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Cardiovascular mortality and morbidity in patients undergoing percutaneous coronary intervention after out-of-hospital cardiac arrest: a systematic review and meta-analysis

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KEYWORDS

- ACS/NSTE-ACS
- miscellaneous
- out-of-hospital cardiac arrest

Abstract

Aims: The aim of this meta-analysis was to appraise the burden of cardiovascular mortality and morbidity among patients undergoing percutaneous coronary intervention (PCI) after out-of-hospital cardiac arrest (OHCA).

Methods and results: This was a meta-analysis of studies assessing the cardiovascular mortality or at least one other pre-defined outcome in OHCA patients undergoing PCI. Forty-nine studies with a total of 301,902 patients (73,634 OHCA and 228,268 non-OHCA patients) were included. Compared to non-OHCA patients, all-cause mortality was higher in OHCA patients (29% vs 4%). The cause of 39% of deaths among OHCA patients was cardiovascular: PCI was more frequently unsuccessful (9.2% vs 7.6%) and there were higher rates of stent thrombosis (2.9% vs 0.8%), myocardial infarction (1.7% vs 1.4%), relevant bleeding (10.2% vs 2.1%) and stroke (1.7% vs 0.5%). OHCA patients compared to non-OHCA patients had a higher risk of all-cause mortality (risk ratio [RR] 6.4, 95% CI: 5.5-7.4), cardiovascular death (4.6, 1.1-19), unsuccessful coronary revascularisation (1.4, 1.1-1.7), stent thrombosis (3.8, 0.6-22.7), myocardial infarction (1.4, 1.1-1.7), relevant bleeding (3.2, 2.5-4.1) and stroke (3.1, 2.3-4.3).

Conclusions: Almost one third of OHCA patients undergoing PCI die and more than one third of the fatalities are attributable to cardiovascular causes. The burden of ischaemic and bleeding complications was consistently higher and the success rates of PCI lower among OHCA as compared to non-OHCA patients.

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Abbreviations

ACS	acute coronary syndrome
LAD	left anterior descending artery
LCX	left circumflex artery
NSTEMI	non-ST-elevation myocardial infarction
OHCA	out-of-hospital cardiac arrest
PCI	percutaneous coronary intervention
RCA	right coronary artery
STEMI	ST-elevation myocardial infarction

Introduction

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death in the USA and Europe. The global incidence of emergency medical system (EMS)-attended OHCA is estimated to be 95.9 per 100,000 person-years and the survival rate is about 6%[1]. Despite advances in the field of resuscitation and intensive care management, acute mortality remains high[2]. The most frequent cause of in-hospital mortality in OHCA patients is withdrawal of life-sustaining therapy on the basis of poor neurological outcomes. However, it has also been observed that a relevant number of deaths during the initial days after OHCA are caused by persistent unstable haemodynamic conditions[3].

Ischaemic coronary artery disease is the leading cause of OHCA and significant coronary lumen narrowing has been documented in more than 70% of patients according to autopsy[4] or coronary angiography data[5]. Current ACC/AHA and ESC guidelines recommend immediate coronary angiography in OHCA patients with ST-elevation myocardial infarction (STEMI)[6,7], whereas, in resuscitated patients without STEMI, coronary angiography is recommended in selected patients without overt evidence of a non-cardiac cause[6].

Several observational studies and one recent randomised trial[8] investigated the impact of coronary angiography and PCI on all-cause mortality in OHCA patients. However, the cause of death (i.e., cardiovascular vs non-cardiovascular) and the prevalence of ischaemic or bleeding events after PCI are less frequently reported, with heterogeneous results among studies. No systematic review and meta-analysis, with the exception of a single small study[9], has appraised the prevalence of cardiovascular events and their potential impact on prognosis in OHCA patients. This information would enhance our understanding of this condition and help to develop dedicated management strategies for these patients.

Therefore, we conducted a systematic review and meta-analysis of studies reporting the aforementioned clinical outcomes in OHCA patients undergoing invasive management.

Methods

This study was performed based on a pre-specified protocol, available in PROSPERO (CRD 42019135553). Reporting and assessment are according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[10].

SOURCE OF EVIDENCE AND SEARCH

We performed a broad literature search in PubMed, Embase, and Cochrane Library Central Register of Controlled Trials (CENTRAL) which was concluded on 30 April 2020. Screening was performed in two stages by two investigators (A. Spirito and G. Gargiulo) working independently and in duplicate against *a priori* eligibility criteria. Search terms and details of the screening process are available in **Supplementary Appendix 1**.

STUDY INCLUSION

We considered original studies of any design reporting any of the outcomes of interest reported below in an OHCA study population in which at least 70% of patients underwent PCI. The rationale of this cut-off is explained in **Supplementary Appendix 1**. We excluded studies not reporting disease-specific causes of fatalities unless reporting at least one additional outcome of interest. The presence of a "non-OHCA" comparison group at the study level (patients with acute coronary syndrome but without OHCA undergoing PCI) was systematically screened but was not mandatory for study inclusion. We considered only studies with at least two thirds of patients enrolled after the year 2002 under the rationale that drug-eluting stents (DES) were not available and adoption of oral $P2Y_{12}$ inhibitors limited until then, thus not reflecting current practice. Additional exclusion criteria are shown in **Supplementary Appendix 1**.

DATA EXTRACTION AND OUTCOME DEFINITIONS

Data were extracted and summarised at the study level on an Excel spreadsheet for the OHCA and, if present, also for the comparison population (non-OHCA).

The primary outcome of interest was cardiovascular death. Secondary outcomes were all-cause mortality, unsuccessful PCI, stent thrombosis, myocardial infarction, bleeding, stroke and neurological status at discharge. We focused on events which occurred during the index hospitalisation or up to 30 days. For all-cause mortality, we also considered the 6- and 12-month follow-up.

The quality of studies was evaluated according to the Newcastle-Ottawa score. For each study, we also assessed the adherence to 2004 and 2015 Utstein core criteria.

Data extraction and study quality assessment were performed by one reviewer and verification was carried out by a second reviewer. Disagreements among reviewers were resolved through consensus or by third-party adjudication. Items extracted and definitions used for the outcomes are listed in **Supplementary Appendix 1**.

DATA SYNTHESIS

Summary proportion estimates with 95% confidence intervals (CI) and heterogeneity using a random effects model were obtained separately for OHCA and non-OHCA populations. Moreover, after selecting only studies reporting data for both OHCA and non-OHCA populations, we used a random effects model to calculate summary risk ratios (RR) and heterogeneity for each outcome comparing the two groups. We used the I^2 metric to assess the extent of heterogeneity. Among OHCA populations, we evaluated the role of patient and study characteristics by using stratified meta-analyses for the

outcome of cardiovascular and all-cause mortality. Further details about data synthesis are provided in **Supplementary Appendix 1**.

Results

LITERATURE SEARCH AND STUDY SELECTION

We screened 1,618 unique citations. Of these, 400 were judged potentially eligible during screening of titles and abstracts, and 49 deemed eligible after full text review **(Figure 1)**.

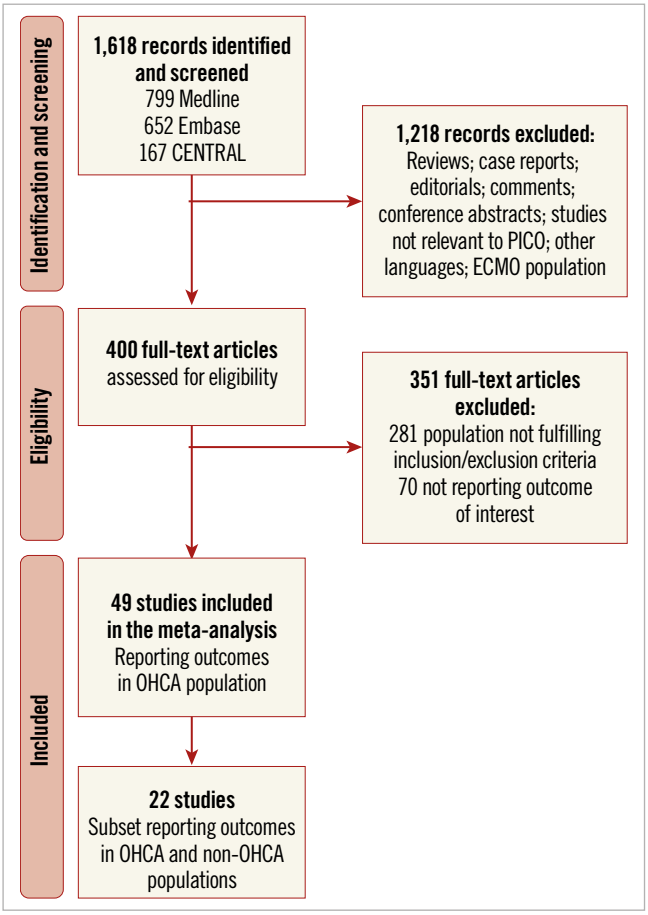

Figure 1. *Flow diagram of the selection of the articles for the systematic review and meta-analysis. ECMO: extracorporeal membrane oxygenation*

Table 1. Summary of selected study and population characteristics.

	Total of 49 studies			
	OHCA		Non-OHCA	
	Studies n=49	Patients n=73,634	Studies n=22	Patients n=228,268
Sample size OHCA group				
>1,000	6 (12)	69,714 (95)	5 (23)	203,407 (89)
104-1,000	9 (18)	2,295 (3)	4 (18)	11,490 (5)
<104	34 (70)	1,625 (2)	13 (59)	13,371 (6)
Number of centres				
Single centre	38 (78)	70,935 (96)	14 (64)	210,792 (92)
Multicentre	11 (22)	2,699 (4)	8 (36)	17,476 (8)
Data collection				
Retrospective	30 (61)	70,505 (96)	10 (45)	201,309 (88)
Prospective	19 (39)	3,129 (4)	12 (55)	26,959 (12)
Geographic area				
Europe	31 (63)	4,566 (6)	11 (50)	43,303 (19)
North America	9 (18)	67,536 (92)	4 (18)	162,686 (71)
Asia, South America, Australia	9 (19)	1,532 (2)	7 (32)	21,350 (10)
Quality of study*				
Good	25 (51)	10,662 (14)	10 (45)	101,618 (45)
Fair	24 (49)	62,972 (86)	12 (55)	126,650 (55)
ECG at presentation				
Only STEMI	22 (45)	10,190 (14)	20 (91)	227,102 (99)
With and without ST-elevation	27 (55)	63,444 (86)	2 (9)	1,166 (1)
Rhythm				
>90% of patients with shockable rhythm	15 (31)	72,350 (98)		
Any rhythm	34 (69)	1,284 (2)		
Therapeutic hypothermia (TH)				
≥90% of patients undergoing TH	17 (35)	640 (1)		
With and without TH	19 (39)	52,970 (72)		
Information not available	13 (27)	19,982 (27)		
State of consciousness after ROSC				
Only unconscious	25 (51)	1,014 (1)		
Conscious and unconscious	16 (33)	53,882 (73)		
Only conscious	1 (2)	42 (<1)		
Information not available	7 (14)	18,696 (25)		

The data represent absolute number and (percentage). *according to Newcastle-Ottawa score. ECG: electrocardiogram; ROSC: return of spontaneous circulation

STUDY CHARACTERISTICS

Among the 49 studies which were published between 2007 and 2020 and included patients from 1997 to 2018, the majority were single-centre (38 studies or 78%), small-scale (34 or 70%), observational (46 or 94%), retrospective (30 or 61%) or conducted in Europe (31 or 63%). According to the Newcastle-Ottawa score, the quality of 25 studies (or 51%) was good **(Table 1, Supplementary Table 1)**.

A total of 22 out of 49 studies (45%) had a comparator group, consisting of patients with ACS (restricted to STEMI in 20 studies) without OHCA undergoing invasive management (non-OHCA group) **(Supplementary Table 2)**.

A further description of the study characteristics is available in **Supplementary Appendix 2** and **Supplementary Table 3**.

POPULATION CHARACTERISTICS

A total of 73,634 OHCA patients were included of whom 71,961 (98%) underwent PCI. Age ranged from 54 to 68 years and 52,143 (71%) patients were male. Among the 49 studies, 40 specified the type of ACS at presentation and 85.6% (20,560 out of 24,033) of the patients had STEMI **(Table 1)**.

The comparator group consisted of 228,268 patients of whom 212,450 (93%) underwent PCI. Age ranged from 56 to 75 years,

164,028 (72%) were male and 227,109 patients (99%) had STEMI **(Table 1)**. OHCA patients compared to those without OHCA more frequently suffered from cardiogenic shock (37% vs 6%) and more often received mechanical support (30% vs 8%). In 4,272 (85%) out of 5,038 OHCA patients in whom information on mechanical support was available, intra-aortic balloon pump was the only assist device used.

SHORT-TERM OUTCOMES

MORTALITY

The proportion of all-cause mortality in OHCA patients obtained from 43 studies was 29% (95% confidence interval [CI]: 27% to 32%, I^2=94%) as compared to 4% (95% CI: 3% to 4%, I^2=97%) in the non-OHCA group (from 18 studies) **(Figure 2A, Supplementary Figure 1)**.

Across the 17 OHCA studies which ascertained causes of mortality, 39% of all fatalities were deemed cardiovascular (95% CI: 24% to 55%, I^2=95%) with an absolute cardiovascular death proportion of 12% (95% CI: 7% to 18%, I^2=93%).

In 2 out of 17 studies which included a comparison group (n=773 OHCA patients and n=12,507 non-OHCA patients), the proportion of cardiovascular death in the non-OHCA group was 4% (95% CI: 4% to 5%), representing 80% of all fatalities (95% CI: 77% to 83%) **(Figure 2A, Figure 2B, Supplementary Figure 2, Supplementary Figure 3)**. The absolute proportion of cardiovascular death was almost fivefold higher in OHCA than non-OHCA patients (risk ratio [RR] 4.6, 95% CI: 1.1 to 19) **(Figure 2C, Supplementary Figure 4)**.

At subgroup analysis we found lower estimated proportions of cardiovascular death in the OHCA population across studies conducted in North America and Europe, with a prospective design or in which more than 50% of patients received a bystander basic life support **(Supplementary Figure 5, Supplementary Table 4)**. Results remained consistent for geographic area when

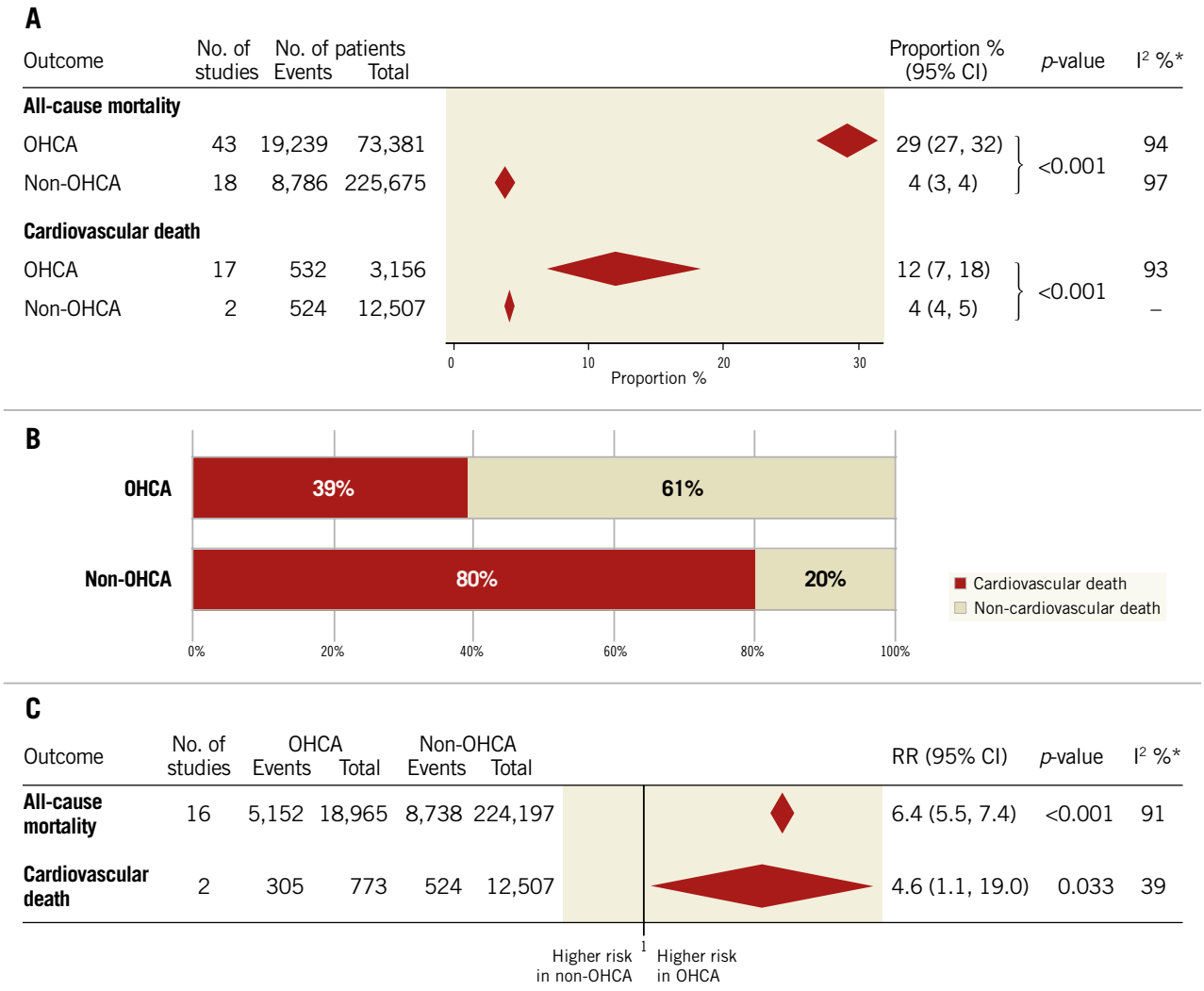

Figure 2. *Summary of proportion estimates of all-cause and cardiovascular death (A), proportion of cardiovascular versus non-cardiovascular death (B) and relative risk for all-cause and cardiovascular death (C) in hospital or at 30 days in OHCA compared to non-OHCA patients. *values around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively.*

all-cause mortality and cardiovascular mortality relative to all-cause mortality were analysed. The proportion of all-cause mortality was also lower in studies of fair quality, published before 2011, in which ≥90% of patients had witnessed arrest, in those including ≥90% of patients with shockable rhythm or in which <30% of patients presented a cardiogenic shock at admission **(Supplementary Figure 6, Supplementary Figure 7, Supplementary Table 4)**.

PCI AND PROCEDURAL FEATURES

PCI was unsuccessful in 9.2% (95% CI: 7.5% to 11.15%, I^2=69%) of the patients with OHCA (across 22 studies) and in 7.6% (95% CI: 6.3% to 9.1%, I^2=97%) of the patients without OHCA (out of 12 studies) **(Figure 3A, Supplementary Figure 8)**. Compared to non-OHCA, unsuccessful PCI was 40% more frequent in OHCA patients (RR 1.4, 95% CI: 1.1% to 1.7%) **(Figure 3B, Supplementary Figure 4)**.

The culprit vessel, reported for both OHCA and non-OHCA patients in ten studies, was more frequently the left main coronary artery (RR 2.8, 95% CI: 1.8-4.4) or left anterior descending artery (LAD) (RR 1.3, 95% CI: 1.2-1.3) or left circumflex artery (LCX) (RR 1.19, 95% CI: 1.03-1.37) and less frequently the right coronary artery (RCA) (RR 0.6, 95% CI: 0.5-0.7) among OHCA patients. The involvement of a coronary artery bypass conduit and the presence of multivessel disease did not

A

Outcome	No. of studies	No. of patients Events	Total	Proportion % (95% CI)	*p*-value	I^2 %*
Unsuccessful PCI						
OHCA	22	1,593	15,060	9.2 (7.5, 11.1)	0.082	69
Non-OHCA	12	8,678	136,745	7.6 (6.3, 9.1)		97
Stent thrombosis						
OHCA	22	2,368	50,435	2.9 (1.7, 4.3)	0.001	51
Non-OHCA	7	89	5,219	0.8 (0.2, 1.5)		60
Myocardial infarction						
OHCA	6	101	7,111	1.7 (1.3, 2.1)	0.066	0
Non-OHCA	5	896	57,079	1.4 (1.0, 2.0)		95
Bleeding (all definitions)						
OHCA	33	9,277	70,452	10.2 (7.8, 12.8)	<0.001	100
Non-OHCA	14	9,133	190,727	2.1 (1.0, 3.5)		100
Bleeding (standard definitions)						
OHCA	14	261	2,185	9.9 (6.8, 13.4)	<0.001	75
Non-OHCA	6	686	18,591	1.3 (0.0, 4.2)		99
Stroke						
OHCA	14	331	24,668	1.7 (1.0, 2.5)	<0.001	86
Non-OHCA	9	1,238	215,889	0.5 (0.4, 0.7)		92

B

Outcome	No. of studies	OHCA Events	Total	Non-OHCA Events	Total	RR (95% CI)	*p*-value	I^2 %*
Unsuccessful PCI	12	1,204	10,497	8,678	136,745	1.4 (1.1, 1.7)	0.001	59
Stent thrombosis	7	22	361	89	5,219	3.8 (0.6, 22.7)	0.142	89
Myocardial infarction	5	100	4,983	896	57,079	1.4 (1.1, 1.7)	0.002	0
Bleeding	14	2,080	16,782	9,046	190,727	3.2 (2.5, 4.1)	<0.001	91
Bleeding (standard)¶	6	175	1,496	470	18,591	6.8 (3.4, 13.5)	<0.001	79
Stroke	9	278	18,457	1,238	215,889	3.1 (2.3, 4.3)	<0.001	74

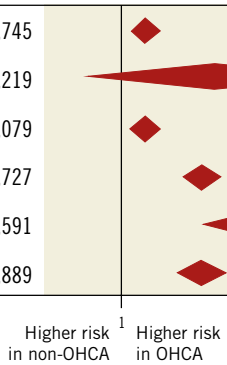

Figure 3. *Summary of proportion estimates (A) and relative risk (B) of secondary outcomes in hospital or at 30 days in OHCA compared to non-OHCA patients. ¶only studies using standard bleeding definition (TIMI, GUSTO, BARC). * values around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively.*

differ between the two groups **(Supplementary Figure 9)**. The use of glycoprotein IIb/IIIa inhibitors, reported in 12/22 and 7/12 studies for OHCA and non-OHCA groups, was 48% and 56%, respectively. The reasons for suboptimal PCI, type of lesion as well as other PCI-related information were largely underreported **(Supplementary Table 5)**.

STENT THROMBOSIS

A total of 2,368 stent thromboses in 50,435 OHCA patients was reported across 22 studies, with a summary proportion estimate of 2.9% (95% CI: 1.70% to 4.3%, I^2=51%), whereas, among 5,219 non-OHCA patients from seven studies, stent thrombosis was observed in 89 cases (0.8%; 95% CI: 0.2% to 1.5%, I^2=60%) **(Figure 3A, Supplementary Figure 10)**.

Across five studies which provided this information, stent thrombosis was associated with greater but statistically not relevant risk of all-cause mortality among OHCA patients (RR 1.63, 95% CI: 0.97 to 2.73) **(Supplementary Figure 11)**.

IN-HOSPITAL RECURRENT MYOCARDIAL INFARCTION

Reinfarction during index hospitalisation occurred in 107 out of 5,050 OHCA patients (nine studies) and in 896 out of 57,079 non-OHCA patients (five studies), providing a summary proportion estimate of 1.4% in both populations **(Supplementary Figure 12)**. After exclusion of stent thrombosis-related myocardial infarction, the summary proportion was 1.7% in the OHCA group with a risk ratio of 1.4 (95% CI: 1.1 to 1.7) compared with non-OHCA patients **(Figure 3B, Supplementary Figure 4)**.

BLEEDING RATES

In-hospital severe or relevant bleeding was reported in 9,277 out of 70,452 OHCA patients across 33 studies with a cumulative proportion of 10% (95% CI: 8% to 13%, I^2=100%) and in 9,133 out of 190,727 non-OHCA patients, leading to a summary proportion of 2% (95% CI: 1% to 4%, I^2=100%) from 14 studies **(Figure 3A, Supplementary Figure 13)**.

The proportions of relevant bleeding in OHCA patients appeared consistent across studies adopting standardised (Bleeding Academic Research Consortium [BARC], Thrombolysis In Myocardial Infarction [TIMI] or Global Registry of Acute Coronary Events [GRACE] scales) or study-specific definitions **(Supplementary Figure 13)**.

When considering only studies presenting a comparison group, we observed a threefold risk increase of severe or relevant bleeding in OHCA versus non-OHCA patients (RR 3.2, 95% CI: 2.5 to 4.1) and a sevenfold increase if the analysis is limited to the six studies that adopted standardised definitions **(Figure 3B, Supplementary Figure 4)**.

STROKE

In OHCA patients 331/24,668 and in non-OHCA patients 1,238/215,889 had a stroke; the summary proportion estimates were 1.7% (95% CI: 1.0% to 2.5%, I^2=86%) and 0.5% (95% CI: 0.4% to 0.7%, I^2=92%), respectively **(Figure 3A, Supplementary Figure 14)**, with an estimated relative risk in OHCA versus non-OHCA patients of 3.1 (95% CI: 2.3 to 4.3) **(Figure 3B, Supplementary Figure 4)**.

NEUROLOGICAL OUTCOMES IN OHCA PATIENTS

Across 20 studies, a poor neurological outcome was observed in 230 out of 1,355 OHCA patients alive at discharge (19%; 95% CI: 14% to 25%, I^2=82%) and it was significantly lower in studies in which the assessment was carried out at one year (10%; 95% CI: 6% to 17%), instead of at discharge or at six months **(Supplementary Figure 15)**.

SIX- AND TWELVE-MONTH FOLLOW-UP

Among patients discharged alive, all-cause mortality at six months was 5.5% (95% CI: 1.6% to 10.9%, I^2=30%) for OHCA patients and 1.9% (95% CI: 1.4% to 2.5%) for non-OHCA patients; at 12-month follow-up it was 6.9% (95% CI: 3.7% to 10.8%, I^2=58%) for OHCA patients and 3.1% (95% CI: 2.3% to 3.9%, I^2=79%) for non-OHCA patients **(Supplementary Figure 16)**. If considering only studies with a comparison group, OHCA patients had a 2.5-fold (95% CI: 0.9 to 6.6) higher risk of death at six months and 1.8-fold (95% CI: 1.01 to 3.34) higher risk at 12 months **(Supplementary Figure 17)**.

REPORTING OF UTSTEIN CORE CRITERIA

Adherence to 2004 or updated 2015 Utstein core criteria for reporting was generally poor **(Supplementary Table 6, Supplementary Appendix 2)**.

Discussion

The salient findings of this systematic review and meta-analysis involving 73,634 OHCA patients who underwent PCI, and 228,268 control patients with ACS but without cardiac arrest, can be summarised as follows:

1. Cardiovascular death occurs almost five times more frequently in OHCA patients and it accounts for 39% of in-hospital fatalities.
2. All-cause mortality was 29% in OHCA and 4% in non-OHCA patients; among OHCA patients who survived to discharge, 19% had a poor neurological outcome.
3. PCI in OHCA patients was more frequently unsuccessful; the culprit lesions appeared more frequently located in the left coronary artery in OHCA as compared to non-OHCA patients, whereas the prevalence of multivessel disease was similar.
4. OHCA patients have higher in-hospital proportions of bleeding and ischaemic events, including myocardial infarction, stent thrombosis and stroke.
5. Adherence to the original or updated Utstein criteria for standardised reporting was generally poor across studies.

The aetiology of OHCA is heterogeneous, but coronary artery disease remains the predominant cause. We focused on patients with OHCA who underwent PCI because we wanted to restrict the analysis to patients in whom the aetiology of OHCA was deemed cardiac. Cardiovascular death had an absolute incidence of 12% and a cardiovascular cause was responsible for 39% of deaths in OHCA patients. Cardiovascular together with all-cause mortality varied greatly across selected studies (from 0 to 55%

and from 7 to 77%, respectively). The selection of patients with favourable prognosis (e.g., witnessed arrest, bystander cardiopulmonary resuscitation, shockable rhythm, undergoing therapeutic hypothermia) greatly influences mortality and explains the heterogeneity observed. This notion was confirmed in the subgroup analysis.

Our meta-analysis confirmed the high prevalence of cardiogenic shock in OHCA patients, which was six times higher than in non-OHCA patients. The most frequent measure of mechanical support was by far intra-aortic balloon pump (IABP); however, this information was largely underreported across included studies. In a randomised study of patients in cardiogenic shock, in which 40% suffered cardiac arrest but did not require prolonged resuscitation, systematic use of IABP did not demonstrate a reduction in mortality[11]. Other forms of mechanical support such as extracorporeal membrane oxygenation (ECMO) or Impella® (Abiomed, Danvers, MA, USA) are being investigated[12,13].

Successful and prompt myocardial revascularisation remains the only evidence-based treatment to mitigate fatality risk in patients with shock and ongoing myocardial ischaemia[6]. Instead, in haemodynamically stable OHCA patients without ST-elevation on ECG, a recent randomised controlled trial did not show any benefit of an early versus delayed invasive strategy[8].

Among OHCA patients, compared to non-OHCA patients, the rate of successful PCI was lower and recurrent myocardial infarction or the occurrence of ST was higher. The broad confidence intervals of risk ratio obtained for stent thrombosis are attributable to the limited number of studies included in this analysis (7 out of 22). Our results showed a trend towards increased mortality for patients experiencing a stent thrombosis.

Oral $P2Y_{12}$ inhibitors show delayed onset and attenuated antiplatelet effects among STEMI patients[14,15] as well as OHCA patients[16,17]. At variance with ACS patients without OHCA[18,19], in the OHCA population the benefit derived from the use of newer $P2Y_{12}$ inhibitors such as prasugrel or ticagrelor is less clear[9]. While the use of parenteral antiplatelet agents may be conceptually appealing to overcome the delay in platelet inhibition[15,20,21], our meta-analysis raises concerns about the liberal use of potent antithrombotic agents in OHCA patients, due to a threefold higher prevalence of relevant bleeding in this population.

We observed that fatality rates remained higher at 12-month follow-up among OHCA as compared to non-OHCA patients. However, this observation is hampered by the limited number of studies reporting mortality rates after hospital discharge.

Finally, our meta-analysis showed a poor adherence to Utstein core criteria across included studies and reinforces the need for standardised reporting and use of validated outcome definitions.

Limitations

The different selection of patients and outcome definitions across studies explain the high degree of heterogeneity observed for almost all clinical endpoints. Moreover, we observed a certain degree of heterogeneity in follow-up length. We tried to overcome these problems by performing a subgroup analysis and stratifying by selection criteria and outcome definition whenever possible. Some thresholds applied in the subgroup meta-analysis were arbitrary, but the results remained consistent if different thresholds were applied. The lack of individual patient data and the absence or underreporting of some important data across studies prevented subgroup analysis of interest (e.g., STEMI vs no-STEMI). The comparison of summary proportion estimates obtained from a different pool of studies for OHCA and non-OHCA populations has to be considered only exploratory. The risk ratio analysis is affected by potential confounders as well, because of the absence of propensity score matching in almost all studies with a comparison group. However, the results obtained with the two methods (proportion meta-analysis and classic meta-analysis) were largely consistent and showed remarkable differences between OHCA and non-OHCA patients. As we selected only OHCA patients undergoing PCI, the results are applicable only to this subgroup of OHCA patients.

Conclusions

Almost one third of OHCA patients undergoing PCI die and more than one third of the fatalities are attributable to cardiovascular causes. In addition, the burden of ischaemic and bleeding complications is consistently higher and the success rates of percutaneous intervention lower among OHCA as compared to non-OHCA patients. Our meta-analysis reinforces the need for high-quality studies adhering to previously proposed standardised criteria for reporting (e.g., Utstein criteria) and suggests the need to investigate new therapeutic strategies affecting neurological but also cardiovascular mortality and morbidity burden in OHCA patients undergoing PCI.

Impact on daily practice

More than one third of the fatalities in OHCA patients undergoing coronary revascularisation are attributable to cardiovascular causes, and the burden of cardiovascular ischaemic and bleeding complications is remarkably higher compared to non-OHCA patients. Dedicated treatment strategies aimed at reducing ischaemic and bleeding risks in this vulnerable and so far largely neglected population are warranted in clinical practice and future clinical studies.

Conflict of interest statement

G. Gargiulo reports personal fees from Daiichi Sankyo, outside the submitted work. M. Valgimigli reports personal fees/grants from AstraZeneca, Terumo, Abbott Vascular, Alvimedica/CLD, Daiichi Sankyo, Opsens, Bayer, CoreFlow, Idorsia Pharmaceuticals Ltd, Universität Basel, Dept. Klinische Forschung, Vifor, Bristol-Myers Squibb SA, iVascular and Medscape, outside the submitted work. S. Windecker reports grants from Amgen, Abbott, Biotronik, Boston Scientific, Bayer, BMS, CSL Behring, Edwards Lifesciences, Medtronic, Polares and Sinomed, outside the submitted work. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Appendix 2. Results.

Supplementary Figure 1. Proportion estimates of in-hospital or 30-day mortality in OHCA and non-OHCA patients.

Supplementary Figure 2. Proportion estimates of cardiovascular death in OHCA and non-OHCA patients.

Supplementary Figure 3. Proportion estimates of cardiovascular death relative to all-cause death for OHCA and non-OHCA patients.

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Supplementary Figure 5. Subgroup analysis for cardiovascular death in the OHCA group.

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Supplementary Figure 15. Proportion of alive patients with poor neurological outcome at discharge.

Supplementary Figure 16. Proportion estimates of all-cause mortality at 6 and 12 months among OHCA and non-OHCA patients discharged alive.

Supplementary Figure 17. Relative risk for all-cause mortality at 6 and 12 months among OHCA and non-OHCA patients discharged alive.

Supplementary Table 1. Study design and OHCA population characteristics in the selected studies.

Supplementary Table 2. Non-OHCA population characteristics in the selected studies.

Supplementary Table 3. Summary of selected study and population characteristics stratified by sample study dimension.

Supplementary Table 4. Non-significant results of stratified meta-analysis.

Supplementary Table 5. Proportion of reporting of some characteristics/outcomes of interest for cardiologists.

Supplementary Table 6. Proportion of reporting of 2004 and 2015 core Utstein criteria.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00221

Supplementary data

Supplementary Appendix 1. Methods

Source of evidence and search

PubMed search terms were: (OHCA OR out of hospital cardiac arrest OR pre-hospital cardiac arrest) AND (coronary angiography OR coronary angiogram OR percutaneous angioplasty OR percutaneous coronary intervention OR "coronary intervention" OR catheterisation). Similar keywords were used for the search in Embase and Cochrane Library for clinical trials.

Screening was performed in two stages: stage 1 encompassed review of titles and abstracts identified from the electronic search, while stage 2 was based upon review of full text articles of those deemed potentially relevant during stage 1.

Study inclusion

The rationale to include studies in which at least 70% of patients underwent PCI is the following: landmark OHCA studies (see reference #4 and #5 in the manuscript) showed that a significant coronary lumen narrowing can be found in 70% of OHCA patients without an obvious cardiac cause. As cardiologists, we are involved in the management of this subgroup of OHCA patients and we wanted to focus our analysis on them. As significant coronary lumen narrowing is underreported among studies compared to the proportion of patients undergoing PCI, we used this latter criterion to select the studies.

We considered studies written in English, German, French, Spanish or Italian. We excluded studies not reporting the number of patients (or percentage) undergoing PCI, reporting exclusively data of patients with refractory cardiac arrest treated with extracorporeal reanimation or including more than 20% of patients after in-hospital cardiac arrest.

Among articles reporting data of overlapping populations (according to the period of recruitment and involved institutions), we gave preference to the reports including the largest number of patients or providing most of the outcomes of interest.

Data extraction and outcome definitions

Items extracted:

- **Publication and study design characteristics**: PMID; year of publication; design; number of sites and country/ies; enrolment period; first author's name; authors' affiliations.
- **Study population characteristics for OHCA and non-OHCA (if applicable):** inclusion and exclusion criteria applied; study sample; OHCA and non-OHCA population sample; number of patients undergoing coronary angiography; number of patients undergoing PCI; number of patients undergoing CABG; number of patients receiving at least one stent; sex; age; shockable rhythm; witnessed arrest; state of consciousness at hospital arrival; n° of patients treated with therapeutic hypothermia and different timing (from begin hypothermia to target temperature, from arrest to begin hypothermia, from ROSC to begin hypothermia); no-flow time (hands off); cardiogenic shock at presentation; need for mechanical support and type (IABP, ECMO, Impella); ECG at presentation; number and type of traumatic injuries following CPR; cause of cardiac arrest and all the items (not already cited above or below) required by 2004 and 2015 core Utstein criteria (for a complete list of the items see **Supplementary Table 6**).

- **Intervention characteristics for OHCA and non-OHCA (if applicable):** use of glycoprotein IIb/IIIa inhibitors; administration of heparin/aspirin/$P2Y_{12}$/bivalirudin and timing (prehospital and/or peri-interventional); patients undergoing thrombolysis; vascular access site (radial or femoral); infarct-related artery; presence of multivessel disease; time to $P2Y_{12}$ administration; multivessel PCI at index procedure; description and/or ACC/AHA classification of coronary lesion; presence of chronic total occlusion.
- **Outcome details for OHCA and non-OHCA (if applicable):** for each of the following outcomes the number of events, timing of assessment and definition used were extracted: cardiovascular death; all-cause mortality; successful PCI; stent thrombosis; myocardial infarction; bleeding; stroke; neurological outcome; mortality at 6 and 12 months.
- **Additionally** we collected: site of bleeding; myocardial infarction caused by stent thrombosis; stent thrombosis followed by death; recurrent cardiac arrest; occurrence of pulmonary embolism or deep venous thrombosis; causes of death (septic shock, multiorgan failure, withdrawal from life-sustaining treatment, neurological).

Definition used for the outcomes:

- We considered as **cardiovascular cause of mortality** the following definitions: cardiac death, caused by arrhythmia or by haemodynamic instability. Multiorgan failure or other causes were not considered as cardiovascular death.
- **Unsuccessful PCI** was defined as TIMI <3 at the end of the PCI.
- We recorded only acute and subacute **stent thrombosis**, definite or probable according to Academic Research Consortium's (ARC) classification. We considered as population at risk for this outcome only those who received a stent during PCI; if this information was not available, all the patients who underwent a PCI were taken as the population at risk.
- We recorded **bleedings** together with the definition/classification used (study-specific or standard) and whenever possible only severe bleedings were considered.
- **Neurological status at discharge** or up to one year after cardiac arrest if classified according to Cerebral Performance Category (CPC) or modified Rankin Scale (mRS) was dichotomised into good (CPC/mRS equal to 1 or 2) and poor neurological outcome (CPC equal to 3 or 4 or mRS between 3 and 5).

Data synthesis

All analyses were performed in Stata 16.0 (StataCorp. 2019. Stata Statistical Software: Release 16. StataCorp LLC, College Station, TX, USA).
We calculated separately in the OHCA and non-OHCA populations the estimated proportion with 95% confidence intervals using the score test (also called Wilson test) with Freeman-Tukey double arcsine transformation. A random effects model with the method of DerSimonian and Laird was applied to obtain the summary estimates and heterogeneity.

Summary risk ratios, derived only from studies reporting data for both OHCA and non-OHCA populations, were obtained using the method of DerSimonian and Laird with the estimate of heterogeneity being taken from the Mantel-Haenszel method.

To assess the extent of heterogeneity in each meta-analysis, we used the I^2 metric (I square). Values around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively.

The p-value estimating the significance of the difference observed in estimated summary proportions and summary risk ratio between OHCA and non-OHCA is derived from a Z-test of the null hypothesis that there is no difference between summary proportions **(Figure 2A, Figure 3B, Supplementary Figure 5-Supplementary Figure 7, Supplementary Table 4)** and that there is no effect on average in random effects meta-analysis **(Figure 2C, Figure 3B, Supplementary Figure 4, Supplementary Figure 9)**, respectively.

Characteristics used for stratified meta-analysis:

Study sample size; data collection (retrospective vs prospective); number of centres (single vs multicentre); year of publication (after versus before 2011); percentage of males, of witnessed cardiac arrest, of patients receiving a bystander basic life support (BLS), with a shockable rhythm; inclusion restricted to patients with sustained ROSC and to unconscious patients; proportion of patients in cardiogenic shock, of patients requiring a mechanical support; proportion of STEMI, of patients treated with PCI, treated with glycoprotein IIb/IIIa inhibitors, type of $P2Y_{12}$ inhibitor used, treatment with therapeutic hypothermia; timing of death assessment; affiliation department of authors (only cardiology, other than cardiology; cardiology and other).

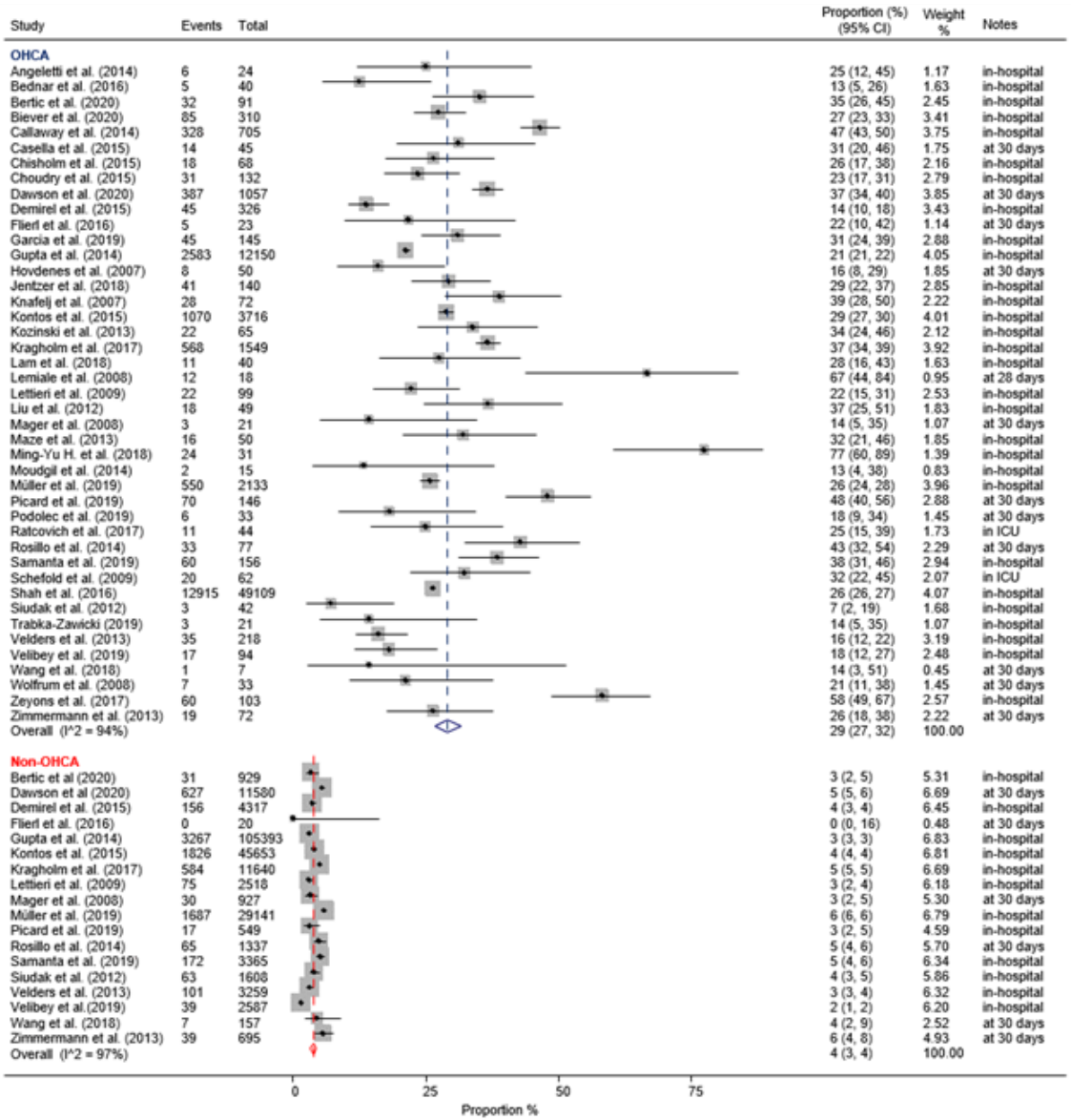
Supplementary Appendix 2. Results

Study characteristics

The six largest studies were retrospective ACS or PCI registries or nationwide inpatient samples and included OHCA patients on an all-comer basis. Conversely, small-scale studies (<104 patients) mainly selected patients undergoing therapeutic hypothermia or unconscious OHCA patients (25 out of 34 studies). Ten out of 15 (67%) large or medium size studies (≥104 patients) included STEMI patients only, whereas the majority of small-scale studies did not restrict the inclusion to STEMI **(Supplementary Table 3)**.

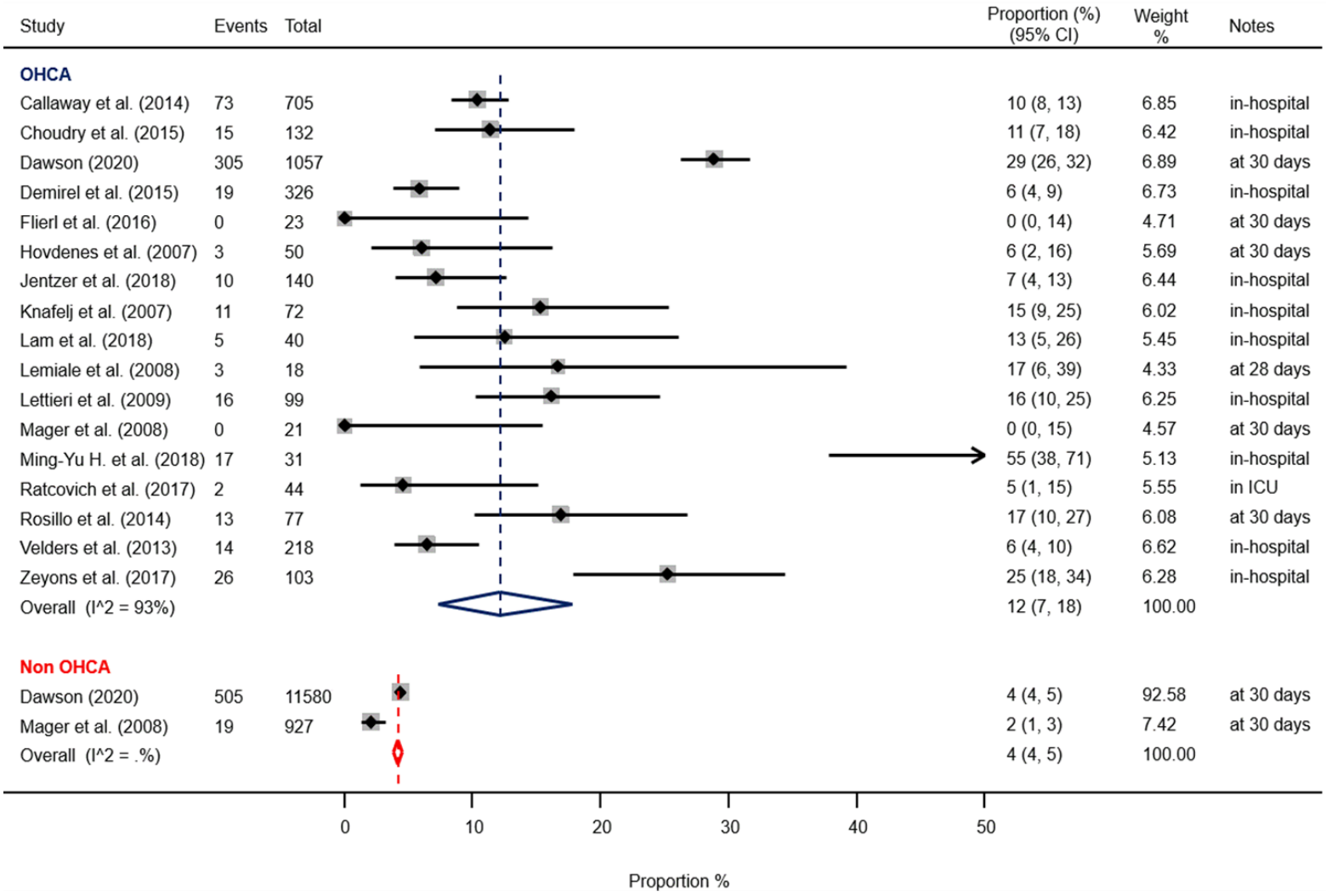
Reporting of Utstein core criteria

Twenty-three out of 28 criteria were reported in around one third of the studies or even less. Only five criteria (age, sex, first monitored rhythm, use of therapeutic hypothermia, use of PCI) were more frequently reported. Neurological status was reported in 24 out of 49 studies (49%), but in 18 studies the assessment was performed at discharge; similarly all-cause death was reported in 43 out of 49 studies (88%), but in only 12 studies (25%) the outcome was assessed at 30 days, whereas the majority reported in-hospital mortality. Some prognostic relevant information such as “witnessed arrest”, “bystander CPR/AED”, timing (“from collapse to begin CPR” or “from call to ambulance arrival” or “from collapse to first shock”) was less reported in studies conducted by cardiologists.



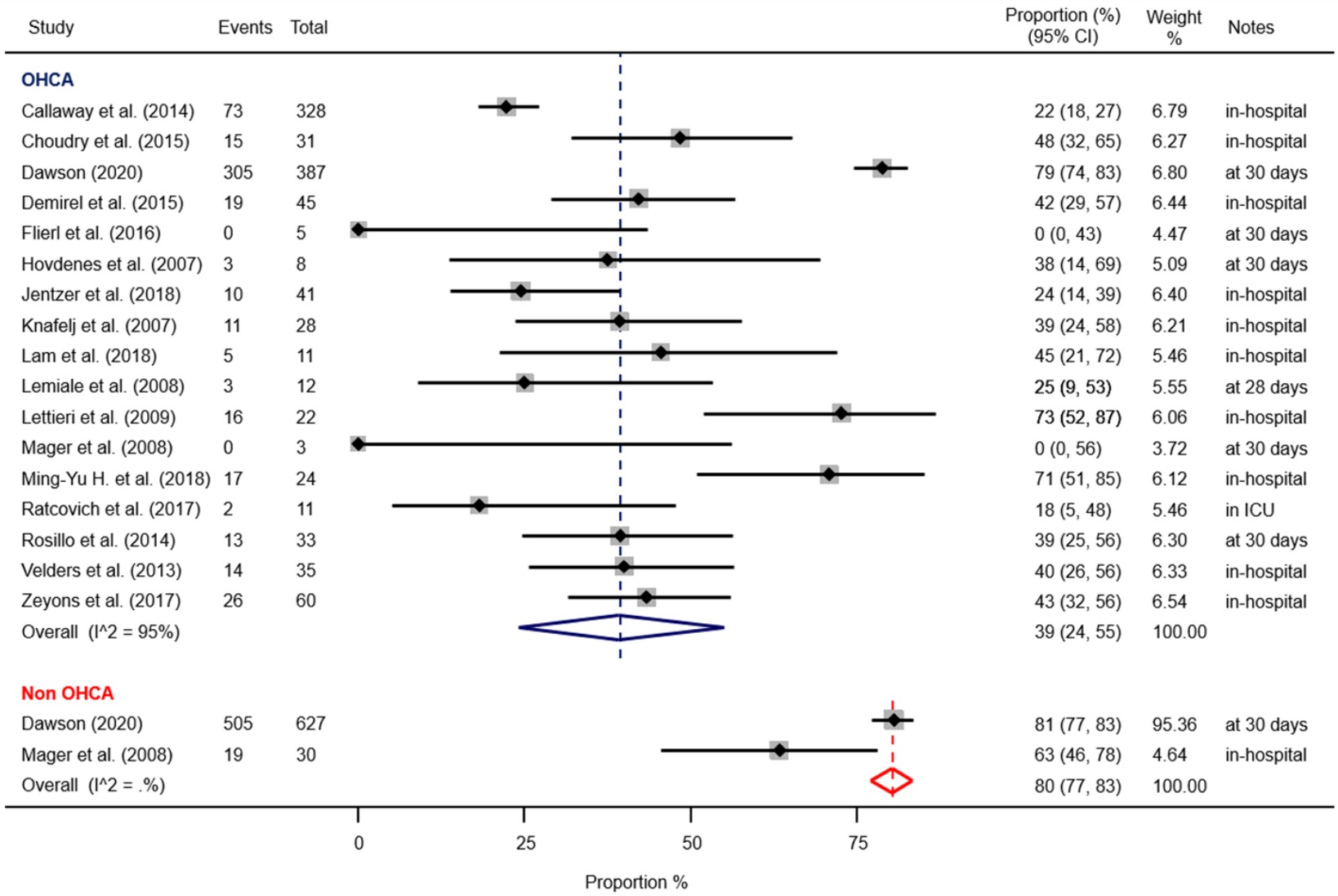
Supplementary Figure 1. Proportion estimates of in-hospital or 30-day mortality in OHCA and non-OHCA patients.

Values of I^2 (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively. ICU: intensive care unit



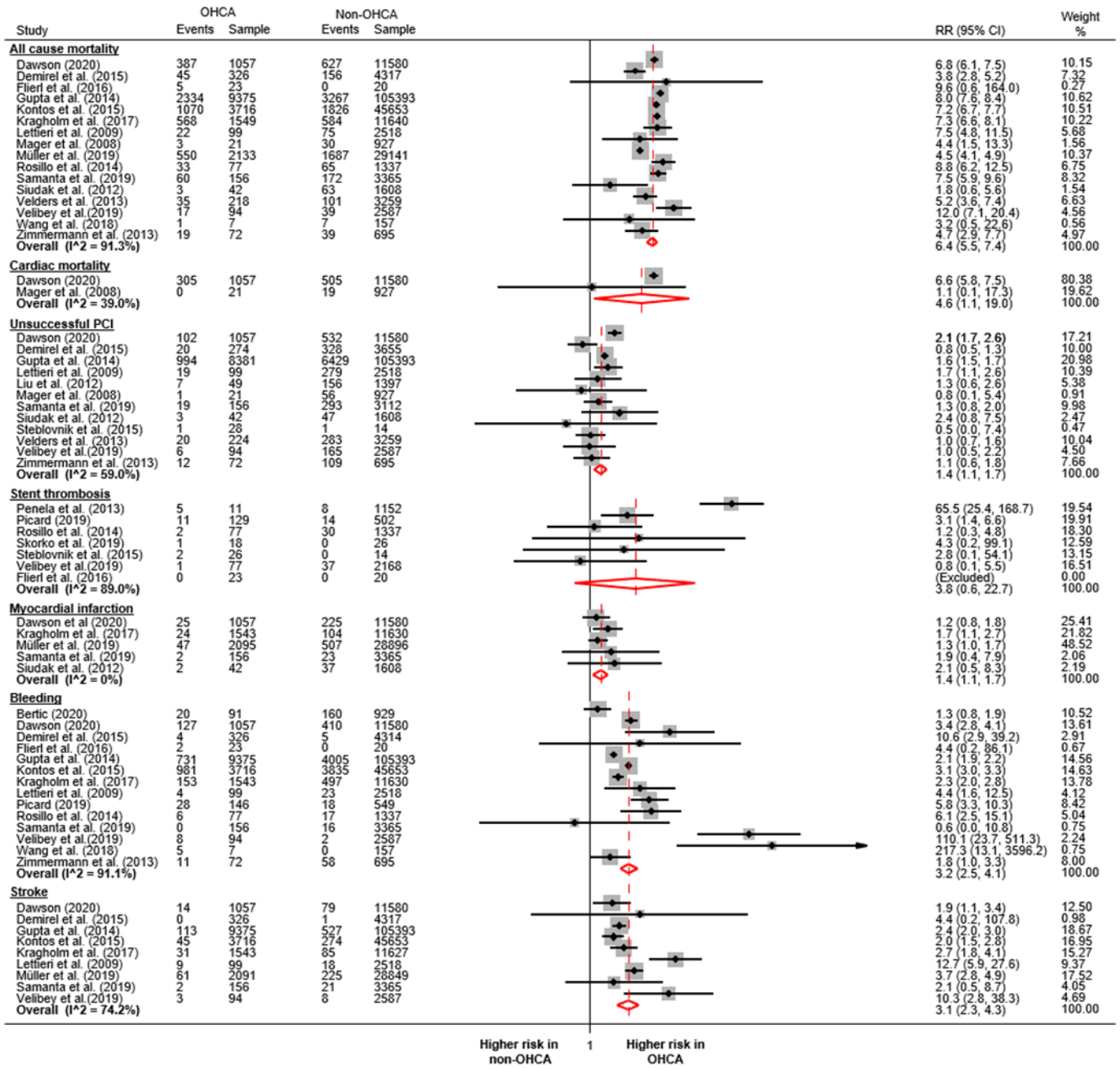
Supplementary Figure 2. Proportion estimates of cardiovascular death in OHCA and non-OHCA patients.

Values of I^2 (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively. ICU: intensive care unit

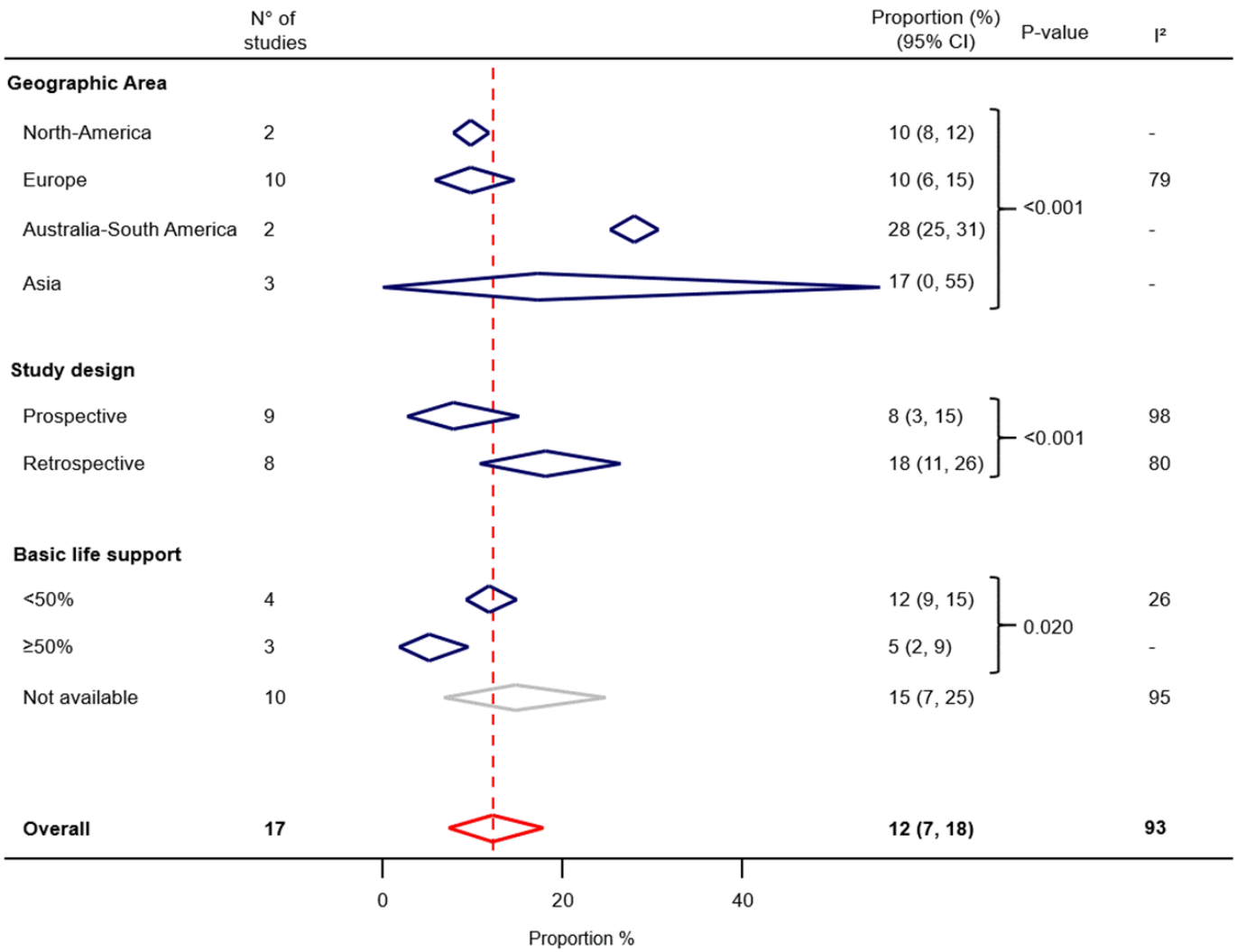


Supplementary Figure 3. Proportion estimates of cardiovascular death (numerator) relative to all-cause death (denominator) for OHCA and non-OHCA patients.

Values of I^2 (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively. ICU: intensive care unit

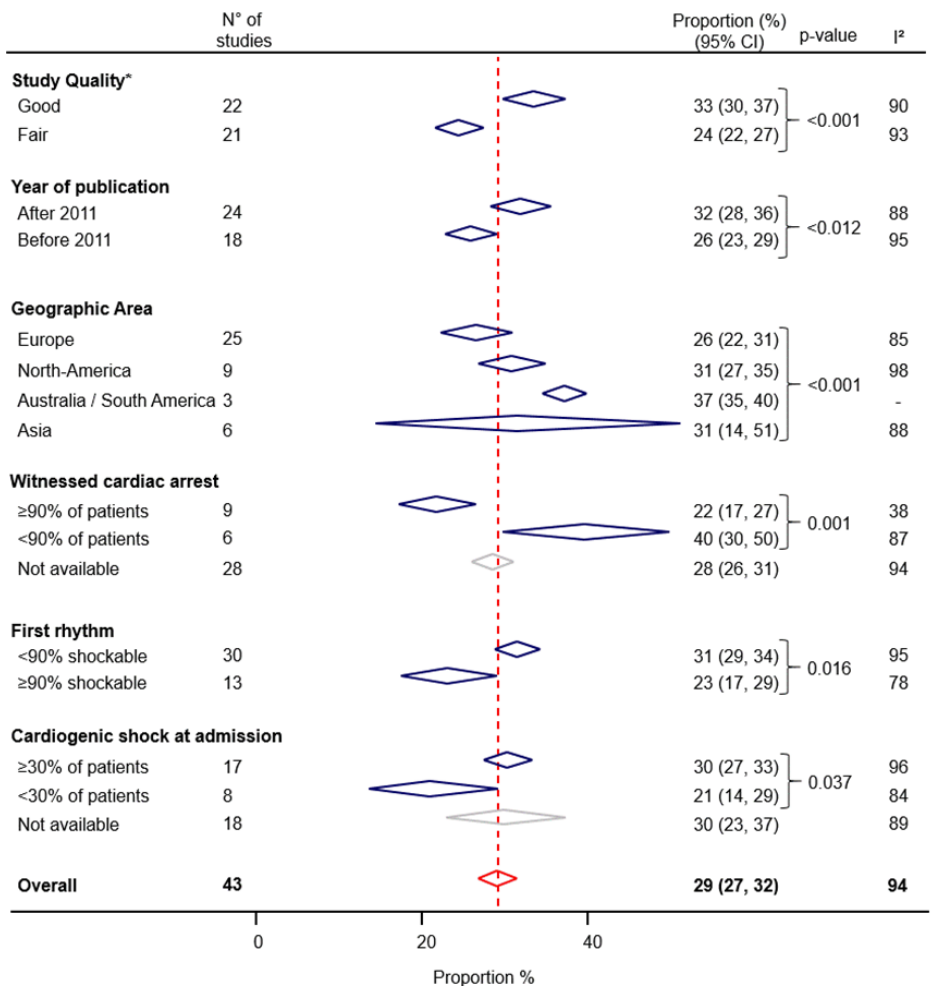


Supplementary Figure 4. Relative risk for the primary and secondary outcomes of OHCA versus non-OHCA patients.



Supplementary Figure 5. Subgroup analysis for cardiovascular death in the OHCA group.

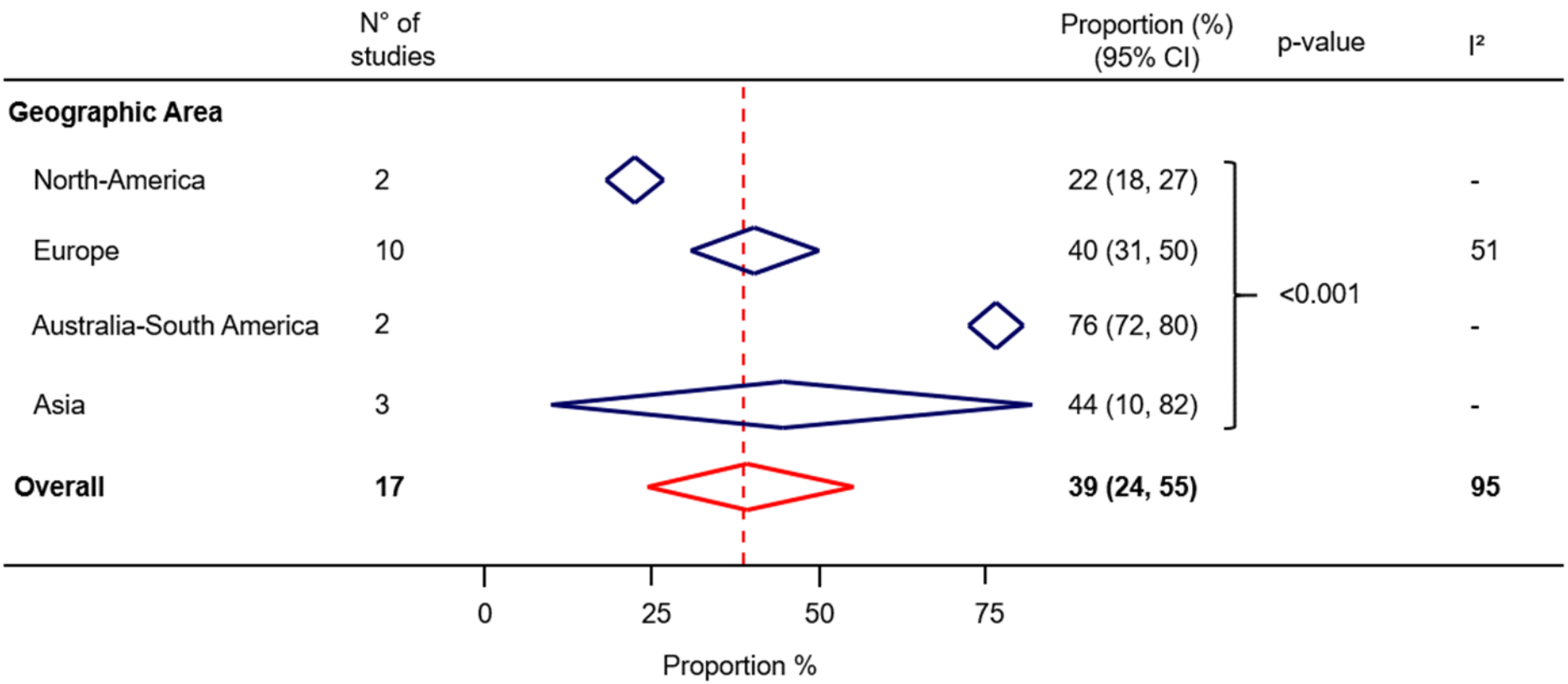
Values of I^2 (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively.



Supplementary Figure 6. Subgroup analysis for all-cause death in the OHCA group.

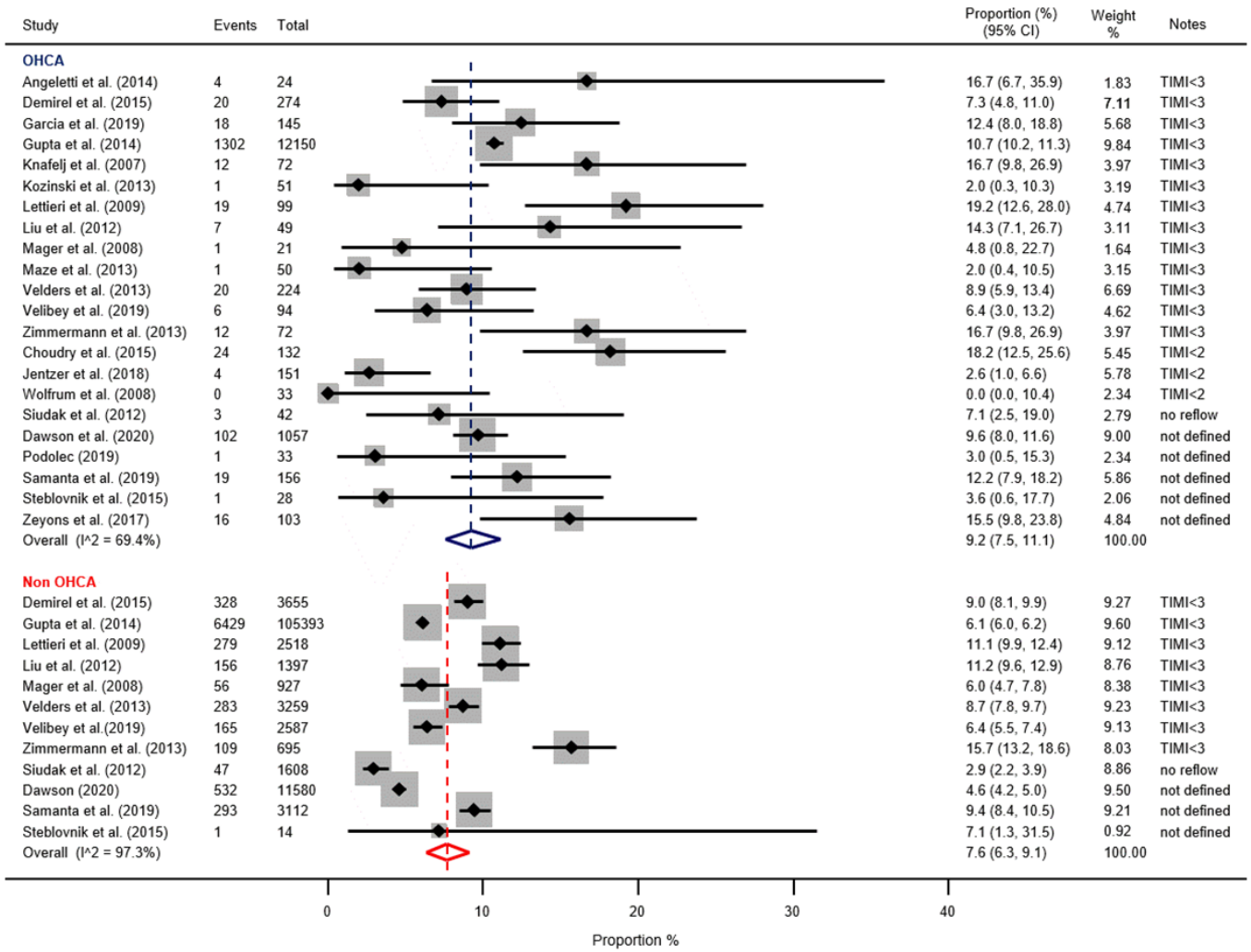
* according to the Newcastle-Ottawa score.

Values of I^2 (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively.



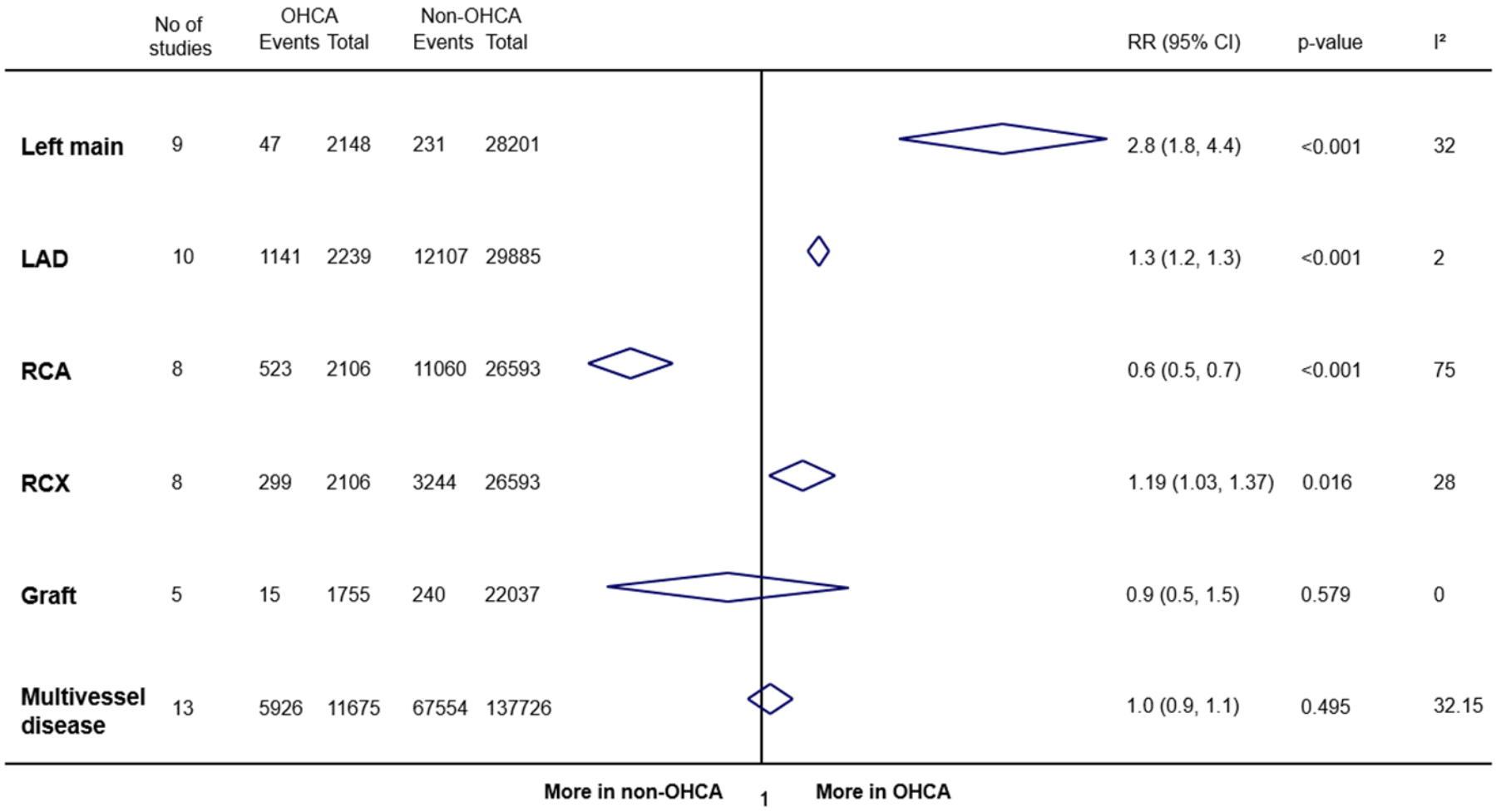
Supplementary Figure 7. Subgroup analysis for cardiovascular death (numerator) relative to all-cause death (denominator) in the OHCA group.

Values of I^2 (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively.



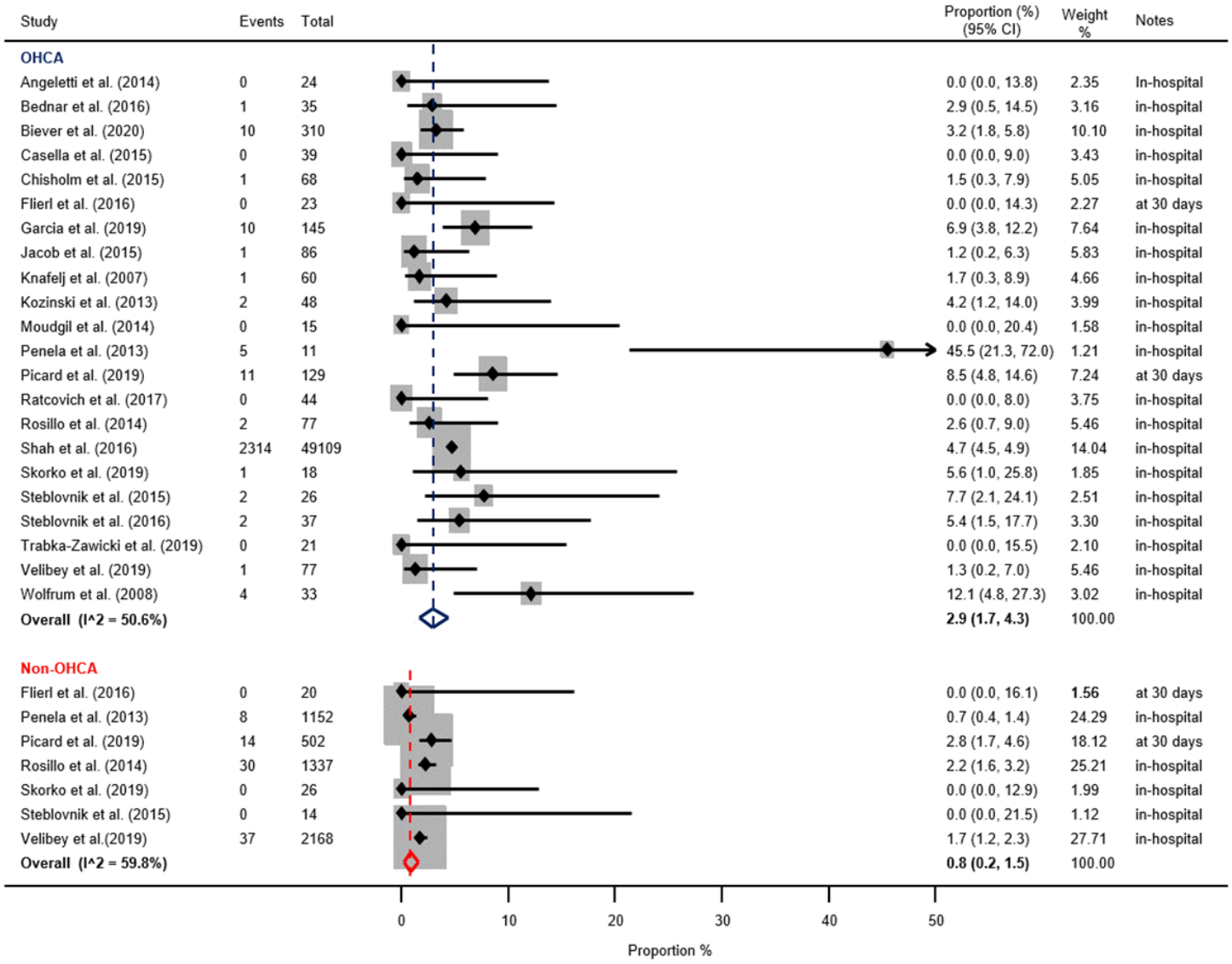
Supplementary Figure 8. Proportion estimate of unsuccessful PCI in OHCA and non-OHCA patients, defined as TIMI <3 at the end of the procedure (if not otherwise specified in notes).

Values of I^2 (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively.



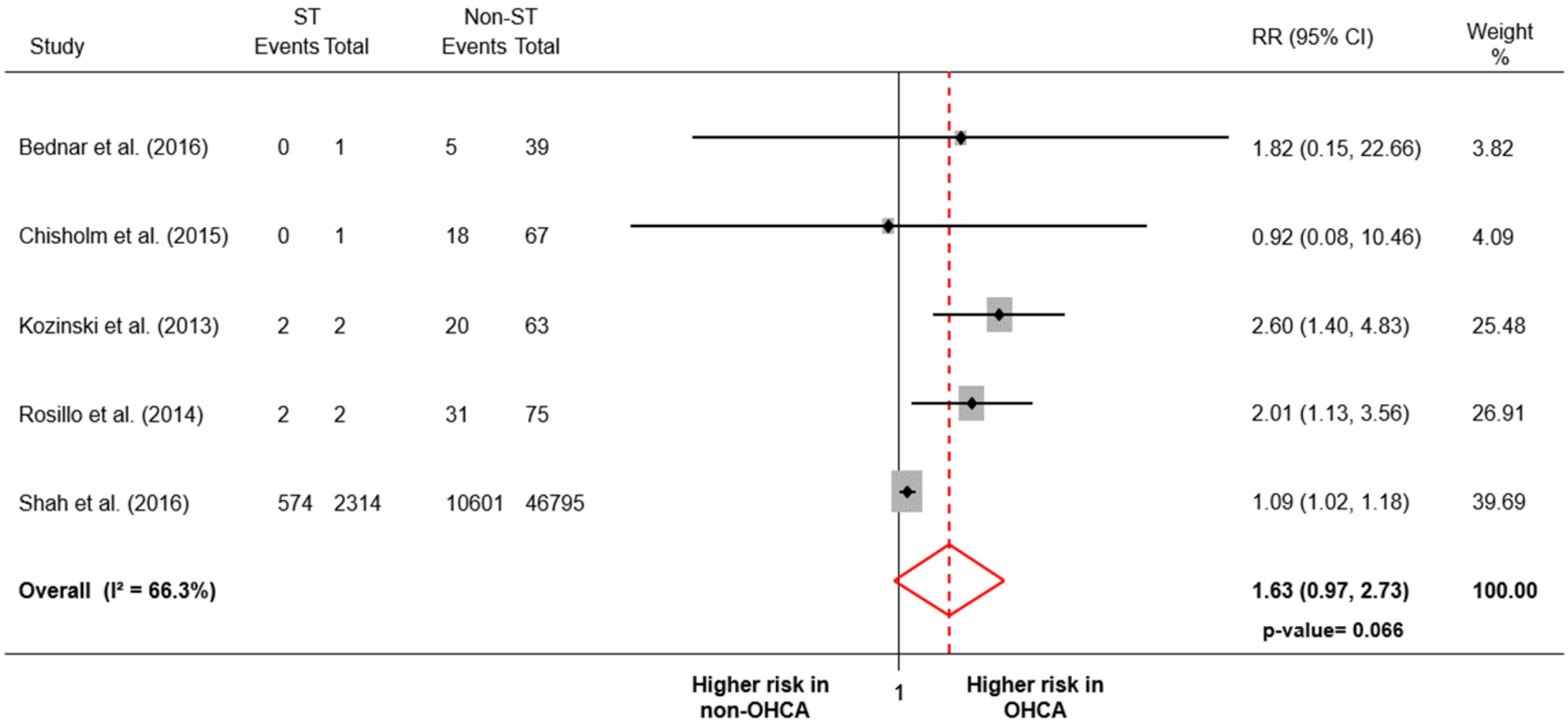
Supplementary Figure 9. Location of culprit lesion: comparison in OHCA versus no-OHCA patients.

Values of I^2 (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively.



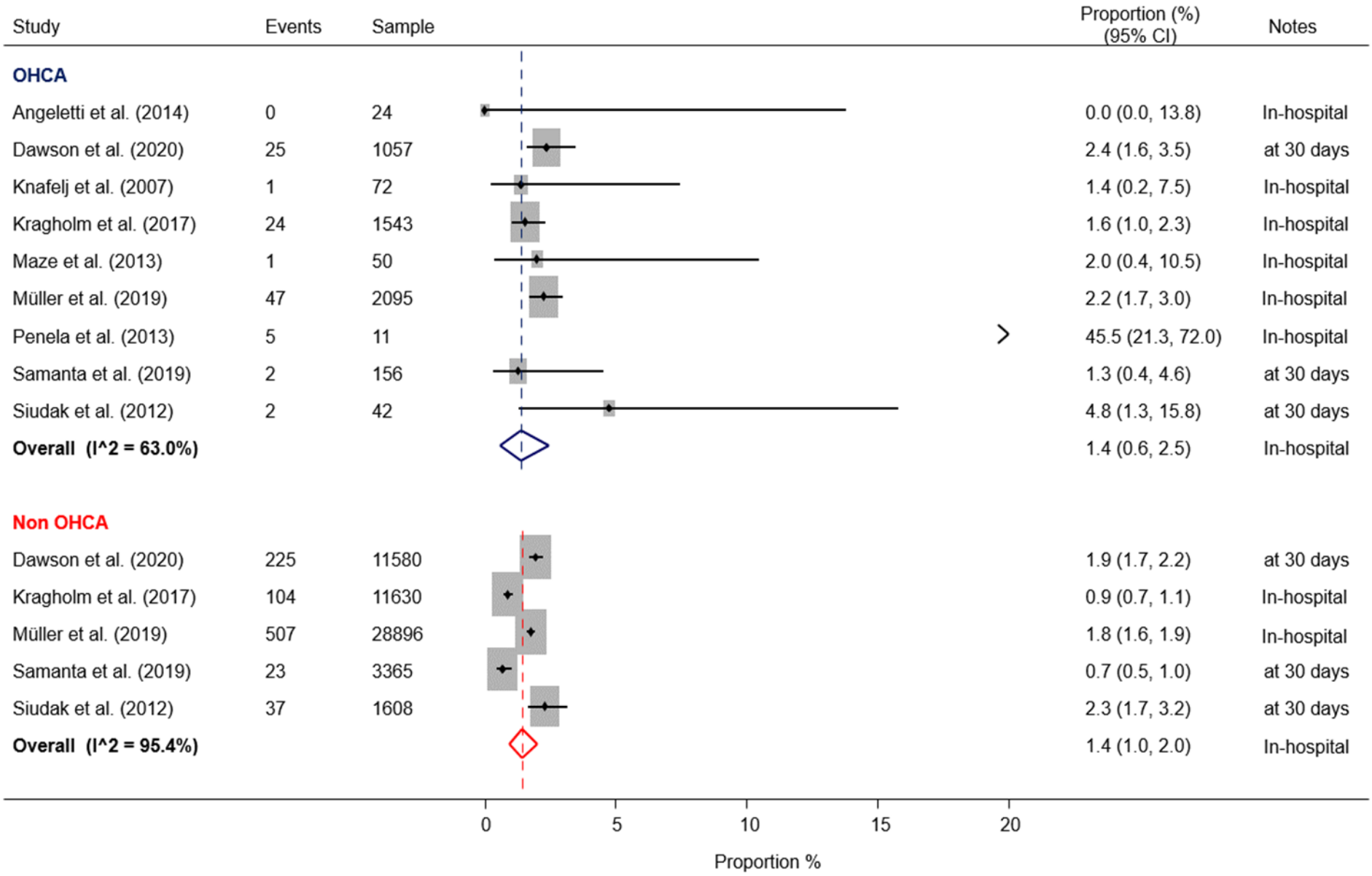
Supplementary Figure 10. Proportion estimates of acute and subacute in-stent thrombosis in OHCA and non-OHCA patients.

Values of I^2 (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively.



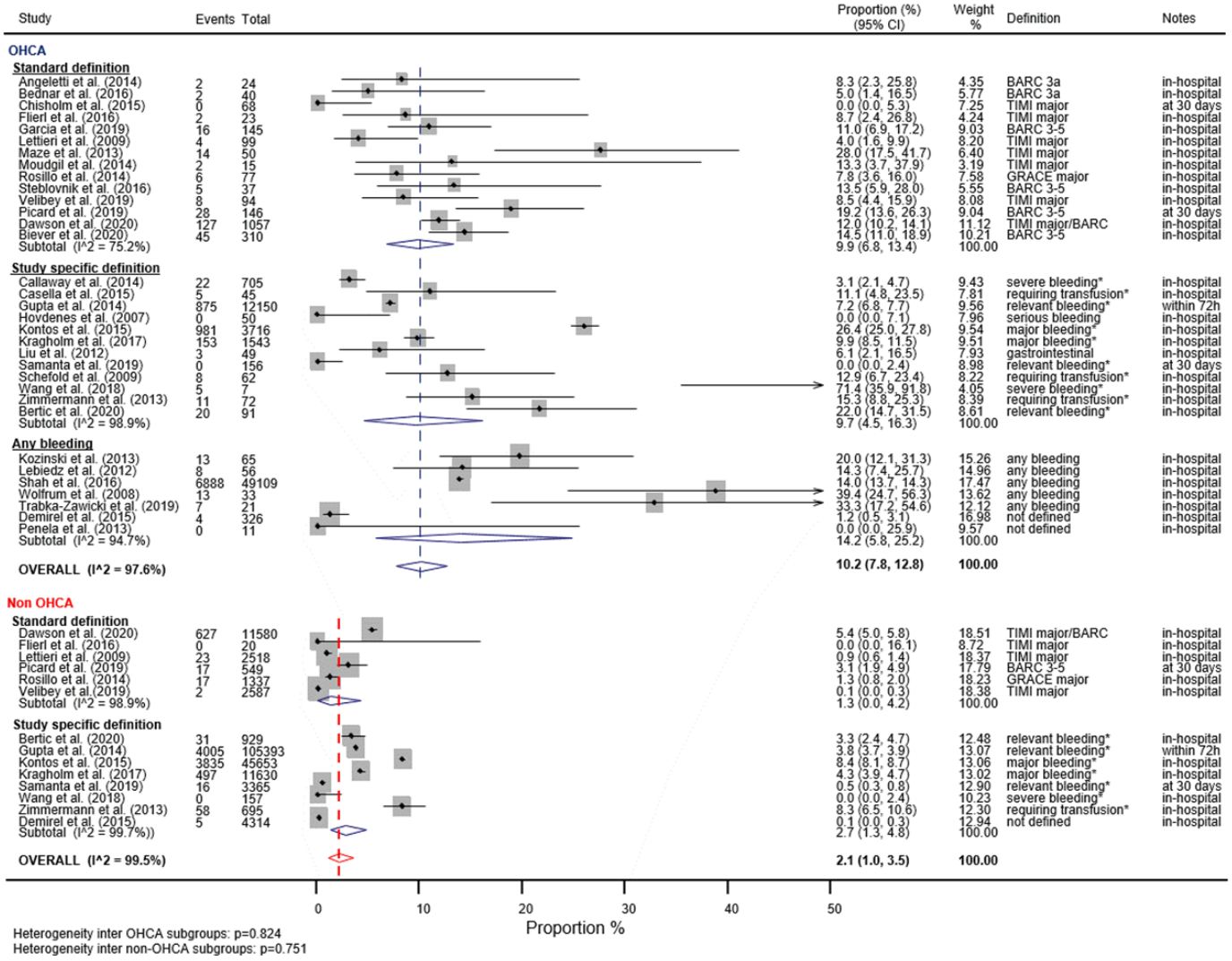
Supplementary Figure 11. All-cause mortality in patients with stent thrombosis (ST) and in patients without stent thrombosis (non-ST) in the OHCA group.

Values of I^2 (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively**.**



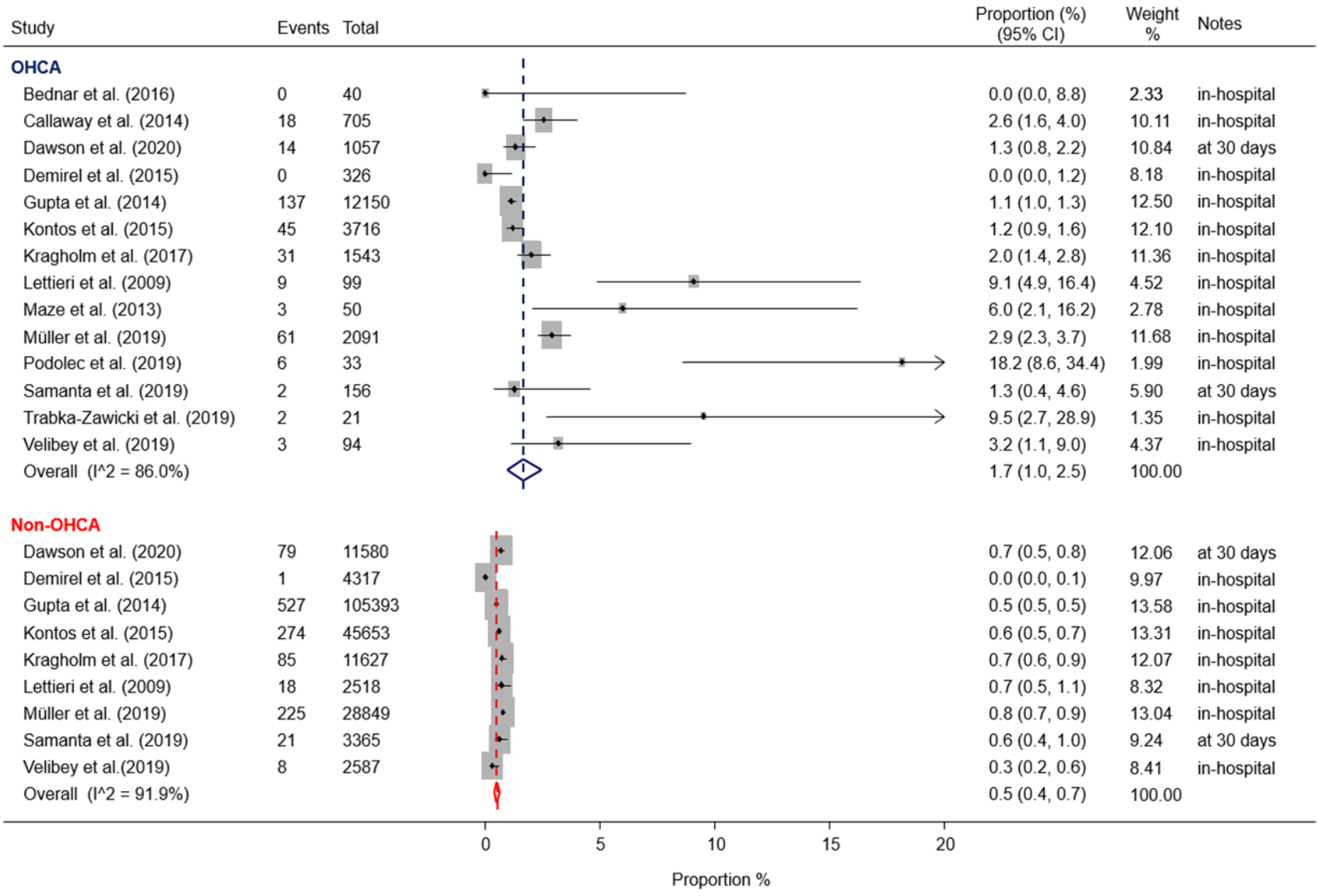
Supplementary Figure 12. Proportion estimate of in-hospital myocardial infarction (including myocardial infarction caused by an ST).

Values of I^2 (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively.



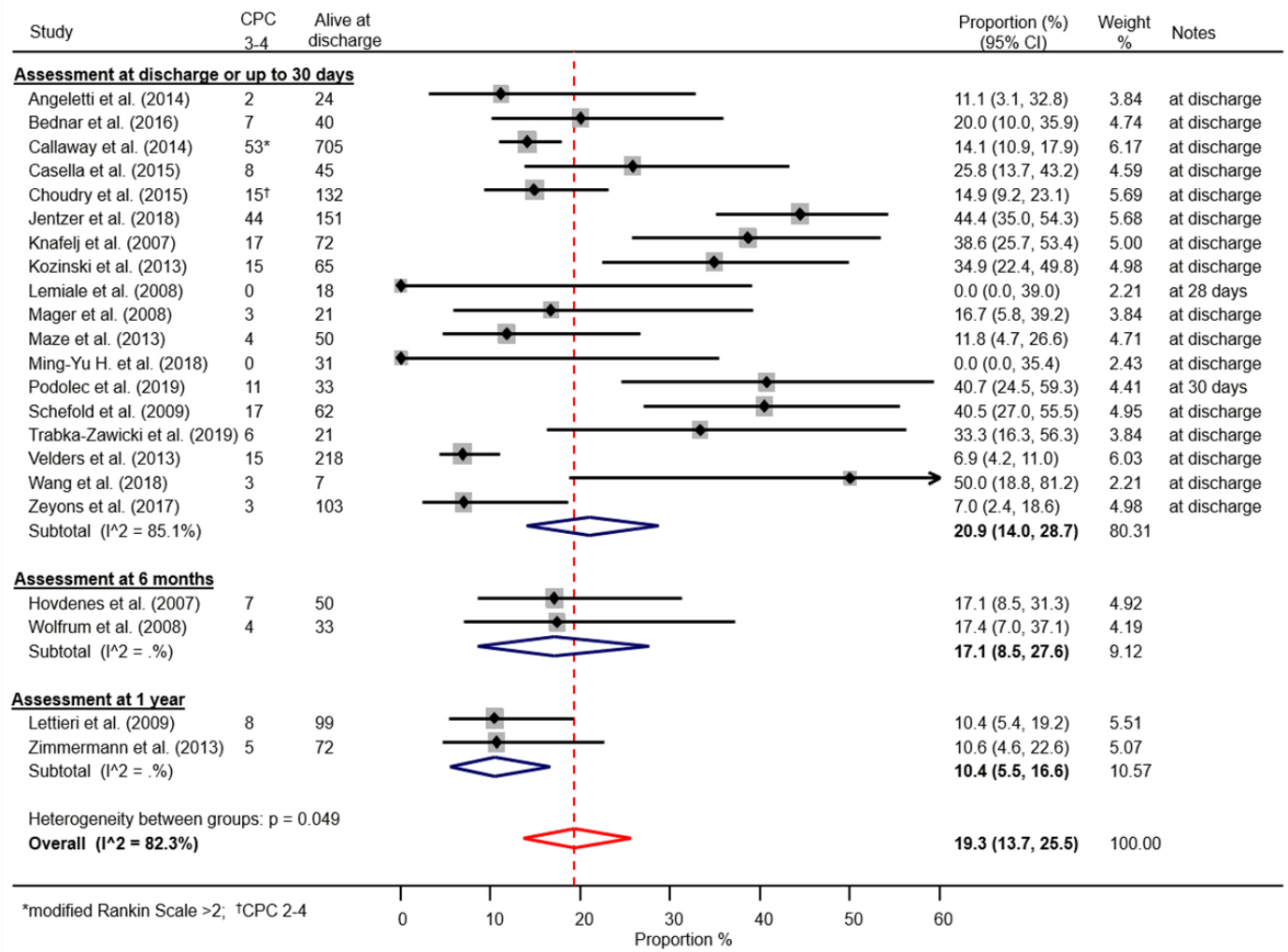
Values of I² (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively.

Supplementary Figure 13. Proportion estimate of in-hospital bleeding events in the OHCA and non-OHCA groups, including subgroup analysis according to bleeding definition.



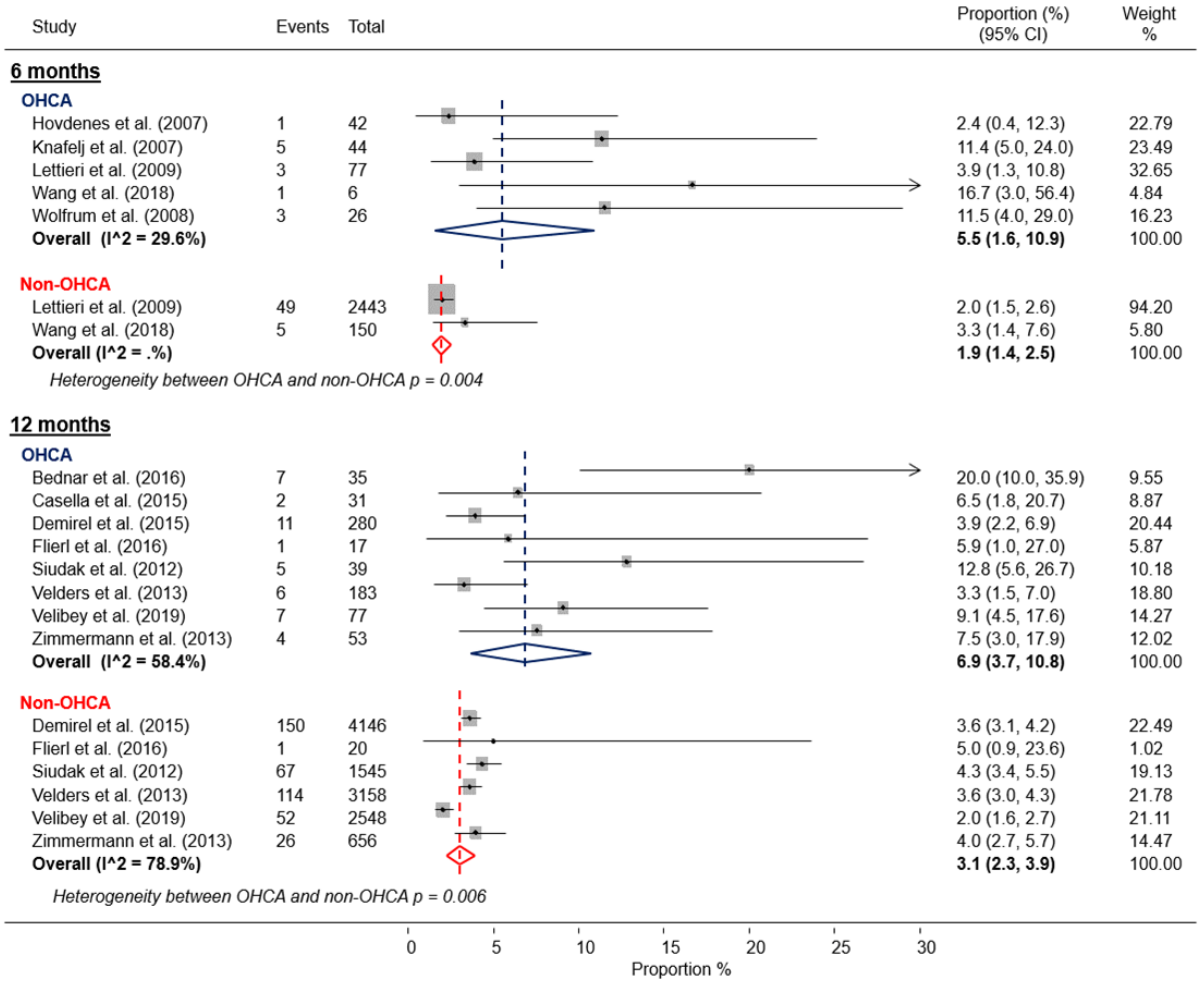
Supplementary Figure 14. Proportion estimate of in-hospital stroke in the OHCA and non-OHCA groups.

Values of I^2 (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively.



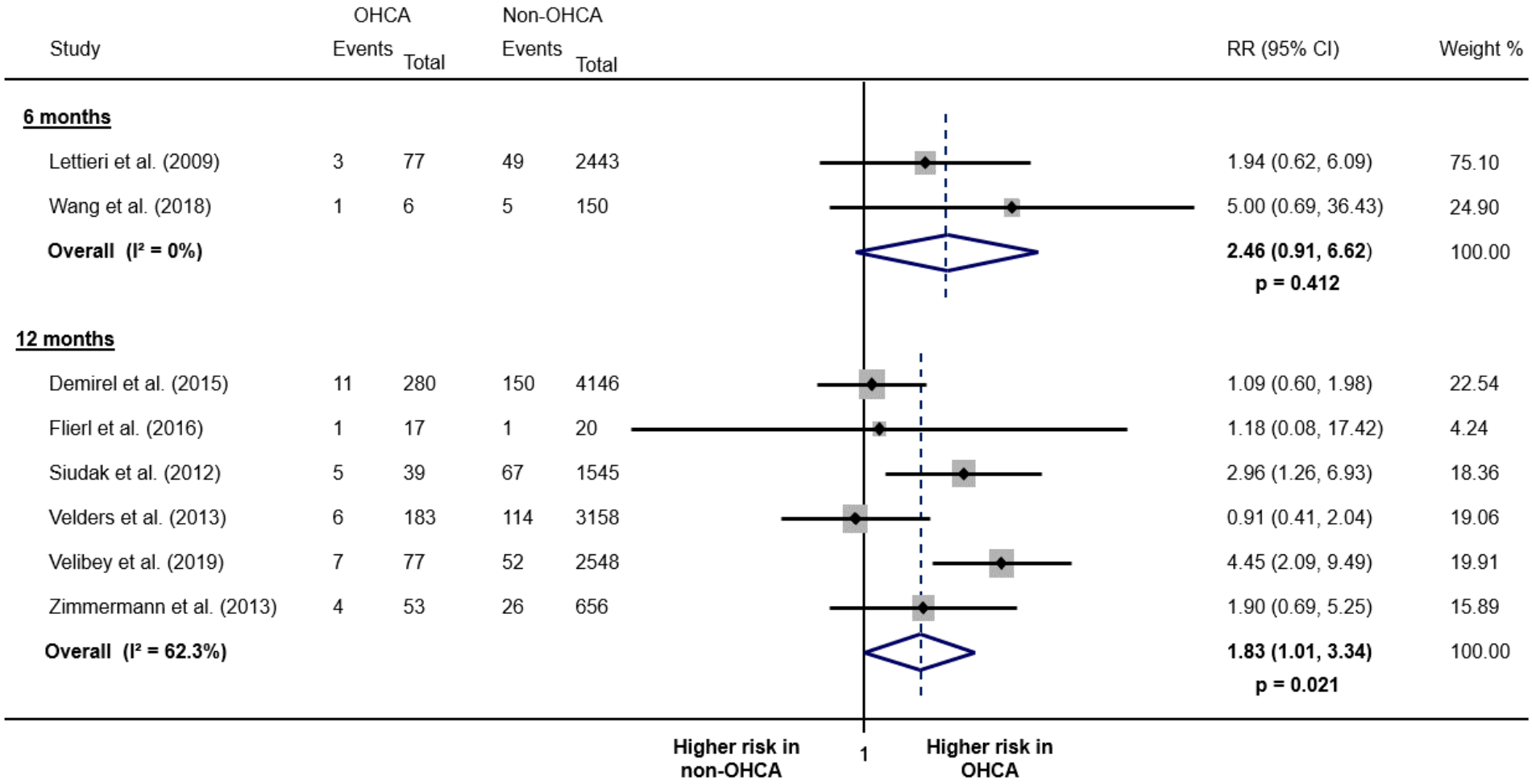
Supplementary Figure 15. Proportion of alive patients with poor neurological outcome at discharge, defined as CPC (Cerebral Performance Category) 3 or 4, including subgroup analysis according to time of assessment.

Values of I^2 (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively.



Supplementary Figure 16. Proportion estimates of all-cause mortality at 6 and 12 months among OHCA and non-OHCA patients discharged alive.

Values of I^2 (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively.



Supplementary Figure 17. Relative risk for all-cause mortality at 6 and 12 months among OHCA and non-OHCA patients discharged alive.

Values of I^2 (I squared) around 25%, 50% and 75% indicate low, intermediate and high heterogeneity among studies, respectively.

Supplementary Table 1. Study design and OHCA population characteristics in the selected studies.

Study	PMID	Sample size	PCI (%)	Recruitment period	Country	Design	Quality of study*	Male (%)	Age	VF/VT (%)	TH (%)	Unconscious (%)	Witnessed (%)	BLS (%)	STEMI (%)	NSTEMI (%)	Shock at admission %	Mechanical support (%)
Angeletti et al (2014)	25002173	24	100	2008-2013	Italy	retrospective	good	96	59	88	100	100	87	-	-	-	33	29
Bednar et al (2016)	26340851	40	87	2011-2014	Czech Republic	prospective	fair	75	65	-	100	100	-	-	57	43	-	-
Bertic et al (2020)	32201581	91	100	2007-2016	Canada	retrospective	good	92	64	-	-	-	-	-	100	-	62	-
Biever et al (2020)	31300835	310	100	2002-2013	Germany	retrospective	good	78	63	-	72	-	-	-	-	-	-	-
Callaway et al (2014)†	24412161	705	73	2007-2009	USA and Canada	Post hoc analysis RCT	good	76	62	77	50	-	85	43	48	52	-	-
Casella et al (2015)†	25522746	45	100	2004-2012	Italy	prospective	good	76	64	89	100	100	96	-	78	22	20	18
Chisholm et al (2015)	24944239	68	100	2010-2013	Denmark	retrospective	good	76	62	96	100	100	-	-	54	46	-	-
Choudry et al (2015)	25326470	132	100	2008-2011	London, UK	retrospective	fair	79	59	95	43	48	91	22	100	0	18	-
Dawson et al (2020)	32209377	1,057	100	2005-2018	Australia	prospective	good	85	61	-	-	-	-	-	100	0	47	-
Demirel et al (2015)	25114328	326	84	2005-2010	Netherlands	prospective	fair	76	60	100	-	-	-	-	100	0	30	21
Flierl et al (2016)	26790884	23	100	2012-2014	Germany	prospective	good	83	61	96	100	100	-	57	-	-	-	35
Garcia et al (2019)	29807760	145	100	2005-2016	Spain	retrospective	good	86	59	74	72	-	-	-	78	22	69	18
Gupta et al (2014)	24513475	12,150	100	2009-2010	North America	retrospective	fair	73	60/64	-	-	-	-	-	77	23	48	35
Hovdenes et al (2007)	17181536	50	72	2003-2005	Norway	retrospective	fair	88	57	100	100	100	94	80	-	-	-	46
Jacob et al (2015)‡	26362487	86	100	2011-2013	Denmark	post hoc analysis RCT	good	87	62	89	89	100	90	80	88	12	10	-
Jentzer et al (2018)†	29223601	151	100	2005-2013	USA	prospective	good	66	61	79	56	-	-	58	64	36	-	-
Knafelj et al (2007)	17383070	72	100	2000-2005	Slovenia	retrospective	fair	82	58	100	44	100	-	35	100	0	-	21
Kontos et al (2015)	25819858	3,716	82	2011-2012	USA	retrospective	good	74	61	-	-	-	-	-	100	0	43	-
Kozinski et al (2013)†	23531402	65	83	2008-2011	Poland	retrospective	good	79	64	80	49	100	-	43	71	29	45	20
Kragholm et al (2017)	29021273	1,549	83	2012-2014	USA	retrospective	good	73	61/59	-	-	-	-	-	100	0	54	-
Lam et al (2018)‡	28766924	40	92	2007-2014	Israel	retrospective	good	76	60	85	-	77	-	-	59	41	-	-

Supplementary Table 1 (continued)

Study	PMID	Sample size	PCI (%)	Recruitment period	Country	Design	Quality of study*	Male (%)	Age	VF/VT (%)	TH (%)	Unconscious (%)	Witnessed (%)	BLS (%)	STEMI (%)	NSTEMI (%)	Shock at admission %	Mechanical support (%)
Lebiedz et al (2012)‡	22120604	56	100	2005-2011	Germany	retrospective	good	83	59	67	100	100	73	57	40	60	-	16
Lemiale et al (2008)	17714849	18	77	2005-2005	France	retrospective	good	78	61	44	100	100	-	-	-	-	56	-
Lettieri et al (2009)	19249431	99	100	2005-2005	Italy	prospective	fair	86	60	91	12	42	88	46	100	0	26	22
Liu et al (2012)†	22613643	49	100	2004-2008	China	retrospective	good	82	54	-	-	29	-	-	100	0	39	37
Mager et al (2008)	19005296	21	100	2001-2006	Israel	prospective	fair	76	57	-	5	-	-	-	100	0	-	19
Maze et al (2013)	22922176	50	100	2004-2011	Canada	retrospective	fair	80	56	96	100	100	84	74	100	0	46	20
Ming-Yu H. et al (2018)	-	31	100	2011-2015	Taiwan	retrospective	good	76	-	-	-	100	-	-	-	-	-	6
Moudgil et al (2014)	25442437	15	93	2011-2012	Canada	prospective	fair	87	56	100	100	100	-	-	-	-	-	-
Müller et al (2019)‡	30447263	2,133	**79**	1997-2017	Switzerland	retrospective	good	78	62	-	33	-	-	-	100	0	36	16
Penela et al (2013)†	23265329	11	100	2010-2012	Spain	retrospective	fair	-	-	100	100	100	-	-	36	64	-	-
Picard et al (2019)	31682901	146	100	2012-2017	France	retrospective	good	85	61	60	73	-	56	89	100	0	65	14
Podolec et al (2019)	31043991	33	100	2011-2016	Poland	Prospective	good	82	66	85	100	100	-	-	61	39	24	-
Ratcovich et al (2017)	28216475	44	100	2014-2015	Denmark	prospective	fair	82	58	-	93	100	-	-	100	0	-	9
Rosillo et al (2014)	24140665	77	100	2008-2012	Bolivia	retrospective	fair	86	61	-	100	100	-	-	100	0	-	30
Samanta et al (2019)	30603662	156	91	2004-2017	Australia	prospective	fair	81	61	100	-	-	-	-	100	0	23	-
Schefold et al (2009)	18255170	62	87	2005-2006	Germany	retrospective	fair	82	56	81	50	100	94	47	-	-	56	-
Shah et al (2016)	27609254	49,109	100	2006-2011	North America	retrospective	fair	68	63	-	2	-	-	-	-	-	34	30
Siudak et al (2012)	21958931	42	100	2005-2007	Europe	retrospective	fair	74	63	83	0	0	-	-	100	0	19	14
Skorko et al (2019)	30716426	18	100	2016-2017	UK	prospective	fair	71	68	100	-	100	100	93	-	-	-	-
Steblovnik et al (2015)	24800722	28	100	2011-2013	Slovenia	prospective	good	68	65	-	100	100	-	-	68	32	-	-
Steblovnik et al (2016)	27994027	37	100	2014-2016	Slovenia	non-randomised CT	fair	-	-	-	100	100	-	-	-	-	46	41
Trabka-Zawicki et al (2019)	28695976	21	100	2014-2015	Poland	prospective	good	81	66	81	100	100	100	67	52	48	19	-

Supplementary Table 1 (continued)

Study	PMID	Sample size	PCI (%)	Recruitment period	Country	Design	Quality of study*	Male (%)	Age	VF/VT (%)	TH (%)	Unconscious (%)	Witnessed (%)	BLS (%)	STEMI (%)	NSTEMI (%)	Shock at admission %	Mechanical support (%)
Velders et al (2013)	23907098	224	100	2006-2009	Netherlands	prospective	fair	79	63	94	42	48	94	-	100	0	31	25
Velibey et al (2019)	30455410	94	100	2009-2014	Turkey	retrospective	fair	83	57	-	-	-	-	-	100	0	-	-
Wang et al (2018)	29521302	7	100	2013-2015	China	retrospective	fair	-	-	100	57	100	100	-	100	0	-	71
Wolfrum et al (2008)	18496378	33	100	2005-2006	Germany	retrospective	fair	82	56/63	100	48	100	91	39	100	0	-	36
Zeyons et al (2017) †	28304194	103	87	2009-2013	France	retrospective	fair	83	64	66	66	-	84	-	85	15	-	38
Zimmermann et al (2013)	22204846	72	100	2001-2008	Germany	retrospective	very good	82	61	-	26	-	100	-	100	0	58	15

* quality of study according to Newcastle-Ottawa score.

† population characteristics refer to the selected subgroup in which >70% of OHCA patients underwent PCI.

‡ population characteristics for the selected PCI subgroup are not available; the data refer to the entire population.

BLS: bystander basic life support; CT: clinical trial; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; RCT: randomised clinical trial; STEMI: ST-elevation myocardial infarction; TH: therapeutic hypothermia; VF: ventricular fibrillation; VT: ventricular tachycardia

Supplementary Table 2. Non-OHCA population characteristics in the selected studies.

Study	PMID	Sample size	PCI (%)	Male (%)	Age	STEMI (%)	NSTEMI (%)	Shock at admission (%)	Mechanical support (%)
Bertic et al (2020)	32201581	929	100	77	66	100	0	4	-
Dawson et al (2020)	32209377	11,580	100	78	64	100	0	7	-
Demirel et al (2015)	25114328	4,317	86	72	64	100	0	2	9
Flierl et al (2016)	26790884	20	100	90	56	100	0	-	0
Gupta et al (2014)	24513475	105,393	100	72	60	100	0	7	9
Kontos et al (2015)	25819858	45,653	87	70	61	100	0	5	-
Kragholm et al (2017)	29021273	11,640	90	67	62/63	100	0	6	-
Lettieri et al (2009)	19249431	2,518	100	77	63	100	0	5	5
Liu et al (2012)	22613643	1,397	100	91	64	100	0	8	5
Mager et al (2008)	19005296	927	100	80	61	100	0	-	5
Müller et al (2019)	30447263	29,141	74	74	65	100	0	3	4
Penela et al (2013)	23265329	1,152	74	-	-	-	-	-	-
Picard et al (2019)	31682901	549	100	81	61	100	0	3	5
Rosillo et al (2014)	24140665	1,337	100	78	64	100	0	-	6
Samanta et al (2019)	30603662	3,365	92	67	61	100	0	7	-
Siudak et al (2012)	21958931	1,608	100	72	64	100	0	3	3
Skorko et al (2019)	30716426	30	87	73	65	100	0	-	-
Steblovnik et al (2015)	24800722	14	100	50	75	50	50	-	-
Velders et al (2013)	23907098	3,259	100	75	63	100	0	5	3
Velibey et al (2019)	30455410	2,587	100	83	57	100	0	-	-
Wang et al (2018)	29521302	157	100	-	-	100	0	-	17
Zimmermann et al (2013)	22204846	695	100	70	63	100	0	9	3

NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction

Supplementary Table 3. Summary of selected study and population characteristics stratified by sample study dimension.

	TOTAL		SMALL*	MEDIUM*	LARGE*
	Studies n=49	**Patients n=73,634**	**34 studies 1,625 pat**	**9 studies 2,295 pat**	**6 studies 69,714 pat**
Rhythm					
≥90% of patients with shockable rhythm	15 (31)	72,350 (98)	11 (32)	4 (44)	4 (44)
Any rhythm	34 (69)	1,284 (2)	23 (68)	5 (56)	5 (56)
Therapeutic hypothermia (TH)					
≥90% of patients undergoing TH	17 (35)	640 (1)	17 (50)	0 (0)	0 (0)
With and without TH	19 (39)	52,970 (72)	11 (32)	6 (67)	6 (67)
Information not available	13 (27)	19,982 (27)	6 (18)	3 (33)	3 (33)
State of consciousness after ROSC					
Only unconscious	25 (51)	1,014 (1)	25 (74)	0 (0)	0 (0)
Conscious and unconscious	16 (33)	53,882 (73)	7 (21)	6 (67)	6 (67)
Only conscious	1 (2)	42 (<1)	1 (3)	0 (0)	0 (0)
Information not available	7 (14)	18,696 (25)	1 (3)	3 (33)	3 (33)
Sustained ROSC					
Excluding patients without sustained ROSC	20 (41)	4,310 (6)	13 (38)	6 (67)	6 (67)
Not specified	29 (59)	69,324 (94)	21 (62)	3 (33)	3 (33)
ECG at presentation					
Only STEMI	22 (45)	10,190 (14)	13 (38)	5 (56)	5 (56)
With and without ST-elevation	27 (55)	63,444 (86)	21 (62)	4 (44)	4 (44)
Data collection					
Retrospective	30 (61)	70,505 (96)	21 (62)	4 (44)	4 (44)
Prospective	19 (39)	3,129 (4)	13 (38)	5 (56)	5 (56)
Authors' affiliation					
Mixed	19 (39)	17,023 (23)	15 (44)	2 (22)	2 (22)
Only cardiology	25 (51)	53,606 (73)	16 (47)	6 (67)	6 (67)
Only ICU/EMS/ED	5 (10)	3,005 (4.1)	3 (9)	1 (11)	1 (11)
Control group (non-OHCA)					
Present	22 (45)	22,089 (30)	22 (62)	4 (44)	4 (44)
Absent	27 (55)	51,545 (70)	12 (38)	5 (56)	5 (56)

The data represent absolute number and (percentage). *small: <104 patients; medium: 104-1,000 patients; large: >1,000 patients.
ECG: electrocardiogram; ED: emergency department; EMS: emergency medical services; ICU: intensive care unit; OHCA: out-of-hospital cardiac arrest; ROSC: return of spontaneous circulation; STEMI: ST-elevation myocardial infarction

Supplementary Table 4. Statistically non-significant results of stratified meta-analysis for the absolute prevalence of cardiovascular death, the prevalence of cardiovascular death (numerator) relative to all-cause death (denominator) and for all-cause death.

	Cardiovascular death (absolute)			Cardiovascular death (relative to all-cause death)			All-cause death		
Subgroup	**N° of studies**	**Proportion estimate**	***p*-value**	**N° of studies**	**Proportion estimate**	***p*-value**	**N° of studies**	**Proportion estimate**	***p*-value**
Sample size			**0.592**			**0.877**			**0.917**
≥104 patients	6	11 (4-20)		6	43 (17-71)		28	29 (23-34)	
<104 patients	11	13 (7-21)		11	40 (27-53)		15	29 (26-32)	
Data collection			**See Supplementary Figure 4**			**0.430**			**0.086**
Prospective				9	34 (12-60)		15	24 (17-31)	
Retrospective				8	45 (36-53)		28	31 (28-33)	
N° of centres			**0.924**			**0.665**			**0.456**
Multicentre	5	13 (5-24)		5	47 (17-79)		11	28 (25-31)	
Single centre	12	12 (6-19)		12	39 (30-49)		32	30 (25-35)	
Year of publication			**0.112**			**0.814**			
After 2011	8	16 (8-27)		8	41 (20-64)				
Before 2011	9	9 (6-12)		9	38 (25-52)				
Quality of study			**0.218**			**0.766**			**See Supplementary Figure 5**
Good	8	16 (7-26)		8	38 (14-66)				
Fair	9	10 (6-15)		9	42 (33-52)				
Affiliation department of the authors			**0.360**			**See Supplementary Figure 6**			
Cardiology	9	9 (3-17)							
Other than cardiology	2	11 (8-13)							
Mixed	6	18 (7-32)							
Percentage of males			**0.479**			**0.592**			**0.181**
≥80% of patients	8	14 (7-21)		8	43 (23-65)		22	31 (26-36)	
<80% of patients	9	10 (6-15)		9	36 (24-49)		20	27 (24, 30)	
Not available	0			0			1	14 (3-51)	
Witnessed cardiac arrest			**0.069**			**0.973**			**See figure S5**
≥90% of patients	3	8 (5-11)		3	43 (32-55)				
<90% of patients	3	16 (8-27)		3	44 (19-71)				
Not available	11	12 (5-21)		11	36 (18-57)				

Supplementary Table 4 (continued)

	Cardiovascular death (absolute)			Cardiovascular death (relative to all-cause death)			All-cause death		
Subgroup	**N° of studies**	**Proportion estimate**	***p*-value**	**N° of studies**	**Proportion estimate**	***p*-value**	**N° of studies**	**Proportion estimate**	***p*-value**
Bystander basic life support		**0.020**	**See Supplementary Figure 4**			**0.151**			**0.637**
≥50% of patients				3	21 (6-40)		6	28 (17-39)	
<50% of patients				4	44 (22-68)		7	31 (22-41)	
Not available				10	43 (26-61)		30	28 (26-31)	
Shockable rhythm			**0.079**			**0.684**			**See Supplementary Figure 5**
≥90% of patients	7	8 (5-12)		7	43 (31-56)				
<90% of patients	10	16 (8-24)		10	38 (17-61)				
ROSC			**0.902**			**0.251**			**0.368**
Only sustained ROSC	10	12 (7-18)		10	34 (22-47)		18	31 (25-38)	
Not only sustained ROSC	7	13 (5-23)		7	49 (28-70)		25	28 (25-31)	
State of consciousness after ROSC			**0.846**			**0.390**			**0.951**
Only unconscious	7	13 (4-25)		7	35 (20-52)		19	29 (23-36)	
Conscious and unconscious	8	13 (6-21)		8	47 (27-68)		16	30 (27-34)	
Not available	2	9 (7-11)		2	24 (20-29)		8	26 (20-33)	
ECG at presentation			**0.554**			**0.332**			**0.247**
Only STEMI	9	11 (4-19)		9	45 (27-64)		22	28 (24, 31)	
With or without ST-elevation	8	14 (7-22)		8	34 (20-48)		21	31 (27, 34)	
Cardiogenic shock at presentation			**0.499**			**0.897**			**See Supplementary Figure 5**
≥30% of patients	3	16 (2-38)		3	51 (16-84)				
<30% of patients	3	10 (5-18)		3	53 (36-70)				
Not available	11	12 (7-18)		11	33 (22-45)				
Need for mechanical support			**0.660**			**0.497**			**0.692**
≥25% of patients	5	10 (3-19)		5	38 (28-48)		11	27 (23-31)	
<25% of patients	6	13 (4-25)		6	45 (27-64)		15	29 (23-35)	
Not available	6	14 (6-24)		6	41 (13-72)		17	31 (27-35)	

Supplementary Table 4 (continued)

	Cardiovascular death (absolute)			Cardiovascular death (relative to all-cause death)			All-cause death		
Subgroup	**N° of studies**	**Proportion estimate**	***p*-value**	**N° of studies**	**Proportion estimate**	***p*-value**	**N° of studies**	**Proportion estimate**	***p*-value**
Patients undergoing PCI			**0.840**			**0.520**			**0.256**
100%	11	11 (6-17)		11	42 (24-61)		29	28 (25-31)	
<100%	6	12 (6-20)		6	34 (22-47)		14	31 (26-37)	
Use of glycoprotein IIb/IIIa inhibitors			**0.954**			**0.771**			**0.756**
≥40% of patients	4	9 (0-25)		4	43 (9-81)		10	28 (24, 32)	
<40% of patients	4	10 (4-17)		4	38 (29-48)		10	30 (21-40)	
Not available	9	14 (8-20)		9	39 (27-51)		23	29 (26-33)	
Type of $P2Y_{12}$ inhibitor used			**0.709**			**0.850**			**0.954**
Only clopidogrel	3	6 (0-17)		3	33 (15-53)		9	28 (22-34)	
All $P2Y_{12}$ inhibitors	5	10 (1-24)		5	38 (11-68)		17	28 (23-32)	
Not available	9	15 (10-21)		9	43 (29-56)		17	31 (27-36)	
Therapeutic hypothermia (TH)			**0.488**			**0.309**			**0.289**
≥90% of patients	5	7 (2-15)		5	27 (14-42)		13	26 (19-33)	
<90% of patients	9	11 (7-15)		8	37 (25-51)		18	30 (26-35)	
Not available	4	22 (7-43)		4	61 (38-82)		12	30 (24-35)	
Outcome assessment timing			**0.656**			**0.596**			**0.774**
At discharge	11	13 (9-18)		11	42 (31-53)		31	29 (26, 31)	
At 30 days	6	9 (1-22)		6	31 (5-65)		11	30 (23, 26)	
At ICU discharge	0			0			1	32 (22, 45)	

ECG: electrocardiogram; ICU: intensive care unit; NSTEMI: non ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; ROSC: return of spontaneous circulation; STEMI: ST-elevation myocardial infarction

Supplementary Table 5. Proportion of reporting of some characteristics/outcomes of interest for cardiologists in 49 studies overall and stratified by department of affiliation of the authors.

	All studies (%) n=49	Cardiology (%) n=25	ICU/EMS/ ED (%) n=5	Mixed (%) n=19
Trauma from reanimation	2 (4)	1 (4)	1 (20)	0 (0)
Pre-hospital antiplatelet/anticoagulant treatment	5 (10)	4 (16)	0 (0)	1 (5)
Direct admission to coronary catheterisation laboratory	1 (2)	0 (0)	0 (0)	1 (5)
Arrest or door-to-balloon	23 (47)	14 (56)	2 (40)	7 (37)
Vascular access	6 (12)	3 (12)	0 (0)	0 (0)
Type of lesion	10 (20)	7 (28)	0 (0)	3 (16)
Chronic total occlusion	2 (4)	0 (0)	0 (0)	2 (11)
Use of glycoprotein IIb/IIIa inhibitors	25 (51)	11 (44)	3 (60)	11 (58)
Type of $P2Y_{12}$ inhibitor	26 (53)	13 (52)	3 (60)	10 (53)
Type of stent (bare metal or drug-eluting stent)	18 (37)	10 (40)	2 (40)	6 (32)
Multivessel PCI	6 (12)	2 (8)	1 (20)	3 (16)

ED: emergency department; EMS: emergency medical services; ICU: intensive care unit; PCI: percutaneous coronary intervention

Supplementary Table 6. Proportion of reporting of 2004 and 2015 core Utstein criteria in the 49 studies overall and stratified by affiliation department of the authors.

	ALL STUDIES	Studies stratified according to affiliation department of the authors		
	N=49	Cardiology (n=25)	ICU/EMS/ED (n=5)	Mixed (n=19)
CORE UTSTEIN CRITERIA 2004				
Cardiac arrest attended	0 (0)	0 (0)	0 (0)	0 (0)
Resuscitation attempted or not	1 (2)	0 (0)	1 (20)	0 (0)
Survived event	4 (8)	1 (4)	1 (20)	2 (11)
Any ROSC	0 (0)	0 (0)	0 (0)	0 (0)
Age	45 (92)	24 (96)	5 (100)	16 (84)
Sex	46 (94)	24 (96)	5 (100)	17 (89)
Witnessed arrest	18 (37)	7 (28)	3 (60)	8 (42)
Witnessed by EMS personnel*	0 (0)	0 (0)	0 (0)	0 (0)
Bystander CPR/AED	16 (33)	7 (28)	4 (80)	5 (26)
First monitored rhythm	31 (63)	15 (60)	4 (80)	12 (63)
Arrest location	3 (6)	1 (4)	1 (20)	1 (5)
Aetiology	8 (16)	1 (4)	2 (40)	5 (26)
Time from collapse to begin CPR* (no flow)	10 (20)	2 (8)	3 (60)	5 (26)
Time from collapse to first shock*	0 (0)	0 (0)	0 (0)	0 (0)
Therapeutic hypothermia (y/n)	37 (76)	18 (72)	5 (100)	14 (74)
30-day survival	12 (24)	7 (28)	1 (20)	4 (21)
Neurological outcome at discharge	18 (37)	7 (28)	3 (60)	8 (42)
CORE UTSTEIN CRITERIA added in 2015				
Population served	8 (16)	0 (0)	0 (0)	5 (26)
System description	4 (8)	0 (0)	0 (0)	4 (21)
Dispatcher-identified cardiac arrest	0 (0)	0 (0)	0 (0)	0 (0)
Dispatcher CPR-instruction	0 (0)	0 (0)	0 (0)	0 (0)
Time from call to ambulance arrival	7 (14)	1 (4)	3 (60)	3 (16)
Time from call to first shock	0 (0)	0 (0)	0 (0)	0 (0)
CPR duration (low flow)	9 (18)	2 (8)	2 (40)	5 (26)
Drugs given	7 (14)	3 (12)	2 (40)	2 (11)
Timing of begin of therapeutic hypothermia	7 (14)	4 (16)	1 (20)	2 (11)
CAG/PCI	49 (100)	25 (100)	5 (100)	19 (100)
Timing of coronary reperfusion	23 (47)	14 (56)	2 (40)	7 (37)

* criteria only present in 2004 and not in 2015. All the numbers reported represent the number of studies and (percentage).

AED: automatic external defibrillation; CAG: coronary angiography; CPR: cardiopulmonary resuscitation; ED: emergency department; EMS: emergency medical services; ICU: intensive care unit; PCI: percutaneous coronary intervention; ROSC: return of spontaneous circulation