Resuscitation 94 (2015) 61–66

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical Paper

Impact of urgent coronary angiography on mid-term clinical outcome of comatose out-of-hospital cardiac arrest survivors presenting without ST-segment elevation☆

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ARTICLE INFO

Article history:
Received 26 March 2015
Received in revised form 23 June 2015
Accepted 29 June 2015

Keywords:
Cardiac arrest
Temperature management
Acute coronary syndrome
Coronary angiography

ABSTRACT

Background: Timing of coronary angiography (CAG) is still controversial in the out-of-hospital cardiac arrest survivors who present without ST-segment elevation.

Methods and results: We analysed a prospective registry of 158 comatose survivors of out-of-hospital cardiac arrest. For further analysis, we included 99 patients without ST-segment elevation on the initial electrocardiogram. All patients underwent temperature management. Urgent CAG (<2 h from admission) was performed in 25% of the patients. A definite cause of the cardiac arrest could be identified during the index hospitalization in 82 patients: 36 had a non-ST-segment elevation acute coronary syndrome (NSTE-ACS) and 46 had a non-ACS diagnosis. Eighty-seven patients (88%) survived the index hospitalization and 65 (66%) were alive at six months. A favourable neurological status (cerebral performance category ≤2) was observed in 56% of the patients at discharge and in 56% after six months of follow-up. Neither the survival nor the neurological outcome differed between the patients in whom the CAG was performed urgently upon the admission and the patients in whom the CAG was initially not performed, regardless of the aetiology of the cardiac arrest. On the other hand, performing an urgent CAG was safe and it did not prolong the average time to achieve an effective hypothermia.

Conclusions: Performing an urgent CAG in comatose cardiac arrest survivors without ST-segment elevation was not associated with better clinical and neurological outcome as compared to the initially conservative approach.

1. Introduction

Out-of-hospital cardiac arrest is often caused by acute myocardial ischaemia.[1] This justifies performing an urgent coronary angiography (with the prospect of revascularization of the culprit lesion) in all the cardiac arrest survivors who present with a suspected or definite acute coronary syndrome (ACS).[2] However, the diagnosis of a non-ST-segment elevation ACS (NSTE-ACS) may be challenging in the post resuscitation comatose patients, especially when the electrocardiographic (ECG) and laboratory findings are inconclusive and the patient's medical history is unknown.[3,4] Thus, the clinicians must often deal with a difficult decision of whether to activate the cath lab immediately upon admission of the patient, or whether to focus initially on achieving a therapeutic hypothermia or on proceeding with differential diagnosis of other possible causes of the cardiac arrest.

This study analysed clinical practice in a large referral centre in the initial management of the post-cardiac arrest patients who did not present with ST-segment elevation myocardial infarction (STEMI). The primary aim was to evaluate whether performing an urgent coronary angiography (CAG) in these patients would have impact on the in-hospital and 6-month mortality and neurological performance as compared to delaying the CAG or not performing a CAG at all. In addition, the study aimed to identify baseline variables which could help to reveal the ischaemic aetiology of the cardiac arrest.

2. Methods

2.1. Study design

We have analysed a prospective registry of 158 consecutive out-of-hospital cardiac arrest survivors who were admitted to our

Abbreviations: ACS, acute coronary syndrome; CAG, coronary angiography; CPC, cerebral performance category; ECG, electrocardiogram; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction.

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2015.06.022.

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http://dx.doi.org/10.1016/j.resuscitation.2015.06.022
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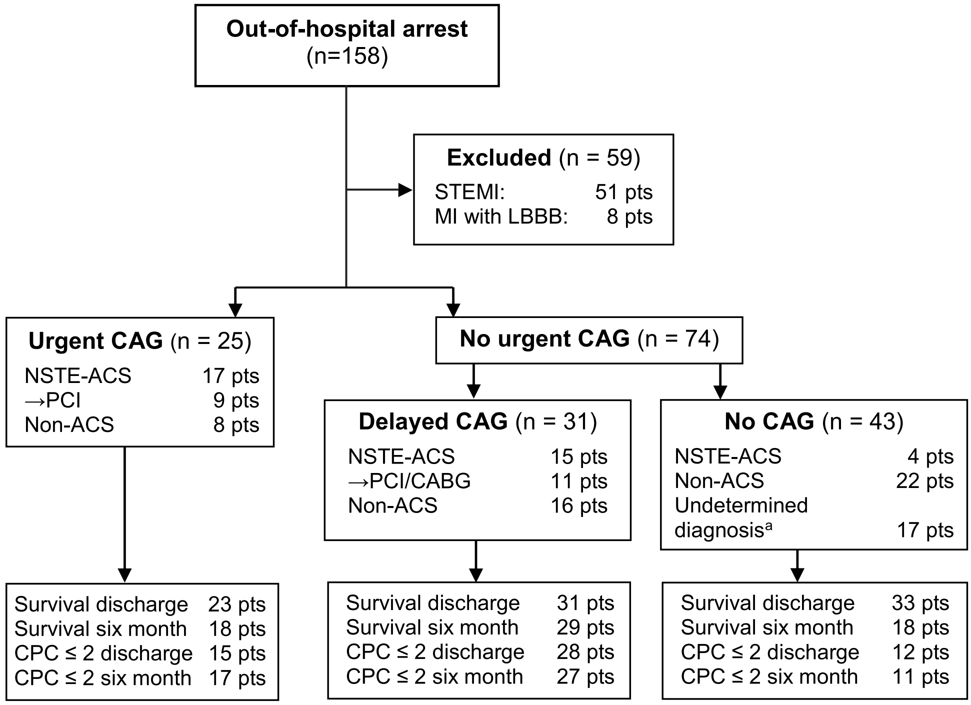

Fig. 1. A study flow chart. ACS = acute coronary syndrome; CAG = coronary angiography; CABG = coronary artery bypass graft; CPC = cerebral performance category; LBBB = left bundle branch block; MI = myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction. [a] Patients excluded from the comparison between NSTE-ACS and non-ACS group.

cardiology intensive care unit between January 2007 and June 2014. Subject's informed consent was not required because of the observational design of the study which was fully anonymized. Patients with acute STEMI or myocardial infarction with left bundle branch block were excluded from further analysis (Fig. 1). In the remaining patients, the cause of the cardiac arrest was not apparent at the initial presentation.

The CAG was considered "urgent" when performed immediately (<2 h) after admission.[5] Indication for performing urgent CAG was based solely on the clinical judgment of attending cardiologists. The cath lab was available 24/7. The decision about performing a delayed CAG or to not perform CAG at all was usually made only after completion of temperature management after reassessing the neurological status.

The patients who underwent an urgent CAG were compared with the patients with delayed or no CAG with regard to the baseline variables, in-hospital and 6-month mortality and cerebral performance category (CPC). Six-month clinical and neurological follow-up were available in all the survivors.

Final diagnoses were made at the time of discharge from the index hospitalization after evaluation of all available clinical and laboratory data, findings of CAG and other diagnostic modalities such as echocardiography, computed tomography angiography, cardiovascular magnetic resonance imaging or electrophysiology study. The diagnosis of ACS was based on the established criteria.[6] In 17 patients, the aetiology of cardiac arrest remained undetermined; in these patients the final diagnosis was usually not pursuit, after a clinical consensus, because of persisting poor neurological status.

All patients underwent temperature management according to the institutional protocol. Based on the contemporary evidence, patients admitted before December 2013 ($n = 89$) were maintained at 32–34 °C for 12–24 h,[7,8] while after December 2013 ($n = 10$) we aimed for a body temperature of 34–36 °C.[9] Target temperature was achieved by means of a hypothermic blanket (Blanketrol, Cincinnati Sub-Zero, USA), ice packs and cold infusions.

2.2. Statistical analysis

Statistical analyses were performed using JMP 10 (SAS Institute Inc., Cary, US). Continuous variables are expressed as mean ± standard deviation or median [interquartile range], according to the normality of the distribution. Categorical variables are expressed as frequency (percentage). Group comparisons were performed using the Student's *t*-test, Mann–Whitney *U* test or chi-square test, as appropriate. Logistic regression was used to identify the predictors of the clinical outcome. *P* value <0.05 was considered statistically significant.

3. Results

Table 1 shows comparison of the investigated baseline and outcome variables among the patient groups. In total, 25 patients (25%) underwent urgent CAG, 31 (31%) underwent a delayed CAG and 43 (43%) did not undergo CAG at all. Percutaneous coronary intervention or coronary artery bypass graft was performed in 20% of all patients; in 9% the revascularization was urgent.

Overall, 88% of patients survived the index hospitalization and 66% were alive at six months. A favourable neurological status (CPC ≤ 2) was observed in 56% of the patients at discharge from the hospitalization and in 56% at six months of follow-up. Neither the survival nor the neurological outcome differed between the patients who underwent urgent CAG upon admission and the patients in whom the CAG was initially delayed or not performed at all. Importantly, the clinical and neurological outcome was not related to the underlying aetiology of the cardiac arrest per se (Table 1).

In a subgroup analysis, the highest 6-month survival rates (100%) and the best neurological performance (CPC ≤ 2 in 94% of the cases) were observed in the non-ACS patients who underwent a delayed CAG. In contrast, the lowest 6-month survival (42%) and the worst neurological outcome (CPC ≤ 2 in 26% of the cases) were observed in the patients in whom the CAG was not performed at all.

Table 1
Association of the urgent, delayed or no coronary angiography with the baseline characteristics, resuscitation parameters, temperature management variables, revascularisation and clinical outcome.

	Coronary angiography				*p*-Value		
	Urgent (*n* = 25)	Delayed (*n* = 31)	No CAG (*n* = 43)	Delayed or no CAG (*n* = 74)	Urgent vs. delayed	Urgent vs. no CAG	Urgent vs. delayed or no CAG
Clinical characteristics							
Age	**59 ± 11**	56 ± 19	59 ± 17	**58 ± 18**	0.48	0.82	**0.85**
Male	**23 (92)**	26 (84)	29 (67)	**55 (74)**	0.36	0.02	**0.06**
Known history of CAD	**10 (40)**	7 (23)	17 (55)	**24 (39)**	0.16	0.27	**0.91**
VF/VT at the first medical contact	**22 (88)**	30 (97)	21 (49)	**51 (69)**	0.21	0.001	**0.06**
Left ventricular ejection fraction (%)[a]	**42 ± 14**	37 ± 15	42 ± 16	**39 ± 15**	0.18	0.90	**0.40**
CPR characteristics[b]							
OHCA witnessed	**12 (86)**	12 (92)	18 (86)	**30 (88)**	0.59	1.00	**0.81**
Basic life support performed	**13 (93)**	13 (100)	18 (86)	**31 (91)**	0.33	0.52	**0.85**
Basic life support time (min)	**8.5 [4.8–10]**	7.0 [5.0–9.5]	6.0 [3.0–10]	**7.0 [4.0–10]**	0.57	0.56	**0.52**
Advanced life support time (min)	**13 [10–16]**	10 [4.0–23]	14 [8.5–23]	**11 [6.7–22]**	0.26	0.91	**0.66**
Time from OHCA to ROSC (min)	**22 [15–25]**	16 [13–30]	21 [14–32]	**19 [13–30]**	0.30	0.97	**0.75**
Troponins at admission							
Troponin I (μg/L)	**0.2 [0.1–1.6]**	0.2 [0.1–0.4]	0.2 [0.1–0.6]	**0.2 [0.1–0.5]**	0.38	0.43	**0.37**
High-sensitivity troponin T (ng/L)	**118 [51–236]**	166 [77–282]	78 [31–129]	**113 [34–213]**	0.44	0.24	**0.72**
ECG at admission							
ST depression ≥0.1 mV in ≥2 leads	**13 (52)**	9 (29)	19 (44)	**28 (38)**	0.08	0.53	**0.21**
Right bundle branch block	**3 (12)**	6 (19)	10 (23)	**16 (22)**	0.46	0.26	**0.29**
Other ECG pattern	**8 (32)**	7 (23)	15 (35)	**22 (30)**	0.43	0.81	**0.83**
Normal ECG	**4 (16)**	13 (42)	5 (12)	**18 (24)**	0.04	0.61	**0.39**
Revascularisation							
Urgent or delayed	**9 (36)**	11 (35)	–	**11 (15)**	0.97	–	**0.02**[c]
Temperature management[b]							
Delay from OHCA to achieve hypothermia (hours)	**3.1 ± 2.6**	3.5 ± 1.7	3.8 ± 2.2	**3.7 ± 2.0**	0.68	0.42	**0.43**
Delay from admission to achieve hypothermia (hours)	**1.6 ± 2.0**	2.4 ± 1.6	1.8 ± 1.4	**2.1 ± 1.5**	0.39	0.84	**0.52**
Uninterrupted hypothermia ≥12 h[d]	**14 (100)**	11 (85)	19 (90)	**30 (88)**	0.13	0.23	**0.18**
Uninterrupted hypothermia ≥24 h	**8 (57)**	9 (69)	13 (62)	**22 (65)**	0.52	0.78	**0.62**
Survival at discharge							
All patients	**23 (92)**	31 (100)	33 (77)	**64 (86)**	0.11	0.11	**0.47**
NSTE-ACS patients[e]	**16 (94)**	15 (100)	1 (25)	**16 (84)**	0.34	0.002	**0.35**
Non-ACS patients[f]	**7 (88)**	16 (100)	18 (82)	**34 (89)**	0.15	0.72	**0.87**
Survival at 6 months							
All patients	**18 (72)**	29 (94)	18 (42)	**47 (64)**	0.03	0.02	**0.44**

Table 1 (*Continued*)

	Coronary angiography				*p*-Value		
	Urgent ($n=25$)	Delayed ($n=31$)	No CAG ($n=43$)	Delayed or no CAG ($n=74$)	Urgent vs. delayed	Urgent vs. no CAG	Urgent vs. delayed or no CAG
NSTE-ACS patients[e]	**12 (71)**	13 (87)	0 (0)	**13 (68)**	0.27	0.01	**0.89**
Non-ACS patients[f]	**6 (75)**	16 (100)	12 (55)	**28 (74)**	0.04	0.31	**0.94**
CPC ≤ 2 at discharge							
All patients	**15 (60)**	28 (90)	12 (28)	**40 (54)**	0.008	0.009	**0.60**
NSTE-ACS patients[e]	**10 (59)**	13 (87)	0 (0)	**13 (68)**	0.08	–	**0.55**
Non-ACS patients[f]	**5 (63)**	15 (94)	11 (50)	**26 (68)**	0.05	0.54	**0.75**
CPC ≤ 2 at 6 months							
All patients	**17 (68)**	27 (87)	11 (26)	**38 (51)**	0.08	0.001	**0.15**
NSTE-ACS patients[e]	**11 (65)**	12 (80)	0 (0)	**12 (63)**	0.34	0.02	**0.92**
Non-ACS patients[f]	**6 (75)**	15 (94)	10 (45)	**25 (66)**	0.19	0.15	**0.61**

ACS = acute coronary syndrome; CAD = coronary artery disease; CAG = coronary angiography; CPC = cerebral performance category; CPR = cardiopulmonary resuscitation; ECG = electrocardiogram; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; OHCA = out-of-hospital cardiac arrest; ROSC = return of spontaneous circulation; VF/VT = ventricular fibrillation/tachycardia.

[a] Left ventricular ejection fraction by echocardiography during 24 h after admission.

[b] Data on cardiopulmonary resuscitation and hypothermia duration known in 48 patients.

[c] Odds ratio 3.2, 95% confidence interval 1.1–9.1.

[d] The hypothermia was terminated prematurely (<12 h) in 4 patients: 1 pt got conscious, 2 pts terminated due to severe hypotension and 1 pt died because of pulsless electrical activity.

[e] Number of patients in the NSTE-ACS group = 36.

[f] Number of patients in the non-ACS group = 46.

However, it must be emphasized that in the latter group the CAG was not performed mostly because of the a priori poor outcome.

The patients who were indicated for an urgent CAG did not differ from the patients who were initially treated conservatively in any of the baseline clinical variables or variables related to the pre-hospital care, although the lowest proportion of initial shockable rhythm was in the patients who were not referred for CAG at all (49%). Importantly, performing an urgent CAG did not delay the average time to achieve an effective therapeutic hypothermia. Besides a minor inguinal hematoma in two patients undergoing a delayed CAG, we observed no complications related to CAG.

The initial presence of a shockable rhythm was associated with better mid-term survival (78% vs. 31%, $p < 0.001$) and neurological status (69% vs. 19%, $p = 0.003$ for CPC ≤ 2). On the other hand, a known history of coronary artery disease was related to worse mid-term survival and neurological outcome (53% vs. 81%, $p = 0.03$ for survival and 38% vs. 77%, $p = 0.02$ for CPC ≤ 2).

Compared to the non-ACS group, the patients with NSTE-ACS were older, they had more often medical history of coronary artery disease, more often shockable rhythm at the first medical contact and more often significant ST-segment depressions or right bundle-branch block on the baseline ECG (Table 2). On the other hand, both groups did not differ in the baseline concentrations of cardiac troponins. Urgent CAG was performed more often in the NSTE-ACS than the non-ACS patients (47% vs. 17%, $p = 0.004$). A complete list of the underlying causes of the cardiac arrest is provided in the Table 3.

4. Discussion

4.1. Major findings

In our registry, two thirds of all out-of-hospital cardiac arrest comatose survivors presented without a clear-cut STEMI or a left bundle branch block myocardial infarction. In these patients, it was usually not apparent at the initial presentation whether the primary cause of the cardiac arrest was a NSTE-ACS or some other cause. However, regardless of the underlying aetiology, clinical and neurological outcome did not differ between the patients who were referred for urgent CAG (based on clinical judgement) and the patients in whom the CAG was initially deferred.

4.2. Selecting patients for urgent coronary angiography

Identification of the cardiac arrest survivors with an ACS could be important because these patients may benefit from urgent coronary revascularisation. In this regard, we have demonstrated that in the setting of post-resuscitated comatose patients, baseline cardiac troponin levels were unable to differentiate between NSTE-ACS and a non-ACS aetiology. Of note, similar finding was reported also by other authors.[4,10–12] On the other hand, we have retrospectively identified five baseline variables that could help to recognize NSTE-ACS with a satisfactory discriminatory power. These include older age, known history of coronary artery disease, presence of a shockable rhythm at the first medical contact and significant ST-segment depressions or right bundle-branch block on the baseline ECG.

4.3. Timing of coronary angiography and clinical outcome

To our surprise, although the above markers of the ischaemic aetiology might seem retrospectively anyhow obvious, in reality their presence did not prompt the clinicians to indicate an urgent CAG. In fact, when the timing of CAG was left solely on the clinical judgment, urgent CAG was performed only in one fourth of the patients. Nonetheless, our most important finding was that the clinical outcome of the patients did not differ between patients treated with urgent CAG or those who were treated initially conservatively.

We can only speculate about the possible explanations for the latter finding. First, the timing of CAG per se might have only a marginal effect on the outcome of the cardiac arrest survivors without STEMI, even if the cause of cardiac arrest is NSTE-ACS. Another explanation is that by considering other factors which are difficult to express in a registry, the attending physicians can

Table 2
Comparison of the patients with non-ST-segment elevation acute coronary syndrome and other aetiology of the cardiac arrest.

	NSTE-ACS (*n* = 36)	Non-ACS (*n* = 46)	*p*-Value	Odds ratio[a] (95% CI)
Clinical characteristics				
Age	66 ± 9.9	50 ± 17	<0.001	1.1/year
Male	32 (89)	35 (76)	0.14	
Known history of CAD	19 (53)	12 (26)	0.01	3.2 (1.3–8.0)
VF/VT at the first medical contact	33 (92)	34 (74)	0.04	3.9 (1.0–15)
Left ventricular ejection fraction (%)	38 ± 13	42 ± 16	0.25	
Troponins at admission				
Troponin I (μg/L)	0.2 [0.1–0.5]	0.2 [0.1–0.6]	0.95	
High-sensitivity troponin T (ng/L)	92 [41–239]	118 [46–252]	0.94	
ECG at admission				
ST-depression ≥1 mm in 2 leads	22 (61)	9 (20)	<0.001	6.5 (2.4–17)
Right bundle branch block	12 (33)	4 (8.7)	0.005	5.3 (1.5–18)
Normal ECG	7 (19)	13 (28)	0.36	
Coronary angiography				
Urgent or delayed CAG	32 (89)	24 (52)	<0.001	7.3 (2.2–24)
Urgent CAG	17 (47)	8 (17)	0.004	4.3 (1.6–12)
Revascularisation				
PCI/CABG	20 (43)	–	–	
PCI	17 (47)	–	–	
CABG	3 (8.3)	–	–	
Clinical outcome				
Survival at discharge	32 (89)	41 (89)	0.97	
Survival at 6 months	25 (69)	34 (74)	0.65	
CPC ≤ 2 at discharge	23 (64)	31 (67)	0.74	
CPC ≤ 2 at 6 months	23 (64)	31 (67)	0.74	

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CAD = coronary artery disease; CAG = coronary angiography; CI = confidence interval; CPC = cerebral performance category; ECG = electrocardiogram; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; VF/VT = ventricular fibrillation/tachycardia.
[a] Values obtained by univariate analysis.

recognize and subsequently indicate to urgent CAG the highest-risk NSTE-ACS patients who may truly benefit from immediate revascularisation. Consequently, the naturally selected high-risk patients who undergo urgent coronary revascularization may have similar outcome as the low-risk patients not undergoing urgent CAG.

The latest ESC guidelines on myocardial revascularization favour routine immediate CAG in all out-of-hospital cardiac arrest survivors irrespective of the ECG pattern, if no obvious non-coronary cause has been identified.[5] The evidence is based on two observational [13,14] and two registry studies.[15,16] In the largest registry, after excluding patients with non-cardiac cause of cardiac arrest, 58% of the patients without ST-segment elevation had a significant coronary artery lesion. Successful urgent coronary angioplasty led to an improved in-hospital survival in these patients.[15] Similarly, Hollenbeck et al. reported benefit of an early CAG at discharge and during variable follow-up in the cardiac arrest survivors without ST-segment elevations who presented with a shockable rhythm.[17]

Our study adds to the evidence by extending both the clinical and neurological follow-up to six months in all patients. In contrast to most previous studies, we excluded from the analyses patients with STEMI, because in these individuals the diagnosis and management is straightforward. On the other hand, we did not exclude the patients with initial non-shockable rhythm because these patients may also suffer from ACS. In contrast to the previous observations we have shown that urgent CAG – indication of which was left on clinical judgment – was not related to the patients' outcome. These contradictory findings could be undoubtedly resolved only by a randomized trial.

Table 3
Final diagnoses made at the time of discharge from the index hospitalization.

Final diagnosis	Number of patients	Coronary angiography		
		Urgent (*n* = 25)	Delayed (*n* = 31)	Not performed (*n* = 43)
NSTE-ACS	36	17	15	4
Undetermined diagnosis	17	0	0	17
Primary arrhythmogenic	11	0	9	2
Dilated cardiomyopathy	10	4	5	1
Ischaemic cardiomyopathy	9	1	1	7
Respiratory insufficiency	6	1	0	5
Hypertrophic cardiomyopathy	3	1	0	2
Heart transplant rejection	2	0	0	2
Epileptic seizure	2	1	1	0
Pulmonary embolism	1	0	0	1
Intoxication	1	0	0	1
Hypokalaemia	1	0	0	1

NSTE-ACS = non-ST-segment elevation acute coronary syndrome.

At last, we have also demonstrated that CAG can be safely realized in the urgent setting of post-resuscitated comatose patients without delaying an effective hypothermia.

4.4. Study limitations

Our study is limited by the retrospective design and a relatively modest size. We are also aware of a possible referral bias, because our institution is primarily a cardiovascular centre. Therefore some ambulance physicians may have referred to our centre preferentially patients with suspected cardiac origin of the arrest. On the other hand, cardiac cause is by default assumed in nearly all out-of-hospital cardiac arrest patients.

5. Conclusions

Performing an urgent CAG in the comatose cardiac arrest survivors without ST-segment elevation or left bundle branch block myocardial infarction was not associated with improved mid-term survival or neurological outcome as compared to an initially conservative approach in which the CAG was indicated only after recovery from the therapeutic hypothermia. Further research should clarify whether the timing of CAG per se can affect clinical outcome of these patients and whether an urgent CAG should be mandatory.

Conflict of interest statement

J. Kautzner served as advisory board member for Biosense Webster, Boston Scientific, Medtronic and St. Jude Medical. He received speaker honoraria from Biosense Webster, Biotronik, Boston Scientific, Hansen Medical, Medtronic and St. Jude Medical. The other authors have no conflict of interest to declare.

Acknowledgement

None.

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