EDITORIAL

Coronary Angiography after Cardiac Arrest — The Right Timing or the Right Patients?

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The treatment of patients who are comatose after out-of-hospital cardiac arrest involves a complex, multidisciplinary approach that includes the use of targeted temperature management, aggressive hemodynamic management, electroencephalographic monitoring, and consideration of coronary angiography.[1] However, studies suggest that despite these interventions, 30 to 50% of these patients die before hospital discharge, and a substantial percentage of long-term survivors have neurologic and cardiac sequelae.[2,3]

Although clinically significant coronary disease is common in patients who have cardiac arrest,[4] the selection of patients for coronary angiography remains controversial. The general consensus is that comatose patients who have had cardiac arrest with evidence of ST-segment elevation myocardial infarction (STEMI) on electrocardiography (ECG) should undergo immediate coronary angiography; beyond this group, however, consensus is elusive. One difficulty in determining which patients should undergo coronary angiography is that identification of patients who have had an arrest from a coronary cause is surprisingly challenging when there is no evidence of STEMI on ECG. A previous observational study has shown that the initial arrest rhythm, troponin levels, and ECG findings are poor predictors of acute coronary lesions that require intervention.[5] Furthermore, even among patients for whom acute coronary syndromes are the cause of the cardiac arrest, the appropriate timing of coronary angiography is unknown. The multicenter, randomized Coronary Angiography after Cardiac Arrest (COACT) trial,[6] the results of which are now reported in the *Journal*, seeks to address the following question: in patients who have had an out-of-hospital cardiac arrest, is a strategy of immediate coronary angiography better than a strategy of delayed angiography with respect to survival at 90 days?

A cohort of 552 patients who were unconscious after cardiac arrest and had an initial shockable rhythm but no evidence of STEMI on ECG were randomly assigned in a 1:1 ratio to undergo immediate coronary angiography after resuscitation or delayed coronary angiography during hospitalization. The median time from arrest to coronary angiography was 2.3 hours in the immediate angiography group and 121.9 hours in the delayed angiography group. Overall survival at 90 days was not significantly different between the two groups (64.5% of patients in the immediate angiography group and 67.2% in the delayed angiography group were alive at 90 days). These results suggest that coronary angiography does not have to be performed immediately in patients who have had cardiac arrest without STEMI. This finding is consistent with results from trials involving patients with acute coronary syndromes with neither STEMI nor cardiac arrest, for whom delayed coronary angiography yielded outcomes similar to those with immediate coronary angiography.

Although the COACT trial represents a carefully performed and well-documented trial conducted in a challenging clinical setting, it is important to highlight a fundamental limitation. Acute unstable coronary lesions were found in less than 20% of the total trial cohort, and coronary interventions were performed in less than 40% of the patients. That is, the majority of patients who had cardiac arrest and underwent angiography did not have clinically significant coronary lesions, and thus only a small fraction of the trial population would be affected by the timing of coronary an-

giography — or the performance of coronary angiography at all. Therefore, the results of the trial should be interpreted with caution. This problem of appropriate patient selection has been a critical limitation in other trials involving patients with cardiac arrest, including the landmark Thrombolysis in Cardiac Arrest (TROICA) trial.[7] In that trial, patients who had out-of-hospital cardiac arrest and were randomly assigned to either thrombolytic therapy or placebo had similar outcomes, yet only a small fraction of these patients probably had acute thrombotic disease.

If the current trial had used more specific inclusion criteria, it could have enriched the cohort for patients with probable coronary disease, and very different outcomes might have resulted. In subgroup analyses, patients over the age of 70 years and patients with a history of coronary disease appeared to be more likely to benefit from immediate coronary angiography than younger patients and patients without a documented history of coronary disease (details are provided in the Supplementary Appendix of the article, available at NEJM.org). In addition, the trial design did not take into account clinical context, such as acute chest pain or other symptoms of coronary ischemia, which are known to often precede a cardiac arrest that has a coronary cause.[8]

The current trial also highlights the challenges inherent in prioritization of interventions after a cardiac arrest. Resuscitation guidelines recommend that targeted temperature management should be implemented promptly after resuscitation; yet often, coronary angiography takes precedence, which leads to delayed use of targeted temperature management. In the COACT trial, the median time to target temperature was 5.4 hours in the immediate angiography group and 4.7 hours in the delayed angiography group; whether this delay attenuated a potential survival benefit of immediate coronary angiography remains unknown. It is also important to stress that most in-hospital deaths that occur among patients who have been resuscitated after cardiac arrest are due to neurologic injury rather than to cardiac complications; in this trial, more than 60% of deaths were due to neurologic injury, which had frequently led to discontinuation of treatment.

The COACT trial represents an important step forward in the care of patients after a cardiac arrest, and the results suggest that for the majority of comatose patients who have had a cardiac arrest without evidence of STEMI, coronary angiography need not be performed immediately. Further work will be required to better define personalized treatment strategies for selected patients after cardiac arrest. Two multicenter investigations are currently under way; the ACCESS trial (ClinicalTrials.gov number, NCT03119571) and the Direct or Subacute Coronary Angiography in Out-of-hospital Cardiac Arrest trial (DISCO; NCT02309151) are investigating the timing of coronary angiography after cardiac arrest. It will be useful to compare the results of these trials with those of the COACT trial.[9,10] The current trial also highlights the daunting challenges that remain in determining how interventions after cardiac arrest can affect patient outcomes. Addressing these challenges will require multidisciplinary efforts, with the important goal of increasing the likelihood of survival and improving quality of life for patients after cardiac arrest.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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ORIGINAL ARTICLE

Coronary Angiography after Cardiac Arrest without ST-Segment Elevation

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ABSTRACT

BACKGROUND

Ischemic heart disease is a major cause of out-of-hospital cardiac arrest. The role of immediate coronary angiography and percutaneous coronary intervention (PCI) in the treatment of patients who have been successfully resuscitated after cardiac arrest in the absence of ST-segment elevation myocardial infarction (STEMI) remains uncertain.

METHODS

In this multicenter trial, we randomly assigned 552 patients who had cardiac arrest without signs of STEMI to undergo immediate coronary angiography or coronary angiography that was delayed until after neurologic recovery. All patients underwent PCI if indicated. The primary end point was survival at 90 days. Secondary end points included survival at 90 days with good cerebral performance or mild or moderate disability, myocardial injury, duration of catecholamine support, markers of shock, recurrence of ventricular tachycardia, duration of mechanical ventilation, major bleeding, occurrence of acute kidney injury, need for renal-replacement therapy, time to target temperature, and neurologic status at discharge from the intensive care unit.

RESULTS

At 90 days, 176 of 273 patients (64.5%) in the immediate angiography group and 178 of 265 patients (67.2%) in the delayed angiography group were alive (odds ratio, 0.89; 95% confidence interval [CI], 0.62 to 1.27; P=0.51). The median time to target temperature was 5.4 hours in the immediate angiography group and 4.7 hours in the delayed angiography group (ratio of geometric means, 1.19; 95% CI, 1.04 to 1.36). No significant differences between the groups were found in the remaining secondary end points.

CONCLUSIONS

Among patients who had been successfully resuscitated after out-of-hospital cardiac arrest and had no signs of STEMI, a strategy of immediate angiography was not found to be better than a strategy of delayed angiography with respect to overall survival at 90 days. (Funded by the Netherlands Heart Institute and others; COACT Netherlands Trial Register number, NTR4973.)

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Out-of-hospital cardiac arrest is a leading cause of death in Europe and the United States. Despite advances in the field of resuscitation and intensive care management, the outcome in patients after cardiac arrest remains poor. A recent study reported mortality of approximately 40% among patients who had been successfully resuscitated after out-of-hospital cardiac arrest associated with ventricular fibrillation or pulseless ventricular tachycardia.[1] Recommended postresuscitation care includes targeted temperature management, vital-organ support, and treatment of the underlying cause of the arrest. However, the cause of arrest is often unclear immediately after the event, and the lack of a definitive diagnosis can lead to uncertainty regarding the appropriate treatment.

The most frequent cause of cardiac arrest is ischemic heart disease, and coronary artery disease has been reported in up to 70% of patients who have been resuscitated and are referred for immediate coronary angiography.[2] If myocardial infarction is the cause of the arrest, immediate percutaneous coronary intervention (PCI) might salvage myocardium, improve circulatory function, and prevent the recurrence of life-threatening arrhythmias. Current European and American guidelines recommend immediate coronary angiography with PCI in patients who present with ST-segment elevation myocardial infarction (STEMI) and cardiac arrest.[3,4]

In patients with cardiac arrest who do not have ST-segment elevation on electrocardiography (ECG), the role of immediate coronary angiography is still a matter of debate. Data from randomized trials are lacking, and observational studies have shown conflicting results regarding the effect of immediate coronary angiography and PCI on outcomes in this patient group.[5-9] At present, international guidelines on cardiopulmonary resuscitation recommend emergency coronary angiography in selected patients after out-of-hospital cardiac arrest, even in the absence of ST-segment elevation.[10,11] It has been advocated, however, that these recommendations need to be substantiated by data from randomized clinical trials.[12,13] The Coronary Angiography after Cardiac Arrest (COACT) trial was designed to test the hypothesis that in patients who are successfully resuscitated after cardiac arrest in the absence of STEMI, a strategy of immediate coronary angiography (and PCI if necessary) would be better than a strategy of delayed angiography with respect to overall survival.

Methods

Trial Design and Oversight

The COACT trial was an investigator-initiated, randomized, open-label, multicenter trial that compared a strategy of immediate coronary angiography with a strategy of delayed angiography in patients who had been successfully resuscitated after cardiac arrest and who did not have ST-segment elevation on ECG. The trial design has been published previously.[14] The protocol, available with the full text of this article at NEJM.org, was designed by the authors and was approved by the trial steering committee and all relevant ethics committees.

The trial was sponsored by the Netherlands Heart Institute, Biotronik, and AstraZeneca. The sponsors of the trial had no role in the design or monitoring of the trial; the selection of the participating centers; the enrollment of participants; the collection, recording, storage, retention, or analysis of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

A clinical research organization (Clinical Research Unit Cardiology VUmc) was responsible for maintaining and monitoring the patient data. A data and safety monitoring committee oversaw the trial. All coronary angiography and PCI procedures were evaluated at an independent core laboratory by personnel who were unaware of the treatment assignments. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol (see the Supplementary Appendix, available at NEJM.org).

Patients

Patients were eligible for the trial if they had had an out-of-hospital cardiac arrest with an initial shockable rhythm and were unconscious after the return of spontaneous circulation. Patients were excluded if they had signs of STEMI on ECG in the emergency department, shock, or an obvious noncoronary cause of the arrest. Further inclusion and exclusion criteria and definitions are provided in the Supplementary Appendix. Deferred written informed consent was obtained from all

enrolled patients with the use of a prespecified procedure (see the Supplementary Appendix).

RANDOMIZATION AND TREATMENT

Patients were screened for eligibility in the emergency department. Eligible patients were randomly assigned in a 1:1 ratio with the use of a Web-based randomization system (Castor EDC) to either immediate angiography or delayed angiography. In the immediate angiography group, coronary angiography was performed as soon as possible and was initiated within 2 hours after randomization. In the delayed angiography group, coronary angiography was performed after neurologic recovery, in general after discharge from the intensive care unit. If a patient who had initially been assigned to the delayed angiography group showed signs of cardiogenic shock, recurrent life-threatening arrhythmias, or recurrent ischemia during hospitalization, urgent coronary angiography was performed.

The choice of anticoagulant and the revascularization strategy were left to the discretion of the treating physicians, although it was recommended that all coronary lesions suspected of being unstable should be treated. (Unstable lesions were defined as coronary lesions with at least 70% stenosis and the presence of characteristics of plaque disruption, including irregularity, dissection, haziness, or thrombus, as assessed by results of coronary angiography.) In patients with multivessel disease, treating physicians were advised to use a revascularization strategy that was based on the local heart team protocol and the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score. The SYNTAX score reflects a comprehensive angiographic assessment of the coronary vasculature, with scores of 22 or lower indicating low anatomical complexity, scores of 23 to 32 indicating intermediate anatomical complexity, and scores of more than 32 indicating high anatomical complexity (0 is the lowest score, and there is no upper limit).[15] If coronary-artery bypass grafting was the treatment of choice for a patient in the immediate angiography group, this procedure could be deferred until after neurologic recovery.

Further postresuscitation care was in line with international resuscitation guidelines.[10] Targeted temperature management was initiated as soon as possible and was performed in accordance with local protocol. The approach to withdrawal of life-sustaining treatment for patients with persistent coma was not prespecified and was based on local practice, which adhered to Dutch and European guidelines.

FOLLOW-UP AND END POINTS

Follow-up data were obtained by means of a telephone interview conducted 90 days after randomization with the patient or a family member or were determined from information acquired from the patient's general physician. The primary end point of the trial was survival at 90 days. Secondary end points included survival at 90 days with good cerebral performance or mild or moderate disability, myocardial injury quantified on the basis of troponin levels, increase in creatine kinase and creatine kinase MB levels (reported as the area under the curve), acute kidney injury defined according to Acute Kidney Injury Network criteria,[16] the need for renal-replacement therapy, time to target temperature, duration of catecholamine or inotropic therapy, neurologic status at discharge from the intensive care unit, markers of shock, recurrence of ventricular tachycardia requiring defibrillation or electrical cardioversion, duration of mechanical ventilation, and major bleeding defined according to Thrombolysis in Myocardial Infarction (TIMI) criteria. A detailed description of biomarker measurements and definitions of outcome measures are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The trial was powered for the primary end point of survival at 90 days. The results of a previous meta-analysis of 10 nonrandomized studies showed that immediate angiography was better than conventional treatment with respect to overall survival (56% vs. 32%; odds ratio, 2.78; 95% confidence interval [CI], 1.89 to 4.10).[17] We therefore hypothesized that in our trial, more patients in the immediate angiography group than in the delayed angiography group would survive to 90 days. We calculated that 251 patients would need to be enrolled in each group to give the trial 85% power to detect a 40% difference between the immediate angiography group and the delayed angiography group in terms of survival to 90 days (45% survival with immediate angiography vs. 32% with delayed angiography), when assessed

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Immediate Angiography Group (N=273)	Delayed Angiography Group (N=265)
Age — yr	65.7±12.7	64.9±12.5
Male sex — no. (%)	223 (81.7)	202 (76.2)
Hypertension — no./total no. (%)	131/269 (48.7)	126/265 (47.5)
Previous myocardial infarction — no. (%)	73 (26.7)	76 (28.7)
Previous CABG — no./total no. (%)	43/272 (15.8)	24/265 (9.1)
Previous PCI — no./total no. (%)	46/272 (16.9)	60/264 (22.7)
Previous coronary artery disease — no. (%)	99 (36.3)	96 (36.2)
Previous cerebrovascular accident — no./total no. (%)	19/272 (7.0)	15/265 (5.7)
Diabetes mellitus — no./total no. (%)	55/272 (20.2)	44/265 (16.6)
Current smoker — no./total no. (%)	50/249 (20.1)	67/249 (26.9)
Hypercholesterolemia — no./total no. (%)	70/270 (25.9)	78/263 (29.7)
Peripheral artery disease — no./total no. (%)	16/272 (5.9)	23/265 (8.7)
Arrest witnessed — no. (%)	218 (79.9)	203 (76.6)
Median time from arrest to basic life support (IQR) — min	2 (1–5)	2 (1–5)
Median time from arrest to return of spontaneous circulation (IQR) — min	15 (9–21)	15 (8–20)
Signs of ischemia on ECG — no./total no. (%)†	168/262 (64.1)	172/248 (69.4)
Median GCS score at admission (IQR)‡	3 (3–3)	3 (3–3)
APACHE IV score§	107±28	105±32
Baseline laboratory values		
pH	7.2±0.1	7.2±0.1
Median lactic acid (IQR) — mmol/liter	5.3 (3.0–8.8)	4.9 (2.8–8.1)
Bicarbonate — mmol/liter	19.4±4.3	19.0±4.5
Base excess	−7.4±6.2	−7.7±6.2
Median partial pressure of oxygen (IQR) — kPa	14.7 (8.9–26.8)	15.3 (10.1–28.2)
Median mixed venous oxygen saturation (IQR) — %	94 (76–98)	94 (75–98)
Median creatinine (IQR) — μmol/liter	102 (90–119)	101 (86–115)
Median creatine kinase (IQR) — U/liter	162 (114–252)	163 (116–248)
Median creatine kinase MB (IQR) — μg/liter	6.0 (4.0–13.2)	6.3 (3.7–19.9)
Median troponin T (IQR) — μg/liter	0.044 (0.029–0.085)	0.053 (0.025–0.116)

* Plus–minus values are means ±SD. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. CABG denotes coronary-artery bypass grafting, IQR interquartile range, and PCI percutaneous coronary intervention.
† Signs of ischemia on electrocardiography (ECG) are defined as depressions of 1 mm or more in two contiguous leads or T-wave inversion in two contiguous leads, or both.
‡ Glasgow Coma Scale (GCS) scores range from 3 to 15, with lower scores indicating a reduced level of consciousness.
§ Acute Physiology and Chronic Health Evaluation (APACHE) IV scores range from 0 to 286, with higher scores indicating a higher risk of death.

by means of a chi-square test at a two-sided significance level of 5%. The sample size was increased by 10% to a total of 552 patients to account for loss of patients to follow-up.

The trial had an adaptive design that allowed for an increase in sample size if the survival benefit was substantial but smaller than the 40% difference mentioned above. The data and safety monitoring committee of the trial was allowed to recommend an increase in the sample size on the basis of the results of an interim analysis of outcomes in the first 400 patients. After this interim analysis, the data and safety monitoring committee advised that the sample size not be increased.

Outcome measures were assessed in all ran-

Table 2. Procedures, Treatments, and Characteristics of Coronary Artery Disease.*

Variable	Immediate Angiography Group (N=273)	Delayed Angiography Group (N=265)
Coronary angiography performed — no. (%)	265 (97.1)	172 (64.9)†
Median time from arrest to coronary angiography (IQR) — hr	2.3 (1.8–3.0)	121.9 (52.0–197.3)
Median time from randomization to coronary angiography (IQR) — hr	0.8 (0.5–1.2)	119.9 (47.2–203.7)
Severity of coronary artery disease — no./total no. (%)		
No clinically significant disease	94/265 (35.5)	59/172 (34.3)
One-vessel disease	72/265 (27.2)	49/172 (28.5)
Two-vessel disease	54/265 (20.4)	35/172 (20.3)
Three-vessel disease	45/265 (17.0)	29/172 (16.9)
Acute unstable lesion — no./total no. (%)‡	36/265 (13.6)	29/172 (16.9)
Acute thrombotic occlusion — no./total no. (%)	9/265 (3.4)	13/172 (7.6)§
Chronic total occlusion — no./total no. (%)	100/265 (37.7)	58/172 (33.7)
Revascularization treatment — no. (%)		
PCI	90 (33.0)	64 (24.2)
CABG	17 (6.2)	23 (8.7)
Pharmacologic or conservative treatment	168 (61.5)	179 (67.5)

* Percentages may not total 100 because of rounding.
† These 172 patients represent 95% of those patients who survived until hospital discharge. A total of 38 of the 172 patients received urgent intervention because of cardiac deterioration.
‡ Unstable lesions were defined as coronary lesions with at least 70% stenosis and the presence of characteristics of plaque disruption, including irregularity, dissection, haziness, or thrombus, as assessed by results of coronary angiography.
§ Six of the 13 patients in the delayed angiography group who had an acute thrombotic occlusion received urgent intervention because of cardiac deterioration.

domly assigned patients, except in those for whom written informed consent was retroactively withdrawn. Categorical data (primary and secondary end points) were compared with the use of the chi-square test or Fisher's exact test and are summarized as numbers and percentages. Odds ratios are reported as effect estimates with 95% confidence intervals. We report the P value only for the primary analysis. The 95% confidence intervals for the secondary end points have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible. Analyses of eight prespecified subgroups were performed. Further details of the statistical analysis are provided in the Supplementary Appendix.

RESULTS

PATIENTS

During the period from January 2015 through July 2018, a total of 552 patients who had been resuscitated after cardiac arrest and who did not have ST-segment elevation on ECG were enrolled at 19 participating centers in the Netherlands (Fig. S1 in the Supplementary Appendix). Screening data were available during the final period of the inclusion phase of the trial, when all centers were enrolling patients (Fig. S2 in the Supplementary Appendix). After exclusion of patients for whom written informed consent was retroactively withdrawn, 538 patients (97.5%) had data available for assessment; 273 of these patients had been assigned to the immediate angiography group and 265 to the delayed angiography group. The baseline characteristics are shown in Table 1. The mean (±SD) age was 65.3±12.6 years, and 79.0% of patients were men.

TREATMENTS

Details about procedures and treatments are provided in Table 2, and in Tables S1 and S2 in the Supplementary Appendix. Coronary angiography was performed in 265 of the 273 patients (97.1%)

Table 3. Clinical Outcomes.*

Outcome	Immediate Angiography Group (N=273)	Delayed Angiography Group (N=265)	Effect Size (95% CI)†
Primary end point			
Survival at 90 days — no. of patients (%)‡	176 (64.5)	178 (67.2)	OR, 0.89 (0.62 to 1.27)
Secondary end points			
Survival with good cerebral performance or mild or moderate disability — no. of patients/total no. (%)	171/272 (62.9)	170/264 (64.4)	OR, 0.94 (0.66 to 1.31)
CPC score at 90 days — no./total no. (%)§			
1	157/272 (57.7)	159/264 (60.2)	Reference
2	14/272 (5.1)	11/264 (4.2)	OR, 1.29 (0.56 to 2.92)
3	4/272 (1.5)	5/264 (1.9)	OR, 0.81 (0.21 to 3.07)
4	0/272	2/264 (0.8)	NA
5	97/272 (35.7)	87/264 (33.0)	OR, 1.13 (0.78 to 1.63)
Survival until hospital discharge — no. of patients (%)	178 (65.2)	182 (68.7)	OR, 0.85 (0.60 to 1.22)
Neurologic status at ICU discharge			
GCS score			
Median (IQR)	15 (14 to 15)	15 (14 to 15)	
Geometric mean (95% CI)	13.7 (13.2 to 14.2)	13.5 (12.9 to 13.7)	1.02 (0.96 to 1.04)
CPC score — no./total no. (%)§			
1	74/258 (28.7)	86/249 (34.5)	Reference
2	59/258 (22.9)	56/249 (22.5)	OR, 1.22 (0.76 to 1.98)
3	36/258 (14.0)	30/249 (12.0)	OR, 1.39 (0.78 to 2.48)
4	4/258 (1.6)	9/249 (3.6)	OR, 0.52 (0.15 to 1.75)
5	85/258 (32.9)	68/249 (27.3)	OR, 1.45 (0.93 to 2.27)
TIMI major bleeding, any grade — no. (%)	7 (2.6)	13 (4.9)	OR, 0.51 (0.20 to 1.30)
Recurrence of ventricular tachycardia resulting in defibrillation or electrical cardioversion — no. (%)	21 (7.7)	16 (6.0)	OR, 1.30 (0.66 to 2.54)
Creatinine kinase			
Median AUC (IQR)	30,099 (9983 to 67,096)	28,006 (11,044 to 74,043)	
Geometric mean (95% CI)	25,694 (21,764 to 30,333)	25,306 (21,140 to 30,291)	1.02 (0.80 to 1.30)
Creatinine kinase MB			
Median AUC (IQR)	930 (402 to 2456)	851 (302 to 2868)	
Geometric mean (95% CI)	975 (793 to 1198)	949 (739 to 1219)	1.03 (0.74 to 1.42)
Troponin T			
Median AUC (IQR)	11.3 (4.4 to 33.5)	10.6 (4.5 to 36.2)	
Geometric mean (95% CI)	11.2 (9.2 to 13.6)	12.8 (10.3 to 16.0)	0.87 (0.64 to 1.16)
Troponin I			
Median AUC (IQR)	154.7 (33.1 to 1762)	183.2 (21.4 to 7278)	
Geometric mean (95% CI)	226.7 (100.1 to 513.2)	315.9 (116.7 to 837.5)	0.72 (0.21 to 2.54)
AKIN classification stage — no./total no. (%)¶			
0	218/244 (89.3)	214/243 (88.1)	Reference
1	12/244 (4.9)	8/243 (3.3)	OR, 1.47 (0.59 to 3.67)
2	4/244 (1.6)	5/243 (2.1)	OR, 0.79 (0.21 to 2.96)
3	10/244 (4.1)	16/243 (6.6)	OR, 0.61 (0.27 to 1.38)

Table 3. (Continued.)

Outcome	Immediate Angiography Group (N=273)	Delayed Angiography Group (N=265)	Effect Size (95% CI)†
Need for renal-replacement therapy — no. (%)	8 (2.9)	11 (4.2)	OR, 0.70 (0.28 to 1.76)
Time to target temperature — hr			
Median (IQR)	5.4 (2.9 to 8.6)	4.7 (2.6 to 7.5)	
Geometric mean (95% CI)	6.5 (5.9 to 7.1)	5.5 (5.0 to 6.0)	1.19 (1.04 to 1.36)
Time to hypothermia: 30.0–35.9°C — hr			
Median (IQR)	6.2 (4.1 to 8.7)	5.1 (3.5 to 8.2)	
Geometric mean (95% CI)	7.1 (6.4 to 7.8)	6.3 (5.7 to 6.9)	1.13 (0.99 to 1.30)
Time to normothermia: 36.0–37.0°C — hr			
Median (IQR)	4.1 (2.2 to 8.4)	2.8 (1.5 to 5.6)	
Geometric mean (95% CI)	5.5 (4.5 to 6.7)	4.2 (3.6 to 5.1)	1.29 (0.99 to 1.68)
Duration of inotropic or catecholamine support — days			
Median (IQR)	1.7 (1.1 to 2.7)	1.9 (1.2 to 2.7)	
Geometric mean (95% CI)	1.6 (1.4 to 1.8)	1.7 (1.5 to 1.9)	0.94 (0.79 to 1.12)
Markers of shock			
Lowest MAP on day 1	61±11	61±13	0.68 (–1.46 to 2.82)‖
Lowest MAP on day 2	62±12	62±11	–0.52 (–2.63 to 1.58)‖
Lowest MAP on day 3	67±15	68±16	–0.94 (–3.85 to 1.96)‖
Lactate on day 1			
Median (IQR)	1.5 (1.1 to 2.4)	1.4 (1.0 to 2.2)	
Geometric mean (95% CI)	1.7 (1.5 to 1.8)	1.5 (1.4 to 1.7)	1.09 (0.96 to 1.23)
Lactate on day 2			
Median (IQR)	1.4 (1.0 to 2.0)	1.3 (1.0 to 2.1)	
Geometric mean (95% CI)	1.5 (1.4 to 1.7)	1.5 (1.4 to 1.6)	1.04 (0.92 to 1.17)
Lactate on day 3			
Median (IQR)	1.3 (1.0 to 1.9)	1.3 (1.0 to 1.8)	
Geometric mean (95% CI)	1.4 (1.3 to 1.5)	1.4 (1.3 to 1.5)	1.00 (0.90 to 1.11)
Duration of mechanical ventilation — days			
Median (IQR)	2.3 (1.4 to 4.1)	2.2 (1.5 to 4.1)	
Geometric mean (95% CI)	2.3 (2.0 to 2.6)	2.4 (2.1 to 2.7)	0.96 (0.80 to 1.14)

* Plus–minus values are means ±SD. The numbers of patients who were assessed for continuous outcomes are provided in Table S6 in the Supplementary Appendix. AUC denotes area under the curve, ICU intensive care unit, MAP mean arterial pressure, NA not applicable, OR odds ratio, and TIMI Thrombolysis in Myocardial Infarction.

† The effect size is the ratio of geometric means unless otherwise noted. The delayed angiography group is used as the reference group for odds ratios and mean differences. The 95% confidence intervals for the secondary end points have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible.

‡ The P value for the primary end point is 0.51.

§ Cerebral Performance Category (CPC) scores range from 1 to 5, with higher scores indicating a worse outcome.

¶ The Acute Kidney Injury Network (AKIN) stages range from 0 to 3, with higher stages indicating more severe renal failure.[16]

‖ The effect size is the mean difference between the immediate angiography group and the delayed angiography group.

in the immediate angiography group and in 172 of the 265 patients (64.9%) in the delayed angiography group. The median time from randomization to coronary angiography was 0.8 hours in the immediate angiography group and 119.9 hours in the delayed angiography group. An acute thrombotic occlusion was found in 3.4% of patients in the immediate angiography group and in 7.6% of patients in the delayed angiography group. PCI was performed in 33.0% of pa-

tients in the immediate angiography group and in 24.2% in the delayed angiography group; coronary-artery bypass grafting was performed in 6.2% and 8.7%, respectively. Patients assigned to the strategy of immediate angiography were more often treated with a glycoprotein IIb/IIIa inhibitor, and patients assigned to the delayed strategy were more likely to be treated with salicylates, a P2Y12 inhibitor, or both.

A total of 13 patients assigned to the immediate angiography group were treated with a delayed strategy, and 3 patients assigned to the delayed angiography group were treated with an immediate strategy (Table S2 in the Supplementary Appendix). A total of 38 patients in the delayed angiography group underwent urgent coronary angiography before their planned procedure.

More than 90% of patients in each group were treated with targeted temperature management and mechanical ventilation. The median time to target temperature among patients who received this treatment was 5.4 hours in the immediate angiography group and 4.7 hours in the delayed angiography group (ratio of geometric means, 1.19; 95% CI, 1.04 to 1.36). Life-sustaining treatment was withdrawn in 76 patients in the immediate angiography group and in 69 patients in the delayed angiography group. Details about the withdrawal of life-sustaining treatment are provided in Tables S4 and S5 in the Supplementary Appendix.

PRIMARY AND SECONDARY END POINTS

Clinical outcomes are reported in Table 3. A total of 176 of 273 patients (64.5%) in the immediate angiography group and 178 of 265 patients (67.2%) in the delayed angiography group survived to 90 days (the primary end point) (odds ratio, 0.89; 95% CI, 0.62 to 1.27; P=0.51) (Table 3 and Fig. 1). Sensitivity analyses showed no significant difference between the groups in the primary outcome. Heterogeneity of treatment effect was suggested in subgroup analyses according to age (P=0.007 for interaction) and history of coronary artery disease (P=0.009 for interaction). No other treatment-by-subgroup interactions were identified. Additional details about primary and secondary end points, sensitivity and subgroup analyses, and causes of death are provided in Tables S6 through S8 and Figs. S3 through S5 in the Supplementary Appendix.

DISCUSSION

In the COACT trial, we examined the effect on clinical outcomes of immediate angiography as compared with delayed angiography in patients who were successfully resuscitated after out-of-hospital cardiac arrest without ST-segment elevation on ECG and who had no obvious noncoronary cause of the arrest. The results of the trial did not show a significant difference between the two treatment groups in the primary end point of survival at 90 days.

Our findings do not corroborate findings of previous observational studies, which showed a survival benefit with immediate coronary angiography in patients who had cardiac arrest without STEMI.[8,18] This difference could be related to the observational nature of the previous studies, which may have resulted in selection bias that favored treating patients who had a presumed better prognosis with a strategy of immediate angiography.

Another explanation for the difference between the results of our trial and those of previous studies is a difference in patient populations. Coronary artery disease was found in 64.5% of patients who underwent immediate coronary angiography in the COACT trial, a finding that is consistent with that in a previous study.[2] However, the vast majority of patients in our trial had stable coronary artery lesions, and thrombotic occlusions were encountered in only 5.0% of patients. This might explain our results, since PCI is associated with improved outcomes in patients with acute thrombotic coronary occlusion (e.g., in patients with STEMI),[3,4] but not in patients with stable coronary artery disease.[19] Our results are also consistent with the results of several randomized trials that showed no survival benefit of immediate coronary angiography as compared with delayed coronary angiography in patients with myocardial infarction without ST-segment elevation who had not presented with cardiac arrest.[20-23]

Another reason for the lack of benefit of early coronary intervention may be that the majority of nonsurvivors died of neurologic complications after the cardiac arrest. This finding is consistent with the results of other resuscitation studies.[24,25] Death from neurologic injury was reported more than three times as frequently as

death from a cardiac cause. In addition, although immediate initiation of targeted temperature management was recommended, and previous studies have shown that initiation of targeted temperature management while urgent PCI is being performed is feasible,[8,26] we found that patients assigned to the immediate angiography group reached their target temperature later than patients in the delayed angiography group. Although the preferred strategy for targeted temperature management is still unclear, and trials that have investigated early targeted temperature management have failed to show benefit,[27,28] one could argue that a later achievement of target temperature might have attenuated any potential benefit gained from immediate coronary angiography.

In the COACT trial, patients who underwent delayed angiography were more likely to receive salicylates or a P2Y12 inhibitor (or both) than patients who underwent immediate angiography. This observation illustrates how the result of immediate coronary angiography can influence treatment, since patients who do not have evidence of coronary artery disease on angiography do not require antiplatelet therapy. In contrast, patients in the immediate angiography group were more likely to be treated with a glycoprotein IIb/IIIa inhibitor, which is more often used in the context of urgent PCI of thrombotic lesions. These differences in antiplatelet strategy between the two groups did not result in a significant difference in TIMI major bleeding.

Several limitations of our trial should be noted. First, we acquired data on patient screening during only the final phase of the trial. Second, because of the nature of the trial, physicians were aware of the assigned group, and this information might have influenced subsequent treatment. Third, our results do not apply to patients with shock, severe renal dysfunction, or persistent ST-segment elevation, since patients with these conditions were excluded from the trial. Fourth, 2.5% of randomly assigned patients could not be assessed because of withdrawal of consent. Finally, the actual overall percentage of patients in the COACT trial who survived was higher than anticipated in the sample-size calculation, which may have affected the power of the trial. The resulting 95% confidence interval does not exclude a 38% harm or a 27% benefit of immediate angiography with respect to the primary end point.

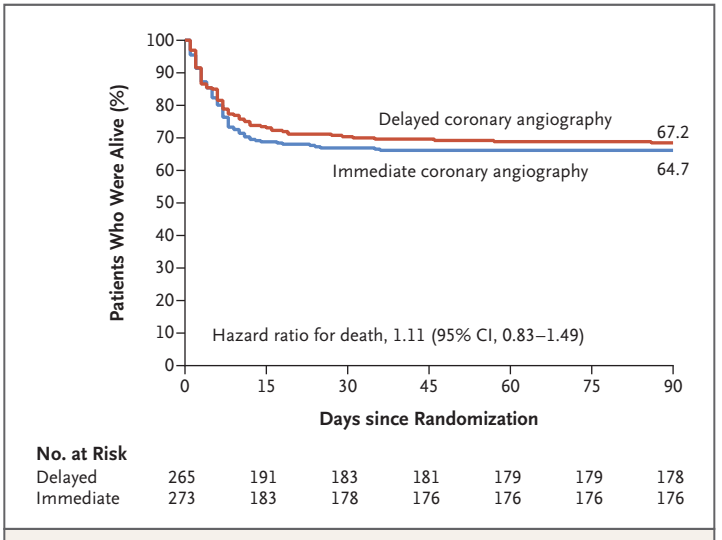

Figure 1. Kaplan–Meier Estimates of Survival among Patients Who Underwent Immediate or Delayed Coronary Angiography after Cardiac Arrest.

There was no significant difference between the two groups in overall survival at 90 days.

In conclusion, in this randomized, multicenter trial involving patients who were successfully resuscitated after out-of-hospital cardiac arrest and who had a shockable rhythm and no signs of STEMI or a noncoronary cause of the arrest, a strategy of immediate angiography was not better than a strategy of delayed angiography with respect to overall survival at 90 days.

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APPENDIX

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