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ORIGINAL RESEARCH

A randomised trial of selective intracoronary hypothermia during primary PCI

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ABSTRACT

BACKGROUND: While experimental data suggest that selective intracoronary hypothermia decreases infarct size, studies in patients with ST-elevation myocardial infarction (STEMI) are lacking.

AIMS: We investigated the efficacy of selective intracoronary hypothermia during primary percutaneous coronary intervention (PCI) to decrease infarct size in patients with STEMI.

METHODS: In this multicentre randomised controlled trial, 200 patients with large anterior wall STEMI were randomised 1:1 to selective intracoronary hypothermia during primary PCI or primary PCI alone. Using an over-the-wire balloon catheter for infusion of cold saline and a pressure-temperature wire to monitor the intracoronary temperature, the anterior myocardium distal to the occlusion was selectively cooled to 30-33°C for 7-10 minutes before reperfusion (occlusion phase), immediately followed by 10 minutes of cooling after reperfusion (reperfusion phase). The primary endpoint was infarct size as a percentage of left ventricular mass on cardiovascular magnetic resonance imaging after 3 months.

RESULTS: Selective intracoronary hypothermia was performed in 94/100 patients randomised to cooling. Distal coronary temperature decreased by 6°C within 43 seconds (interquartile range [IQR] 18-113). The median duration of the occlusion phase and reperfusion phase were 8.2 minutes (IQR 7.2-9.0) and 9.1 minutes (IQR 8.2-10.0), respectively. The infarct size at 3 months was 23.1±12.5% in the selective intracoronary hypothermia group and 21.6±12.2% in the primary PCI alone group (p=0.43). The left ventricular ejection fraction at 3 months in each group were 49.1±10.2% and 50.1±10.4%, respectively (p=0.53).

CONCLUSIONS: Selective intracoronary hypothermia during primary PCI in patients with anterior wall STEMI was feasible and safe but did not decrease infarct size compared with standard primary PCI. (ClinicalTrials.gov: NCT03447834)

KEYWORDS: cooling; hypothermia; infarct size; MVO; myocardial reperfusion injury; STEMI

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ST-elevation myocardial infarction (STEMI) remains a major health problem and may lead to death or heart failure[1]. Early restoration of blood flow limits infarct size and improves long-term outcomes[1,2]. The treatment of choice in STEMI patients is early reperfusion and revascularisation by primary percutaneous coronary intervention (PCI)[3]. Paradoxically, reperfusion may also cause myocardial injury and increase infarct size. This is termed myocardial reperfusion injury[4]. Currently, no therapy exists to reduce such injury in humans[4-6].

There is general agreement that reperfusion injury occurs during the first minutes of reperfusion, and preventive therapy before reperfusion may be cardioprotective[4].

In animal models of myocardial infarction, hypothermia of 30-33°C reduces reperfusion injury and infarct size[7,8]. Importantly, this effect was only noted when hypothermia was established before reperfusion[9-12]. In contrast, studies in humans applying systemic cooling have not been able to confirm this protective effect[13].

To overcome the intrinsic limitations of systemic cooling, we developed and tested a novel method to provide intracoronary hypothermia selectively to the infarct area just prior to reperfusion[14,15]. This method was feasible and safe in a human pilot study[16]. Compared to systemic cooling, the target temperature of the threatened myocardium is achieved more rapidly by intracoronary cooling, within minutes and without noticeable side-effects[17]. In 2 of 4 patients with inferior STEMI and an occluded right coronary artery, symptomatic atrioventricular conduction disturbances were observed, one of which necessitated treatment with a temporary pacemaker. In 6 patients with large anterior STEMI, no complications were observed. Consequently, we conducted the randomised, controlled EUROpean Intracoronary Cooling Evaluation in patients with ST-elevation myocardial infarction trial (EURO-ICE) as a proof-of-principle study to investigate the ability of selective intracoronary hypothermia to decrease infarct size in patients with anterior wall STEMI[18].

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Impact on daily practice

Myocardial reperfusion injury is a logical target to further decrease infarct size and improve clinical outcomes in patients with ST-elevation myocardial infarction. There is general agreement that reperfusion injury occurs during the first minutes of reperfusion, and as such, new therapies should be active in the myocardium at risk before reperfusion occurs. Selective intracoronary infusion, the technique used in the present study, allows for administration of drugs into the distal myocardium before reperfusion. New (pharmacological) therapies targeting reperfusion injury should consider using this technique to ensure adequate release in the myocardium at risk before reperfusion.

Methods

STUDY DESIGN

The trial protocol was approved by the institutional review boards of each participating site, and the study was conducted in accordance with the Declaration of Helsinki.

EURO-ICE was a prospective, multicentre randomised controlled trial to evaluate the effect of selective intracoronary hypothermia on infarct size as determined by cardiovascular magnetic resonance imaging (CMR) at 3 months. Patients with anterior wall STEMI and an occlusion of the proximal or mid-left anterior descending artery (LAD) with Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 flow were randomised 1:1 to selective intracoronary hypothermia plus primary PCI versus standard primary PCI (control group), respectively[18]. The trial was conducted at 8 sites in Europe **(Supplementary Table 1)**.

A data safety monitoring board (DSMB) had access to all data. Interim analyses, for which the investigators were blinded, were performed by the DSMB after the inclusion of 40 and 100 patients, respectively. CMR studies were analysed by an independent core laboratory, blinded to treatment (University of Glasgow Imaging Core Laboratory, United Kingdom). During the study, the authors had no access to outcome data, including CMR results. After the last CMR had been analysed by the core laboratory, the authors had unrestricted access to all data.

STUDY POPULATION

Patients were eligible if they were admitted for anterior wall STEMI with a summed ST-segment deviation of ≥5 mm on the qualifying electrocardiogram and presented within 6 hours after onset of symptoms. Patients were required to be conscious and capable of providing informed consent.

Major exclusion criteria were age <18 or >80 years, cardiogenic shock, previous anterior wall myocardial infarction, previous bypass surgery, severe concomitant disease with a life expectancy of less than 1 year, known contraindications to CMR, or inability to understand and give informed consent. The flowchart is shown in **Supplementary Figure 1**, and **Supplementary Table 2** provides a list of all inclusion and exclusion criteria.

TRIAL PROCEDURES

Primary PCI was performed according to usual care. If the initial coronary angiogram demonstrated an occlusion in the proximal or mid-LAD with TIMI grade 0 or 1 flow, then the patient was eligible for the study. After a short

Abbreviations

CMR	cardiovascular magnetic resonance imaging
LAD	left anterior descending artery
LVM	left ventricular mass
MVO	microvascular obstruction
OTWB	over-the-wire balloon
PCI	percutaneous coronary intervention
PW	pressure wire
STEMI	ST-elevation myocardial infarction

verbal explanation, informed consent was obtained, and randomisation was performed. In case of randomisation to standard primary PCI, predilatation and stenting were performed as usual, and the procedure was finished according to regular routine.

In case of randomisation to selective intracoronary hypothermia, a regular guidewire was advanced beyond the culprit lesion, immediately followed by an over-the-wire balloon (OTWB) that was inflated to 4 atm at the location of the occlusion to prevent reperfusion. Next, a 0.014" coronary pressure wire (PW) capable of also measuring temperature (PressureWire [Abbott]) was equalised for pressure at the tip of the guiding catheter while simultaneously zeroing the blood temperature. Thereafter, it was positioned next to the regular guidewire in the balloon-occluded distal coronary artery **(Central illustration)**. If necessary, the balloon was deflated for a few seconds to pass the PW into the distal LAD, after which the balloon was quickly reinflated to re-occlude the coronary artery.

Thereafter, the regular guidewire in the OTWB was removed, and the central lumen of the OTWB was connected to two parallel contrast infusion pumps **(Supplementary Appendix 1)**, one filled with saline at room temperature and the other filled with saline at 4°C **(Central illustration)**. Next, the intracoronary hypothermia protocol was performed as described below. Tympanic temperature was measured to monitor systemic temperature.

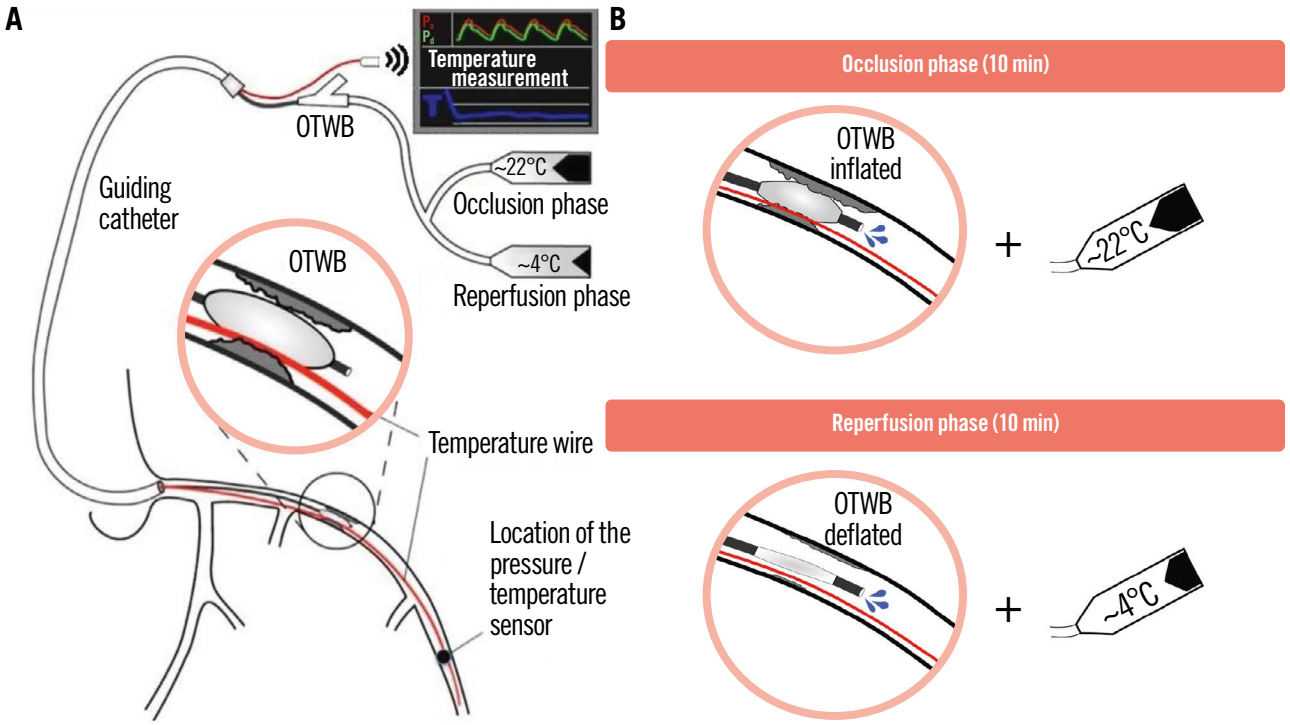
As an alternative to the use of a regular guidewire and OTWB, followed by introduction of the PW, it was also permitted to start the procedure with just a PW, cross the occlusion, and advance a specifically designed 2.7 Fr monorail balloon-infusion catheter (CoolCell catheter [CCC] [Hexacath]) to the site of the occlusion and inflate the balloon to 4 atm. No regular wire was then necessary, thus simplifying the procedure **(Supplementary Figure 2)**.

INTRACORONARY HYPOTHERMIA PROTOCOL

Hypothermia was initiated for 7-10 minutes before the onset of reperfusion (occlusion phase, OTWB inflated) and continued for 10 minutes after reperfusion (reperfusion phase, balloon deflated). The first pump, filled with saline at room temperature, was connected to the central lumen of the OTWB, and infusion was started at a flow rate of 20-25 ml/min. If necessary, this flow rate was adjusted based

EuroIntervention — Central **Illustration**

Selective intracoronary hypothermia during primary PCI in patients with anterior wall STEMI.



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A) A schematic overview of the instrumentation for selective intracoronary hypothermia is shown. The close-up shows the positioning of the balloon within the occlusion after removal of the regular guidewire in order to enable saline infusion through the central lumen of the over-the-wire balloon. The sensor-tipped pressure temperature wire is indicated in red. B) The occlusion phase (balloon inflated) and the reperfusion phase (balloon deflated) are shown with the associated saline temperatures. OTWB: over-the-wire balloon

upon the continuous measurement of the distal coronary temperature to maintain a temperature of approximately 6°C below body temperature, corresponding to a myocardial temperature in the infarcted area of roughly 4°C below body temperature during that occlusion phase (heat transport by conduction)[19]. After these 7-10 minutes, the balloon was deflated, and reperfusion was started. Just before deflating the balloon, the infusion was switched to saline at 4°C using the second infusion pump. Switching the temperature of the saline to 4°C during the reperfusion phase was necessary, because during the reperfusion phase, partial or complete reperfusion occurs, and the cooler saline mixes with warmer blood. In this way, an adequate reduction in the distal and myocardial temperatures can be maintained during the reperfusion phase **(Figure 1, Supplementary Figure 3)**. It has been demonstrated in previous animal experiments that, during the reperfusion phase, coronary and myocardial temperatures are almost equal (heat transport by convection)[15]. The distal coronary pressure was measured continuously.

After the intracoronary infusions, the OTWB (or CCC) was removed, and PCI was finished using the PW as a guidewire. Medical treatment before and after the intervention followed contemporary guidelines.

ENDPOINTS

The primary endpoint of the EURO-ICE trial was infarct size as a percentage of left ventricular mass (LVM) assessed at 3 months by CMR using late gadolinium enhancement (LGE) analysis. Key secondary endpoints were a composite of all-cause mortality or hospitalisation for heart failure at 3 months and at 1 year. Subgroup analyses were performed for the primary endpoint, and results were visualised as a forest plot for the prespecified characteristics. For a complete overview of the endpoints see **Supplementary Table 3**.

CARDIOVASCULAR MAGNETIC RESONANCE IMAGING

CMR at 1.5 Tesla was performed between 2 and 7 days and again at 3 months after the index STEMI. The protocol

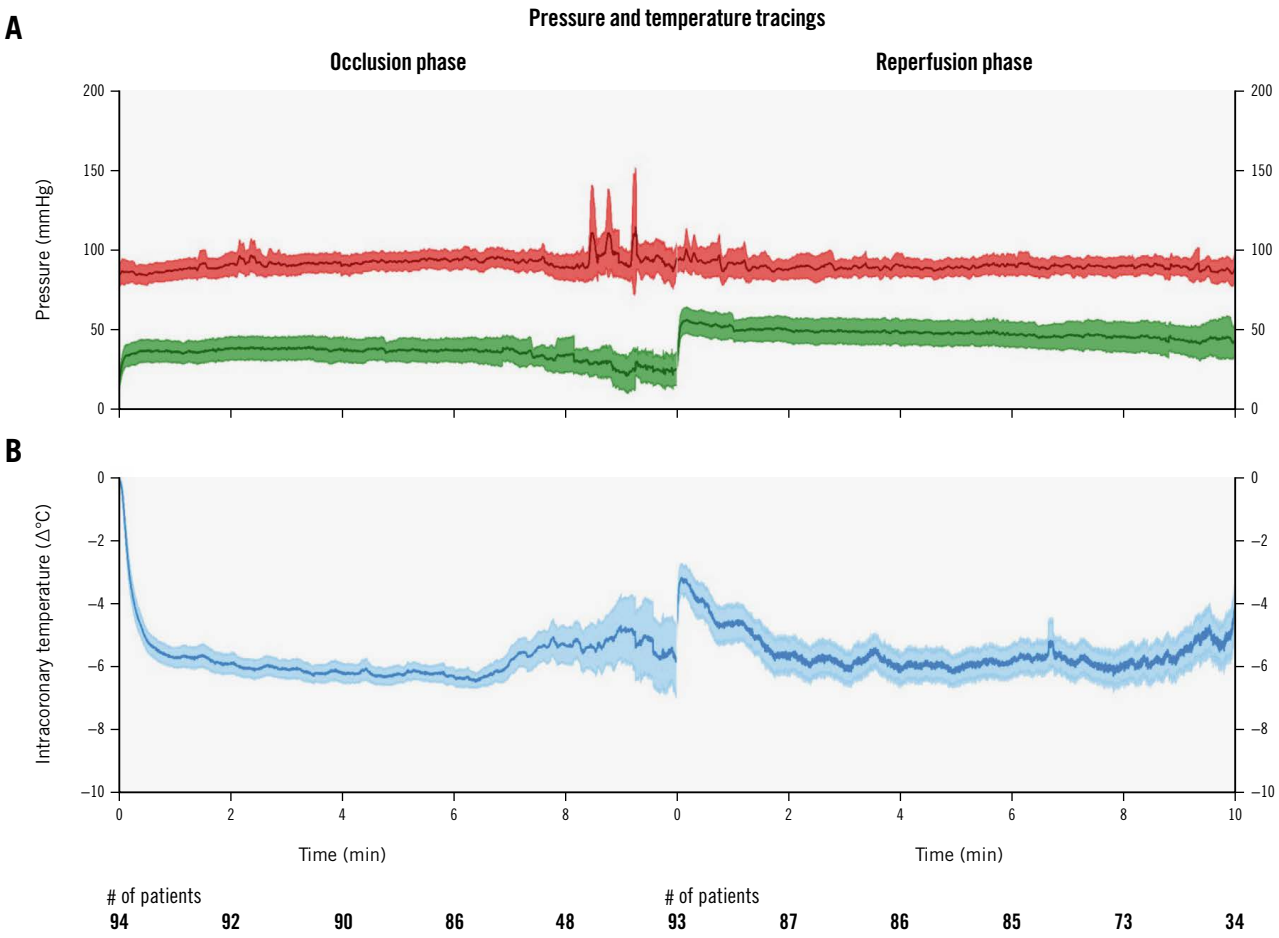

Figure 1. *Composite tracing of all patients showing aortic pressure (red), distal coronary pressure (green) and intracoronary temperature (blue) during treatment with selective intracoronary hypothermia. Tracings are displayed as means with 95% confidence intervals (shading). Time in minutes is indicated on the horizontal axis with the number of patients participating at that timepoint written below. A) The procedure consisted of two parts: the occlusion phase with the inflated balloon and infusion of saline at room temperature, immediately followed by the reperfusion phase with the deflated balloon (allowing reperfusion) and infusion of saline at 4°C. B) Intracoronary temperature is expressed as °C relative to body temperature.*

included T2* imaging (precontrast), T1 mapping (pre- and post-contrast), first pass myocardial perfusion imaging after administration of gadobutrol contrast media (Gadovist [Bayer]; 1.5 mmol/ml solution for injection), cine steady-state free precession imaging (SSFP), and finally, LGE imaging 10-15 minutes after contrast administration. LVM and function were calculated from the short-axis cine images. LGE imaging was used to calculate infarct size and to identify microvascular obstruction (MVO). Infarct size and MVO were expressed in grams and as a percentage of LVM. The T2* images were used to identify intramyocardial haemorrhage (IMH), and contrast-enhanced cine SSFP measured the area at risk. The **Supplementary Appendix 2** provides a detailed description of the acquisition techniques, CMR parameters, and analyses.

SAMPLE SIZE AND STATISTICS

All endpoints were analysed in the intention-to-treat (ITT) population.

Since this study only included patients with anterior wall STEMI due to a proximal or mid-LAD occlusion, it was assumed that the mean infarct size in the control arm would roughly correspond to 25% of LVM. Assuming a normal distribution of infarct size with a mean of 25% in the control arm and a standard deviation of 15%, plus typical statistical assumptions (unpaired 2-tailed t-test, alpha of 0.05, and power 0.80), a sample size of 91 subjects per arm would be needed to detect an absolute reduction of 6.25% of LVM, i.e., a 25% relative reduction of infarct size. To account for patients lost-to-follow up, 200 patients were planned for the study.

The secondary endpoints of clinical outcomes at 3 months and at 1 year were compared by applying the chi-square or Fisher's exact test to a 2x2 table of binary events per group. Similarly for the secondary endpoints involving imaging or blood samples, unpaired 2-tailed t-tests or Mann-Whitney U tests were used to compare values between the groups.

Predefined analyses included tests for heterogeneity of effect by lesion location (proximal vs mid-LAD occlusion), TIMI flow grade (0 vs 1), and assumed clinical characteristics (binary or using the cohort median as the threshold).

Finally, because the cooling procedure is not trivial in itself and because it was difficult to anticipate protocol deviations, per-treatment and per-protocol analyses for the primary endpoint were part of the statistical protocol.

Results

PATIENT CHARACTERISTICS

Patients were recruited between January 2019 and June 2022 in 8 European heart centres.

Baseline characteristics are presented in **Table 1**. The mean age (±standard deviation) of the patients was 62±11 years, and 86% were male.

Risk factors were equally distributed in both groups, and the summed ST-deviation on the qualifying electrocardiogram was 16 mm (interquartile range [IQR] 10-23) in the selective intracoronary hypothermia group and 13 mm (IQR 9-19) in the control group (p=0.07).

Angiography revealed the culprit occlusion in the proximal LAD in 51% of the patients and in the mid-LAD in 49% in the selective intracoronary hypothermia group, and in 49% and 51% in the control group, respectively (p=0.78).

Table 1. Baseline characteristics in both groups.

	Selective intracoronary hypothermia during primary PCI (N=100)	Standard primary PCI (N=100)	*p*-value
Age, years	61.7±9.9	61.6±11.2	0.92
Sex			0.55
Male	87	84	
Female	13	16	
Medical history			
Hypertension	33	33	1.00
Current smoker	34	37	0.66
Diabetes mellitus	14	10	0.38
Dyslipidaemia	38	34	0.56
Family history of CVD	33	42	0.19
Prior myocardial infarction	6	1	0.05
Prior PCI	6	4	0.52
Body temperature before procedure, °C	36.3±0.8	36.3±0.8	0.96
Coronary angiography			
Left main disease	1	0	0.32
Multivessel disease	24	24	>0.99
Anterior wall STEMI			
∑ ST deviation, mm	16 (10-23)	13 (9-19)	0.07
Culprit occlusion			0.78
Proximal LAD	51	49	
Mid-LAD	49	51	
Pre-PCI TIMI grade flow			0.32
0	83	88	
1	17	12	
Symptom onset-to-balloon time*, min	149 (117-213)	156 (120-206)	0.81
Door-to-balloon time*, min	37 (33-44)	22 (18-26)	<0.001

Data are given as mean±SD, n, or median (IQR). *In the selective intracoronary hypothermia during primary PCI group, symptom onset-to-balloon time and door-to-balloon time include the duration of the occlusion phase. CVD: cardiovascular disease; IQR: interquartile range; LAD: left anterior descending artery; PCI: percutaneous coronary intervention; SD: standard deviation; STEMI: ST-elevation myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction

The door-to-balloon time was 15 minutes longer in the hypothermia group compared with the control group: 37 (IQR 33-44) versus 22 minutes (IQR 18-26), respectively (p<0.001). Taking into account that the median duration of the occlusion phase was 8 minutes **(Table 2)**, this indicates that an additional 7 minutes were needed for the specific instrumentation required for the cooling procedure.

PROCEDURAL RESULTS FOR PRIMARY PCI

Successful stenting was performed in 95 patients in the selective intracoronary hypothermia group and 95 patients

Table 2. Procedural data related to selective intracoronary hypothermia.

	Selective intracoronary hypothermia during primary PCI (N=94)
Hypothermia – occlusion phase	
Time to target temperature, sec	43 (18-113)
Duration of occlusion phase, min	8.2 (7.2-9.0)
Δ body temperature§, °C	–0.1 (–0.5 to 0.0)
Rate of infusion, ml/min	20 (20-25)
Infused volume of saline, ml	162 (140-200)
Atrial fibrillation	0/94
Sustained VT or VF#	2/94
Hypothermia – reperfusion phase	
Duration of reperfusion phase, min	9.1 (8.2-10.0)
Δ body temperature§, °C	–0.3 (–0.7 to 0.1)
Rate of infusion, ml/min	20 (15-20)
Infused volume of saline, ml	144 (123-200)
Atrial fibrillation	0/94
Sustained VT or VF#	3/94

Data are given as median (IQR) or n/N. §The difference in body temperature before the start of the procedure. #Necessitating defibrillation. PCI: percutaneous coronary intervention; VF: ventricular fibrillation; VT: ventricular tachycardia

in the control group. Patients were treated with current-generation drug-eluting stents. In the hypothermia arm, stenting was performed after completion of the hypothermia protocol. At the discretion of the interventional cardiologist, additional predilatation or direct stenting were both allowed.

No patients died during the procedure. Ventricular fibrillation occurred in 9 patients in the selective intracoronary hypothermia group versus 7 patients in the control group **(Supplementary Figure 4)** (p=0.60). Atrial fibrillation occurred in 0 versus 3 patients, respectively (p=0.08). Haemodynamic deterioration during the procedure occurred in 3 versus 2 patients, respectively (p=0.65). Two cases of acute stent thrombosis were encountered in the selective intracoronary hypothermia group versus 1 case in the control group (p=0.56).

PROCEDURAL RESULTS FOR SELECTIVE INTRACORONARY HYPOTHERMIA

The target temperature was achieved within 43 seconds (IQR 18-113) after the start of infusion. The duration of the occlusion phase was 8.2 minutes (IQR 7.2-9.0). The mean distal intracoronary temperature and distal coronary pressure for all patients are shown in **Figure 1**. The systemic temperature changed during the occlusion phase by –0.1ºC (IQR –0.5 to 0.0). The total infused volume of saline at room temperature was 162 ml (IQR 140-200) at a rate of 20 ml/min (IQR 20-25). No notable changes were observed in heart rate or aortic pressure.

The duration of the reperfusion phase was 9.1 minutes (IQR 8.2-10.0). The mean intracoronary temperature and distal coronary pressure for all patients during this phase are also shown in **Figure 1**. The systemic temperature changed by –0.3ºC (IQR –0.7 to 0.1). The total volume of cold saline used in the reperfusion phase was 144 ml (IQR 123-200) at a rate of 20 ml/min (IQR 15-20). Again, no notable changes were observed in heart rate or aortic pressure **(Figure 1)**.

All details of cooling are presented in **Table 2**. An example of an individual patient's recording during a complete cooling procedure is presented in **Supplementary Figure 3**.

PRIMARY ENDPOINT AND CMR RESULTS

Infarct size as a percentage of LVM at 3 months was available in 89 patients randomised to selective intracoronary hypothermia and in 97 patients randomised to the control group. Reasons for not performing CMR at 3 months are mentioned in **Supplementary Figure 1**.

Infarct size was 23.1±12.5% of LVM in the selective intracoronary hypothermia group and 21.6±12.2% in the control group (p=0.43). Absolute infarct size was 26.1±17.8 g in the selective intracoronary hypothermia group and 24.5±15.7 g in the control group (p=0.52). Left ventricular ejection fraction (LVEF) at 3 months was 49.1±10.2% in the selective intracoronary hypothermia group and 50.1±10.4% in the control group (p=0.53).

The myocardial salvage index was 0.54±0.24 in the selective intracoronary hypothermia group and 0.55±0.25 in the control group (p=0.82). All CMR results are presented in **Table 3** and **Supplementary Table 4**.

The predefined analysis for heterogeneity showed a larger infarct size for proximal versus mid-LAD in both groups, with no difference between the selective intracoronary hypothermia and control groups **(Supplementary Table 5)**. This was the same for TIMI grade 0 versus 1 flow. A forest plot of all predefined subanalyses of the primary endpoint is shown in **Supplementary Figure 5**.

The prespecified per-treatment analysis and per-protocol analysis did not significantly change the findings of the study **(Supplementary Table 6, Supplementary Table 7)**.

SECONDARY ENDPOINTS AND CLINICAL FOLLOW-UP

All-cause mortality or hospitalisation for heart failure at 1 year occurred in 3 patients in the selective intracoronary hypothermia group and in 2 patients in the control group (p=0.65). One patient died in the selective intracoronary hypothermia group 6 weeks after the index admission because of intracranial haemorrhage and 1 patient died after 11 months because of respiratory failure due to COVID-19. No patients in the control group died.

Subacute stent thrombosis occurred in 1 patient in the selective intracoronary hypothermia group after 6 days; there were no cases of this in the control group.

During the index admission, no differences were present in the maximum creatine kinase (CK) level or maximum troponin level **(Table 3)**. The maximum CK-MB isoenzyme (CK-MB) was 260 U/l (IQR 185-400) in the selective intracoronary hypothermia group and 239 U/l (IQR 99-322) in the control group (p=0.043). N-terminal pro-brain natriuretic peptide (NT-proBNP) at 3 months was 355 (IQR 144-667) pg/ml in the selective intracoronary hypothermia group and 264 (IQR 114-527) pg/ml in the control group (p=0.25). At 1 year, both NT-proBNP and LVEF (determined by echocardiography) were similar in both groups.

Table 3. Primary endpoint and key secondary endpoints at the index admission and at 3-month follow-up.

	Selective intracoronary hypothermia during primary PCI (N=100)	Standard primary PCI (N=100)	*p*-value
Primary endpoint			
Infarct size at 3 months, % of LVM	23.1±12.5	21.6±12.2	0.43
Secondary laboratory endpoints during index admission			
Maximum troponin level, ng/l	5,749 (3,019-9,382)	5,887 (2,365-8,979)	0.78
Maximum CK level, U/l	2,460 (1,380-3,674)	1,926 (712-3,228)	0.06
Maximum CK-MB level, U/l	260 (185-400)	239 (99-322)	0.043
Secondary clinical endpoints at 3 months			
Composite of all-cause mortality or hospitalisation for heart failure	2	1	0.56
All-cause mortality	1	0	
Hospitalisation for heart failure	1	1	
Secondary laboratory endpoints at 3 months			
NT-proBNP level, pg/ml	355 (144-667)	264 (114-527)	0.25
Secondary CMR endpoints			
Infarct size at 3 months, g	26.1±17.8	24.5±15.7	0.52
Ejection fraction, %	49.1±10.2	50.1±10.4	0.53
Myocardial salvage index	0.54±0.24	0.55±0.25	0.82
MVO, % of LVM	2.81±4.46	2.25±5.34	0.44
IMH present	49 (55)	39 (42)	0.08
Secondary clinical endpoints at 1 year			
Composite of all-cause mortality or hospitalisation for heart failure	3	2	0.65
All-cause mortality	2	0	
Hospitalisation for heart failure	1	2	
Implantation of ICD	1	1	
Secondary laboratory endpoints at 1 year			
NT-proBNP level, pg/mL	192 (92-432)	183 (48-374)	0.56
Secondary echocardiography endpoint at 1 year			
Ejection fraction, %	52.1±10.5	50.9±9.6	0.44

Data are given as mean±SD, median (IQR), n, or n (%). CK: creatine kinase; CK-MB: creatine kinase MB isoenzyme; CMR: cardiovascular magnetic resonance imaging; g: grams; ICD: implantable cardioverter-defibrillator; IMH: intramyocardial haemorrhage; IQR: interquartile range; LVM: left ventricular mass; MVO: microvascular obstruction; NT-proBNP: N-terminal pro-brain natriuretic peptide; PCI: percutaneous coronary intervention; SD: standard deviation

Discussion

The EURO-ICE trial demonstrated that selective intracoronary hypothermia during primary PCI in patients with large anterior wall STEMI was feasible and safe but did not reduce infarct size.

EURO-ICE is the largest hypothermia trial in patients with STEMI. As opposed to previous trials that investigated systemic cooling methods, we studied a technique of selective intracoronary cooling. This was performed using standard PCI equipment and consisted of 7-10 minutes of cooling of the threatened myocardium before the occluded coronary artery was opened, followed by an additional 10 minutes of cooling after reperfusion had been established.

The prevention of reperfusion injury in order to decrease myocardial infarct size remains a challenge. Previous attempts hitherto in humans using systemic hypothermia have been disappointing[20-25].

Although our technique of selective intracoronary hypothermia has several advantages compared to the systemic cooling methods used in previous trials, it remains unclear why selective intracoronary hypothermia was not effective to reduce infarct size in EURO-ICE. While the protocol was based on successful experimental studies, it cannot be excluded that the time intervals of cooling, depth of cooling, or other methodological issues related to humans affected the results. Moreover, it should be noted that the clinical outcomes, in patients randomised either to selective intracoronary hypothermia or to standard primary PCI, were better than expected. Infarct size, mortality and hospitalisation for heart failure were all low compared to historical data for patients with large anterior wall STEMI[26].

Of particular interest is the relation between selective intracoronary hypothermia and rhythm disturbances. Using systemic hypothermia, atrial fibrillation occurs in approximately 40% of patients[24], whereas atrial fibrillation did not occur in any of the patients who underwent cooling in our study. This may also have contributed to the observed difference in the incidence of cardiogenic shock between the EURO-ICE trial (incidence of cardiogenic shock in the cooling

arm: 1%) and previously published systemic cooling trials (incidence of cardiogenic shock in the cooling arm: 10.3%)[25].

Importantly, there was no difference in the incidence of ventricular fibrillation between the selective intracoronary hypothermia group and the control group **(Supplementary Figure 4)**. The door-to-balloon time was longer in the selective intracoronary hypothermia group compared to the control group, but this did not result in a larger infarct size.

In the present study, no shivering was observed in the cooled patients even though no antishivering medications were used. In previous published (systemic) hypothermia trials, however, 20% of cooled patients had uncontrolled shivering despite pretreatment with antishivering medication (oral buspirone and intravenous pethidine)[25].

Limitations

Our study has several limitations. First, the population was highly selective, and only patients with large anterior wall STEMI and a proximal or mid-LAD stenosis were included. However, there is no reason to suspect that the outcome would be any different in inferior wall STEMI. Second, our study was limited to patients with TIMI grade 0 or 1 flow. Patients with TIMI grade 2 or 3 flow were not included, because those patients had spontaneous reperfusion, and we believed that any advantage of cooling would not be pronounced in such cases. Third, although the cooling intervals were based on animal studies, it cannot be excluded that prolongation of the reperfusion phase may have been necessary and that, in fact, "delayed" reperfusion injury may have occurred in our study. Fourth, in 6 patients randomised to selective intracoronary hypothermia, the cooling protocol was not started at all. The main reason for this was an inability to place the PW into the distal LAD. This may have influenced the overall results. Fifth, LGE assessment for the primary endpoint could have been influenced by other causes for late enhancement, such as previous inferior infarction or myocarditis.

A major advantage of the technique used in this study is the possibility to have selective access to the infarct area before reperfusion occurs. A number of pharmacological therapies (such as cyclosporine, gap junction inhibitors and adenosine) have been investigated to prevent reperfusion injury during STEMI[26,27]. In those studies, positive results from animal experiments could not be reproduced in humans. An important limitation in all of these studies was the fact that in humans it was difficult to deliver the respective drug to the myocardium at risk before reperfusion occurred, making it doubtful that the drug would have any timely effect. The technique used in the present study allows for the administration of drugs into the distal myocardium before reperfusion occurs.

Conclusions

The EURO-ICE trial demonstrates that selective intracoronary hypothermia during primary PCI – started shortly before and continued for 10 more minutes after reperfusion – in patients with large anterior wall ST-elevation myocardial infarction is feasible and safe but does not decrease infarct size compared to primary PCI alone.

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Conflict of interest statement

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Supplementary Figure 5. Forest plot of predefined subanalyses of the primary endpoint.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-01042

Supplementary data

Supplementary Appendix 1. Saline infusion protocol and infusion pumps.

Saline was infused through the central lumen of the 0.014“ over the wire balloon (OTWB) or the central lumen of the CoolCell® catheter, respectively. For the infusion of saline, high pressure contrast injector pumps with infusion mode were used.
Typically, infusion was started at a rate of 20 ml/min. This could then be adjusted based on the temperature feedback by the Pressure-Temperature guidewire (PressureWire™ X, Abbott, USA). The accuracy of that sensor for temperature recording is 0.02 °C (Nico et al. Coronary thermodilution to assess flow reserve: validation in humans. *Circulation* 2002;105:2482-6). The maximum pressure of the infusion pumps was limited to 600 PSI. Typically, with an infusion rate of 20 ml/min, the generated pressure was 350 PSI. Infusion pumps of several trademarks can be used, such as in this study the Medrad® Mark V ProVis pump (Bayer, Leverkusen, Germany) and the Nemoto Rempress pump (Nemoto Kyorindo Co., Ltd., Tokyo, Japan).

Supplementary Appendix 2. Cardiovascular magnetic resonance imaging acquisition standard operating procedure.

Title: Selective intracoronary hypothermia in patients with ST-segment elevation myocardial infarction to reduce infarct size	Version: 2.0
Authors: Colin Berry, Kenneth Mangion, Vanessa Orchard	
Date: 12 April 2019	

Purpose
To describe the cardiac magnetic resonance (CMR) imaging scan protocol for the intra-coronary hypothermia trial, EUROpean Intracoronary Cooling Evaluation in Patients With ST-elevation Myocardial Infarction (EURO-ICE).
To optimize CMR acquisition for the primary outcome of the trial, infarct size as revealed by late gadolinium enhancement 3 months after ST-elevation myocardial infarction (STEMI).

Scope
All sites and all individuals who acquire and/or analyze CMR data as a part of the clinical trial.

Key points

CMR scanner: 1.5 Tesla field strength with a standard (e.g. 8-element) phased array cardiac surface coil. CMR should be performed twice – 2 – 7 days (baseline) and 3 months (follow-up) post-MI:

Baseline – CMR should be planned for 5 days post-STEMI. The scan should not be performed earlier than 2 days. If circumstances prevent the scan being performed within 2 – 7 days, the CMR scan should still be performed whenever feasible either before day 2 or after day 7. In all cases, the CMR should *still be performed* even if after 7 days. There is no upper limit to the

time from the index event, although the data will be qualified if the scan is performed after 7 days.

Follow-up – 3 months±2 weeks.

The primary outcome of the trial is infarct size (% left ventricular (LV) mass) on the follow-up CMR scan, as revealed by late gadolinium enhancement 10-15 minutes after gadolinium contrast (0.15 mmol/L) administration. The late enhancement short axis left ventricular stack is the key part of the CMR examination since infarct size (%LV mass) is the primary outcome of the trial. In order to obtain information on myocardial perfusion, the default approach for contrast administration will be a dual bolus (0.05 mmol/L first pass then after the first pass scan, administer 0.10 mmol/L).

CMR set-up

CMR imaging will be obtained in patients who have given written informed consent and who have satisfied the local safety criteria for CMR.

CMR safety check including renal function.

Contra-indications to MRI: ferrous metal foreign body, severe claustrophobia.

Patients with renal dysfunction should still undergo CMR. Renal dysfunction is not a contraindication to CMR but a GFR<30 ml/min is a contraindication to gadolinium contrast administration. There participants should undergo a non-contrast CMR scan with a full LV stack of T2* maps.

NB. STEMI patients with renal dysfunction during the acute admission: since renal function may improve, it may be reasonable to defer the scan for a couple of days to permit a recovery in renal function.

CMR protocol

Please ensure the same slice positions are used throughout the scan. The protocol includes pre-contrast and post-contrast imaging. Gadolinium contrast is given early in the protocol to ensure that infarct size (primary outcome) is secured.

	Stage	Guidance	Time
			Min
Pre-contrast	**Patient preparation**	Patient instructions, scanner set-up, load the pump injector, check IV access is functional, acquire the ECG	5 / 5
Pre-contrast	**Localisers and planning**	X3 orthogonal bright-blood, 2Ch, 3Ch, 4Ch	5 / 10
Pre-contrast	**T2* (pre-contrast)**	SA full LV stack (8 - 10 slices) T2* multi-echo GRE	7 / 17
Pre-contrast	**T1 map (pre-contrast)**	SA single slice (mid-infarct zone) MOLLI preferred, or ShMOLLI	2 / 19
Post-contrast	**First pass perfusion**	**Inject Gadovist, Dose 1** – 0.05 mmol/kg FLASH sequence 3 SAX per R-R interval over 1.5 min	4 / 23
Post-contrast		**Inject Gadovist Dose 2** – 0.10 mmol/kg	1 / 24
Post-contrast		Wait 3 minutes for contrast equilibration	3 / 27
Post-contrast	**Cine-SSFP**	SA full stack 8 – 10 slices aligned to the Use the T2* SAX slice positions; single LAX	8 / 35
Post-contrast	**Late enhancement**	Start at t = 10 min post Dose 2 SA full stack aligned to the T2* positions	8 / 43
Post-contrast	**T1 (post-contrast)**	Start at t ≥ 15 min post Dose 2 SA single slice (mid-infarct zone) MOLLI	2 / 45
	End of study	Patient briefing	5 / 50

Schematic illustration of the CMR acquisition protocol

CMR protocol pre-contrast

<u>Localisers and planning</u>

The CMR protocol includes three orthogonal 'white blood' sequences (axial, sagittal and coronal) and long axis cine imaging (vertical long axis, horizontal long axis and 3 chamber

view) to permit identification of the LV outflow tract (LVOT). The localizer acquisitions should be conducted according to the site's best practice.

T2* imaging

T2* maps should be obtained using a dedicated T2* map sequence. Excluding the LVOT and apex, acquire a full stack to permit volumetric measurement of myocardial haemorrhage (T2* infarct core).

NB. If the patient is tolerating the scan poorly then abandon T2 imaging in order to give gadolinium contrast to secure late enhancement imaging for infarct size (primary outcome of the trial).*

Typical T2* imaging parameters: T2* multi-echo GRE (preferred) or T2*-map
Bandwidth ~814 (x8) Hz/pixel; flip angle 18°; matrix 256x115 pixels; spatial resolution 2.6 x 1.6 x 10 mm; slice thickness 8 mm with 2 mm gap.

T1 map – pre-contrast

Three short axis T1-maps (basal, mid and apical positions) should be acquired.
A single T1 mapping method, e.g. MOLLI, should be designated for the protocol in your site. MOLLI is most widely available, and therefore this method is preferred. Ensure that this T1 map pulse sequence is always used including at baseline and follow-up.
Typical T1 imaging parameters:

Contrast administration: a two bolus approach

The intravenous contrast agent is gadobutrol (Gadovist®, Bayer; 1.5 mmol/ml solution for injection) which should be administered in two doses (see Appendix 3 for weight-adjusted contrast volume). First dose injection (D1 = 0.05 mmol/kg) should be given to initiate the first-pass of contrast and the second dose, D2 = 0.1 mmol/kg 'top-up' injection, should be given immediately after the first-pass. Therefore, the total dose of gadobutrol is 0.15 mmol/kg.
An automated pump injector (e.g. Medrad) should be used for intravenous injection of gadolinium. The injection rate should be 4 ml/sec.

CMR protocol after contrast administration with split dosing

Dose 1: 0.05 mmol/kg of Gadovist for first pass perfusion

Next, 3-of-5 short axis slices for first pass gadolinium contrast perfusion CMR will be acquired, ideally, at the same slice positions from the T2* scans. However, on occasion, alignment may not occur due to the size of heart on systole. First-pass perfusion at rest for 'wash-in' MVO quantification will be performed with a fast low-angle shot (FLASH) sequence run simultaneously with the contrast injection. 'Normal' standard sequence, i.e. non WIP implementation, for 3 SAX per RR interval over 1.5 min is used.
Typical first-pass imaging parameters:
Saturation recovery with inversion pulse. T1 101 ms; TR/TE 194/0.98 ms; acquisition window 1000 ms. 1 concatenation; 3 *SAX* slices. If three slices cannot be acquired within the R-R cycle then use 2 concatenations.

Dose 2: 0.10 mmol/kg of Gadovist as top up:

Cardiac mass & function, incorporating area-at-risk imaging with 'contrast cine-SSFP'

Wait 2 – 3 minutes following the second dose of contrast to enable contrast equilibration. This time could be used to set-up the cine-LV stack.
The cine-CMR for LV mass and function will be collected during the interval between the 3 min scan and late enhancement imaging. Cine-CMR should be acquired with a short axis LV stack, slices aligned to T1 maps, from MV to apex (usually 10 slices in total). Extra slices are acquired basally to MV that incorporate LVOT and also potentially to apex (usually 10 slices in total).
Steady-state free precession (SSFP) cine breath-hold sequences (with parallel imaging acceleration) will be used. The heart will be imaged in multiple parallel short-axis (SAX) planes 8-mm thick separated by 2 mm gaps, equating to approximately 10 slices and 30 cardiac phases.
Typical SSFP imaging parameters:
Voxel size 2.0 x 2.0 x 8.0 mm; TR/TE 39.6/1.12 ms; flip angle 55o, matrix 192 x 192 pixels; slice thickness 8 mm, with 2 mm gap.

Late enhancement
Late MVO and scar will be imaged 10-15 minutes after intravenous Gadovist contrast administration using, in general, a motion-corrected T1-weighted phase-sensitive inversion recovery radiofrequency pulse sequence. A full stack, aligned to T2* scans (or cines), and three long axis views (vertical long axis, horizontal long axis and 3 chamber view) will be acquired. Where patient tolerance is limited, then a single long axis view would suffice. Phase-sensitive inversion recovery CMR techniques reduce variability relating to myocardial nulling which is required for late gadolinium enhancement imaging of infarct vs. unaffected myocardium. If a phase-sensitive protocol is not used, a modified Look-Locker inversion time scout will be performed prior to using an inversion recovery turbo gradient echo sequence. Phase swops will be performed where appropriate to rule out artefact.

Poor breath-holding: A single shot technique or navigated late gadolinium enhancement CMR will be used as an option for poor breath holders.
Typical LGE / MVO imaging parameters with PSIR:
Matrix 192 x 256 pixels; flip angle 25o; TE 3.36 ms; bandwidth 130 Hz/pixel; echo spacing 8.7ms and trigger pulse 2. The voxel size is 1.8 x 1.3 x 8 mm. Inversion times individually adjusted to optimize nulling of apparently normal myocardium (typical values, 200 to 300 ms).

Post-contrast T1 mapping
Three short axis T1-maps (basal, mid and apical positions) that must match the same slice positions as the pre-contrast T1-map scans, >15 min after top-up injection of contrast.

CMR follow-up scan
MR scans at 3 months follow-up must involve the same scan protocol as was used in the baseline CMR scan.
Renal function should be known or checked.

CMR annotation
All MRIs must be anonymized prior to upload to the eCRF with all patient identifiers removed. The method used is the same as that for other data such as the ECGs and angiograms, the required method is detailed below:
ID: TRIAL-NAME_Site-ParticipantNo_YYYYMMDD
Name: CMR_TIMEPOINT

Imaging analysis was undertaken using Medis software, University of Glasgow Imaging Core Laboratory.

Supplementary Table 1. Participating centres and co-principal investigators.

Participating centers	Co-principal investigator
Catharina Hospital, Eindhoven, The Netherlands	Luuk C Otterspoor
Cardiovascular Center Aalst, Onze Lieve Vrouwe Clinic, Aalst, Belgium	Bernard De Bruyne
Golden Jubilee National Hospital, Glasgow, United Kingdom	Richard Good
Rigshospitalet, Copenhagen, Denmark	Thomas Engstrøm
Örebro University, Örebro, Sweden	Ole Fröbert
Essex Cardiothoracic Centre, Basildon, United Kingdom	Thomas R Keeble
Skäne University Hospital, Lund, Sweden	David Erlinge
Belgrade University School of Medicine, Belgrade, Serbia.	Branko Beleslin

Supplementary Table 2. Inclusion and exclusion criteria.

Inclusion criteria
Age 18-80 years
STEMI anterior wall, $\sum$ ST-deviation $\geq$ 5mm
Onset of symptoms < 6 hours
Culprit occlusion in proximal (syntax segment 6) or mid (syntax segment 7) LAD artery
Pre PCI TIMI grade flow should be 0 or 1
Exclusion criteria
Age <18 or >80 years
Pre PCI TIMI grade flow 2 or 3
Culprit occlusion in distal LAD (syntax segment 8) artery
Cardiogenic shock or hemodynamic instability
History of severe left ventricular function and/or severe valvular disease
History of previous anterior wall myocardial infarction or bypass surgery
Very tortuous or calcified coronary arteries, i.e. complex coronary anatomy
Severe comorbidity with life expectancy of less than 1 year
Inability to understand and give informed consent
Contra-indication for MRI
Pregnancy

Supplementary Table 3. Secondary endpoints of the EURO-ICE study, excluding CMR endpoints.

Index admission
Peak value of troponin T
Peak value of CK
Peak value of CK-MB
3 months
Composite of all-cause mortality and hospitalization for heart failure
All-cause mortality
Hospitalization for heart failure
Cardiac death
NT-proBNP
LVEF measured by echocardiography (biplane Simpson's method)
WMSI by echocardiography
1 year
Composite of all-cause mortality and hospitalization for heart failure
All-cause mortality
Implantation of cardioverter defibrillator for primary prevention
Implantation of cardioverter defibrillator for secondary prevention
Implantation of cardioverter defibrillator for both primary and secondary prevention
Hospitalization for heart failure
Cardiac death
NT-proBNP
LVEF measured by echocardiography (biplane Simpson's method)
WMSI by echocardiography

CK creatine kinase; CK-MB creatine kinase MB isoenzyme; NT-proBNP N-terminal proB-type natriuretic peptide; LVEF Left ventricular ejection fraction; WMSI wall motion score index

Supplementary Table 4. Cardiovascular magnetic resonance imaging endpoints.

	Selective intracoronary hypothermia during PPCI (N=100)	Standard PPCI (N=100)	P-value
Primary end point			
- IS at 3 months, %LVM (SD)	23.1±12.5	21.6±12.2	0.43
Secondary CMR end points (days 2 – 7)			
- AAR, %LVM (SD)	48.5±10.4	46.5±12.2	0.25
- MVO, %LVM (SD)	2.8±4.5	2.2±5.3	0.44
- IMH present, n (%)	49 (55)	39 (42)	0.08
- Baseline IS, %LVM (SD)	30.6±14.0	27.9±13.0	0.18
- Baseline IS, g (SD)	41.1±21.4	36.0±21.1	0.11
- Baseline MSI, (SD)	0.38±0.25	0.41±0.25	0.54
- Baseline LVEDV, mL (SD)	182.9±39.7	169.3±38.8	0.02
- Baseline LVESV, mL (SD)	102.4±30.5	94.3±31.6	0.08
- Baseline LVEF, % (SD)	44.1±9.2	44.5±9.8	0.80
- Baseline GLS, % (SD)	-11.4±5.0	-11.2±5.1	0.75
- Baseline WMSI (SD)	1.69±0.33	1.62±0.33	0.13
Secondary CMR endpoint at 3 months			
- IS, g (SD)	26.1±17.8	24.5±15.7	0.52
- MVO, %LVM (SD)	0.02±0.15	0.06±0.33	0.37
- IMH present, n (%)	2 (2)	4 (4)	0.47
- Final MSI, (SD)	0.54±0.24	0.55±0.25	0.82
- Final LVEDV, mL (SD)	186.7±49.5	175.4±45.5	0.11
- Final LVESV, mL (SD)	95.7±40.5	94.7±59.3	0.89
- Final LVEF, % (SD)	49.1±10.2	50.1±10.4	0.53
- Final GLS, % (SD)	-16.3±6.5	-15.7±5.5	0.50
- Final WMSI (SD)	1.43±0.36	1.39±0.35	0.39

PPCI primary percutaneous coronary intervention; IS infarct size; %LVM percentage of left ventricular mass; CMR cardiovascular magnetic resonance imaging; AAR area at risk; MVO microvascular obstruction; IMH intramyocardial hemorrhage; MSI myocardial salvage index; LVEDV left ventricular end-diastolic volume; LVESV left ventricular end-systolic volume; LVEF left ventricular ejection fraction; GLS global longitudinal strain; WMSI wall motion score index

Supplementary Table 5. Subgroup analyses for the primary endpoint.

	Selective intracoronary hypothermia during PPCI (N=94)	Standard PPCI (N=106)	P-value
Primary endpoint			
- **IS at 3 months, %LVM (SD)**	**23.1±12.5**	**21.6±12.2**	**0.43**
- Male sex	22.8±11.6	20.9±12.6	0.31
- Female sex	24.7±19.0	25.4±9.8	0.91
- Diabetes, yes	17.3±8.5	18.4±10.1	0.80
- Diabetes, no	23.9±12.8	22.0±12.4	0.34
- History of previous PCI, yes	27.5±14.5	21.5±6.3	0.47
- History of previous PCI, no	22.8±12.4	21.6±12.4	0.53
- History of previous MI, yes	24.2±9.4	18.6±*NA*	0.62
- History of previous MI, no	23.0±12.7	21.6±12.3	0.47
- Proximal LAD	26.0±13.7	23.2±13.5	0.33
- Mid LAD	20.0±10.4	20.1±10.9	0.95
- TIMI grade flow 0	23.7±12.8	21.4±12.4	0.24
- TIMI grade flow 1	20.1±11.0	23.5±11.1	0.43
- Age (<median of cohort)	23.2±13.0	20.9±12.1	0.40
- Age (≥median of cohort)	22.9±12.1	22.2±12.4	0.77
- STB time (<median of cohort)	22.0±13.7	18.9±12.0	0.25
- STB time (≥median of cohort)	23.6±11.2	23.9±12.4	0.90

PPCI primary percutaneous coronary intervention; IS infarct size; %LVM percentage of left ventricular mass; PCI percutaneous coronary intervention; MI myocardial infarction; LAD left anterior descending artery; TIMI thrombolysis in myocardial infarction; STB symptom onset to balloon.

Supplementary Table 6. Per-treatment analysis.

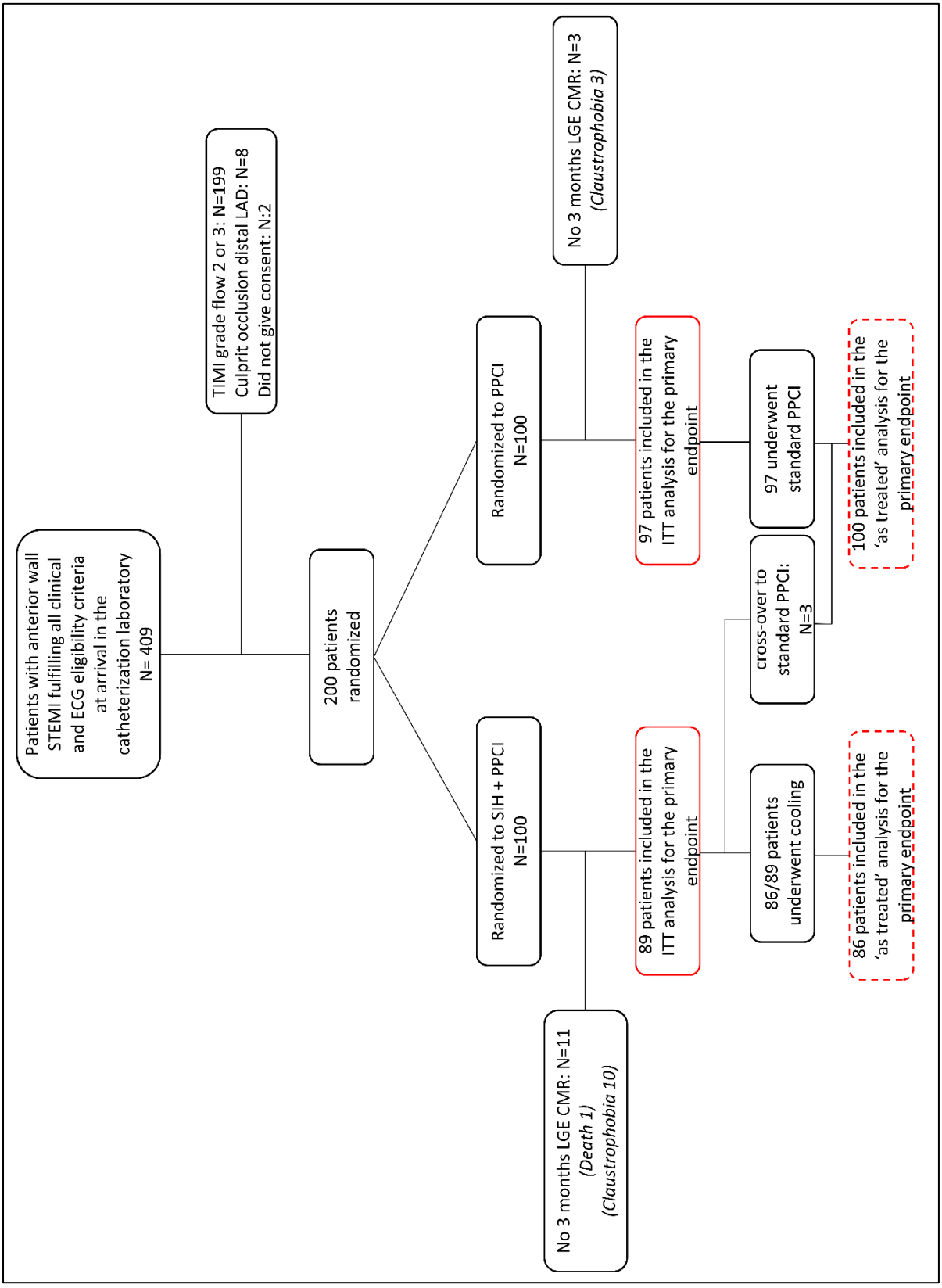
	Selective intracoronary hypothermia during PPCI (N=94)	Standard PPCI (N=106)	P-value
Primary endpoint			
- IS at 3 months, % of LVM (SD)	22.9±12.6	21.8±12.1	0.54
Secondary CMR endpoints			
- IS at 3 months, grams (SD)	25.9±18.0	24.6±15.6	0.60
- LVEF, % (SD)	49.2±10.2	50.0±10.4	0.61
- MSI (SD)	0.54±0.24	0.55±0.25	0.95
- MVO present, % of LVM	2.8±4.5	2.3±5.3	0.45
- IMH present, n (%)	48 (55)	40 (42)	0.08

PPCI primary percutaneous coronary intervention; IS infarct size; LVM left ventricular mass; CMR cardiovascular magnetic resonance; LVEF left ventricular ejection fraction; MSI myocardial salvage index; MVO microvascular obstruction; IMH intramyocardial hemorrhage

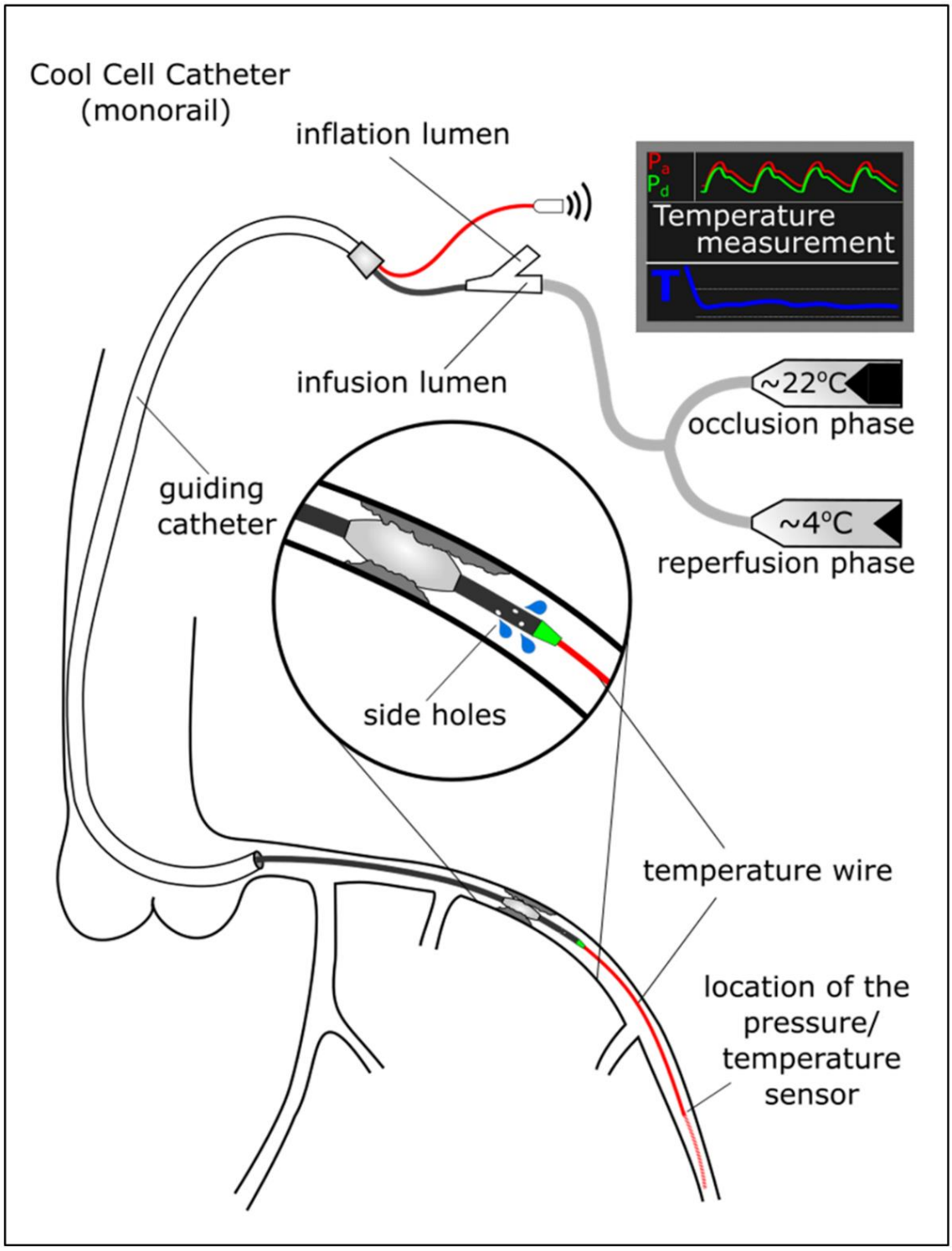
Supplementary Table 7. Per-protocol analysis.

	Selective intracoronary hypothermia during PPCI (N=63)	Standard PPCI (N=106)	P-value
Primary endpoint			
- IS at 3 months, % of LVM (SD)	23.6±13.1	21.8±12.1	0.37
Secondary CMR endpoints			
- IS at 3 months, grams (SD)	27.0±18.4	24.6±15.6	0.39
- LVEF, % (SD)	48.9±10.4	50.0±10.4	0.55
- MSI (SD)	0.53±0.26	0.55±0.25	0.76
- MVO present, % of LVM	2.7±4.2	2.3±5.3	0.60
- IMH present, n (%)	32 (55)	40 (42)	0.12

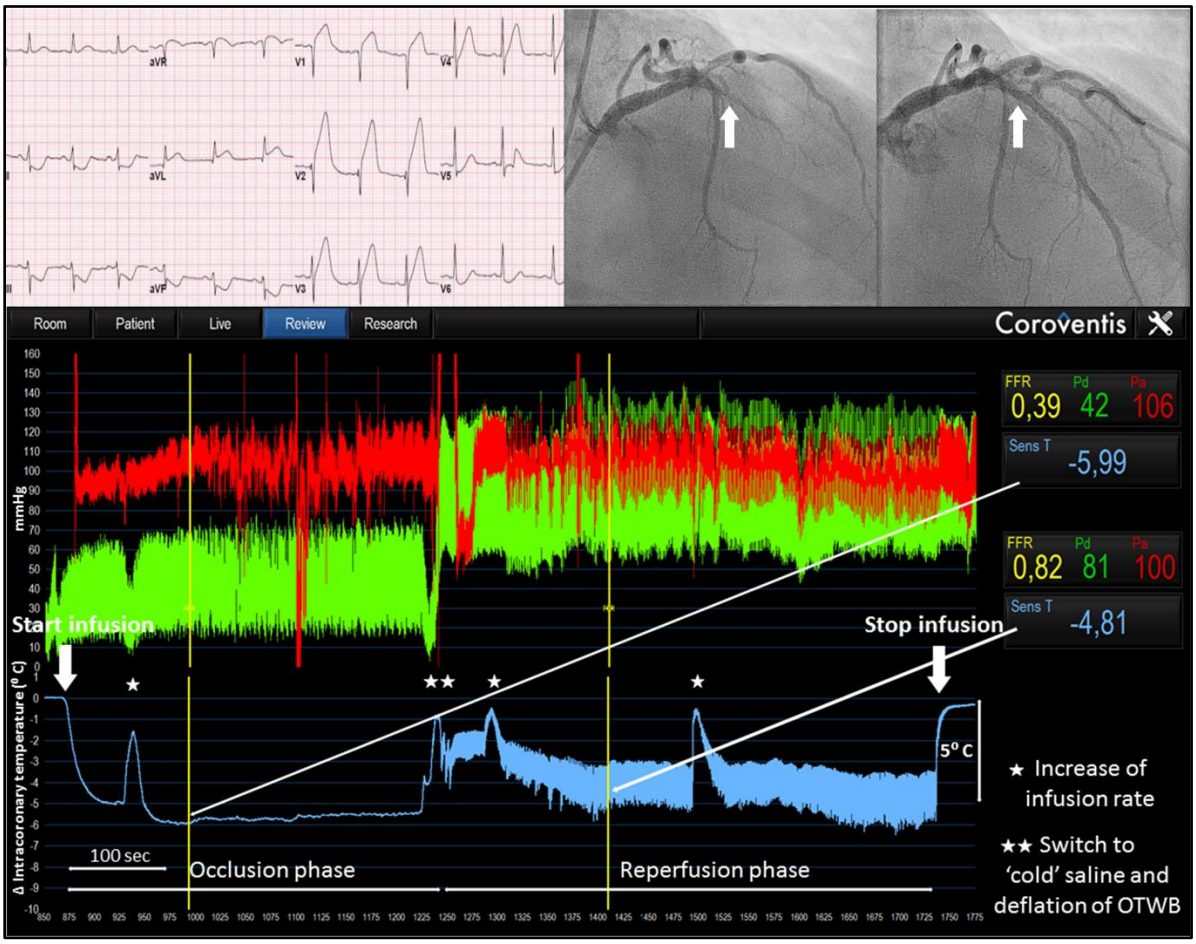
PPCI primary percutaneous coronary intervention; IS infarct size; LVM left ventricular mass; CMR cardiovascular magnetic resonance; LVEF left ventricular ejection fraction; MSI myocardial salvage index; MVO microvascular obstruction; IMH intramyocardial hemorrhage



Supplementary Figure 1. Flowchart of the EURO-ICE study.



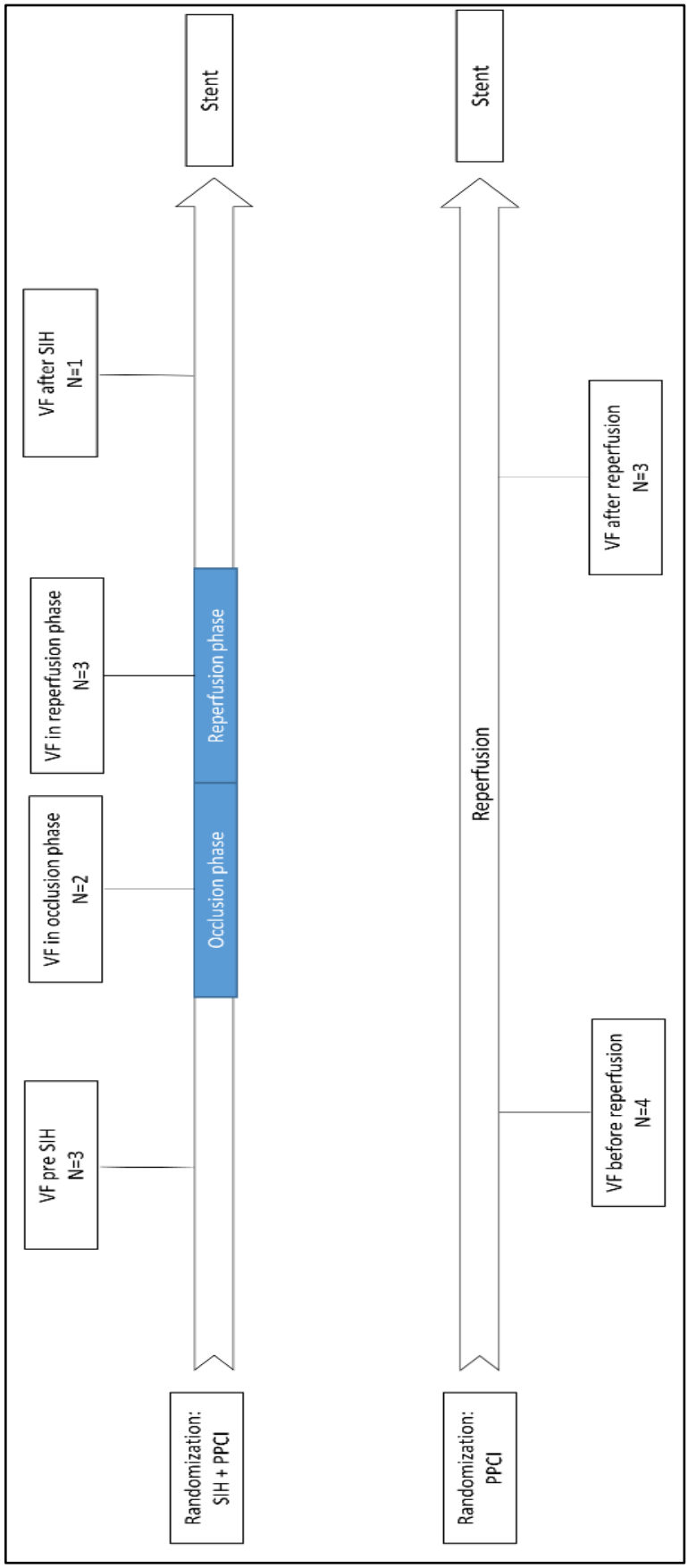
Supplementary Figure 2. Instrumental setup using the CoolCell catheter.
Instrumentation in the 34 patients in whom a new specifically designed 2.7F monorail-balloon-infusion catheter (CoolCell® catheter, Hexacath, Paris) was used to facilitate the instrumentation. The sensor-tipped pressure-temperature wire is used now as primary guidewire, the CoolCell® catheter (CCC) is advanced over this wire as a monorail system, the balloon is inflated to 4 atm, and infusion can take place through the infusion lumen of the CCC. No second wire is necessary. In those 34 patients in whom the CCC was used, door-to-balloon time was 36 (IQR 31 – 41) minutes vs 39 (35 – 45) minutes in the patients in whom an OTWB was used (P=0.036)



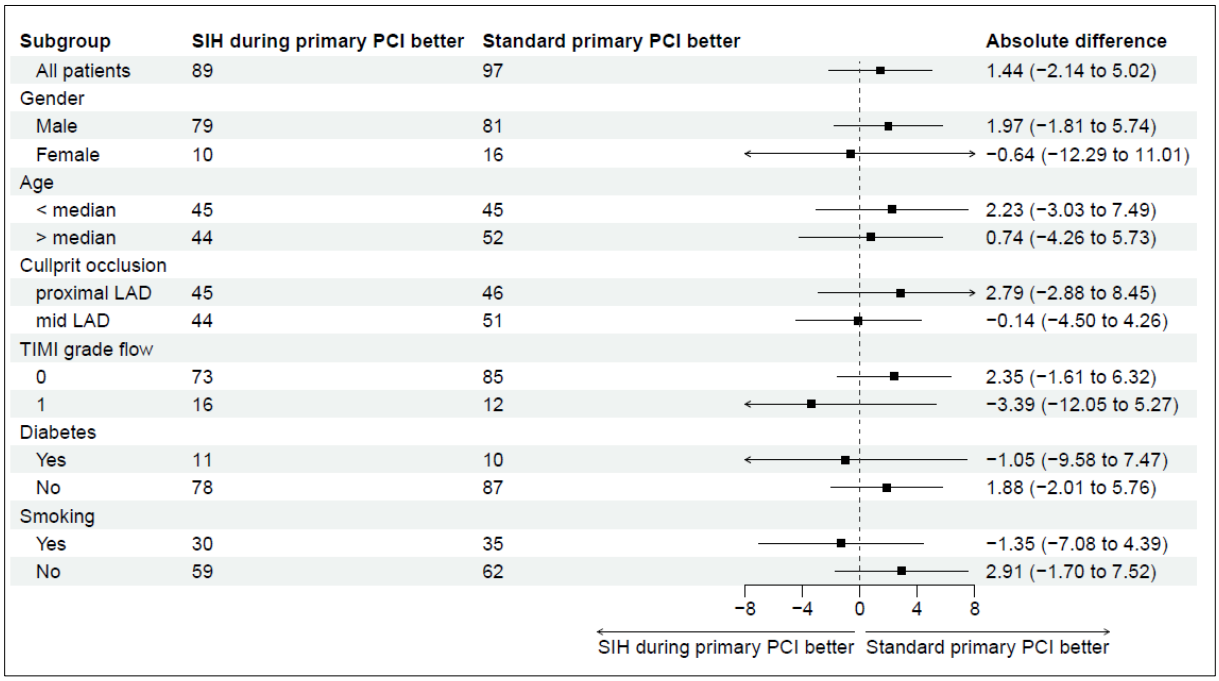
Supplementary Figure 3. Example of the cooling and interventional procedure in a patient randomised to selective intracoronary hypothermia.

*Upper left pane*l: ECG at admission. *Upper right panels*: occlusion in proximal LAD artery with TIMI grade flow 0 at the first angiogram and PCI result after stenting. *Lower panel:* CoroFlow (Coroventis, Uppsala, Sweden) tracing with recordings of aortic pressure (in red), distal intracoronary pressure (green), and intracoronary temperature relative to body temperature (blue). The horizontal axis represents time. The occlusion phase of the cooling procedure is visible on the left part of the recording and the reperfusion phase on the right part. Within 60 seconds from the start of saline infusion at room temperature, distal intracoronary temperature decreases to 5°C below body temperature. The asterisk indicates increase of infusion rate to decrease the temperature further to 6°C below body temperature. The double asterisk marks the switch of infusion pumps to saline of 4°C, whereafter the balloon is deflated. Infusion rate is now adjusted twice (indicated by the single asterisks) to achieve and maintain a distal coronary temperature of approximately 5°C below body temperature. At the end of the reperfusion phase, infusion is stopped and temperature returns quickly to normal.

In this patient, full reperfusion occurs immediately as can be observed by the rapid rise of distal coronary pressure, phasic pattern of the distal coronary temperature and necessity of increasing the infusion rate of cold saline to reach the target temperature.



Supplementary Figure 4. Incidence of ventricular fibrillation in both groups during the different phases of the interventional procedure.



Supplementary Figure 5. Forest plot of predefined subanalyses of the primary endpoint.