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Clinical paper

Direct or subacute coronary angiography in out-of-hospital cardiac arrest (DISCO)—An initial pilot-study of a randomized clinical trial

Ludvig Elfwén[a,1,], Rickard Lagedal[b,1], Per Nordberg[c], Stefan James[d], Jonas Oldgren[d], Felix Böhm[e], Peter Lundgren[f,g], Christian Rylander[h], Jan van der Linden[i], Jacob Hollenberg[c], David Erlinge[j], Tobias Cronberg[k], Ulf Jensen[a], Hans Friberg[l], Gisela Lilja[k], Ing-Marie Larsson[b], Ewa Wallin[b], Sten Rubertsson[b,2], Leif Svensson[c,2]*

[a] *Department of Clinical Science and Education, Södersjukhuset, Karolinska Institute, Sweden*
[b] *Department of Surgical Sciences/Anesthesiology and Intensive Care Medicine, Uppsala University, Sweden*
[c] *Department of Medicine, Center for Resuscitation Science, Karolinska Institute, Solna, Sweden*
[d] *Uppsala Clinical Research Center and Department of Medical Sciences, Cardiology, Uppsala University, Sweden*
[e] *Division of Cardiology, Department of Medicine, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden*
[f] *Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden*
[g] *Prehospen — Centre for Prehospital Research, University of Borås, Sweden*
[h] *Department of Anaesthesiology and Intensive Care Medicine, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden*
[i] *Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden*
[j] *Department of Cardiology, Clinical Sciences, Lund University, Lund, Sweden*
[k] *Lund University, Skane University Hospital, Department of Clinical Sciences, Division of Neurology, Lund, Sweden*
[l] *Department of Anesthesiology and Intensive Care Medicine, Skane University Hospital, Lund University, Lund, Sweden*

Abstract

Background: The clinical importance of immediate coronary angiography, with potentially subsequent percutaneous coronary intervention (PCI), in out-of-hospital cardiac arrest (OHCA) patients without ST-elevation on the ECG is unclear. In this study, we assessed feasibility and safety aspects of performing immediate coronary angiography in a pre-specified pilot phase of the 'DIrect or Subacute Coronary angiography in Out-of-hospital cardiac arrest' (DISCO) randomized controlled trial (ClinicalTrials.gov ID: NCT02309151).

Methods: Resuscitated bystander witnessed OHCA patients >18 years without ST-elevation on the ECG were randomized to immediate coronary angiography versus standard of care. Event times, procedure related adverse events and safety variables within 7 days were recorded.

Results: In total, 79 patients were randomized to immediate angiography (n = 39) or standard of care (n = 40). No major differences in baseline characteristics between the groups were found. There were no differences in the proportion of bleedings and renal failure. Three patients randomized to immediate angiography and six patients randomized to standard care died within 24 h. The median time from EMS arrival to coronary angiography was 135 min in the immediate angiography group.

* Corresponding author at: Ludvig Elfwén, Department of Cardiology, Södersjukhuset, 118 52 Stockholm, Sweden.
E-mail address: Ludvig.elfwen@sll.se (L. Elfwén).

[1] Equal author contribution.
[2] Shared last authorship.

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In patients randomized to immediate angiography a culprit lesion was found in 14/38 (36.8%) and PCI was performed in all these patients. In 6/40 (15%) patients randomized to standard of care, coronary angiography was performed before the stipulated 3 days.

Conclusion: In this out-of-hospital cardiac arrest population without ST-elevation, randomization to a strategy to perform immediate coronary angiography was feasible although the time window of 120 min from EMS arrival at the scene of the arrest to start of coronary angiography was not achieved. No significant safety issues were reported.

Keywords: Out-of-hospital, Cardiac arrest, Coronary angiography, Percutaneous coronary intervention

Introduction

Ischemic heart disease, acute or chronic, is the most common cause of out-of-hospital cardiac arrest OHCA.[1] Early revascularization by percutaneous coronary intervention (PCI) of occluded coronary arteries or significant coronary stenoses may therefore have the potential to improve cardiac function, organ perfusion and survival. On the other hand, there might be a significant risk to transport often hemodynamically unstable OHCA patients within and between hospitals to perform coronary angiography at an early stage.

Observational data show that up to 30% of OHCA patients without ST elevation on presenting ECG, have a coronary occlusion.[2,3] Thus, an important clinical issue to address is how to identify which of these patients that would benefit from early coronary angiography and subsequent PCI.

Current European and American resuscitation guidelines recommend that it is reasonable to perform emergent coronary angiography for selected adult patients with a suspected cardiac cause of the arrest but without ST-elevation.[4,5] However, there are limited data supporting this recommendation. Recently, the results from the COACT trial could not show any benefit of immediate coronary angiography in this patient population, however the study might have been underpowered.[6,7]Together with the DISCO trial, there are several ongoing randomized clinical studies (ACCESS, ClinicalTrials.gov number, NCT03119571 and TOMAHAWK, ClinicalTrials.gov number NCT02750462) with similar design.[8]

The aim of this study, a pre-specified analysis of the pilot phase of the ongoing large randomized clinical national multicenter DISCO-trial,[9] was primarily to investigate feasibility and safety aspects of randomizing to a strategy of performing immediate coronary angiography in unconscious OHCA patients without ST-elevations compared with standard of care in patients admitted primarily to the intensive care unit with subsequent coronary angiography.

Methods

Study design

The design of the DIrect or Subacute Coronary angiography in Out-of-hospital cardiac arrest (DISCO) trial, a national, pragmatic, multicenter, randomized clinical study has been described previously.[9] In the pilot phase of the study, consecutive OHCA patients with ST-elevation were also included as a control population. Those patients were not randomized but enrolled and followed only for observation and comparison regarding differences in timeframes, logistics and safety.

Ethical considerations

The study was approved by the regional ethical committee in Stockholm, Sweden (Identification number 2014/1170-31/1) and registered at ClinicalTrials.gov (NCT02309151).

Patients

Witnessed OHCA patients over 18 years of age with return of spontaneous circulation (ROSC) admitted alive to hospital were screened with 12-lead ECG as early as possible, i.e. in the ambulance or at the latest in the emergency room. Patients without ST-segment elevation or presumed new left bundle branch block were eligible for randomization. Exclusion criteria included obvious non-cardiac causes, terminally ill patients with a life expectancy less than one year, expected time to coronary angiography more than 120 min, known pregnancy and patients not unconscious (Glasgow coma scale >8).

Randomization

Patients who met inclusion and had no exclusion criteria were randomly assigned in a 1:1 ratio either to immediate coronary angiography or to a strategy where patients were admitted primarily to the intensive care unit with a potential coronary angiography performed at a later stage (i.e. pre-specified not before 3 days). Randomization was performed through a web-based study module with blocks of five.

Study organization

The DISCO study is an academically initiated study led by researchers at Uppsala University, Uppsala, and the Center for Resuscitation Science, Karolinska Institutet, Stockholm; Sweden. The Uppsala Clinical Research Center (UCR), Sweden, is the clinical and data coordinating center.

Treatment protocol — coronary angiography and PCI

Immediate coronary angiography group

The study protocol stated that PCI should be performed immediately on the presumed culprit lesion. The protocol also stated that PCI should preferably be carried out on all significant stenoses that were accessible to PCI during the acute angiography. Significant stenosis was defined as a stenosis of >50% as assessed by the operator. The choice of antithrombotic treatment followed local routines of the participating hospitals and under discretion of the treating physician.

Participating hospitals had similar post-resuscitation protocols according to post-resuscitation guidelines.[5]

Standard of care group
According to the study protocol, coronary angiography should not be performed earlier than 3 days after the cardiac arrest unless circulatory instability (cardiogenic shock), ventricular arrhythmias (sustained VT or VF) or ECG changes (ST-elevation) indicative of cardiac ischemia occurred.

Data collection

Data collection was performed according to a prespecified clinical report form (CRF). Coronary angiography and PCI data were collected from the Swedish Coronary Angiography and Angioplasty Register (SCAAR). Each study site was monitored by independent research nurses according to Good Clinical Practice standards.

Feasibility

Prehospital and in-hospital timeframes
All time measurements from the cardiac arrest to Emergency Medical Services (EMS) arrival, time to randomization, time to cardiac catheterization and time to ICU arrival were collected.

Randomization and informed consent issues

Logistical problems regarding the randomization and informed consent procedures from the patients or next of kin were reported.

Cross over (adherence to protocol)

Patients in the standard of care group performing coronary angiography earlier than three days because of circulatory instability (cardiogenic shock), ventricular arrhythmias (sustained VT or VF) or new ST-elevation were analyzed regarding the reason for earlier catheterization.

Presenting electrocardiogram, ECG

The presenting ECG and the decision to randomize or not, based on the ECG interpretation, was collected from the EMS or at the latest in emergency room. ECG patterns were reported as ST-elevation, ST-depression, left bundle branch block, right bundle branch block, Q-waves, T-wave inversion or others which included normal ECG findings.

Safety aspects

Bleedings were reported as major or minor according to a prespecified protocol.[10] Minor bleedings defined as observed bleeding with decrease in hemoglobin, >30 g/L but less than 50 g/L. Major bleeding defined as bleeding with decrease in hemoglobin >50 g/L. Comparison was made regarding renal failure and the need for renal replacement therapy.

Coronary angiography and PCI findings
All possible adverse events related to the intervention such as bleedings, procedure related cardiac arrest and ventricular arrhythmias were recorded.

Secondary transportations
Cases of secondary transportations between primary and tertiary hospitals were observed regarding safety issues such as new cardiac arrest during transportation and time to coronary angiography.

24-h mortality
The 24-h mortality rate was used as a safety measure to detect any differences between the study groups.

Statistical analysis

The sample size of the pilot phase with about 80 randomized patients was predefined in the protocol and was chosen as reasonably appropriate to assess feasibility of a strategy to perform immediate coronary angiography in OHCA patients and to assess important safety aspects. The main DISCO trial is powered to detect a 20% relative difference in 30-day survival and is planned to recruit 1006 patients.

The analyses were based on all randomized patients without ST-elevations. In addition, we report data from the observation group with ST-elevations for comparisons regarding procedure related side effects.

Categorical variables are presented as total numbers of patients and proportions (%) in each group. Continuous variables are presented as medians and interquartile ranges (IQR). Due to the limited number of patients presented in this pilot study no comparative statistics were performed, and no outcome data were analyzed regarding primary and secondary outcomes of the main study.

Results

A total of 79 patients were randomized from January 1, 2015 to October 15, 2017 of which 39 were in the immediate angiography group and 40 in the standard of care group. An additional 39 patients were enrolled in the observational ST-elevation non-randomized group (Fig. 1). Among patients admitted after an OHCA at the participating sites, approximately 12% were randomized. The exact number of patients that were screened for eligibility in the study cannot be presented. The main reasons for not participating in the study were obvious non-cardiac causes and unwitnessed cardiac arrest.

Baseline characteristics

Baseline characteristics are presented in Table 1. The most common location of the CA was at home in the both randomized groups. Patients were predominantly men. Ventricular fibrillation was the primary ECG rhythm in 52.6% of the immediate angiography group and 55% in the standard of care group. Heart failure, previous stroke, and previous cancer were numerically somewhat more frequent in the immediate angiography group.

Presenting electrocardiogram, (ECG)
As seen in Table 1 right bundle branch block was numerically more frequent in the immediate angiography group compared to the standard of care group (26.5% versus 17.5%) and ST-depression was more commonly found in the standard of care group (15% versus 13.2%). Other ECG changes, including normal ECG and unspecific ECG changes, were numerically more common in the standard of care group compared to the immediate angiography group (40.0% versus 34.2%).

Feasibility

Prehospital and in-hospital event times
Event times in all treatment groups are presented in Table 2. The median time from the CA to EMS arrival was 8 min (Q1–Q3: 6–13) in the

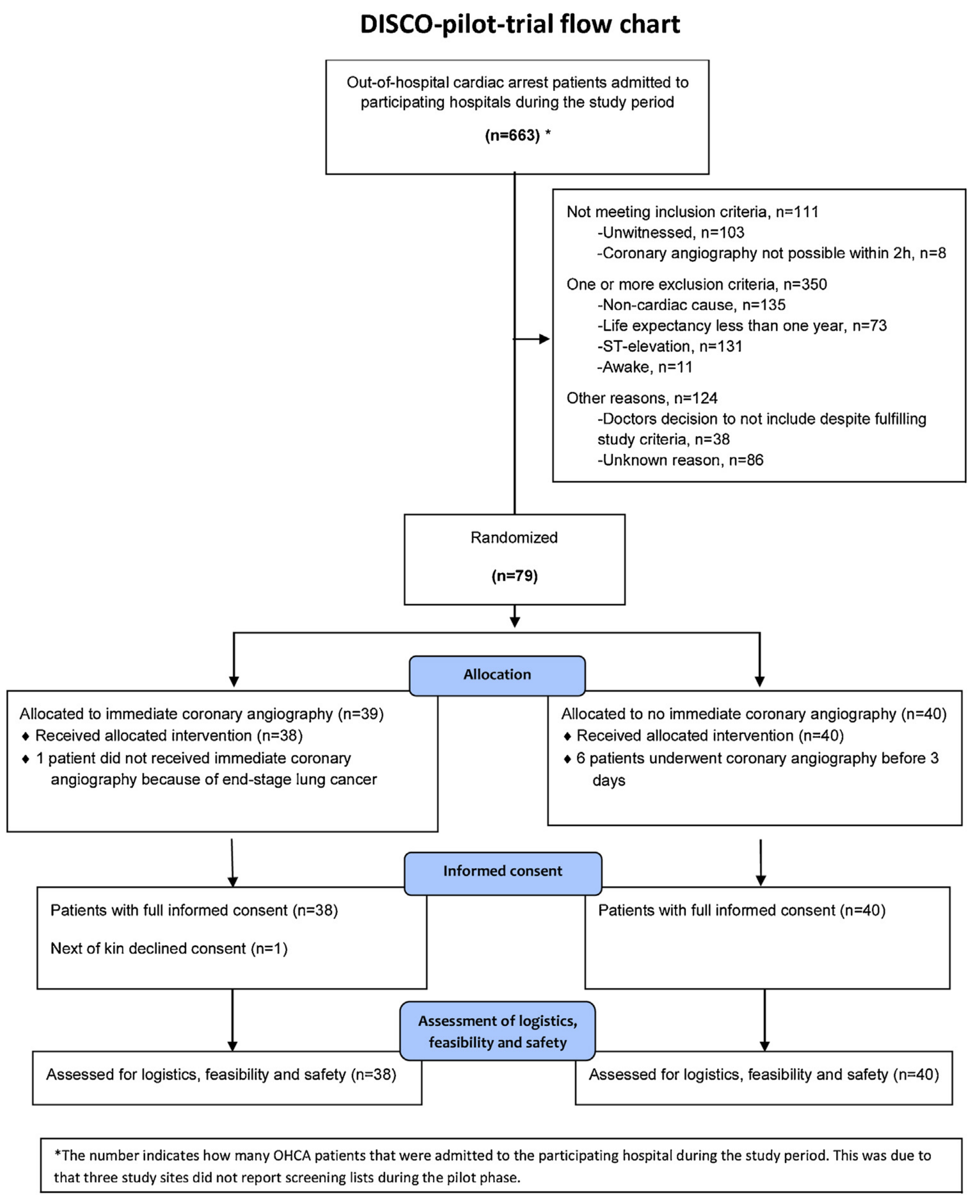

Fig. 1 – DISCO-pilot-trial flow chart.

immediate angiography group and 9 min (Q1–Q3: 6–12) in the standard of care group. Median time from CA to ROSC was 20 min (Q1–Q3: 14–35) in the immediate angiography group and 25 min (Q1–Q3: 19–34) in the standard of care group. The median time from EMS arrival to coronary angiography was 135 min (Q1–Q3: 106–178) in the immediate angiography group (Table 2).

Randomization and informed consent issues

The inclusion and exclusion criteria on scene were in 10 of the randomized patients later reevaluated (mainly due to non-witnessed and awake patients) as not fulfilling the study criteria, but still presented in this early assessment of the study according to intention to treat. In one deceased patient, the next of kin later declined study participation. One patient was randomized to immediate coronary angiography, but after having a dialogue with next of kin, the clinician decided not to perform coronary angiography due the exclusion criterion end-stage metastatic lung cancer.

Cross-over

In the standard of care group 6 of 40 (15%) patients underwent coronary angiography earlier than 3 days after the cardiac arrest. In two of those patients new onsets of symptoms and ST-elevation were detected during repeated ECG's after randomization and coronary angiography was therefore performed after 3.5 and 35 h respectively from randomization. In one patient, high troponin elevations were detected after six hours, interpreted as a high probability of an occluded coronary vessel by the clinician in charge and the patient underwent coronary angiography 26 h after randomization. In another patient, an acute echocardiography indicated a new onset of ischemia and a coronary angiography was therefore performed 48 h after randomization. In three of these six patients PCI was performed. In two

Table 1 – Baseline characteristics.

Group of characteristics	Characteristics	No ST elevation		ST elevation
		Immediate CAG n = 38	Standard care n = 40	Observation n = 39
	Age years median (Q1–Q3)	71 (62–78)	70 (61–77)	62 (53–71)
	Male	22 (57.9%)	31 (77.5%)	35 (89.7%)
Pre-hospital characteristics	Location of arrest—home	22 (57.9%)	25 (62.5%)	18 (46.2%)
	Bystander CPR	28 (73.7%)	30 (75.0%)	27 (69.2%)
	Initial rhythm VT/VF	20 (52.6%)	22 (55.0%)	29 (74.4%)
	Initial rhythm asystole	8 (21.1%)	4 (10.0%)	7 (17.9%)
	Initial rhythm PEA	7 (18.4%)	13 (32.5%)	2 (5.1%)
	Initial rhythm unknown	3 (7.9%)	1 (2.5%)	1 (2.6%)
Medical history	Ischemic heart disease	9 (23.7%)	10 (25.0%)	7 (17.9%)
	Previous myocardial infarction	6 (15.8%)	8 (20.0%)	7 (17.9%)
	Previous PCI	4 (10.5%)	7 (17.5%)	6 (15.4%)
	Previous CABG	3 (7.9%)	3 (7.5%)	0 (0%)
	Heart failure	7 (18.4%)	6 (15.0%)	3 (7.7%)
	COPD	7 (18.4%)	7 (17.5%)	0 (0%)
	Previous Stroke	6 (15.8%)	4 (10.0%)	1 (2.6%)
	Cancer	7 (18.4%)	6 (15.0%)	2 (5.1%)
	Diabetes	6 (15.8%)	10 (25.0%)	6 (15.4%)
Measurements at emergency room	Pulse rate, bpm, median, (Q1–Q3)	95 (80–117)	90 (73–111)	98 (79–110)
	Systolic blood pressure (mmHg) median (Q1–Q3)	130 (107–149)	125 (109–161)	120 (91–142)
	Glasgow Coma Scale, median (Q1–Q3)	3 (3–4)	3 (3–3)	3 (3–3)
First arterial blood gas	pH (Q1–Q3)	7.2 (7.1–7.3)	7.2 (7.1–7.3)	7.2 (7.0–7.3)
	PaO2 (kPa), median, (Q1–Q3)	16.2 (11.1–39.8)	18.5 (12.1–35.4)	17.5 (11.0–35.6)
	PaCO2 (kPa) median (Q1–Q3)	5.7 (4.7–8.5)	5.9 (5.1–8.0)	5.8 (5.1–7.5)
	Lactate (mmol/L) (Q1–Q3)	7.9 (5.7–9.9)	7.5 (5.7–9.7)	8.5 (5.1–12.0)
Presenting ECG	ST-elevation	2 (5.2%)	0 (0%)	37 (94.9%)
	ST-depression	5 (13.2%)	6 (15.0%)	1 (2.6%)
	Right bundle branch block	10 (26.3%)	7 (17.5%)	0 (0%)
	Known Left bundle branch block	5 (13.2%)	4 (10.0%)	1 (2.6%)
	New Left bundle branch block	0 (0%)	1 (2.5%)	1 (2.6%)
	Q-wave	1 (2.6%)	1 (2.5%)	0 (0%)
	T-wave inversion	1 (2.6%)	2 (5.0%)	0 (0%)
	Other, incl normal	13 (34.2%)	16 (40.0%)	0 (0%)
ECG rhythm	Sinus rhythm	26 (68.4%)	25 (62.5%)	31 (79.5%)
	Atrial fibrillation	9 (23.7%)	11 (27.5%)	4 (10.3%)
	Ventricular tachycardia	1 (2.6%)	0 (0%)	0 (0%)
	Other, incl AV-block	2 (5.2%)	3 (7.5%)	3 (7.7%)

Categorical variables are presented as numbers (%). Continuous variables are presented as medians (Q1–Q3). Abbreviations: CPR: Cardio pulmonary resuscitation, VT: Ventricular Tachycardia, VF: Ventricular fibrillation, PEA: Pulseless electric activity, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass grafting, COPD: Chronic obstructive pulmonary disease.

Table 2 – Time periods.

Median times (Q1–Q3)	No ST elevation		ST elevation
	Immediate CAG n = 38	Standard of care n = 40	Observation, STEMI n = 39
Time from cardiac arrest to EMS arrival (min)	8 (6–13)	9 (6–12)	8 (4–12)
Time from cardiac arrest to ROSC (min)	20 (14–35)	25 (19–34)	25 (17–30)
Time from EMS arrival to vessel puncture (min)	135 (106–178)		
Time from cardiac arrest to randomization (min)	79 (65–96)	76 (63–92)	NA
Time from randomization to angio (min)	69 (42–94)	NA	NA
Time from ER arrival to ICU arrival (min)	155 (85–212)	104 (85–134)	176 (143–210)
Time from ER arrival to vessel puncture (min)	98 (68–133)	NA	NA

Times are presented as medians (Q1–Q3). Abbreviations: EMS: Emergency medical service, ROSC: Return of spontaneous circulation, CA: Cardiac arrest, ICU: Intensive care unit, ER: Emergency room, NA: Not answered.

Table 3 – Coronary angiography and PCI.

	Immediate CAG n = 38	Observation (STEMI) n = 39
Radial access	17 (44.7%)	13 (33.3%)
Femoral access	18 (47.4%)	23 (59.0%)
Access not answered	3 (7.9%)	3 (7.7%)
Culprit lesion identified	14 (36.8%)	26 (66.7%)
Culprit vessel, LAD	5 (13.2%)	18 (46.2%)
Culprit vessel, LCX	3 (7.9%)	2 (5.1%)
Culprit vessel, RCA	4 (10.5%)	6 (15.4)
Culprit vessel, Other	2 (5.3%)	0 (0%)
Culprit vessel, Chronic total occlusion (CTO)	2 (5.3%)	1 (2.6%)
PCI of any vessel	15 (39.5%)	26 (66.7%)
General success	14 (93%)	26 (100%)
Significant stenosis outside identified culprit vessel	7 (18.4%)	13 (33.3%)
Complete revascularization, multi-vessel disease[a]	2 (28.6%)	4 (30.1%)
Complication related to intervention		
New cardiac arrest at PCI-unit	3 (7.9%)	2 (5.1%)
Arrhythmias (VT/VF) requiring treatment at PCI-unit	2 (5.3%)	2 (5.1%)
Bleeding minor	0 (0%)	0 (0%)
Bleeding major	0 (0%)	0 (0%)
Cardiac tamponade	0 (0%)	0 (0%)
Deceased at PCI-unit	0 (0%)	0 (0%)

Categorical variables are presented as numbers (%). Abbreviations: LAD: Left artery descending, LCX: Left circumflex artery, RCA: Right coronary artery, PCI: Percutaneous coronary intervention, VT: Ventricular tachycardia, VF: Ventricular fibrillation.

[a] Complete revascularization of those identified as significant stenosis outside identified culprit vessel.

patients coronary angiography was performed earlier than three days without any reason specified in the CRF.

Coronary angiography and PCI findings (Table 3)

Of the 39 patients randomized to immediate angiography, 38 received the allocated intervention. In the immediate angiography group a culprit lesion was found in 14/38 patients (36.8%) and PCI was performed in 15/38 patients (39.5%) and assessed as successful in 14/15 (93%) patients. Multi-vessel disease with at least one additional significant stenosis, except culprit, was found in 6/38(15.8%) patients in the immediate angiography group. Full revascularization, as recommended in the protocol, was carried out in only two of these six patients (33.3%). Chronic total occlusion (CTO) was deemed as culprit in two patients (5.9%) in the immediate angiography group. Among patients allocated to the standard of care group, 12 (30%) patients underwent coronary angiography after 3 days.

Safety aspects (Table 4)

One patient in the standard of care group was diagnosed with subarachnoid hemorrhage at day one and two patients in the observation STEMI group were also diagnosed with subarachnoid hemorrhage after coronary angiography. In none of these patients, the bleedings were considered as related to the intervention.

No patients suffered from procedure related death in the coronary angiography lab. Three patients in the immediate coronary angiography group had a new cardiac arrest in the coronary angiography lab with ventricular fibrillation requiring defibrillation.

Three minor bleedings were reported in both the immediate angiography and standard of care groups (7.9% versus 7.5%). No minor bleeding was reported in the observational STEMI group. There were no major bleeding events reported in the randomized groups, but in the observational STEMI group, two major bleeding events occurred (5.1%).

Two patients in the standard of care group were treated with intra-aortic balloon pump (IABP) for circulatory support versus no patient in the immediate angiography group.

Transportation

Transportation between primary and tertiary hospitals occurred in 7 out of 38 cases (18.4%) due to the lack of 24/7 coronary angiography services in two of the participating study centers. No serious event occurred during the transport from the primary hospital to the tertiary center. However, one patient had a new cardiac arrest after the re-transportation back to the primary hospital, which occurred two hours after PCI was performed. The patient achieved ROSC but deceased the following day in the ICU.

24-h mortality

The mortality at 24 h was 7.9% (n = 3) in patients randomized to immediate angiography and 15% (n = 6) in patients randomized to standard care. The corresponding 24-h mortality in the observational STEMI group was 10.3% (n = 4).

Discussion

The main findings of this study were that randomization to a strategy to perform immediate coronary angiography in OHCA patients without ST-elevations was feasible and without evident safety issues.

Feasibility of the intervention

One of the inclusion criteria was that coronary angiography should be possible to perform within 120 min from EMS arrival at the scene of the

Table 4 – Safety/ICU parameters.

		No ST elevation		ST elevation
		Immediate CAG n = 38	Standard of care n = 40	Observation, n = 39
Parameters at ICU arrival	Pulse rate (bpm) (Q1–Q3)	82 (70–92)	86 (71–105)	90 (75–97)
	Mean arterial pressure (mmHg) (Q1–Q3)	76 (70–85)	73 (63–84)	80 (69–90)
	Core temperature (°C) (Q1–Q3)	35.9 (34.8–36.4)	36.1 (35.1–36.4)	35.3 (34.4–35.8)
	Arterial blood gas-pH (Q1–Q3)	7.3 (7.3–7.4)	7.3 (7.2–7.4)	7.3 (7.3–7.4)
	Arterial blood gas-PaO2 (kPa) (Q1–Q3)	11.1 (9.7–15.0)	11.6 (8.4–14.4)	13.4 (10.1–17.8)
	Creatinine (μmol/L) (Q1–Q3)	104 (81–134)	102 (90–130)	96 (84–118)
	Cystatine C (μmol/L) (Q1–Q3)	1.3 (1.0–1.6)	1.0 (0.8–1.4)	1.0 (0.7–1.3)
Measures at ICU				
	TTM 36 °C	12 (31.6%)	17 (45.9%)	13 (33.3%)
	TTM 33 °C	9 (23.7%)	11 (29.7%)	15 (38.5%)
	Refractory lactate acidosis at 20–28 h	8 (21.1%)	10 (25%)	7 (17.9%)
	Creatinine 3 days after CA (μmol/L) (Q1–Q3)	100 (72–179)	100 (84–182)	80 (67–96)
	Cystatin C 3 days after CA (μmol/L) (Q1–Q3)	1.2 (1.0–1.9)	1.1 (0.8–1.6)	1.0 (0.7–1.2)
	Renal failure requiring CRRT	1 (2.6%)	1 (2.5%)	2 (5.1%)
	Pneumonia	21 (55.3%)	14 (35.0%)	19 (48.7%)
	Norepinephrine required (any ICU day)	29 (76.3%)	35 (87.5%)	36 (92.3%)
	Adrenalin required (any ICU day)	4 (10.5%)	5 (12.5%)	3 (7.7%)
	Levosimendan required (any ICU day)	3 (7.9%)	8 (20.0%)	7 (17.9%)
	Dobutamin required (any ICU day)	7 (18.4%)	2 (5.0%)	9 (23.1%)
	Isoprenalin required (any ICU day)	1 (2.6%)	2 (5.0%)	2 (5.1%)
Antiplatlet drugs first 24 h				
	Acetylsalicylic acid	16 (42.1%)	12 (30.0%)	26 (66.7%)
	Clopidogrel	4 (10.5%)	4 (10.0%)	4 (10.3%)
	Ticagrelor	7 (18.4%)	5 (12.5%)	27 (69.2%)
	Cangrelor	4 (10.5%)	0 (0%)	2 (5.1%)
Adverse events				
	Need for mechanical circulatory support	0 (0%)	2 (5.0%)	4 (11.1%)
	Bleedings, minor	3 (7.9%)	3 (7.5%)	0
	Bleedings, major	0	0	2 (5.1%)
	Subarachnoid hemorrhage	0	1 (2.5%)	2 (5.1%)
	Ventricular arrhythmias, VT or VF	1 (2.6%)	2 (5.0%)	7 (17.9%)
	Brady arrhythmias requiring pacemaker	0	1 (2.5%)	1 (2.6%)
ICU outcome measures				
	Time in ventilator (hours) (Q1-Q3)	61 (32–127)	75 (41–113)	72 (40–152)
	Time in ICU (days) (Q1–Q3)	4 (1–6)	3 (2–6)	4 (2–9)
	Decision of Do Not Resuscitate (DNR)	13 (34.2%)	16 (40.0%)	10 (25.6%)
	Decision of palliative care	13 (34.2%)	12 (30.0%)	10 (25.6%)
	Deceased at 24 h from cardiac arrest	3 (7.9%)	6 (15.0%)	4 (10.3%)

Categorical variables are presented as numbers (%). Continuous variables are presented as medians (Q1–Q3). TTM: Target temperature management, CA: Cardiac arrest, CRRT: Continuous renal replacement therapy, ICU: Intensive care unit, VT: ventricular tachycardia, VF: ventricular fibrillation.

arrest. This was not achieved in the majority of patients as the median time to coronary angiography in this pilot phase was 135 min (Q1–Q3: 106–178). As a consequence of this, the study protocol for the main study was modified with the amendment that coronary angiography should be possible to perform within 120 min from randomization.

A culprit lesion was identified and treated with PCI in 37% of the patients randomized to immediate coronary angiography, which is a similar proportion compared to earlier observational studies.[11–13]

According to the protocol, PCI should be carried out in culprit lesions and was recommended in all significant stenoses during the acute angiography. However, only two patients, randomized to immediate coronary angiography, had this “complete revascularization strategy”. After the recently published results from the Culprit-Shock trial,[14] suggesting higher risk of immediate multivessel PCI, the study protocol was changed to culprit-lesion-only PCI. Subsequent evaluation with Fractional Flow Reserve and PCI of non-culprit lesions at a later stage is left to decide according to local clinical routine.

In the standard of care group six patients performed coronary angiography earlier than 3 days after CA and in four patients the reasons were outside the protocol such as considerable Troponin elevations and echocardiography-findings suggesting ischemia. However, in a pragmatic study as the DISCO-trial it is difficult to prevent such clinically based decisions.

Safety aspects

Most of the complications reported including pneumonia and the requirement of vasopressors or inotropic drugs were expected in this group of patients. The adverse events related to coronary angiography and PCI were low in all groups. The rate of bleedings and signs of renal failure were low and did not differ between the randomized groups. Three patients with cerebral hemorrhage as a primary cause of the cardiac arrest were included in the study. The strategy of immediate angiography may confer a risk of delaying the diagnose of non-cardiac causes of the arrest. Furthermore, an immediate invasive approach with PCI against non-culprit stenosis and subsequent administration of anti-platelet drugs might be deleterious for a patient with cerebral hemorrhage. On the other hand, an immediate angiography that excludes culprit lesions might promote a more aggressive search for alternative causes for the arrest and the possibility to find and treat more uncommon causes.

Transportation

One important question is whether OHCA patients should be transported directly to hospitals with 24/7 coronary angiography capabilities in line with the concept of “Cardiac Arrest centers”.[15] Most hospitals around the world do not have a 24/7 angiography service, and this strategy is still debatable. However, transportation from primary receiving hospital to tertiary hospital after resuscitated OHCA could potentially be hazardous with risk of recurrent ventricular arrhythmias and new cardiac arrests. In this pilot phase, secondary transportation from the primary hospital to a tertiary hospital for immediate coronary angiography was safe in the seven patients that were transferred. Due to the limited number of patients this important concern will be more thoroughly addressed in the main phase of the study. However, one patient, randomized to immediate coronary angiography, suffered a new cardiac arrest after transportation back to the primary hospital. The decision to re-transportation the patients earlier (one hour after PCI) than routine occurred due to the shortage of ICU-beds at the tertiary hospital.

Challenges and experiences

First, the proportion of coronary culprit lesions in patients without ST-elevation was about 37% which is similar to data from observational studies.[12,16] Thus, the presented data establish the heterogeneity of resuscitated OHCA patients without ST-elevations compared to those patients with ST-elevation that have a higher probability of coronary cause of the cardiac arrest. This heterogeneity has previously been described in a consensus report[17] which recommend a short “ER-stop” for evaluating the need for immediate coronary angiography in these patients.

Second, the overall recruitment rate was low and only 12% of the patients that were admitted to the participating hospitals were randomized. Thus, it is crucial to further facilitate cooperation between cardiologists, emergency care physicians and ICU-doctors to succeed in this type of trial. It is also important to find the key players at a local level to facilitate patient enrolment.

Third, there is an apparent risk of selection bias if clinicians tend to only randomize patients with low risk of having an occluded coronary artery. Thus, it is both challenging and important to convince clinicians to include patients in the study to close the evidence gap even if some clinicians may have a strong belief in performing immediate coronary angiography in all OHCA patients. Otherwise, there is a strong risk of selection bias.

Fourth, the randomization was performed at a later stage than expected. The aim was to randomize patients already prehospitally in order to facilitate early coronary angiography, i.e. within 120 min. However, this was not fully achieved and the time window for performing coronary angiography has been extended to 120 min from randomization.

Limitations

We found no major adverse events in the population studied. However, the number of patients might be too small to determine important clinical safety issues and differences.

Conclusion

In this population of bystander witnessed out-of-hospital cardiac arrest patients without ST-elevation, a strategy to perform immediate coronary angiography was feasible although the time window of 120 min from EMS arrival at the scene of the arrest to start of coronary angiography was not achieved. No significant safety issues were reported.

Conflict of interest statement

None of the authors had any conflict of interest.

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