The ACCESS Trial
NCT03119571

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TITLE: ACCESS to the cardiac catheterization laboratory in patients without ST-segment elevatio myocardial infarction resuscitated from out-of-hospital ventricular fibrillation cardiac arrest

Supported by: The National Heart, Lung, and Blood Institute (NHLBI)

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Information Type:

☐ Initial Protocol
☒ Protocol Amendment

Protocol Amendment Details:

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Revision History

Revision Date	Release Date	Reason for Change
10/27/2017	11/07/2017	Grammar/clarity, ECG guidelines, removal of ALFI, HUE 3, and T-GDS Assessments
10/25/2018	11/20/2018	Blinding mRS and CPC outcome assessment at hospital discharge and 3 months, Inclusion of transfers and patients age 76-80, timing and reporting of SAEs, power and sample size calculations, futility analysis

ACCESS Protocol Signature Page v3.0:

I have read this protocol and any updates provided within and I agree to conduct the study as described and in accordance with other material supplied to me. In addition, I agree to conduct the study in compliance with all applicable regulations and guidelines.

If changes in personnel occur during completion of this protocol, I will be responsible for identifying appropriate trained individuals to carry out the responsibilities of the protocol and will notify the Clinical Coordinating Center promptly of these changes.

_____
Investigator Name (Print)

_____ _____
Investigator Name (Signature) Date

List of Abbreviations

ACLS	advanced cardiac life support
AE	Adverse Event
AED	automated external defibrillator
AKI	Acute kidney injury
CABG	Coronary artery bypass grafting
CCL	cardiac catheterization laboratory
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CPC	Cerebral Performance Category
CPR	cardiopulmonary resuscitation
CRF	Case Report Form
HHS	Department of Health and Human Services
DNAR	Do not attempt resuscitation
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, HHS
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ED	emergency department
EMS	emergency medical services
EMT	emergency medical technicians
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
IABP	Intra-aortic balloon pump
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IEC	Independent or Institutional Ethics Committee
IRB	Institutional Review Board
ISM	Independent Safety Monitor
JAMA	Journal of the American Medical Association
LAR	Legally Authorized Representative
MODS	Multiple organ dysfunction syndrome
MOP	Manual of Procedures
MRC	Minnesota Resuscitation Consortium
mRS	modified Rankin Scale score
N	Number (typically refers to subjects)
NEJM	New England Journal of Medicine
NIAID	National Institute of Allergy and Infectious Diseases, NIH, HHS
NIH	National Institutes of Health
STEMI	ST-segment elevation myocardial infarction on 12-lead ECG
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, HHS
OHCA	out-of-hospital cardiac arrest
OHRP	Office for Human Research Protections
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, HHS
PCI	percutaneous coronary intervention
PEA	pulseless electrical activity
PI	Principal Investigator
ROSC	return of spontaneous circulation

List of Abbreviations - *continued*

SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SDCC	Statistical and Data Coordinating Center
VF	ventricular fibrillation
VT	ventricular tachycardia
WHO	World Health Organization

Title: **ACCESS to the cardiac catheterization laboratory in patients without ST-segment elevation myocardial infarction resuscitated from out-of-hospital ventricular fibrillation cardiac arrest**

Population: *Up to 520 patients. 18-80 years old*

Number of Sites: *Up to 30 hospitals*

Study Duration: *5 years*

Subject Duration: *3 months post hospital discharge*

STUDY SUMMARY

ACCESS to the cardiac catheterization laboratory (CCL) in patients without ST-segment elevation myocardial infarction resuscitated from out-of-hospital ventricular fibrillation cardiac arrest (The ACCESS Trial)

Primary Aim
Determine survival to hospital discharge with Modified Rankin Scale Score (mRS) ≤ 3 in adult (18-80 years old) patients resuscitated from out-of-hospital VT/VF cardiac arrest who do not have ST-segment elevation on emergency department 12-lead ECG (no-STEMI) randomized to receive either: 1) initial CCL admission, or 2) initial ICU admission.

Hypothesis: The corresponding hypothesis is that a large proportion of all resuscitated patients presenting with VT/VF have ischemic heart disease as the underlying cause for their cardiac arrest and that a strategy to facilitate prompt revascularization in all patients presenting with VT/VF who do not have ST-segment elevation on emergency department 12-lead ECG will improve survival with good neurological outcome.

Primary Endpoint
Survival to hospital discharge with mRS ≤ 3

Secondary Aims
Determine secondary assessments of survival, left ventricular function, hospital duration, and rehabilitation in-hospital and assessment of survival and functional status at 3 months in both groups.

Hypothesis: The corresponding hypothesis is that initial CCL admission will result in improved secondary assessment values at 3 months.

Secondary Endpoints
In-hospital secondary endpoints: Survival to hospital discharge, CPC score, mean peak troponin level, mean ejection fraction, mean length of ICU stay, mean hospitalization duration, the incidence of and mean length of rehabilitation.

3-month post-hospital discharge secondary endpoint: Survival to 3 months, survival to 3 months with mRS ≤ 3, functional status at 3 months (mRS score and CPC score) , incidence and length

of rehabilitation, incidence of congestive heart failure, incidence of re-hospitalization over 3 months, and incidence and time to return to work.

Pragmatic Clinical Trial
The ACCESS Trial will randomize patients to receive one of two standard treatments currently practiced in the United States: either, 1) initial CCL admission, or 2) initial ICU admission. Other than randomizing to one of these two standard treatments, care is not otherwise specified and is completely at the discretion of the treating clinician, including coronary interventions, if any, hemodynamic support, medications, therapeutic hypothermia, and all other interventions and clinical care.

Inclusion Criteria
Adult patients (18-80 years old) resuscitated from VT/VF OHCA with no-STEMI on emergency department 12-lead ECG and either a direct EMS transport or transferred from an outside hospital: a) covered by the local community consultation and public notification process, and b) transferred within 4 hours and 30 minutes from initial hospital arrival (time from initial emergency department arrival to participating hospital arrival [either ED or ICU, whichever is first]), and c) transferred to the participating hospital's ED or ICU.

Exclusion Criteria
1) Non-shockable initial out-of-hospital cardiac arrest rhythm (pulseless electrical activity or asystole), 2) Valid do not attempt resuscitation orders (DNAR), 3) Blunt, penetrating, or burn-related injury, drowning, electrocution or known overdose, 4) Known prisoners, 5) Known pregnancy, 6) ST-segment elevation on emergency department 12-lead ECG, 7) Absolute contraindications to emergent coronary angiography including, a) known anaphylactic reaction to angiographic contrast media, b) active gastrointestinal or internal bleeding, or c) severe concomitant illness that drastically shortens life expectancy or increases risk of the procedure,8) Suspected or confirmed intracranial bleeding, 9) refractory cardiac arrest prior to randomization, 10) patients meeting ACCESS Trial eligibility criteria transferred from an outside hospital: a) not covered by the local community consultation and public notification process, or b) transferred more than 4 hours and 30 minutes from initial hospital arrival (time from initial emergency department arrival to participating hospital arrival [either ED or ICU, whichever is first]), or c) transferred directly to the participating hospital's ED or ICU, and 11) unavailability of the cardiac catheterization laboratory.

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

According to a recently published Institute of Medicine report titled, "Strategies to Improve Cardiac Arrest Survival: A Time to Act", approximately 395,000 cases of cardiac arrest occur outside of a hospital setting each year in the United States.[12] On average, less than 6 percent survive, resulting in over 360,000 deaths per year.[12] Consequently, the national public health burden of this problem in terms of prevalence and mortality is enormous, representing the third leading cause of death in the nation.[12] Victims are generally between 50-70 years old.[13, 14] Evidence demonstrates most victims are not markedly aged or infirm, but rather active members of society, living at home, gainfully employed, and most often seemingly healthy.[15] This sudden, unexpected loss of life among victims of cardiac arrest is devastating and leads to tremendous family suffering and community loss.

Although ventricular tachycardia/ventricular fibrillation (VT/VF) constitutes only 30-35% of all cardiac arrests, more than 80% of all cardiac arrest survivors with favorable neurological function present with VT/VF, making it the presenting cardiac arrest rhythm with the highest survival rate and the greatest opportunity for improvements in treatment and outcome for this devastating public health problem.[16, 17] A potential reason for the relatively high survival rate from VT/VF cardiac arrest is its underlying *reversible* cause. Observational studies demonstrate approximately 30% of VT/VF patients that are initially successfully resuscitated from cardiac arrest have ST-segment elevation myocardial infarction (STEMI).[18-21] Seventy percent of resuscitated patients from VT/VF cardiac arrest **do not have** ST-segment elevation myocardial infarction on their 12-lead electrocardiogram (no-STEMI). These patients have been shown to have a 25-30% incidence of acute coronary occlusion and an additional 15% incidence of non-thrombotic treatable coronary stenosis.[18, 22 23] Thus, approximately 75% of all patients resuscitated from VT/VF cardiac arrest have been shown to have ischemic heart disease, potentially treatable by timely percutaneous coronary intervention (PCI).[24-30]

A protocol of early access to the cardiac catheterization laboratory (CCL) implemented through the Minnesota Resuscitation Consortium (MRC) in Minneapolis/St. Paul, Minnesota analyzed that experience during an 18 month period (1/1/13-6/30/15). Patients resuscitated from VT/VF cardiac arrest with no-STEMI that went to the CCL within 6 hours had a 66% (86/130) survival with favorable neurological function (Cerebral Performance Category [CPC] ≤2) compared to 52% (37/73) of the patients that went after 6 hours or never gained access to the CCL (OR 2.13 [1.06, 4.28] p=0.03, adjusted for age, sex, race location of arrest, bystander CPR, and witnessed arrest). Patients that gained access to the CCL compared to patients that never got access to the CCL had a higher survival (76% versus 50%, adjusted OR 3.76 [1.83,7.75], p=0.0003) and survival with favorable neurological function (68% versus 35%, adjusted OR 4.84 [2.3,10.2] p<0.0001). The most important factor associated with survival was the presence of revascularization with patients that received PCI and/or CABG having an adjusted OR of 2.8 (CI 1.54, 5.06), p=0.0007 for survival with favorable neurological function compared to patients that did not receive revascularization.[31]

Despite this, consistent hospital-based delivery of emergent PCI in patients successfully resuscitated from cardiac arrest in Minneapolis/St. Paul continues to remain underutilized and highly variable. Further, this experience reflects practice throughout the United States as identified in the Institute of Medicine report.[12] Variability in clinical practice can be ascribed to: 1) the unreliability of the 12-lead ECG to identify the presence of acute coronary occlusion[18], 2) provider concerns regarding public reporting of negative CCL outcomes[32], and 3) current, exclusive

reliance on observational data, its associated potential selection bias, and the absence of a randomized clinical trial. Since no definitive randomized trial has ever been performed, it is therefore unknown whether timely CCL access in resuscitated VT/VF cardiac arrest patients without ST-segment elevation on emergency department 12-lead ECG results in higher survival with preserved neurologic function compared with delayed or no access to the CCL.

Variation in Clinical Practice. Despite the presence of strong agreement that resuscitated VT/VF cardiac arrest patients with STEMI should gain early access to the CCL, the community of interventional cardiology has mixed responses to the need for no-STEMI patients to gain early access to the CCL. The majority of no-STEMI patients in the United States are admitted to the intensive care unit (ICU) and have cardiology consultation. A few cities and sites have established more aggressive protocols with early access to the CCL regardless of 12-lead ECG findings, providing an alternative treatment approach.[22, 23, 31, 33, 34] While interventional cardiologists acknowledge the promising data showing increased survival and high frequency of significant coronary artery disease in this patient population, most believe that a change of practice should be guided by a randomized trial because all registries have an inherent selection bias that no statistical adjustment can eliminate completely. Therefore, physicians base their treatment on individual interpretation of non-conclusive data leading to wide variation in clinical practice.[1,27, 35-37]

Table 1. Stated reasons why patients did not go to the CCL within 2-6 hours

Stated reason in the medical record, n=52
Patient or family refused or patient was DNR, n=3 (5.8%)
Physician denial, n=42 (80.8%)
Concern for poor neurological function (n=14)
No ischemic features on ECG (n=11)
Cardiology did not recommend catheterization, no clear reason given (n=6)
Other non-ischemic etiology thought to be more likely (n=10)
Patient was receiving other therapies that delayed catheterization laboratory (n=1)
No Reason n=6 (11.5%)
Expired prior to arrival to catheterization lab, n=1 (1.9)

Reasons for not accepting patients early to the CCL. In a recently submitted manuscript reviewing observational results of the MRC early CCL protocol, reasons were identified why patients were denied early access to the CCL. The reasons given by most cardiologists were based on the absence of randomized data showing benefit and the unfounded perception that CCL access may complicate neurological outcomes. Many cardiologists preferred to wait an extended period of time until the neurological outcome would be known before proceeding to the CCL (Table 1)

	Overall N=263	STEMI N=104	No-STEMI N=159	P value
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/or CABG	142 (54%)	75 (72%)	67 (42%)	<.0001
Location of stents placed				
1 area	115 (44%)	69 (66%)	46 (29%)	
2 areas	13 (5%)	5 (5%)	8 (5%)	
3 areas	1 (0.4%)	1 (1%)	0 (0%)	
No stents placed	133 (51%)	29 (28%)	104 (65%)	

Table 2. Angiographic data and revascularization details for patients that went to the CCL **regardless** of the time. The overall prevalence of disease distribution associated with clinical revascularization is shown for patients presenting with STEMI and **with No ST elevation**. CAD: Defined as the presence of >70% stenosis in the coronary angiography report by the clinician Cardiologists unrelated to the "culprit" lesion Garcia et al. JACC 2015 Under review (The MRC two year experience).

Prevalence of coronary artery disease (CAD) in no-STEMI patients and observational data suggesting benefit of early access to the CCL.

1. **The prevalence of CAD in resuscitated VF/VT patients with no-STEMI on 12-lead ECG.** Whether early recognition of underlying ischemia and urgent resolution of that ischemia by CCL revascularization would result in improved functionally favorable survival may depend on the prevalence of significant CAD in this patient

population. Kern et al published that 82/247 (33.3%) patients with no-STEMI that had coronary angiography had a culprit lesion identified. Of those, 66/82 (80.5%) had successful PCI. In comparison, patients with STEMI had higher rates of culprit lesions identified 154/192 (80%) and 93% had PCI.[23] The MRC experience reported that prevalence of CAD was higher with 42 % of patients gaining access to the CCL receiving revascularization compared to only 72% of patients with STEMI.[31] (Table 2) Based on those two cohorts of patients representing different metropolitan areas and hospitals it is clear that the prevalence of disease in the no-STEMI population is high enough that early coronary angiography will have significant yield and will lead to interventions to reverse ischemia in 30-50% of patients. Whether an early invasive strategy will result in higher functionally favorable survival can only be definitively answered with a randomized clinical trial.

	All No STE N=203	MRC Protocol N=130	MRC Protocol deviations N=73	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**

Table 3 Effect of early access to the CCL for patients with No STE post ROSC and the effect on survival with favorable neurological function. 2013-2014 MRC Data (JACC under review)

Table 4. ROC PRIMED data showing that although only 19.2% of patients gained access to the CCL early they had a significant survival advantage. C.W. Callaway et al. / Resuscitation 85 (2014) 657–663

Association of interventions with outcomes.

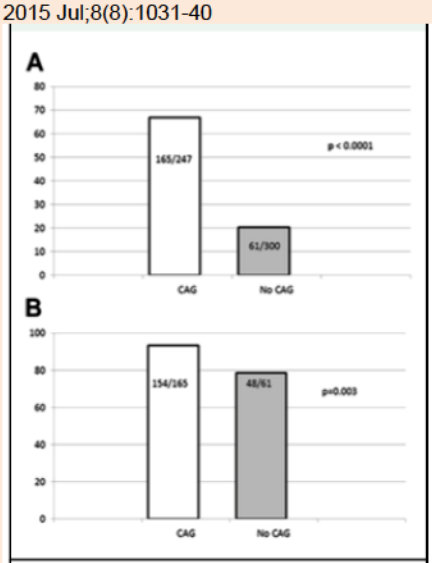
	Survival to hospital discharge (*N* = 1368)			MRS < 3 (*N* = 1006)		
	N	Odds ratio	Adjusted odds ratio[a]	*N*	Odds ratio	Adjusted odds rat
Early coronary angiography (*N* = 765)	495 (64.7%)	4.08 (3.65, 4.56)	1.69 [1.06,2.70]	413 (54.0%)	4.32 (3.81, 4.90)	1.87 [1.15, 3.04]
Reperfusion subjects (PCI or fibrinolytics) (*N* = 705)	377 (62.4%)	5.30 (4.74, 5.93)	1.94 [1.34, 2.82]	324 (53.6%)	5.98 (5.27, 6.78)	2.14 [1.46, 3.14]
Induced hypothermia (*N* = 1566)	637 (40.7%)	1.60 (1.43, 1.78)	1.36 [1.01, 1.83]	476 (30.4%)	1.56 (1.38, 1.77)	1.42 [1.04, 1.94]

[a] Adjusted for sex, first rhythm, witnessed collapse, bystander CPR, ROC site, advance airway inserted by EMS, public location of collapse, age, hospital cases per epinephrine dose, mean CPR fraction, intervals from 911 call to EMS arrival, EMS arrival to return of pulses, and depart scene to ED arrival.

2. **The MRC experience.**

In Minneapolis/St. Paul (MSP), where the only community-wide (as opposed to single, hospital-based) clinical protocol for early access to the CCL currently exists in the US, patients between 18-75 years old resuscitated from VT/VF with no-STEMI received early access to the CCL only two thirds of the time (130/203 or 64%). That observation underscores that even in this community, patients receive both treatments with randomness that is based on receiving cardiology preferences. The beneficial effect of early access to the CCL was sustained after adjusting for age, sex, race, year, location of arrest, bystander CPR, witnessed arrest and past medical history of PCI, coronary artery bypass grafting, myocardial infarction, diabetes, hypertension, hyperlipidemia, or tobacco use.[31] (Table 3)

Figure 1. Kern et al. JACC Cardiovasc Interv. 2015 Jul;8(8):1031-40



Coronary angiography 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)**. CAG = coronary angiography.

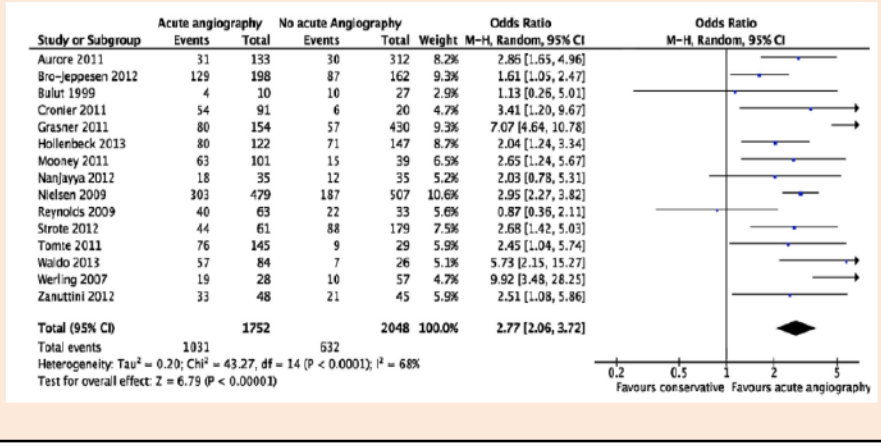
3. The ROC PRIMED experience. Dr. Clif Callaway (Co-I), reported in a recent publication from the ROC PRIMED database, the effect of early access to the CCL on functionally favorable survival. In the ROC PRIMED study (the largest study performed and published today in the US), only 19.2% (765/ 3981) of patients admitted to the hospital were investigated in the CCL and, of those, 705 (92%) had reperfusion therapy.[38] This observation underscores that the majority of the hospitals in the US and Canada do not access the CCL based on organized protocols but rather as a sporadic, random strategy. The data for this small, subpopulation was also consistent with many other case series showing that early access to the CCL had a positive association with survival to hospital discharge with mRS≤3. It had the strongest association with survival of any hospital-based intervention - greater than therapeutic hypothermia. (Table 4)

4. INTCAR Registry. Similarly, Dr. Kern (Co-I), recently published the effect of early coronary angiography and possible PCI in 548 patients with no-STEMI from the INTCAR-Cardiology Registry. Access to the CCL resulted in a survival benefit as shown in Figure 1. [23, 34]

5. **Meta-analysis.** A recent meta-analysis by Camuglia et al.[39] confirmed the MRC clinical observations, reaffirming that the published observational studies and MRC protocol driven results are consistent. It is evident that early access to the CCL with timely revascularization, when needed, is associated with a significant increase in the odds ratio for survival and functionally favorable survival. (Figure 2)

Early coronary angiography and PCI improves functionally favorable survival. There are no randomized human studies to address whether early coronary angiography and PCI improve functionally favorable survival from cardiac arrest. For this reason, investigators performed the first and only animal randomized trial of early versus delayed revascularization in pigs with ischemic (LAD balloon occlusion) cardiac arrest and resuscitation.[40] The hypothesis was that early PCI hemodynamic stabilization leads to less hypotension, hypoxia and metabolic abnormalities and would improve 24-hour survival and neurological outcomes. Total occlusion of the mid LAD was induced by balloon inflation in 27 pigs. After 5 minutes, VF was induced and left untreated for 8 minutes. If return of spontaneous circulation (ROSC) was achieved within 15 minutes of CPR (21/27 animals), animals were randomized to a total of either 45 minutes (group A) or 4 hours (group B) of LAD occlusion. Animals without ROSC after 15 minutes of CPR were classified as refractory VF (group C). In those pigs, CPR was continued up to 45 min of total LAD occlusion at which point coronary reperfusion was performed. CPR was continued until ROSC or another 10 min of CPR had been performed. Primary endpoints for groups A and B were 24-hour survival and functional assessment by cerebral performance category (CPC). The primary endpoint for group C was ROSC before or after reperfusion. Early, compared to late, reperfusion improved survival (10/11 versus 4/10, p = 0.02), mean CPC (1.4 ± 0.7 versus 2.5 ± 0.6, p = 0.017), LVEF (43 ± 13 versus 32 ± 9%, p = 0.01), troponin I (37 ± 28 versus 99 ± 12, p = 0.005) and CK-MB (11 ± 4 versus 20.1 ± 5, p = 0.031) at 24 hours after ROSC. In animals with refractory VF, ROSC was achieved only after reperfusion (in 4/6 animals). Investigators concluded that early reperfusion therapy significantly improves 24-hour survival rates and neurological status in a porcine model of VF cardiac arrest due to acute myocardial infarction.

Figure 2. Meta-analysis of the effect of acute angiography after VF/VT cardiac arrest on survival.



Window of Opportunity to Provide Potential Benefit (references 1-6 in red are for this section)

Coronary angiography and PCI have been shown to have a larger benefit when they are applied as early as possible. Optimal timing for CCL access is considered to be 90 minutes from emergency department arrival but benefits from PCI and coronary angiography can be seen up to 4 hours from hospital arrival based on STEMI randomized trials and meta-analyses. The benefits of revascularization diminish after 6 hours and are not present after 24 hours. Furthermore, in NSTEMI populations, the benefits have been confirmed up to 24-72 hours and a survival benefit has been realized with early access to the CCL for ambulatory patients.[1, 2 3-5]

In the proposed study population, an estimated 25-50% of patients will be identified to have significant, treatable CAD. The presence of "culprit" or "thrombotic occlusions" varies and has been reported as 25-40% in various cohorts. An additional group of patients will be identified as having culprit non-occlusive lesions. In those patients, intervention within 24 hours has been

shown to improve outcomes and patients with higher risk factors (such as Troponin, CHF, dynamic ST changes and ongoing chest pain) realize the larger benefit. [1]

The duration of myocardial ischemia before reperfusion, has been shown by Tarantini, et al [3], to be related with transmural myocardial necrosis and severe microvascular obstruction. Maximum injury appears to be plateauing after 6 -8 hours of ischemia; making it unlikely that clinical outcomes will improve further if reperfusion is achieved after those limits.

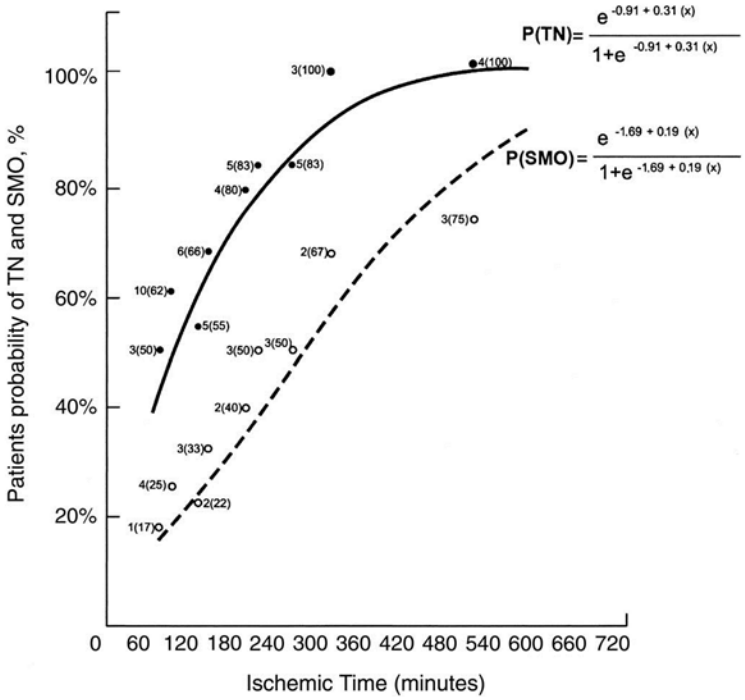
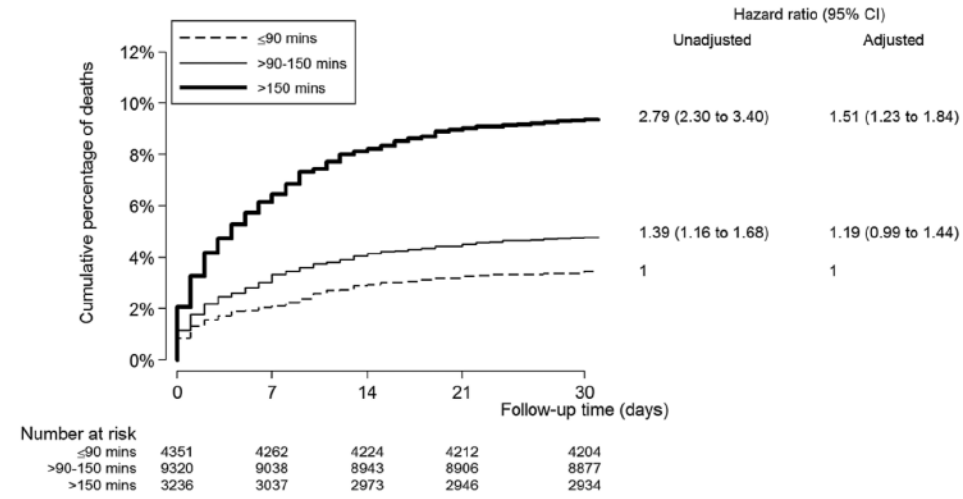


Figure 3. Relationship between ischemic time and in-hospital (patient) probability of transmural necrosis (TN) or severe microvascular dysfunction (SMO) assessed with logistic regression model. The coefficients of both equations have been computed for 30-min intervals. **Filled circles** □ observed TN rate expressed in number (%); **open circles** □ observed SMO rate expressed in number (%).

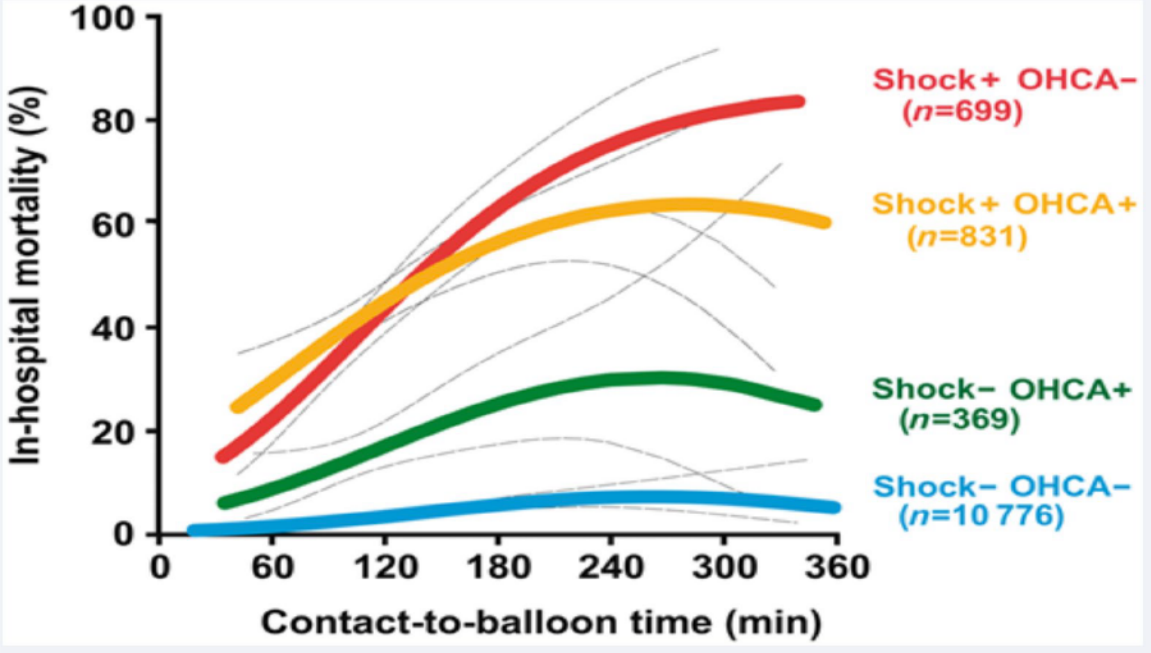


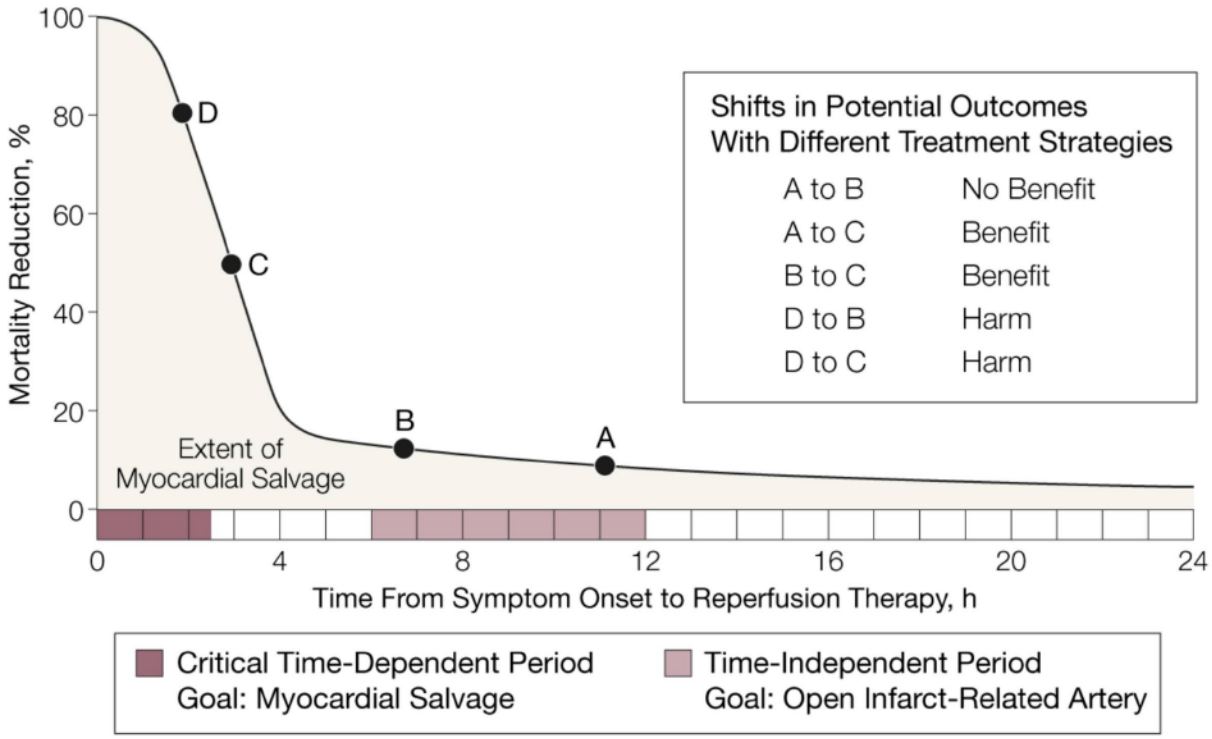
Varcoe RW, *et al*. *Heart* 2017;**103**:117–124. doi:10.1136/heartjnl-2016-309658

The figure 4, above shows how delayed reperfusion leads to worse outcomes and worse survival corroborating the basic pathophysiological observation in patients with acute myocardial infarction[4]. The Kaplan Meier Plot is showing 30-day mortality by door to balloon time (with 90 and 150 min as cut points).

Figure 4 clearly shows that >150 minutes is diminishing the potential advantage.

The therapeutic window and its tail, suggest that a 6-hour window exists with patients with STEMI and shock and OHCA in Figure 5 below. The effect of PCI plateaus at 4-6 hours.[5]





Based on Gersh et al. mortality decreases when reperfusion therapy is applied within 4-6 hours from onset of symptoms. As it can be seen on figure 6 above, after 6 hours the benefit is clearly decreased.[6]

The analysis, above, demonstrates the potential for direct benefit of initial cardiac catheterization laboratory (CCL) admission up to 6 hours for transfer patients. For all patients, however, the sooner the artery is opened following arrival at the treating hospital, the greater the likelihood for potential benefit. The likelihood of benefit diminishes and the likelihood of harm increases with greater delay following arrival at the treating hospital. This “time is muscle” concept continues to define the therapeutic window for this study, with the additional clarification as 90 minutes from arrival at the treating (participating) hospital.

The desired therapeutic effect is opening of an occluded artery. The same previous estimates for mobilizing the cardiac catheterization laboratory team (30 minutes) and opening the artery (15 minutes) continue to apply. Accordingly, any transfer patient arriving at the participating hospital ≤ 4 hours and 30 minutes of arrival at the first hospital’s emergency department (ED) will be considered as eligible for study entry (6 hours – 90 minutes [45 minutes to contact the family and 45 minutes to mobilize the CCL and open the artery]).

Upper Age Limit of 80 Years **(references 1-25 in blue are for this section)**

The prevalence and proportion of elderly patients undergoing or being referred for coronary revascularization is increasing.[1,2] Currently, a quarter of all patients treated with percutaneous coronary intervention (PCI) are aged >75 years. [1,2] Further, cardiovascular disease remains the leading cause of morbidity and mortality amongst the elderly.[3] Interventional cardiologists were initially reluctant to perform revascularization procedures in the elderly because of the perceived comparative increased risk to reduced benefit obtained by revascularization in this subset of

patients. However, there has been a paradigm shift in the treatment of this group of patients, with a quarter of all percutaneous coronary interventions (PCI) performed in patients aged ≥75 years and 12% performed in those aged ≥80 years.[4,5]
Increasing age is associated with greater PCI risk. [6,7] Increased coronary medial calcification and multi-vessel disease in elderly patients make PCI more technically challenging. [6,7] Hypercoagulability of older patients, caused by elevated levels of activated factors such as VII, IX and X and increased platelet reactivity may increase risk of acute stent thrombosis. [8,9] Reduced lean body mass, reduction in first pass metabolism and liver cytochrome P450 activity, and age-dependent decline in renal function may lead to an increase in bleeding complications. [10] Co-morbidities increase with age. [11]

However, development of revascularization protocols, improvements in operator technique, guide-catheter and guide-wire technology combined with the use of evidence-based drug therapies, including, the use of dual anti-platelet, high-intensity statin therapy, and glycoprotein IIb/IIIa inhibitors, has dramatically reduced mortality figures.[12] In an observational study using the National Cardiovascular Disease Registry (NCDR) CathPCI Registry, Singh *et al.* demonstrated an overall reduction in mortality to 1.2%.[13] The decline in mortality was greatest in the oldest patient group, emphasizing the improvements made to PCI technique and adjunctive management.[13] Mortality was less than one percent for patients >80 years with no risk factors but reached 7.2% for patients>80 years with left ventricular ejection fraction (LVEF) <35%.[14]

Observational studies looking at the uptake of PCI to treat elderly patients with acute coronary syndromes (ACS) suggest the interventional community are changing their practice in accordance with the growing evidence in this subset of patients and treating more elderly people with percutaneous revascularization. Khera *et al.* used the United States Nationwide Inpatient Sample to examine temporal trends in PCI uptake from 2001-2010.[15] Patients were divided into age groups: 65-79 and >80 years. The use of PCI for STEMI increased 33.5% and 22% in each group respectively. A decreased in-hospital mortality was also seen in the >80 age group (150 per 1000), which was apparent in the 65-79 age group (115 per 1000), suggesting the greatest benefit of PCI is when it is performed in the elderly population when compared with other age groups. Additionally, PCI is not only useful in terms of preventing death, but specifically in the elderly, it brings about most improvement in physical health at 6 months when compared to younger people.[16]

Over a third of all patients admitted with a non-ST-elevation myocardial infarction (NSTEMI) are greater than seventy-five years of age.[17] Liistro *et al.* examined outcomes of patients presenting with NSTEMI undergoing revascularization (CABG or PCI), and found that death (3.1% vs 0.3% p=0.02) and death plus non-fatal myocardial infarction (5.6% vs 1% p=0.01) were significantly more common amongst those aged >75 years, when compared to a younger cohort (<75 years). However, percutaneous revascularization in the elderly population led to a comparable 30-day all-cause mortality (1.9% vs 0%, p=0.1) and medium term (mean duration 10.7 months) cardiac mortality (2.9% vs 1.1%, p<0.01).[18]

In a study by De Servi *et al.*, an aggressive treatment strategy (involving angiography within 4 days in NSTEMI patients, followed by revascularization where possible) was followed in 39% >75 years and 56% in the<75years group (p=<0.001).[19] At 30-days following NSTEMI, revascularization had been performed in 30% of patients in the older group and 48% in the younger group (p=<0.001). In-hospital 30-day mortality rates were almost four times as high in the older group, with adoption of a conservative strategy being an independent predictor of adverse outcome (OR 2.31), highlighting the importance of revascularization in this high-risk cohort in modifying and optimizing outcome. In addition, the GRACE registry assessed

outcomes in patients across all ages who underwent revascularization following NSTEMI. This reaffirmed the improved outcome with revascularization, with a significant reduction in 6-month mortality demonstrated in all age ranges: under 70 years (OR 0.52, 95% CI 0.37-0.72), 70-80 years (0.38, 0.26-0.54) and over 80 years (0.68, 0.49-0.95). (Figure 1)[20]

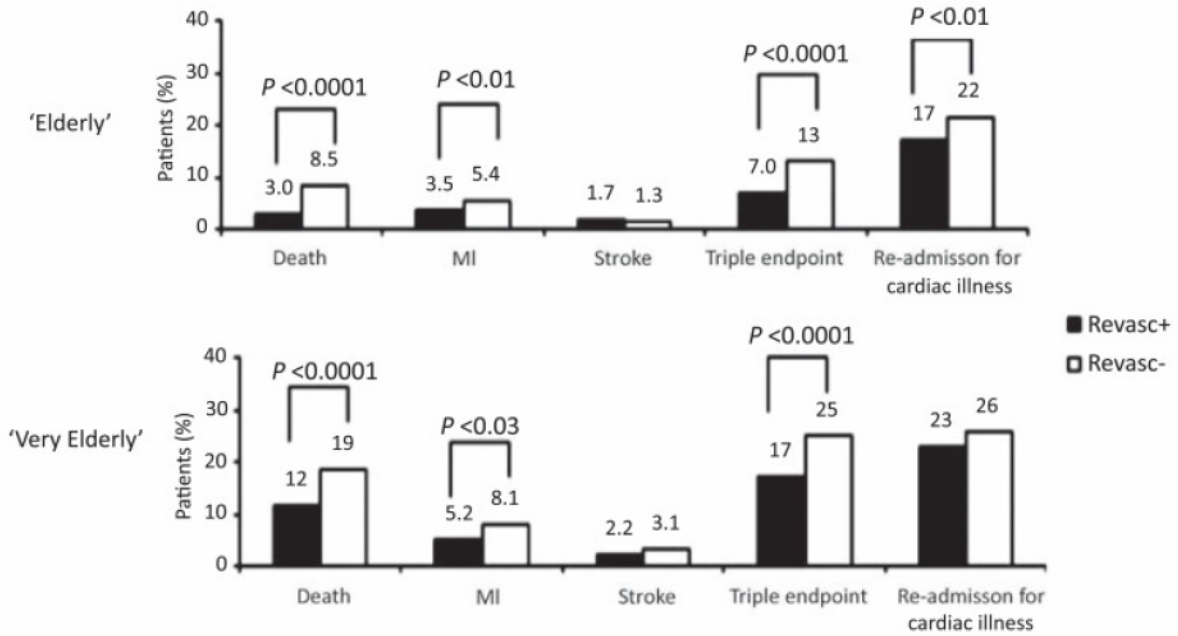


Figure 1: Improved outcomes in both NSTEMI elderly (aged 70-80 years) and NSTEMI very elderly (> 80 years old) groups undergoing percutaneous revascularization from the GRACE registry of Acute Coronary Events. Devlin *et al*.[20]

The direct benefit of PCI in the elderly appears to be sustained even in the condition of angina. Investigators of the Trial of Invasive versus Medical therapy in Elderly – (TIME) study evaluated treatment options in patients with chronic symptomatic coronary artery disease already on two anti-anginal drugs. (Figure 2)[21] All enrolled patients were aged > 75 years, and randomized to angiography ± revascularization or medical therapy. While symptoms and quality of life improved in both groups, major adverse cardiac events were significantly reduced in the PCI treated cohort (19% vs. 49%, p=0.0001) (Figure 2) Furthermore, when PCI is compared to CABG in the setting of stable CAD, meta-analysis data has shown that PCI is associated with a reduced 30-day mortality (5.4% 95% CI 4.4-6.6% vs 7.2% 95% CI 6.3-8.2%), with equivalent rates of 1-year survival (87% 95% CI 84-91% vs. 86% 95% CI 83-88%).[22] These data demonstrate a percutaneous revascularization strategy, in the presence of failed medical therapy, leads to acceptable short and medium term outcomes in comparison with CABG, in the context of stable angina.

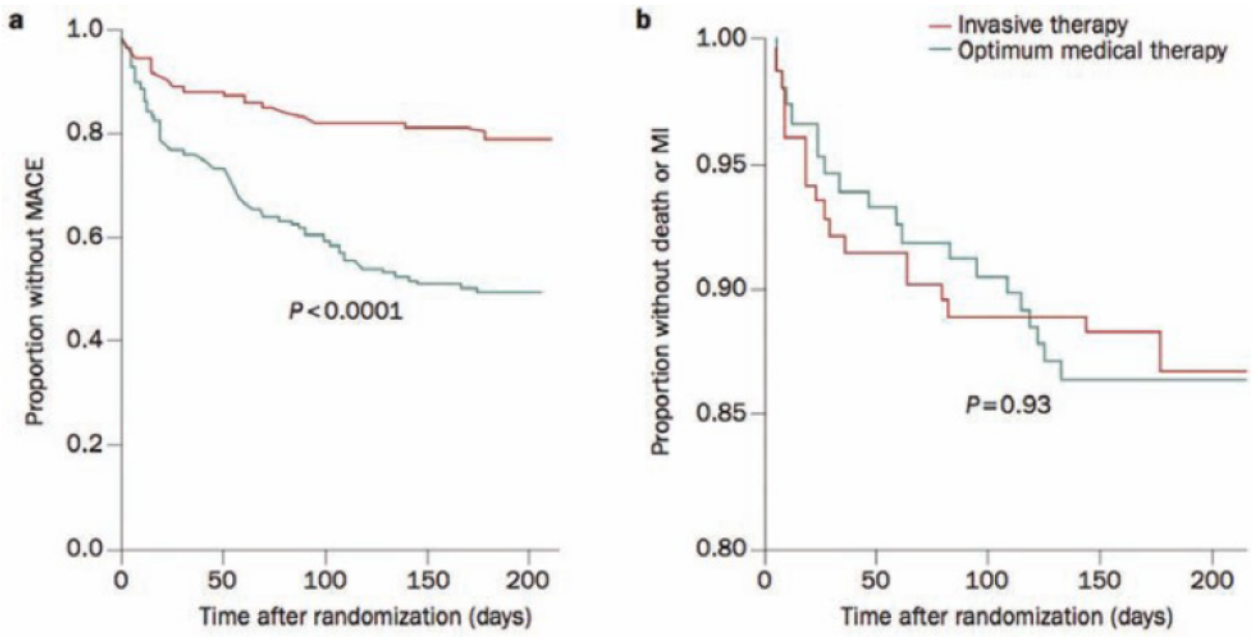


Figure 2: Outcomes associated with invasive and optimum medical therapy for coronary artery disease among patients aged >75 years. A. Event-free survival. B. Time to death or nonfatal MI. Abbreviations: MACE, major adverse cardiac event (death, recurrent MI, or rehospitalization for acute coronary syndromes); MI, myocardial infarction.

Multiple groups have published assessments of the relationship between survival from out-of-hospital cardiac arrest and age. Wissenberg et al, with data from the Danish Cardiac Arrest Registry, compared patients of working age (18 to 65 years), early senior age (66-80 years), and late senior age (>80 years) and found that patients age 66-80 years old survived in 30% of cases of cardiac arrest related to a shockable rhythm. Importantly, the survival rate was increasing from 2001 through 2011 which was the last year assessed.[23] Similarly, Hirlekar et al. assessed survival in elderly patients after in-hospital cardiac arrest finding that patients age 70-79 years were discharged alive in 28% overall and in 58% of VF/VT arrest. Of those, 92% were discharged with CPC 1-2[24] multiple studies have demonstrated that in cardiac arrest survivors, neurological outcome is similar irrespective of age.[23-25]
Based on data from the Minnesota Resuscitation Consortium, there are 10-15 cases/year involving patients aged 76-80 with out-of-hospital VF/VT arrest in addition to the 100-120 cases/year that meet the current ACCESS criteria. Over the last 3 years, patients 76-80 years old had an average 31% survival rate to hospital discharge with CPC 1 or 2. The survival rate, although lower than the younger population, confers benefit to this patient population. Furthermore, early access to the CCL within 4 hours for this age group confers the same observed absolute survival increase when going to the CCL (43.3% with initial CCL admission versus 27% with no CCL admission) with 44% of all patients getting early CCL access. There were 43 total patients aged 76-80 years old in our database over a 3 year period of time.

In summary, there has been an increasing prevalence of revascularization in the elderly as improvements in revascularization protocols, improvements in operator technique, and use of evidence-based drug therapies have dramatically reduced mortality. As would be expected, due to age-associated pathophysiological changes and increased co-morbid conditions, the elderly are a higher-risk group for mortality and adverse events following PCI when compared to younger patients. However, despite the higher risk, coronary artery disease treated by PCI (as opposed to no intervention) is likely to afford increased direct benefit to older patients with

greater relative improvements in survival and functional status than when compared with younger patients.

The management of older patients will still need to be guided based on the findings of the ACCESS trial in the future. However, exclusion criteria for age >75 eliminate these patients. We therefore propose to modestly increase the age inclusion criteria from 18-75 years old to 18-80 years old. Very elderly patients > 80 years old will be excluded from the trial.

Professional guideline organizations identify need for a randomized clinical trial Both the American Heart Association (AHA) and the American College of Cardiology (ACC) are encouraging early access to the CCL but cannot strongly recommend it due to the absence of a randomized clinical trial. The recent published ACC statement concludes: "Randomized controlled trials of early PCI in post-cardiac arrest patients without ST-segment elevation are needed."[33] Further, due to the higher mortality of this population and the adverse effect of public reporting of CCL mortality outcomes there is a significant counterincentive to allow access to the CCL for this population. In order to eliminate that issue, conclusive evidence is needed that such an approach improves outcomes. When and if the benefit is established, we will be able to generate a separate category for this population in national reporting databases. Both AHA and ACC have underscored that important point. The ACC statement concluded: "We emphasize our viewpoint and explicitly recommend without reservation that PCI outcomes in cardiac arrest patients not be included in public reporting. A national platform for tracking outcomes of cardiac arrest patients undergoing PCI is needed and should distinguish patients with and without ST-segment elevation." [32]

The American Heart Association 2010 Guideline stated: "It is reasonable to include cardiac catheterization and coronary angiography in standardized post-cardiac arrest protocols as part of an overall strategy to improve neurologically intact survival in this patient group (Class IIa, LOE B) and appropriate treatment of ACS or STEMI, including PCI or fibrinolysis, should be initiated regardless of coma (Class I, LOE B). Angiography and/or PCI need not preclude or delay other therapeutic strategies including therapeutic hypothermia (Class IIa, LOE B).[10]

In the same document, the AHA guidelines acknowledged the value of early CCL access and possible PCI. The guidelines stated: "Cardiac angiography and PCI, when used as part of a standardized advanced post–cardiac arrest protocol, may result in improved survival to hospital discharge. Acute coronary artery occlusion is frequent in survivors of out-of-hospital cardiac arrest. PCI is feasible following ROSC, and almost 50% of cardiac arrest survivors have an acute thrombotic occlusion, or culprit lesion, that is amenable to reperfusion. In addition, successful PCI can result in improved cardiac ejection fraction and survival. Cardiac catheterization alone (without PCI) has been associated with improved neurologically intact survival. Although coronary artery occlusion after cardiac arrest is associated with ST elevation or LBBB, specific ECG findings may also be conspicuously absent."[10]

Clinical Equipoise

Thus, wide variation in clinical practice exists in the United States, with no-STEMI patients treated with either: 1) initial CCL admission, or 2) initial ICU admission. There are strong proponents for each of these two strategies contending the prospect of direct benefit for patients for either approach. For initial CCL admission this includes, but is not limited to identifying coronary artery lesions and promptly reperfusing; recognizing other etiologies; optimizing hemodynamics and cardiac performance; placing mechanical hemodynamic support, if needed; and, knowing the "absence" of coronary artery disease could benefit by informing subsequent patient management. For initial ICU admission this includes, but is not limited to rapidly stabilizing by correction of acidosis, optimizing ventilation and providing systemic hemodynamic support; identifying other

etiologies; targeting performing coronary angiography at a time when the patient is more stable or when clinical judgment suggests coronary artery disease as the culprit of the arrest. Thus, there is the prospect of direct benefit to patients for either of these approaches. The clinical and underlying physiologic validity of the treating clinician's decision to intervene in any individual case with one of these two treatment options is unknown. Observational data supports potential benefit for no-STEMI patients receiving early CCL treatment, but it is subject to inherent selection bias that no statistical adjustment can eliminate completely. Professional guidelines organizations recommend implementation of a randomized clinical trial as proposed in this study. Given this state of our current collective understanding, clinical equipoise exists for the proposed randomized clinical trial, which will provide the only reliable data on which clinical practice can be based and consistently provided.

Significance

An estimated 120–130,000 patients suffer VT/VF cardiac arrest each year.[7-11] Of these, 50–60% survive to hospital admission (60,000–78,000 patients/year) and 70% of these **do not** have ST-segment elevation on 12-lead ECG (42,000 – 54,600 patients/year). With a realistic estimate of an absolute 15% increase in VT/VF functionally favorable survival rate with initial CCL admission, an additional 6300 to 8200 patients could be saved each year in the United States alone.

3 OBJECTIVE

The objective is to evaluate survival to hospital discharge with mRS ≤3, as well as 3 month morbidity, survival, and functional recovery in the two randomized treatment groups.

4 STUDY DESIGN

The ACCESS Trial is a pragmatic, prospective, clinical study, randomizing adult (18-80 years old) patients resuscitated from out-of-hospital VT/VF cardiac arrest who do not have ST-segment elevation acute myocardial infarction on emergency department 12-lead ECG (no-STEMI) and are either direct EMS transports or transferred from an outside hospital: a) covered by the local community consultation and public notification process, and b) transferred within 4 hours and 30 minutes from initial hospital arrival (time from initial emergency department arrival to participating hospital arrival [either ED or ICU, whichever is first], and c) transferred to the participating hospital's ED or ICU to receive either: 1) initial CCL admission, or 2) initial ICU admission.

5 STUDY POPULATION

5.1 Selection of the Study Population

Adult patients (18-80 years old) resuscitated from out-of-hospital VT/VF cardiac arrest will be initially identified in the emergency department. The research coordinator will determine patient eligibility. Prior to being eligible for the ACCESS study all inclusion criteria need to be met and none of the exclusion criteria.

5.1.1 Inclusion of Women and minorities

The ACCESS Trial has been designed to screen 100% of eligible study subjects with the condition of interest from participating study sites (adults [18-80 years old] resuscitated from out-of-hospital VT/VF cardiac arrest with no ST-segment elevation on emergency department 12-lead ECG). There are no gender or racial/ethnic exclusions. Eligible subjects of all gender and racial/ethnic subgroups will be offered participation in the study. We therefore expect gender and ethnic/racial proportions reflecting the demographic characteristics of the participating study sites. The following targeted/planned enrollment table was generated based on the gender and racial/ethnic characteristics of the geographic regions served by the participating study sites and the anticipated number of study subjects per site.

5.1.2 Targeted/Planned Enrollment Table of the ACCESS Trial

Race	Male (N)	Female (N)	Total (N)
American Indian/Alaska Native	4	4	8
Asian	14	16	30
Black/African American	28	32	60
Hawaiian/Pacific Islander	2	3	5
White	202	205	407
Multirace	5	5	10
Ethnicity	**Male (N)**	**Female (N)**	**Total (N)**
Hispanic (Latino/Latina)	38	40	78
Non-Hispanic	216	226	442

5.1.3 Exclusion of Children

The incidence of coronary artery disease and frequency of VT/VF cardiac arrest in children is extremely low. For these reasons, children < 18 years old are necessarily excluded from inclusion in the ACCESS Trial as they are unlikely to benefit from study inclusion.

5.1.4 Justification of Exclusion Criteria

Adults >80 years old have increased CCL and cardiac arrest mortality and are unlikely to benefit from study inclusion. Non-shockable cardiac arrest rhythms, valid do not resuscitate orders (DNR), blunt, penetrating, or burn-related injury, drowning, electrocution or known overdose, known pregnancy, absolute CCL contraindications, known or suspected intracranial bleeding, refractory cardiac arrest prior to randomization, patients meeting ACCESS Trial eligibility criteria initially seen in an outside hospital and then transferred to an ACCESS Trial participating hospital more

than 4 hours and 30 minutes later, and unavailability of the cardiac catheterization laboratory are excluded because they are not the condition of interest and are also unlikely to benefit from study inclusion. Patients with ST-segment elevation on 12-lead ECG are not the condition of interest. Known prisoners are excluded from studies utilizing exception from informed consent under emergency circumstances as defined in 45 CFR Part 46. Patients transferred from an outside hospital not covered by the community consultation and public notification process or transferred directly to the CCL for immediate PCI cannot be included in the study.

5.2 Inclusion/Exclusion Criteria

Inclusion Criteria:

- Adult presumed or known to be 18-80 years old
- Resuscitated from OOHCA
- Initial cardiac arrest rhythm of pulseless VT/VF (including patients treated with an AED) or unknown shockable rhythm
- No ST-segment elevation MI (No STEMI or STEMI-equivalent syndrome) on ED 12-lead ECG (as interpreted by a physician)
  - 12-lead ECG Criteria
    - STEMI

      Leads V2 and V3: New STE at the J point in at least 2 contiguous leads ≥ 2 mm (0.2 mV) in men, or ≥ 1.5 mm (0.15 mV) in women in leads V_2–V_3

      OR: ≥ 1 mm (0.1 mV) in other contiguous chest or limb leads

      OR: New left bundle branch block (LBBB) considered as a STEMI equivalent by the treating clinician
  - Either a direct EMS transport or transferred from an outside hospital:

    a) covered by the local community consultation and public notification process, and

    b) transferred within 4 hours and 30 minutes from initial hospital arrival (time from initial emergency department arrival to participating hospital arrival [either ED or ICU, whichever is first]), and

    c) transferred to the participating hospital's ED or ICU.

Exclusion Criteria:

- Initial non-shockable out-of-hospital cardiac arrest rhythm (pulseless electrical activity or asystole)
- Valid do not resuscitate orders (DNR),
- Blunt, penetrating, or burn-related injury, drowning, electrocution or known overdose,
- Known prisoners

- Known pregnancy,
- ST-segment elevation on ED 12-lead ECG (as interpreted by a physician)
- Absolute contraindications to emergent coronary angiography including,
  - known anaphylactic reaction to angiographic contrast media,
  - active gastrointestinal or internal bleeding, or
  - severe concomitant illness that drastically shortens life expectancy or increases risk of the procedure.
- Suspected or confirmed intracranial bleeding
- Refractory cardiac arrest (prior to randomization)
- Patients meeting ACCESS Trial eligibility criteria transferred from an outside hospital:
  - not covered by the local community consultation and public notification process, or
  - transferred > 4 hours and 30 minutes from initial hospital arrival (time from initial emergency department arrival to participating hospital arrival [either ED or ICU, whichever is first]), or
  - transferred directly to the participating hospital's CCL
- Unavailability of the cardiac catheterization laboratory

6 CLINICAL AND LABORATORY ASSESSMENTS

6.1 Schedule of Events

Assessment	Screening	Enrollment Randomization	Hospitalization	Discharge from Hospital	3 month visit[1] (±14 Days)
Inclusion/Exclusion	X				
Consent [2]	X				
Demographics		X			
Medical History		X			
Pre-hospital data		X			
Glasgow Coma Score at time of eligibility		X			
Randomization		X			
Hospital data			X		
Ejection Fraction (EF)[3]				X	
Trop I[4]			X	X	
Labs: Creatinine, eGFR[5]			X	X	
Blood Gases:PaCOx[4], SaO2[4], pH[4], HCO3[4]			X		
Blinded mRS score				X	X
Blinded CPC Score				X	X
AE/SAE reporting			X	X	X

*Ejection fraction (EF), Trop I, Labs, and blood gas values will be acquired only if obtained as a component of clinical care.

[1] Calculated from day of Discharge
[2] Documentation of EFIC process required if used
[3] EF should be result reported closest to discharge date
[4] Peak Troponin during hospitalization
[5] Value to be reported closest to admission and/or closest to discharge

7 STUDY SCHEDULE

7.1 Screening

All adult (18-80 years old) patients successfully resuscitated from out-of-hospital VT/VF cardiac arrest transported to the emergency department with no ST-segment elevation on emergency department 12-lead ECG will be considered eligible for entry in the study. The research coordinator will review and confirm all inclusion and exclusion criteria. If all inclusion criteria are met and none of the exclusion criteria are applicable the subject is eligible for the study.

7.2 Consenting

The subject may enter the trial by one of two informed consent approaches; consent by the subject or family member/legally authorized representative (LAR) or by exception of informed consent (EFIC).

Upon subject arrival to the ED the coordinator has a 45 minute window to obtain written informed consent. A good faith effort will be made to contact family or the LAR to obtain written informed consent. If all efforts to contact family or LAR within 45 minutes fail, patients will be considered eligible for study entry under EFIC.

If the LAR is contacted in-person within 45 minutes of subject ED arrival, the Investigator/designee will explain the nature and scope of the study, potential risk and benefits of participation, and answer questions for the subject or family member/LAR. If the subject or family member/LAR agrees to participate, the informed consent form (ICF) must be signed and personally dated by the subject or their family member/LAR. The Investigator/designee must also sign the ICF prior to subject enrollment.

If the LAR can only be contacted by telephone with 45 minutes of ED arrival, the Investigator/designee will explain the nature and scope of the study, potential risk and benefits of participation, and answer questions for the subject or family member/LAR. If the subject or family member/LAR does not object to participation in research, the patient will be entered in the study under the EFIC process.

If the LAR cannot be contacted within 45 minutes of ED arrival, the patient will be entered in the study under the EFIC process.

7.3 Randomization/Baseline

Randomization will occur after documentation that inclusion and exclusion criteria are met and informed written consent has been obtained, notification of the patient/family/LAR has occurred and they do not object to participation in the study, or documentation that a good faith effort was done to contact the subject's family member.
The Investigator/designee will then log into a website and randomize the subject to one of the two groups and notify the appropriate treating clinicians. If the subject is randomized to initial cardiac catheterization laboratory (CCL) admission, institutional guidelines to activate/notify the CCL of the subject will be followed. If the subject is randomized to initial ICU admission, institutional guidelines for these subjects for admission to the intensive care unit or the equivalent will be followed.

If the EFIC process is used, the subject will be randomized under HHS regulation 45 CFR Part 46, exception from informed consent under emergency circumstances (EFIC). Following randomization of a patient under HHS regulation 45 CFR Part 46, exception from informed consent under emergency circumstances, research personnel will continue to make every effort to contact family or subject's LAR, to notify them of their family member's participation in the study. If contact occurs after entry of the subject under EFIC but prior to emergency department admission to the CCL or ICU, research personnel will review the informed consent process with the family/LAR. If the family/LAR consents to study participation, the subject will continue with the intervention to which they were randomized and included in the evaluable study population. If at any point the family/LAR withdraws consent to study participation the treating physician will be notified. In such cases, continued treatment will be at the discretion of the treating clinician. If family/LAR contact does not occur prior to emergency department admission to the CCL or intensive care unit, the patient will continue with the intervention to which they were randomized. The family/LAR will be subsequently notified consistent with 45 CFR Part 46 regulations.

7.3.1 Baseline Assessments: See MOP for full detailed list for all time points

- EMS incident number
- Location Type
- Arrest Witnessed by anyone
- Arrest After Arrival of any 911 Responder
- Who Initiated CPR
- Was an AED Applied Prior to EMS Arrival
- Who First Applied the AED
- Who First Defibrillated the Patient
- First Known Arrest Rhythm of Patient
- Did the patient have ROSC in the field at any time
- Did subject rearrest at any time prior to transfer to ED
- Was Hypothermia Care Provided in the Field
- Estimated time of Arrest
- Time of 1st Defibrillation Shock
- Time of 1st CPR by anyone
- Total number of shocks (AED +EMS):
- Advanced Airway Successfully Placed in the Field
- Vascular Access
- Medication Administered in the field
- Response and Treatment Times
- Time of ED admission
- ED 12-lead ECG interpreted by treating physician
- Glasgow Coma Score at time of eligibility assessment (3-15)
- ED procedures
- ED Hemodynamic Support
- Blood pressure

- Hypothermia
- Subjects vital status on discharge from the ED

7.4 Follow-up and Final Visits

7.4.1 Admission Assessments:

- Catheterization lab data
  - Angiogram upload
  - Did the subject go to the CCL
  - Subject vital status
  - Date of arrival to CCL
  - Time of arrival to CCL
  - Date/Time of PCI/Thrombectomy
  - Chronic Coronary Artery disease (existing 50%) stenosis location/s
  - ACUTE coronary artery disease location/s of culprit vessel/s
  - Number of stents placed
  - Vessel location of stents
- Hypothermia assessment
- Procedures during hospitalization (LVAD, CABG, ECMO, IABP, ICD)
- Ejection fraction per ECHO assessment before discharge or last before death
- Length of relevant events
  - ICU stay
  - Ventilator duration
  - Hospitalization length
  - Total time to awakening
  - IABP duration
- AE/SAE

7.4.2 Discharge Assessments:

- Survival status
- mean peak troponin level
- mean ejection fraction
- mean length of ICU stay
- mean hospitalization duration
- incidence of and mean length of rehabilitation.
- Blinded CPC score
- Blinded mRS score
- Lab values
- AE/SAE

7.4.3 3 Month Phone Call Assessment:

- Survival to 3 months

- Survival to 3 months with mRS ≤ 3
- Functional status at 3 months (blinded)
    - mRS score
    - CPC score
- Incidence and length of rehabilitation
- Incidence of congestive heart failure
- Incidence of re-hospitalization over 3 months
- Incidence and time to return to work.
- AE/SAE assessment

7.5 Functional status and Neurological Assessment Details

7.5.1 Cerebral Performance Category (CPC)

CPC 1: Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.
CPC 2: Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.
CPC 3: Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
CPC 4: Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
CPC 5: Brain death: apnea, areflexia, EEG silence, etc.

7.5.2 Modified Rankin Scale Score (mRS)

The mRS has face validity and can be determined via review of the clinical record, in-person or over the telephone.[59, 60] The mRS has concurrent validity with other measures of neurological recovery after stroke and brain injury.[61, 62] mRS has prior use in a cohort of neurosurgical patients with in-hospital cardiac arrest,[42] in a cohort of survivors of out-of-hospital cardiac arrest[43] and is currently the accepted standard for cardiac arrest clinical trials.[63, 64] It is scaled from zero (no symptoms) to six (death), with a score of ≤3 indicating a moderate functional disability or better and conventionally taken to be consistent with favorable neurological and functional outcome.[65] Patients who die before hospital discharge will be assigned a mRS of 6. This will be conducted by certified, blinded personnel.

7.6 Criteria for Discontinuation or Withdrawal of a Subject (or a Cohort), if applicable

Subjects/LARs have the right to withdraw from research at any time (45 CFR 46 [A] [8]). If the subject/LAR decides to withdraw from all components of the research study, investigators will discontinue interacting or intervening with the subject in order to obtain data about him/her for the research study. Discontinuation or withdrawal of a subject may also occur because of study closure due to DSMB review.

8 ASSESSMENT OF OUTCOME MEASURES[41]

8.1 Primary Outcome Measures

Survival to hospital discharge with mRS ≤ 3 [42-44]

8.2 Secondary Outcome Measures

- *In-hospital secondary endpoints:* Survival to hospital discharge, mRS score, CPC score, mean peak troponin level, mean ejection fraction, mean length of ICU stay, mean hospitalization duration in patients who survive to hospital discharge, and the incidence of and mean length of rehabilitation.
- *3-month post-hospital discharge secondary endpoints:* Survival to 3 months, survival to 3 months with mRS ≤ 3, functional status at 3 months (mRS score and CPC score), incidence and length of rehabilitation, incidence of congestive heart failure, incidence of re-hospitalization over 3 months, and incidence and time to return to work.[45-47]

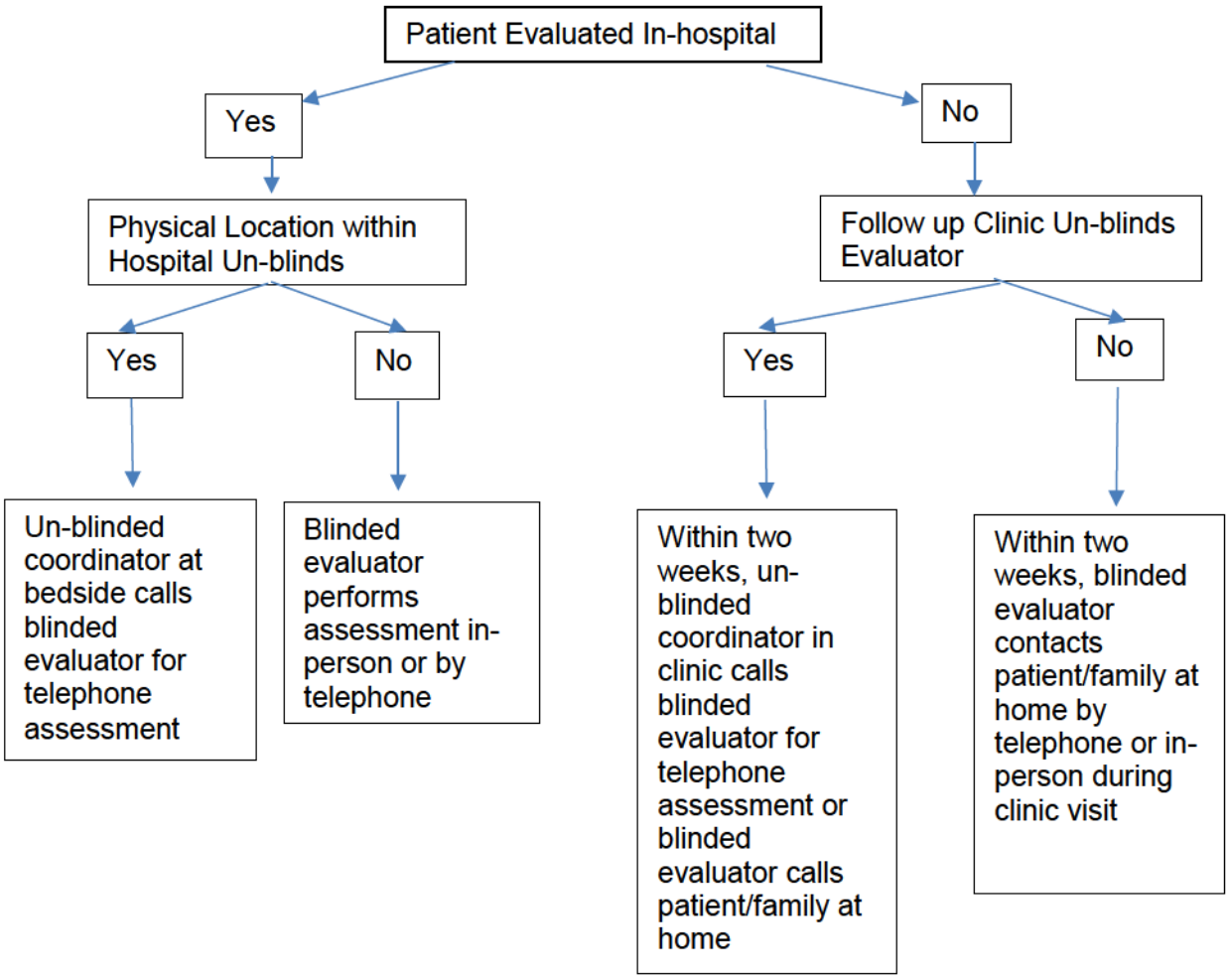
  Pre-specified Subgroup Analyses:
  The primary study endpoint will be compared between:
  - Males versus females, and
  - Study subjects < 55 versus ≥ 55 years old

8.3 Blinding mRS and CPC Classification at Hospital Discharge and 3 Months

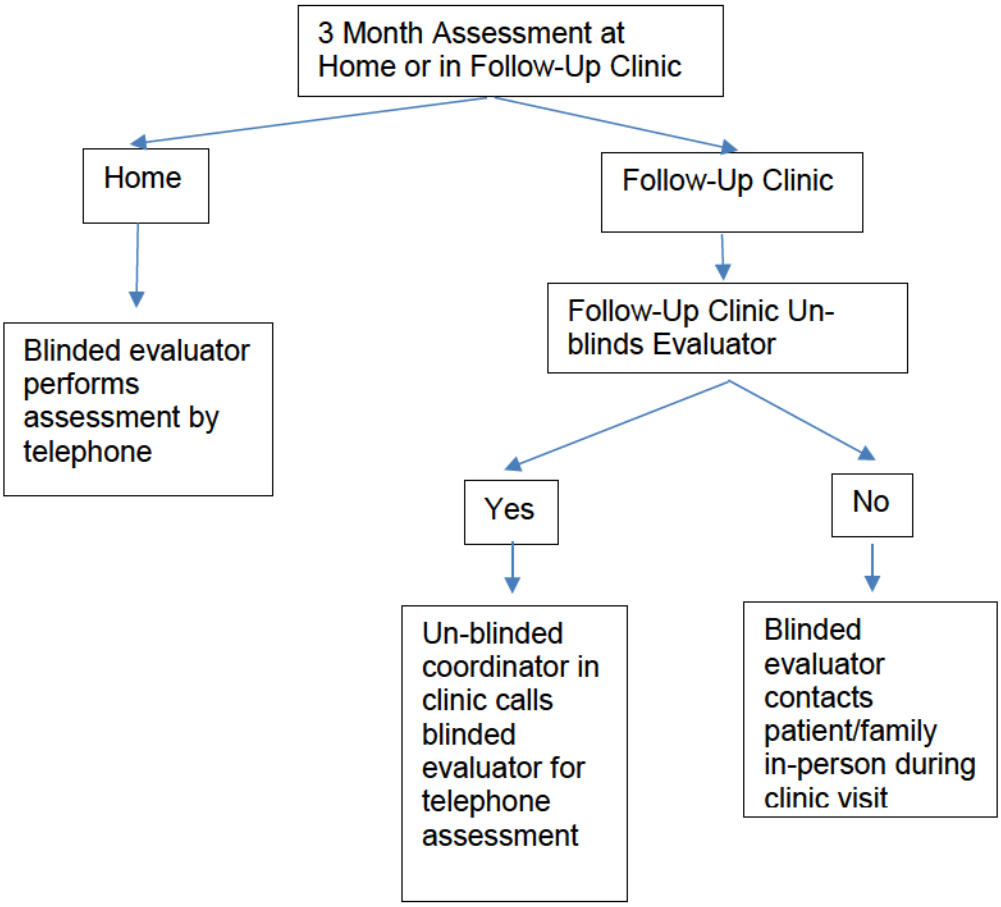
a) **Blinded assessment of mRS and CPC classification at hospital discharge and 3 months will be accomplished as follows:** Hospital chart/medical record review will not be used to obtain mRS and CPC classifications at either hospital discharge or 3 months. At hospital discharge, the following approach will be used: 1) if the physical location of the patient within the hospital does not un-blind the evaluator, then the blinded evaluator will determine the mRS and CPC in person or by telephone, 2) if the physical location of the patient within the hospital will un-blind the evaluator, an un-blinded research coordinator at the patient's bedside will call a blinded evaluator who will obtain the mRS and CPC from the patient/family by telephone, and 3) if the patient is missed prior to hospital discharge, a blinded evaluator will contact the patient/family by telephone or in-person (e.g. on a follow-up clinic visit) and determine the mRS and CPC within 2 weeks of hospital discharge. The 3-month blinded assessment will be accomplished by assigning an mRS-qualified staff person without knowledge of randomized treatment assignment to contact the patient or family, by telephone or in person (e.g. on a follow-up clinic visit) 3 months following hospital discharge to obtain both the mRS and CPC classifications. If the type of follow-up clinic un-blinds the evaluator, an un-blinded research coordinator at the patient' side will call a blinded evaluator who will obtain the mRS and CPC from the patient/family by telephone during that clinic visit. The medical record will not be reviewed to obtain this information.

b) **Algorithms for blinded assessment**

Blinded mRS and CPC Assessment at Hospital Discharge



Blinded mRS and CPC Assessment at 3 months



9 SAFETY ASSESSMENT AND REPORTING

Data and Safety Monitoring Board (DSMB) and Monitoring Strategy

Selected and convened by the NHLBI, an independent DSMB will help ensure the safety of the trial by monitoring adverse outcomes throughout the trial and by reviewing outcome data for both efficacy and possible harm. In addition, the Board will review the results of the interim analyses (see below). The DSMB must review and approve the protocol before the study can commence. The DSMB will evaluate the rate of adverse events between the treatment and control arms at intervals to be determined by the DSMB, expected to be approximately every three to four months (after evaluation of cohorts of 82 patients; see below). The DSMB will also monitor primary and secondary study outcomes between the treatment and control groups. The SDCC will forward DSMB recommendations to study investigators, the Institutional Review Boards, the Food and Drug Administration, and the NIH in accordance with federal regulations 45 CFR Part 46 Subpart A and 21 CFR 312.

Safety and Data Monitoring Plan

An independent Clinical Events Committee (CEC) will be established to evaluate and classify adverse events and to determine whether adverse events potentially unique to initial CCL admission were the result of CCL intervention or the consequences of the underlying cardiac arrest. Similarly, the CEC will evaluate and classify adverse events and to determine whether adverse events potentially unique to initial ICU admission were the result of ICU intervention or the consequences of the underlying cardiac arrest. The safety and data monitoring plan for this trial is centered on reports to the DSMB. The DSMB will be given password-protected access to the database of deaths and occurrences of survival to hospital discharge with mRS ≤ 3 and occurrences of serious adverse events attributable to initial CCL and ICU admission. This data will be updated on an expedited basis. Members of the DSMB and/or statistical staff at the SDCC may request a conference call or meeting of the group at any time. Interim monitoring will be summarized by posterior (Bayesian) probability distributions.[39a] This permits direct calculation of the probabilities of treatment superiority, which in turn determine the trial's stopping rules. The DSMB, in deciding on recommendations regarding continuation of the trial, must weigh risks versus benefits. This will be facilitated by comparisons of the ratios of serious adverse events (including deaths) to good outcomes between each of the treatment groups. If these ratios differ significantly between the two groups (after appropriate adjustment for multiple comparisons), the DSMB will be obligated to consider recommending stopping the trial.

9.1 Definition of Adverse Event (AE)

An AE is any untoward medical occurrence in a subject undergoing a study related procedure and believed reasonably to be caused by the study related procedure.

Expected Adverse Events

Significant adverse events resulting from the initial, sudden cessation of cardiac activity and resulting global ischemia are common in the cardiac arrest patient population. Significant adverse events are thus expected to be frequent in both treatment arms. Nonetheless, investigators will monitor adverse events in both groups to more sensitively characterize the outcome of each standard treatment and carefully monitor study subject safety throughout the trial.

The ACCESS Trial randomizes study subjects to one of two standards of care and has no study intervention. All adverse events occurring as a result of either standard of care will be considered expected.

Reportable (or Pre-defined) Adverse Events Common to Both Treatment Arms

- Infection/sepsis
  - Infection: any infection requiring intervention by the treating clinicians
  - Sepsis: systemic inflammatory response syndrome in response to an infectious process (confirmed by the treating clinicians)
- Acute kidney injury (AKI) (Confirmed by the treating clinicians)
  - Increase in serum creatinine ≥0.3 mg/dl (≥26.5 µmol/) within 48 hours, or
  - Increase in serum creatinine ≥1.5 times baseline, or
  - Urine volume < 0.5 ml/kg/h for 6 hours
- Liver failure/injury
  - Rapid development of hepatocellular dysfunction in a patient without known prior liver disease (confirmed by the treating clinicians)
- Cardiogenic shock
  - Intervention required to maintain adequate hemodynamics (confirmed by the treating clinicians)
- Multiple organ dysfunction syndrome (MODS)
  - Two or more organs in which homeostasis cannot be maintained without intervention (confirmed by the treating clinicians)
- Seizure activity
  - Documented by EEG or clinical assessment
  - Confirmed by the treating clinicians
- Recurrent cardiac arrest

9.2 Definition of Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that:

- Death
- Life-threatening adverse event
- Requires or prolongs hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly/birth defect.
- Requires medical or surgical intervention to prevent the above outcomes.

Examples of SAEs include but are not limited to pulmonary embolism, sustained ventricular tachycardia, and stroke.

Examples of SAE due to cardiac catheterization lab procedure include but are not limited to injury to coronary artery, dissection or perforation, pericardial effusion or tamponade, bleeding requiring transfusion, and acute renal failure secondary to contrast dye.

Unexpected Serious Adverse Events (USAE)
These will be defined as any serious unexpected adverse effect on health or safety or any unexpected life-threatening problem associated with the randomized treatment received if that effect or problem was not previously identified in nature, severity, or degree of incidence in the investigation plan, or any other unexpected serious problem associated with the randomized treatment received that relates to the rights, safety or welfare of subjects. USAEs will be monitored and reported in all randomized subjects.

Classification of Adverse Events
Serious adverse events (SAE) common to both treatment groups will be considered expected adverse events, documented in all randomized patients, and routinely reported to the Institutional Research Board (IRB) (if required by local institutional guidelines) and the DSMB. The relatedness and expectedness of all adverse events will be reviewed by the site investigator and reported in the database. Adverse events potentially unique to initial CCL or ICU admission will be considered Serious Adverse Events requiring expedited reporting consistent with federal guidelines. Presentations to the DSMB will be comparisons of the ratio of SAEs (including deaths) to favorable outcomes between the two treatment groups. If these ratios, after adjustment for multiple comparisons, are found to be significantly different between the two groups, the DSMB will be obligated to consider a recommendation to stop the study or to revise the protocol.

9.3 Reporting Procedures

Clinical Events Committee (CEC)
An independent CEC will be established to determine whether adverse events potentially unique to initial CCL and ICU admission were the result of CCL or ICU intervention or the consequences of the underlying cardiac arrest. CEC decisions will be forwarded to the DSMB.

Notifications are comprised of an email to the CEC, NHLBI, and DSMB with available information on the date and nature of the event, the site Investigator's evaluation of the severity, expectedness, and relatedness to study treatment group; and an assessment of the event given the information known at the time of the initial reporting.

Event specific reports are formal written reports providing the details of the event (including circumstances surrounding the event, laboratory testing, concomitant medications, and any formal diagnoses made via medical intervention). These reports include an assessment of the severity, expectedness, and relatedness to study treatment group as well as any available status update on the patient. Additional reporting will be required to document resolution of the event or documentation of longer adverse effects or damage.

Serious Adverse Event Reporting
The investigator should report all SAEs to the SDCC as soon as possible but no later than 7 calendar days from the day study personnel became aware of the event or as per the investigative site's local requirements if the requirement is more stringent than those outlined. SAEs that are unexpected AND associated with the CCL or ICU as well as deaths are to be reported to the SDCC within 72 hours of research team acknowledgment.

Scheduled cumulative trial reports are prepared semi-annually by the SDCC. These are used by the DSMB to assess recruitment, subject safety, and continued trial feasibility. These reports include total numbers of AE/SAE experienced in the overall trial. The information provided includes both new events reported since the last DSMB meeting and cumulative events reported during the life of the trial.

Reporting Timeframe for events which are unexpected AND associated with CCL or ICU The SDCC will notify the CEC, NHLBI, and DSMB within 72 hours of learning of the event; with an event specific report filed no later than 7 days post SDCC notification. For all other reportable events, the SDCC will notify the CEC, NHLBI, and DSMB no later than 15 days of learning of the event; with an event specific report filed no later than 30 days post notification. Cumulative trial reports (which include all events) will be generated for review by the CEC, NHLBI, and DSMB at semi-annual DSMB meetings.

9.4 Halting Rules

The DSMB is obligated to formally vote on stopping the trial if at any of their scheduled meetings or special ad hoc meetings, the posterior probability (Bayesian) of either treatment being superior exceeds 99.9%. The DSMB's decision will be forwarded as a recommendation to the trial's Principal Investigators and to the Sponsor [NHLBI]. If the trial's enrollment limit (48 months; 520 patients) is reached, this threshold will be eased slightly to 97.6%. [53]

9.5 Guidelines for Futility

Futility refers to situations in the conduct of a clinical trial in which the probability of achieving the pre-specified level of evidence required to confirm the clinical hypothesis, which we will call the probability of success, is so low that there is not sufficient reason to continue. For the present context, a 'successful' trial is one in which the cardiac cath lab is confirmed to have a higher response rate than the ICU. Both enrollment and current evidence of the treatment effect play a role in whether a study is futile. These guidelines pertain only to futility in regards to the current evidence about the treatment effect. Enrollment considerations for futility may need to be taken into account on an ad hoc basis during the course of the trial as well.

One common approach for statistical futility monitoring uses conditional power. This is the probability of success conditional on the current data assuming future patient outcomes follow the targeted alternative. Another common approach for statistical futility monitoring uses predictive power. This is the probability of success conditional on the current data assuming future patient outcomes follow the current posterior predictive distribution. Conditional power reflects how likely the trial is to succeed assuming the original response rates for the two arms under the targeted alternative, whereas predictive power reflects how likely the trial is to succeed given the current posterior information about the actual response rates in the two arms. Both of these power figures may be estimated using a Monte Carlo simulation for the remainder of the trial in which future outcomes are drawn from the appropriate distributions. The estimate is the proportion of these simulated trials that were successful. For these calculations, we assume the enrollment target of n=520 is achievable.

There are situations in which the conditional and predictive power is zero. That is, for all possible realizations of the future patient outcomes, the trial will fail to confirm the hypothesis. It is more likely that the conditional and predictive power is greater than zero, however. The

presentation of conditional and predictive power to the DSMB is intended as a statistical guideline, not as an absolute mandate. The DSMB is free in any situation to make recommendations about the trial. That said, we suggest the DSMB make a formal judgement should both conditional power drop below 25% and predictive power drop below 1%. We call these 'alert levels.' In this case, the DSMB may consider still continuing the trial to bolster evidence for the equivalence of the two interventions.

We conducted Monte Carlo simulations of the trial and found that under the Big Win (0.65 versus 0.50) there is about a 1% chance of simultaneously reaching both alert levels at an interim analysis, whereas there is about a 3% chance under the Modest Win (0.65 versus 0.53) and 60% chance under the Null (0.57 versus 0.57). Adhering to the proposed alert levels by stopping the trial for futility will not materially affect the trial's power under the Big Win and Modest Win scenarios as simultaneously hitting these alert levels is highly unlikely under these alternative scenarios. The main impact of adhering to the proposed futility guideline is a much higher chance of stopping the trial early for futility under the null scenario, and other scenarios in which the response rates differ by much less than 0.12.

10 CLINICAL MONITORING STRUCTURE.

10.1 Site Monitoring Plan

The SDCC will conduct periodic on-site monitoring visits during the course of the study. At a minimum, the SDCC will ensure that the monitor reviews eligibility, safety, and outcome data within the first 3-6 months and then 10% of randomly selected subjects thereafter at each site in accordance with the protocol, accepted standards of Good Clinical Practice (International Conference on Harmonization E6), and all applicable federal, state, provincial, and local laws, rules, and regulations relating to the conduct of the clinical trial.

During the trial, the SDCC may utilize remote and /or site risk-based monitoring to ensure that the protocol and good clinical practices (GCP) are being followed. Electronic monitoring will consist of reviewing and evaluating: conformance to IRB and consent form requirements with sampling of consents in 5% of subjects for entry criteria. The SDCC will determine data accuracy using a number of statistical-based approaches to identify potential data errors. Source documents, such as documentation of entry criteria, may be queried and reviewed by members of the SDCC and CCC to identify data irregularities and to confirm that the data recorded on the case report forms is accurate. Sites that fail to meet the standards for acceptable performance will undergo follow-up action, which will be determined by the severity of the discrepancies and may include repeat on-site monitoring, probation, or suspension, For-cause monitoring will occur if irregularities are identified and if necessary will be supplemented by site visits by members of the SDCC or CCC staff. The investigator and the clinical site will allow SDCC/CCC staff and appropriate regulatory authorities direct access to source documents to perform this verification.

11 STATISTICAL CONSIDERATIONS

11.1 Study Outcome Measures

Primary outcome
Success is defined as survival with good cognitive function (modified Rankin Scale score ≤ 3) at the time of discharge from the hospital.

Secondary Outcomes
3-month post-hospital discharge secondary endpoint: Survival to 3 months, survival to 3 months with mRS ≤ 3, functional status at 3 months (mRS score and CPC score), incidence and length of rehabilitation, incidence of congestive heart failure, incidence of re-hospitalization over 3 months, and incidence and time to return to work.
In-hospital secondary endpoints: Survival to hospital discharge, mRS score, CPC score, mean peak troponin level, mean ejection fraction, mean length of ICU stay, mean hospitalization duration, the incidence of and mean length of rehabilitation.

Transformations: The primary outcome, as well as the secondary outcomes of survival to 3 months, survival to 3 months with mRS ≤ 3, incidence of congestive heart failure and incidence of re-hospitalization within 3 months, are all dichotomous. Quantitative variables, such as mRS score, CPC score, mean peak troponin levels, and ejection fraction, will be analyzed without transformation. Time-to-event variables such as length of ICU stay, hospital stay, length of rehabilitation, and time to return to work will be analyzed using survival analytic methods (Kaplan-Meier/log-rank statistics, Cox regression).

11.2 Sample Size Considerations

Randomization Scheme
The trial employs a Bayesian adaptive trial design and randomization approach.[22, 48] This permits direct calculation of the probabilities of treatment superiority, which in turn determine the trial's stopping rules. The adaptive randomization scheme permits the trial to stop early if justified by an "early win" by either arm, thus minimizing[49] the trial's sample size (subject to the usual Type I error controls). The randomization ratio changes at regular intervals, biasing the ratio in favor of the treatment that is currently more successful in the trial. This treats the patients in the trial more ethically by exposing fewer of them to the inferior treatment, while still answering the trial's primary question and without compromising statistical integrity.[50]

The design assumes an accrual rate averaging 20 to 25 patients per month for a maximum of 42 months (at most 520 patients). The first 82 patients will be randomized 1:1 between the CCL and ICU arms; 82 is thus the minimum possible sample size for this trial. After this, patients will be randomized in proportion to the current posterior (Bayesian) probability that each treatment is the best, given the results observed so far. This means that the randomization ratio is itself random; however, we will only consider changing the ratio every 4 months (~82 patients). Posterior probabilities of superiority will be computed using validated, customized programs written in R (R Development Core Team, 2018)[66], and for certain analyses, the well-validated and documented OpenBUGS software (http://www.openbugs.net/), and randomization probabilities will then be updated accordingly. These probabilities will be used to create the randomization schedule for the next 4-month period, which will be available to trial staff via a password-protected private website. The ratio will never be permitted to exceed 3:1 in either direction. Because the randomization ratio changes over time, data analysis will be stratified by time-intervals where the ratio is fixed, to avoid confounding of treatment group with time.[49, 51-53]

As mentioned above, DSMB reports will be created approximately every three to four months (i.e., after each cohort of 82 patients has enrolled), and the posterior probability (Bayesian) of treatment (or control) superiority will be computed. If this probability exceeds 99.9% at any monitoring point, the DSMB will formally vote on whether the trial should be stopped early and the corresponding winning treatment will be announced.

Allocation concealment
To avoid selection bias and other confounders, allocation concealment will be achieved by central randomization and an optional paper-based method with concealed assignments.

Blinding
It is impossible in this trial to blind the randomized treatment assignment to the patient or to hospital personnel responsible for patient care. However, blinding to treatment assignment of the endpoint evaluator to functional assessment at 3 months will be implemented to remove observer bias from outcome evaluation and increase validity of the study findings. Thus, blinding has been implemented to the extent possible.

Sample Size and Study Duration
1) In each of three different scenarios, study power was evaluated with a maximum sample size of 520 and a maximum Type I error rate of 0.05:Scenario 1 ("big win"): This scenario assumes a 65% good outcome in the CCL arm, but only 50% good outcome in the ICU arm, a 15% improvement with initial CCL admission.
2) Scenario 2 ("modest win"): This scenario assumes 65% good outcome in the CCL arm, but raises the ICU arm good outcome rate to 53%, reducing the CCL arm's improvement to just 12%.
3) Scenario 3 ("null"): This scenario assumes both arms have the same 57% good outcome rate; this is the scenario used to check Type I error (false positive rate).

The analysis is Bayesian, but uses strictly noninformative prior distributions; i.e., no external or historical information is allowed to influence the trial's results.[54-56]

The posterior probability threshold for stopping the trial at any of the planned interim monitoring points was 0.999, and the final threshold was set to 0.976. Averaging over 5,000 simulated trials produced the following estimates: In *Scenario 1*, the trial correctly selected the CCL arm as superior 89.6% of the time and required an average sample size of 511 patients. In *Scenario 2*, the trial correctly selected the CCL arm 73.5% of the time. In both *Scenario 1* and *2*, the average proportion of patients assigned to the CCL arm was 67%. In the null *Scenario 3*, either arm was incorrectly selected as superior 4.8% of the time (with roughly half of the errors in each direction).

11.3 Analysis Plan

Primary Efficacy Analyses

- Once the trial has stopped, the results in both treatment groups will be summarized by their posterior (Bayesian) probability distributions. For the primary endpoint, the primary summary will be the posterior probability that CCL is superior to ICU or vice versa. We will also obtain summaries of each of the two individual posteriors, i.e., point and 95% interval estimates of the probability of survival to hospital discharge with mRS ≤ 3 in both treatment groups.

Bayesian analyses will be supervised by Drs. Murray and Zhang, while Dr. Connett and his staff will take the lead on classical analyses, both here and throughout the trial. Note that, because the ratio of treatment assignments (CCL versus ICU) will probably be changed at various time points, analysis will be stratified by time periods (using, for example, a Mantel-Haenszel approach). This is to account for confounding of treatment assignment with seasonal effects and effects in secondary analyses due to exclusions after randomization.

Secondary Efficacy Analyses:

***In-hospital secondary* endpoints**

- Survival to hospital discharge: We will use both Bayesian and classical Cox proportional hazards regression to compare the survival distributions in the two groups, reporting on the statistical significance of any differences we find.
- MRS score, CPC score, mean peak troponin level, mean length of ICU stay, mean hospital duration, incidence of and mean length of rehabilitation: We will use both Bayesian and classical one-sample methods to report point and 95% interval estimates of the average values at discharge in the two groups separately, and corresponding two-sample test methods to compare the values in patients surviving to discharge in the two groups, reporting on the statistical significance of any differences we find.

3-month post-hospital discharge secondary endpoints

- Survival to 3 months: We will use both Bayesian and classical one-sample binary data methods to report point and 95% interval estimates of the probability of survival to 3 months in the two groups separately, and corresponding two-sample binomial test methods to compare the 3-month survival probabilities in the two groups, reporting on the statistical significance of any differences we find.
- Survival to 3 months with mRS ≤ 3: The same analyses will be performed as the unmodified 3- month survival, but with the added restriction on mRS score.

Functional status at 3 months:

- MRS score and CPC score: We will use both Bayesian and classical one-sample methods to report point and 95% interval estimates of the average values at 3 months in the two groups separately, and corresponding two-sample test methods to compare the values in the two groups, reporting on the statistical significance of any differences we find.
- Incidence of rehabilitation, congestive heart failure, re-hospitalization, and return to work: We will use both Bayesian and classical one-sample binary data methods to report point and 95% interval estimates of the probability of the endpoint in the two groups separately, and corresponding two-sample binomial test methods to compare the endpoint probabilities in the two groups, reporting on the statistical significance of any differences we find.
- Length of rehabilitation and time to return to work: We will use both Bayesian and classical one-sample methods to report point and 95% interval estimates of the median times to event for these variables in the two groups separately, and corresponding survival-analytic methods (Kaplan-Meier and associated tests) to compare the outcomes in the two groups, reporting any on the statistical significance of any differences we find.

Safety Analysis

The incidence of adverse events will be recorded for all patients in the safety population and presented by randomized arm to the DSMB for their review during the conduct of the study, as well as summarized and compared across randomized arms in the final report of study results. Events will be reported in two categories: those which commonly occur due to cardiac arrest, and those which are attributable either cardiac catheterization or ICU care. The statistical significance of the differences in safety signal incidence between the two randomized groups will be reported, using both p-values and posterior probabilities. However, assessment of the statistical significance of differences in nonfatal events plays a lesser role than differences in the primary study outcome (survival to hospital discharge with mRS ≤3) in the two randomized groups. Hence, emphasis is placed on the presentation of primary study results, with statistical tests provided for guidance on the precision of estimates as indicated. The DSMB must weigh risks against benefits. Thus interim presentations to the DSMB will include comparisons between the groups of the frequency and ratio of serious adverse events (including deaths) to favorable outcomes. Similar considerations apply to the study investigators in publications of study results when the trial is completed. The specific measures listed that potentially reflect the safety of the CCL group or ICU group may or may not affect survival to hospital discharge with mRS ≤3.

Subgroup Analyses

Males versus females: We will use Bayesian[2] and classical methods to compare the incidence of safety signals in men and women, Separate analyses as described above will be undertaken within each gender. These analyses will include comparisons of treatment effect between the genders to ascertain whether there is evidence of a treatment-gender interaction.

Age < 55 versus ≥ 55 years old: We will use Bayesian[1] and classical methods to compare the incidence of safety signals in persons under age 55 at study entry with those who were older than 55 at study entry. Separate analyses will be performed within each of these age groups, with the objective of ascertaining whether there is evidence for an interaction between treatment and age group.

Comparison Populations

Intention-to-Treat

Analysis of primary and secondary efficacy outcomes will be conducted on an *intention-to-treat* basis, that is, according to the treatment assignment to which study subjects were randomized. For patients who are not evaluable at the time of hospital discharge or at the 3-month time point (because, for example, they have withdrawn from the study and refuse further follow-up), methods of multiple imputation will be employed to enable analysis in the presence of missing data.

As-Treated

Analysis of primary and secondary efficacy outcomes will also be conducted on an *as-treated* basis. In this analysis, each patient's treatment assignment will be based on the treatment the patient actually received, rather than the treatment to which the patient was randomized. Patients who receive cardiac catheterization within 6 hours of their first emergency department arrival will be considered treated as randomized to initial CCL admission. Patients who do not receive cardiac catheterization or receive cardiac catheterization > 6 hours from their first emergency department arrival will be considered randomized to initial ICU admission.

Per-Protocol

Analysis of primary and secondary efficacy outcomes will also be conducted on a per-protocol basis. In order to be included in the per-protocol analyses, patients must fulfill the terms of eligibility, randomization, and outcome assessment as originally allocated.

Safety Population

Evaluation of safety will be made comparing the incidence of common adverse events in all patients randomized to one of the two treatment groups and evaluating adverse events unique to all patients randomized to early CCL activation and treatment.

12 ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in this trial each site will permit authorized representatives of the ACCESS Trial and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital and prehospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, recorded data from automated instruments, radiographs, and coronary artery catheterization reports and radiographs.

13 QUALITY CONTROL AND QUALITY ASSURANCE

We will institute the following quality assurance and quality control procedures:

13.1 Central Training for site personnel

A 1-2 day training session for all coordinators will be held on site in Minneapolis (or via WebEx) prior to start-up of the study. This will include a detailed review of the protocol, consent of a legally authorized representative (LAR) of the patient when obtainable, exception from informed consent for those patients for whom proxy consents cannot be obtained, determination of eligibility, use of the web-based data collection system, required baseline data, randomization procedures, review of required in-hospital data, reporting of laboratory results, documentation and reporting of adverse events (including deaths), post-discharge follow-up and mRS testing, 3-month follow-up, management of error corrections, documentation of protocol violations and deviations, and other protocol specific requirements

13.2 MOP

Development of a detailed Manual of Procedures (MOP) and Case Report Forms (CRF): A detailed and indexed MOP will be constructed and maintained on the study's internal website by the SDCC. Case report forms will exactly parallel REDCap™ data entry screens.

13.3 Site Visits

SDCC staff will visit participating sites. See section 10

13.4 Interactive editing of data

The web-based data collection system will make use of REDCap™, which permits extensive editing of the data at the time of data entry. In addition, after data are received at the SDCC, prospective edits of the data for consistency will be carried out. Requests for error correction will be sent to site coordinators by e-mail.

13.5 Reporting

Reporting on completeness, timeliness, rates of errors, protocol deviations and protocol violations will be posted to the study's website, with daily updates.

13.6 Conference Calls

Conference calls with site coordinators and other staff will be scheduled by the SDCC on a monthly basis.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Protection Against Risk

In accordance with federal regulations and as described above in the DSMB and safety and data monitoring plan, we will develop an adverse event reporting system to identify and treat any potential adverse events. We intend to closely monitor the clinical course of all patients enrolled in this trial to identify any expected or unexpected adverse events. Data regarding adverse events will be collected in both a structured (standard form) and open (describing any difficulties encountered) format. An additional risk to subjects in this proposal pertains to the potential for a breach in patient confidentiality. All study personnel involved in data collection and analysis will be required to sign a confidentiality agreement as required by the institutional review board. In addition, subjects will be identified in the database by a study number and links to specific identifiers will be kept in a separate secure location. Database files will be maintained on a password protected computer in a secure location and backed up remotely.

14.2 Institutional Review Board

The local IRB(s) with Federal Wide Assurance covering the participating hospital(s) will assure supervision of the protocol, community consultation, public notification, adverse event reporting, and all regulatory aspects of the study.

14.3 Informed Consent Process

This study proposes two approaches to informed consent for patients resuscitated from VT/VF cardiac arrest who, most often, will be comatose and unable to provide informed consent: 1) if the patient is alert and oriented or comatose with a family member/legally authorized representative (LAR) present within the first 45 minutes of arrival in the emergency department (ED) or intensive care unit (ICU), research personnel will approach the patient/LAR and obtain prospective, written informed consent, and 2) if the patient is comatose and a family member/legally authorized representative (LAR) is not present within the first 45 minutes after arrival in the emergency department, the patient will be randomized under HHS regulation 45 CFR Part 46, exception from informed consent under emergency circumstances (EFIC). The therapeutic window in this study is considered to be 90 minutes.

A therapeutic window of 90 minutes has been determined based on the national ACC/AHA recommendations for STEMI patients of a door to balloon time of 90 minutes.[8,9] CCL mobilization requires approximately 30 minutes' notice (to mobilize the CCL team and transfer the patient from the emergency department to the cardiac catheterization laboratory) and an additional 15 minutes is required to acquire vascular access, define coronary anatomy, and intervene. Thus, potential benefit to the patient may occur if CCL evaluation and intervention occurs within this *target* of 90 minutes of ED or ICU arrival.

Following randomization of a patient under HHS regulation 45 CFR Part 46, exception from informed consent under emergency circumstances, research personnel will continue to make every attempt to contact family and the patient's LAR, to notify them of their family member's participation in the study. If contact occurs after entry of the subject under EFIC but prior to emergency department transfer to the CCL or intensive care unit, research personnel will review

the informed consent process with the LAR. If the LAR consents to study participation, the patient will continue with the intervention to which they were randomized and included in the evaluable study population. If the LAR does not consent to study participation, the treating physician will be notified. In such cases, continued treatment will be at the discretion of the treating clinician. If LAR contact does not occur prior to emergency department transfer to the CCL or intensive care unit, the patient will continue with the intervention to which they were randomized and included in the evaluable study group. The family member(s)/LAR will be subsequently notified consistent with 45 CFR Part 46 regulations.

14.4 Qualification of Study for Exception from Informed Consent under Emergency Circumstances (Federal Regulations 45 CFR Part 46)

This study qualifies for exception from informed consent required for emergency research as outlined in HHS regulation 45 CFR Part 46. For one standard intervention (CCL treatment), optimal outcome occurs if CCL treatment is accomplished within a target of 90 minutes of arrival at the treating hospital. Mobilizing the CCL team generally takes 30 minutes, necessarily followed by another 15 minutes for successful catheter access, angiography, identification of pathological coronary anatomy, and then treatment. The other standard treatment, ICU admission is not time sensitive. For these reasons, the time available for investigators to approach the legally authorized representative for written informed consent) is dictated by CCL treatment and defined as 45 minutes. In this setting, the patients are most often unconscious and/or unable to participate in the informed consent process. As a result, the patient is unable to provide consent for study enrollment. Legal next-of-kin are often not available during the first 45 minutes of emergency department evaluation and treatment. Taken together, these issues provide sufficient support for an exception from consent in order to evaluate an intervention that holds potential benefit to this patient population. We have outlined below each criterion stipulated in the regulations for this exception and how our study design applies to these criteria.

45 CFR Part 46 Exception from informed consent requirements for emergency research

- **The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.** The proposed trial randomizes patients resuscitated from VT/VF cardiac arrest and no ST-segment elevation on emergency department 12-lead ECG and are either direct EMS transports or transferred from an outside hospital: a) covered by the local community consultation and public notification process, and b) transferred within 4 hours and 30 minutes from initial hospital arrival (time from initial emergency department arrival to participating hospital arrival [either ED or ICU, whichever is first], and c) transferred to the participating hospital's ED or ICU to receive either: 1) initial CCL admission, or 2) initial ICU admission, which are current standards of care in the United States.
  As reviewed in this proposal, observational data implies an approximate 50% incidence of acute coronary occlusion and ischemic heart disease in cardiac arrest patients successfully resuscitated from VT/VF cardiac arrest, an inability to reliably detect acute coronary occlusion and ischemic

heart disease on emergency department 12-lead ECG and, therefore, significant potential survival benefit with initial CCL admission in this patient population. However, observational results are subject to selection bias and other unmeasured confounders. No definitive randomized trial has ever been performed. It is therefore unknown if initial CCL admission in resuscitated VT/VF cardiac arrest patients without ST-segment elevation myocardial infarction on emergency department 12-lead ECG results in improved survival or outcome compared with initial ICU admission. We propose a large randomized trial focused on evaluation of these two standards of care in the VT/VF cardiac arrest population, with sufficient statistical power to detect differences in functionally favorable survival.

- **Obtaining informed consent is not feasible because:**
  The subjects will not be able to give their informed consent as a result of their medical condition;
  The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
  There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
  The CCL treatment is thought to be most beneficial if administered within 90 minutes of arrival in the ED or ICU. Mobilizing the CCL team generally takes 30 minutes, necessarily followed by an additional 15 minutes to achieve successful catheter access, angiography, identification of pathological coronary anatomy, and then treatment. For these reasons, the time available for investigators to approach the legally authorized representative for written informed consent) is dictated by CCL treatment and defined as 45 minutes. In this setting the patient is most often unconscious and unable to provide consent for study enrollment. Legal next-of-kin are often not available during the first 45 minutes of emergency department/hospital stabilization, treatment, and disposition. Since we are studying out-of-hospital cardiac arrest, which is frequently the first manifestation of cardiovascular disease, there is no way to prospectively identify individuals who are likely to become eligible for this trial.
  Participation in the research holds out the prospect of direct benefit to the subjects because:
  There are strong proponents for each of these two strategies contending the prospect of direct benefit for patients for either approach. For initial CCL admission this includes, but is not limited to identifying coronary artery lesions and promptly reperfusing; recognizing other etiologies; optimizing hemodynamics and cardiac performance; placing mechanical hemodynamic support, if needed; and, knowing the" absence" of coronary artery disease could benefit by informing subsequent patient management. For initial ICU admission this includes, but is not limited to rapidly stabilizing by correction of acidosis, optimizing ventilation and providing systemic hemodynamic support; identifying other etiologies; targeting performing coronary angiography at a time when the patient is more stable or when clinical judgment suggests coronary artery disease as the culprit of the arrest. Thus, there is the prospect of direct benefit to patients for either of these approaches.

Subjects are facing a life-threatening situation that necessitates intervention;

As defined, these patients with cardiac arrest are facing a life-threatening situation that requires timely intervention.

Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

Both treatments evaluated in this study are associated with potential risks and benefits and are well established practices in the United States. We contend that these risks are reasonable in light of the potential benefits outlined in this proposal and the current poor outcome for patients resuscitated from out-of-hospital cardiac arrest.

The clinical investigation could not practicably be carried out without the waiver.

- This study could not be conducted without the waiver of consent because legal next-of-kin are often not available during the first 45 minutes following arrival at the participating hospital, potential benefit to the patient may occur if cardiac catheterization laboratory intervention occurs within 90 minutes, and potential benefit to the patient may be significantly reduced or lost if cardiac catheterization laboratory intervention does not occur within that targeted time frame.
- **The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.**

  This study proposes two approaches to informed consent for patients resuscitated from VT/VF cardiac arrest who, most often, will be comatose and unable to provide informed consent: 1) if the patient is alert and oriented or comatose with a family member/legally authorized representative (LAR) present within the first 45 minutes of arrival in the emergency department (ED), research personnel will approach the patient/LAR and obtain prospective, written informed consent, and 2) if the patient is comatose and a family member/legally authorized representative (LAR) is not present within the first 45 minutes after arrival in the emergency department, the patient will be randomized under HHS regulation 45 CFR Part 46, exception from informed consent under emergency circumstances (EFIC). The therapeutic window in this study is considered to be 45 minutes.

  A therapeutic window of 90 minutes has been determined based on the national ACC/AHA recommendations for STEMI patients of a door to balloon time of 90 minutes.[8,9] CCL mobilization requires approximately 30 minutes' notice (to mobilize the CCL team and transfer the patient from the emergency

department to the cardiac catheterization laboratory) and an additional 15 minutes is required to acquire vascular access, define coronary anatomy, and intervene. Thus, potential benefit to the patient may occur if CCL evaluation and intervention occurs within this *target* of 90 minutes of emergency department arrival.

Following randomization of a patient under HHS regulation 45 CFR Part 46, exception from informed consent under emergency circumstances, research personnel will continue to make every attempt to contact family and the patient's LAR, to notify them of their family member's participation in the study. If contact occurs after entry of the subject under EFIC but prior to emergency department transfer to the CCL or intensive care unit, research personnel will review the informed consent process with the LAR. If the LAR consents to study participation, the patient will continue with the intervention to which they were randomized and included in the evaluable study population. If the LAR does not consent to study participation, the treating physician will be notified. In such cases, continued treatment will be at the discretion of the treating clinician. If LAR contact does not occur prior to emergency department transfer to the CCL or intensive care unit, the patient will continue with the intervention to which they were randomized and included in the evaluable study group. The family member(s)/LAR will be subsequently notified consistent with 45 CFR Part 46 regulations.

Study investigators are committed to attempting to contact a legally authorized representative within the first 45 minutes following ED or ICU arrival at the participating hospital. Research personnel will work with emergency department/ICU social services and/or the chaplain to repeatedly attempt to contact a LAR following patient arrival at the participating hospital. Specifics of each attempt and communication with social services and the chaplain will be documented and made part of the patient's permanent research record. If these repeated attempts fail to identify and contact a LAR, the patient will be considered for study entry under EFIC.

Therefore, we propose to use exception from informed consent as a needed component of the informed consent process, public notification, community consultation, patient notification of enrollment, and waiver of documented informed consent to review clinical records. If legal representatives are not available after randomization and emergency department disposition, research personnel will attempt to contact the subject's legal representative as soon as feasible and a summary of these efforts will be documented in the patient's chart. If the subject becomes competent during the study period, then he/she will be approached by research personnel for notification of enrollment.

- **The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 45 CRF part 46. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has**

reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation. All procedures and consent forms will be approved by the designated local Institutional Review Board (IRB) prior to the onset of the trial.

- **Additional protections of the rights and welfare of the subjects will be provided, including, at least:**
  Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
  Community consultation as specified and approved by the local IRB will be undertaken prior to final IRB approval to begin patient entry. Since the population eligible for enrollment includes all citizens in the study regions it will not be possible to target any particular small group.
  The community consultation plan for each study site will have to be individualized to fit the local community. Feedback from the community will be obtained by research personnel regarding any concerns they may have about potential enrollment. If requested, bracelets or medic-alert-type necklaces will be made available that could be worn by members of the community who do not want to participate.
  Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
  Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results; Public disclosures will be performed both prior to study enrollment and at the completion of the study in the form of multimedia press releases. These will include plans for the study including potential risks and benefits and a summary of the results of the study upon completion. In the event that the press releases are not widely circulated, advertisements will also be placed in local papers describing the study, as approved by the local IRB.
  Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; An independent data monitoring committee will exercise oversight of the study.
  If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this Information available to the IRB at the time of continuing review;
  We expect that almost all patients who meet the enrollment criteria will be unconscious. Research personnel will make every attempt to contact family/LAR within the first 45 minutes following arrival in the ED or ICU as described previously in this section. Following randomization at 45 minutes, research personnel will continue their efforts to contact the family/LAR

consistent with HSS regulation 45 CFR Part 46. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

14.5 Subject Confidentiality

All data sent to the SDCC via the REDCap™ data capture system will be de-identified in compliance with HIPAA regulations. Each patient in the trial will be assigned an ID in the form of 'A-12345-6', where 'A' denotes the treating center, '12345' is a numeric ID, and '6' is a check digit which is included to filter out errors in keying. In addition, we will require a suffix of the form 'C-41', where 'C' is the first letter of the patient's last name, and '41' is the year of birth. This suffix greatly reduces the chances of errors of patient information on forms and correspondence. The same (uninformative) identifiers will be used for any centrally stored lab specimens. Access to patient records at the SDCC will be restricted to the SDCC's data managers and to statistical analysts. No patient files can be copied to computers other than the SDCC's REDCap™/ORACLE servers. No patient data will be released to any third parties outside the SDCC.

15 DATA HANDLING AND RECORD KEEPING

15.1 Data Management Responsibilities

Data collection from the time of randomization, through the hospital stay, and through longer-term follow-up will be the responsibility of personnel at the ED, CCL, and ICU where the patient is treated. As noted below, the primary tool for data capture and transmission to the SDCC will be REDCap™. The REDCap™ data entry system can create PDF printable versions case-report forms which exactly parallel the data entry screens. REDCap™ automatically creates a data dictionary and schemas for all aspects of study data. Personnel will maintain printed copies of all REDCap™ case-report forms in folders at the sites where patients are seen and treated; such folders will include original copies of lab reports, ECG tracings, radiologic reports, and other source documents.

Adverse events, as described elsewhere in this protocol, must be thoroughly documented and submitted through the REDCap™ software within 72 hours of the event. Expert assessment of the severity and seriousness of the adverse event is required of the Principal Investigator at the treating site. For serious AEs, a text description of the event and its sequelae will be required.

At the SDCC, the REDCap™ data will be stored in an ORACLE™ data management system, which will permit additional editing and error correction beyond what can be done interactively. The ORACLE database is secure and backed up, with off-site storage, on a daily basis. Access to the ORACLE database at the SDCC is restricted to data managers and data analysts, requiring secure passwords. Specific identifiers, such as name, hospital number, SSNs, telephone numbers and addresses of patients, will not be permitted to be transmitted to the SDCC. The SDCC's database must comply with HIPAA regulations at all times.

All data analysis is the responsibility of the statistical staff at the SDCC. The REDCap™ database is accessible to programs in SAS, R, and other data analysis packages, and it permits construction of formatted analysis files which include variable labels and sources.

15.2 Data Capture Methods

REDCap™ web-based data capture software will be employed to collect data for transmission to the SDCC. REDCap™, developed by the CTSA at Vanderbilt University [https://redcap.vanderbilt.edu/] is a flexible, user-friendly, secure data entry and data management package which permits a complete range of interactive editing capabilities. Coordinators and data entry personnel at each of the participating sites will be trained by the SDCC in the use of the software, which will be accessed by logging onto to a secure, password-protected, menu-driven web site established and maintained at the SDCC in Minneapolis. REDCap™ data entry screens parallel very closely printed forms which can be completed by site personnel from data sources (laboratory results, physiologic measurements, ECG information, interviews, and others) prior to entry into interactive data entry sessions. In this trial it is expected that data will be entered into the REDCap™ system within 24 hours of obtaining the data.

15.3 Types of Data

- Laboratory data such as enzymes and biomarkers related to the cardiac event; serum troponin; blood gases; ECG reports, ejection fractions, blood pressure, heart and respiratory rate.
- Data derived from prehospital incident reports and hospital patient care reports.

- Data derived from the mRS and CPC
- Data based on interviews with patients during the hospital stay, at the time of discharge, and at 3-month's post-discharge
- Data on patient deaths from (1) hospital discharge summaries, (2) death certificates, (3) witnesses to the death; (4) autopsy reports if available.
- Data on findings from the CCL
- Data on major procedures (such as CABG) carried out during the hospital stay

15.3.1 Dates and Times

Because dates are crucial in accurate determination of the efficacy of treatment and documentation of adverse events, dates of the following events will be recorded and stored in the central database:

1) Date and time of occurrence of the cardiac arrest
2) Date and time of arrival at the Emergence Department
3) Date and time of randomization
4) Date and time of admissions to the ICU
5) Date and time of arrival at the Coronary Catheterization Laboratory
6) Dates of occurrence of any serious adverse events
7) Date of discharge from the hospital
8) Dates or re-admission to the hospital
9) Dates of occurrence of follow-up visits
10) Date and time of death

15.4 Timing/Reports

See sections 8.3, 12 above. Monitoring reports on patient accrual by site, on in-hospital follow-up, adherence to protocol, timeliness and accuracy of data submission, adherence to protocol, post-hospitalization of follow-up will be posted by the SDCC to the study's internal website with frequent updates. Reports of study progress will be prepared by the SDCC for meetings and conference calls of study investigators and site coordinators.

Reports on study progress, data quality and completeness, and adverse events will be prepared by the SDCC for meetings or conference calls of the DSMB every 3-4 months. DSMB reports will be split into two sections: The Open Report, which includes data on study progress and operations, and the Closed Report, which includes data on the primary and secondary endpoints in the study. The Open Report section can be accessed by the study's Principal Investigators, all DSMB members, and NHLBI investigators. The Closed Report will be available only to SDCC statisticians, DSMB members, and the NHLBI project office.

15.5 Study Records Retention

Data records for the ACCESS trial will be stored at the SDCC for at least 10 years after completion of the study. All data are anonymized, with records indexed by alphanumeric IDs; no names, SSNs, hospital record numbers, phone numbers, addresses or other identifiers will be stored at the SDCC.

15.6 Protocol Deviations

Protocol deviations and violations will be detected in part by careful review at the SDCC of submitted data on an ongoing basis. Serious protocol violations (e.g., failure to adhere to consent procedures, eligibility errors, errors in carrying out the randomized treatment assignment, and errors that could potentially affect patient safety) will require detailed documentation by site personnel and may require additional information from the site principal investigator. Serious protocol violations will be summarized by the SDCC and reported to the DSMB and the NHLBI project office and the originating site's IRB within 72 hours of the information becoming available.

16 PUBLICATION POLICY

See MOP

17 LITERATURE REFERENCES

REFERENCES

1. Berry SM, Carlin BP, Lee JJa and Muller P. Bayesian Adaptive Methods for Clinical Trials. *3Boca Raton, FL: Chapman and Hall/CRC Press*. 2011.
2. Thall PF and Wathen JK. Practical Bayesian adaptive randomisation in clinical trials. *European journal of cancer*. 2007;43:859-66.
3. Youngquist ST, Kaji AH, Lipsky AM, Koenig WJ and Niemann JT. A Bayesian sensitivity analysis of out-of-hospital 12-lead electrocardiograms: implications for regionalization of cardiac care. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*. 2007;14:1165-71.
4. Thall PF and Simon R. Practical Bayesian guidelines for phase IIB clinical trials. *Biometrics*. 1994;50:337-49.
5. Dixon DO and Simon R. Bayesian subset analysis. *Biometrics,*. 1991;47:871-881.
6. Carlin BP and Louis TA. Bayesian Methods for Data Analysis 3rd ed. *Boca Raton, FL: Chapman and Hall/CRC Press*. 2009.
7. Cummins RO and Hazinski MF. The most important changes in the international ECC and CPR guidelines 2000. *Resuscitation*. 2000;46:431-7.
8. Morrison LJ, Deakin CD, Morley PT, Callaway CW, Kerber RE, Kronick SL, Lavonas EJ, Link MS, Neumar RW, Otto CW, Parr M, Shuster M, Sunde K, Peberdy MA, Tang W, Hoek TL, Bottiger BW, Drajer S, Lim SH and Nolan JP. Part 8: advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*. 2010;122:S345-421.
9. Nadkarni VM, Nolan JP, Billi JE, Bossaert L, Bottiger BW, Chamberlain D, Drajer S, Eigel B, Hazinski MF, Hickey RW, Jacobs I, Kloeck W, Montgomery WH, Morley PT, O'Connor RE, Okada K, Shuster M, Travers AH and Zideman D. Part 2: international collaboration in resuscitation science: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*. 2010;122:S276-82.
10. O'Connor RE, Brady W, Brooks SC, Diercks D, Egan J, Ghaemmaghami C, Menon V, O'Neil BJ, Travers AH and Yannopoulos D. Part 10: acute coronary syndromes: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S787-817.
11. Sayre MR, Koster RW, Botha M, Cave DM, Cudnik MT, Handley AJ, Hatanaka T, Hazinski MF, Jacobs I, Monsieurs K, Morley PT, Nolan JP and Travers AH. Part 5: adult basic life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*. 2010;122:S298-324.
12. Medicine. IO. Strategies to Improve Cardiac Arrest Survival: A Time to Act. *The National Academies Press*. 2015.
13. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics C and Stroke Statistics S. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28-e292.
14. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, Gabrielli A, Silvers SM, Zaritsky AL, Merchant R, Vanden Hoek TL and Kronick SL. Part 9: post-

cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S768-86.
15. Rea TD and Paredes VL. Quality of life and prognosis among survivors of out-of-hospital cardiac arrest. *Current opinion in critical care*. 2004;10:218-23.
16. Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, Rea T, Lowe R, Brown T, Dreyer J, Davis D, Idris A and Stiell I. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA : the journal of the American Medical Association*. 2008;300:1423-31.
17. Aufderheide TP, Nichol G, Rea TD, Brown SP, Leroux BG, Pepe PE, Kudenchuk PJ, Christenson J, Daya MR, Dorian P, Callaway CW, Idris AH, Andrusiek D, Stephens SW, Hostler D, Davis DP, Dunford JV, Pirrallo RG, Stiell IG, Clement CM, Craig A, Van Ottingham L, Schmidt TA, Wang HE, Weisfeldt ML, Ornato JP and Sopko G. A trial of an impedance threshold device in out-of-hospital cardiac arrest. *The New England journal of medicine*. 2011;365:798-806.
18. Spaulding CM, Joly LM, Rosenberg A, Monchi M, Weber SN, Dhainaut JF and Carli P. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *The New England journal of medicine*. 1997;336:1629-33.
19. Wagner H, Terkelsen CJ, Friberg H, Harnek J, Kern K, Lassen JF and Olivecrona GK. Cardiac arrest in the catheterisation laboratory: a 5-year experience of using mechanical chest compressions to facilitate PCI during prolonged resuscitation efforts. *Resuscitation*. 2010;81:383-7.
20. Davies MJ and Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. *The New England journal of medicine*. 1984;310:1137-40.
21. Cronier P, Vignon P, Bouferrache K, Aegerter P, Charron C, Templier F, Castro S, El Mahmoud R, Lory C, Pichon N, Dubourg O and Vieillard-Baron A. Impact of routine percutaneous coronary intervention after out-of-hospital cardiac arrest due to ventricular fibrillation. *Critical care*. 2011;15:R122.
22. Noc M, Fajadet J, Lassen JF, Kala P, MacCarthy P, Olivecrona GK, Windecker S and Spaulding C. Invasive coronary treatment strategies for out-of-hospital cardiac arrest: a consensus statement from the European Association for Percutaneous Cardiovascular Interventions (EAPCI)/Stent for Life (SFL) groups. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2014;10:31-7.
23. Kern KB, Lotun K, Patel N, Mooney MR, Hollenbeck RD, McPherson JA, McMullan PW, Unger B, Hsu CH, Seder DB and Registry IN-C. Outcomes of Comatose Cardiac Arrest Survivors With and Without ST-Segment Elevation Myocardial Infarction: Importance of Coronary Angiography. *JACC Cardiovascular interventions*. 2015;8:1031-40.
24. Garot P, Lefevre T, Eltchaninoff H, Morice MC, Tamion F, Abry B, Lesault PF, Le Tarnec JY, Pouges C, Margenet A, Monchi M, Laurent I, Dumas P, Garot J and Louvard Y. Six-month outcome of emergency percutaneous coronary intervention in resuscitated patients after cardiac arrest complicating ST-elevation myocardial infarction. *Circulation*. 2007;115:1354-62.
25. Gorjup V, Radsel P, Kocjancic ST, Erzen D and Noc M. Acute ST-elevation myocardial infarction after successful cardiopulmonary resuscitation. *Resuscitation*. 2007;72:379-85.
26. Knafelj R, Radsel P, Ploj T and Noc M. Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. *Resuscitation*. 2007;74:227-34.
27. Noc M. Urgent coronary angiography and percutaneous coronary intervention as a part of postresuscitation management. *Critical care medicine*. 2008;36:S454-7.
28. Anyfantakis ZA, Baron G, Aubry P, Himbert D, Feldman LJ, Juliard JM, Ricard-Hibon A, Burnod A, Cokkinos DV and Steg PG. Acute coronary angiographic findings in survivors of out-of-hospital cardiac arrest. *American heart journal*. 2009;157:312-8.

29. Dumas F, Cariou A, Manzo-Silberman S, Grimaldi D, Vivien B, Rosencher J, Empana JP, Carli P, Mira JP, Jouven X and Spaulding C. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. *Circulation Cardiovascular interventions*. 2010;3:200-7.
30. Sideris G, Voicu S, Yannopoulos D, Dillinger JG, Adjedj J, Deye N, Gueye P, Manzo-Silberman S, Malissin I, Logeart D, Magkoutis N, Capan DD, Makhloufi S, Megarbane B, Vivien B, Cohen-Solal A, Payen D, Baud FJ and Henry P. Favourable 5-year postdischarge survival of comatose patients resuscitated from out-of-hospital cardiac arrest, managed with immediate coronary angiogram on admission. *European heart journal Acute cardiovascular care*. 2014;3:183-91.
31. Garcia S, Drexel T, Bekwelem W, Raveendran G, Caldwell E, Klann L and Yannopoulos D. Early Access to the Cardiac Catheterization Laboratory for Patients Resuscitated from Cardiac Arrest due to a Shockable Rhythm: The Minnesota Resuscitation Consortium Twin Cities Unified Protocol. *JAHA* 2015;Accepted manuscript.
32. Peberdy MA, Donnino MW, Callaway CW, Dimaio JM, Geocadin RG, Ghaemmaghami CA, Jacobs AK, Kern KB, Levy JH, Link MS, Menon V, Ornato JP, Pinto DS, Sugarman J, Yannopoulos D, Ferguson TB, Jr., American Heart Association Emergency Cardiovascular Care C, Council on Cardiopulmonary CCP and Resuscitation. Impact of percutaneous coronary intervention performance reporting on cardiac resuscitation centers: a scientific statement from the American Heart Association. *Circulation*. 2013;128:762-73.
33. Rab T, Kern KB, Tamis-Holland JE, Henry TD, McDaniel M, Dickert NW, Cigarroa JE, Keadey M, Ramee S and Interventional Council ACoC. Cardiac Arrest: A Treatment Algorithm for Emergent Invasive Cardiac Procedures in the Resuscitated Comatose Patient. *Journal of the American College of Cardiology*. 2015;66:62-73.
34. Kern KB. Usefulness of cardiac arrest centers - extending lifesaving post-resuscitation therapies: the Arizona experience. *Circ J*. 2015;79:1156-63.
35. Waldo SW, Armstrong EJ, Kulkarni A, Hoffmayer K, Kinlay S, Hsue P, Ganz P and McCabe JM. Comparison of clinical characteristics and outcomes of cardiac arrest survivors having versus not having coronary angiography. *The American journal of cardiology*. 2013;111:1253-8.
36. Voicu S, Sideris G, Deye N, Dillinger JG, Logeart D, Broche C, Vivien B, Brun PY, Capan DD, Manzo-Silberman S, Megarbane B, Baud FJ and Henry P. Role of cardiac troponin in the diagnosis of acute myocardial infarction in comatose patients resuscitated from out-of-hospital cardiac arrest. *Resuscitation*. 2012;83:452-8.
37. Strote JA, Maynard C, Olsufka M, Nichol G, Copass MK, Cobb LA and Kim F. Comparison of role of early (less than six hours) to later (more than six hours) or no cardiac catheterization after resuscitation from out-of-hospital cardiac arrest. *The American journal of cardiology*. 2012;109:451-4.
38. Callaway CW, Schmicker RH, Brown SP, Albrich JM, Andrusiek DL, Aufderheide TP, Christenson J, Daya MR, Falconer D, Husa RD, Idris AH, Ornato JP, Rac VE, Rea TD, Rittenberger JC, Sears G, Stiell IG and Investigators ROC. Early coronary angiography and induced hypothermia are associated with survival and functional recovery after out-of-hospital cardiac arrest. *Resuscitation*. 2014;85:657-63.
39. Camuglia AC, Randhawa VK, Lavi S and Walters DL. Cardiac catheterization is associated with superior outcomes for survivors of out of hospital cardiac arrest: Review and meta-analysis. *Resuscitation*. 2014.
40. Sideris G, Magkoutis N, Sharma A, Rees J, McKnite S, Caldwell E, Sarraf M, Henry P, Lurie K, Garcia S and Yannopoulos D. Early coronary revascularization improves 24h survival and neurological function after ischemic cardiac arrest. A randomized animal study. *Resuscitation*. 2014;85:292-8.

41. Becker LB, Aufderheide TP, Geocadin RG, Callaway CW, Lazar RM, Donnino MW, Nadkarni VM, Abella BS, Adrie C, Berg RA, Merchant RM, O'Connor RE, Meltzer DO, Holm MB, Longstreth WT and Halperin HR. Primary outcomes for resuscitation science studies: a consensus statement from the American Heart Association. *Circulation*. 2011;124:2158-77.
42. Rabinstein AA, McClelland RL, Wijdicks EF, Manno EM and Atkinson JL. Cardiopulmonary resuscitation in critically ill neurologic-neurosurgical patients. *Mayo Clinic proceedings*. 2004;79:1391-5.
43. van Alem AP, de Vos R, Schmand B and Koster RW. Cognitive impairment in survivors of out-of-hospital cardiac arrest. *American heart journal*. 2004;148:416-21.
44. Folstein MF, Folstein SE and McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research*. 1975;12:189-98.
47. Stiell I, Nichol G, Wells G, De Maio V, Nesbitt L, Blackburn J and Spaite D. Health-related quality of life is better for cardiac arrest survivors who received citizen cardiopulmonary resuscitation. *Circulation*. 2003;108:1939-44.
49. Zhang J, Carlin BP, Neaton JD, Soon GG, Nie L, Kane R, Virnig BA and Chu H. Network meta-analysis of randomized clinical trials: reporting the proper summaries. *Clinical trials*. 2014;11:246-62.
50. Dixon DO and Simon R. Bayesian subset analysis. *Biometrics*. 1991;47:871-81.
51. Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, Frangakis C, Hogan JW, Molenberghs G, Murphy SA, Neaton JD, Rotnitzky A, Scharfstein D, Shih WJ, Siegel JP and Stern H. The prevention and treatment of missing data in clinical trials. *The New England journal of medicine*. 2012;367:1355-60.
52. Murray TA, Carlin BP and Lystig TC. Bayesian adaptive design for device surveillance. *Clinical trials*. 2013;10:5-18.
53. Berry SM, Carlin BP and Connor J. Bias and trials stopped early for benefit. *JAMA : the journal of the American Medical Association*. 2010;304:156; author reply 158-9.
54. Carlin BP and Hodges JS. Hierarchical proportional hazards regression models for highly stratified data. *Biometrics*. 1999;55:1162-70.
55. Carlin BP, Kadane JB and Gelfand AE. Approaches for optimal sequential decision analysis in clinical trials. *Biometrics*. 1998;54:964-75.
56. Carlin BP and Sargent DJ. Robust Bayesian approaches for clinical trial monitoring. *Statistics in medicine*. 1996;15:1093-106.
57. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, Afzal R, Chrolavicius S, Jolly SS, Widimsky P, Avezum A, Rupprecht HJ, Zhu J, Col J, Natarajan MK, Horsman C, Fox KA, Yusuf S and Investigators T. Early versus delayed invasive intervention in acute coronary syndromes. *The New England journal of medicine*. 2009;360:2165-75.
58. Swahn E, Alfredsson J, Afzal R, Budaj A, Chrolavicius S, Fox K, Jolly S, Mehta SR, de Winter R and Yusuf S. Early invasive compared with a selective invasive strategy in women with non-ST-elevation acute coronary syndromes: a substudy of the OASIS 5 trial and a meta-analysis of previous randomized trials. *European heart journal*. 2012;33:51-60.
59. Newcommon NJ, Green TL, Haley E, Cooke T and Hill MD. Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin Scale. *Stroke; a journal of cerebral circulation*. 2003;34:377-8; author reply 377-8.
60. Merino JG, Lattimore SU and Warach S. Telephone assessment of stroke outcome is reliable. *Stroke; a journal of cerebral circulation*. 2005;36:232-3.
61. Weimar C, Kurth T, Kraywinkel K, Wagner M, Busse O, Haberl RL, Diener HC and German Stroke Data Bank C. Assessment of functioning and disability after ischemic stroke. *Stroke; a journal of cerebral circulation*. 2002;33:2053-9.

62. Hop JW, Rinkel GJ, Algra A and van Gijn J. Changes in functional outcome and quality of life in patients and caregivers after aneurysmal subarachnoid hemorrhage. *Journal of neurosurgery*. 2001;95:957-63.
63. Stiell IG, Callaway C, Davis D, Terndrup T, Powell J, Cook A, Kudenchuk PJ, Daya M, Kerber R, Idris A, Morrison LJ and Aufderheide T. Resuscitation Outcomes Consortium (ROC) PRIMED cardiac arrest trial methods part 2: rationale and methodology for "Analyze Later vs. Analyze Early" protocol. *Resuscitation*. 2008;78:186-95.
64. Aufderheide TP, Kudenchuk PJ, Hedges JR, Nichol G, Kerber RE, Dorian P, Davis DP, Idris AH, Callaway CW, Emerson S, Stiell IG and Terndrup TE. Resuscitation Outcomes Consortium (ROC) PRIMED cardiac arrest trial methods part 1: rationale and methodology for the impedance threshold device (ITD) protocol. *Resuscitation*. 2008;78:179-85.
65. Nichol G, Stiell IG, Hebert P, Wells GA, Vandemheen K and Laupacis A. What is the quality of life for survivors of cardiac arrest? A prospective study. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*. 1999;6:95-102.
66. R Development Core Team (2018). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria, <https://www.R-project.org>.

References – Transfer Patients

1. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, Afzal R, Chrolavicius S, Jolly SS, Widimsky P, Avezum A, Rupprecht HJ, Zhu J, Col J, Natarajan MK, Horsman C, Fox KA, Yusuf S and Investigators T. Early versus delayed invasive intervention in acute coronary syndromes. *The New England journal of medicine*. 2009;360:2165-75.
2. Kruk M, Kadziela J, Reynolds HR, Forman SA, Sadowski Z, Barton BA, Mark DB, Maggioni AP, Leor J, Webb JG, Kapeliovich M, Marin-Neto JA, White HD, Lamas GA and Hochman JS. Predictors of outcome and the lack of effect of percutaneous coronary intervention across the risk strata in patients with persistent total occlusion after myocardial infarction: Results from the OAT (Occluded Artery Trial) study. *JACC Cardiovascular interventions*. 2008;1:511-20.
3. Tarantini G[1], Cacciavillani L, Corbetti F, Ramondo A, Marra MP, Bacchiega E, Napodano M, Bilato C, Razzolini R, Iliceto S. Duration of Ischemia is a Major Determinant of Transmurality and Severe Microvascular Obstruction after Primary Angioplasty: A Study Performed with Contrast-Enhanced Magnetic Resonance. J AM Coll Cardiol. 2005 Oct 4;46(7):1229-35.
4. Varcoe RW, Clayton TC, Gray HH, de Belder MA, Ludman PF, Henderson RA, British Cardiovascular Intervention Society (BCIS) and the National Institute for Cardiovascular Outcomes Research (NICOR). Impact of call-to-balloon time on 30-day mortality in contemporary practice. Heart. 2017 Jan15;103(2):117-124.
5. Scholz KH, Maier SKG, Maier LS, Lengenfelder B, Jacobshagen C, Jung J, Fleischmann C, Werner GS, Olbrich HG, Ott R, Mudra H, Seidl K, Schulze PC, Weiss C, Haimerl J, Friede T and Meyer T. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: results from the German prospective, multicentre FITT-STEMI trial. *European heart journal*. 2018;39:1065-1074.
6. Gersh BJ, Stone GW, White HD, Holmes DR. Pharmacological Facilitation of Primary Percutaneous Coronary Intervention for Acute Myocardial Infarctions the Slope of the Curve the Shape of the future?. *JAMA*. 2005;293(8):979–986.

References – Upper Age Limit of 80 Years Old

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018 Mar 20;137(12):e67-e492.
2. Vandermolen S, Abbott J, De Silva K. What's Age Got to do with it? A Review of Contemporary Revascularization in the Elderly. Curr Cardiol Rev. 2015;11(3):199-208.
3. Alexander K.P., Roe M.T., Chen A.Y., Lytle B.L., Pollack C.V., Jr, Foody J.M., Boden W.E., Smith S.C., Jr, Gibler W.B., Ohman E.M., Peterson E.D., CRUSADE Investigators Evolution in cardiovascular care for elderly patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. J. Am. Coll. Cardiol. 2005;46(8):1479–1487.
4. Singh M., Peterson E.D., Roe M.T., Ou F.S., Spertus J.A., Rumsfeld J.S., Anderson H.V., Klein L.W., Ho K.K., Holmes D.R. Trends in the association between age and in-hospital mortality after percutaneous coronary intervention: National Cardiovascular Data Registry experience. Circ. Cardiovasc. Interv. 2009;2(1):20–26.
5. Bauer T., Möllmann H., Weidinger F., Zeymer U., Seabra-Gomes R., Eberli F., Serruys P., Vahanian A., Silber S., Wijns W., Hochadel M., Nef H.M., Hamm C.W., Marco J., Gitt A.K. Predictors of hospital mortality in the elderly undergoing percutaneous coronary intervention for acute coronary syndromes and stable angina. Int. J. Cardiol. 2011;151(2):164–169.
6. Sangiorgi G., Rumberger J.A., Severson A., Edwards W.D., Gregoire J., Fitzpatrick L.A., Schwartz R.S. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. J. Am. Coll. Cardiol. 1998;31(1):126–133.
7. Batchelor W.B., Anstrom K.J., Muhlbaier L.H., Grosswald R., Weintraub W.S., O'Neill W.W., Peterson E.D. National Cardiovascular Network Collaboration. Contemporary outcome trends in the elderly undergoing percutaneous coronary interventions: results in 7,472 octogenarians. J. Am. Coll. Cardiol. 2000;36(3):723–730.
8. Mari D., Mannucci P.M., Coppola R., Bottasso B., Bauer K.A., Rosenberg R.D. Hypercoagulability in centenarians: the paradox of successful aging. Blood. 1995;85(11):3144–3149.
9. Terres W., Weber K., Kupper W., Bleifeld W. Age, cardiovascular risk factors and coronary heart disease as determinants of platelet function in men. A multivariate approach. Thromb. Res. 1991;62(6):649–661.
10. Vaughan L., Zurlo F., Ravussin E. Aging and energy expenditure. Am. J. Clin. Nutr. 1991;53(4):821–825.
11. Fried L.P., Tangen C.M., Walston J., Newman A.B., Hirsch C., Gottdiener J., Seeman T., Tracy R., Kop W.J., Burke G., McBurnie M.A. Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J. Gerontol. A Biol. Sci. Med. Sci. 2001;56(3):M146–M156.
12. Singh M., Peterson E.D., Roe M.T., Ou F.S., Spertus J.A., Rumsfeld J.S., Anderson H.V., Klein L.W., Ho K.K., Holmes D.R. Trends in the association between age and in-hospital mortality after percutaneous coronary intervention: National Cardiovascular Data Registry experience. Circ. Cardiovasc. Interv. 2009;2(1):20–26.

13. Singh M., Peterson E.D., Roe M.T., Ou F.S., Spertus J.A., Rumsfeld J.S., Anderson H.V., Klein L.W., Ho K.K., Holmes D.R. Trends in the association between age and in-hospital mortality after percutaneous coronary intervention: National Cardiovascular Data Registry experience. Circ. Cardiovasc. Interv. 2009;2(1):20–26.
14. Santana J.O., Haft J.I., LaMarche N.S., Goldstein J.E. Coronary angioplasty in patients eighty years of age or older. Am. Heart J. 1992;124(1):13–18.
15. Khera S., Kolte D., Palaniswamy C., Mujib M., Aronow W.S., Singh T., Gotsis W., Silverman G., Frishman W.H. ST-elevation myocardial infarction in the elderly--temporal trends in incidence, utilization of percutaneous coronary intervention and outcomes in the United States. Int. J. Cardiol. 2013;168(4):3683–3690.
16. Li R., Yan B.P., Dong M., Zhang Q., Yip G.W., Chan C.P., Zhang M., Zhang Q., Sanderson J.E., Yu C.M. Quality of life after percutaneous coronary intervention in the elderly with acute coronary syndrome. Int. J. Cardiol. 2012;155(1):90–96.
17. De Servi S., Cavallini C., Dellavalle A., Santoro G.M., Bonizzoni E., Marzocchi A., Politi A., Pesaresi A., Mariani M., Chierchia S. ROSAI-2 Investigators. Non-ST-elevation acute coronary syndrome in the elderly: treatment strategies and 30-day outcome. Am. Heart J. 2004;147(5):830–836. doi: 10.1016/j.ahj.2003.12.016.
18. Liistro F., Angioli P., Falsini G., Ducci K., Baldassarre S., Burali A., Bolognese L. Early invasive strategy in elderly patients with non-ST elevation acute coronary syndrome: comparison with younger patients regarding 30 day and long term outcome. Heart. 2005;91(10):1284–1288.
19. De Servi S., Cavallini C., Dellavalle A., Santoro G.M., Bonizzoni E., Marzocchi A., Politi A., Pesaresi A., Mariani M., Chierchia S. ROSAI-2 Investigators. Non-ST-elevation acute coronary syndrome in the elderly: treatment strategies and 30-day outcome. Am. Heart J. 2004;147(5):830–836.
20. Devlin G., Gore J., Elliott J., et al. Management and 6-month outcome in elderly and very elderly patients with high-risk non-ST-elevation acute coronary syndromes. Eur. Heart J. 2008;29:1275–1282.
21. TIME Investigators. Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial. Lancet. 2001;358(9286):951–957. doi: 10.1016/S0140-6736(01)06100-1.
22. McKellar S.H., Brown M.L., Frye R.L., Schaff H.V., Sundt T.M., III Comparison of coronary revascularization procedures in octogenarians: a systematic review and meta-analysis. Nat. Clin. Pract. Cardiovasc. Med. 2008;5(11):738–746.
23. Wissenberg M, Folke F, Hansen CM, Lippert FK, Kragholm K, Risgaard B, Rajan S, Karlsson L, Søndergaard KB, Hansen SM, Mortensen RN, Weeke P, Christensen EF, Nielsen SL, Gislason GH, Køber L, Torp-Pedersen C. Survival After Out-of-Hospital Cardiac Arrest in Relation to Age and Early Identification of Patients With Minimal Chance of Long-Term Survival. Circulation. 2015 May 5;131(18):1536-45.
24. Hirlekar G, Karlsson T, Aune S, Ravn-Fischer A, Albertsson P, Herlitz J, Libungan B. Survival and neurological outcome in the elderly after in-hospital cardiac arrest. Resuscitation 2017 Sep;118:101-106.
25. Winther-Jensen M, Kjaergaard J, Hassager C, Bro-Jeppesen J, Nielsen N, Lippert FK, Køber L, Wanscher M, Søholm H. Resuscitation and post resuscitation care of the very old after out-of-hospital cardiac arrest is worthwhile. Int J Cardiol. 2015 Dec 15;201:616-23.