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

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Background Patients experiencing out-of-hospital cardiac arrest (OHCA) without ST-segment elevation are a heterogenic group with a variety of underlying causes. Up to one-third of patients display a significant coronary lesion compatible with myocardial infarction as OHCA trigger. There are no randomized data on patient selection and timing of invasive coronary angiography after admission.

Methods and results The TOMAHAWK trial randomly assigns 558 patients with return of spontaneous circulation after OHCA with no obvious extracardiac origin of cardiac arrest and no ST-segment elevation/left bundle-branch block on postresuscitation electrocardiogram to either immediate coronary angiography or initial intensive care assessment with delayed/selective angiography in a 1:1 ratio. The primary end point is 30-day all-cause mortality. Secondary analyses will be performed with respect to initial rhythm, electrocardiographic patterns, myocardial infarction as underlying cause, neurological outcome, as well as clinical and laboratory markers. Clinical follow-up will be performed at 6 and 12 months. Safety end points include bleeding and stroke.

Conclusion The TOMAHAWK trial will address the unresolved issue of timing and general indication of angiography after OHCA without ST-segment elevation. (Am Heart J 2019;209:20-8.)

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Out-of-hospital cardiac arrest (OHCA) is a frequent cause of death. It is estimated that, in Europe, approximately 38 per 100,000 residents annually experience OHCA treated by emergency medical services.[1] The most frequent underlying etiology is acute myocardial infarction, being responsible for up to about 50% of cases.[2]

Prognosis is generally poor, and only few patients survive up to hospital admission. In a large OHCA registry, return of spontaneous circulation (ROSC) was achieved in only 18.0%, and hospital admission rate was as low as 14.6%.[3] However, mere hospital admission is by no means a guarantee of favorable clinical outcome. The final hospital discharge rate varies between 5.1% and 9.8%, reflecting an in-hospital mortality of up to 65%.[3,4] Furthermore, a relevant subset of patients surviving to hospital discharge will display cognitive impairment.[5] Optimal postresuscitation management, pre- and intrahospital, is therefore of vital importance.

While acute coronary lesions as underlying cause of cardiac arrest can be found in approximately 90% of OHCA patients with ST-segment elevation, patients without post-resuscitation ST-segment elevation on the electrocardiogram (ECG) represent a more heterogeneous group with a variety of etiologies, including noncardiac causes.[6-8] However, acute coronary syndrome is still suggested as the most frequent OHCA trigger in this patient subset. In OHCA patients admitted to the intensive care unit (ICU) without obvious extracardiac etiology and no ST-segment elevation on the ECG after ROSC, approximately 30% reveal at least 1 significant coronary stenosis considered relevant to proceed with percutaneous coronary intervention (PCI).[6] Therefore, coronary angiography in these patients seems to be reasonable. However, it must be emphasized that no randomized trials have studied—let alone proven—the clinical benefit of revascularization in these patients, yet.

Another open issue is the optimal timing of angiography in OHCA survivors without ST-segment elevation on the postresuscitation ECG. Registry studies have shown a potential benefit of early coronary angiography/PCI in these patients.[9,10] Further observational data indicate a survival benefit only in patients with low risk score of poor neurological outcome, whereas other showed no benefit of early coronary angiography with respect to overall survival.[11,12] It must be kept in mind that a relevant proportion of OHCA survivors without ST-segment elevation will have other etiologies than acute coronary syndrome. Immediate unselected coronary angiography will put these patients at the risk of complications of the procedure without any benefit and possibly account for delay in making the correct diagnosis. Again, there is a lack of randomized studies, and it remains unclear whether coronary angiography should be performed immediately in all patients after hospital admission or if a more selective approach is warranted with potential angiography later depending on the subsequent clinical course.

The TOMAHAWK trial (Immediate Unselected Coronary Angiography versus Delayed Triage in Survivors of Out-of-Hospital Cardiac Arrest without ST-segment Elevation) will address the unresolved issue of timing and general indication of coronary angiography after OHCA without ST-segment elevation.

Study objectives and design

The TOMAHAWK study is a prospective, randomized, international, multicenter, open-label trial with the primary objective to examine whether survivors of OHCA without ST-segment elevation should undergo immediate coronary angiography for treating or ruling out acute coronary events or whether initial intensive care evaluation should guide clinical triage. The study flowchart is shown in Figure 1. The trial is registered at ClinicalTrials.gov (NCT02750462).

Patient population and timeline

A total of 558 patients will be enrolled at currently 37 study sites in Germany and Denmark. Figure 2 shows the geographical distribution of the study centers. All sites have 24/7 PCI services. Patients ≥30 years with documented resuscitated OHCA of possible cardiac origin and ROSC without ST-segment elevation are eligible for inclusion. A detailed list of in- and exclusion criteria is displayed in Table I.

Recruitment started in November 2016 and is estimated to be completed in 2020.

Informed consent

As eligible patients will not be able to give full informed consent before randomization, a stepwise informed consent process has been validated and approved by all ethical committees of the participating study sites.

In the acute setting upon hospital admission, 2 physicians assess the supposed patient will. If there is agreement between the 2 physicians, the patient may be randomized. In case a legal representative has been appointed in the past, this person will be asked to provide informed consent. In the subacute stage, the patient (if possible) or an authorized legal representative will be asked for final informed consent. The informed consent process is slightly different in the participating center in Denmark by reason of different local ethical and legal requirements.

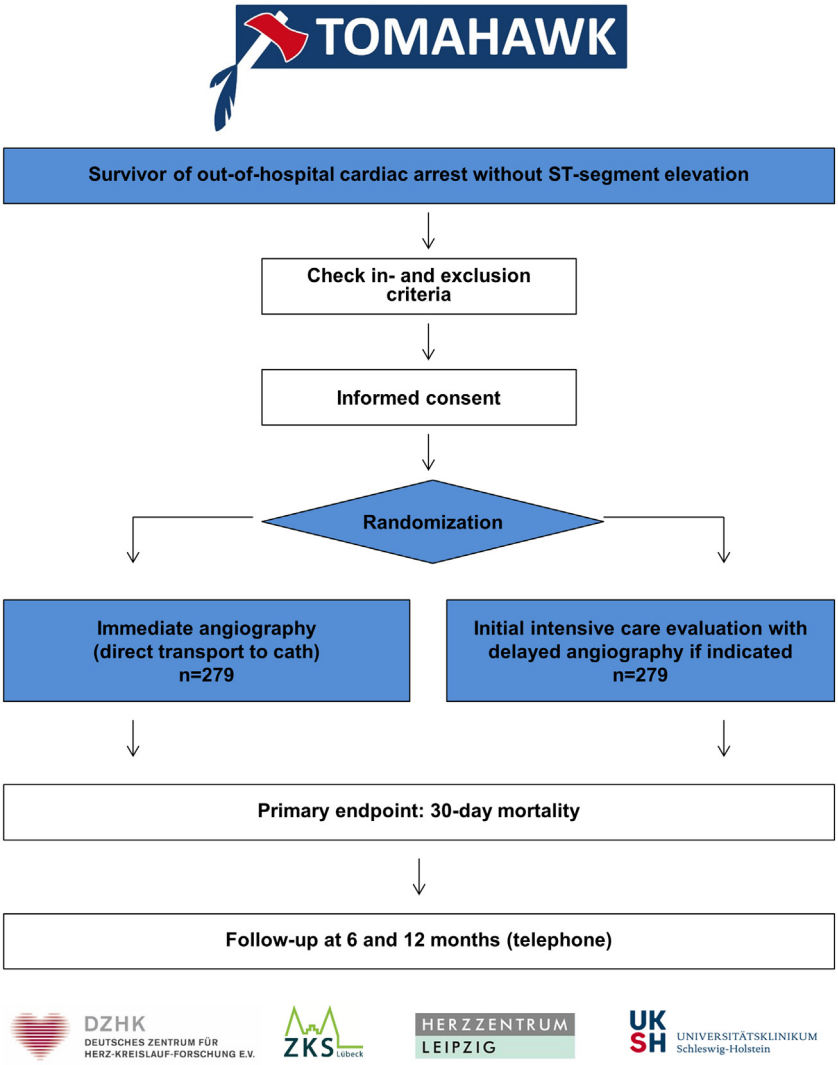
Randomization

Randomization is to be performed as soon as possible after hospital admission. Eligible patients are assigned to immediate coronary angiography or initial intensive care assessment and delayed/selective angiography in a 1:1 ratio. Randomization is carried out blockwise with randomly changing blocks and stratified for trial site via a Web-based system (secuTrial).

Patient treatment

Patients randomized to immediate coronary angiography will be transported to the catheterization laboratory

Figure 1



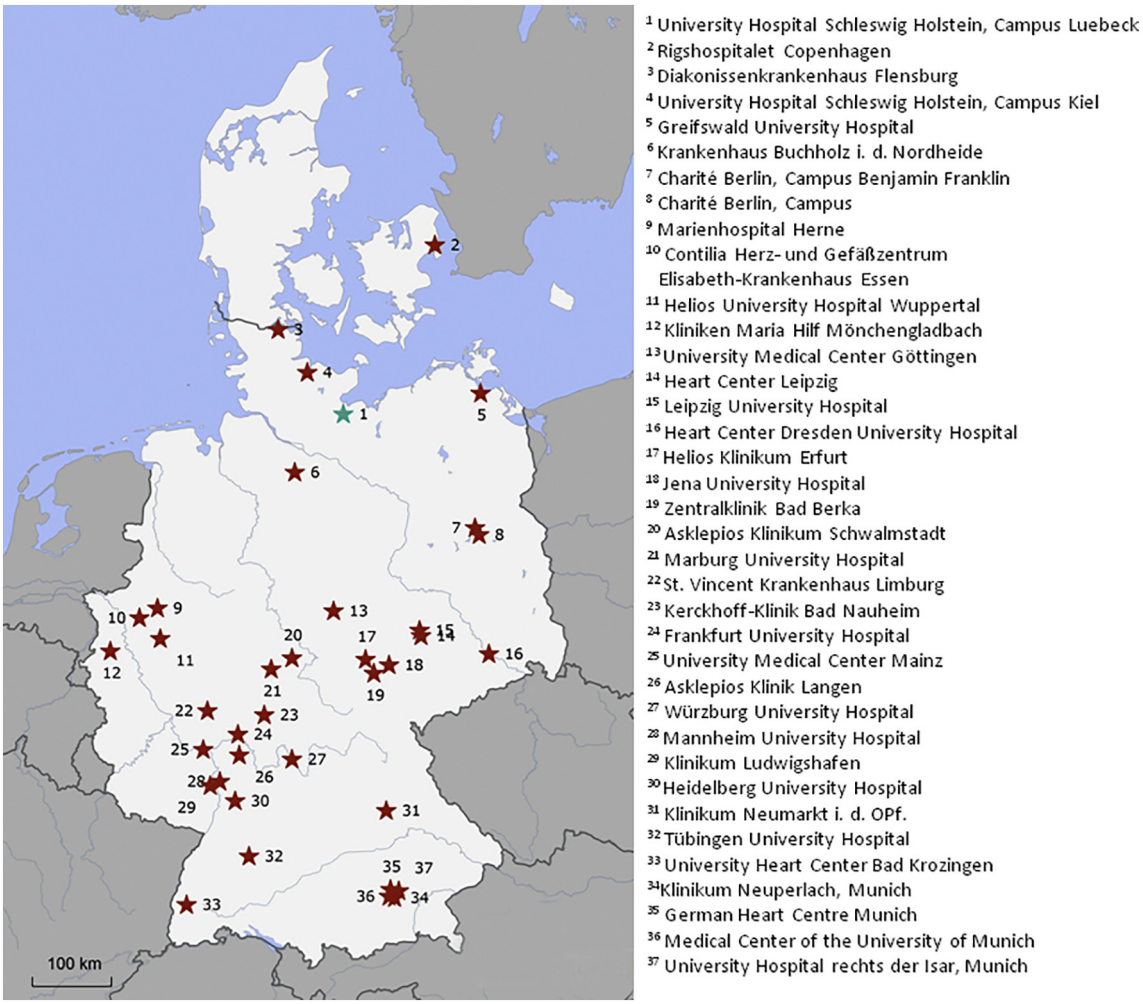
Study flow.

as soon as possible after hospital admission for evaluation of coronary anatomy. It is recommended to keep time in the emergency department and/or ICU to a minimum (preferably immediate transport to the catheterization laboratory bypassing the emergency department and/or ICU). Every effort should be made to keep the time from presentation in the hospital and visualization of coronary anatomy as short as possible.

Patients assigned to the delayed/selective coronary angiography group will first be transported to the ICU for further evaluation and stratification of OHCA etiology. Further triage will depend on the results of clinical examination and objective testing and will be left to the individual physician according to clinical judgment. If a high likelihood of an acute coronary trigger for OHCA persists, the treating physician may proceed to coronary angiography after a minimum delay of 24 hours after the onset of cardiac arrest. Coronary angiography is allowed ≤24 hours in case of a *large myocardial infarction* (defined as an increase in cardiac troponin I or T ≥70× upper limit of normal or CKMB ≥10× upper limit of normal >6 hours after the onset of cardiac arrest), electrical instability possibly caused by acute myocardial ischemia, development of cardiogenic shock, or new ST-segment elevation.

If clinical examination and further testing make a coronary etiology unlikely, angiography can be either delayed until later in the hospital course (eg, after the results of non-invasive stress testing are available) or a strategy of invasive cardiac catheterization can be abandoned altogether.

Figure 2



Geographical distribution of study sites.

Revascularization

Revascularization is to be attempted in both groups if at least 1 major coronary artery has pathology deemed clinically relevant by the operator (ie, significant stenosis, occlusion, ulceration, and/or thrombus consistent with plaque rupture). Given the high-risk features of the study population, it is recommended that a percutaneous approach as opposed to coronary artery bypass grafting is favored whenever possible. The ultimate choice between PCI and coronary artery bypass grafting is, however, left to the discretion of the individual operator. Interventional technique (eg, stent choice) is left to the discretion of the operator; also, revascularization of nonculprit lesions may be carried out at a later time point as staged procedure, depending on remaining symptoms or inducible ischemia.

Concomitant therapy

Postresuscitation care in the ICU will be the same for both groups and will follow published guidelines.[13,14] All comatose patients should undergo targeted temperature management (TTM) starting as soon as possible and maintained for at least 24 hours. In patients randomized to immediate angiography/PCI, TTM should be initiated before and maintained during the invasive procedure and thereafter.

Neurological assessment

Neurological outcome will be assessed by cerebral performance category (CPC). Clinical neuroprognostic tests (ie, pupillary light response, corneal reflex, following eye movements, motor response to pain, pharyngeal coughing reflex) will be documented daily on ICU. Moreover, the results of somatosensory evoked potentials, cerebral computed

Table I. Inclusion and exclusion criteria

Inclusion criteria
• Documented resuscitated OHCA of possible cardiac origin and ROSC
• Age ≥30 y
• Informed consent
Exclusion criteria
• ST-segment elevation or left bundle-branch block
• No ROSC 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 extracardiac 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

tomographic/magnetic resonance scans, neuron-specific enolase, and electroencephalography will be recorded.

Follow-up

Clinical events will be assessed at discharge and at 30 days, 6 months, and 12 months after randomization by direct questioning if the patient is still hospitalized or a structured telephone interview. Clinical events will be verified by original source data. At 6 and 12 months, quality of life will be assessed by the EuroQol 5D questionnaire.

End points

The primary end point of the TOMAHAWK study is 30-day all-cause mortality.

Secondary end points are as follows:

- Myocardial infarction at 30 days
- Severe neurological deficit (CPC 3-5) at 30 days, 6 months, and 12 months
- Composite end point of all-cause mortality and/or severe neurological deficit at 30 days
- Length of ICU stay
- Length of hospital stay
- Serial Simplified Acute Physiology Score (SAPS) II score
- All-cause death within 6 and 12 months of follow-up
- Myocardial infarction (possibly recurrent) at 6 and 12 months of follow-up
- Rehospitalization for congestive heart failure within 30 days, 6 months, and 12 months of follow-up
- Peak release of myocardial enzymes
- Quality of life at 6 and 12 months assessed by the EuroQol 5D questionnaire
- Moderate and severe bleeding (Bleeding Academic Research Consortium (BARC) definition types 2-5)[15]
- Stroke
- Acute renal failure requiring renal replacement therapy

Safety aspects of the study will be monitored by a dedicated Data Safety and Monitoring Board (DSMB) consisting of 3 members with pertinent expertise in the management of OHCA and/or large-scale clinical trials (2 clinicians and 1 biostatistician). Members of the DSMB will not be participants or directly involved in the practical conduct of the study. Clinical end points will be adjudicated by a clinical event committee consisting of clinicians with pertinent expertise who are not participants in the study. Event adjudication will be performed using treatment-arm–blinded source data.

Substudies

Angiography. The angiography substudy will assess differential effects of the treatment groups on angiographic parameters and their impact on patient outcome. A comprehensive angiographic analysis will be carried out according to established and standardized methods, including incidence of coronary artery disease, culprit lesions and nonculprit lesions, pre- and postprocedural Thrombolysis in Myocardial Infarction flow, and angiographic grading scores to determine the complexity of coronary artery disease. Digitalized coronary angiographies will be sent to a central angiographic core laboratory for blinded analysis.

Electrocardiogram. The ECG substudy will explore the value of different postresuscitation ECG abnormalities such as ST-segment depression and bundle-branch block for the prediction of acute coronary syndrome as the trigger for OHCA. The principal objective is to identify ECG patterns which provide a high negative predictive value for ruling out an acute coronary etiology.

Data and statistical analysis

Sample size calculation and data analysis

Prior evidence is limited. As at the time of designing the study protocol there was only 1 single registry trial reporting on clinical outcome according to the timing of angiography exclusively in OHCA survivors without ST-segment elevation, this study presented the basis for sample size determination.[16] The trial reported 30-day mortality of 34% in patients undergoing emergency angiography and 46% with delayed/selective angiography. Using these data, a total of 558 patients were calculated to reject the null hypothesis of no difference between groups (2-sided χ^2 test, power 80%, 1 interim analysis, global $\alpha = .05$, α at final analysis = .0342, 5% maximum dropout rate per group). A group sequential plan according to Wang and Tsiatis was used that minimizes the average sample size under the alternative hypothesis at $\delta = 0.41$.[17] This plan is equivalent to using the α-spending function of Hwang et al at $\gamma = -0.13$.[18] Predefined subgroup analyses will be performed for gender, diabetes, age (<65 and ≥ 65), TTM (carried out vs not carried out), shockable versus nonshockable rhythm, time from arrest to ROSC ($<$ vs $\geq$ median), and confirmed myocardial infarction as OHCA trigger.

The primary analysis will be based on the intention-to-treat principle. A patient is included in the intention-to-treat population if randomized to either treatment group. The per-protocol population will be analyzed as sensitivity analysis. The per-protocol population includes only patients who have received a treatment according to the initial allocation. However, to account for potential immortal time bias, patients in group 1 (immediate angiography) who die before the start of angiography will be included in the per-protocol analysis although they did not receive the allocated treatment.

Study organization and funding

The TOMAHAWK trial is fully supported by the German Center for Cardiovascular Research (DZHK). The sponsor of the trial is the University Hospital of Schleswig-Holstein, Campus Luebeck. TOMAHAWK follows a standard study organization including steering committee, DSMB, and clinical event committee. Project management is located at the Center for Clinical Trials Luebeck which also conducts on-site monitoring. All statistical analyses will be performed by the Institute for Medical Biometry and Statistics at the University of Luebeck.

Discussion

Indication and timing of coronary angiography in patients after OHCA with suspected cardiac cause of the event and without ST-segment elevation have never been studied in a prospective randomized fashion. Evidence therefore is limited. Two treatment strategies in this patient subgroup are debated: (1) immediate unselected coronary angiography in all patients and (2) initial intensive care assessment with optimal post–cardiac arrest care and further diagnostic measures with possible coronary angiography depending on results.

Taking into account that acute myocardial infarction with up to 33% represents the major cause of cardiac arrest in OHCA patients without ST-segment elevation, rapid coronary revascularization might provide several advantages.[6,7] In the acute setting, it may lead to hemodynamic and electrical stabilization, possibly improving cerebral and overall organ perfusion. Over the long term, aborting myocardial injury or keeping the possible infarct size small might prevent development of heart failure and late complications such as arrhythmias.

On the other hand, although the risk of diagnostic coronary angiography and potential PCI might seem low, its true hazard in patients after OHCA has never been systematically studied. Depending on the time of whole-body ischemia and the duration until ROSC, most OHCA patients develop post–cardiac arrest syndrome consisting of post–cardiac arrest brain injury, post–cardiac arrest myocardial dysfunction, and systemic ischemia/reperfusion response.[19] Patients after OHCA in which coronary angiography including possible PCI is directly performed at admission might therefore be put at a higher risk of cerebral damage, renal impairment, bleeding, stent thrombosis, and other complications due to general inflammation including an activated coagulation/anticoagulation, fibrinolysis/antifibrinolysis system, and a compromised blood-brain barrier. This may be particularly consequential as, according to registry data, 2 of 3 patients do not display a culprit lesion considered relevant as OHCA trigger.[6] These patients will be put at risk of the coronary procedure and a potential delay in further differential diagnosis and treatment of OHCA etiologies other than myocardial infarction. Additionally, in all patients, the time to initiation of TTM may be prolonged or the TTM chain may be temporarily interrupted owing to issues during patient transport or invasive procedure, although studies indicated no delay of TTM due to invasive coronary treatment.[20]

Current international guidelines recommend urgent coronary angiography as a class IIa level of evidence C recommendation in patients after OHCA without ST-segment elevation in case there is a suspicion of ongoing myocardial infarction.[8] This recommendation is based on registry data indicating a significant survival benefit in patients undergoing urgent coronary angiography.[6,10,21] However, selection bias in retrospective analyses may be high, and not to be ignored, diagnosis of ongoing myocardial ischemia represents a major challenge in patients after OHCA due to limited sensitivity of diagnostic tools.[22] Additionally, other studies have shown no mortality benefit of early coronary angiography including a subanalysis of a large randomized TTM trial.[12,16] This trial compared TTM at 33°C versus 36°C after cardiac arrest. A dedicated post hoc analysis included 544 patients without ST-segment elevation. Half of these patients received early coronary angiography (within 6 hours) with no significant benefit regarding survival at a median follow-up of 427 days compared to those without early coronary angiography including a propensity-matched analysis.

A very recently published retrospective study analyzed 1,410 OHCA patients with presumed cardiac cause with regard to a benefit of early coronary angiography in dependence on the Cardiac Arrest Prognosis score.[11] This score provides a high discrimination value in stratifying neurological outcome after OHCA.[23] According to this trial, patients only have a benefit from early coronary angiography with respect to survival at hospital discharge when the prognosis risk score is low regardless of the presence of ST-segment elevation. On the opposite, in patients at intermediate- or high-risk score, no association of early coronary angiography and mortality was shown. By reason of the retrospective design, selection bias again might be high. Still, the above-mentioned results encourage the approach to include the neurological prognosis in determining further treatment including coronary angiography. Nevertheless, no study so far showed an adverse correlation of early coronary angiography and survival or neurological outcome in patients after OHCA.

The primary end point of TOMAHAWK is 30-day all-cause mortality. However, secondary end points such as neurological outcome and safety end points such as stroke and bleeding will allow a good overall assessment of the patients enrolled.

Table II. Ongoing randomized clinical trials comparing early coronary angiography with a delayed or selective approach in OHCA patients without ST-segment elevation

Title/identifier*	Country	Sample size	Main inclusion criteria	Treatment arms	Primary outcome
Immediate Unselected Coronary Angiography Versus Delayed Triage in Survivors of OHCA Without ST-Segment Elevation (TOMAHAWK) NCT02750462	Germany, Denmark	558	• OHCA of presumed cardiac cause • Sustaining ROSC at hospital admission • Age ≥30 y	Immediate after hospital admission **vs** delayed/selective CAG	30-d survival
Coronary Angiography after Cardiac Arrest (COACT)[29] NTR 4973	Netherlands	552	• Comatose patients (GCS <8) with ROSC after OHCA • Ventricular tachycardia or ventricular fibrillation during arrest • Age >18 y	CAG within 120 min after randomization **vs** CAG after neurological recovery	90-d mortality
Emergency Versus Delayed Coronary Angiogram in Survivors of Out-of-hospital Cardiac Arrest (EMERGE) NCT02876458	France	970	• OHCA with ROSC and no obvious non-cardiac cause of arrest • Age ≥18 y	CAG at admission **vs** CAG after 48 to 96 h after admission	Survival with no or minimal neurological sequel (CPC 1 or 2) at 180 d
Direct or Subacute Coronary Angiography for Out-of-hospital Cardiac Arrest (DISCO)[30] NCT02309151	Sweden	1006	• Witnessed OHCA • Sustained ROSC >20 min • Age >18 y	CAG as soon as possible after hospital admission **vs** delayed/selective CAG (soonest at 24 h after hospital admission)	30-d survival
Expedited transfer to a cardiac arrest centre for non-ST elevation out of hospital cardiac arrest (ARREST) ISRCTN96585404	United Kingdom	860	• Witnessed OHCA with ROSC and no obvious noncardiac cause • Age ≥18 y	Direct transport for heart attack center with immediate CAG **vs** standard of care	30-d mortality
Early Coronary Angiography Versus Delayed Coronary Angiography (PEARL) NCT02387398	United States	240	• OHCA with ROSC and suspected cardiac etiology • Age ≥18 y	CAG within 120 min after hospital admission **vs** no CAG within the first 6 h from admission	Safety and Efficacy of early CAG at 180 d
Coronariography in out of hospital cardiac arrest (COUPE) NCT02641626	Spain	166	• OHCA with ROSC and GCS ≤8 • Rule out of obvious noncardiac cause (CT scan and transthoracic echocardiogram) • Age ≥18 y	CAG as soon as possible after randomization **vs** CAG after extubation and good neurologic prognosis	Survival with good neurological outcome (CPC 1 or 2) at 30 and 180 d
ACCESS to the Cardiac Cath Lab in Patients Without STEMI Resuscitated From Out-of-hospital VT/VF Cardiac Arrest NCT03119571	United States	864	• Resuscitated from OHCA with initial cardiac arrest rhythm of pulseless ventricular tachycardia/ventricular fibrillation • Age 18-75 y	Initial admission to cardiac catheterization laboratory **vs** Admission to intensive care unit for evaluation	Survival with good neurological outcome (mRS ≤3) at hospital discharge

CAG, coronary angiography; *GCS*, Glasgow Coma Scale; *mRS*, Modified Rankin Scale.
* Identifiers registered in https://www.clinicaltrials.gov, http://www.trialregister.nl, or https://www.isrctn.com.

Next to the potential timing of coronary angiography, a desirable aim in patients after OHCA without ST-segment elevation is to enhance the power of predicting acute coronary syndrome as underlying cause. Several observational data failed to provide a diagnostic predictor for coronary occlusion with a satisfactory sensitivity and specificity. Coronary occlusion was found in 23%-33% of patients even though no ST-segment elevation was present

on ECG.[6,7,24] On the other hand, ST-segment elevations predict an acute coronary lesion in only 85%-96% of the patients.[6,7] Troponin measurement showed a sensitivity and specificity of only 66% in predicting acute myocardial infarction.[25] Furthermore, evidence of the predictive value of echocardiographic findings is lacking. There is solely 1 small retrospective study where regional wall motion abnormalities showed 68% sensitivity and 52% specificity in prediction of coronary artery disease.[26] A retrospectively developed diagnostic score for acute myocardial infarction in OHCA patients without ST-segment elevation was published by Zeyons et al[27]: A combination of ST-segment elevation, chest pain before cardiac arrest, and an initial shockable rhythm showed a significantly higher diagnostic value than ST-segment elevation alone. So far, no external validation has been performed. In the absence of ST-segment elevation, the score cannot provide adequate support regarding a decision for or against coronary angiography. The above-mentioned predefined substudies of the TOMAHAWK trial aim to obtain further data on this question next to evaluating several other aspects of OHCA patients without ST-segment elevation.

TOMAHAWK will only address patients in stable hemodynamic and electric conditions, as immediate coronary angiography in unstable patients represents, despite limited evidence, a class I recommendation according to current guidelines (level of evidence C).[28] To take this recommendation into account, several circumstances are defined where the treating physician is allowed to proceed to coronary angiography within 24 hours after the onset of cardiac arrest even if the patient is randomized to the late/selective group. Despite sensitivity being low, troponin was defined in addition to hemodynamic or electrical instability and new ST-segment elevations as one criterion indicating early coronary angiography based on the expert consensus document of Moussa et al.[29] This definition was created for patients with postprocedural myocardial infarction. However, it is the best eminent definition available for patients after cardiopulmonary resuscitation.

Parallel to TOMAHAWK, several ongoing randomized trials examine the effect of early coronary angiography in OHCA patients without ST-Segment elevation. Studies exceeding 100 patients are listed in Table II. These trials share many design characteristics which will create a major opportunity of data pooling to gain a high level of evidence and an important improvement in the treatment of OHCA patients.

Conclusion

Evidence on early coronary angiography/PCI in patients after OHCA with presumed cardiac cause of cardiac arrest and no signs of ST-segment elevation is limited. Current guidelines are based on retrospective data only. The randomized TOMAHAWK trial is designed to compare immediate coronary angiography to a delayed/selective approach after intensive care triage in these patients.

CRediT authorship contribution statement

Steffen Desch: Conceptualization, Methodology, Investigation, Writing - original draft, Supervision, Project administration, Funding acquisition, Visualization. **Anne Freund:** Investigation, Writing - original draft, Supervision, Project administration, Visualization. **Tobias Graf:** Investigation, Resources, Writing - review & editing. **Stephan Fichtlscherer:** Investigation, Resources, Writing - review & editing.
Hendrik Haake: Investigation, Resources, Writing - review & editing. **Michael Preusch:** Investigation, Resources, Writing - review & editing. **Fabian Hammer:** Investigation, Resources, Writing - review & editing. **Ibrahim Akin:** Investigation, Resources, Writing - review & editing. **Martin Christ:** Investigation, Resources, Writing - review & editing. **Christoph Liebetrau:** Investigation, Resources, Writing - review & editing. **Carsten Skurk:** Investigation, Resources, Writing - review & editing. **Stephan Steiner:** Investigation, Resources, Writing - review & editing. **Ingo Voigt:** Investigation, Resources, Writing - review & editing. **Roland Schmitz:** Investigation, Resources, Writing - review & editing. **Harald Mudra:** Investigation, Resources, Writing - review & editing. **Jakob Ledwoch:** Investigation, Resources, Writing - review & editing, Project administration. **Niels Menck:** Investigation, Resources, Writing - review & editing. **Jan Horstkotte:** Investigation, Resources, Writing - review & editing. **Klaus Pels:** Investigation, Resources, Writing - review & editing.
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Suzanne de Waha-Thiele: Investigation, Resources, Writing - review & editing. **Denise Olbrich:** Project administration, Supervision. **Inke König:** Methodology, Formal analysis, Resources. **Kathrin Klinge:** Project administration, Supervision.
Holger Thiele: Conceptualization, Methodology, Investigation, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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