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

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55 **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.

64 **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 65 66 (n=119) and without therapeutic hypothermia (n=375). At median follow-up (16.0) 67 [0.2-33.3] months), there was no difference in the adjusted mortality rate between groups 68 (51.3% with hypothermia vs 48.0% without hypothermia; HR_{adi}1.08 95%CI [0.77–1.53]; 69 p=0.659). There was a higher frequency of bleeding in the hypothermia group (6.7% vs 70 1.1%; OR_{adi} 7.99 95%CI [2.05-31.2]; p=0.002), without difference for the rest of 71 periprocedural complications. At 6-month follow-up, adjusted all-cause mortality rate 72 was similar between groups (46.2% with hypothermia vs 44.5% without hypothermia; 73 HR_{adi}1.02 95%CI [0.71-1.47]; p=0.900). Also, no differences were observed in the 74 adjusted mortality rate between 6 months and median follow-up (9.4% with hypothermia 75 vs 6.3% without hypothermia; HR_{adi}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.

79 ABBREVIATIONS

- 80 ACS, Acute coronary syndrome
- 81 COPD, Chronic obstructive pulmonary disease
- 82 CPR, Cardiopulmonary resuscitation
- 83 eCRF, electronic case report form
- 84 EKG, Electrocardiogram
- 85 EMS, Emergency medical system
- 86 ESCC, Emergency system coordinating center
- 87 ERC, European Resuscitation Council
- 88 FMC, First medical contact
- 89 ICU, Intensive care unit
- 90 IPD, Individual patient data
- 91 IHCA, In-hospital cardiac arrest
- 92 MI, Myocardial infarction
- 93 OHCA, Out-of-hospital cardiac arrest
- 94 PCI, Percutaneous coronary intervention
- 95 PPCI, Primary percutaneous coronary intervention
- 96 RCT, Randomized controlled trials
- 97 ROSC, Return of spontaneous circulation
- 98 STEMI, ST-segment elevation myocardial infarction
- 99 TIA, Transient ischemic attack
- 100 TIMI, Thrombolysis in myocardial infarction
- 101 TTM, Targeted Temperature Management
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105 INTRODUCTION

106 Cardiac arrest is a major cause of morbidity and mortality worldwide, accounting for
107 275.000 individuals per year with out-of-hospital cardiac arrest (OHCA) in Europe and
108 290.000 patients per year with in-hospital cardiac arrest (IHCA) in the United States.[1,
109 2] In both settings, mortality remains high, only approximately 10% survival in OHCA
110 and 30% survival in IHCA, with a modest improvement in IHCA and no changes in
111 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]

118 Targeted therapeutic hypothermia (i.e., active cooling of comatose patients after 119 ROSC) has been widely used based on its potential neuroprotective effects, such as 120 cerebral metabolism slowdown and reperfusion injury reduction.[6] The current 121 European Resuscitation Council (ERC) 2021 guidelines recommends targeted 122 hypothermia with a target temperature between 32–36°C for at least 24 hours in adults 123 who remain unresponsive after ROSC regardless of the setting or initial heart rhythm.[7, 124 8]. These recommendations are based on the results of early randomized controlled trials 125 (RCTs) suggesting improved outcomes in patients with OHCA and initial shockable 126 rhythms.[9, 10] However, recent RCTs have found contrasting results, with one RCT 127 suggesting an improvement in survival with favourable neurological outcomes at 90 days 128 after cardiac arrest with non-shockable rhythm.[11] In contrast, the other largest RCTs 129 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 6months 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.

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136 METHODS

137 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.

144

145 *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.

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156 **Procedures**

157 After achieving ROSC, patients were treated with immediate post-resuscitation care. The 158 patients included in the study suffered cardiac arrest and had suspected STEMI based on 159 the diagnostic EKG. They were transferred to PPCI centers according to the regional 160 STEMI network protocols for emergent coronary angiography. [15] All patients 161 underwent coronary angiography, but the decision to proceed with PCI was established 162 by the treating medical team based on patient's clinical presentation and results from 163 coronary angiography. If PCI was performed, it was done according to the local practices 164 and current recommendations of the European Society of Cardiology (ESC) guidelines at 165 the moment of the procedures. [16, 17]

166 The decision to apply therapeutic hypothermia was taken following each center's 167 local intensive care unit (ICU) protocol. Therefore, therapeutic hypothermia (active 168 cooling with a target temperature of 32-36°C for at least 24h) was applied differently among hospitals – either with surface cooling pads (Arctic SunTM system) or endovascular 169 170 invasive devices (CoolGard system). [18-20] Although these local protocols were 171 different, all of them followed the existing recommendations of the ERC guidelines for 172 the inclusion period described previously. [7, 8, 21] When patients arrived at the ICU, 173 they received standard treatments, including mechanical ventilation and vasoactive 174 support. All patients were treated with sedative and analgesic agents at recommended 175 doses adjusted for managing mechanical ventilation. Neuromuscular relaxation was 176 achieved with neuromuscular blocking drug infusion to avoid muscular tremors. 177 According to local practices, patients who did not receive therapeutic hypothermia had 178 conventional post-resuscitation treatment at the corresponding ICU center.

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181 Data capture and managing

182 A predefined electronic Case Report Form (eCRF) was implemented since the inception 183 of the STEMI network. Study data elements were collected by the local investigators 184 (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 185 186 clinical outcomes (Supplementary Appendix). All the data were obtained from the 187 medical records. The quality of the data included in the registry was verified by means of 188 external audits. Data on patient's vital status was obtained through the national social security database up to December 31st, 2020. 189

190 *Definition and outcomes*

191 The primary endpoint was all-cause death at median follow-up. The key secondary 192 endpoint was six-month all-cause death. Exploratory outcomes included periprocedural 193 complications (pre and 24h post PPCI); such as ventricular fibrillation, ventricular 194 tachycardia, asystole, atrial fibrillation (AF), any bleeding, any shock, acute stent thrombosis, and reinfarctions. The occurrence of these events was ascertained and 195 196 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, 197 time delays are defined according to the ESC STEMI guidelines published in 2017.[16] 198

199 Statistical analysis

All analyses were stratified by patients treated with or without therapeutic hypothermia.

201 Continuous variables are presented as mean and standard deviation (or medians and
202 interquartile ranges whenever appropriate) and were compared with independent
203 samples *t* test. Categorical variables were expressed as absolute and relative frequency
204 and were compared with chi–square or Fisher exact tests as appropriate.

For the primary endpoint (all-cause death), number and percentage of patients, 205 survival curves using Kaplan-Meier estimates, and hazard ratio (HR) (95% confidence 206 207 interval [CI]) using Cox regression model are displayed. In addition, HR and p-value 208 were calculated from Cox proportional hazards models adjusted for possible 209 confounders that were considered of clinical and statistical significance (p<0.05). For 210 in-hospital complications, number and percentage of patients with event and odds ratio 211 (OR) (95% confidence interval [CI]) using logistic regression model are displayed. In 212 addition, OR and p-value were calculated from logistic proportional hazards models 213 adjusted for confounders that were considered of clinical significance.

214 A landmark analysis was performed, studying two time periods, 6-month 215 follow-up (0-180 days) and beyond 6-month follow-up (180 days to end of study). 216 Subgroup analyses included the following variables: gender, age greater than 65 years, 217 OHCA and IHCA, shockable and non-shockable rhythm in the first assistance, initial 218 EKG with ST-segment elevation, shock on admission, fibrinolysis, total ischemic time, 219 PCI performed, number of vessels diseased, treated vessels and mechanical circulatory 220 support/intra-aortic balloon pump. Two-tailed p-value <0.05 was considered as 221 significant. The SAS v.9.4 software was used for all analyses.

222

223 **RESULTS**

224 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**).

235 A total of 409 patients (82.8%) had an OHCA while 85 patients (17.2%) had an 236 IHCA. Most of the patients (79.3%) had a shockable rhythm in the first medical 237 assistance. Patients in the hypothermia group were more commonly assisted in the first 238 place by the EMS (89.9% vs 80.5%; p=0.045) and had a higher incidence of ventricular 239 fibrillation in the first medical contact (85.7% vs 61.6%; p=0.001) compared to those 240 without hypothermia. By contrast, the group without therapeutic hypothermia had had a 241 higher frequency of initial Killip Class IV in the hospital arrival compared to the group 242 with hypothermia (48.5% vs 32.7%; p=0.032). However, in the first medical contact there 243 were not differences between groups regarding shock status (20.5% vs 21%, p= 0.911)

244 (Table 2).

245 Periprocedural complications

246 In the hypothermia group, there was a higher frequency of bleeding complications (6.7% 247 vs 1.1%; OR_{adi} 7.99 95%CI [2.05–31.2]; p=0.002) and a trend towards a higher frequency 248 of atrial fibrillation (6.7% vs 1.9%; OR_{adi}3.05 95%CI [0.98–9.49]; p=0.055) compared to 249 the group without hypothermia. Again, there were no differences in patients with 250 stablished cardiogenic shock after cardiac catheterization procedure between 251 normothermia and hypothermia group (15.9% vs 23.5%, p= 0.193). There were no 252 significant differences between the groups in the other assessed periprocedural outcomes 253 (Table 3).

254 Long-term mortality

255 The overall median follow-up was 16.0 (0.2-33.3) months, without differences between 256 groups (13.6 [0.3–29.6] with hypothermia vs 16.7 [0.1–34.5] without hypothermia; 257 p=0.899). The primary endpoint (adjusted all-cause mortality rate at median follow-up) 258 was comparable between the group with and without hypothermia (51.3% vs 48.0%; 259 HR_{adi}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 260 261 hypothermia; HR_{adi}1.02 95%CI [0.71–1.47]; p=0.900) (Figure 2). In the landmark 262 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}2.02 263 264 95%CI [0.69–5.92]; p=0.200) (Figure 3).

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266 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).

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273 **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) therapeutic hypothermia was associated with a higher rate of periprocedural bleeding; 4)
there were no prespecified subgroups in whom hypothermia was associated with better
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 benefits303 in OHCA patients and initial shockable rhythms. [9,10] However, in the recent TTM1

304 and TTM2 trials hypothermia at 33°C in patients with cardiac arrest did not improve 305 survival. [12, 13] An individual patient data (IPD) metanalysis of these trials, including 306 2800 patients, did not find a benefit of hypothermia versus temperature control in terms 307 of survival (49.4% vs. 47.9%; RR 1.03; 95%CI [0.96–1.11]; P=0.41) or poor functional 308 outcome (54.3% vs. 54.0%; RR 1.01; 95%CI [0.94–1.08]; P=0.88), both at 6 months.[14] 309 Our data confirm the observation of these landmark RCTs. Within suspected STEMI 310 patients, we did not find a difference in the adjusted mortality between the patients treated 311 with hypothermia and those without at 6 months; questioning the contemporary role of 312 hypothermia in patients with cardiac arrest who achieved ROSC in the real-world 313 scenario.

314 Although several significant advances in cardiac arrest interventions have been 315 achieved in the last decades, including improvement in revascularization, telephone-316 assisted cardiopulmonary resuscitation (CPR), availability of public defibrillators, 317 bystander CPR training, and improved ambulance response, the survival rate after a 318 cardiac arrest is still significantly low. [22] Even though our study analysed the data from 319 patients who achieved ROSC - a better clinical scenario among all patients with cardiac 320 arrest - the overall survival rate at 6 months was 55.1% (OHCA: 47.4% and IHCA: 321 68.5%). Therefore, pursuing new technologies that improve survival represents an unmet 322 clinical need. Among these breakthrough technologies, geolocation assistance, drone 323 defibrillators, wearable technology, gender-specific research, and community-initiated 324 extracorporeal membrane oxygenation; could potentially cause an inflection in the 325 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

329 achieving ROSC and treated with hypothermia than those without. [23] In contrast, severe 330 hypothermia (i.e., core temperature <28°C) has been related to an increased risk of 331 bleeding events. [24] We found an 8-fold higher risk of any bleeding in patients with 332 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 333 334 and 2 out of 3 had PCI. Hence, they received therapeutic doses of several antithrombotic 335 therapies (heparinoids and antiplatelets) and were exposed to an invasive procedure that 336 can lead to access site bleeding. Therefore, our data might suggest that in patients achieving ROSC after cardiac arrest and undergoing coronary angiography, hypothermia 337 338 could be associated with a higher risk of any bleeding. Nevertheless, due to the low 339 frequency of bleeding events, these outcomes should be interpreted with caution.

340 We performed subgroup analyses to identify if any group of patients could benefit 341 from hypothermia. We did not find any subgroup in which patients treated with 342 hypothermia had lower mortality than those without hypothermia. Of note, non-shockable 343 rhythms have been under represented in these studies; since >75% of cardiac arrests have 344 pulseless electrical activity or asystole as the initial rhythm. Moreover, a dedicated RCT 345 including 548 patients with initial non-shockable rhythm found a higher 90-day survival 346 with favourable neurological outcomes in the hypothermia group compared to those 347 without hypothermia. [11] Our study included ~80% of patients with shockable rhythm 348 (being hypothermia more frequently applied when ventricular fibrillation was present in 349 the first medical contact as recommended by the ERC guidelines [25]) and $\sim 20\%$ of 350 patients with non-shockable rhythm in the first medical assistance. Nevertheless, we did 351 not find any benefit in terms of mortality on hypothermia over normothermia in patients 352 with shockable or non-shockable rhythm in the first medical assistance (Pinteraction=0.636). 353 Similar results were found in the IPD of the TTM and TTM2 trials. [14]

354 Limitations

355 This study has several limitations that should be acknowledged. First, this is an 356 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 357 358 between groups. It has to be considered that the initial decision to perform hypothermia 359 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 360 361 hypothesis-generating. However, pre-hospital and in-hospital clinical and angiographic 362 data were prospectively collected by the participating centers and externally audited by 363 the coordinating center, representing a large contemporary population with cardiac arrest 364 and supporting the robustness of the findings. The rationale for including only Catalonian 365 inhabitants is supported by the selection of mortality as the primary outcome, as only 366 inhabitants were available for follow-up. Second, after hospital discharge only the vital 367 status was assessed - without available data about neurological status. Nevertheless, 368 mortality is an unambiguous endpoint and was available in all the included patients. 369 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 370 temperature targets or methods could have had an impact on outcomes. However, in the 371 372 most recent randomized controlled clinical trials (TTM1, TTM2 and Hyperion) [11-13] 373 the participant centers also applied different methods of hypothermia and they did not 374 find any difference on outcomes. Nonetheless, over the observation period, the 375 participating centers followed different local protocols that were based on the ERC 376 recommendations at the time of inclusion [25, 26]. Fourth, we did not include in our 377 registry specific potentially relevant clinical data; such as time from cardiac arrest to 378 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.

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385 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.

392

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394 None

395

396 CONFLICT OF INTEREST STATEMENT

Dr.Angiolillo declares that he has received consulting fees or honoraria from Abbott, 397 398 Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, 399 Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, Novartis, PhaseBio, PLx 400 Pharma, Pfizer, Sanofi and Vectura; D.J.A. also declares that his institution has received 401 research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, 402 Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry 403 Co., Merck, Novartis, and the Scott R. MacKenzie Foundation. Dr Sabaté declares that 404 he has received consulting fees from Abbott Vascular and iVascular outside the submitted 405 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	Hypothermia	Normothermia	Р
	N = 494	N = 119	N = 375	Ĩ
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	Р
First medical contact				
Patient delay ¹ (minute), median (IQR)	19 (10–36)	16 (10-30)	20 (10-39)	0.199
1 st medical contact	17 (10 00)	10 (10 20)	20 (10 0))	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	Р
Time from FMC to hospital	76 (57–99)	78 (63–96)	75 (54–100)	0.197
(minute), median (IQR)	/0 (3/-99)	/0 (03-90)	75 (54-100)	
Killip class				0.028
Ι	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 \geq 70%	196 (44.2%)	51 (44.0%)	145 (44.3%)	
>1 -vessel disease with stenosis \geq 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 2 nd 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	Hypothermia	Normothermia	р
	N = 494	N = 119	N = 375	r
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				

³Time 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.

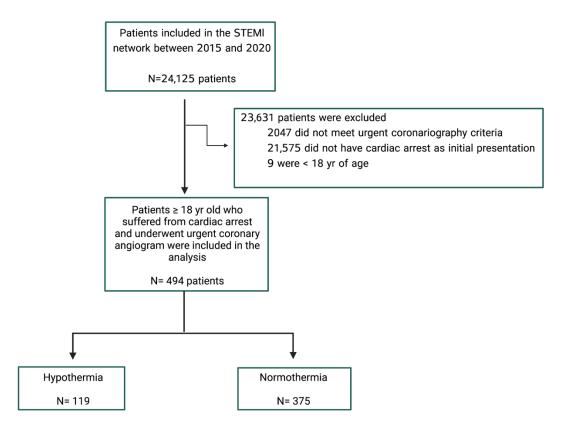
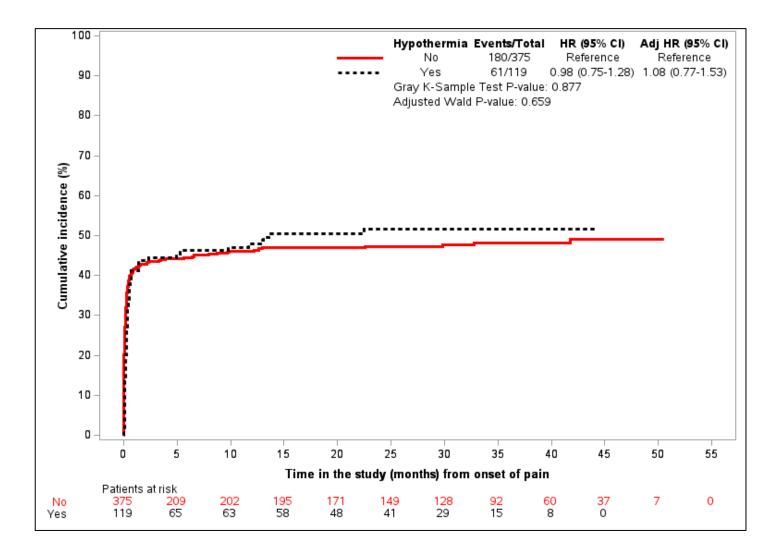
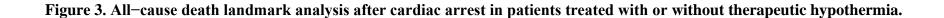
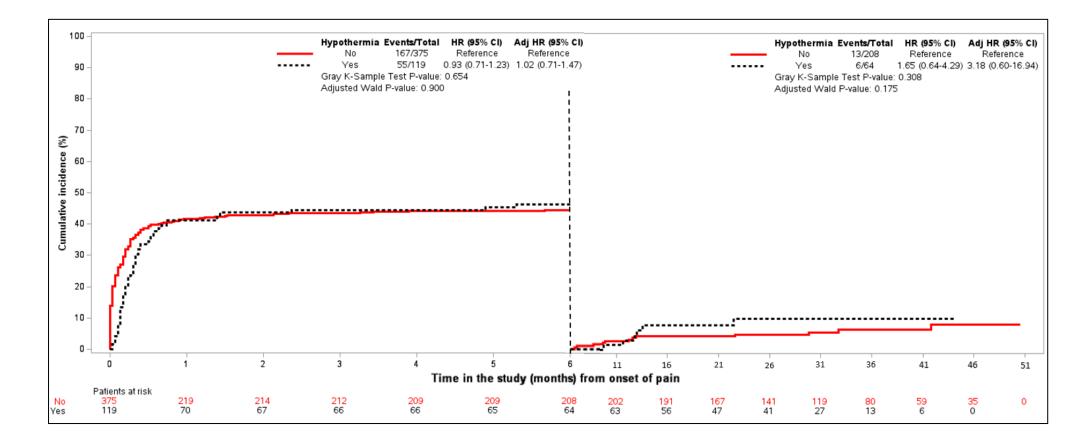


Figure 2. All-cause death after cardiac arrest in patients treated with or without therapeutic hypothermia.







	Нуре	othermia	Norm	othermi	ia		
Outcome	Died	Survived	Died	Survive	d	HR [IC95%]; p	P for interaction
Overall	61	58	180	195	-	1.08 [0.77 - 1.53]; p=0.659	
Sex Male Female	49 12	51 7	150 30	161 34		0.92 [0.66 - 1.27]; p=0.597 ⁻ 1.33 [0.68 - 2.59]; p=0.411 -	0.335
Age <65 years ≥65 years	33 28	41 17	90 90	135 60	+	1.05 [0.70 - 1.56]; p=0.813 - 0.89 [0.59 - 1.37]; p=0.607 -	0.508
Type of 1st assitances In-hospital Out of hospital	3 58	9 49	25 155	52 143		0.77 [0.23 - 2.54]; p=0.663 [—] 0.92 [0.68 - 1.25]; p=0.601 -	0.698
Shockable rhythm Yes No	50 11	52 6	105 75	143 52	+	1.11 [0.79 - 1.55]; p=0.552 - 0.96 [0.51 - 1.81]; p=0.902 -	
Initial ECG with ST elevation Yes No	36 25	40 18	100 80	124 71	±	0.98 [0.67 - 1.44]; p=0.924 0.99 [0.63 - 1.55]; p=0.963 -	0.953
Shock on admission Present Not present	18 43	7 51	50 130	27 168	+	0.96 [0.56 - 1.64]; p=0.871 - 0.97 [0.69 - 1.37]; p=0.869 -	
Fibrinolysis Yes No	4 57	1 57	7 173	1 194	-	0.55 [0.16 - 1.90]; p=0.341 0.97 [0.72 - 1.31]; p=0.864	0.500
Total ischemia time <148 minutes ≥148 minutes	20 27	16 23	52 49	66 58	<u>+</u>	1.29 [0.77 - 2.17]; p=0.329 - 1.08 [0.67 - 1.72]; p=0.764 _	
PCI Yes No	48 13	41 17	109 71	132 63	-	1.13 [0.80 - 1.58]; p=0.498 = 0.70 [0.39 - 1.26]; p=0.237 =	0.156
Number of vessels diseased None One vessel More than one	13 26 22	14 25 19	66 63 51	59 82 54	1	0.81 [0.45 - 1.47]; p=0.487 1.16 [0.73 - 1.83]; p=0.530 0.96 [0.58 - 1.58]; p=0.869	0.609
Treated vessels None One vessel More than one	16 43 2	19 39 0	80 90 10	74 114 7	-	0.76 [0.45 - 1.31]; p=0.333 1.13 [0.79 - 1.63]; p=0.498 1.50 [0.32 - 3.00]; p=0.604	0.422
MCS/Intra-aortic balloon pump Yes No	6 55	4 54	21 159	10 185	-	0.67 [0.27 - 1.66]; p=0.380 - 1.02 [0.75 - 1.38]; p=0.916 -	0.353
				I	0.0 0.5 1.0 1.5 2.0 2.5 3.0 Favors Favors Hypothermia Normothermia		

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

Supplementary appendix

Figure S1. Dedicated case report form.

Generalitat de Catalunya Departament de Salut	Case report F	orm - Codi IAM						
	HOS	PITAL] _ Co	odi IAM hospital assist	ance data		
Patient identifiers	C-			-, но	spital confirms Codi IAM:		Date and time of cardiology evaluation	
CIP:	Name		1	1i ∣⊑	Yes		Date: Time:	
	Name			🗆	No			
Clinical record number				Ca	rdiology codi IAM hospital d	iagnosis	Fibrinolysis codi IAM hospital	Reasons to not perform fibrinolysis
Clinic episode	<u>L</u>			Li □	STEMI	RBBB	Yes	No criteria
	Date of birth	<u>, M Y</u>			NSTEMI	LBBB	No	Time window
	Age	Gender Ma	male		Posterior STEMI suspicion	LBBB	Date and time of codi IAM hospital fibrinolysis	
Country	Age				Left main suspicion		Date: Time:	Not available
	Region			Ca	theterization laboratory	Killip	Type of FB:	Fibrinolysis outcome (90 minutes)
Municipality		Other identifiers					Not indicated	Complete reperfusion
District		Financial entity	1		PPCI	<u> </u>	TNK	Incomplete reperfusion
Telephone numbers		Health identifier			Rescue PCI		Other	No reperfusion
		Type of health identifier			PCI post effective fibrinolysis	IV IV	Not available	Not available
ID Codi IAM:					(24h)			
5110		Yes No	Observations:	í l⊨	Other PCI PCI not indicated		Arrival to catheterization laboratory	Type snd number of stents
EMS number		Case validation	-	=	Coronary angiogram without PC		Date Time	BMS
New Codi IAM activation within	n first 24h?	No Yes 🦳 🚽	Reinfarction	AVV 3PP	hospital complications and p		Date and time of wire crossing	DES
		l	In-stent thrombosis		Mechanical ventilation	Targeted therapeutic	Date: Time:	000
First medical contact facility	First medical contact team	Date and time of chest pain	Hospital contact 24h prior to episode	de Rey	Shock	hypothermia	5 a.o.	
EMS	EMS	Date: Time:		Full	Asystole	Mechanical complication	TIMI flow PRE POST	Reasons to not perform PCI
Home	No codi IAM hospital		Past medical history		Pulmonary edema		0	Non significant lesions
Primary care center	Cedi IAM hespital	Cardiac arrest situation:	Smoker		AV Block	1. VSD	1	Require other treatment
Emergency primary care center No codi IAM hospital	Primary care center Not available	Date and time of first assistance	DL HTA		Bleeding	2. Free wall rupture	2	Medical decision
Codi IAM hospital	First assistance unit		DM		VF	3. Mitral chord rupture	3	Patient refusal
Not available			CVA/TIA		VT	4. Papillary muscle rupture		Coronary embolism
EKG in first assistance	CAP	Date and time of first EKG Date: Time:	Previous MI Previous PCI		Atrial fibrillation Other tachvarrhythmias	5. Cardiac tamponade	Number of vessels diseased	Coronary dissection Failed PCI
EMS EMS	CUAP/CAC		Previous CABG		Beinfarction		No coronary lesions Non significant lesion < 70%	Exitus during or pre PCI
No codi IAM hospital	Informació no disponible	Therapeutic decision First assistance	In-stent thrombosis		In-stent trhombosis		1 vessel disease > 70%	Codi IAM refusal
H. Codi IAM EKG diagnosis		Fibrinolysis Other hospital transl	ler Antiplatelet		Exitus		2 vessel disease ≥ 70%	Other
STEMI	Left main suspicion	Not clear, Codi IAM Not available	Anticoagulant				3 vessel disease ≥ 70%	
NSTEMI	Pacemaker rhythm	hospital transfer		Det	ibrillation/cardioversion	Ventricular assistance		
LBBB	Not diagnostic EKG	Date and time of first decision	Fibrinolysis (first assistance)		Yes	IABP	Left main disease	
	Not available	Date and time of fibrinolysis	Yes		No	_	Number of vessels treated	
	- Low Street and	Date Time	No No			Impella		
Complications and procedures in			Reasons to not perform fibrinolysis	Sta	ged PCI	ECMO	Date and time of exitus	
	Shock Asystole	Defibrillation/cardioversion	PPCI decision No criteria		Yes	Levitronix Other	Date Time	
L	AV block	Exitus Yes No	Time window					
	Bleeding	Date and time of exitus in the first assistance	Contraindications		al diagnosis Anterior STEMI	Pericarditis	Date and time of acute episode	Patient destination Codi IAM Hospital admission
Other tachyarrhytmias	Pulmonary edema	Date Time:	Not available	」 ⊨	Inferior STEMI	Myopericarditis		Return to reference hospital
Codi IAM hospital arrival d	data но:	SPITAL:] -	Lateral STEMI	Tako Tsubo	Date and time of return to reference hospital	Return to other hospital
Clinical record number		Date and time of hospital arrival	Transfer		Posterior STEMI	Pulmonary embolism	Date Time	Discharge
Admission number		Date Time	EMS primary transfer		Left main disease	Aortic dissection		Exitus
Admission department			Intrahospital EMS		NSTEMI	Unspecific chest pain	Clinical observations:	Not available
Emergency room	Catheterization laboratory Other departments	Other situations The patient is already admitted when	Own transfer Other emergency transfer	∣ ∣⊨	Unstable angina	Other		
Coronary unit	Not available	Codi IAM activation	C ower emergency nansier		Other diagnosis		RETURN HOSPITAL:	

Outcome	Hype Died	othermia Survived	Norm Died	othermia Survived	a 	HR [IC95%]; p	P for interaction
Overall	55	64	167	208	+	1.02 [0.71 - 1.47]; p=0.900	
Sex Male Female	43 12	57 7	141 26	170 38	•	0.84 [0.60 - 1.19]; p=0.332 = 1.48 [0.75 - 2.94]; p=0.263 =	0.152
Age <65 years ≥65 years	31 24	43 21	87 80	138 70	*	1.01 [0.67 - 1.53]; p=0.948 - 0.84 [0.53 - 1.33]; p=0.463 -	0.526
Type of 1st assitances In-hospital Out of hospital	3 52	9 55	22 145	55 153	-	0.85 [0.25 - 2.83]; p=0.788 = 0.87 [0.64 - 1.20]; p=0.401 =	
Shockable rhythm Yes No	44 11	58 6	98 69	150 58	+	1.03 [0.72 - 1.46]; p=0.889 = 1.01 [0.53 - 1.91]; p=0.976 =	0.919
Initial ECG with ST elevation Yes No	33 22	43 21	94 73	130 78	+	0.94 [0.64 - 1.40]; p=0.775 - 0.94 [0.58 - 1.51]; p=0.786 -	0.924
Shock on admission Present Not present	17 38	8 56	47 120	30 178	+	0.94 [0.54 - 1.63]; p=0.818 - 0.92 [0.64 - 1.32]; p=0.638 -	
Fibrinolysis Yes No	3 52	2 62	7 160	1 207	-	0.44 [0.11 - 1.71]; p=0.234 - 0.95 [0.69 - 1.29]; p=0.721 _	0.344
Total ischemia time <148 minutes ≥148 minutes	18 25	18 25	47 47	71 60	-	1.23 [0.72 - 2.12]; p=0.451 - 1.02 [0.63 - 1.65]; p=0.943 _	
PCI Yes No	44 11	45 19	103 64	138 70	+	1.06 [0.75 - 1.51]; p=0.738 - 0.66 [0.35 - 1.26]; p=0.206 -	0.182
Number of vessels diseased None One vessel More than one	13 25 17	14 26 24	60 60 47	65 85 58	-	0.89 [0.49 - 1.61]; p=0.689 1.15 [0.72 - 1.83]; p=0.557 0.78 [0.45 - 1.37]; p=0.388	0.572
Treated vessels None One vessel More than one	14 40 1	21 42 1	73 85 9	81 119 8	-	0.73 [0.41 - 1.30]; p=0.286 1.09 [0.75 - 1.59]; p=0.653 0.74 [0.09 - 5.84]; p=0.772	0.471
MCS/Intra-aortic balloon pump Yes No	6 49	4 60	21 146	10 198		0.67 [0.27 - 1.66]; p=0.380 - 0.97 [0.70 - 1.34]; p=0.838 -	
				ŀ	0.0 0.5 1.0 1.5 2.0 2.5 3.0 Favors Favors lypothermia Normothermia		

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

Outcome	Hype Died	othermia Survived	Norm Died	othermia Survived	HR [IC95%]; p	P for interaction
Overall	6	58	13	195	2.02 [0.69 - 5.92]; p=0	.200
Sex Male Female	6 0	51 7	4 9	34 161	2.25 [0.79 - 6.39]; p=0	.128
Age <65 years ≥65 years	2 4	41 17	3 10	135 60	2.21 [0.37 - 13.2]; p=0 1.38 [0.43 - 4.41]; p=0	.386] 0.594
Type of 1st assitances In-hospital Out of hospital	0 6	9 49	3 10	52 143	1.75 [0.63 - 4.82]; p=0	.281
Shockable rhythm Yes No	6 0	52 6	7 6	143 52	2.47 [0.830 - 5]; p=0.1	06
Initial ECG with ST elevation Yes No	3 3	40 18	6 7	124 71	1.69 [0.42 - 6.78]; p=0 1.65 [0.43 - 6.37]; p=0	.460] 0.996
Shock on admission Present Not present	1 5	7 51	3 10	27 168	1.38 [0.14 - 13.4]; p=0 1.74 [0.59 - 5.12]; p=0	.783 .316] 0.841
Fibrinolysis Yes No	1 5	1 57	0 13	1 194	1.41 [0.50 - 3.97]; p=0	.517
Total ischemia time <148 minutes ≥148 minutes	2 2	16 23	5 2	66 58	2.20 [0.40 - 12.1]; p=0 2.86 [0.40 - 20.7]; p=0	.364 .298] 0.834
PCI Yes No	4 2	41 17	6 7	132 63	2.70 [0.74 - 9.86]; p=0 1.02 [0.21 - 4.93]; p=0	.133 .977] 0.430
Number of vessels diseased None One vessel More than one	0 1 5	14 25 19	6 3 4	59 82 54	1.38 [0.14 - 13.5]; p=0 3.38 [0.90 - 12.6]; p=0	.783 .076 0.790
Treated vessels None One vessel More than one	2 3 1	19 39 0	7 5 1	74 114 7	1.07 [0.22 - 5.17]; p=0 2.21 [0.51 - 9.56]; p=0	.929]0.358 289]0.358
MCS/Intra-aortic balloon pump Yes No	0 6	4 54	0 13	10 185	1.70 [0.64 - 4.50]; p=0	.287
					0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 avors Favors othermia Normothermia	

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