Long-term survival after cardiac arrest in patients undergoing emergent coronary angiography

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ABSTRACT (word count: 248)

Aim: To determine long-term survival of patients after cardiac arrest undergoing emergent coronary angiography and therapeutic hypothermia.

Methods: We analysed data from patients treated within the regional STEMI Network from January 2015 to December 2020. The primary endpoint was all-cause mortality at median follow-up. Secondary endpoints were periprocedural complications (arrhythmias, pulmonary edema, cardiogenic shock, mechanical complication, stent thrombosis, reinfarction, bleeding) and 6-month all-cause death. A landmark analysis was performed, studying two time periods; 0–6 months and beyond 6 months.

Results: From a total of 24,125 patients in the regional STEMI network, 494 patients who suffered from cardiac arrest were included and divided into two groups: treated with (n=119) and without therapeutic hypothermia (n=375). At median follow−up (16.0 [0.2−33.3] months), there was no difference in the adjusted mortality rate between groups (51.3% with hypothermia vs 48.0% without hypothermia; HR_{adj}1.08 95%CI [0.77−1.53]; p=0.659). There was a higher frequency of bleeding in the hypothermia group (6.7% vs 1.1%; OR_{adj} 7.99 95%CI [2.05−31.2]; p=0.002), without difference for the rest of periprocedural complications. At 6-month follow−up, adjusted all-cause mortality rate was similar between groups (46.2% with hypothermia vs 44.5% without hypothermia; HR_{adj}1.02 95%CI [0.71−1.47]; p=0.900). Also, no differences were observed in the adjusted mortality rate between 6 months and median follow−up (9.4% with hypothermia vs 6.3% without hypothermia; HR_{adj}2.02 95%CI [0.69−5.92]; p=0.200).

Conclusions: In a large cohort of patients with cardiac arrest within a regional STEMI network, those treated with therapeutic hypothermia did not improve long−term survival compared to those without hypothermia.

ABBREVIATIONS

ACS, Acute coronary syndrome

COPD, Chronic obstructive pulmonary disease

CPR, Cardiopulmonary resuscitation

eCRF, electronic case report form

EKG, Electrocardiogram

EMS, Emergency medical system

ESCC, Emergency system coordinating center

ERC, European Resuscitation Council

FMC, First medical contact

ICU, Intensive care unit

IPD, Individual patient data

IHCA, In−hospital cardiac arrest

MI, Myocardial infarction

OHCA, Out-of-hospital cardiac arrest

PCI, Percutaneous coronary intervention

PPCI, Primary percutaneous coronary intervention

RCT, Randomized controlled trials

ROSC, Return of spontaneous circulation

STEMI, ST−segment elevation myocardial infarction

TIA, Transient ischemic attack

TIMI, Thrombolysis in myocardial infarction

TTM, Targeted Temperature Management

INTRODUCTION

Cardiac arrest is a major cause of morbidity and mortality worldwide, accounting for 275.000 individuals per year with out−of−hospital cardiac arrest (OHCA) in Europe and 290.000 patients per year with in−hospital cardiac arrest (IHCA) in the United States.[1, 2] In both settings, mortality remains high, only approximately 10% survival in OHCA and 30% survival in IHCA, with a modest improvement in IHCA and no changes in OHCA over the last decade despite advances in treatments and technology.[1, 3, 4]

After cardiac arrest, there is a combination of several complex pathophysiological events, beginning from the initial global ischemia to the subsequent reperfusion injury in patients who achieve a return of spontaneous circulation (ROSC). This chain of events has been labelled as post−cardiac arrest syndrome.[5] Among these, hypoxic brain injury is an important cause of neurological disability and mortality without an effective treatment or improvement in prognosis over the last decades.[4]

Targeted therapeutic hypothermia (i.e., active cooling of comatose patients after ROSC) has been widely used based on its potential neuroprotective effects, such as cerebral metabolism slowdown and reperfusion injury reduction.[6] The current European Resuscitation Council (ERC) 2021 guidelines recommends targeted hypothermia with a target temperature between 32–36ºC for at least 24 hours in adults who remain unresponsive after ROSC regardless of the setting or initial heart rhythm.[7, 8]. These recommendations are based on the results of early randomized controlled trials (RCTs) suggesting improved outcomes in patients with OHCA and initial shockable rhythms.[9, 10] However, recent RCTs have found contrasting results, with one RCT suggesting an improvement in survival with favourable neurological outcomes at 90 days after cardiac arrest with non−shockable rhythm.[11] In contrast, the other largest RCTs found no survival benefit of hypothermia to 33°C over 36°C after OHCA at 6-month

follow-up. [12-14] Of note, none of them has evaluated long-term survival beyond 6 months in patients with cardiac arrest treated with therapeutic hypothermia.

The aim of this study was to determine the long-term survival of patients with cardiac arrest treated with or without hypothermia within the regional 'Codi IAM' ST−elevation myocardial infarction (STEMI) network.

METHODS

Data collection

From January 2015, data from all patients activated in the regional STEMI network in Catalonia (Spain) were prospectively collected in a dedicated registry. [15] The database comprising the registry belongs to the Health Department of the Catalonia Government and includes demographic, clinical, and therapeutic data. It conforms to the ethical and legal requirements for research purposes. This study was approved by the institutional review board (IRB) of each participant hospital.

Patient population and follow−up

This was an observational, multicentric study based on prospectively collected data from consecutive patients treated within the STEMI Network between January 2015 and December 2020. Patients were included according to the following inclusion criteria: Adults (≥18 years old) residing in Catalonia who presented a cardiac arrest (OHCA or IHCA) and achieved ROSC with suspected STEMI who underwent emergent coronary angiography with or without PCI and were treated with or without therapeutic hypothermia according to the treating medical team criteria.

Procedures

After achieving ROSC, patients were treated with immediate post−resuscitation care. The patients included in the study suffered cardiac arrest and had suspected STEMI based on the diagnostic EKG. They were transferred to PPCI centers according to the regional STEMI network protocols for emergent coronary angiography. [15] All patients underwent coronary angiography, but the decision to proceed with PCI was established by the treating medical team based on patient's clinical presentation and results from coronary angiography. If PCI was performed, it was done according to the local practices and current recommendations of the European Society of Cardiology (ESC) guidelines at the moment of the procedures. [16, 17]

The decision to apply therapeutic hypothermia was taken following each center's local intensive care unit (ICU) protocol. Therefore, therapeutic hypothermia (active cooling with a target temperature of 32-36ºC for at least 24h) was applied differently among hospitals – either with surface cooling pads (Arctic Sun^{TM} system) or endovascular invasive devices (CoolGard system). [18-20] Although these local protocols were different, all of them followed the existing recommendations of the ERC guidelines for the inclusion period described previously. [7, 8, 21] When patients arrived at the ICU, they received standard treatments, including mechanical ventilation and vasoactive support. All patients were treated with sedative and analgesic agents at recommended doses adjusted for managing mechanical ventilation. Neuromuscular relaxation was achieved with neuromuscular blocking drug infusion to avoid muscular tremors. According to local practices, patients who did not receive therapeutic hypothermia had conventional post−resuscitation treatment at the corresponding ICU center.

Data capture and managing

A predefined electronic Case Report Form (eCRF) was implemented since the inception of the STEMI network. Study data elements were collected by the local investigators (catsalut.gencat.cat). The data elements are focused on the previous history, clinical status of the patient in the different levels of care (out−hospital, transfer, and in−hospital), and clinical outcomes (**Supplementary Appendix**). All the data were obtained from the medical records. The quality of the data included in the registry was verified by means of external audits. Data on patient's vital status was obtained through the national social security database up to December 31st, 2020.

Definition and outcomes

The primary endpoint was all−cause death at median follow−up. The key secondary endpoint was six−month all−cause death. Exploratory outcomes included periprocedural complications (pre and 24h post PPCI); such as ventricular fibrillation, ventricular tachycardia, asystole, atrial fibrillation (AF), any bleeding, any shock, acute stent thrombosis, and reinfarctions. The occurrence of these events was ascertained and reported by the local investigators of each participating center in a prospective manner by means of a dedicated case report form (**Figure S1**). In patients presenting with STEMI, time delays are defined according to the ESC STEMI guidelines published in 2017.[16]

Statistical analysis

All analyses were stratified by patients treated with or without therapeutic hypothermia. Continuous variables are presented as mean and standard deviation (or medians and interquartile ranges whenever appropriate) and were compared with independent samples *t* test. Categorical variables were expressed as absolute and relative frequency and were compared with chi−square or Fisher exact tests as appropriate.

For the primary endpoint (all−cause death), number and percentage of patients, survival curves using Kaplan−Meier estimates, and hazard ratio (HR) (95% confidence interval [CI]) using Cox regression model are displayed. In addition, HR and p−value were calculated from Cox proportional hazards models adjusted for possible confounders that were considered of clinical and statistical significance ($p<0.05$). For in−hospital complications, number and percentage of patients with event and odds ratio (OR) (95% confidence interval [CI]) using logistic regression model are displayed. In addition, OR and p−value were calculated from logistic proportional hazards models adjusted for confounders that were considered of clinical significance.

A landmark analysis was performed, studying two time periods, 6−month follow−up (0–180 days) and beyond 6−month follow−up (180 days to end of study). Subgroup analyses included the following variables: gender, age greater than 65 years, OHCA and IHCA, shockable and non-shockable rhythm in the first assistance, initial EKG with ST−segment elevation, shock on admission, fibrinolysis, total ischemic time, PCI performed, number of vessels diseased, treated vessels and mechanical circulatory support/intra−aortic balloon pump. Two−tailed p−value <0.05 was considered as significant. The SAS v.9.4 software was used for all analyses.

RESULTS

Patient population

From January 2015 to December 2020, 24,125 patients were included in the regional STEMI network database. Out of these, 560 patients with cardiac arrest were included in the study. Among them, 66 patients were excluded from the analysis (64 patients achieved ROSC but died before STEMI network activation; in 2 patients, age was not available).

The remaining 494 patients were finally included in the analysis and divided into two groups: treated with hypothermia (n=119) and without hypothermia (n=375) (**Figure 1**).

Baseline characteristics showed a lower frequency of active smokers (51.3% vs 39.2%; p=0.020), and a higher frequency of previous myocardial infarction (MI) (16.3% vs 7.6%; p=0.018) and previous percutaneous coronary intervention (PCI) (12.3% vs 5.9%; p=0.049) in the therapeutic hypothermia group (**Table 1**).

A total of 409 patients (82.8%) had an OHCA while 85 patients (17.2%) had an IHCA. Most of the patients (79.3%) had a shockable rhythm in the first medical assistance. Patients in the hypothermia group were more commonly assisted in the first place by the EMS (89.9% vs 80.5%; p=0.045) and had a higher incidence of ventricular fibrillation in the first medical contact (85.7% vs 61.6%; p=0.001) compared to those without hypothermia. By contrast, the group without therapeutic hypothermia had had a higher frequency of initial Killip Class IV in the hospital arrival compared to the group with hypothermia (48.5% vs 32.7%; p=0.032). However, in the first medical contact there were not differences between groups regarding shock status (20.5% vs 21%, p= 0.911) (**Table 2**).

Periprocedural complications

In the hypothermia group, there was a higher frequency of bleeding complications (6.7% vs 1.1%; OR_{adj} 7.99 95%CI [2.05−31.2]; p=0.002) and a trend towards a higher frequency of atrial fibrillation (6.7% vs 1.9%; OR_{adj}3.05 95%CI [0.98−9.49]; p=0.055) compared to the group without hypothermia. Again, there were no differences in patients with stablished cardiogenic shock after cardiac catheterization procedure between normothermia and hypothermia group (15.9% vs 23.5%, p= 0.193). There were no significant differences between the groups in the other assessed periprocedural outcomes (**Table 3**).

Long−term mortality

The overall median follow−up was 16.0 (0.2−33.3) months, without differences between groups (13.6 [0.3−29.6] with hypothermia vs 16.7 [0.1−34.5] without hypothermia; p=0.899). The primary endpoint (adjusted all-cause mortality rate at median follow−up) was comparable between the group with and without hypothermia (51.3% vs 48.0%; HR_{adj}1.08 95%CI [0.77−1.53]; p=0.659). Similarly, the 6-month adjusted all-cause mortality, was similar between groups (46.2% with hypothermia vs 44.5% without hypothermia; HR_{adj}1.02 95%CI [0.71−1.47]; p=0.900) (**Figure 2**). In the landmark analysis, no differences were observed in the adjusted mortality rate between 6 months and median follow−up (9.4% with hypothermia vs 6.3% without hypothermia; HR_{adj}2.02 95%CI [0.69−5.92]; p=0.200) (**Figure 3**).

Subgroup analyses

In the entire study period, none of the explored tests of interaction for subgroups, showed a statistically significant difference (**Figure 4**). There were no significant interactions in any subgroup when the analysis was performed either up to 6 month−follow−up (i.e., from cardiac arrest to 6-month follow-up) or beyond (i.e., from 6−month follow−up to the end of study) (**Figure S2** and **Figure S3**).

DISCUSSION

Our main findings can be summarized as follows: 1) despite recent advances in cardiovascular medicine care; survival rates after cardiac arrest (including OHCA and IHCA) remain at almost 50% in a contemporary cohort of patients included in a regional STEMI network registry; 2) in patients with suspected STEMI who suffered cardiac arrest, therapeutic hypothermia had no positive effect on mid or long-term survival; 3)

279 therapeutic hypothermia was associated with a higher rate of periprocedural bleeding; 4)
280 there were no prespecified subgroups in whom hypothermia was associated with better
281 long-term survival.

282 In the most recent and larger RCTs that evaluated therapeutic hypothermia after
283 cardiac arrest, researchers reported outcomes at 6 months follow-up. Therefore, the
284 results of therapeutic hypothermia beyond this time point are unknown. Our study focused
285 on assessing the long-term outcomes after cardiac arrest in patients undergoing coronary
286 angiography in patients with suspected STEMI. We analysed a large and contemporary
287 dataset including almost 500 patients with a median follow-up of 16 (0.2−33.3) months
288 and a maximum follow-up of 50 months. At median follow-up, we did not find any
289 difference in the mortality rate between patients treated with hypothermia and those
290 without hypothermia. Our study extends the knowledge that therapeutic hypothermia may
291 have no benefit in mortality beyond the previously reported mid-term outcomes of 6
292 months.

293 Moreover, we performed a landmark analysis to analyse the outcomes between 6
294 months and the end of follow-up. During this period, we did not find any differences in
295 the mortality rate between patients treated with and without hypothermia. The potential
296 reasons for these observations remain elusive. However, it can be argued that the vast
297 majority of the fatal events occur within the 6 months after the cardiac arrest (~92.1%),
298 and the potential benefit, if any, to be obtained at long-term follow-up is marginal.
299 Notably, we did not find any mortality benefit in patients treated with hypothermia over
300 those treated without hypothermia either in the complete study or landmark analyses (i.e.,
301 0-6 months and beyond 6 months).

302 In the early RCTs, therapeutic hypothermia was associated with survival benefits
303 in OHCA patients and initial shockable rhythms. [9,10] However, in the recent TTM1

and TTM2 trials hypothermia at 33ºC in patients with cardiac arrest did not improve survival. [12, 13] An individual patient data (IPD) metanalysis of these trials, including 2800 patients, did not find a benefit of hypothermia versus temperature control in terms of survival (49.4% vs. 47.9%; RR 1.03; 95%CI [0.96−1.11]; P=0.41) or poor functional outcome (54.3% vs. 54.0%; RR 1.01; 95%CI [0.94−1.08]; P=0.88), both at 6 months.[14] Our data confirm the observation of these landmark RCTs. Within suspected STEMI patients, we did not find a difference in the adjusted mortality between the patients treated with hypothermia and those without at 6 months; questioning the contemporary role of hypothermia in patients with cardiac arrest who achieved ROSC in the real-world scenario.

Although several significant advances in cardiac arrest interventions have been achieved in the last decades, including improvement in revascularization, telephone-assisted cardiopulmonary resuscitation (CPR), availability of public defibrillators, bystander CPR training, and improved ambulance response, the survival rate after a cardiac arrest is still significantly low. [22] Even though our study analysed the data from patients who achieved ROSC - a better clinical scenario among all patients with cardiac arrest - the overall survival rate at 6 months was 55.1% (OHCA: 47.4% and IHCA: 68.5%). Therefore, pursuing new technologies that improve survival represents an unmet clinical need. Among these breakthrough technologies, geolocation assistance, drone defibrillators, wearable technology, gender-specific research, and community-initiated extracorporeal membrane oxygenation; could potentially cause an inflection in the prognosis of patients with cardiac arrest. [22]

In our study, patients treated with hypothermia had higher rates of periprocedural bleeding complications than those without hypothermia. Previously, bleeding complications have been numerically but not statistically more frequent in patients

achieving ROSC and treated with hypothermia than those without. [23] In contrast, severe hypothermia (i.e., core temperature <28°C) has been related to an increased risk of bleeding events. [24] We found an 8-fold higher risk of any bleeding in patients with hypothermia regardless of the use of fibrinolytic therapy (i.e., tenecteplase). Since all the patients of the study had STEMI suspicion, all of them underwent coronary angiography and 2 out of 3 had PCI. Hence, they received therapeutic doses of several antithrombotic therapies (heparinoids and antiplatelets) and were exposed to an invasive procedure that can lead to access site bleeding. Therefore, our data might suggest that in patients achieving ROSC after cardiac arrest and undergoing coronary angiography, hypothermia could be associated with a higher risk of any bleeding. Nevertheless, due to the low frequency of bleeding events, these outcomes should be interpreted with caution.

We performed subgroup analyses to identify if any group of patients could benefit from hypothermia. We did not find any subgroup in which patients treated with hypothermia had lower mortality than those without hypothermia. Of note, non-shockable rhythms have been under represented in these studies; since >75% of cardiac arrests have pulseless electrical activity or asystole as the initial rhythm. Moreover, a dedicated RCT including 548 patients with initial non-shockable rhythm found a higher 90-day survival with favourable neurological outcomes in the hypothermia group compared to those without hypothermia. [11] Our study included ~80% of patients with shockable rhythm (being hypothermia more frequently applied when ventricular fibrillation was present in the first medical contact as recommended by the ERC guidelines[25]) and ~20% of patients with non-shockable rhythm in the first medical assistance. Nevertheless, we did not find any benefit in terms of mortality on hypothermia over normothermia in patients with shockable or non-shockable rhythm in the first medical assistance ($P_{interaction}$=0.636). Similar results were found in the IPD of the TTM and TTM2 trials. [14]

Limitations

This study has several limitations that should be acknowledged. First, this is an observational study including only Catalonian inhabitants with suspected STEMI who suffered cardiac arrest. In our study there is an imbalance in the number of patients between groups. It has to be considered that the initial decision to perform hypothermia or normothermia in patients who suffered cardiac arrest was at each center's discretion; which confers an inherent selection bias. Thus far, its results should be considered hypothesis-generating. However, pre−hospital and in−hospital clinical and angiographic data were prospectively collected by the participating centers and externally audited by the coordinating center, representing a large contemporary population with cardiac arrest and supporting the robustness of the findings. The rationale for including only Catalonian inhabitants is supported by the selection of mortality as the primary outcome, as only inhabitants were available for follow-up. Second, after hospital discharge only the vital status was assessed – without available data about neurological status. Nevertheless, mortality is an unambiguous endpoint and was available in all the included patients. Third, we did not have specific data about the different temperature targets or the exact method and timing of therapeutic hypothermia. It remains unclear if the different temperature targets or methods could have had an impact on outcomes. However, in the most recent randomized controlled clinical trials (TTM1, TTM2 and Hyperion) [11-13] the participant centers also applied different methods of hypothermia and they did not find any difference on outcomes. Nonetheless, over the observation period, the participating centers followed different local protocols that were based on the ERC recommendations at the time of inclusion [25, 26]. Fourth, we did not include in our registry specific potentially relevant clinical data; such as time from cardiac arrest to ROSC, whether the cardiac arrest had been witnessed or assisted by bystander, or arterial

pH/lactate level. Finally, although we performed several adjustments given the nature of a registry; data impact of unmeasured confounding variables cannot be completely ruled out.

CONCLUSIONS

In this large and contemporary cohort of patients with in- or out-of-hospital cardiac arrest with suspected STEMI, those patients treated with hypothermia did not have better long−term survival than those without. In a landmark analysis, therapeutic hypothermia was not associated with better survival between 0 to 6 months or beyond. The maintained low survival rates after a cardiac arrest should be a call for action to investigate and implement efficient therapeutic interventions for these patients.

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CONFLICT OF INTEREST STATEMENT

Dr.Angiolillo declares that he has received consulting fees or honoraria from Abbott, Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, Novartis, PhaseBio, PLx Pharma, Pfizer, Sanofi and Vectura; D.J.A. also declares that his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, and the Scott R. MacKenzie Foundation. Dr Sabaté declares that he has received consulting fees from Abbott Vascular and iVascular outside the submitted work. Other authors have nothing to declare.

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FIGURE LEGENDS

Figure 1. Study patient flow chart.

Shown is the flowchart of patient inclusion in the study. STEMI, ST−segment elevation myocardial infarction

Figure 2. All−cause death after cardiac arrest in patients treated with or without hypothermia.

Shown are Kaplan-Meier estimates of probability of death until a median follow-up of 16 months after cardiac arrest among patients treated with or without hypothermia and the number of patients at risk at each time point. Data are of 494 patients for whom survival status was available. The P value was calculated by means of Cox regression.

Figure 3. All−cause death landmark analysis after cardiac arrest in patients treated with or without hypothermia.

Shown are Kaplan-Meier estimates of probability of death in two time periods (0-180 days and beyond 6 months) after cardiac arrest among patients treated with or without therapeutic hypothermia and the number of patients at risk at each time point. The P value was calculated by means of Cox regression.

Figure 4. Long−term all−cause death at 6 months stratified by subgroup.

Shown are long-term all-cause death at 6 months stratified by subgroup among patients treated with or without therapeutic hypothermia. The P value was calculated by means of Cox regression.

TABLES

Table 1. Baseline characteristics.

	Total N = 494	Hypothermia N = 119	Normothermia N = 375	P
Demographic data				
Age (years), mean (SD)	60.80 (12.33)	60.00 (11.14)	61.05 (12.69)	0.468
Age≥65 years	195 (39.5%)	45 (37.8%)	150 (40.0%)	0.747
Gender (males)	411 (83.2%)	100 (84.0%)	311 (82.9%)	0.780
Clinical history				
Smoker	208 (42.1%)	61 (51.3%)	147 (39.2%)	0.020
Hypertension	228 (46.2%)	54 (45.4%)	174 (46.4%)	0.845
Dyslipidaemia	195 (39.5%)	46 (38.7%)	149 (39.7%)	0.834
Diabetes mellitus	102 (20.6%)	21 (17.6%)	81 (21.6%)	0.353
Stroke/TIA	22 (4.5%)	3 (2.5%)	19 (5.1%)	0.241
Previous MI	70 (14.2%)	9 (7.6%)	61 (16.3%)	0.018
Previous PCI	53 (10.7%)	7 (5.9%)	46 (12.3%)	0.049
Previous coronary surgery	13 (2.6%)	4 (3.4%)	9 (2.4%)	0.568
Chronic liver disease	4 (0.8%)	0 (0.0%)	4 (1.1%)	0.577
Chronic kidney disease	9 (1.8%)	4 (3.4%)	5 (1.3%)	0.149
COPD	19 (3.8%)	3 (2.5%)	16 (4.3%)	0.388
Previous medical treatment				
Dual antiplatelet therapy	13 (2.6%)	1 (0.8%)	12 (3.2%)	0.161
Antiplatelet	75 (15.2%)	18 (15.1%)	57 (15.2%)	0.984
Anticoagulant	40 (8.1%)	11 (9.2%)	29 (7.7%)	0.599

Data are shown as n (%), unless otherwise indicated.
COPD, Chronic obstructive pulmonary disease; PCI, Percutaneous Coronary Intervention; MI, Myocardial Infarction; SD, standard deviation; TIA, Transient ischemic attack.

Table 2. Medical assistance characteristics.

	Total N = 494	Hypothermia N = 119	Normothermia N = 375	P
First medical contact				
Patient delay[1] (minute), median (IQR)	19 (10−36)	16 (10−30)	20 (10−39)	0.199
1st medical contact				0.045
EMS	409 (82.8%)	107 (89.9%)	302 (80.5%)	
No STEMI network hospital	39 (7.9%)	4 (3.4%)	35 (9.3%)	
STEMI network hospital	23 (4.7%)	2 (1.7%)	21 (5.6%)	
Primary care centre	23 (4.7%)	6 (5.0%)	17 (4.5%)	
Fibrinolysis	13 (2.6%)	5 (4.2%)	8 (2.1%)	0.219
EKG	481 (97.4%)	117 (98.3%)	364 (97.1%)	0.457
Time from FMC to EKG (minute), median (IQR)	15 (5−27)	18 (7−30)	15 (4−27)	0.213
EKG diagnosis				0.147
ST elevation	300 (62.5%)	76 (65.0%)	224 (61.7%)	
Non−diagnostic	74 (15.4%)	12 (10.3%)	62 (17.1%)	
Right bundle branch block	31 (6.5%)	12 (10.3%)	19 (5.2%)	
Left bundle branch block	30 (6.3%)	7 (6.0%)	23 (6.3%)	
ST depression	28 (5.8%)	7 (6.0%)	21 (5.8%)	
Suspected left main disease	14 (2.9%)	2 (1.7%)	12 (3.3%)	
Pacemaker rhythm	2 (0.4%)	0 (0.0%)	2 (0.6%)	
Suspected posterior MI	1 (0.2%)	1 (0.9%)	0 (0.0%)	
Events during FMC				
Ventricular fibrillation	333 (67.4%)	102 (85.7%)	231 (61.6%)	0.001
Ventricular tachycardia	59 (11.9%)	9 (7.6%)	50 (13.3%)	0.091
Atrial fibrillation	27 (5.5%)	7 (5.9%)	20 (5.3%)	0.818
Other arrhythmias	20 (4.0%)	5 (4.2%)	15 (4.0%)	0.993
Bleeding	1 (0.2%)	0 (0.0%)	1 (0.3%)	1.000
Shock	102 (20.6%)	25 (21.0%)	77 (20.5%)	0.911
Asystole	109 (22.1%)	22 (18.5%)	87 (23.2%)	0.280
AV block	28 (5.7%)	5 (4.2%)	23 (6.1%)	0.472
Acute pulmonary edema	7 (1.4%)	0 (0.0%)	7 (1.9%)	0.133
Death	3 (0.6%)	0 (0.0%)	3 (0.6%)	1.000
Hospital arrival	491 (99.4%)	119 (100.0%)	372 (99.2%)	1.000

	Total N = 494	Hypothermia N = 119	Normothermia N = 375	P
Time from FMC to hospital (minute), median (IQR)	76 (57−99)	78 (63−96)	75 (54−100)	0.197
Killip class				0.028
I	219 (49.4%)	66 (58.4%)	153 (46.4%)	
II	21 (4.7%)	8 (7.1%)	13 (3.9%)	
III	6 (1.4%)	2 (1.8%)	4 (1.2%)	
IV	197 (44.5%)	37 (32.7%)	160 (48.5%)	
Angiography procedure				
PCI	330 (67.2%)	89 (74.8%)	241 (64.8%)	0.107
Coronary angiography without PCI	145 (29.5%)	28 (23.5%)	117 (31.5%)	
System delay[2] (minute), median (IQR)	120 (95−153)	125.5 (106−155)	118 (91−150)	0.066
Total ischemic time[3] (minute), median (IQR)	148 (117−199)	155 (125−199)	145 (114−199)	0.177
TIMI flow pre−procedure				0.333
TIMI 0	189 (47.3%)	52 (46.8%)	137 (47.4%)	
TIMI 1	29 (7.3%)	4 (3.6%)	25 (8.7%)	
TIMI 2	48 (12.0%)	14 (12.6%)	34 (11.8%)	
TIMI 3	134 (33.5%)	41 (36.9%)	93 (32.2%)	
TIMI flow post−procedure*				0.332
TIMI 0	9 (2.7%)	1 (1.1%)	8 (3.3%)	
TIMI 1	4 (1.2%)	0 (0.0%)	4 (1.6%)	
TIMI 2	12 (3.6%)	2 (2.2%)	10 (4.1%)	
TIMI 3	308 (92.5%)	87 (96.7%)	221 (90.9%)	
Left main disease	32 (6.5%)	12 (10.1%)	20 (5.4%)	0.080
Number of vessels diseased				0.572
No angiographic lesions	80 (18.1%)	19 (16.4%)	61 (18.7%)	
Non−significant lesions (stenosis <70%)	21 (4.7%)	5 (4.3%)	16 (4.9%)	
1−vessel disease with stenosis ≥70%	196 (44.2%)	51 (44.0%)	145 (44.3%)	
>1−vessel disease with stenosis ≥70%	146 (32.9%)	41 (35.4%)	105 (32.1%)	
Number of vessels treated, mean (SD)	1.00 (0.39)	0.97 (0.28)	1.02 (0.42)	0.385
No treatment	20 (6.2%)	5 (5.6%)	15 (6.4%)	
1−vessel treated	286 (88.0%)	82 (92.1%)	204 (86.4%)	
>1−vessel treated	19 (5.8%)	2 (2.2%)	17 (7.2%)	
Number of conventional stents, mean (SD)	0.44 (0.65)	0.36 (0.62)	0.49 (0.66)	0.151
Number of drug-eluting stents, mean (SD)	1.03 (0.67)	0.91 (0.64)	1.07 (0.68)	0.089
PCI in 2nd stage	9 (1.8%)	3 (2.5%)	6 (1.6%)	0.523
Procedures in the catheterization laboratory				
Intra−aortic balloon counterpulsation	35 (7.1%)	9 (7.6%)	26 (7.0%)	0.832
Mechanical circulatory support	12 (2.4%)	3 (2.5%)	9 (2.4%)	0.940

	Total N = 494	Hypothermia N = 119	Normothermia N = 375	P
Follow-up				
Time from event to last follow-up (months) Median (IQR)	16.0(0.2−33.3)	13.6 (0.3−29.6)	16.7 (0.1−34.5)	0.899

Data are shown as n (%), unless otherwise indicated.
[1]Time from symptom onset to first medical contact (FMC)
[2]Time from first medical contact to angiography
[3]Time from symptom onset to coronary flow restoration
[*] TIMI flow post procedure is not available in all patients since PCI was not performed in 100% of cases
ACS, Acute Coronary Syndrome; EMS, Emergency Medical Services; EKG, Electrocardiogram; ICU, Intensive Care Unit; PCI, Percutaneous Coronary Intervention; SD, Standard Deviation; STEMI, ST−Elevation Myocardial Infarction; TIMI, Thrombolysis In Myocardial Infarction

Table 3. Clinical outcomes.

	Hypothermia N = 119	Normothermia N = 375				
Time from cardiac arrest to follow-up (months), median (IQR)	13.6 (0.3-29.6)	16.7 (0.1-34.5)				
All-cause death			**HR (95%CI)***	**P ***	**HR (95%CI)****	**P ****
Entire study period	61 (51.3%)	180 (48.0%)	0.98 (0.73-1.31)	0.879	1.08 (0.77-1.53)	0.659
Up to 6 months	55 (46.2%)	167 (44.5%)	0.93 (0.71-1.23)	0.654	1.02 (0.71-1.47)	0.900
> 6 months	6 (9.4%)	13 (6.3%)	1.65 (0.64-4.29)	0.308	2.02 (0.69-5.92)	0.200
Periprocedural complications			**OR (95%CI)¥**	**P¥**	**OR (95%CI)¥¥**	**P¥¥**
Cardiogenic shock	28 (23.5%)	59 (15.9%)	1.64 (0.99-2.74)	0.053	1.47 (0.82-2.60)	0.193
Ventricular fibrillation	18 (15.1%)	52 (14.0%)	1.11 (0.62-1.98)	0.731	1.10 (0.59-2.05)	0.754
Ventricular tachycardia	14 (11.8%)	25 (6.7%)	1.87 (0.94-3.72)	0.076	1.71 (0.83-3.54)	0.144
Asystole	3 (2.5%)	23 (6.2%)	0.40 (0.12-1.34)	0.137	0.42 (0.12-1.48)	0.177
Atrial fibrillation	8 (6.7%)	7 (1.9%)	3.78 (1.34-10.7)	0.011	3.05 (0.98-9.49)	0.055
AV block	1 (0.8%)	13 (3.5%)	0.24 (0.03-1.82)	0.166	0.28 (0.03-2.34)	0.240
Bleeding	8 (6.7%)	4 (1.1%)	6.68 (1.98-22.6)	0.002	7.99 (2.05-31.2)	0.002
Acute pulmonary edema	2 (1.7%)	9 (2.4%)	0.70 (0.15-3.26)	0.645	1.16 (0.22-6.07)	0.864
Other arrhythmias	2 (1.7%)	6 (1.6%)	1.05 (0.21-5.28)	0.952	0.99 (0.17-5.62)	0.991
Acute stent thrombosis	1 (0.8%)	5 (1.3%)	0.63 (0.07-5.42)	0.672	0.36 (0.04-3.62)	0.387
Mechanical complication	1 (0.8%)	3 (0.8%)	1.05 (0.11-10.2)	0.965	3.17 (0.07-136.1)	0.548
Reinfarction	0 (0.0%)	3 (0.8%)	-	0.953	-	0.709
Free wall rupture	1 (0.8%)	1 (0.3%)	3.17 (0.20-51.1)	0.416	-	0.695
Cardiac tamponade	0 (0.0%)	2 (0.5%)	-	0.961	-	0.976

Data are shown as n (%), unless otherwise indicated.

* Univariate Cox regression

** Multivariate cox regression adjusted by gender, age, type of 1st medical contact, shockable rhythm in 1st medical contact, initial EKG with ST elevation, shock on admission, fibrinolysis, total ischemia time, PCI performed, number of vessels disease, number of vessels treated and mechanical circulatory support/intra-aortic balloon pump.

¥ Logistic regression

¥¥ Multivariate logistic regression adjusted by gender, age, type of 1st medical contact, shockable rhythm in 1st medical contact, initial EKG with ST elevation, shock on admission, fibrinolysis, total ischemia time, PCI performed, number of vessels disease, number of vessels treated and mechanical circulatory support/intra-aortic balloon pump.

FIGURES

Figure 1. Study patient flow chart.

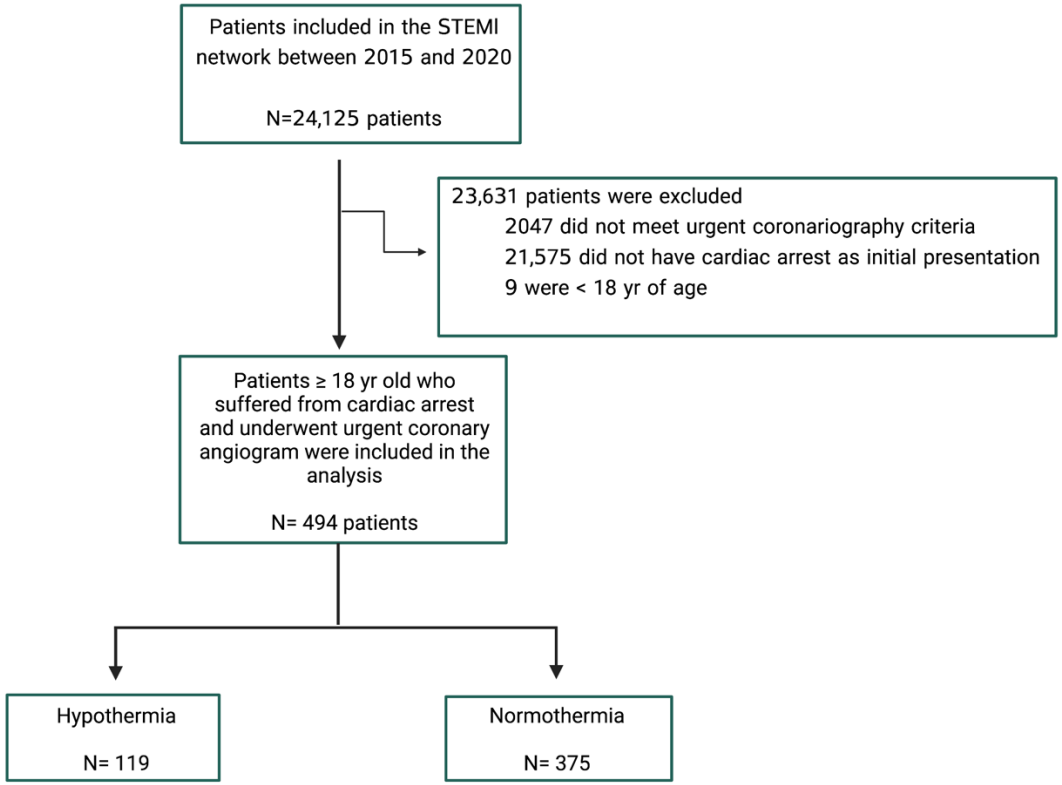


Figure 2. All−cause death after cardiac arrest in patients treated with or without therapeutic hypothermia.

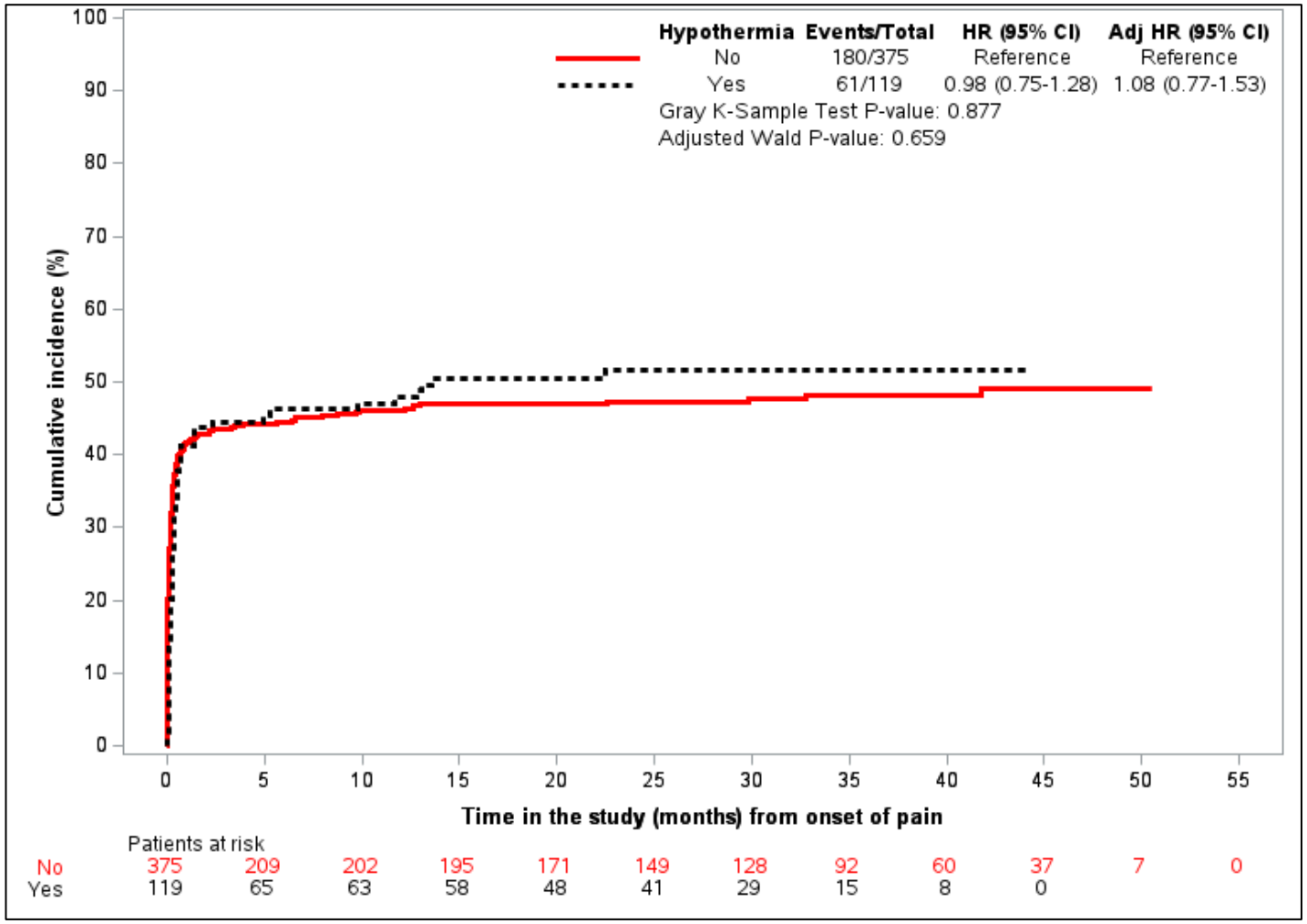


Figure 3. All−cause death landmark analysis after cardiac arrest in patients treated with or without therapeutic hypothermia.

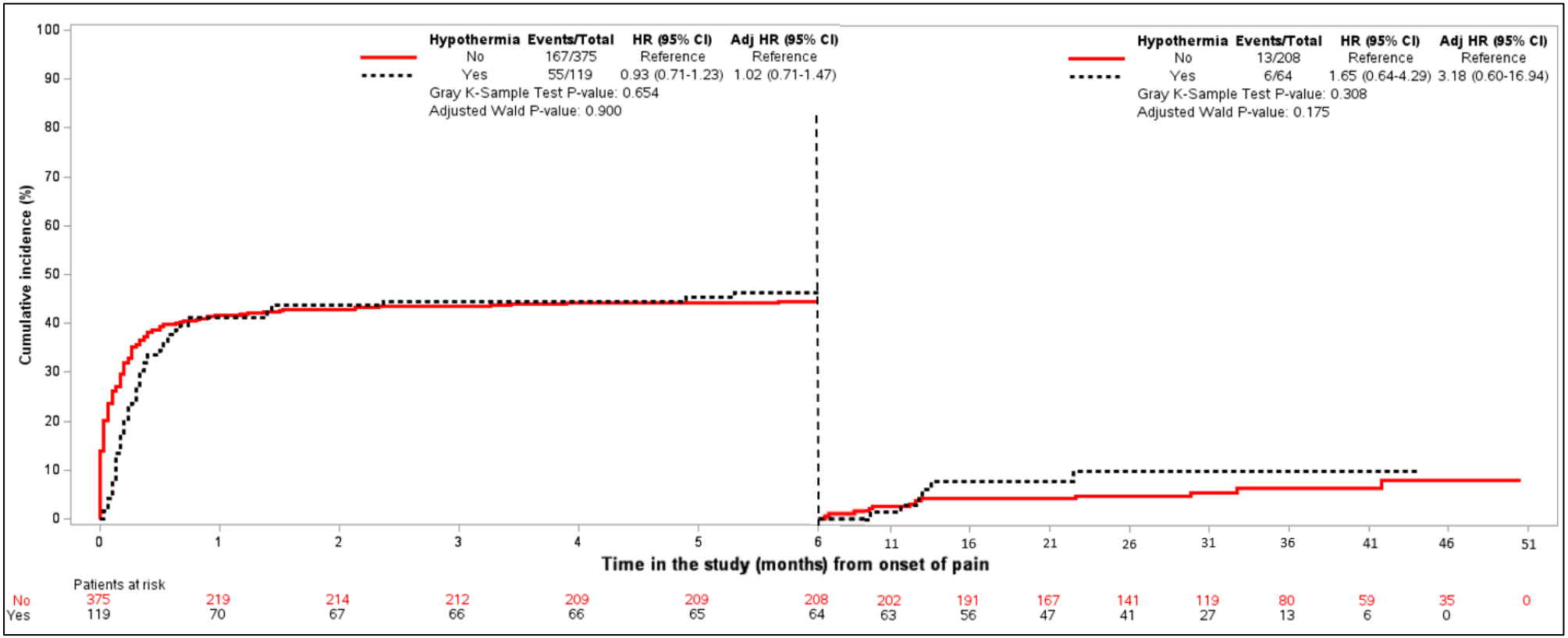
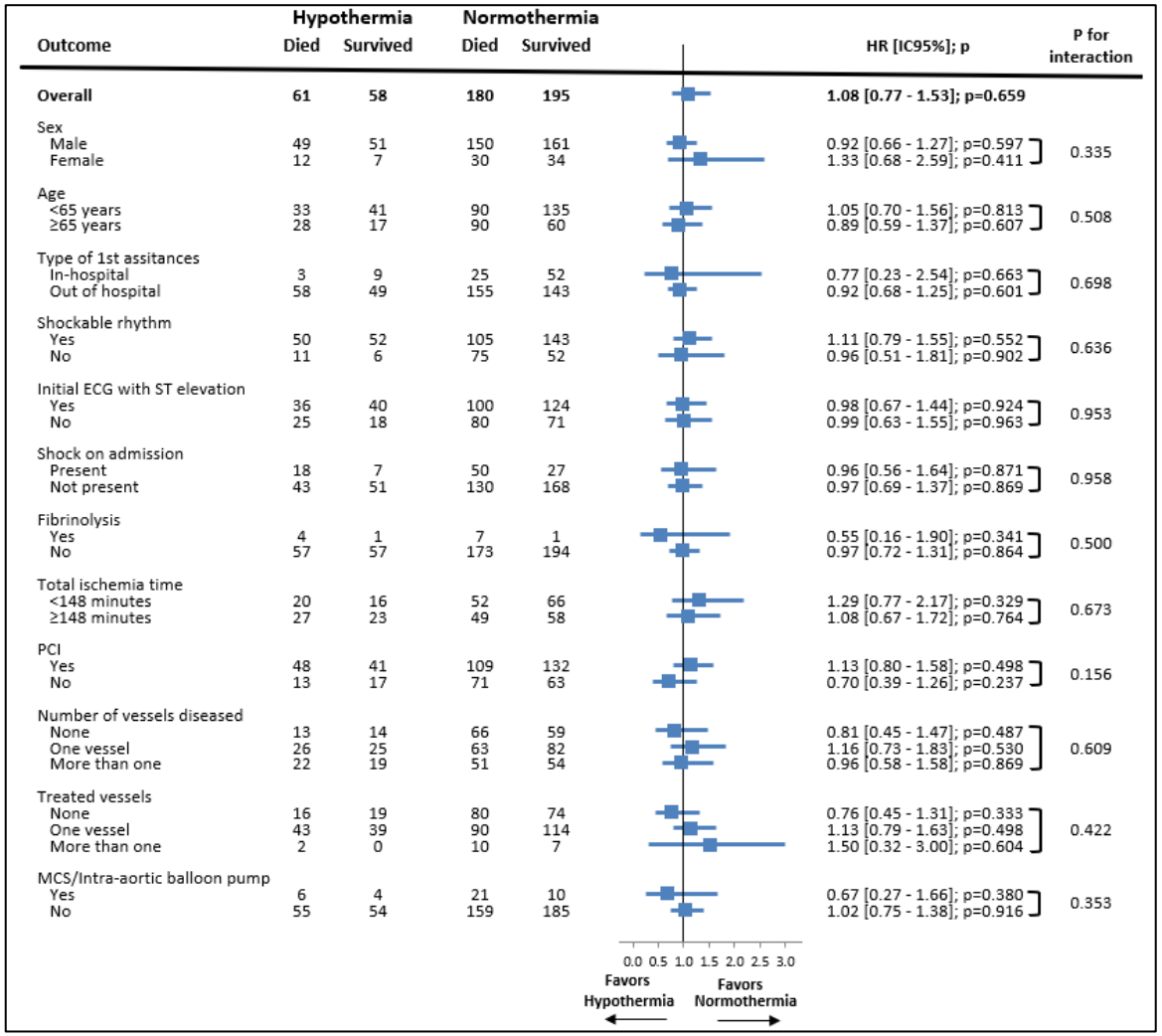


Figure 4. Long−term all−cause death stratified by subgroup.



Supplementary appendix

Figure S1. Dedicated case report form.

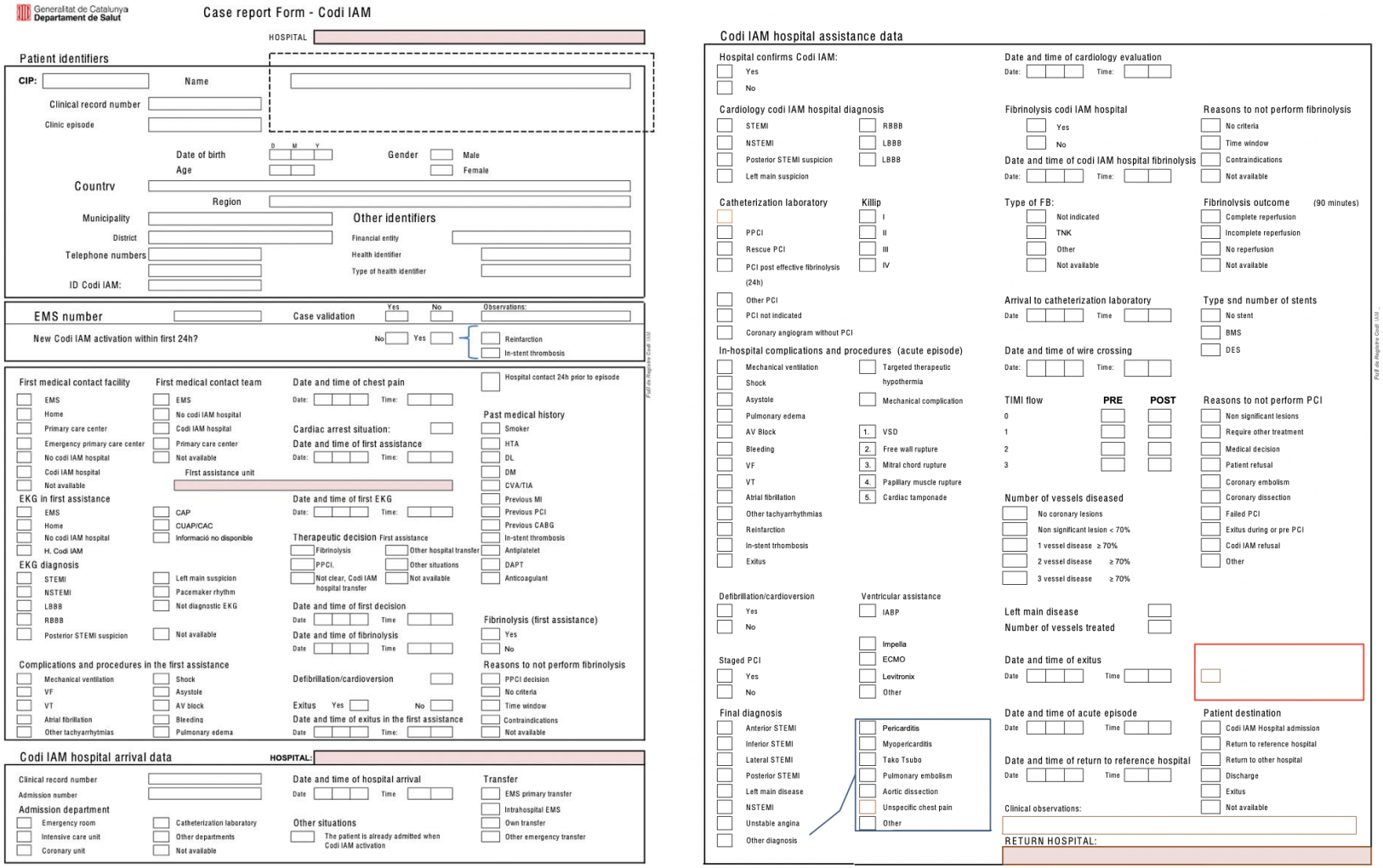


Figure S2. All−cause death between 0 to 6 moths stratified by subgroup.

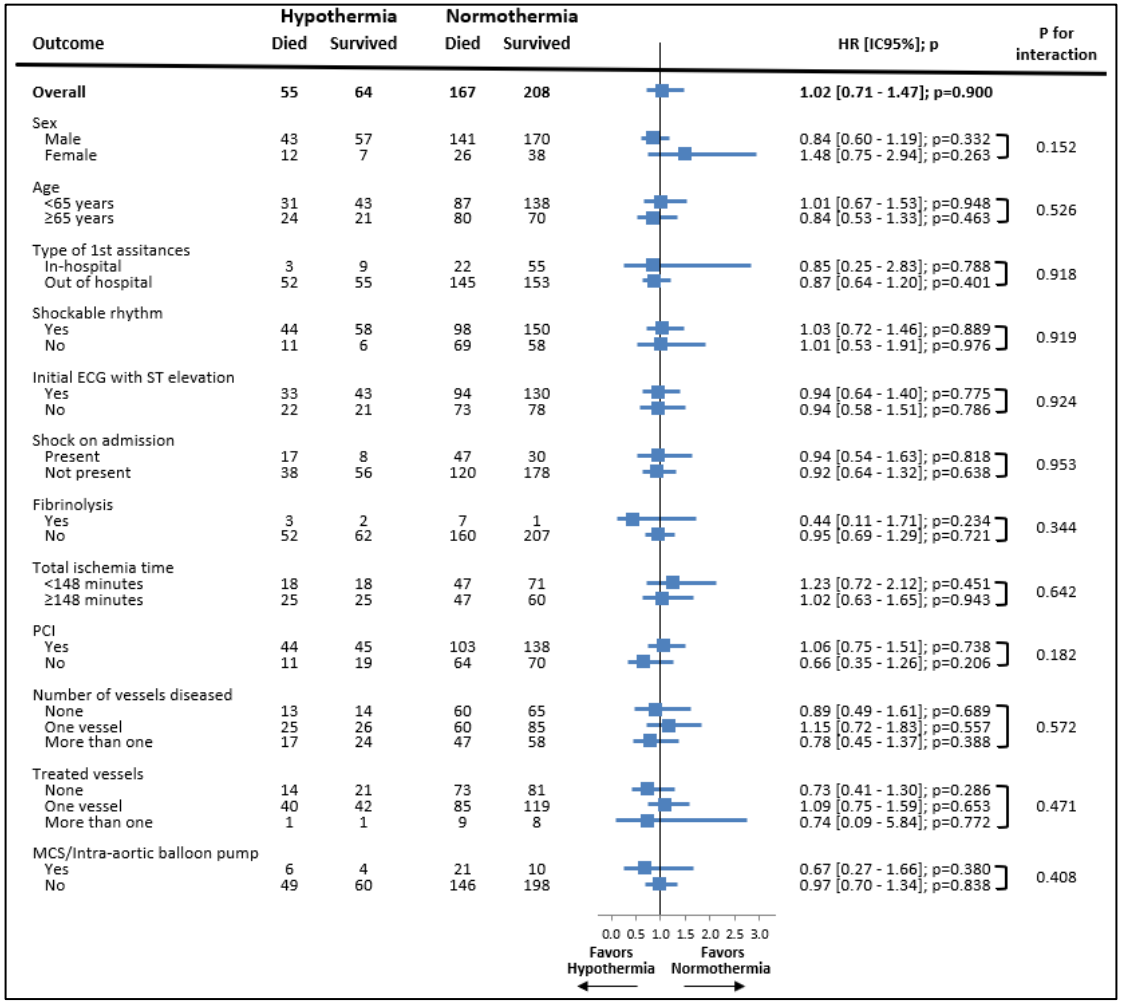


Figure S3. All−cause death beyond 6 moths stratified by subgroup.