Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Desch S, Freund A, Akin I, et al. Angiography after out-of-hospital cardiac arrest without ST-segment elevation. N Engl J Med. DOI: 10.1056/NEJMoa2101909

SUPPLEMENTARY APPENDIX

TABLE OF CONTENTS

Study Organization

Principal Investigator

- Steffen Desch, MD; Heart Center Leipzig at the University of Leipzig and Leipzig Heart Institute, Leipzig, Germany + Universitäres Herzzentrum Lübeck, Lübeck, Germany + Deutsches Zentrum für Herz-Kreislauf-Forschung e.V. (DZHK), Germany

Steering Committee

- Steffen Desch, MD; Heart Center Leipzig at the University of Leipzig and Leipzig Heart Institute, Leipzig, Germany + Universitäres Herzzentrum Lübeck, Lübeck, Germany + Deutsches Zentrum für Herz-Kreislauf-Forschung e.V. (DZHK), Germany
- Anne Freund, MD; Heart Center Leipzig at the University of Leipzig and Leipzig Heart Institute, Leipzig, Germany + Deutsches Zentrum für Herz-Kreislauf-Forschung e.V. (DZHK), Germany
- Holger Thiele, MD; Heart Center Leipzig at the University of Leipzig and Leipzig Heart Institute, Leipzig, Germany

Project Management

- Kathrin Klinge, PhD; Zentrum für Klinische Studien, Universität Lübeck, Lübeck, Germany

Monitoring

- Sabine Brett; Zentrum für Klinische Studien, Universität Lübeck, Lübeck, Germany

Data Management, Statistical Analysis

- Inke R. König, PhD; Institut für Medizinische Biometrie und Statistik, Universität Lübeck, Lübeck, Germany
- Maren Vens, PhD; Institut für Medizinische Biometrie und Statistik, Universität Lübeck, Lübeck, Germany
- Frank Sandig; Institut für Medizinische Biometrie und Statistik, Universität Lübeck, Lübeck, Germany

Clinical Event Committee

- Ulrich Tebbe (chair), MD; Institut Klinische Forschung GmbH, Detmold, Germany
- Michael Oeff, MD; Brandenburg, Germany
- Karl Georg Häusler, MD; Universitätsklinikum Würzburg, Würzburg, Germany

Data Safety Monitoring Board

- Guido Michels (chair), MD; St.-Antonius-Hospital, Eschweiler, Germany
- Karl Werdan, MD; Universität Halle-Wittenberg, Halle, Germany
- Joachim Gerß (statistician), PhD; Universität Münster, Germany

Homepage

https://tomahawk.dzhk.de/

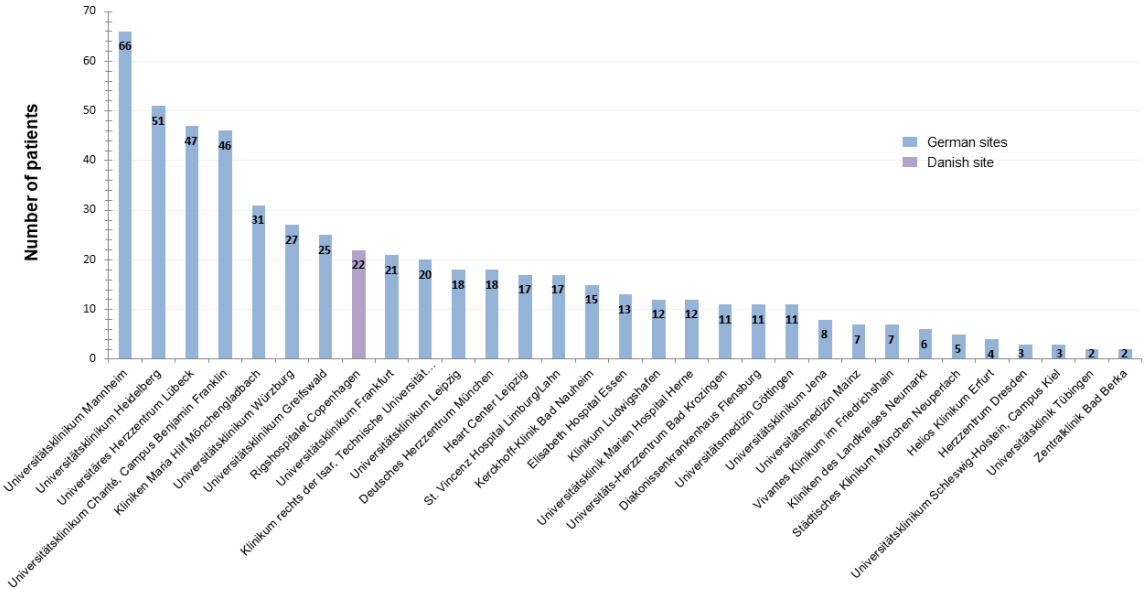
Study Sites and Investigators

1. Universitätsklinikum Mannheim, Mannheim, Germany: Ibrahim Akin, MD; Michael Behnes, MD; Uzair Ansari, MD (66 patients)
2. Universitätsklinikum Heidelberg, Heidelberg, Germany: Michael R. Preusch, MD; Jan Stiepak, MD (51 patients)
3. Universitäres Herzzentrum Lübeck, Lübeck, Germany: Tobias Graf, MD; Karolin Schmoll, MD; Georg Fuernau, MD; Thomas Stiermaier, MD; Ingo Eitel, MD; Suzanne de Waha-Thiele, MD (47 patients)
4. Universitätsklinikum Charité, Campus Benjamin Franklin, Berlin, Germany: Ulf Landmesser, MD; Carsten Skurk, MD; Thomas Wurster, MD; Wulf Knie, MD (46 patients)
5. Kliniken Maria Hilf, Mönchengladbach, Germany: Hendrik Haake, MD; Jürgen vom Dahl, MD; Christian Kotzlowski, MD (31 patients)
6. Universitätsklinikum Würzburg, Würzburg, Germany: Peter Nordbeck, MD; Octavian Maniuc, MD; Maria Moritz, MD (27 patients)
7. Universitätsklinikum Greifswald, Greifswald, Germany: Fabian Hammer, MD; Stephan B. Felix, MD; Peter Abel, MD; Daniel Beug, MD (25 patients)
8. Rigshospitalet, Copenhagen, Denmark: Christian Hassager, MD; Jesper Kjaergaard, MD; Thomas Engstrøm, MD (22 patients)
9. Universitätsklinikum Frankfurt, Frankfurt, Germany: Stephan Fichtlscherer, MD; Mariuca Vasa-Nicotera, MD; Stephan Heyl, MD (21 patients)
10. Klinikum rechts der Isar, Technische Universität, München, Germany: Jakob Ledwoch, MD; Christian Kupatt, MD; Petra Hoppmann, MD; Christian Bradaric, MD (20 patients)
11. Universitätsklinikum Leipzig, Leipzig, Germany: Karsten Lenk, MD; Ulrich Laufs, MD; Daniel Lavall, MD (18 patients)
12. Deutsches Herzzentrum, München, Germany: Michael Joner, MD; Patrick Mayr, MD; Anna-Lena Lahmann, MD (18 patients)
13. Heart Center Leipzig, University Hospital, Leipzig, Germany: Steffen Desch, MD; Holger Thiele, MD; Anne Freund, MD; Janine Pöss, MD; Mohamed Abdel-Wahab, MD; Philipp Lurz, MD; Alexander Jobs, MD (17 patients)
14. St. Vincenz Hospital, Limburg/Lahn, Germany: Stephan Steiner, MD; Stefanie Weigel, MD (17 patients)
15. Kerckhoff-Klinik, Bad Nauheim, Germany: Christoph Liebetrau, MD; Maren Weferling, MD; Catharina Hamm, MD (15 patients)

16. Elisabeth Hospital Essen, Germany: Ingo Voigt, MD; Thomas Schmitz, MD (13 patients)
17. Klinikum Ludwigshafen, Ludwigshafen, Germany: Uwe Zeymer, MD; Ralph Winkler, MD (12 patients)
18. Universitätsklinik Marien Hospital Herne, Klinikum der Ruhr-Universität Bochum, Herne, Germany: Michael Brand, MD; Hans-Joachim Trappe, MD (12 patients)
19. Universitäts-Herzzentrum, Bad Krozingen, Germany: Roland Schmitz, MD; Christian Valina, MD; Simon Schöchlin, MD (11 patients)
20. Diakonissenkrankenhaus Flensburg, Flensburg, Germany: Christoph Garlichs, MD; Jan Horstkotte, MD (11 patients)
21. Universitätsmedizin Göttingen, Göttingen, Germany: Claudius Jacobshagen, MD; Tim Seidler, MD; Gerd Hasenfuß, MD (11 patients)
22. Universitätsklinikum Jena, Jena, Germany: Sylvia Otto, MD; Sven Möbius-Winkler, MD; P. Christian Schulze, MD (8 patients)
23. Universitätsmedizin Mainz, Mainz, Germany: Tommaso Gori, MD (7 patients)
24. Vivantes Klinikum im Friedrichshain, Berlin, Germany: Stephan Kische, MD (7 patients)
25. Kliniken des Landkreises Neumarkt, Neumarkt, Germany: Peter Grewe, MD; Klaus Pels, MD (6 patients)
26. Städtisches Klinikum München Neuperlach, München, Germany: Stefan Sack, MD; Harald Mudra, MD (5 patients)
27. Helios Klinikum Erfurt, Erfurt, Germany: Niels Menck, MD; Norman Klöppner, MD; Stefan Löser, MD; Philipp Lauten, MD (4 patients)
28. Herzzentrum Dresden, Dresden, Germany: Axel Linke, MD; Norman Mangner, MD; Felix Woitek, MD (3 patients)
29. Universitätsklinikum Schleswig-Holstein, Campus Kiel, Kiel: Derk Frank, MD; Matthias Lutz, MD; Norbert Frey, MD (3 patients)
30. Universitätsklinik Tübingen, Tübingen, Germany: Tobias Geisler, MD; Michal Droppa, MD (2 patients)
31. Zentralklinik Bad Berka, Bad Berka, Germany: Marc-Alexander Ohlow, MD (2 patients)

There were 8 additional sites which were initiated but did not enroll patients.

Graphical presentation of enrollment by site



Cardiac versus general intensive care unit

Patients were treated in either cardiac intensive care units OR general medical intensive care units at each hospital. In case of a medical intensive care unit under the responsibility of the cardiology department, this was also counted as a cardiac intensive care unit.

Type of intensive care unit	Number of sites
Cardiac intensive care unit	17
General medical intensive care unit	14

Inclusion and Exclusion Criteria

Inclusion criteria

- Documented resuscitated OHCA of possible cardiac origin and return of spontaneous circulation
- Age ≥30 years
- Informed consent

Exclusion criteria

- ST-segment elevation or left bundle branch block
- No return of spontaneous circulation upon hospital admission
- Severe hemodynamic or electrical instability requiring immediate coronary angiography/intervention (delay clinically not acceptable)
    - Life-threatening arrhythmia possibly caused by acute myocardial ischemia
    - Cardiogenic shock (defined by clinical and hemodynamic criteria)
- Obvious extra-cardiac etiology such as traumatic brain injury, primary metabolic or electrolyte disorders, intoxication, overt hemorrhage, respiratory failure due to known lung disease, suffocation, drowning
- In-hospital cardiac arrest
- Known or likely pregnancy
- Participation in another intervention study interfering with the research questions of the TOMAHAWK trial

Definitions of Analysis Populations

Patients with invalid written informed consent and/or who withdrew informed consent themselves or by a legal representative and demanded the complete deletion of data were excluded from all data sets.

Intention-to-treat population

Patients were included in the intention-to-treat population if randomized to either treatment group. Patients severely violating any in- or exclusion criteria were excluded according to the statistical analysis plan. This affected a total of 4 patients violating exclusion criteria (2 with in-hospital cardiac arrest and 2 with ST-segment elevation myocardial infarction). In one STEMI case the study physicians were unaware of the fact that STEMI is an exclusion criterion. In the second case, the patient was presented to the emergency room by emergency medical service presenting two post-resuscitation ECGs. Randomization was performed after evaluation of one of the two ECGs showing no significant ST-elevation. However, the second presented ECG showed significant ST-segment elevations and the patient was subsequently treated for STEMI. In the 2 cases with in-hospital cardiac arrest the study physicians were unaware of the fact that in-hospital cardiac arrest is an exclusion criterion.

The decision to exclude patients severely violating inclusion or exclusion criteria from the intention-to-treat population in the final analysis was made by the Steering Committee and the lead statistician upon the first cases (first STEMI, first in-hospital cardiac arrest) and was constituted in the statistical analysis plan. This was based on the consideration, that these patients were included by human error in an emergency setting. Risk of introducing bias by exclusion of these patients post-randomization was therefore seen as minimal. Mistakenly inclusion of the patients was reported immediately by the respective study sites without the influence of possible events occurring in the further clinical course.

Per-protocol population

The per-protocol population includes all patients who received treatment according to the initial allocation and as described in the protocol. However, to account for potential immortal time bias, patients assigned to immediate angiography who died before the start of angiography (and did thus not receive the allocated treatment) were still included in the per-protocol population.

Safety population

The safety population was used for the analysis of safety events. Patients in the safety analysis were analyzed as treated, i.e.

- Patients in group 1 (immediate angiography) who did not undergo coronary angiography but survived for up to 24h after randomization were analyzed as patients in group 2 (delayed/selective angiography).
- Patients in group 2 (delayed/selective angiography) who underwent coronary angiography before a minimum delay of 24 h after the onset of cardiac arrest and did not meet any of the criteria under which coronary angiography was allowed ≤ 24 h were analyzed as patients in group 1 (immediate angiography).

Sample Size Calculation

Sample size determination was based on a registry study reporting on clinical outcome according to the timing of angiography exclusively in OHCA survivors without ST-segment elevation.[1] The study reported a 30-day mortality of 34% in patients undergoing emergency angiography and 46% with delayed/selective angiography. For sample size calculation, the following parameters were used:

- Significance level $\alpha = 0.05$ (two-sided)
- Treatment allocation 1:1
- Rate in immediate angiography group = 0.34 per 30 days, rate in delayed/selective angiography group =0.46 per 30 days
- Accrual time = 0.001
- Dropout rate per group = 0.05 per 30 days
- Anticipated effect size hazard ratio = 0. 674
- Power at anticipated effect at final analysis $1-\beta = 0.8$.

In addition, one interim analysis was planned at an information rate of 0.5 using the alpha spending function of Hwang et al. with $\gamma = -0.13$ which is equivalent to using a group sequential plan according to Wang and Tsiatis which minimizes the average sample size under the null hypothesis at $\delta = 0.41$.[2] Thus, a total of 558 patients (i.e. 279 subjects per group) were calculated with an interim analysis for efficacy after 109 events. The significance level at interim analysis was 0.0242 (two-sided) and 0.0342 (two-sided) at final analysis. The power with the anticipated effect at interim analysis was 0.42. Sample size calculation was performed using Addplan version 6.1.

Additional Details of Statistical Analysis

For binary secondary endpoints relative risks and corresponding 95% confidence intervals using the score method were used. No multiplicity adjustments were made to the confidence intervals. Continuous secondary outcomes were analyzed giving the Hodges-Lehmann estimator for location shift median of differences and corresponding 95% Hodges-Lehmann confidence intervals.

Since the primary endpoint is a time-to-event endpoint no imputation was performed.

All statistical analyses were pre-specified in a statistical analysis plan and performed by the Institute for Medical Biometry and Statistics at the University of Lübeck using SAS® 9.4. Figures were created using R 3.5.1 or higher.

Handling of Missing Values, Missing Data

As the primary endpoint of all-cause mortality was assessed early after the onset of the disease (at 30 days), it was not expected that there would be a relevant proportion of patients with missing primary endpoint data. Time to event endpoints were considered censored at the last observation, if this did not constitute an event. Thus, there were no missing values, and patients who were lost to follow-up were treated equal to those with administrative censoring. The standard assumption underlying this decision is that the censoring is non-informative of survival. In the present study, this means that it was assumed that patients did not favorably drop out of the study because they were either too ill to further participate or because they no longer required treatment. In the present cohort of patients, this seems highly plausible.

Nonetheless, additional sensitivity analyses were performed to compare the result of the primary endpoint with two alternative scenarios (in line with Rothmann et al.)[3]: 1) worst-case scenario: In this scenario, lost-to-follow-up patients are set to have died at the time point of the last observation, instead of being censored. This therefore assumes an informative drop out in the direction that patients drop out because of mortality that is not assessed within the study; 2) worst-comparison scenario: Again, lost-to-follow-up patients are set to have died at the time point of the last observation, instead of being censored. However, to mimic the most extreme case, this is only done in patients in the experimental group, thus artificially increasing the possible effect to its maximum. This therefore assumes that there is a non-informative drop out of patients in the control group, but an informative drop out of patients in the experimental group. As suggested by Walton[4], both analyses can be performed to assess the robustness of the original results, with the worst-comparison analysis invoking maximal stress to the results.

Both analyses were performed with the following results: Within the worst-case scenario, the original HR shifted from 1.28 (1.00-1.63) to 1.24 (0.97-1.57), thus strengthening the primary result. Within the worst-comparison scenario, the HR then shifted to 1.35 (1.06-1.72). Thus, the first analysis shifted the result further in the direction of the null hypothesis, the latter slightly in the direction of the alternative hypothesis, as expected. Nominally, the latter scenario would be associated with a p value below significance, but the estimated HR is still well within the original confidence interval, and all three confidence intervals are largely overlapping. Thus, also keeping in mind that the worst-comparison scenario makes strong and clinically unrealistic assumptions about the informative drop out only in the experimental group, these results can be viewed as confirmation of the robustness of the original results.
To minimize the risk of differential rates of missing data across treatment arms as well as the overall amount of missing data, missingness in core variables was compared descriptively between sites and arms.
Variables with >25% missing values in the complete respective analysis set are used in univariate description only without imputation. For all non-time-to-event outcomes, missing values were rare, thus a detailed investigation of the missingness mechanism would not be robust and biases in a complete case analysis unlikely. We therefore refrained from imputation of any of these exploratory endpoints.

For the secondary endpoint “Severe neurological deficit (CPC score 3-5) at 30 days, an additional sensitivity analysis was performed by calculating relative risk estimates with 95% confidence intervals after using different imputation methods:

1. Median imputation: All missings were imputed by the median, i.e., the more frequent category, in this case “no severe neurological deficit”. This resulted in RR 1.53 (0.84-2.80).
2. Worst case imputation for all: All missings were imputed by the worst outcome, i.e., “severe neurological deficit”. This resulted in RR 1.13 (0.71-1.78).
3. Worst case imputation (“severe neurological deficit”) for missings in experimental group, best case imputation (“no severe neurological deficit”) for missings in control group. This resulted in RR 2.04 (1.16-3.59).

Thus, scenarios 1 and 2 validate the original result. Scenario 3 assumes the worst case in that the worst outcome is assumed for the experimental but the best outcome for the control group. This assumption can be considered unlikely for our study setting.
The CPC score was only assessed in patients alive at 30 days.
To further illustrate the clinical profile of patients alive and not lost-to-follow-up at 30 days (in which the CPC score was assessed) the baseline characteristics of surviving patients are shown below.

	Immediate angiography (n=113)	Delayed/selective angiography (n=131)
Age (years); median (IQR)	65 (52 - 73)	65 (56 - 76)
Female sex; n/total (%)	28/113 (24.8)	40/131 (30.5)
Body mass index (kg/m²); median (IQR)	26.2 (24.5 - 27.8)	26.1 (24.5 - 29.3)
Diabetes mellitus; n/total (%)	21/107 (19.6)	28/127 (22.1)
Hypertension; n/total (%)	60/105 (57.1)	76/119 (63.9)
Current smoker; n/total (%)	26/62 (41.9)	28/75 (37.3)
Dyslipidemia; n/total (%)	27/100 (27.0)	42/118 (35.6)
Known coronary artery disease; n/total (%)	30/100 (30.0)	51/117 (43.6)
Prior myocardial infarction; n/total (%)	19/104 (18.3)	27/115 (23.5)
Prior percutaneous coronary intervention; n/total (%)	16/103 (15.5)	33/113 (29.2)
Prior coronary bypass surgery; n/total (%)	8/106 (7.6)	18/122 (14.8)
Known periperal artery disease; n/total (%)	8/97 (8.3)	9/114 (7.9)
Prior stroke or transitory ischemic attack; n/total (%)	9/103 (8.7)	10/114 (8.8)
Arrest witnessed; n/total (%)	102/113 (90.3)	115/127 (90.6)
Shockable first monitored rhythm; n/total (%)	74/102 (72.6)	93/122 (76.2)
Bystander cardiopulmonary resuscitation; n/total (%)	68/96 (70.8)	88/115 (76.5)
Time from arrest to basic life support (min); median (IQR)	1.5 (0.5 - 7)	1 (0 - 5)
Time from arrest to return of spontaneous circulation (min); median (IQR)	17 (10 - 26)	16 (10 - 25)
Prehospital extracorporaeal life support; n/total (%)	2/110 (1.8)	1/131 (0.8)
Glasgow Coma Scale; median (IQR)	3 (3 - 3)	3 (3 - 3)
Systolic blood pressure on admission (mmHg); median (IQR)	115 (100 - 130)	115 (100 - 131)
Left ventricular ejection fraction on admission; median (IQR)	48 (40 - 56)	42 (30 - 50)
Lab values on admission		
ph; median (IQR)	7.27 (7.20 - 7.33)	7.29 (7.20 - 7.35)
Lactate (mmol/L); median (IQR)	3.6 (1.7 - 6.3)	3.9 (2.3 - 5.8)
Creatinine (µmol/L); median (IQR)	103 (88 - 124)	101 (88 - 124)
Troponin T (µg/L); median (IQR)	0.08 (0.03 - 0.19)	0.05 (0.03 - 0.10)
Troponin I (µg/L); median (IQR)	0.10 (0.03 - 0.40)	0.20 (0.09 - 0.58)
Blood glucose (mmol/L); median (IQR)	11.2 (9.0 - 13.3)	10.8 (8.8 - 13.7)

Informed Consent

In the acute setting upon hospital admission, two physicians assessed the supposed patient's willingness to participate in the study. If there was agreement between the two physicians, the patient was then randomized. In case a legal representative had been appointed in the past, this person was asked to provide informed consent. In the subacute stage, the patient (if possible) or an authorized legal representative was asked for final informed consent.

The informed consent process was slightly different in the participating center in Denmark because of national ethical and legal requirements. In Denmark, patients could be randomized acutely without formal consent at the time of randomization. Thereafter, the study physician had to obtain written informed consent from a near relative as soon as possible (but after randomization). In addition and also after randomization, acceptance from a physician who knew about the trial - but who was not involved in the trial - was also necessary. If the patient woke up with an acceptable neurological status written informed consent had to be obtained from the patient to keep him/her in the trial and use the data.

Endpoint List

Endpoint	*Reported in current manuscript*
Primary endpoint	
30-day all-cause mortality	Yes
Secondary endpoints	
Myocardial infarction at 30 days	Yes
Myocardial infarction (possibly recurrent) at 6 and 12 months	No
Severe neurological deficit (CPC categories 3–5) at 30 days*	Yes
Severe neurological deficit (CPC categories 3–5) at 6 and 12 months*	No
Composite endpoint of all-cause mortality and/or severe neurological deficit at 30 days	Yes
All-cause death at 6 and 12 months	No
Rehospitalization for congestive heart failure at 30 days	Yes
Rehospitalization for congestive heart failure at 6 and 12 months	No
Length of ICU stay	Yes
Length of hospital stay†	No
Serial SAPS II‡	Yes
Peak release of myocardial enzymes	Yes
Quality of life at 6 and 12 months	No
Safety endpoints	
Moderate and severe bleeding (BARC definition types 2-5) at 30 days	Yes
Stroke at 30 days	Yes
Acute renal failure requiring renal replacement therapy at 30 days	Yes

BARC=Bleeding Academic Research Consortium

*The Cerebral Performance Category (CPC) score evaluates neurological outcome and ranges from 1 to 5. Scores of 3, 4 and 5 reflect poor outcome (severe neurological disability, persistent vegetative state or brain death).

†Length of hospital stay will be reported at a later time point since a relevant percentage of patients was still in hospital at 30 days (immediate angiography 38/257 [14.8%]; delayed/selective angiography: 42/253 [16.6%]).

‡The Simplified Acute Physiology Score (SAPS) II measures the severity of disease in patients admitted to intensive care units and ranges from 0 (best) to 163 (worst).

Outcome Definitions

Myocardial reinfarction

The definitions of myocardial infarction and reinfarction were based on the 3rd Universal Definition of Myocardial Infarction.[5] Thus, myocardial reinfarction was defined according to the specific situation.

Re-MI ***<24 h***	**Re-MI** ***24 h – 7 days***	**Re-MI** ***>7 days***
Symptoms, such as angina pectoris for ≥20 minutes, most likely due to myocardial ischemia ***and or*** new ST-elevation ≥1 mm in ≥2 contiguous leads or new left bundle branch block ***or*** angiographic evidence of re-occlusion of a previously open coronary artery or graft	Symptoms, such as angina pectoris for ≥20 minutes, most likely due to myocardial ischemia ***and or*** if cardiac markers are still elevated, new increase ≥20% from the last non-normalized measurement ***or*** if cardiac markers are normalized, application of the "universal definition" for myocardial infarction (see next column)	"Universal definition" for myocardial infarction **1.** Rise and/or fall of cardiac biomarkers above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following: • Symptoms of ischemia • ECG changes indicative of new ischemia • Development of pathological Q waves in ECG • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality **2.** Sudden, unexpected cardiac death with ST-elevation and presumably new LBBB or evidence of fresh thrombus by coronary angiography, but death

Re-MI *<24 h*	Re-MI *24 h – 7 days*	Re-MI *>7 days*
		occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. **3.** Peri-PCI myocardial infarction: increases of biomarkers > 3 of the upper reference level **4.** Peri-CABG myocardial infarction: increases of biomarkers > 5 of the upper reference level plus new pathological Q waves or new LBBB or angiographically documented new graft or native coronary artery occlusion **5.** Pathological findings of acute myocardial infarction

Bleeding

Bleeding was classified according to the BARC criteria:[6]

Type	Bleeding definition
Type 0	no bleeding
Type 1	bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2	any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the

	following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3	
Type 3a	Overt bleeding plus hemoglobin drop of 3 to <5 g/dL (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding
Type 3b	Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial hemorrhage (does not include stroke, microbleeds or hemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision
Type 4	CABG-related bleeding Perioperative intracranial bleeding within 48 h Reoperation after closure of sternotomy for the purpose of controlling bleeding Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period† Chest tube output ≥2L within a 24-h period
Type 5	Fatal bleeding
Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Stroke

Stroke was defined as an acute new neurological deficit ending in death or lasting longer than 24 hours, and classified by a physician as a stroke.

1. Primary hemorrhagic - defined as an intracerebral hemorrhage or subdural hematoma
    a. Intracerebral hemorrhage - Stroke with focal collections of intracerebral blood seen on brain imaging (CT or MRI) or a post-mortem examination, not felt to represent hemorrhagic conversion. Subarachnoid hemorrhage should be included in this category.
    b. Subdural hematoma - High density fluid collection in subdural space on brain images or blood in the subdural space on autopsy.
2. Non-hemorrhagic cerebral infarction - Stroke without focal collections of intracerebral blood on brain imaging.
3. Non-hemorrhagic infarction with hemorrhagic conversion - Cerebral infarction with blood felt to represent hemorrhagic conversion and not a primary hemorrhage.
4. Uncertain - Any stroke without brain imaging (CT or MRI) or autopsy documentation of type, or if tests are inconclusive.

Neurological outcome

Defined according to the Cerebral Performance Categories (CPC) scale[7]

CPC grade	
1	Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.
2	Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.
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.
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.
5	Brain death: apnea, areflexia, EEG silence, etc.

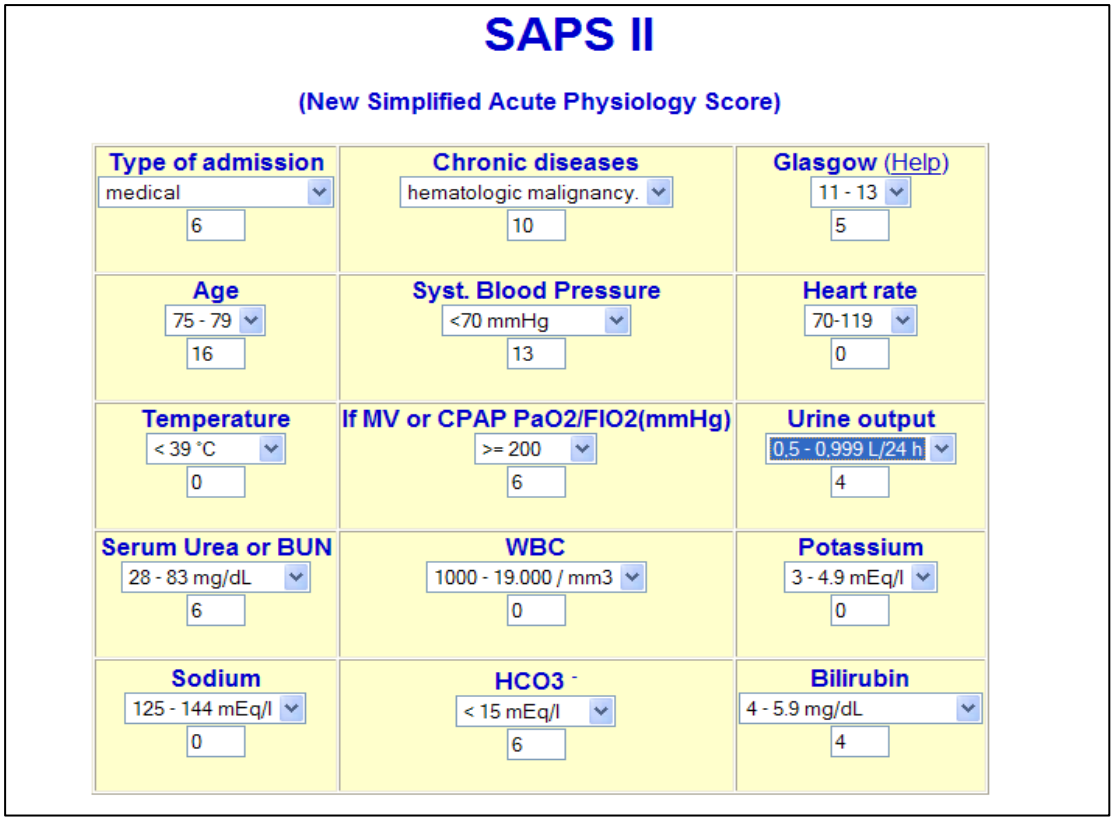
New congestive heart failure

Occurrence of congestive heart failure after hospital discharge:

Defined as re-hospitalization due to new or worsening heart failure >24 h after hospital discharge.

Simplified Acute Physiology Score II (SAPS II)

The disease severity was assessed by the SAPS II (http://www.sfar.org/scores2/saps2.html).[8] This score is evaluated on a routine basis in all hospitals in Germany. Individual parameters of the SAPS II are as follows:



SAPS II

(New Simplified Acute Physiology Score)

Type of admission medical 6	**Chronic diseases** hematologic malignancy. 10	**Glasgow** (Help) 11 - 13 5
Age 75 - 79 16	**Syst. Blood Pressure** <70 mmHg 13	**Heart rate** 70-119 0
Temperature < 39 °C 0	**If MV or CPAP PaO2/FIO2(mmHg)** >= 200 6	**Urine output** 0,5 - 0,999 L/24 h 4
Serum Urea or BUN 28 - 83 mg/dL 6	**WBC** 1000 - 19.000 / mm3 0	**Potassium** 3 - 4.9 mEq/l 0
Sodium 125 - 144 mEq/l 0	**HCO_3^-** < 15 mEq/l 6	**Bilirubin** 4 - 5.9 mg/dL 4

Interim analysis

An interim analysis was performed after 109 primary endpoint events. Based on the interim analysis a dedicated Data Safety Monitoring Board gave a formal recommendation to either continue or stop/pause the trial based on the following criteria:

- an observed difference in the primary outcome measure between treatment groups in the interim analysis according to predefined rules ($p<0.0242$),
- an observed difference in serious adverse events between treatment groups,
- the evaluation of safety reports shows that the risk-benefit ratio is no longer considered acceptable,
- results from other studies show benefit or harm with any of the interventions and the risk-benefit ratio is no longer considered acceptable.

In total, 222 patients were included in the interim analysis. The endpoint of all-cause death occurred in 57/112 patients (50.9%) assigned to immediate coronary angiography and in 52/110 (47.3%) allocated to delayed/selective coronary angiography. All-cause death was not significantly different between treatment groups (hazard ratio 1.09; 95% confidence interval 0.74-1.60; log-rank p=0.4643). There were no safety concerns. Thus, the Data Safety Monitoring Board decided not to stop the trial.

Reasons for Crossover

A total of 46 patients underwent coronary angiography within the first 24h albeit randomized to the delayed/selective strategy. Reasons were as follows:

Crossovers compatible with study protocol (see study protocol for definitions)

#		#	
1	Development of cardiogenic shock	13	Development of cardiogenic shock
2	New ST-segment elevation	14	Large myocardial injury
3	New ST-segment elevation	15	Development of cardiogenic shock
4	New ST-segment elevation	16	Development of cardiogenic shock
5	Development of cardiogenic shock	17	Development of cardiogenic shock
6	Development of cardiogenic shock	18	Large myocardial injury
7	Development of cardiogenic shock	19	Development of cardiogenic shock
8	Development of cardiogenic shock	20	New ST-segment elevation
9	Electrical instability	21	Large myocardial injury
10	Large myocardial injury	22	Development of cardiogenic shock
11	Large myocardial injury	23	Electrical instability
12	New ST-segment elevation	24	Large myocardial injury

Crossovers violating study protocol

For the majority of crossover patients not fulfilling the protocol-specified allowed reasons for early catheterization the study sites could not deliver a plausible reason for the protocol violation.

#		#	
1	No plausible reason provided by study site	12	No plausible reason provided by study site
2	No plausible reason provided by study site	13	No plausible reason provided by study site
3	Increase in biomarkers of myocardial injury without fulfilling the definition of large myocardial injury as defined in the protocol	14	No plausible reason provided by study site
4	No plausible reason provided by study site	15	No plausible reason provided by study site
5	No plausible reason provided by study site	16	No plausible reason provided by study site

6	No plausible reason provided by study site	17	No plausible reason provided by study site
7	Increase in biomarkers of myocardial injury without fulfilling the definition of large myocardial injury as defined in the protocol	18	No plausible reason provided by study site
8	No plausible reason provided by study site	19	Awake patient with diagnosis of non ST-elevation myocardial infarction
9	Increase in biomarkers of myocardial injury without fulfilling the definition of large myocardial injury as defined in the protocol	20	No plausible reason provided by study site
10	No plausible reason provided by study site	21	No plausible reason provided by study site
11	Emergency surgery for aortic aneurysm. Interdisciplinary decision to perform preoperative coronary angiography.	22	No plausible reason provided by study site

There was also 1 patient in the immediate group who did not receive coronary angiography within the first 24 hours.

The reason was as follows:

#	
1	No plausible reason provided by study site

Adverse Events and Serious Adverse Events

Adverse events and serious adverse events of any nature were collected over the study course. A total of 328 serious adverse events were reported in the immediate angiography group and 295 in the delayed/selective group. Further, a total 209 adverse events were reported in the immediate angiography group and 191 in the delayed/selective group.

Additional analyses incorporating competing risks

Additional analyses for several endpoints were performed accounting for the competing risk of all-cause mortality. Effect sizes were calculated as estimation of hazard ratios with corresponding 95% confidence intervals from the Cox model and estimation of hazard ratios with corresponding 95% confidence intervals while taking the competing risk of mortality into account using the approach by Fine & Gray.[9] Results are shown in the table below, where the original results are shown as relative risks (RR), and the new results as hazard ratios (HR) or hazard ratios with competing risks (HR-C):

	Immediate angiography (n=265)	Delayed/selective angiography (n=265)	Effect Size (95% CI)
Secondary endpoints (efficacy) Myocardial infarction; n/total (%)	0/248 (0)	2/250 (0.8)	RR 0 (0-1.93) HR 0 (0-inf) HR-C 0 (0-inf)
Rehospitalization for congestive heart failure; n/total (%)	1/246 (0.4)	1/249 (0.4)	RR 1.00 (0.19-1.85) HR 1.01 (0.06-16.13) HR-C 1.01 (0.06-16.06)
Secondary endpoints (safety) Moderate and severe bleeding (BARC definition types 2-5); n/total (%)	12/260 (4.6)	8/232 (3.4)	RR 1.34 (0.57-3.14) HR 1.34 (0.55-3.28) HR-C 1.34 (0.55-3.27)
Stroke; n/total (%)	4/258 (1.6)	5/242 (2.1)	RR 1.13 (0.33-3.84) HR 1.11 (0.22-5.50) HR-C 1.11 (0.22-5.46)
Acute renal failure requiring renal replacement therapy; n/total (%)	49/259 (18.9)	38/241 (15.8)	RR 1.14 (0.78-1.68) HR 1.21 (0.78-1.86) HR-C 1.21 (0.79-1.86)

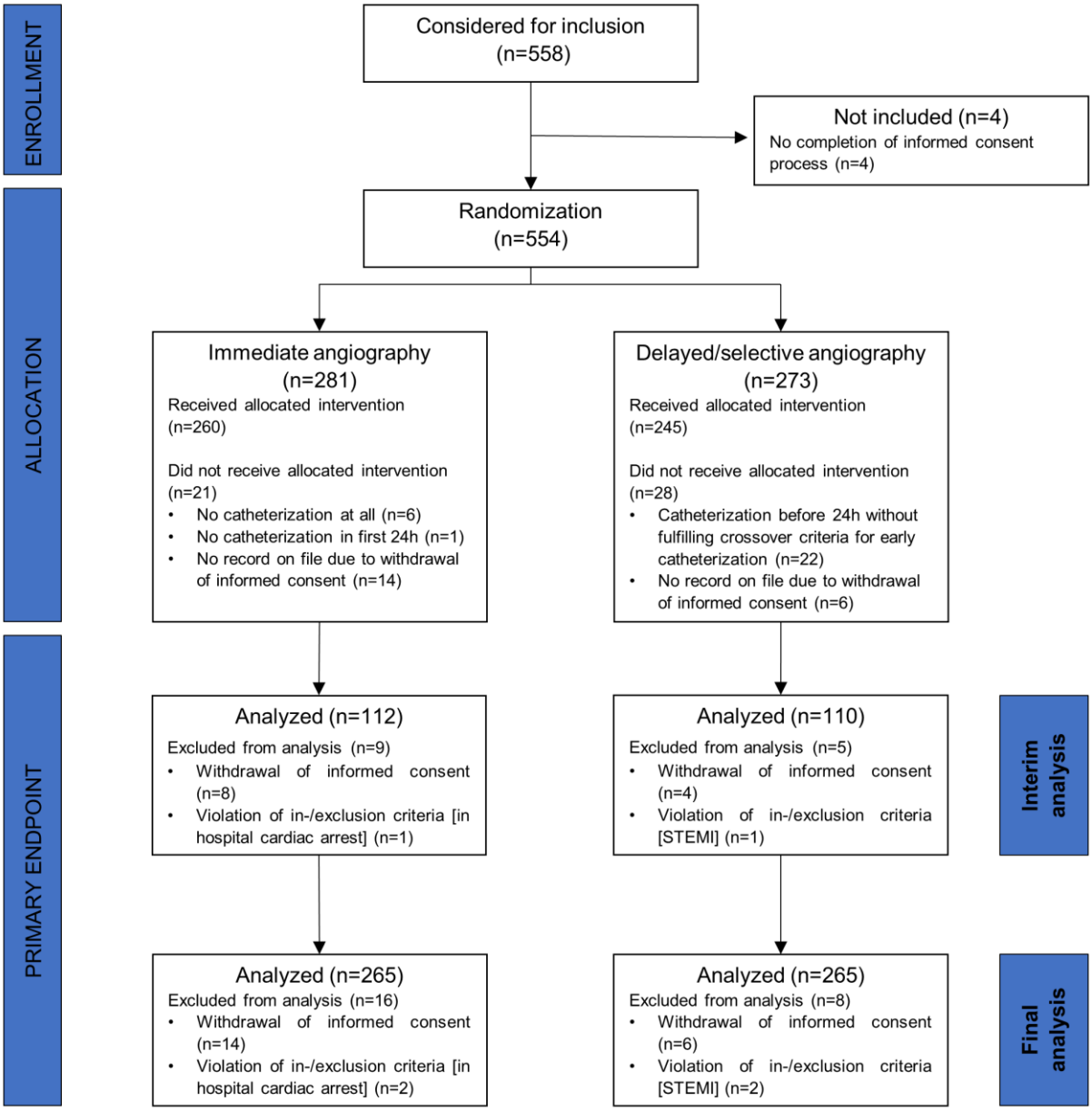
CI=confidence interval; RR=relative risk; HR=hazard ratio; HR-C=hazard ratio with competing risks; BARC=Bleeding Academic Research Consortium

The results show that the effect estimators are very similar. Also, they show that the estimation from both time-to-event models is less precise, owing to the small number of

events, thus leading to wider confidence intervals. In the case of myocardial infarction, the time-to-event models did not converge, given that no event was observed in one group.

Supplementary Figures

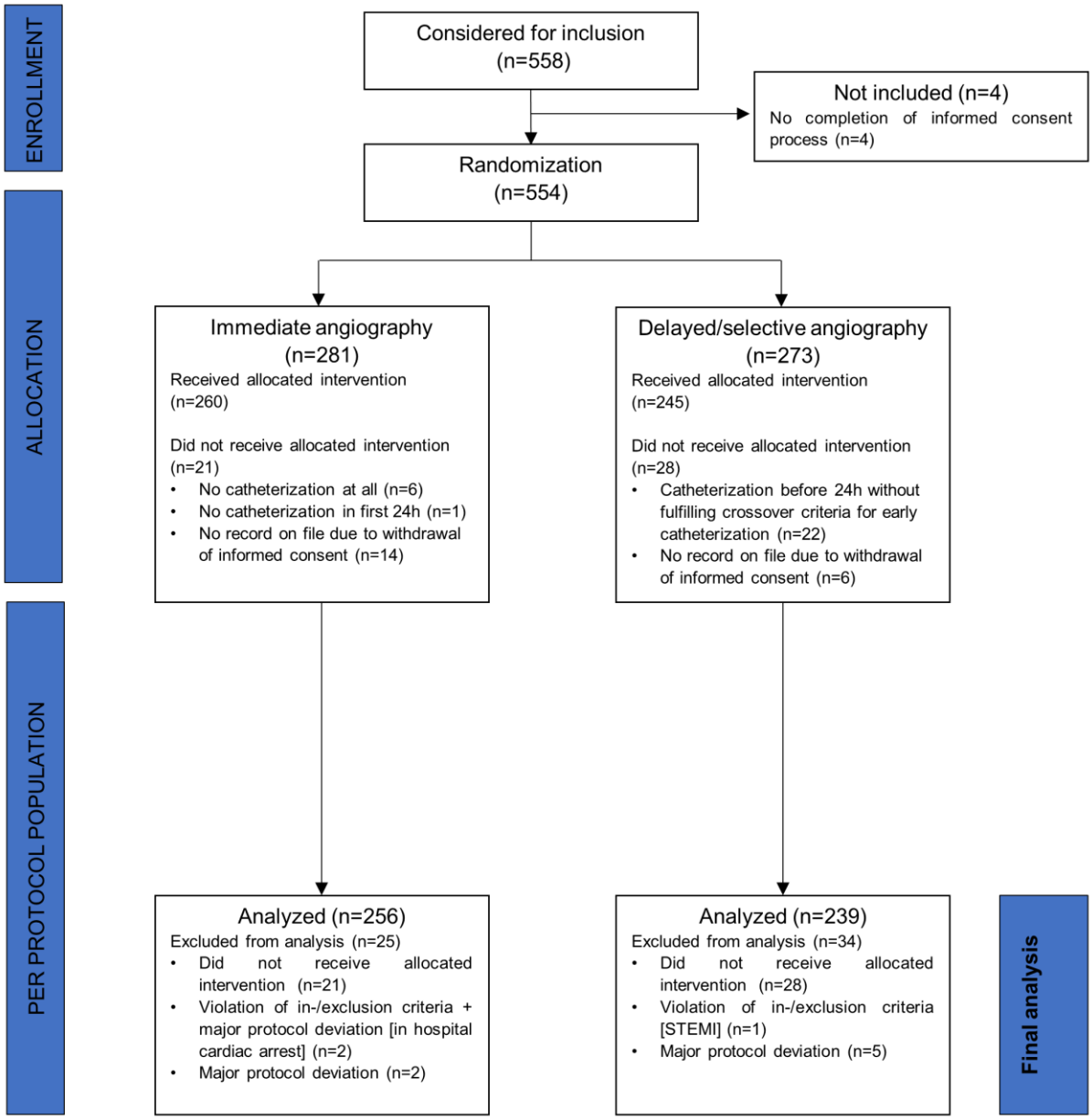
Figure S1 – Study Flow Chart for Intention-to-Treat Population*



*Please see also Table S5 for further information on study screening.

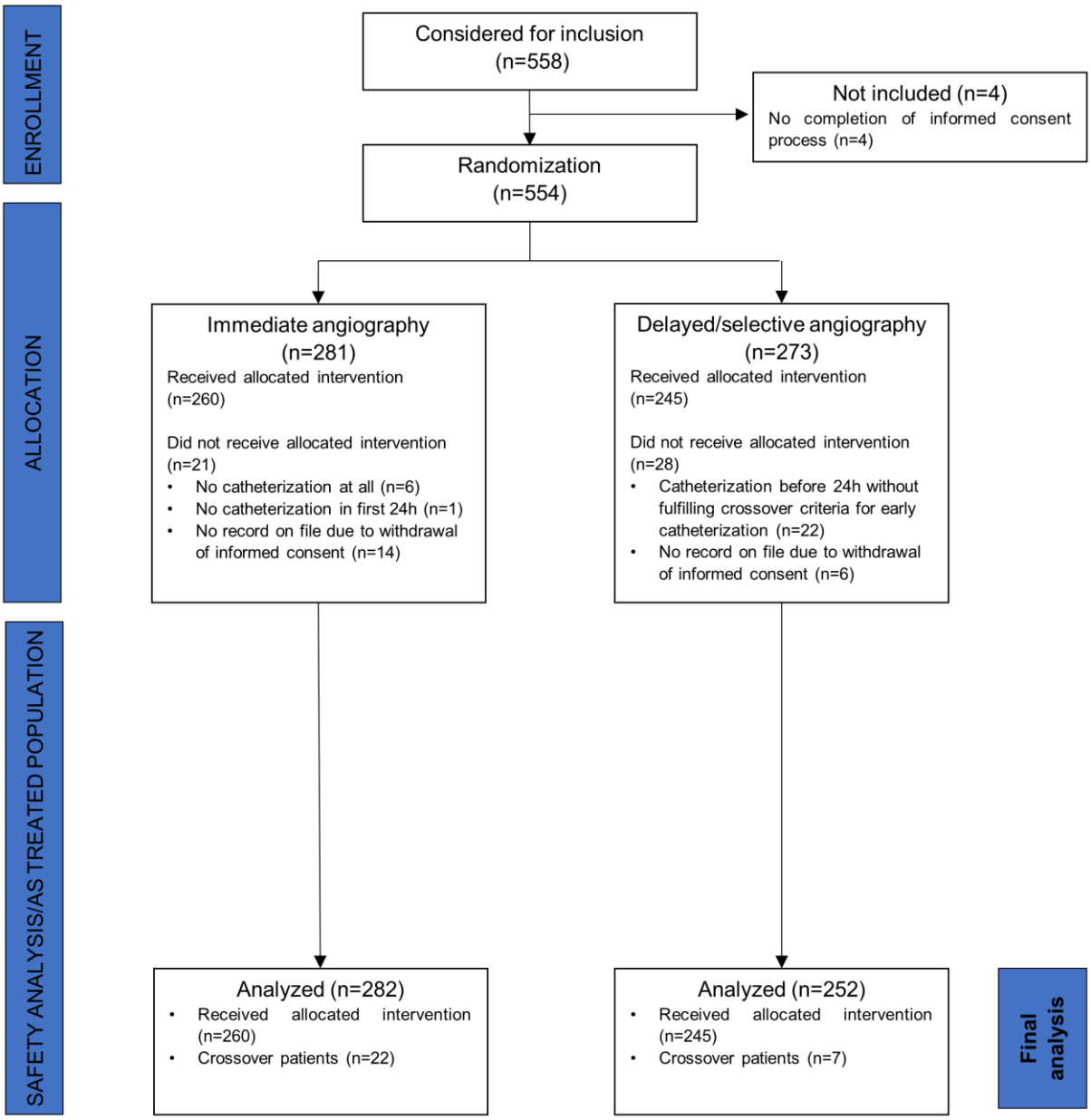
STEMI=ST-elevation myocardial infarction

Figure S2 – Study Flow Chart for Per-Protocol Population



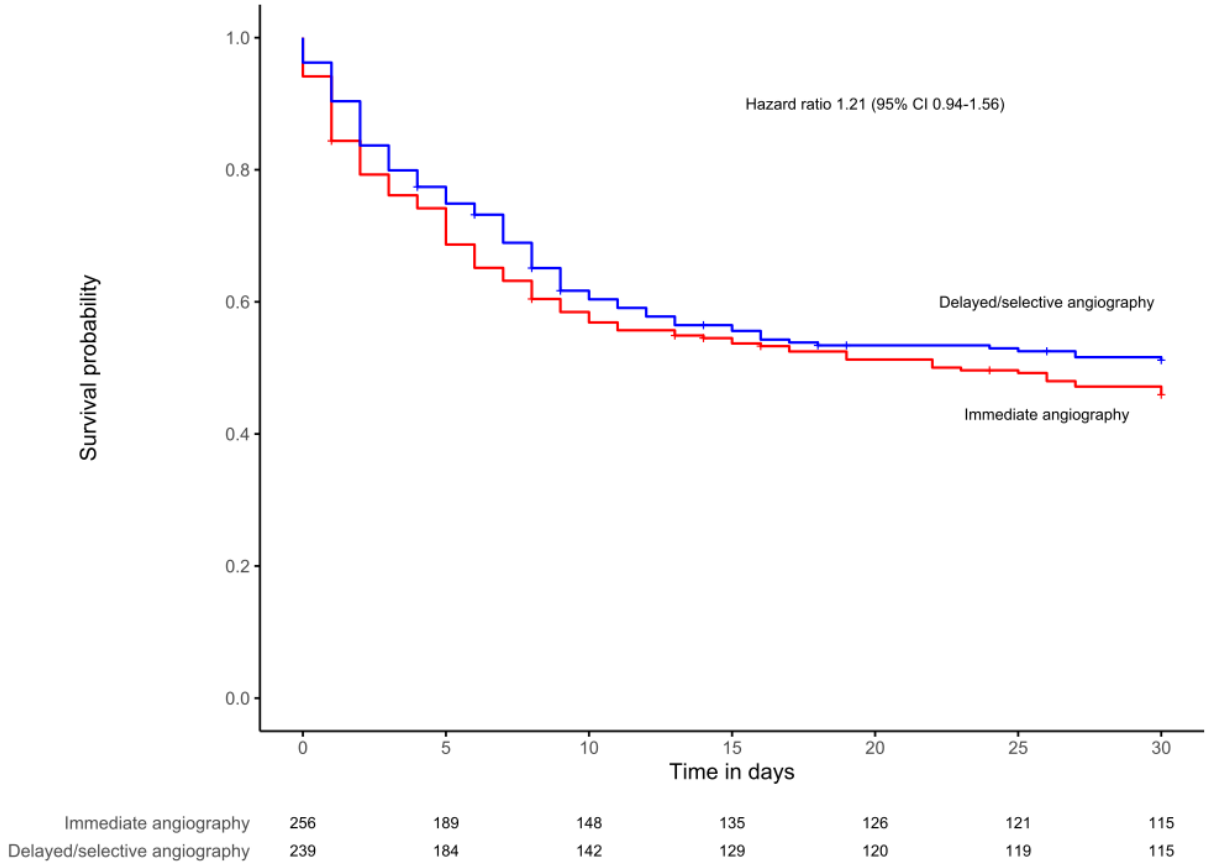
STEMI=ST-elevation myocardial infarction

Figure S3 – Study Flow Chart for Safety Population (as Treated)*



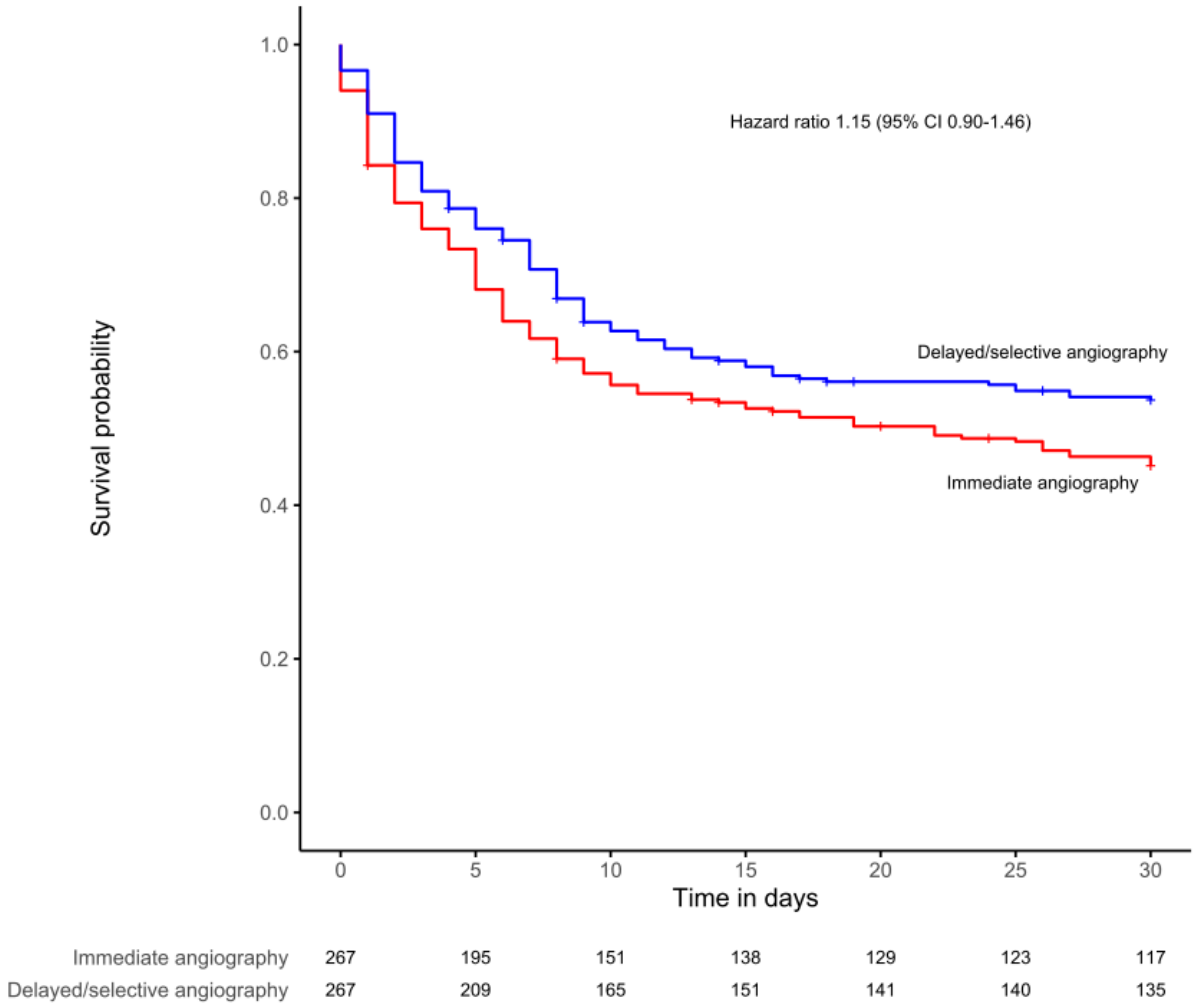
*The safety analysis was performed according to the as treated principle. In this analysis, a total of 7 patients randomized to the immediate angiography group and 22 patients randomized to the delayed/selective group switched treatment arms (crossover patients).

Figure S4 – Time-to-Event Curves through 30 Days for the Primary Endpoint All-Cause Mortality in Per-Protocol Population



Event rates represent Kaplan-Meier estimates.

Figure S5 – Time-to-Event Curves through 30 Days for the Primary Endpoint All-Cause Mortality in Safety (As Treated) Population



Event rates represent Kaplan-Meier estimates.

Supplementary Tables

Table S1 – Medication on Admission

	Immediate angiography	Delayed/selective angiography
Aspirin, n/total (%)	75/212 (35.4)	85/218 (39.0)
Thienopyridine, n/total (%)	62/211 (29.4)	58/218 (26.6)
Vitamin K antagonist, n/total (%)	5/211 (2.4)	6/218 (2.8)
Direct oral anticoagulant, n/total (%)	32/211 (15.2)	42/218 (19.3)
Beta blocker, n/total (%)	102/210 (48.6)	114/218 (52.3)
Angiotensin converting enzyme inhibitor, n/total (%)	82/211 (38.9)	80/218 (36.7)
Angiotensin 1 receptor antagonist, n/total (%)	22/210 (10.5)	29/217 (13.4)
Statin, n/total (%)	90/211 (42.7)	98/217 (45.2)
Oral antidiabetic agent, n/total (%)	7/211 (3.3)	16/219 (7.3)
Insulin, n/total (%)	21/211 (10.0)	24/220 (10.9)
Loop diuretic, n/total (%)	46/209 (22.0)	63/217 (29.0)
Thiazide, n/total (%)	9/210 (4.3)	15/217 (6.9)
Mineralocorticoid receptor antagonist, n/total (%)	34/211 (16.1)	36/217 (16.6)
Calcium channel blocker, n/total (%)	31/211 (14.7)	41/217 (18.9)
Non-steroidal anti-inflammatory drug, n/total (%)	12/211 (5.7)	10/217 (4.6)
Antidepressant, n/total (%)	11/211 (5.2)	9/217 (4.2)
Bronchodilator therapy, n/total (%)	20/211 (9.5)	27/217 (12.4)

Table S2 – Medication at 30 Days

	Immediate angiography	Delayed/selective angiography
Aspirin, n/total (%)	58/111 (52.3)	69/128 (53.9)
Thienopyridine, n/total (%)	48/110 (43.6)	50/127 (39.4)
Vitamin K antagonist, n/total (%)	7/110 (6.4)	4/128 (3.1)
Direct oral anticoagulant, n/total (%)	22/110 (20.0)	32/128 (25.0)
Unfractionated heparin, n/total (%)	5/111 (4.5)	10/127 (7.9)
Low molecular weight heparin, n/total (%)	17/111 (15.3)	9/125 (7.1)
Beta blocker, n/total (%)	80/110 (72.7)	97/127 (76.4)
Angiotensin converting enzyme inhibitor, n/total (%)	62/111 (55.9)	68/126 (54.0)
Angiotensin 1 receptor antagonist, n/total (%)	18/110 (16.4)	24/126 (19.1)
Statin, n/total (%)	71/111 (64.0)	81/126 (64.3)
Oral antidiabetic agent, n/total (%)	9/109 (8.3)	14/127 (11.0)
Insulin, n/total (%)	15/109 (13.8)	17/127 (13.4)
Loop diuretic, n/total (%)	39/110 (35.5)	57/126 (45.2)
Thiazide, n/total (%)	6/107 (5.6)	12/126 (9.5)
Mineralocorticoid receptor antagonist, n/total (%)	26/110 (23.6)	30/126 (23.8)
Calcium channel blocker, n/total (%)	26/110 (23.6)	25/127 (19.7)
Non-steroidal anti-inflammatory drug, n/total (%)	7/111 (6.3)	5/125 (4.0)
Antidepressant, n/total (%)	11/111 (9.9)	15/126 (11.9)
Bronchodilator therapy, n/total (%)	13/110 (11.8)	11/126 (8.7)

Table S3 – Serial Simplified Acute Physiology Score II

	Immediate angiography	Delayed/selective angiography
SAPS II; median (IQR)*		
ICU day 1	65 (48-77), n=230	64 (48-78), n=234
ICU day 2	60 (44-73), n=217	62 (45-74), n=237
ICU day 3	55 (40-68), n=189	54 (40-67), n=215
ICU day 4	52 (35-63), n=176	49 (34-62), n=197
ICU day 5	50 (33-62), n=160	46 (30-62), n=178
ICU day 6	50 (33-62), n=160	46 (30-62), n=178
ICU day 7	48 (31-64), n=115	48 (31-63), n=143

IQR=interquartile range; ICU=intensive care unit

*The Simplified Acute Physiology Score (SAPS) II measures the severity of disease in patients admitted to intensive care units and ranges from 0 (best) to 163 (worst).

Table S4 – Causes of Death at 30 Days*†

	Immediate angiography	Delayed/selective angiography
All-cause death; n/total (%)	143/265 (54.0)	122/265 (46.0)
Cardiovascular death; n/total (%)	49/140 (35.0)	35/121 (28.9)
Primary cause of death; n/total (%)*		
Neurological injury/anoxic brain injury	52/138 (37.7)	49/117 (41.9)
Cardiogenic shock	35/138 (25.4)	28/117 (23.9)
Infection/septic shock	10/138 (7.3)	16/117 (13.7)
Stroke (ischemic and hemorrhagic)	3/138 (2.2)	2/117 (1.7)
Sudden cardiac death	6/138 (4.4)	0/117 (0)
Hemorrhagic shock	1/138 (0.7)	0/117 (0)
Other	31/138 (22.5)	22/117 (18.8)

*Information on the primary cause of death was available in 255 of 265 deceased patients.

†Withdrawal of life-sustaining therapies was left to the discretion of the treating physicians. The following question was asked in the case report form: “Did results of neuroprognostic tests lead to discontinuation of treatment?”

Discontinuation of treatment was reported in 29/258 patients (11.4%) in the immediate angiography group after a median of 5 days (interquartile range 3-6) and in 28/256 patients (10.9%) in the delayed/selective angiography group after a median of 6 days (interquartile range 3-7).

Table S5 – Study Screening*

Number of patients screened	278
Number of patients not included	213
ST-elevation myocardial infarction	76
No cardiac cause of out-of-hospital cardiac arrest	37
Intra-hospital cardiac arrest	29
No sustained return of spontaneous circulation	34
Hemodynamic or electrical instability	16
Participation in another trial	1
Age <30 years	1
Other	19

*Initial screening was conducted via the corresponding registry of the trial. Thereafter, screening logs were maintained during the early phase of the trial but were discontinued as continuation was seen as a major challenge for participating sites due to the contribution of a large number of physicians 24/7, partly from different departments at the respective sites. The Steering Committee was also concerned that the entries in the screening logs would be distorted this way.

However, complete screening logs are available for selected study sites for the first 8-17 months of their respective recruitment. These might serve to give an impression of the distribution of included patients and exclusion criteria and are displayed above.

References

1. Bro-Jeppesen J, Kjaergaard J, Wanscher M, et al. Emergency coronary angiography in comatose cardiac arrest patients: do real-life experiences support the guidelines? Eur Heart J Acute Cardiovasc Care 2012;1:291-301.

2. Wang SK, Tsiatis AA. Approximately optimal one-parameter boundaries for group sequential trials. Biometrics 1987;43:193-9.

3. Rothmann MD, Koti K, Lee KY, Lu HL, Shen YL. Missing data in biologic oncology products. J Biopharm Stat 2009;19:1074-84.

4. Walton MK. Addressing and advancing the problem of missing data. J Biopharm Stat 2009;19:945-56.

5. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551-67.

6. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. Circulation 2011;123:2736-47.

7. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480-4.

8. Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270:2957-63.

9. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999:496-509.