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# Selective intracoronary hypothermia in patients with ST-elevation myocardial infarction. Rationale and design of the EURO-ICE Trial.

## *Short title: Intracoronary hypothermia in STEMI*

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**CLASSIFICATIONS**

STEMI, Other technique, MRI, Myocardial infarction.

**ABBREVIATIONS**

| | |
|---|---|
| STEMI | ST-elevation myocardial infarction |
| PPCI | Primary percutaneous coronary intervention |
| SIH | Selective intracoronary hypothermia |
| IS | Infarct size |
| LAD | Left anterior descending |
| TIMI | Thrombolysis-In-Myocardial-Infarction |
| OTWB | Over-the-wire balloon |
| CMR | Cardiovascular magnetic resonance imaging |

## INTRODUCTION

In ST-elevation myocardial infarction (STEMI), early restoration of blood flow, preferably by primary percutaneous coronary intervention (PPCI), is paramount to limit infarct size (IS) and improve long-term outcomes [1]. However, reperfusion by itself may also cause damage to the myocardium and increase IS. This has been termed myocardial reperfusion injury [2].

In animal models of acute myocardial infarction, it has been demonstrated that hypothermia decreases IS [3]. In contrast, human studies applying systemic cooling methods have not yet been able to confirm this protective effect.

Recently, we developed a new method to provide selective intracoronary hypothermia during PPCI [4]. The EUROpean Intracoronary Cooling Evaluation in patients with ST-elevation myocardial infarction (EURO-ICE) trial will assess the efficacy of this method.



## METHODS

### Study objectives

The primary objective of the EURO-ICE trial is to evaluate the effect of selective intracoronary hypothermia (SIH) on IS.

### Study design

EURO-ICE is a prospective, multicenter, randomized controlled, proof-of-principle study. Two hundred patients with anterior wall STEMI and an occlusion of the proximal or mid left anterior descending (LAD) artery with Thrombolysis-In-Myocardial-Infarction grade flow 0 or 1 will be randomized in 1:1 fashion to SIH during PPCI versus standard PPCI. Respectively, for the study flowchart and a complete overview of all in- and exclusion criteria we refer to ‘supplementary figure 1’ and ‘supplementary table 1’ of the appendix.

**Selective intracoronary hypothermia**

When randomized to the experimental arm, SIH will be performed as described by Otterspoor et al [4]. First, the occlusion is crossed with a regular guidewire. Hereafter, an over-the-wire balloon (OTWB) is advanced into the LAD artery and inflated at the site of the occlusion. Next, a pressure/temperature wire (PressureWire X™, Abbott, Minneapolis, Minnesota, USA) is advanced into the distal LAD for continuous recording of pressure and temperature. After the guidewire is removed from the central lumen of the OTWB, this lumen is connected to two infusion pumps filled with saline at room temperature and 4° C, respectively (figure 1).

First, saline at room temperature is infused during 7-10 minutes at a flow rate of 15-30 mL/min (*occlusion phase*) to maintain a distal coronary temperature of 6-8° C below body temperature. Next, the OTWB is deflated and the infusion continues for 7-10 more minutes, using the second infusion pump filled with saline at 4° C (*reperfusion phase*). The flow rate can be varied to maintain a distal coronary temperature between 4-6° C below body temperature.

Finally, the OTWB is retracted and the procedure continues per routine with placement of (a) drug-eluting stent(s).



**Endpoints**

The primary endpoint of the study is infarct size as a percentage of left ventricular mass after 3 months assessed by cardiovascular magnetic resonance imaging, using late gadolinium enhancement analyses. Evaluation of the primary endpoint will be performed in the Glasgow Imaging Core Laboratory by experienced reviewers, blinded to treatment allocation of the patients.

Key secondary endpoints are a composite of all-cause mortality and hospitalization for heart failure at 3 months and at 1 year. For a complete overview of all endpoints we refer to the supplementary appendix.

**Sample size and statistics**

Since this study only includes patients with anterior wall STEMI due to a proximal or mid LAD artery occlusion, we assume IS in the control arm will correspond to a mean of approximately 25% of left ventricular mass [5]. Assuming a normal distribution of IS with a mean of 25% in the control arm and a standard deviation of 15%, plus typical statistical assumptions (unpaired, two-tailed t-test, alpha of 0.05, power 0.80), a sample size of 91 subjects per arm is sufficient to detect an absolute reduction of 6.25%; i.e. relative reduction of 25%. To account for patients lost to follow-up 200 patients will be enrolled.

The secondary endpoints of 3- and 12-month clinical outcomes will be compared by applying a chi-squared or Fisher exact test to a 2x2 table of binary events/group. Similarly, for the secondary endpoints involving imaging or blood samples, an unpaired, two-tailed t-test or Mann-Whitney U test will be used to compare values between the groups.



**Organization/ethical concerns**

The study protocol is approved at each participating center by their local ethics committee and/or internal review board. All investigators will adhere to the principles of the Declaration of Helsinki. An independent data safety and monitoring board (DSMB) will oversee safety and a blinded interim analysis of IS will be performed after 40 patients have been included and thereafter as judged appropriate.

**DISCUSSION**

Despite early revascularization through PPCI in patients with STEMI, large infarctions still occur frequently. Consequently, mortality after STEMI remains high and many patients develop complications such as heart failure [5].

A logical target for therapy beyond PPCI is the attenuation of myocardial reperfusion injury. In contrast to preclinical studies, human trials applying systemic cooling have failed to demonstrate

a decrease in IS, most likely due to an inability to reach the therapeutic target temperature before reperfusion.

SIH overcomes most limitations of systemic cooling. Hypothermia is administered selectively into the infarcted area, with a rapid and sufficient decrease of the myocardial temperature before reperfusion occurs (supplementary appendix).

After having tested this method in a small safety and feasibility pilot study in humans [4], we have designed the EURO-ICE study.

**LIMITATIONS**

Importantly, although the procedure will be prolonged by approximately 20 minutes in the experimental arm, ischemic time will only be prolonged by 7 to 10 minutes. The hypothesized beneficial effects of hypothermia should at least counterbalance the prolongation of the ischemic time.



**CONCLUSIONS**

The EURO-ICE trial is a European multicenter, randomized controlled, proof-of-principle study comparing SIH during PPCI with standard PPCI in 200 patients with anterior wall STEMI.

**IMPACT ON DAILY PRACTICE**

The EURO-ICE trial investigates whether SIH during PPCI decreases IS. If such beneficial effect can be demonstrated, this will translate into a lower risk of complications, such as heart failure and mortality, and will be a next step in PPCI for patients with STEMI.

**FUNDING**

The EURO-ICE trial is an investigator-initiated trial without any commercial purpose or pursuit of profit by the sponsor of the study, CATHREINE BV. The trial is financed by a research grant from Abbott. Their support remains limited to funding only, with no influence on study design, data collection or analysis, or final manuscript publication.

**CONFLICT OF INTEREST STATEMENT**

BDB reports grants from Abbott, Boston Scientific and Biotronik AG and receives consulting fees from Abbott, Opsens, and Boston Scientific, outside the submitted work and has equity of Siemens, GE, Bayer, Philips, HeartFlow, Edwards Life Sciences and Celyad. TE reports personal fees from Bayer, BMS and Abbott, outside the submitted work. CB reports grants from Abbott, Siemens Healthcare and Coroventis, outside the submitted work. NP reports consultancy fees from Abbott and Opsens, institutional grants from Abbott and Hexacath, outside the submitted work and has equity of Philips, ASML, Heartflow and GE Health. All other authors have nothing to disclose.

**Figure 1.** Schematic drawing of the instrumentation for selective intracoronary hypothermia. *OTWB:* over-the-wire balloon catheter; *LAD:* left anterior descending artery (*adapted from reference 4, with permission of the author)*

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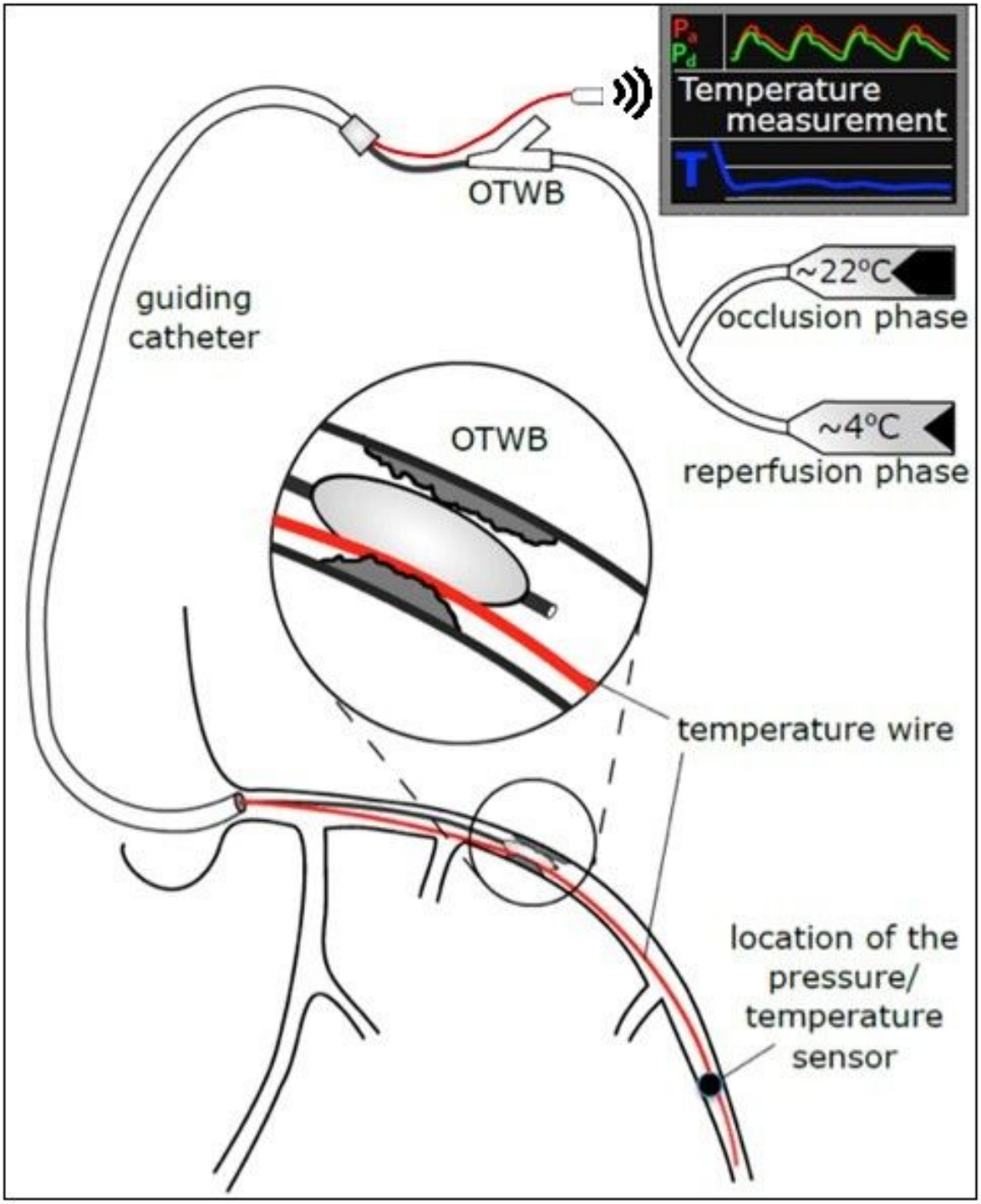
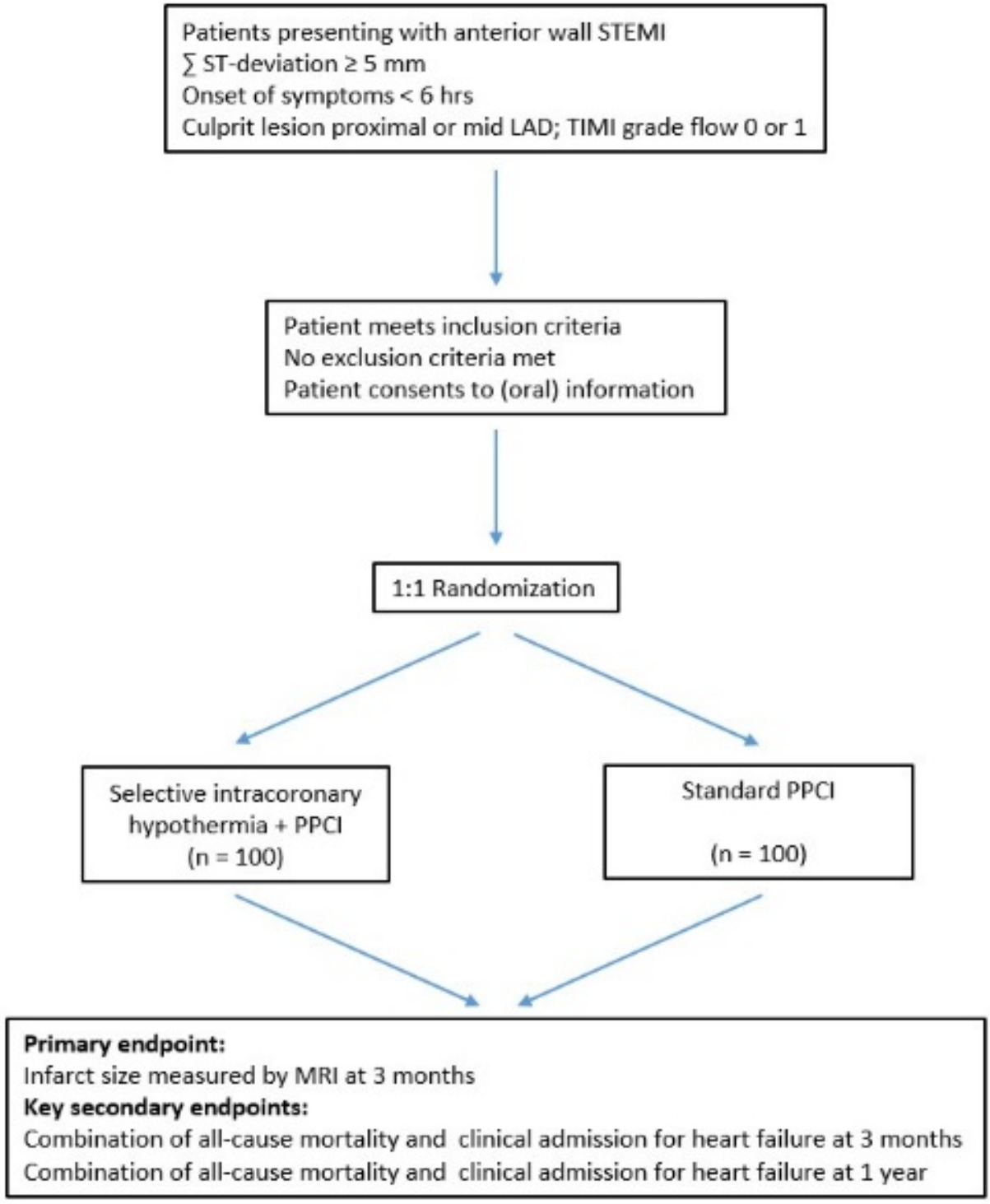

Temperature measurement
OTWB
guiding catheter
~22°C
occlusion phase
~4°C
reperfusion phase
OTWB
temperature wire
location of the pressure/ temperature sensor

**SUPPLEMENTARY APPENDIX EURO-ICE**

Table of Contents

**STUDY FLOWCHART OF THE EURO-ICE TRIAL**




*Supplementary Figure 1. Study flowchart*

## INCLUSION AND EXCLUSION CRITERIA

| **Inclusion criteria** |
|---|
| Age 18-80 years |
| STEMI anterior wall, ∑ ST-deviation ≥ 5mm |
| Onset of symptoms < 6 hours |
| Culprit lesion in proximal (segment 6) or mid (segment 7) LAD artery |
| TIMI grade flow should be 0 or 1 |
| **Exclusion criteria** |
| Age <18 or >80 years |
| Cardiogenic shock or hemodynamic instability |
| Severe conduction disturbances necessitating implantation of a temporary pacemaker |
| 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 1. Inclusion and exclusion criteria*

## ENDPOINTS AND PRESPECIFIED SUBGROUP ANALYSES

### Primary endpoint

The primary endpoint is final Infarct size as a percentage of total left ventricular mass after 3 months, assessed by MRI with late gadolinium enhancement (LGE) 10-15 minutes after contrast administration.

### Secondary endpoints

- Composite of all-cause mortality and hospitalization for heart failure at 3 months
- Composite of all-cause mortality and hospitalization for heart failure at 1 year
- All-cause mortality at 3 months
- All-cause mortality at 1 year
- Implantation of cardioverter defibrillator for primary prevention at 1 year
- Implantation of cardioverter defibrillator for secondary prevention at 1 year
- Implantation of cardioverter defibrillator for both primary and secondary prevention at 1 year
- Hospitalization for heart failure at 3 months
- Hospitalization for heart failure at 1 year
- Cardiac death at 3 months
- Cardiac death at 1 year
- Peak value of high-sensitivity troponin T (hs-TnT) while inpatient
- Peak value of creatine kinase (CK) while inpatient
- Peak value of creatine kinase-MB mass (CK-MB) while inpatient
- N-terminal pro-brain natriuretic peptide (NT-proBNP) at 3 months
- N-terminal pro-brain natriuretic peptide (NT-proBNP) at 1 year
- Left ventricular ejection fraction measured by echocardiography (biplane Simpson's method) at 3 months

- Left ventricular ejection fraction measured by echocardiography (biplane Simpson's method) at 1 year
- Wall motion score index (WMSI) by echocardiography at 3 months
- Wall motion score index (WMSI) by echocardiography at 1 year

### Secondary MRI efficacy endpoints at baseline (5-7 days after the index event)

- Late microvascular obstruction (MVO) extent in percentage of LVmass
- Late MVO (presence / absence)
- Initial infarct size (IS), assessed with LGE, 10-15 minutes after contrast administration
- Initial myocardial salvage index (MSI, area-at-risk minus initial infarct size/area-at-risk, AAR)
- Initial left ventricular end-diastolic volume index (LVEDVI)
- Initial left ventricular end-systolic volume index (LVESVI)
- Initial left ventricular global longitudinal strain (GLS)
- Initial left ventricular circumferential strain (GCS)
- Initial left ventricular ejection fraction (LVEF)
- Systolic wall thickening in the culprit artery territory
- Wall motion score index (WMSI)
- Myocardial hemorrhage (presence/absence)

### Secondary MRI efficacy endpoints at follow-up (3 months after the index event)

- Final infarct size in grams
- Final MSI (AAR-final IS/AAR)
- Change in IS, 3 months after procedure
- Final left ventricular end-diastolic volume index (LVEDVI)
- Final left ventricular end-systolic volume index (LVESVI)

- Final left ventricular ejection fraction (LVEF)
- Final left ventricular global longitudinal strain (GLS)
- Final left ventricular circumferential strain (GCS)
- Change in left ventricular end-diastolic volume index (LVEDVI)
- Change in left ventricular end-systolic volume index (LVESVI)
- Change in left ventricular ejection fraction (LVEF)
- Change in left ventricular global longitudinal strain (GLS)
- Change in left ventricular circumferential strain (GCS)

### Pre-specified subgroup analyses

To exclude for important influence on specific endpoints, a subgroup analysis will be performed. These designated endpoints will be compared without adjustment for other covariates. These subgroups comprise of categorical or continuous data. When these covariates are continuous data, a threshold (median or other) will be used to create a binary variable.



Categorical subgroups

- Diabetes status (yes versus no; 2 categories)
- Gender (male versus female; 2 categories)
- Geographic location (participating sites; categories is number of participating sites)
- History of previous PCI (yes versus no; 2 categories)
- History of previous myocardial infarction (yes versus no; 2 categories)
- Number of diseased vessels (1 versus 2 versus 3; 3 categories)
- Lesion location (proximal versus mid LAD artery; 2 categories)
- TIMI grade flow (0 versus 1; 2 categories)

Continuous subgroups

- Age (binary using median of cohort for threshold)
- Symptom-onset-to-balloon time (binary using median of cohort for threshold)
- Achieved decrease in distal temperature (binary using median of cohort for threshold)
- Previous ejection fraction (binary using ejection fraction of 50% for threshold)

## DEFINITIONS

*All-cause mortality* is defined as all deaths, regardless of the cause of death.

*Hospitalization for heart failure* is defined as an event which requires hospitalization for at least 24 hours in any inpatient unit or ward in the hospital, because the patient has clinical signs of heart failure, including dyspnea, orthopnea and increasing fatigue or signs and/or symptoms of volume overload. Treatment should at least consist of intravenous drug administration, such as diuretics or vasoactive agents.

*Cardiac death* is defined as any sudden death, death related to acute myocardial infarction, arrhythmia or congestive heart failure, death secondary to a cerebrovascular accident, or death directly related to PCI, even if the ultimate cause of death is not clearly a cardiac event (e.g., infection).



## ADVANTAGES OF SELECTIVE INTRACORONARY HYPOTHERMIA VS SYSTEMIC COOLING

Applying selective intracoronary hypothermia overcomes several limitations of systemic cooling. First, hypothermia is directed selectively to the area at risk, which guarantees rapid and sufficient cooling within 100 seconds, hence achieving the target temperature before reperfusion. This point has proven to be crucial in reducing reperfusion injury in previous animal studies. Second, because hypothermia is achieved locally, systemic side effects such as shivering and volume overload are avoided. In addition, we showed that temperature

change is neglectable in the adjacent healthy myocardium. Third, the pressure/temperature wire in the coronary artery allows for continuous monitoring of the distal pressure and precise control and adjustment of the target coronary temperature to enhance the precision and safety of the procedure. Fourth, the intracoronary method requires a coronary angiogram prior to the decision to treat with hypothermia. Therefore, unnecessary cooling is avoided in cases with existing TIMI grade flow 2 or 3, where cooling is not effective anymore. Fifth and final, selective intracoronary hypothermia reaches the infarct area directly. This is in contrast to many negative studies in humans to reduce reperfusion injury in which the protective agents were administered intravenously most of the time and hence not able to reach the target area because of the occlusion in the culprit artery.



**COOL CELL CATHETER**

In the near future, the instrumentation for this procedure will be more practical by use of a dedicated monorail infusion catheter with a balloon at its tip, the so called Cool Cell Catheter (Hexacath, Paris, France). The Cool Cell Catheter is in process of CE-approval presently and will be used in this trial when available.

When using the Cool Cell Catheter, the procedure starts by advancing a pressure/temperature wire across the culprit lesion into the distal LAD artery, after equalizing it in the proximal LCA. Immediately thereafter, the Cool Cell Catheter is advanced over this pressure/temperature wire and the balloon is inflated at the site of the occlusion. Because it is a monorail infusion catheter, the lumen of the Cool Cell Catheter can be used for infusion of saline in the distal LAD artery. The rest of the procedure is the same as described in the article.

## EURO-ICE TRIAL ORGANIZATION, LEADERSHIP, COMMITTEES AND CORE LABORATORY

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*MRI Core Laboratory:* Glasgow Imaging Core Laboratory, Glasgow, United Kingdom. The reviewers of the MRI Core Laboratory are blinded to the randomization code of the patients.

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