paul, a community that provides early access to the CCL after OHCA, patients between 18 and 75 years of age resuscitated from VF/pVT with no ST-segment elevation on ECG received early access to the CCL only two-thirds of the time (130 of 203, 64%). That observation underscores the point that even with consensus throughout an entire community, patients are still treated with discretion according to the receiving cardiologist's preference. Notably, in this setting, early access to the CCL was associated with improved functionally favorable survival after adjustment for a variety of demographic and resuscitation characteristics, including age, sex, race, year, location of arrest, bystander CPR, witnessed arrest, medical history of PCI, CABG, myocardial infarction, diabetes mellitus, hypertension, hyperlipidemia, and tobacco use (Table 3).[16]

The Resuscitation Outcomes Consortium Prehospital Resuscitation Using an Impedance Valve and Early Versus Delayed Analysis Experience (Large North American Prehospital Clinical Trials Network)

Reporting from the PRIMED (Resuscitation Outcomes Consortium Prehospital Resuscitation Using an Impedance Valve and Early vs Delayed Analysis) database, Callaway et al[11] assessed the effect of early access to the CCL on functionally favorable survival. In one of the largest cardiac arrest studies to date in North America, only 19% (765 of 3981) of patients admitted to the hospital were investigated in the CCL, and of those, 705 (92%) had revascularization treatment. This observation demonstrates that most hospitals in the United States and Canada do not access the CCL on the basis of organized protocols but rather as a sporadic strategy that may incorporate clinical judgment, clinician bias, and resource availability. The data from this study were also consistent with many other case series showing that early access to CAG had a positive association with functionally favorable survival.[33,34,36] Early access to CAG had the strongest association with survival of any hospital-based intervention, including therapeutic hypothermia (adjusted OR, 1.87 [95% CI, 1.15–3.04] versus 1.42 [95% CI, 1.04–1.94], respectively).

International Cardiac Arrest Registry Experience

Similarly, Kern et al[20] reported the association between early CAG and clinically appropriate PCI on outcomes in 548 patients with no ST-segment elevation on ECG after OHCA who were enrolled in INTCAR (International

Table 3. Effect of Early Access to the CCL for Patients With No STEMI After ROSC and the Effect on Survival With Favorable Neurological Function

	All No STEMI (n=203), n (%)	MRC Protocol (n=130), n (%)	MRC Protocol Deviations (n=73), n (%)	Adjusted OR* (95% CI)	*P* Value
Discharged alive	145 (71)	95 (73)	50 (68)	1.73 (0.80–3.74)	0.16
CPC 1 or 2	125 (62)	86 (66)	39 (53)	2.77 (1.31–5.85)	0.01

CCL indicates cardiac catheterization laboratory; CPC, Cerebral Performance Category; MRC, Minnesota Resuscitation Consortium; OR, odds ratio; ROSC, return of spontaneous circulation; and STEMI, ST-segment–elevation myocardial infarction.

Cardiac Arrest Registry). Access to the CCL resulted in a survival benefit, as shown in Figure 4.

Transport to PCI-Capable Centers for Early CAG

Given the observed potential benefits of early CAG and revascularization, studies have examined the strategies of emergency medical services (EMS) when transporting patients resuscitated from OHCA. Kragholm et al[45] assessed the effect of PCI centers and bypassing hospitals without PCI capabilities on survival by using the CARES data. Of 1507 patients with out-of-hospital ROSC, 1359 (90%) were transported to PCI centers, and 148 (10%) were transported to non-PCI hospitals. A total of 873 patients (60%) bypassed the nearest non-PCI hospital. Survival to hospital discharge was higher among those transported to PCI centers (34% versus 15%; adjusted OR, 2.47 [95% CI, 2.08–2.92]). Compared with patients taken to non-PCI hospitals, odds of survival were higher for patients taken to the nearest PCI center (OR, 3.07 [95% CI, 1.90–4.97]), including patients bypassing closer hospitals for transport to PCI centers (OR, 3.02 [95% CI, 2.01–4.53]). Adjusted survival remained significantly better across transport times of 1 to 5, 6 to 10, 11 to 20, 21 to 30, and >30 minutes. Further randomized studies are necessary to fully exclude selection bias and to evaluate the benefits of preferential transport to PCI centers.

Current Treatment Guidelines

The present consensus in the cardiology community on the need for early CAG to facilitate timely reperfusion applies only to those with ST-segment elevation. Current STEMI guidelines strongly recommend (Class I; Level of Evidence B-NR) early catheterization and reperfusion for postarrest patients manifesting ST-segment elevation, even if the patient remains comatose.[46,47] However, there is no consensus about the value and necessity of early catheterization for resuscitated patients without ST-segment elevation despite nonrandomized data suggesting at least a modest prevalence of sig-

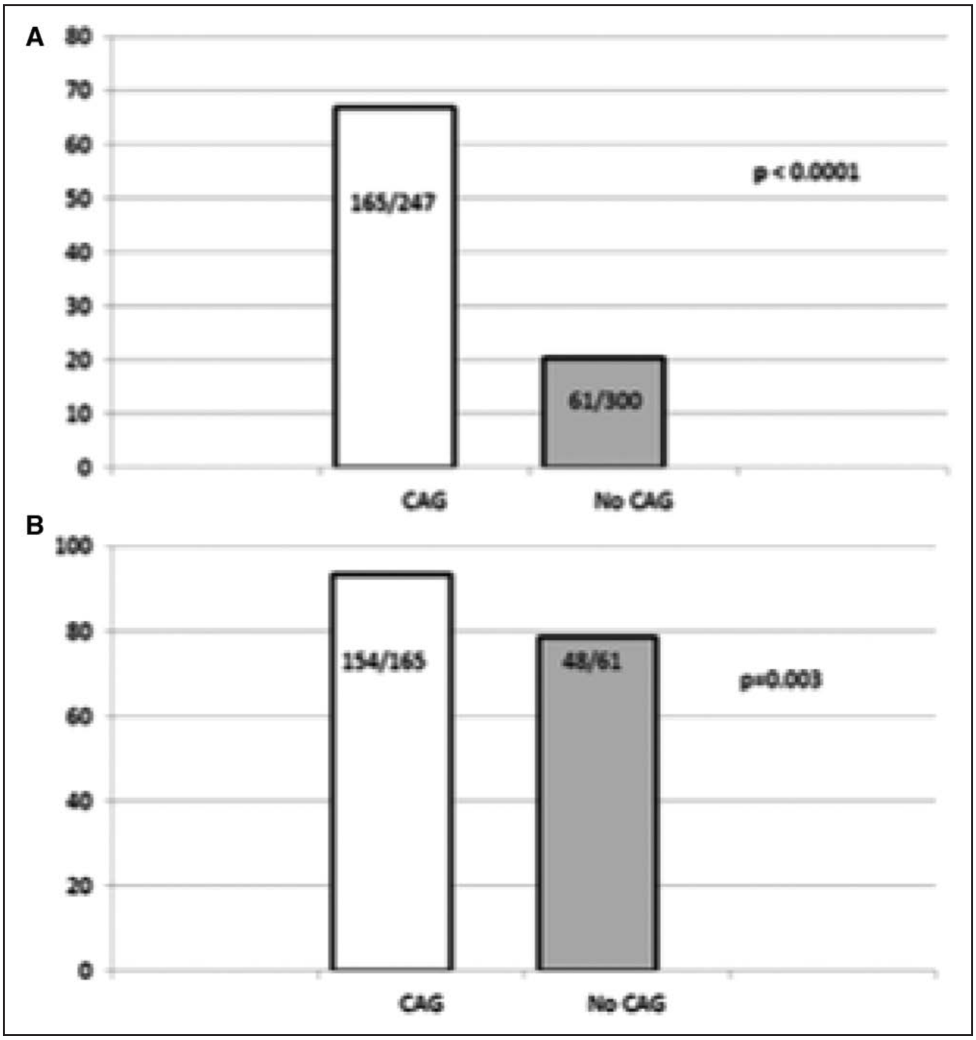

Figure 4. Coronary angiography (CAG) is associated with improved survival to hospital discharge among patients without ST-segment–elevation myocardial infarction (A) and with good neurological function (Cerebral Performance Category 1 or 2) among survivors without ST-segment elevation myocardial infarction (B).
Reprinted from Kern et al[20] with permission from the American College of Cardiology Foundation. Copyright © 2015, American College of Cardiology Foundation.

nificant CAD in this subgroup. Some have advocated for randomized clinical trials before committing to this approach for all postarrest patients.[48–51]

Randomized Controlled Trials

The potential biases and limitations from nonrandomized registry cohort studies are well described. Nine separate randomized clinical trials evaluating the potential survival benefit of early CAG after arrest in patients without ST-segment elevation are now planned or underway. Table 4 highlights the similarities and differences among the trials.[52–59] These randomized clinical trials will collectively enroll >5000 patients over the next 5 years and will help define clinical practice in the future.

Nonshockable Rhythms and Early CAG

In past years, the epidemiology of OHCA has changed such that nonshockable rhythms (bradyasystole and PEA) are now more prevalent.[60] Nonshockable OHCA is more commonly associated with noncardiovascular disease and thus might be less expected to manifest remediable coronary lesions as its cause.[61] In addition, most reports of emergent cardiac catheterization have excluded patients with obvious noncardiac causes of OHCA. The discretionary selection of patients for cardiac catheterization after OHCA represents the greatest potential bias for all observational studies, regardless of the presenting arrest rhythm. Accordingly, the proportion of patients with OHCA caused by nonshockable arrhythmias has been small in these reports, representing ≈20% to 25% of the study populations.[62] Moreover, studies that have included a broader group of patients with OHCA undergoing cardiac catheterization have not separately described angiographic findings in the subgroup with nonshockable rhythms. Notably, a small observational report described a similar prevalence of obstructive CAD among resuscitated patients who were selected for catheterization, regardless of their presenting rhythm or postresuscitation ECG findings. The presence of obstructive coronary artery lesions ranged from ≈50% of patients across VF/pVT, asystole, and PEA subgroups in the absence of ST-segment elevation to >90% across subgroups when ST-segment elevation was present.[62] In the total study population, performance of cardiac catheterization was associated with improved survival after OHCA regardless of the presenting rhythm. These findings suggest that there is potential benefit from CAG in all patients who are resuscitated from OHCA and require further study.

Resuscitated Patients With OHCA and Coronary Revascularization in the CCL

When CAD is observed in patients resuscitated from OHCA, revascularization can be achieved safely with PCI in most cases, with 68% to 80% of patients receiving PCI in observational cohorts.[16,20] In select patients, CABG may also be feasible. These observational studies demonstrate that patients who receive early coronary revascularization with PCI or CABG have a greater likelihood of survival, with ORs ranging from 2 to 5.[9,11,16]

Although no single study has confirmed an association between the severity of CAD and the likelihood of survival, comparisons can be made between patients resuscitated in the field and patients with refractory VF/pVT treated with extracorporeal CPR (ECPR). Those with OHCA resuscitated in the field have multivessel CAD in 52% of cases[16] compared with 70% of cases for refractory VF/pVT arrest.[7] Rates of chronic total occlusions were similar between these cohorts, with 25% in resuscitated patients[20] and 33% in shock-refractory patients.[7]

Spaulding et al[9] showed that in a cohort of 84 patients resuscitated from VF/pVT arrest, 60 (71%) had significant CAD and 40 (48%) had total coronary arterial occlusion. Angioplasty was attempted in 37 patients and was successful in 28. Overall survival to hospital discharge of these 80 patients was 38%. After multivariate analysis, a successful PCI was an independent predictor of survival (OR, 5.2 [95% CI, 1.1–24.5]; *P*=0.04).

Similarly, multiple case series have addressed the issue of procedural success and survival in resuscitated patients who subsequently present with STEMI. In 2004, Bendz et al[10] reported angiographic findings for 40 such consecutive patients. The most common culprit lesion was found in the left anterior descending artery (50%), and PCI was successful in 95% of the cases. Survival to hospital discharge was 72%, and all patients were alive 2 years later. Gorjup et al[31] reported similar results in 135 patients, with a PCI success rate of 87% and survival rate to hospital discharge of 67%. Overall, 53% had functionally favorable survival with CPC 1 or 2.

Data from the PROCAT registry, describing 435 patients who underwent CAG after OHCA, showed that at least 1 significant coronary artery lesion was present in 304 patients (70%).[15] Significant coronary lesions were identified in 96% of patients with STEMI and in 58% of patients with no ST-segment elevation. Coronary revascularization was an independent predictor of survival with an OR of 2.06 (95% CI, 1.15–3.66) regardless of ECG findings, as shown in Figure 5.

Similarly, Garcia et al[16] demonstrated that revascularization (PCI/CABG) was independently associated with survival to hospital discharge and neurological recovery in 315 patients resuscitated from VF/pVT OHCA regardless of the presence or absence of ST-segment elevation (Table 5).

In a similar French cohort of 695 patients without ST-segment elevation who underwent immediate CAG after OHCA, Dumas et al[14] reported that patients with

Table 4. Randomized Clinical Trials of CAG for OHCA

Protocol Titles	PIs	Country and Clinical Centers, n	Start–End Dates	Projected No.	Primary Comparison	Primary End Point	Secondary End Points	Status
DISCO (pilot), NCT02309151	Prof Sten Rubertsson/ Per Nordberg, MD, PhD	Sweden 15	December 2014–March 2017	80	Immediate (≤2 h) vs delayed CAG in postarrest pts without ST-segment elevation	Composite: Care deviations: LOS First medical contact-Admit Prognostic factors: pH, lactate, O_2 saturation Supportive care Cardiac fx: echocardiogram, biomarkers SAEs: bleeding, vascular, rearrest	Survival at 30 d Survival with good neurological fx at 30 d Survival with good neurological fx at 6 mo Cardiac fx (echocardiogram)	Recruiting
COACT, NTR4973	Prof Jorrit S. Lemkes	Netherlands 14	December 1, 2014–December 1, 2017	552	Immediate (≤2 h) vs delayed CAG in postarrest pts without ST-segment elevation	Survival at 90 d	Neurological fx of survival at 90 d CK-MB Renal injury Recurrent VF/pVT Biomarkers of shock	Recruiting
PEARL, NCT02387398	Prof Karl B. Kern	US, Slovenia, Australia 5	December 2015–November 2018	140	Early (≤2 h) vs delayed (>6 h) CAG in postarrest pts without ST-segment elevation	Composite: Safety: rearrest, bleeding, pulmonary edema, hypotension, renal injury, pneumonia Efficacy: survival at DC, LV function (LVEF), regional WMS	Survival to 30 and 180 d ECG 30 and 180 d GCS, mRS, and CPC; survival at 30 and 180 d	Recruiting
COUPE, NCT02641626	Prof Ana Viana-Tejedor	Spain NA	January 2016–July 2019	166	Urgent vs delayed CAG in postarrest pts without ST-segment elevation	Composite of in-hospital survival and 6-mo survival with favorable neurological function (CPC 1 or 2)	Safety: MACEs, including death; recurrent MI; bleeding; and ventricular arrhythmias	Recruiting
TOMAHAWK, NCT02750462	Prof Steffen Desch	Germany NA	August 2016–August 2018	558	Immediate vs delayed CAG in postarrest pts without ST-segment elevation	All-cause mortality at 30 d	None specified	Recruiting
EMERGE, NCT 02876458	Prof Christian Spaulding	France 21	December 2016–June 2019	970	Immediate vs delayed (48–72 h) CAG in postarrest pts without ST elevation	Survival with CPC 1 or 2 at 180 d	Shock Recurrent VF/pVT Change in LVEF (baseline to 180 d) LOS	Recruiting
DISCO-2 (pivotal trial), NCT02309151	Prof Sten Rubertsson, Per Nordberg, MD, PhD	Sweden 15	September 2017–September 2020	1006	Immediate (≤2 h) versus delayed CAG in postarrest pts without ST-segment elevation	30-d survival	Survival at discharge from ICU, at 30 d, and at 180 d Echocardiogram at 24 h, 72 h, and 180 d CPC and mRS score at discharge from ICU, at 30 d, and at 180 d	Unknown

(*Continued*)

Table 4. Continued

Protocol Titles	PIs	Country and Clinical Centers, n	Start–End Dates	Projected No.	Primary Comparison	Primary End Point	Secondary End Points	Status
ACCESS, NCT03119571	Prof Demetris Yannopoulos, Prof Tom Aufderheide	US 26	November 2016–June 2021	20	Initial CCL admission vs initial ICU admission in postarrest pts with VF/pVT without ST-segment elevation	Survival to hospital DC with mRS score ≤3	Survival to DC and 3 mo CPC status at DC and 3 mo mRS score at 3 mo Mean peak TpI Mean LVEF ICU and hospital LOS LOS at rehabilitation Functional status at 3 mo. Incidence of heart failure Time to return to work	Recruiting
Cardiac Catheterization in Cardiac Arrest, NCT02587494	Prof Shahar Lavi	Canada Not known	December 2015–December 2018	75	Early (<12 h) vs late (>24 h) CAG in postarrest pts without ST-segment elevation	Composite: Death and poor neurological outcome (CPC 3–5)	Survival at 30 d CPC at 30 d AKI MI Stent thrombosis Bleeding Composite of death and poor neurological outcome (CPC 3–5) at 1 y CVA Heart failure LOS and cost	Not yet recruiting

ACCESS indicates Access to the Cardiac Catheterization Laboratory in Patients Without ST-Segment Elevation Myocardial Infarction Resuscitated From Out-of-Hospital Cardiac Arrest; AKI, acute kidney injury; ALF, acute liver failure; CAG, coronary angiography; CCL, cardiac catheterization laboratory; CK-MB, creatine kinase-MB; COACT, Coronary Angiography After Cardiac Arrest; COUPE, Coronariography in Out-of-Hospital Cardiac Arrest; CPC, Cerebral Performance Category; CVA, cerebrovascular accident; DC, discharge; DISCO, Direct or Subacute Coronary Angiography in Out-of-Hospital Cardiac Arrest: A Randomized Study; EMERGE, Emergency Versus Delayed Coronary Angiogram in Survivors of Out-of-Hospital Cardiac Arrest With No Obvious Noncardiac Cause of Arrest; LOS, length of stay; LV, left ventricular; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; MI, myocardial infarction; mRS, modified Rankin Scale; NA, not available; OHCA, out-of-hospital cardiac arrest; PEARL, A Randomized Pilot Clinical Trial for Early Coronary Angiography Versus No Early Coronary Angiography for Post-Cardiac Arrest Patient With No ST-Segment Elevation on Their ECG; PI, principal investigator; pts, patients; SAE, serious adverse event; TOMAHAWK, Immediate Unselected Coronary Angiography Versus Delayed Triage in Survivors of Out-of-Hospital Cardiac Arrest Without ST-Segment Elevation; TpI, troponin I; VF/pVT, pulseless ventricular fibrillation/ventricular tachycardia; and WMS, wall motion score.

an identifiable lesion and successful PCI had 43% functionally favorable survival compared with 33% of the patients who had no identifiable coronary cause of their arrest (*P*=0.03). Successful PCI was again an independent factor associated with good neurological survival.[14]

Sideris et al[63] in 2014 reported the 5-year outcomes of a total of 300 comatose patients resuscitated predominantly from shockable rhythms who had CAG on admission. PCI was attempted in 91% of patients with significant lesions and was successful in 93% of attempts. Survival to discharge was 32%. After discharge, overall 5-year survival was 82%. Survival from admission to 5 years was 37.4±5.2% for patients with significant coronary lesions and 20.7±3.0% for those without (hazard ratio, 1.5 [95% CI, 1.12–2.0]; *P*=0.0067). This study suggests that survivors are expected to live 5 years, especially if they have had culprit lesions identified and PCI performed (Figure 6A). Geri et al[64] reported the longest follow-up for patients who received early CAG and showed that patients with CAD and PCI had higher short- and long-term survival up to 10 years compared with patients with no CAD (Figure 6B).

Multiple case series among resuscitated patients with OHCA who had ST-segment elevation on the initial ECG have consistently shown high procedural success with PCI and survival rates varying from 60% to 80%, with almost 90% of those patients surviving with favorable neurological outcomes (Table 6).

Complete revascularization also may be important to optimize patient outcomes[73]; however, most patients resuscitated from cardiac arrest rarely receive multivessel PCI in the postarrest setting.[16,74] Although data are limited, patients with ongoing cardiogenic shock after OHCA may also benefit from multivessel PCI.[74]

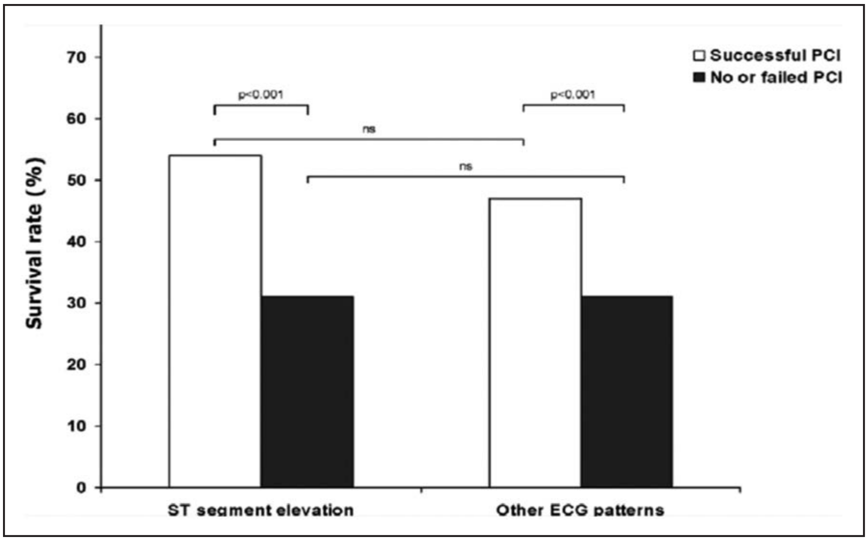

Figure 5. **PROCAT registry (Parisian Region Out of Hospital Cardiac Arrest) associated successful percutaneous coronary intervention (PCI) with better survival regardless of the presence or absence of ST-segment elevation.**

The survival benefit associated with early revascularization after cardiac arrest may arise from 2 separate mechanisms. VF/pVT arrest is widely accepted to be of ischemic origin in most cases. Therefore, correcting the underlying ischemic pathogenesis may prevent future arrhythmias and rearrest, leading to improved survival. Second, revascularization would be expected to alleviate ischemia, which may promote cardiac recovery and prevent prolonged hemodynamic instability after cardiac arrest. This is the proposed mechanism by which revascularization is believed to improve survival in the setting of post-STEMI cardiogenic shock and led to recommendations for emergent revascularization in the setting of cardiogenic shock after an acute coronary event.[46,75] The results of ongoing randomized trials may significantly inform these proposed mechanisms of benefit.

A summary of the factors associated with favorable outcomes after OHCA is shown in Table 7.

Arrest or Rearrest in the CCL

Cardiac arrest is infrequent in the CCL itself. Historical reports estimate an incidence of ≈1%,[81,82] but such calculations are dependent on the severity of illness among the population undergoing CAG and intervention. In 2002, Anderson et al[82] reported >100 000 procedures from the American College of Cardiology–National Cardiovascular Data Registry and found an overall in-hospital death rate of 1% to 5% among those with acute myocardial infarction and 6% if the catheterization was done urgently. Mehta et al[83] reported a VF/pVT incidence of 4% during PCI for acute myocardial infarction in the Primary Angioplasty in Myocardial Infarction trials. Today's CCL typically treats sicker patients with greater risk for serious complications, including cardiac arrest and death. More contemporary reports suggest that more than half (55%) of all PCIs are nonelective and that close to 20% are performed in clinically unstable patients.[84] The best estimate for current PCI-related in-hospital mortality, a surrogate for refractory cardiac arrest in the CCL, is 2% to 3%.

Manual chest compressions have been the primary technique for sustaining circulation during cardiac arrest. However, performing high-quality manual chest compressions in the CCL while attempting to recanalize an acutely occluded coronary artery can be challenging. Barriers include unsafe radiation to the chest compressor's hands, obstruction of the interventionist's view, frequent interruptions of chest compressions, and poor CPR quality.

One potential solution is to use a mechanical chest compressor. Mechanical chest compressions afford the

Table 5. **Association Between Revascularization and Survival to Hospital Discharge and Good Neurological Function**

	Overall (n=315), n (%)	PCI or CABG (n=139), n (%)	No PCI or CABG (n=176), n (%)	Unadjusted OR (95% CI)	*P* Value	Adjusted OR* (95% CI)	*P* Value
Discharged alive	227 (72)	112 (79)	115 (66)	1.88 (1.13–3.14)	0.015	2.55 (1.32–4.93)	0.005
CPC 1 or 2	197 (63)	102 (72)	95 (55)	2.09 (1.31–3.36)	0.002	3.04 (1.36–5.66)	0.0005

Outcomes are based on the presence or absence of revascularization regardless of timing to cardiac catheterization laboratory access. CABG indicates coronary artery bypass graft; CPC, cerebral performance category; OR, odds ratio; and PCI, percutaneous coronary intervention.

*Adjusted for age, sex, race, history of PCI, CABG, myocardial infarction, diabetes mellitus, hypertension, congestive heart failure, hyperlipidemia, tobacco use, year, location of arrest, and bystander cardiopulmonary resuscitation witnessed arrest.

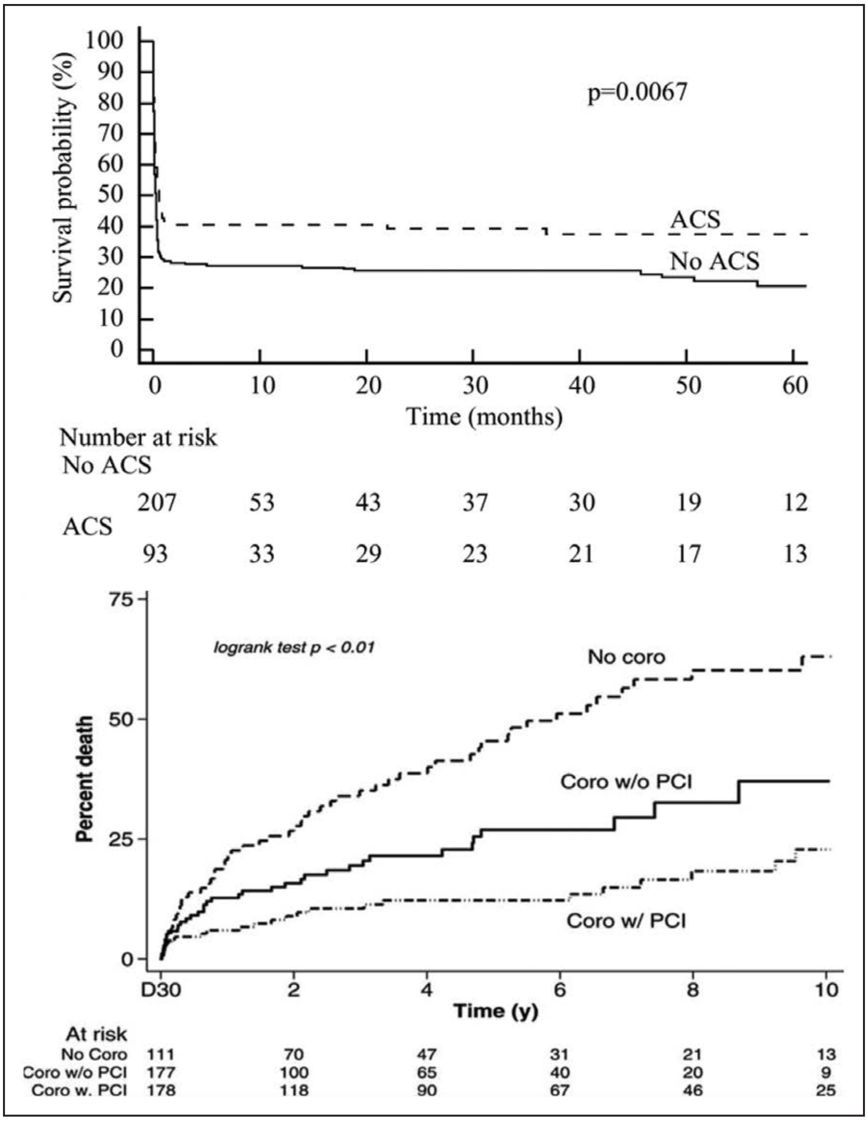

Figure 6. Long-term survival after resuscitated out-of-hospital cardiac arrest (OHCA) attributable to pulseless ventricular fibrillation/ventricular tachycardia in relation to the presence of acute coronary syndrome (ACS) and coronary angiography.
A, The 5-year outcomes of patients surviving cardiac arrest and coronary angiography (Coro). Patients are divided on the basis of the presentation of ACS or not. Reprinted from Sideris et al.[63] Copyright © 2014, SAGE Publications, Ltd. Reprinted by Permission of SAGE Publications, Ltd. **B**, Up to 10 years of follow-up for patients who gained access to the cardiac catheterization laboratory after resuscitated OHCA. PCI indicates percutaneous coronary intervention. Reprinted from Geri et al.[64] Copyright © 2015, American Heart Association, Inc.

opportunity to initiate PCI or percutaneous circulatory support during ongoing CPR in patients with refractory cardiac arrest. Wagner et al[85,86] reported 2 sequential case series of using mechanical CPR in the CCL among a combined total of 75 patients undergoing PCI. In the first of these studies, 88% (28 of 32) of the patients included in the mechanical chest compression cohort had their coronary or cardiac intervention performed during mechanical chest compressions with an 80% success rate.[86] In the second study, 86% (37 of 43) of patients with refractory cardiac arrest had their cardiac procedure or PCI successfully completed during ongoing mechanical CPR.[85] Overall, functionally favorable survival after refractory cardiac arrest was 25% (19 of 75) with 87% 1-year survival. Venturini et al[87] also reported their experience with 43 patients receiving CPR in the CCL. Nearly half (20 of 43) of these patients arrested in the CCL, whereas the other patients were brought to the CCL in refractory cardiac arrest with ongoing chest compressions. Of the 43 patients, 22 had venoarterial extracorporeal membrane oxygenation (VA-ECMO) initiated during mechanical chest compressions and were more likely to achieve ROSC than those not receiving VA-ECMO (100% versus 53%; P=0.003), demonstrating that initiation of such percutaneous extracorporeal life support was feasible and safe during mechanical chest compression–assisted resuscitation in the CCL.[87]

Other therapeutic options for patients arresting in the CCL include percutaneously placed left ventricular assist devices. Large animal preclinical studies have shown that Impella can support systemic circulation without chest compressions during ischemic VF cardiac arrest but that intravascular volume loading is required.[88] Derwall et al,[89] using a porcine model of VF, found that this device can generate coronary perfusion pressures of 20 mm Hg, twice that of manual chest compressions. Compared with chest compressions alone, this increased hemodynamic support translated into a significant survival advantage at 24 hours (2 of 10 versus 9 of /10; P=0.003) in animals.

Table 6. Case Series With Early Access to CAG and PCI for Resuscitated Patients After OHCA and STEMI on the First Postresuscitation ECG

	Survival	Survival With Good Neurological Status
Borger van der Berg et al,[65] 2003	39/42	NA
Keelan et al,[66] 2003	11/15	9/11
Bendz et al,[10] 2004	29/40	NA
Quintero-Moran et al,[67] 2006	18/27	NA
Gorjup et al,[31] 2007	90/135	72/90
Garot et al,[30] 2007	102/186	88/102
Richling et al,[68] 2007	24/46	22/24
Markusohn et al,[69] 2007	19/25	17/19
Werling et al,[70] 2007	9/13	NA
Pleskot et al,[71] 2008	14/20	11/14
Hosmane et al,[32] 2009	63/98	58/63
Anyfantakis et al,[72] 2009	35/72	33/35
Reynolds et al,[62] 2009	52/96	NA
Overall, n/N (%)	505/815 (62)	310/358 (87)

Presenting rhythm was ventricular fibrillation/pulseless ventricular tachycardia in >95% of the cases. CAG indicates coronary angiography; NA, not available; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

Percutaneous VA-ECMO has been used for refractory cardiac arrest in the CCL. Case series and reports have documented successful resuscitation attempts and left ventricular support with such technology after standard therapies have failed.[90,91] This approach requires a multidisciplinary team and careful selection of appropriate candidates.

Today, mechanical chest compression devices and mechanical circulatory support devices are most commonly used in tandem, often sequentially. The "2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care" included treatment recommendations for cardiac arrest in the CCL, indicating that mechanical piston devices may be considered in specific settings in which the delivery of high-quality manual compressions may be challenging or dangerous for the provider (Class IIb; Level of Evidence C-EO). It also recommended providing chest compressions to patients in cardiac arrest during PCI and that it may be reasonable to use VA-ECMO as a rescue treatment when initial therapy is failing for cardiac arrest that occurs during PCI (Class IIb; Level of Evidence C-LD).[92,93] Because feasibility and preliminary efficacy have now been demonstrated, these approaches are becoming more commonly applied in the CCL.

Refractory OHCA and the Role of the CCL

Definition of Refractory VF/pVT

Advanced perfusion/reperfusion strategies using early EMS transport and initiation of ECMO, followed by CAG

Table 7. Factors Favorable for Successful Recovery After OHCA

Factor	Magnitude of the Effect (OR)
Witnessed arrest[15,36,76–78]	1.8–7.7
Shockable initial rhythm[15,36,76–80]	5–15
Bystander CPR[36,77,78]	1.6–2.0
CPR for <30 min[36]	1.8
Tissue perfusion: lactic acid <7[15]	3.1
Age <60 y[39,76–78]	1.5–2.7
Age <85 y[76,78]	2.2–2.4
Early CAG[11,12,36,39,80]	1.6–2.8
STEMI on ECG[20,36,80]	1.9–3.3
Successful PCI[15,16,36,39]	2.1–2.6

CAG indicates coronary angiography; CPR, cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

and PCI when needed, have been shown to result in a 43% functionally intact survival rate for patients with out-of-hospital refractory VF/pVT.[7] The definition of refractory VF/pVT can be chosen as a point along a theoretical continuum of failed response to standard care. Physicians have historically chosen the point of administration of initial antiarrhythmic as the point of labeling the VF as refractory. As the emergency response strategies evolve, different definitions may become prominent, and others may become obsolete. Along the time continuum of resuscitation efforts, interventions may be applied either too early or too late. For example, implementing a novel strategy too late along this continuum may not offer benefit because the patient is already too severely compromised. If it occurs too early, expensive resources may be mobilized unnecessarily. For these reasons, most of the investigations currently involving patients with refractory cardiac arrest choose a decision point, whether time or procedure based (eg, number of shocks), for optimal implementation. Common US EMS-based definitions suggest either 15 to 20 minutes of unsuccessful standard resuscitation or 3 unsuccessful shocks.[22,94] We use this definition of refractory VF/pVT throughout this review.

CAD and Refractory VF/pVT Cardiac Arrest

Published data with VA-ECMO–supported angiographic evaluation in patients with refractory VF/pVT OHCA establish that there is a high burden of CAD in this population.[7,23] The prevalence of complex CAD, combined with the relatively high survival rates in selected patients undergoing revascularization, supports the contention that the severity of underlying coronary artery pathology may be causally associated with the inability of standard resuscitation efforts to achieve ROSC in the majority of patients (Figure 7).[7]

VA-ECMO–Facilitated CAG/Angioplasty

Efforts to treat patients with refractory cardiac arrest have led to the use of ECMO to facilitate return

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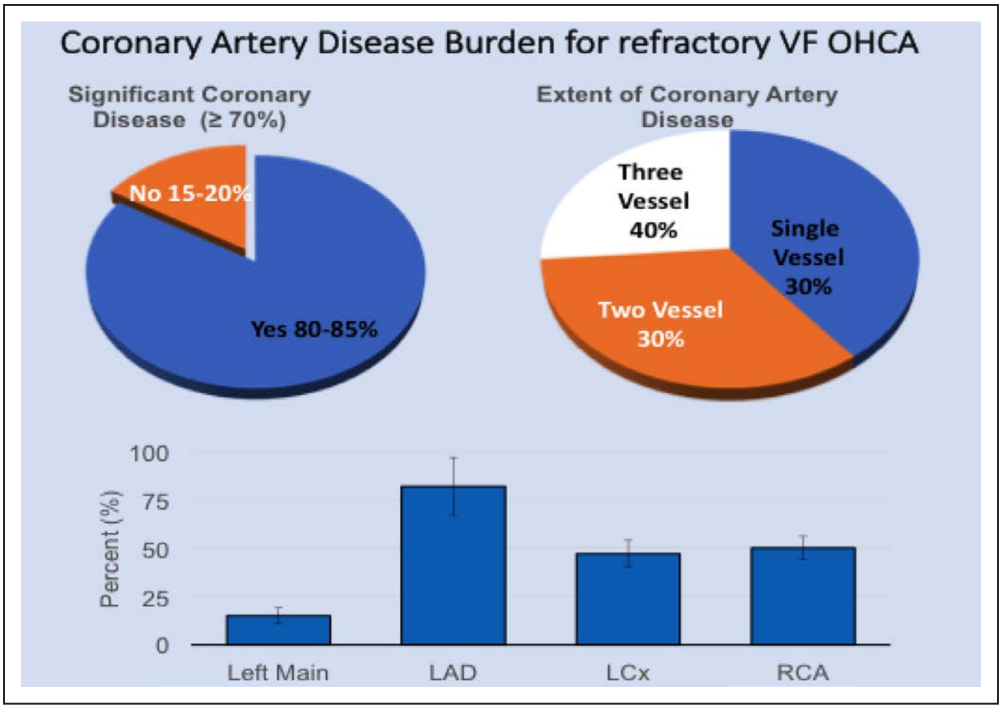

Figure 7. Coronary artery burden is shown as an average based on the published literature in the United States, Japan, France, and Australia.
The largest proportion of patients have significant coronary artery disease, and at least 70% of those have ≥2 vessels involved. The predominant vessel involved is the left anterior descending (LAD), followed by equal distribution between left circumflex (LCx) and right coronary artery (RCA). The left main artery is rarely involved. OHCA indicates out-of-hospital cardiac arrest; and VF, ventricular fibrillation.

of normal perfusion and to support further resuscitation efforts, including CAG and PCI. Multiple cohorts have shown that such an approach is feasible in selected patients. Because time to initiation of ECPR is a critical predictor of survival, 2 major approaches to limit time to ECPR have been implemented. The first approach uses rapid EMS mobilization and transportation to the closest highly equipped emergency department or CCL, used in Asia, Australia, Canada, and the United States. The second approach mobilizes ECMO-equipped emergency response units to the field with initiation of ECMO undertaken at the site of the arrest, used in Paris, France.

VA-ECMO for Refractory VF/pVT OHCA: Survival and Favorable Neurological Outcomes

Among 2885 adults in the 2016 Extracorporeal Life Support Organization registry database, survival to discharge after ECPR for cardiac arrest that was refractory to conventional resuscitation was 29%.[95] Such outcomes have varied widely in other published studies, principally drawn from non-US cohorts, mainly in Asia.[24,25,96–99] Several studies of patients unresponsive to standard resuscitation who received VA-ECMO (and PCI when indicated) found worse outcomes with OHCA versus in-hospital cardiac arrest (IHCA). Kagawa et al[96] analyzed data for 86 patients with OHCA or IHCA unresponsive to CPR who received VA-ECMO (and PCI when indicated). Survival to day 30 was 29% overall, 17% (7 of 42) for OHCA versus 41% (18 of 44) for IHCA, and 37% (17 of 46) for patients presenting with VF/pVT versus 20% (8 of 40) for patients with nonshockable rhythms. Compared with VA-ECMO recipients who did not survive to day 30, survivors had a significantly shorter time interval from collapse to initiation of VA-ECMO (40 [interquartile range, 25–51] minutes versus 54 [interquartile range, 34–74] minutes; *P*=0.002) but also a higher rate of intra-arrest PCI (88% versus 70%; *P*=0.04). Wang et al[24] retrospectively described a cohort of 230 patients who had received VA-ECMO over a study period of 5 years (31 patients with OHCA and 199 with IHCA). No significant differences were observed between OHCA and IHCA in rate of survival to hospital discharge (39% versus 31%; *P*>0.05) or functionally favorable survival (26% versus 25%; *P*>0.05). As in the former study, the duration of ischemia (from collapse to VA-ECMO) was a strong predictor for survival. The authors attributed the high survival rate in patients with OHCA compared with previous studies[96,97,100,101] to a well-organized and rapid-response EMS system, efficiency in handling patient transportation and resuscitation, and an equipped cart in the emergency department rather than in the intensive care unit, which shortened the duration of ischemia.[24] In Australia, Stub et al[21] treated 26 patients with refractory prolonged cardiac arrest with the CHEER protocol (mechanical CPR, hypothermia, ECMO, and early reperfusion) during a period of 32 months. Of 15 patients with IHCA, all had ROSC with VA-ECMO, and

9 (60%) survived. In 11 patients with OHCA (all with VF), ROSC was achieved in 2 patients before VA-ECMO was initiated and in 8 of 9 patients placed on VA-ECMO. A total of 5 patients (45%) with OHCA survived, including 3 of 9 patients who were placed on VA-ECMO. Avalli et al[100] reported their experience with VA-ECMO support in patients with refractory cardiac arrest (IHCA, n=24; OHCA, n=18). Survival to discharge from intensive care was 46% (11 of 24) for IHCA and 6% (1 of 18) for OHCA (P<0.05). At 6 months, survival rates with good neurological outcomes were 38% (9 of 24) for IHCA and 6% (1 of 18) for OHCA. Haneya et al[101] analyzed a total of 85 consecutive adult patients with refractory cardiac arrest treated with VA-ECMO. Thirty-day survival was 42% (25 of 59) in patients with IHCA and 15% (4 of 26) in patients with OHCA (P<0.02). Duration of CPR, as a possible surrogate for ischemic time, was an independent risk factor for mortality. In the United States, Johnson et al[102] reported 26 cases of people with cardiac arrest who received VA-ECMO (and reperfusion when indicated) over a 7-year period, of whom 11 (42%) presented with VF/pVT. Of 15 patients with OHCA, 1 patient (7%) who presented with VF/pVT survived to discharge and made a full neurological recovery. Survival to discharge was 27% (3 of 11) for IHCA.

In South Korea, Kim et al[99] found similar rates of survival to hospital discharge among patients with OHCA with prolonged conventional CPR compared with patients who received VA-ECMO (19% [86 of 444] versus 16% [9 of 55], respectively). However, propensity score matching of patients who received≥21 minutes of CPR duration showed neurological outcomes at 3 months to be more favorable with VA-ECMO than with conventional CPR (15% versus 8%). In an observational study, Maekawa et al[97] analyzed data from 162 adult Japanese patients with witnessed OHCA of presumed cardiac origin who had undergone CPR for >20 minutes before receipt of VA-ECMO. Survival to discharge was 32% (17 of 53) with VA-ECMO and 6% (7 of 109) with conventional CPR. Matched propensity analysis showed significantly higher neurologically intact survival at 3 months with VA-ECMO compared with conventional CPR (29% versus 8%; P=0.018). In the SAVE-J trial (Study of Advanced Cardiac Life Support for Ventricular Fibrillation With Extracorporeal Circulation in Japan), a prospective observational study of patients with OHCA with VF/pVT performed in Japan over a 3-year period, Sakamoto et al[25] compared patients admitted to 26 hospitals providing VA-ECMO with those admitted to 20 hospitals that did not provide VA-ECMO. In per-protocol analysis, overall 1-month survival was 29% (68 of 234) with VA-ECMO versus 6% (9 of 159) without VA-EMCO. CPC scores of 1 or 2 were achieved at 1 month in 14% (32 of 234) of patients who received VA-ECMO versus 2% (3 of 159) of those without VA-ECMO (P<0.0001) and at 6 months in 12% (29 of 234) versus 3% (5 of 159), respectively (P=0.002). In Austria, Schober et al[103] found that functionally favorable survival was 14% with VA-ECMO and 6% with conventional CPR.

Several studies have compared the potential impact of VA-ECMO between patients with refractory VF/pVT and those with nonshockable rhythms. Leick et al[104] found that 30-day survival was 38% in ECMO recipients who presented with VF/pVT and 35% in patients presenting with nonshockable rhythms. The door–to–VA-ECMO initiation time was the only significant and independent predictor of 30-day mortality. In Denmark, Fjølner et al[105] found that in patients admitted with witnessed, refractory, normothermic OHCA treated with VA-ECMO, 33% survived to hospital discharge, all with CPC 1 or 2. Survival to hospital discharge was 56% in patients with VF/pVT as the initial rhythm and 17% in patients presenting with PEA or asystole. In patients with refractory OHCA who received VA-ECMO in Lyon, France, Pozzi et al[26] found that survival to discharge was 32% (6 of 19) among those with VF/pVT and 0% (0 of 49) in patients with nonshockable rhythms (P<0.001). In a study in Paris by Lamhaut et al,[106] although overall survival in patients with refractory OHCA and VA-ECMO was only 14% (21 of 156), early field application of VA-ECMO within 60 minutes after a 9-1-1 call and careful selection of patients improved survival from 8% to 29%. Failure to subsequently perform CAG was the strongest predictor of mortality (OR, 7.1), and only patients presenting with VF/pVT ultimately survived. In 62 consecutive adult patients treated with the Minnesota Refractory VF/pVT Protocol, Yannopoulos et al[7] reported that 45% (28 of 62) of patients were discharged alive and 42% (26 of 62) were discharged with functionally favorable survival (CPC 1 or 2), all of which were functionally intact (CPC 1) at 3 months. Table 8 is a summary of the published series as of today.

The Advanced Reperfusion Strategies for Refractory Cardiac Arrest (2018–2023)

The National Institutes of Health has funded a definitive randomized trial for extracorporeal life support for refractory VF arrest. The primary end point of the ARREST trial (Advanced Reperfusion Strategies for Refractory Cardiac Arrest) is survival to hospital discharge with a modified Rankin Scale score ≤3. Secondary end points include survival at 6 months and cost per life saved. The study is powered to detect an absolute survival difference of 25% (15% versus 40%).

Importance of Quality of CPR

For patients who are treated for refractory OHCA, the inability to achieve ROSC and the continuation of a low-flow state impose a significant ischemic burden, worsening the initial injuries to vital organs. Several studies

Table 8. Survival in Patients With Refractory OHCA Treated With Advanced Perfusion Techniques (ECMO and PCI)

	Enrollment, y	VA-ECMO Cannulation	Patients, n (%)		Survival Rates		
			OHCA	VF/pVT	All OHCA, n (%)	CPC 1–2, n (%)	VF/pVT, n (%)
Kagawa et al,[96] 2012	7.5	ED	42	23 (55)	7 (17)*	6 (14)*	17/46 (37)†
Avalli et al,[100] 2012	5	ED/ICU/CCL	18	16 (89)	1 (5.5)*	1 (5.5)*	…
Haneya et al,[101] 2012	5	ED	26	12 (46.2)	4 (15)‡	27/85 (32)†	…
Leick et al,[104] 2013	2	CCL	28	8 (28.6)	11 (39)*	8 (28.5)*	…
Maekawa et al,[97] 2013	4.5	ED	53	32 (60.4)	17 (32.1)‡	8 (15.1)‡	…
Wang et al,[24] 2014	5.5	ED	31	15 (48.4)	12 (38.7)‡	8 (25.8)‡	…
Johnson et al,[102] 2014	7	ED	15	11/26 (42)*	1 (6.6)‡	3/26 (11.5)†‡	…
Sakamoto et al,[25] 2014	3	ED	234	234 (100)	68 (29)*§	32 (13.7)*§	68 (29)*§
Kim et al,[99] 2014	7.5	ED	55	31 (56.4)	9 (16.4)‡	8 (14.5)‡	…
Stub et al,[21] 2015	3	ED	11	11 (100)	5 (45)‡	5 (45)‡	5 (45)‡
Pozzi et al,[26] 2016	4	ED	68	19 (28)	6 (8.8)‡	3 (15.8)‡	6 (31.5)‡
Lee et al,[98] 2016	4	ED	23	20 (87)	10 (43.5)*	7 (30.4)*	8 (40)*
Fjølner et al,[105] 2017	3.5	CCL	21	9 (43)	7 (33)‡	7 (33)‡	5 (55.6)‡
Lamhaut et al,[106] 2017	4	Field vs ED	156	81 (58)‖	21 (13.5)‡	21 (13.5)‡	21 (25.9)‡
Schober et al,[103] 2017	10	ED	7	4/7 (57)	1 (14)¶	…	…
Yannopoulos et al,[7] 2017	1	CCL	62	62 (100)	28 (45)‡	26 (42)‡	28 (45)‡

CCL indicates cardiac catheterization laboratory; CPC, Cerebral Performance Category; ECMO, extracorporeal membrane oxygenation; ED, emergency department; ellipses (…), data not available; ICU, intensive care unit; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; and VF/pVT, ventricular fibrillation/pulseless ventricular tachycardia.

*Thirty-day survival.
†Percentage includes OHCA plus in-hospital cardiac arrest.
‡Survival to hospital discharge.
§This is per-protocol analysis. Intention-to-treat analysis was 32 of 260 (12.3%).
‖One hundred thirty-nine patients with available data.
¶Six-month survival.

that have emerged from the Resuscitation Outcomes Consortium have confirmed the importance of maintaining optimal parameters for chest compression rate and depth and minimizing pauses in compressions on survival outcomes. Although randomized trials to date have not shown a significant benefit of mechanical over manual CPR in OHCA, mechanical CPR may be of benefit when transport from field to hospital is required during ongoing CPR to maintain quality compressions and to better ensure crew safety.

The Effect of Time in Prolonged Resuscitation Attempts: Evidence of a Golden Hour of Response

The ability to achieve ROSC with modern CPR declines sharply after the first 10 to 15 minutes of a resuscitation attempt, with 80% of survivors achieving ROSC before 15 minutes of resuscitative efforts. Within 30 minutes after the start of resuscitative efforts, 95% of survivors have achieved ROSC.[17–19] These data have been used to support termination of traditional resuscitative efforts, often ≈30 minutes.[107,108] Conversely, programs using VA-ECMO support have now demonstrated significant survival in patients receiving 50 to 60 minutes of resuscitative efforts. Patients who achieve ROSC either spontaneously or with ECMO support within 50 to 60 minutes after the 9-1-1 call appear to have higher survival rates compared with patients who require >60 minutes of CPR with or without the addition of VA-ECMO.[7,106,109] Therefore, efforts to facilitate earlier VA-ECMO implementation are justified, requiring consideration of system reorganization to minimize low-flow (CPR) time.

Multisystemic Injury and Complexity of Postarrest Care

Although VA-ECMO provides a very promising new intervention for OHCA, full patient recovery requires both careful selection of possible candidates and a supporting system of care after the intervention. Odds of survival after cardiac arrest increase in hospitals that have a full complement of cardiovascular interventional capabilities, even when patients do not require these specific interventions.[110,111] This observation suggests that the culture of care itself plays an important role in outcome and differs between sites. It also suggests that greater experience improves care for patients with acute cardiovascular collapse.

Postcardiac arrest intensive care must address multisystem organ failure.[112] The most common cause of death after reversal of cardiac arrest remains early withdrawal of life-sustaining therapy because of pre-

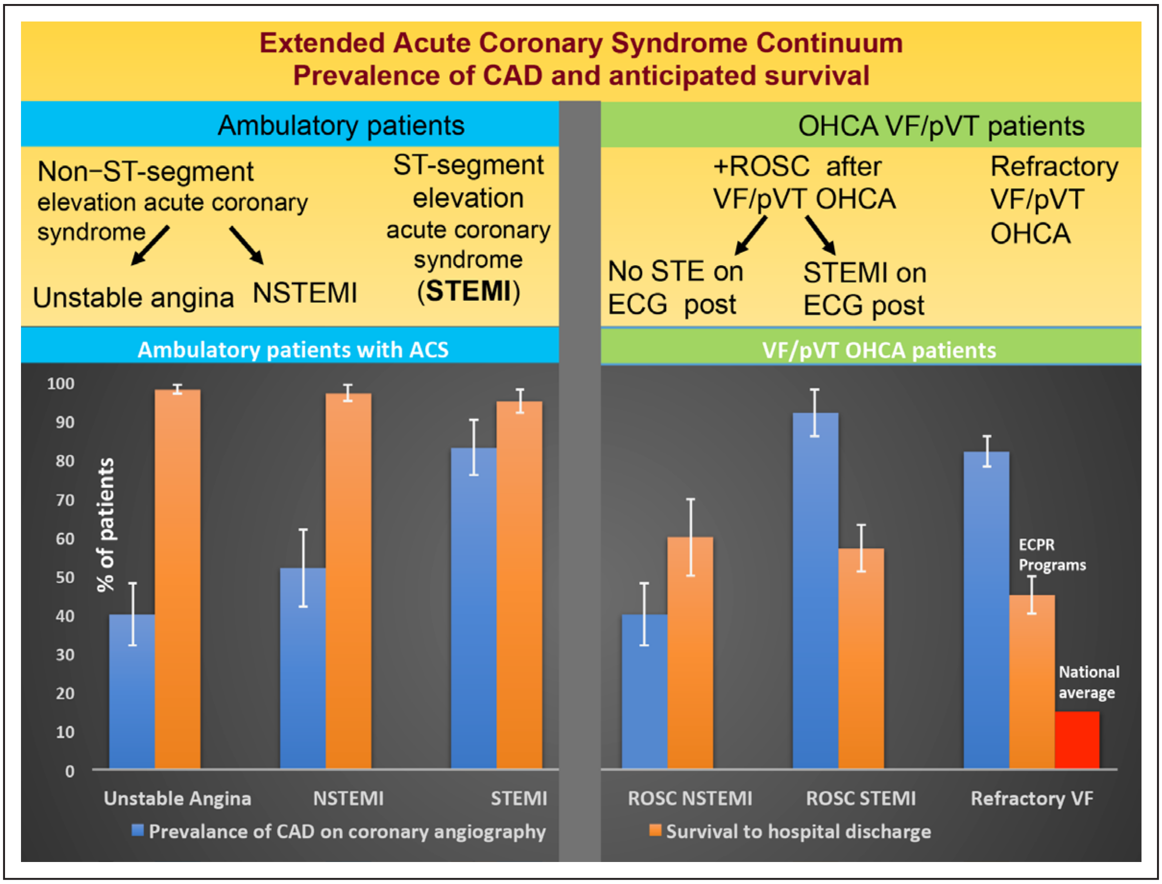

Figure 8. Expansion of the acute coronary syndrome (ACS) continuum to include the patients with out-of-hospital cardiac arrest (OHCA) who present with ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT).
Patients are divided into ambulatory and OHCA arrest. Anticipated survival rates and prevalence of coronary artery disease (CAD; >70% stenosis acute and chronic) are based on published randomized trials. ECPR indicates extracorporeal cardiopulmonary resuscitation; NSTEMI, non–ST-segment–elevation myocardial infarction; ROSC, return of spontaneous circulation; STE, ST-segment elevation; and STEMI, ST-segment–elevation myocardial infarction.

sumed poor neurological prognosis.[110] Accurate neurological prognostication is not possible before 72 hours from cardiac arrest and likely requires longer periods of support and observation before such a determination is made. This remains an area of ongoing research. Neurocritical care expertise can be essential to prevent premature withdrawal of life-sustaining treatment for patients with potential for recovery.[113]

Every organ system is affected by ischemia/reperfusion.[114] Multidisciplinary critical care, including access to comprehensive medical and surgical support services for all organ systems, may be necessary for any postarrest patient. Additional neuropsychological resources and rehabilitation services are also essential to sustain the survival gains that are achieved early with aggressive ECPR-based programs.

CONCLUSIONS

CAD is a common substrate, and its severity is a potential trigger for OHCA, especially in the case of shockable rhythms. Patients with VF/pVT OHCA should be considered at the highest severity of a continuum of acute coronary syndromes. Patients with VF/pVT have a significant burden of CAD: acute, chronic, or acute on chronic (Figure 8).

Current guidelines recommend early CAG and reperfusion for postarrest patients manifesting ST-segment elevation after ROSC is achieved. However, because of a lack of conclusive randomized data and ongoing perceived clinical equipoise, there is no consensus guideline on the use of CAG and coronary revascularization in patients without ST-segment elevation on ECG. Multiple randomized trials addressing this question are underway. Until their completion, there is a significant body of observational studies that address the role of the CCL in this population.

The current evidence suggests that early access to the CCL in patients resuscitated from VF/pVT cardiac arrest is associated with 2- to 3-fold higher functionally favorable survival rates than more conservative approaches of late or no access to the CCL. This body of evidence, with potential for unmeasured selection bias, suggests that patients resuscitated from OHCA, especially those with presenting shockable rhythms, should be considered for early CAG, identification of reversible causes, and revascularization when indicated.

The burden of complex CAD appears even higher in patients with refractory VF/pVT OHCA. The emergence of advanced perfusion/reperfusion strategies and early deployment of VA-ECMO and PCI when needed have shown promising results and have been associated with a 2- to 4-fold (8%–15% to 30%–45%) increase in survival in observational studies. Expansion of this approach is likely to occur in the future. Randomized trials are necessary to inform this expansion and to develop best practices to maximize the efficiency of care. The ARREST trial will address survival and cost per life saved in the United States, but results will be not available until 2023. On the basis of the available evidence, healthcare systems planning to initiate extracorporeal life support–based resuscitation for refractory OHCA should implement system-structural protocols that target a 9-1-1 call to VA-ECMO support interval of <60 minutes. They should also provide multidisciplinary postresuscitation critical care, including comprehensive medical and surgical support services. This will be critical for the effective expansion of extracorporeal life support programs.

The effect of early CCL access in nonshockable rhythms remains undefined.

PCI, mechanical circulatory support, and comprehensive postresuscitation care may provide substantial benefit. However, they are also resource intensive, requiring careful consideration. Furthermore, efforts should be undertaken with an understanding of the resource requirements to fully optimize the entire chain of survival.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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