

University of Groningen

Cost Analysis From a Randomized Comparison of Immediate Versus Delayed Angiography After Cardiac Arrest

Camaro, Cyril; Bonnes, Judith L.; Adang, Eddy M.; Spoormans, Eva M.; Janssens, Gladys N.; van der Hoeven, Nina W.; Jewbali, Lucia S.; Dubois, Eric A.; Meuwissen, Martijn; Rijpstra, Tom A.

Published in:
Journal of the American Heart Association

DOI:
[10.1161/JAHA.121.022238](https://doi.org/10.1161/JAHA.121.022238)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Camaro, C., Bonnes, J. L., Adang, E. M., Spoormans, E. M., Janssens, G. N., van der Hoeven, N. W., Jewbali, L. S., Dubois, E. A., Meuwissen, M., Rijpstra, T. A., Bosker, H. A., Blans, M. J., Bleeker, G. B., Baak, R., Vlachojannis, G. J., Eikemans, B. J., van der Harst, P., van der Horst, I. C., Voskuil, M., ... van Royen, N. (2022). Cost Analysis From a Randomized Comparison of Immediate Versus Delayed Angiography After Cardiac Arrest. *Journal of the American Heart Association*, 11(5), [022238]. <https://doi.org/10.1161/JAHA.121.022238>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).



The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

ORIGINAL RESEARCH

Cost Analysis From a Randomized Comparison of Immediate Versus Delayed Angiography After Cardiac Arrest

Cyril Camaro , MD; Judith L. Bonnes, MD, PhD; Eddy M. Adang, PhD; Eva M. Spoormans, MD; Gladys N. Janssens, MD; Nina W. van der Hoeven, MD; Lucia S. Jewbali , MD; Eric A. Dubois , MD, PhD; Martijn Meuwissen, MD, PhD; Tom A. Rijpstra, MD, PhD; Hans A. Bosker, MD, PhD; Michiel J. Blans , MD, PhD; Gabe B. Bleeker, MD, PhD; Rémon Baak, MD; George J. Vlachojannis , MD, PhD; Bob J. Eikemans, MD; Pim van der Harst , MD, PhD; Iwan C. van der Horst, MD, PhD; Michiel Voskuil, MD, PhD; Joris J. van der Heijden, MD; Bert Beishuizen, MD, PhD; Martin Stoel, MD, PhD; Hans van der Hoeven, MD, PhD; José P. Henriques, MD, PhD; Alexander P. Vlaar, MD, PhD; Maarten A. Vink, MD, PhD; Bas van den Bogaard, MD, PhD; Ton A. Heestermans, MD, PhD; Wouter de Ruijter , MD, PhD; Thijs S. Delnoij, MD, PhD; Harry J. Crijns , MD, PhD; Gillian A. Jessurun, MD, PhD; Pranobe V. Oemrawsingh , MD, PhD; Marcel T. Gosselink, MD, PhD; Koos Plomp, MD; Michael Magro , MD, PhD; Paul W. Elbers , MD, PhD; Peter M. van de Ven, PhD; Jorrit S. Lemkes , MD, PhD; Niels van Royen , MD, PhD

BACKGROUND: In patients with out-of-hospital cardiac arrest without ST-segment elevation, immediate coronary angiography did not improve clinical outcomes when compared with delayed angiography in the COACT (Coronary Angiography After Cardiac Arrest) trial. Whether 1 of the 2 strategies has benefits in terms of health care resource use and costs is currently unknown. We assess the health care resource use and costs in patients with out-of-hospital cardiac arrest.

METHODS AND RESULTS: A total of 538 patients were randomly assigned to a strategy of either immediate or delayed coronary angiography. Detailed health care resource use and cost-prices were collected from the initial hospital episode. A generalized linear model and a gamma distribution were performed. Generic quality of life was measured with the RAND-36 and collected at 12-month follow-up. Overall total mean costs were similar between both groups (EUR 33 575±19 612 versus EUR 33 880±21 044; $P=0.86$). Generalized linear model: (β , 0.991; 95% CI, 0.894–1.099; $P=0.86$). Mean procedural costs (coronary angiography and percutaneous coronary intervention, coronary artery bypass graft) were higher in the immediate angiography group (EUR 4384±3447 versus EUR 3028±4220; $P<0.001$). Costs concerning intensive care unit and ward stay did not show any significant difference. The RAND-36 questionnaire did not differ between both groups.

CONCLUSIONS: The mean total costs between patients with out-of-hospital cardiac arrest randomly assigned to an immediate angiography or a delayed invasive strategy were similar during the initial hospital stay. With respect to the higher invasive procedure costs in the immediate group, a strategy awaiting neurological recovery followed by coronary angiography and planned revascularization may be considered.

REGISTRATION

URL: <https://trialregister.nl>; Unique identifier: NL4857.

Key Words: coronary angiography ■ health care costs ■ non-ST-segment-elevation myocardial infarction ■ out-of-hospital cardiac arrest

Correspondence to: Niels van Royen, MD, PhD, Radboud University Medical Center, Geert Grooteplein 10, 6525 GA Nijmegen, PO BOX 9100, 6500 HB Nijmegen, The Netherlands. E-mail: niels.vanroyen@radboudumc.nl

Supplemental Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.022238>

For Sources of Funding and Disclosures, see page 8.

© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Coronary angiography in patients without ST-segment–elevation myocardial infarction who are successfully resuscitated after out-of-hospital cardiac arrest can be performed immediately or after neurologic recovery
- Data of health care resource use and costs may provide information for policymaking and help in final decision making choosing either early or delayed coronary angiography in these patients
- In this analysis, no significant difference was seen in mean total costs, but higher procedure costs were seen in the immediate invasive coronary angiography group compared with a delayed invasive strategy.

What Are the Clinical Implications?

- In patients successfully resuscitated after out-of-hospital cardiac arrest without signs of ST-segment elevation on the ECG, a more conservative strategy awaiting neurological recovery followed by planned coronary angiography (and a subsequent revascularization strategy) reduces procedural costs.

Nonstandard Abbreviations and Acronyms

ARREST	Advanced Reperfusion Strategies for Patients With Out-of-Hospital Cardiac Arrest and Refractory Ventricular Fibrillation
CAG	coronary angiography
COACT	Coronary Angiography After Cardiac Arrest
DISCO	Direct or Subacute Coronary Angiography in Out-of-Hospital Cardiac Arrest
FRISC	Fast Revascularisation During Instability in Coronary Artery Disease II
OHCA	out-of-hospital cardiac arrest
RITA-3	Third Randomised Intervention Trial of Unstable Angina
TACTICS	Treat Angina With Aggrstat and Determine Cost of Therapy With an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction (TIMI) 18
TOMAHAWK	Immediate Unselected Coronary Angiography Versus Delayed Triage in Survivors of Out-of-Hospital Cardiac Arrest Without ST-Segment Elevation

The outcome of patients with out-of-hospital cardiac arrest (OHCA) remains poor, with survival to hospital discharge ranging between 10% and 30%.¹ Even after the return of spontaneous circulation has been achieved, mortality is still around 40%.² The leading cause of in-hospital mortality is poor neurologic outcome, which cannot be predicted in the early phase after cardiac arrest.³

While international guidelines recommend emergency coronary angiography (CAG) and percutaneous coronary intervention (PCI) in selected patients after OHCA,^{3,4} the right timing of intervention is still under debate.^{5,6} However, emergency angiography in patients without a coronary or ischemic cause of the OHCA can further delay evidence-based interventions on survival such as targeted temperature management and hemodynamic support. The COACT (Coronary Angiography After Cardiac Arrest) trial (Netherlands Trial Register number NL4857) was designed to address this issue. In this investigator-initiated, randomized, open-label, multicenter trial, a strategy of immediate CAG was compared with a strategy of delayed angiography in patients who had been successfully resuscitated after cardiac arrest and did not have ST-segment elevation on ECG.⁷ With respect to 90-day survival no significant difference was seen between the 2 groups.⁸ Also, no improvement in 1-year clinical outcome was observed.⁹ A recent meta-analysis of 3581 patients (11 studies) also found no significant difference in 30-day mortality, neurological outcome, and PCI rate between early versus nonearly CAG in OHCA without ST-segment elevation.¹⁰

In case of equivalence with regard to health outcomes, it is important to assess the costs related to either strategy. Significant differences in costs between the 2 modalities can provide information for policymaking and help in final decision making about the implementation of either an immediate or delayed angiography strategy in patients after OHCA without ST-segment elevation. Total costs related to managing patients with OHCA are mainly driven by in-hospital costs and length of stay at the intensive care unit (ICU) during the initial hospitalization.^{11,12} We performed a prespecified cost-consequence analysis based on the hospital stay and collected RAND-36 quality-of-life scores at 12 months.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. Details of the COACT trial have been published previously.⁷⁻⁹ In summary, the COACT was a multicenter, randomized, controlled, open-label trial involving 19 hospitals in the Netherlands. Between January 2015 and July 2018, a total of 552 comatose

patients with OHCA with an initial shockable rhythm and without ST-segment elevation on the ECG were randomized in a 1:1 ratio to undergo immediate or delayed coronary angiography. The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act and the statements of the Dutch Central Committee on Research Involving Human Subject. The COACT was approved by each site's institutional review board and local ethics committees, and each patient provide written informed consent for participation in the study. Antithrombotic and revascularization strategies were left to the discretion of the treating physicians and followed prevailing guideline recommendations.⁴ Unstable coronary lesions, including a stenosis of at least 70%, were recommended to treat by the study protocol. Postresuscitation care, including targeted temperature management, was in line with current resuscitation guidelines.³ Patients were followed up by telephone interview conducted 90 days and 1 year after randomization.

Health Care Resource Use and Cost-Prices

Resource use data were collected for all patients included. Data from the following important cost-intensive procedures during hospital stay were collected: CAG (immediate or delayed), coronary revascularization by PCI, coronary artery bypass grafting and implantable cardioverter-defibrillator implants. PCI was categorized as immediate (acute), elective, or staged.

Health care costs were evaluated from the perspective of the Dutch health care system. In the health care system of the Netherlands, there is a supplementary tariff for emergency (acute) PCIs, but this is irrespective of the time the procedure is performed. The cost-prices of ICU, cardiac care unit, and ward stay were determined per day according to the 2018 reference list of the Dutch National Healthcare Institute.¹³ Hospital procedure costs are based on standard 2018 list prices and the diagnosis-treatment combination to transparency, the current reimbursement system in the Netherlands. This diagnosis-treatment combination to transparency is comparable with the diagnosis-related group system in other countries. A short explanation of the Dutch health care system is mentioned in Data S1. See Table S1 for a detailed description of the average prices of ICU, cardiac care unit, and ward days and the list prices for health care activities and procedures.

Subgroup Analysis

Mean total costs were compared between the immediate and delayed angiography groups for the following subgroups: age ≥ 70 years and < 70 years, male, female, known diabetes, prior myocardial infarction, prior coronary artery

bypass grafting, patients who survived until 90 days to discharge, and patients who did not survive.

Statistical Analysis

Continuous data were summarized as means \pm SD or medians (interquartile ranges [IQRs]). Categorical data were summarized by frequencies and percentages. Categorical variables are reported as (relative) frequencies and compared using the chi-squared test or Fisher's exact test, whichever was most appropriate. For the cost analysis, mean differences and 95% CIs for differences were calculated (univariable analysis).

Cost is usually a parameter with a skewed distribution. To take this into account as well as possible heteroscedasticity, an additional cost analysis was performed using a generalized linear model and a gamma distribution specifying the relationship between the variance and the mean. All data analyses were performed using SPSS Statistics version 25 (IBM, Armonk, New York).

Quality of Life

Generic quality of life for those patients included in this cost analysis was measured with the RAND-36 and collected at 12-month follow-up.

RESULTS

After exclusion of patients without available written consent, 538 patients were eligible for inclusion in the COACT trial. In total, 17 patients were excluded from the present analysis (8 in the immediate and 9 in the delayed angiography group) because of missing data (no hospital admission or ICU data). Thus, data from 521 patients were available for cost analysis: 265 patients in the immediate angiography group and 256 patients in the delayed group. Baseline characteristics are shown in Table 1. Both groups showed no difference with respect to demographic and clinical characteristics. In most patients, the cardiac arrest was witnessed by bystanders and the median time to basic life support was within 5 minutes. Patients were predominantly men. The procedures are outlined in Table 2. Revascularization was mainly performed by PCI, but most patients were treated conservatively. No significant difference was observed with respect to survival at 90 days and survival until hospital discharge. As in the main trial, patients were categorized according to the group they were originally assigned to (ie, intention to treat). An as-treated analysis yielded similar results (see Tables S2–S4).

Health Care Resource Use

Table 3 shows the health care resource use in each group. Similar length of stay in both groups was seen

Table 1. Baseline Characteristics

Baseline characteristics	Immediate angiography group (N=265)	Delayed angiography group (N=256)
Age, y, median (IQR)	68 (58–75)	66 (57–74)
Male sex, n (%)	216 (82)	194 (76)
Hypertension, n (%)	129 (49)	122 (48)
Previous myocardial infarction, n (%)	69 (26)	74 (29)
Previous CABG, n (%)	40 (15)	23 (9)
Previous PCI, n (%)	43 (16)	59 (23)
Previous coronary artery disease, n (%)	94 (36)	93 (36)
Previous CVA, n (%)	19 (7)	15 (6)
Diabetes, n (%)	54 (21)	41 (16)
Current smoker, n (%)	49 (20)	66 (27)
Hypercholesterolemia, n (%)	70 (27)	76 (30)
Peripheral artery disease, n (%)	16 (6)	23 (9)
Arrest witnessed, n (%)	212 (80)	195 (76)
Median time from arrest to BLS, min (IQR)	2 (1–5)	2 (1–5)
Median time from arrest to ROSC, min (IQR)	15 (8–20)	15 (8–20)
APACHE IV score	108±27	106±31

APACHE indicates acute physiology and chronic health evaluation; BLS, basic life support; CABG, coronary artery bypass graft; CAG, coronary angiography; CVA, cerebrovascular accident; IQR, interquartile range; PCI, percutaneous coronary intervention; and ROSC, return of spontaneous circulation.

in the duration of ICU hospitalization (both median 5 days). Thirty-five (13%) patients randomly assigned to the delayed angiography group underwent immediate angiography or PCI. More than one-third (35%) of the participants did not undergo angiography in the delayed group versus 3% in the immediate group. PCI (acute or staged) was performed in a significantly higher proportion of patients in the immediate angiography group (33% versus 24%; $P=0.02$). On the other hand, coronary artery bypass grafting was more often performed in the delayed group (6.4% versus 8.6%; $P=0.35$). No statistically significant difference was observed in the rates of implantable cardioverter-defibrillator implantation and renal support therapy.

Costs

The cost drivers at discharge are depicted in Table 4 and shown in the Figure. Overall total costs were similar between groups (immediate angiography group, EUR 33 575±19 612 versus delayed angiography group, EUR 33 880±21 044; $P=0.86$). Applying the prespecified generalized linear model for overall costs showed similar results (β , 0.991; 95% CI, 0.894–1.099; $P=0.86$). Subgroup analysis also showed no difference in costs for any of the subgroups (Table 5).

The costs for individual components differed. The mean costs of invasive coronary procedures (CAG, PCI, and coronary artery bypass grafting) were higher in the immediate group (EUR 4384±3447 versus EUR 3028±4220; $P<0.001$). Costs of hospitalization were

Table 2. Procedures

Procedural characteristics	Immediate angiography group (N=265)	Delayed angiography group (N=256)	P value
CAG performed, n (%)	258 (97)	166 (65)	<0.001
Time from arrest to CAG, h, median (IQR)	2.3 (1.8–3.0)	123.7 (52.0–200.1)	<0.001
Time from randomization to CAG, h, median (IQR)	0.8 (0.5–1.2)	122.2 (48.2–209.7)	<0.001
Revascularization, n (%)			
PCI	89 (34)	62 (24)	0.02
CABG	17 (6)	22 (9)	0.35
Conservative treatment	161 (61)	173 (68)	0.11
Survival, n (%)			
Survival at 90 d	171 (65)	172 (67)	0.52
Survival until hospital discharge	173 (65)	176 (69)	0.40

CABG indicates coronary artery bypass graft; CAG, coronary angiography; IQR, interquartile range; and PCI, percutaneous coronary intervention.

Table 3. Health Care Resource Use

Health care resource use	Immediate angiography group (N=265)	Delayed angiography group (N=256)	P value
Invasive coronary procedures, n (%)			
None	7 (3)	89 (35)	<0.001
Immediate CAG only	154 (58)	11 (4)	<0.001
Immediate CAG with acute PCI	61 (23)	19 (7)	<0.001
Immediate CAG with staged PCI	20 (8)	1 (0.4)	<0.001
Immediate CAG with acute PCI and staged PCI	6 (2)	0 (0)	<0.001
Immediate CAG with acute PCI and planned CABG	2 (0.8)	1 (0.4)	1.000
Immediate CAG with planned CABG	15 (6)	3 (1.2)	0.005
Delayed CAG only	0 (0)	73 (29)	<0.001
Delayed CAG with direct PCI	0 (0)	29 (11.3)	<0.001
Delayed CAG with staged PCI	0 (0)	12 (5)	<0.001
Delayed CAG with planned CABG	0 (0)	18 (7)	<0.001
Hospitalization days, median (IQR)			
Intensive care unit	5 (3–7)	5 (3–7)	0.62
Ward	7 (0–16)	9 (0–17)	0.30
Total length of stay	13 (7–22)	15 (8–23)	0.16
Other procedures, n (%)			
ICD implantation	104 (39)	103 (40)	0.82
Renal support therapy	7 (3)	11 (4)	0.30

CABG indicates coronary artery bypass graft; CAG, coronary angiography; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; and PCI, percutaneous coronary intervention.

EUR 16 167±13 308 versus EUR 16 683±13 643 ($P=0.66$) for ICU admission; and EUR 5000±5888 versus EUR 5942±8200 ($P=0.13$) for the ward days. Total length of stay was median 13 days in the immediate group versus median 15 days in the delayed group ($P=0.16$).

Quality of Life

Quality-of-life values were obtained in 230 of the 318 included patients who survived until 1 year. No difference was found between the 2 treatment groups at 1 year. The median for the RAND-36 questionnaire physical component score was 49 (IQR, 42–55) in the immediate angiography group and 51 (IQR, 46–55) in the delayed group ($P=0.57$). The mental component

of the RAND-36 reveals a median of 51 (IQR, 43–57) in the immediate angiography group and 50 (IQR, 43–56) in the delayed group ($P=0.55$). In Table S5, the baseline characteristics are shown for the patients in which the RAND-36 is available (N=230) and not available (N=88). This analysis did not show any difference. Also, the total costs showed no significant difference for those patients for whom the RAND-36 is available (see Table S6).

DISCUSSION

Our key finding is that of the initial hospital stay, mean total costs are similar for strategies of either immediate or delayed CAG with or without subsequent PCI

Table 4. Health Care Costs: Mean Total Costs (SD) in EURO

Health care costs	Immediate angiography group (N=265)	Delayed angiography group (N=256)	P value	Mean difference in total cost (95% CI)
Total costs	33 575±19 612	33 880±21 044	0.86	–305 (–3804 to 3195)
Costs, invasive coronary procedures	4384±3447	3028±4220	<0.001	1356 (694 to 2018)
Costs, intensive care unit length of stay	16 167±13 308	16 683±13 643	0.66	–517 (–2836 to 1803)
Costs, ward days	5000±5888	5942±8200	0.13	–941 (–2167 to 284)
Costs, ICD implantations	8024±10 002	8226±10 046	0.82	–202 (–1928 to 1523)

ICD indicates implantable cardioverter-defibrillator.

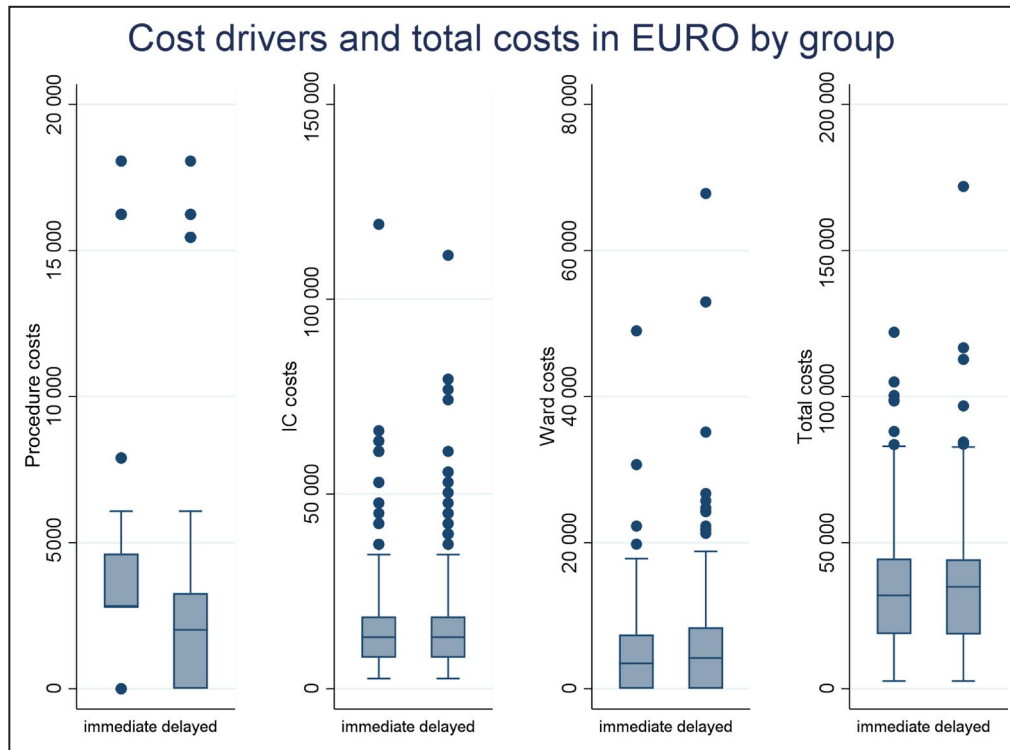


Figure. Cost drivers and total costs in EURO by group. Box plots of procedure costs, intensive care unit costs, ward costs, and total costs between the immediate and delayed angiography group. IC indicates intensive care.

in patients with OHCA without ST-segment elevation. However, the immediate strategy resulted in higher invasive procedure costs associated with higher rates of CAG, additional PCI, and staged PCI. A total of 35% of the patients in the delayed group did not receive

CAG compared with 3% in the immediate angiography group. On the one hand, this difference could be explained by early death rates before angiography could take place in the delayed group. On the other hand, CAG in this group was often withheld because

Table 5. Subgroups: Mean Total Costs (SD) in EURO

Subgroups	Immediate angiography group	Delayed angiography group	P value	Mean difference in total cost (95% CI)
Age<70 y (N=312)	34956±20162 N=150	37816±20836 N=162	0.22	-2860 (-7434 to 1714)
Age≥70 y (N=209)	31774±18804 N=115	27096±19730 N=94	0.08	4678 (-592 to 9949)
Female (n=111)	30 270±18 310 N=49	31 444±19 219 N=62	0.75	-1174 (-8306 to 5957)
Male (n=410)	34325±19859 N=216	34658±21584 N=194	0.87	-333 (-4357 to 3691)
Diabetes (N=95)	27 027±19 846 N=54	30 120±21 243 N=41	0.47	-3094 (-11509 to 5322)
Previous MI (n=143)	34 127±20 083 N=69	34 330±23 285 N=74	0.96	-203 (-7415 to 7009)
Previous CABG (n=63)	32 864±18 410 N=40	26 704±14 325 N=23	0.17	6160 (-2762 to 15081)
Patients who survived at 90 days (N=343)	40 857±18914 N=171	40 856±20119 N=172	1.00	0 (-4147 to 4148)
Patients who did not survive (N=172)	20 329±12 768 N=94	19 594±14 811 N=84	0.72	734 (-3346 to 4814)

CABG indicates coronary artery bypass graft; and MI, myocardial infarction.

Downloaded from http://ahajournals.org by on May 16, 2022

of an alternative noncardiac diagnosis. Patients who did survive and did not undergo angiography were those with neurological sequelae, comorbidities, and the use of noninvasive imaging. Thirty-five (13%) patients randomly assigned to the delayed angiography group underwent immediate angiography or PCI. This crossover to an immediate invasive procedure was explained by development of hemodynamic unstable conditions or dynamic ECG changes (ST-segment elevation). More PCI procedures were observed in the immediate group, which can be explained by the urge of the intervention team to treat a possible culprit lesion. The higher costs in the immediate strategy group were balanced by the higher duration of total length of stay and a higher (nonsignificant) cost of implantable cardioverter-defibrillator implantations in the delayed angiography group. Moreover, invasive costs are only a small part (8%–13%) of the total costs. This would explain the equivalence of mean total costs in both groups. Data regarding cardiac rehabilitation were not documented. However, the 1-year follow-up of the COACT trial did not show any difference with regard to rehospitalization, and no difference in cardiac function as assessed by echocardiography or cardiac magnetic resonance imaging was found between the immediate and the delayed invasive group.⁹ Therefore, the experimental and control group seem to converge with regard to disease burden, and consequently health care consumption, within a year.

Costs might be saved when evaluating only those patients with good neurological recovery. From the doctor's perspective, work during out-of-office hours should be taken into consideration. During these circumstances, staffing is limited and each coronary intervention is labor intensive, which eventually leads to more costs. There is no harm in terms of mortality when patients are scheduled in a controlled environment during daily office hours. Also, the duration of hospital admittance can be reduced hypothetically by better up-front diagnosis at the emergency department. A standard total-body computed tomography scan before ICU admittance might help in the early identification of a noncardiac cause of the cardiac arrest.

In patients with non–ST-segment–elevation acute coronary syndrome, cost-effectiveness trials without a setting of prehospital cardiac arrest reveal conflicting results. The TACTICS (Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy —Thrombolysis in Myocardial Infarction [TIMI] 18) trial randomly assigned 2220 patients with unstable angina pectoris or non–ST-segment–elevation myocardial infarction to an early invasive strategy or conservative management. Early CAG was preferred in terms of cost per year of life gained (\$12 739; range, \$8371–\$25 769) compared

with a conservative strategy.¹⁴ In a cost-effectiveness analysis in patients with non–ST-segment–elevation acute coronary syndrome included in the RITA-3 (Third Randomised Intervention Trial of Unstable Angina), mean incremental cost per quality-adjusted life year gained was most likely to benefit intermediate- and high-risk patients.¹⁵ However, in the FRISC (Fast Revascularisation During Instability in Coronary Artery Disease II) trial an early interventional strategy was not cost-effective in the short-term.¹⁶ In a more recent economic analysis, a strategy of early invasive CAG versus medical management showed no benefit in elderly patients (>75 years) diagnosed with non–ST-segment–elevation myocardial infarction in terms of cost-effectiveness and quality-adjusted life year gained.¹⁷

Exploratory subgroup analyses suggested that sex did not affect mean total costs. In a previous analysis, sex did not affect the clinical outcome as well.¹⁸

Several other and ongoing trials should be mentioned. Their results will add further knowledge regarding the timing of coronary angiography in patients with an OHCA. The TOMAHAWK (Immediate Unselected Coronary Angiography Versus Delayed Triage in Survivors of Out-of-Hospital Cardiac Arrest Without ST-Segment Elevation) trial results have recently been published and show no benefit of immediate versus delayed coronary angiography with regard 30-day risk of death. In contrast to the COACT trial, this study included both patients with shockable and nonshockable initial cardiac rhythms.^{19,20} The ongoing DISCO (Direct or Subacute Coronary Angiography in Out-of-Hospital Cardiac Arrest) study is an international multicenter trial recruiting 1006 patients with OHCA randomly assigned to CAG as soon as possible versus delayed/selective CAG.²¹ The ARREST (Advanced Reperfusion Strategies for Patients With Out-of-Hospital Cardiac Arrest and Refractory Ventricular Fibrillation) trial investigates direct transport to a cardiac arrest center and immediate CAG versus transport to the nearest emergency department.²² We are eagerly awaiting the results of these trials and a cost analysis. Also, health economic implications might add further evidence.

Study Limitations

The COACT trial was not powered on the outcome “cost,” and the present analysis is a post hoc analysis. Our cost analysis includes patient-level resource consumption only from the initial hospital stay. Neurological status at discharge (cerebral performance score, Glasgow Coma Scale score) did not differ between the treatment arms; therefore, we presume a similar rehabilitation process and subsequent similar work disability.

No quality-of-life scores were obtained at 90 days. However, RAND-36 quality-of-life scores were available at 12 months. As a result, we opted for a cost-consequence analysis instead of a cost-effectiveness analysis. In the latter case, it is essential that costs and effects are evaluated over the same time frame. Moreover, we chose to show only results based on empirical data from our research and therefore not to make assumptions about costs or effect behavior, which are not supported by empirical data (eg, extrapolation of cost to reach a 12-month time frame, or shrink quality-adjusted life year scores to a 90-day time frame).

CONCLUSIONS

During the initial hospital admittance, no significant difference in total health care costs is observed between the immediate and delayed coronary angiography strategy group in patients successfully resuscitated after OHCA with an initial shockable rhythm, but without ST-segment elevation. With respect to the higher invasive procedure costs in the immediate group, a strategy awaiting neurological recovery followed by coronary angiography and planned revascularization may be considered.

ARTICLE INFORMATION

Received May 12, 2021; accepted January 11, 2022.

Affiliations

Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands (C.C., J.L.B., N.v.R.); Department of Health Evidence, Radboudumc Technology Center for Health Economics, Nijmegen, the Netherlands (E.M.A.); Department of Cardiology, Amsterdam University Medical Center, location VUmc, Amsterdam, the Netherlands (E.M.S., G.N.J., N.W.v.d.H., J.S.L., N.v.R.); Department of Cardiology and Intensive Care Medicine, Erasmus Medical Centre, Rotterdam, the Netherlands (L.S.J., E.A.D.); Department of Cardiology (M.M.); and Department of Intensive Care Medicine (T.A.R.), Amphia Hospital, Breda, the Netherlands; Department of Cardiology (H.A.B.); and Department of Intensive Care Medicine (M.J.B.), Rijnstate Hospital, Arnhem, the Netherlands; Department of Cardiology (G.B.B.); and Department of Intensive Care Medicine (R.B.), Haga Hospital, Den Haag, the Netherlands; Department of Cardiology, Maasstad Hospital Rotterdam and University Medical Centre Utrecht, Utrecht, the Netherlands (G.J.V.); Department of Intensive Care Medicine, Maasstad Hospital, Rotterdam, the Netherlands (B.J.E.); Department of Cardiology, University Medical Center Groningen and University Medical Centre Utrecht, Groningen and Utrecht, the Netherlands (P.v.d.H.); Department of Critical Care, University Medical Center Groningen and Maastricht University Medical Center+, Groningen and Maastricht, the Netherlands (I.C.v.d.H.); ; Department of Intensive Care Medicine, Maastricht University Medical Center+, Maastricht, the Netherlands (I.C.v.d.H., T.S.D.); Department of Cardiology (M.V.); and Department of Intensive Care Medicine (J.J.v.d.H.), University Medical Center Utrecht, Utrecht, the Netherlands; Department of Intensive Care Medicine (B.B.); and Department of Cardiology (M.S.), Medisch Spectrum Twente, Enschede, The Netherlands; Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, the Netherlands (H.v.d.H.); Department of Cardiology (J.P.H.); and Department of Intensive Care Medicine (A.P.V.), Amsterdam University Medical Center, Amsterdam, the Netherlands; Department of Cardiology (M.A.V.); and Department of Intensive Care Medicine (B.v.d.B.), OLVG, Amsterdam, the Netherlands; Department of Cardiology (T.A.H.); and Department of Intensive Care Medicine (W.d.R.),

Noord West Ziekenhuisgroep, Alkmaar, the Netherlands; Department of Cardiology, Maastricht University Medical Center+, Maastricht, the Netherlands (T.S.D., H.J.C.); Department of Cardiology, Scheper Hospital, Emmen, the Netherlands (G.A.J.); Department of Cardiology, Haaglanden Medical Center, Den Haag, the Netherlands (P.V.O.); Department of Cardiology, Isala Hospital, Zwolle, the Netherlands (M.T.G.); Department of Cardiology, Tergooi Hospital, Blaricum, the Netherlands (K.P.); Department of Cardiology, Elisabeth-Tweesteden Hospital, Tilburg, the Netherlands (M.M.); Department of Intensive Care Medicine, Amsterdam University Medical Center, location VUmc, Amsterdam, the Netherlands (P.W.E.); and Department of Epidemiology and Data Science, Amsterdam University, Amsterdam, the Netherlands (P.M.v.d.V.).

Sources of Funding

This work was supported by unrestricted research grants from the Netherlands Heart Institute, Biotronik, and AstraZeneca.

Disclosures

None.

Supplemental Material

Data S1
Tables S1–S6

REFERENCES

- Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. *Resuscitation*. 2010;81:1479–1487. doi: 10.1016/j.resuscitation.2010.08.006
- Patel N, Patel NJ, Macon CJ, Thakkar B, Desai M, Rengifo-Moreno P, Alfonso CE, Myerburg RJ, Bhatt DL, Cohen MG. Trends and outcomes of coronary angiography and percutaneous coronary intervention after out-of-hospital cardiac arrest associated with ventricular fibrillation or pulseless ventricular tachycardia. *JAMA Cardiol*. 2016;1:890–899. doi: 10.1001/jamacardio.2016.2860
- Welsford M, Nikolaou NI, Beygui F, Bossaert L, Ghaemmaghami C, Nonogi H, O'Connor RE, Pichel DR, Scott T, Walters DL, et al. Part 5: acute coronary syndromes: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation*. 2015;132(Suppl 1):S146–S176. doi: 10.1161/CIR.0000000000000274
- Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42:1289–1367. doi: 10.1093/eurheartj/ehaa575
- Noc M, Fajadet J, Lassen JF, Kala P, MacCarthy P, Olivecrona GK, Windecker S, Spaulding C. Invasive coronary treatment strategies for out of hospital cardiac arrest: a consensus statement from the European Association for Percutaneous Cardiovascular Interventions. *EuroIntervention*. 2014;10:31–37. doi: 10.4244/EIJV10I1A7
- Patterson T, Perkins GD, Hassan Y, Moschonas K, Gray H, Curzen N, de Belder M, Nolan JP, Ludman P, Redwood SR. Temporal trends in identification, management, and clinical outcomes after out-of-hospital cardiac arrest: insights from the myocardial ischaemia national audit project database. *Circ Cardiovasc Interv*. 2018;11(6):e005346. doi: 10.1161/CIRCINTERVENTIONS.117.005346
- Lemkes JS, Janssens GN, Straaten H-V, Elbers PW, van der Hoeven NW, Tijssen JGP, Otterspoor LC, Voskuil M, van der Heijden JJ, Meuwissen M, et al. Coronary angiography after cardiac arrest: rationale and design of the COACT trial. *Am Heart J*. 2016;180:39–45. doi: 10.1016/j.ahj.2016.06.025
- Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, et al. Coronary angiography after cardiac arrest without ST-segment elevation. *N Engl J Med*. 2019;380:1397–1407. doi: 10.1056/NEJMoa1816897
- Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen MM, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, et al. Coronary angiography after cardiac arrest without ST-segment elevation: One-year outcomes of the COACT randomized clinical trial. *JAMA Cardiol*. 2020;5:1–8. doi: 10.1001/jamacardio.2020.3670

10. Verma BR, Sharma V, Shekhar S, Kaur M, Khubber S, Bansal A, Singh J, Ahuja KR, Nazir S, Chetrit M, et al. Coronary angiography in patients with out-of-hospital cardiac arrest without ST-segment elevation: a systematic review and meta-analysis. *JACC Cardiovasc Interv.* 2020;13:2193–2205. doi: 10.1016/j.jcin.2020.07.018
11. Petrie J, Easton S, Naik V, Lockie C, Brett SJ, Stümpfle R. Hospital costs of out-of-hospital cardiac arrest patients treated in intensive care; a single centre evaluation using the national tariff-based system. *BMJ Open.* 2015;5:e005797. doi: 10.1136/bmjopen-2014-005797
12. Geri G, Scales DC, Koh M, Wijeyesundera HC, Lin S, Feldman M, Cheskes S, Dorian P, Isaranuwachai W, Morrison LJ, et al. Healthcare costs and resource utilization associated with treatment of out-of-hospital cardiac arrest. *Resuscitation.* 2020;153:234–242. doi: 10.1016/j.resuscitation.2020.04.032
13. Hakkaart-van Roijen L, Van der Linden N, Bouwmans CAM, Kanters TA, Tan SS. *Costing manual: Methodology of costing research and reference prices for economic evaluations in healthcare [in Dutch: Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg]*. Institute for Medical Technology Assessment: Erasmus University Rotterdam; 2015. <https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg>
14. Mahoney EM, Jurkowitz CT, Chu H, Becker ER, Culler S, Kosinski AS, Robertson DH, Alexander C, Nag S, Cook JR, et al. Cost and cost-effectiveness of an early invasive vs conservative strategy for the treatment of unstable angina and non-ST-segment elevation myocardial infarction. *JAMA.* 2002;288:1851–1858. doi: 10.1001/jama.288.15.1851
15. Henriksson M, Epstein DM, Palmer SJ, Sculpher MJ, Clayton TC, Pocock SJ, Henderson RA, Buxton MJ, Fox KA. The cost-effectiveness of an early interventional strategy in non-ST-elevation acute coronary syndrome based on the RITA 3 trial. *Heart.* 2008;94:717–723. doi: 10.1136/hrt.2007.127340
16. Janzon M, Levin LA, Swahn E. Cost-effectiveness of an invasive strategy in unstable coronary artery disease; results from the FRISC II invasive trial. The Fast Revascularisation during InStability in Coronary artery disease. *Eur Heart J.* 2002;23(31–40): doi: 10.1053/euhj.2001.2695
17. Simpson J, Javanbakht M, Vale L. Early invasive strategy in senior patients with non-ST-segment elevation myocardial infarction: is it cost-effective? – a decision – analytic model and value of information analysis. *BMJ Open.* 2019;9(e030678):10.1136/bmjopen-2019-030678
18. Spoormans EM, Lemkes JS, Janssens GN, van der Hoeven NW, Jewball LSD, Dubois EA, van de Ven PM, Meuwissen M, Rijpstra TA, Bosker HA, et al. Sex differences in patients with out-of-hospital cardiac arrest without ST-segment elevation: a COACT trial substudy. *Resuscitation.* 2020;158:14–22. doi: 10.1016/j.resuscitation.2020.10.026
19. Desch S, Freund A, Graf T, Fichtlscherer S, Haake H, Preusch M, Hammer F, Akin I, Christ M, Liebetau C, et al. Immediate unselected coronary angiography versus delayed triage in survivors of out-of-hospital cardiac arrest without ST-segment elevation: design and rationale of the TOMAHAWK trial. *Am Heart J.* 2019;209:20–28. doi: 10.1016/j.ahj.2018.12.005
20. Desch S, Freund A, Akin I, Behnes M, Preusch MR, Zelniker TA, Skurk C, Landmesser U, Graf T, Eitel I, et al. TOMAHAWK investigators. angiography after out-of-hospital cardiac arrest without ST-segment elevation. *N Engl J Med.* 2021;385:2544–2553. doi: 10.1056/NEJMoa2101909
21. Lagedal R, Elfswén L, James S, Oldgren J, Erlinge D, Östlund O, Wallin E, Larsson I-M, Lilja G, Cronberg T, et al. Design of DISCO: direct or subacute coronary angiography in out-of-hospital cardiac arrest study. *Am Heart J.* 2018;197:53–61. doi: 10.1016/j.ahj.2017.11.009
22. Patterson T, Perkins A, Perkins GD, Clayton T, Evans R, Nguyen H, Wilson K, Whitbread M, Hughes J, Fothergill RT, et al. Rationale and design of: a randomized trial of expedited transfer to a cardiac arrest center for non-ST elevation out-of-hospital cardiac arrest: the ARREST randomized controlled trial. *Am Heart J.* 2018;204:92–101. doi: 10.1016/j.ahj.2018.06.016

SUPPLEMENTAL MATERIAL

Data S1.

Short explanation of the Dutch healthcare system

The healthcare system in Netherlands is based on social mandatory insurance for all residents and the Health Insurance Act (Zorgverzekeringswet ; ZVW) applies for hospital care.

Hospitals negotiate with the insurance companies to determine prices for procedures and other health services covered by the ZVW act and information on reimbursement tariffs is not publicly available. These health services with negotiable tariffs are referred to as ‘B-segment’ or ‘free-segment’ health care products. However, for certain expensive treatments (e.g. percutaneous coronary interventions, coronary artery bypass graft, ICD implantations) maximum standard tariffs apply. The Dutch Healthcare Authority (NZA) determines these tariffs by periodic cost surveys. For the analysis in this manuscript, these standard NZa tariffs are applied for invasive procedures and are outlined in supplementary table 1 - *the 2018 reference list of the Dutch National Healthcare Institute*

Table S1. The 2018 reference list of the Dutch National Healthcare Institute.

Health care resource use costs (EURO)	
ICU per day	2649
Ward/CCU per day (weighted average)	495
Invasive Procedures costs (EURO)	
Immediate CAG only	2800
Immediate CAG with acute PCI	4624
Immediate CAG with staged PCI	6074
Immediate CAG with acute PCI and staged PCI	7898
Immediate CAG with acute PCI and planned CABG	18061
Immediate CAG with planned CABG	16237
Delayed CAG only	2016
Delayed CAG with direct PCI	3274
Delayed CAG with staged PCI	5290
Delayed CAG with planned CABG	15453
ICD implantation	20446

ICU=intensive care unit, CCU=cardiac care unit, CAG=coronary angiography,

PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting,

ICD=implantable cardioverter-defibrillator

Table S2. Baseline characteristics (as treated).

Baseline characteristics	Immediate angiography (N=292)	Delayed angiography (N=229)	P-value
Age (years), median (IQR)	67 (57-75)	67 (57-75)	0.963
Male sex, N (%)	238 (82)	172 (75)	0.077
Hypertension, N (%)	139 (48)	112 (49)	0.854
Previous myocardial infarction, N (%)	74 (25)	69 (30)	0.224
Previous CABG, N (%)	38 (13)	25 (11)	0.458
Previous PCI, N (%)	48 (17)	54 (24)	0.043
Previous coronary artery disease, N (%)	100 (34)	87 (38)	0.376
Previous CVA, N (%)	21 (7)	13 (6)	0.481
Diabetes Mellitus, N (%)	57 (20)	38 (17)	0.380
Current Smoker, N (%)	61 (23)	54 (25)	0.550
Hypercholesterolemia	76 (26)	70 (31)	0.259
Peripheral artery disease, N (%)	20 (7)	19 (8)	0.540
Arrest witnessed, N (%)	235 (81)	172 (75)	0.141
Median time from arrest to BLS (min), IQR	2 (1-5)	2 (1-5)	0.881
Median time from arrest to ROSC (min), IQR	14 (8-20)	15 (8-20)	0.805
APACHE IV score	110 (90-128)	106 (83-130)	0.304

IQR= interquartile range, CABG=coronary artery bypass graft, PCI=percutaneous coronary intervention, CVA= cerebrovascular accident, BLS=basic life support, CAG=coronary angiography, APACHE = Acute Physiology And Chronic Health Evaluation, ROSC = return of spontaneous circulation

Table S3. Procedures (as treated).

Procedural characteristics	Immediate angiography (N=292)	Delayed angiography (N=229)	P-value
CAG performed, N (%)	291 (100)	133 (58)	<0.001
Revascularization, N (%)			
PCI	110 (38)	41 (18)	<0.001
CABG	21 (7)	18 (8)	0.774
Conservative treatment	164 (56)	170 (74)	<0.001
Survival, N (%)			
Survival at 90 days	192 (66)	151 (66)	0.965
Survival until hospital discharge	192 (66)	157 (69)	0.499

CAG=coronary angiography, IQR=interquartile range, PCI=percutaneous coronary

intervention, CABG=coronary artery bypass graft

Table S4. Health care costs (as treated). Mean total costs (SD) in EURO.

Health care costs	Immediate angiography (N=292)	Delayed angiography (N=229)	P-value	Mean difference in total cost (95% CI)
Total costs	34237 ± 19940	33071 ± 20796	0.516	1167 (-2357 to 4690)
Costs invasive coronary procedures	4610 ± 3538	2580 ± 4053	<0.001	2030 (1375 to 2684)
Costs intensive care unit length of stay	16858 ± 13856	15862 ± 12952	0.402	996 (-1339 to 3332)
Costs ward days	5067 ± 6389	5968 ± 7955	0.152	-901 (-2136 to 333)
Costs ICD implantations	7702 ± 9924	8660 ± 10125	0.279	-958 (-2695 to 778)

ICD=implantable cardioverter-defibrillator

Table S5. Baseline characteristics RAND36.

Baseline characteristics	RAND36 not available (n=88)	RAND36 available (n=230)	P-value
Age (years), median (IQR)	62 (51-70)	64 (55-72)	0.168
Male sex, N (%)	73 (83)	181 (79)	0.397
Hypertension, N (%)	42 (48)	100 (44)	0.515
Previous myocardial infarction, N (%)	24 (27)	53 (23)	0.431
Previous CABG, N (%)	14 (16)	19 (8)	0.045
Previous PCI, N (%)	19 (22)	38 (17)	0.292
Previous coronary artery disease, N (%)	32 (36)	73 (32)	0.433
Previous CVA, N (%)	3 (3)	11 (5)	0.765
Diabetes Mellitus, N (%)	14 (16)	22 (10)	0.110
Current Smoker, N (%)	25 (30)	49 (22)	0.162
Hypercholesterolemia	25 (28)	59 (26)	0.648
Peripheral artery disease, N (%)	4 (5)	18 (8)	0.302
Arrest witnessed, N (%)	76 (86)	181 (79)	0.120
Median time from arrest to BLS (min), IQR	2 (1-4)	2 (1-5)	0.983
Median time from arrest to ROSC (min), IQR	10 (8-15)	12 (7-20)	0.287
APACHE IV score	89 (68-106)	105 (84-121)	<0.001

IQR= interquartile range, CABG=coronary artery bypass graft, PCI=percutaneous coronary intervention, CVA= cerebrovascular accident, BLS=basic life support, CAG=coronary angiography, APACHE = Acute Physiology And Chronic Health Evaluation, ROSC = return of spontaneous circulation

Table S6. Total costs in patients with available RAND36.

RAND 36	Immediate angiography group	Delayed angiography group	P-value	Mean difference in total cost (95% CI)
RAND 36 available	40416 ± 17938	40239 ± 19567	0.933	177 (-3966 to 4320)