# CHILL-MI

## Rapid Endovascular Catheter Core Cooling Combined with Cold Saline as an Adjunct to Percutaneous Coronary Intervention for the Treatment of Acute Myocardial Infarction

**ClinicalTrials.gov number:**
**NCT01379261**


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# Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

| Affiliation/Financial Relationship | Company |
| --- | --- |
| • Speaker´s Honoraria | • Philips, ZOLL |

# Insights from animal studies

Hypothermia:

- Inhibits necrosis of cardiomyocytes and apoptotic cell death[1]
- Protects the myocardium through a reduction in metabolism[1]

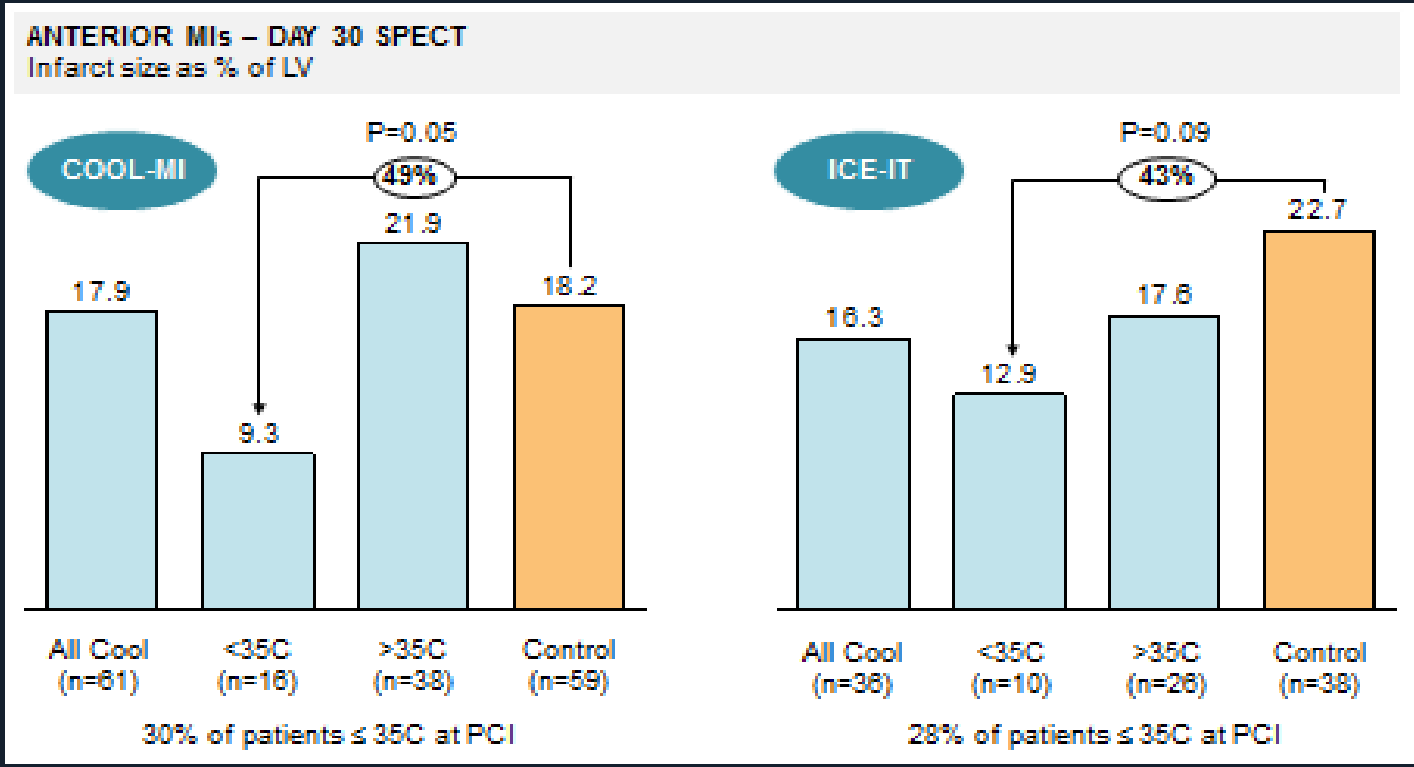
- Protects during ischemia[2]
- Reduces reperfusion injury[3]
- Has minimal effect when initiated after reperfusion[3]
- Improves survival in cardiogenic shock[4]

[1]Verma et al. *Circulation, 2002;* Tissier et al. *Cardiovascular Research*, 2010
[2] Duncker et al. *Am J Physiol*, 1996, Dae et al. *Am J Physiol*, 2002, Götberg et al . *BMC CV Disord*. 2008
[3] Götberg et al . *Basic Research in Cardiology*, 2011
[4] Götberg et al,. *Rescusitation*, 2010

# Early clinical trials

## COOL-MI [1]

## ICE-IT [2]




- **Primary endpoints not achieved in the studies**
- **Only 1/3 of the patients reached ≤35˚ C at the time of reperfusion.**
- **In anterior STEMI patients cooled to ≤35ºC before reperfusion, a trend for reduction in infarct size was observed in both trials**



1 O'Neill, *TCT 2003*
2 Grines, *TCT 2004*

# Combination Hypothermia for Rapid Cooling

- Pressurized cold saline (4ºC) IV infusion to ”kick start” cooling
- Endovascular cooling catheter with temperature sensor placed in vena cava

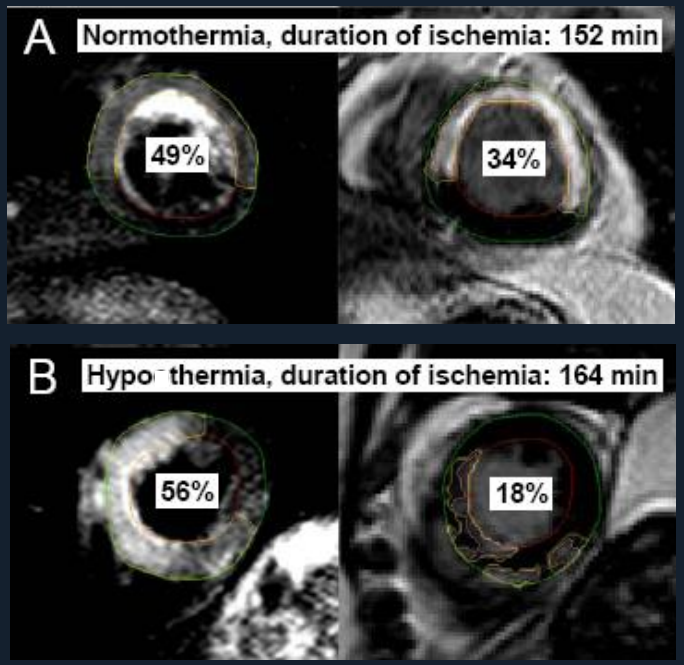

**Anterior: 10 mL/kg**
**Inferior: 20 mL/kg**


**InnerCool RTx Endovascular Cooling System (Philips Healthcare)**

# RAPID MI-ICE Pilot Study

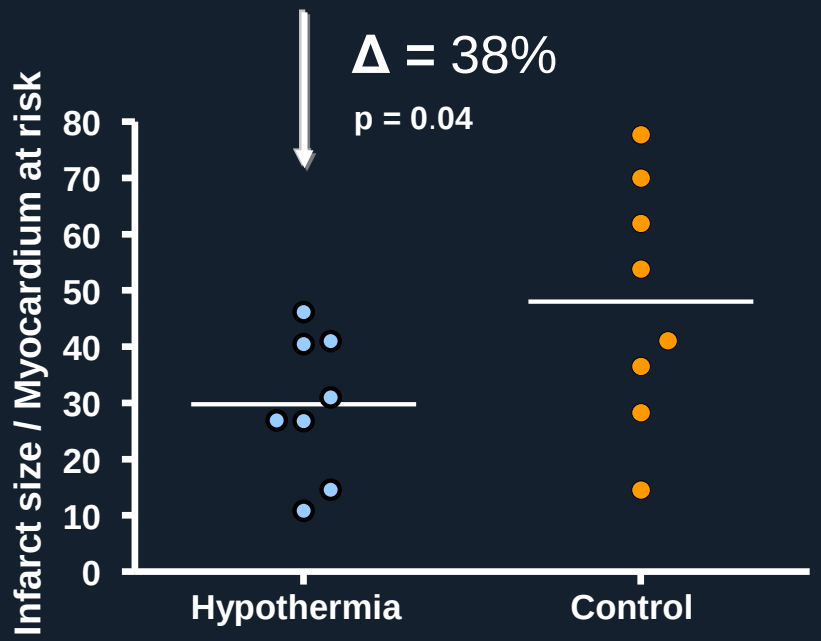
**Infarct size (IS)/Myocardium at Risk (MaR) measured with cardiac MRI was reduced by cold saline and endovascular cooling**

## MRI




MaR IS

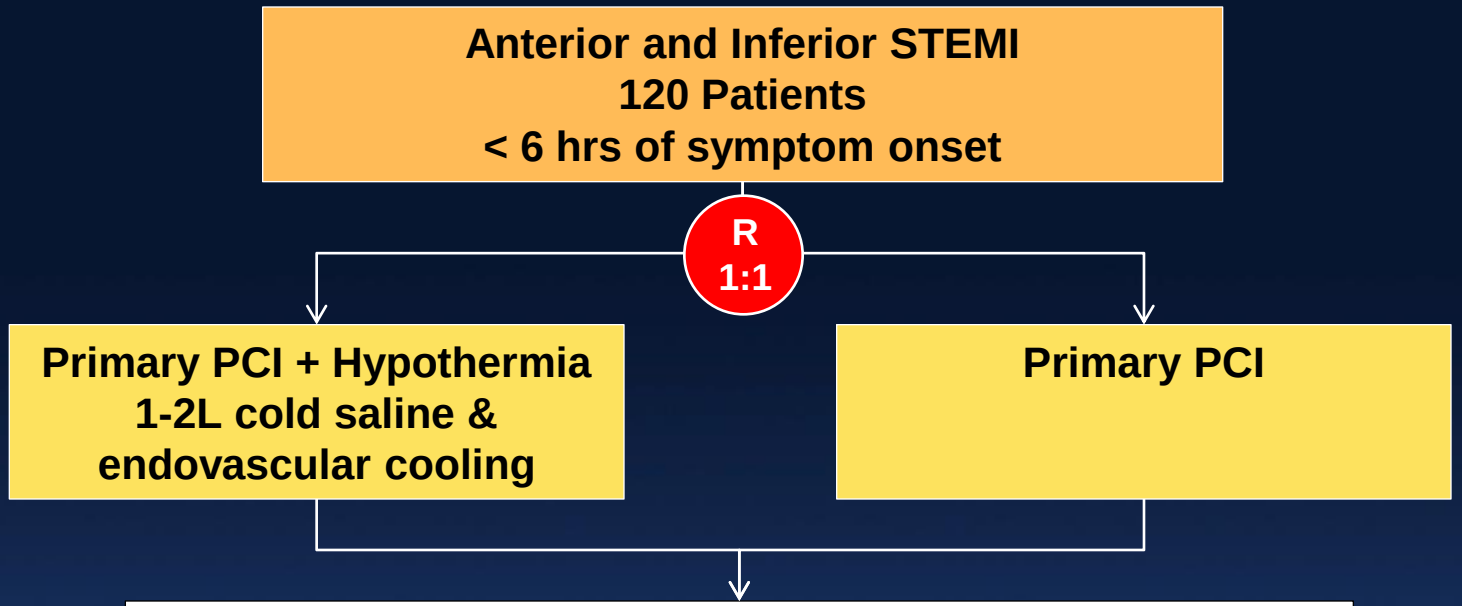
## IS/ MaR






Götberg et al. *Circulation Cardiovascular Interventions*, 2010

# CHILL-MI: Study Design




**Primary Endpoint:**

Infarct size/myocardium at risk (IS/MaR)
assessed by cardiac MRI at 4±2 days

**Key Secondary Endpoints:**

IS/MaR in patients with anterior and inferior infarctions
IS/MaR assessed by cardiac MRI at 6 months
Death & Heart Failure within 45 days

**Safety Endpoints:**

Incidence of heart failure, pulmonary edema, infections and bleeding
(TIMI definition) within 45 days

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# CHILL-MI: Study organisation

**Co-Principal Investigators:**

- David Erlinge, Lund, Sweden
- Göran Olivecrona, Lund, Sweden

**Sponsor:**

- Philips

**ARO and CEC:**

- Uppsala Clinical Research Center (UCR), Sweden

**MRI core-lab:**

- Imacor, Lund, Sweden

**DSMB (chairman):**

- Dan Atar, Oslo, Norway

**Participating sites:**

- Lund, Sweden, *Coordinating*
- Vienna, Austria
  PI: Irene Lang & Michael Holzer
- Uppsala, Sweden
  PI: Stefan James
- Stockholm, Sweden
  PI: Ulf Jensen
- Gothenburg, Sweden
  PI: Elmir Omerovic
- Copenhagen, Denmark
  PI: Peter Clemmensen
- Aarhus, Denmark
  PI: Hans Erik Bötker
- Innsbruck, Austria
  PI: Bernhard Metzler
- Ljubljana, Slovenia
  PI: Marko Noc

# CHILL-MI: Power Analysis

- Based on a mean infarct size as percent of myocardium at risk in the control group of 48% and a standard deviation in both groups of 17.7 % (based on RAPID MI-ICE pilot), 72 evaluable patients would give 80% power to detect a 25% relative reduction (RR) in the hypothermia group, using a 2-sided test at the 5% significance level.

- To account for uncertainty in variability and dropout rate, a sample size of 120 patients was chosen, estimated to give 90% power after 20% dropout.

# Key Inclusion/Exclusion criteria

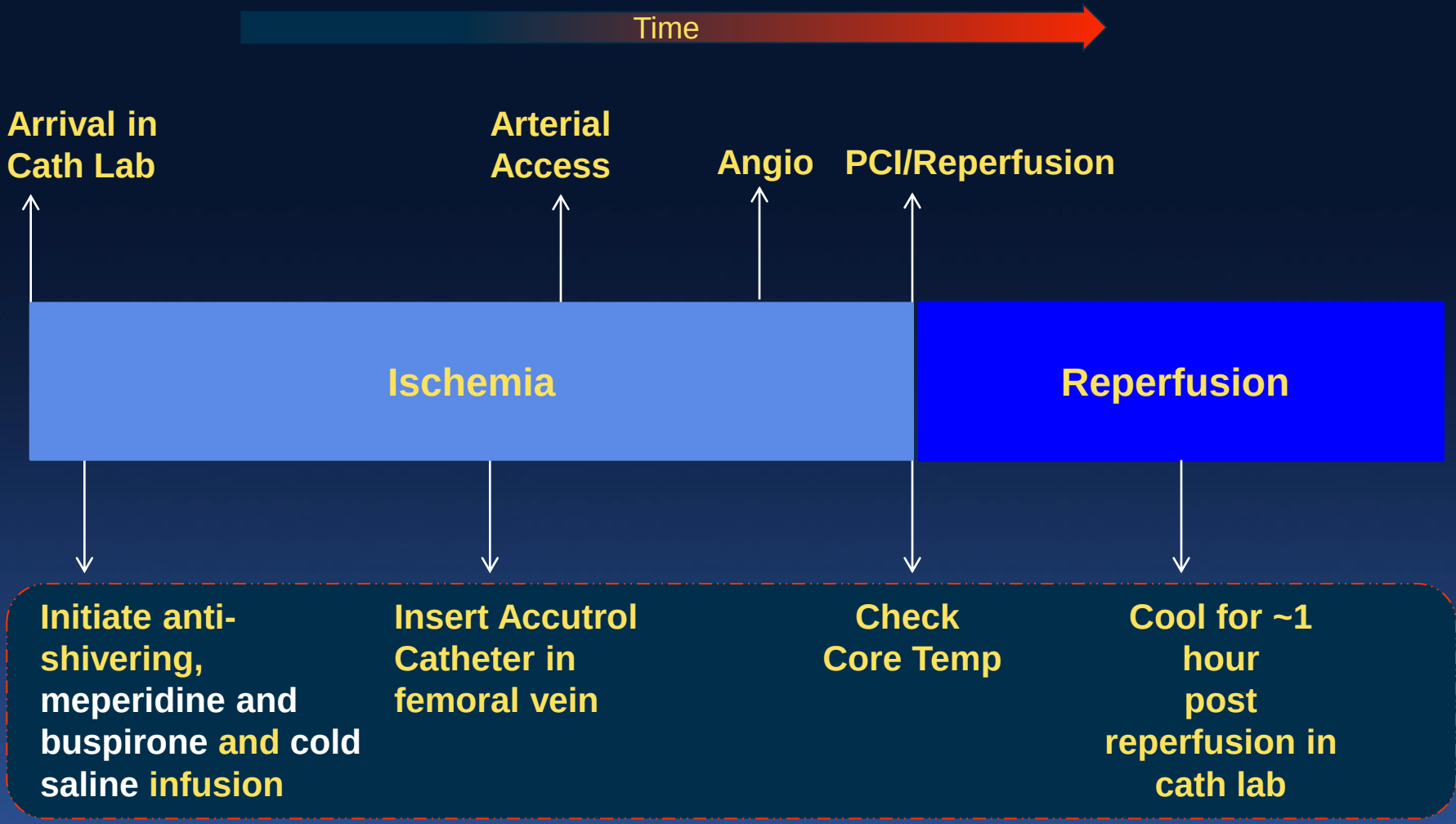
*Key Inclusion criteria:*

- Anterior or large inferior STEMI with ST-segment elevation in two contiguous leads and a duration of symptoms of < 6h

*Key exclusion criteria:*

- Patients with cardiac arrest,
- Previous AMI
- Previous PCI or CABG
- Known congestive heart failure
- End stage kidney disease or hepatic failure
- Killip class II-IV

# CHILL-MI: Cath Lab Work Flow



# CHILL-MI: Demographics

| Variable | Hypothermia (n=61) | Control (n=59) |
|---|---|---|
| Age | 57(37-79) | 59 (30-75) |
| Women | 13 (21%) | 8 (14%) |
| Hypertension | 17 (28%) | 7 (12%) |
| Diabetes | 8 (13%) | 3 (5%) |
| Hyperlipidemia | 10 (16%) | 1 (2%) |
| Current smoker | 28 (46%) | 23 (39%) |
| BMI ($kg/m^2$) | 28.4 ± 4.9 | 27.0 ± 3.3 |
| Anterior STEMI | 23 (38%) | 28 (48%) |
| Inferior STEMI | 38 (62%) | 30 (52%) |

p-values not significant for any variable

# CHILL-MI: Medication & Procedures

| Variable | Hypothermia (n=61) | Control (n=59) |
|---|---|---|
| Initial TIMI flow 0/1 | 54 (89%) | 48 (81%) |
| Initial TIMI flow 2/3 | 7 (11%) | 11 (19%) |
| TIMI 3 flow post PCI | 57 (93%) | 53 (90%) |
| Thrombectomy | 35 (59%) | 41 (69%) |
| GpIIb/IIIa | 14 (23%) | 22 (34%) |
| Bivalirudin | 35 (57%) | 31 (52%) |
| Ticagrelor/Prasugrel | 54 (89%) | 67 (84%) |
| Aspirin | 61 (100%) | 59 (100%) |
| Buspirone 30 mg | 44 (71%) | 0 |
| Meperidine/Pethidine | 114 ± 67 mg | 0 |
| DES | 44 (75%) | 50 (86%) |

p-values not significant for any variable

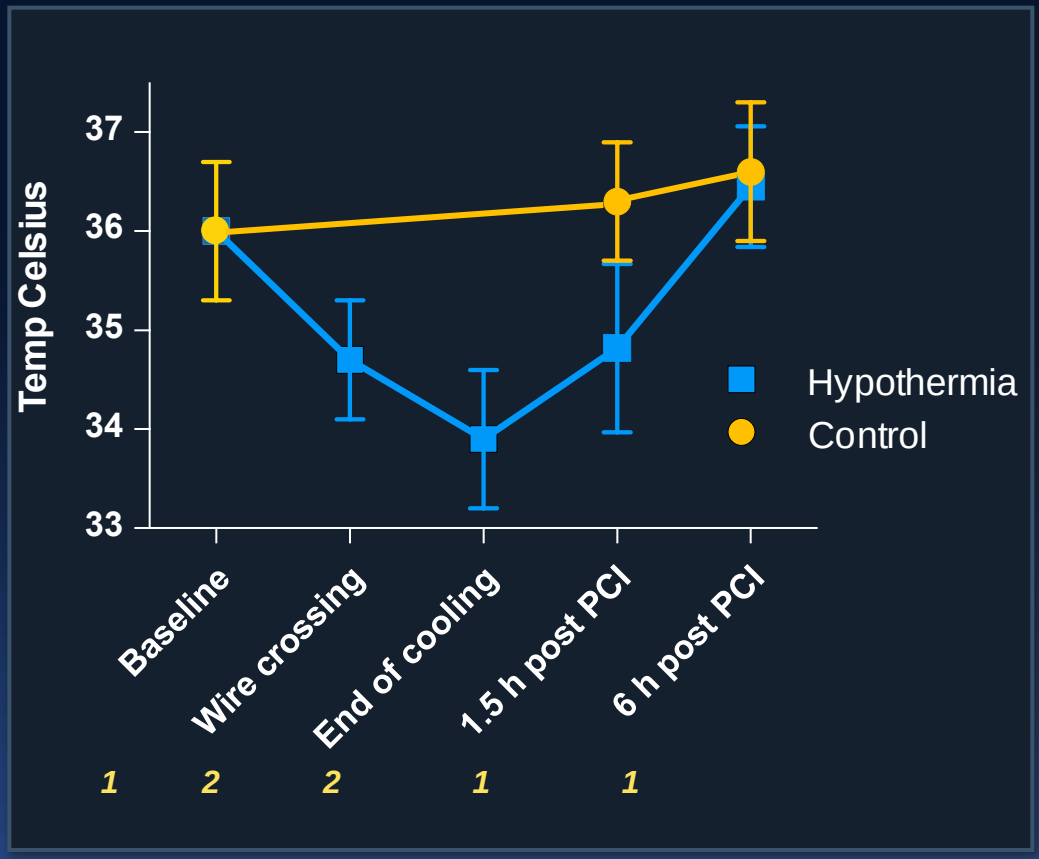
# CHILL-MI: Cooling Performance

- Mean core temp at reperfusion: 34.7°C
- Mean catheter cooling rate: 6 C°/hr

- Patients ≤35.0 C at reperfusion: 77%
- Patients ≤35.4 C at reperfusion: 92%

- Symptom to randomization
  - Hypothermia 132 (±64)
  - Control 129 (±56)

- Randomization to balloon
  - Hypothermia 42 min
  - Control 33 min
  - Increase 9 min




1 tympanic temp.
2 catheter temp.

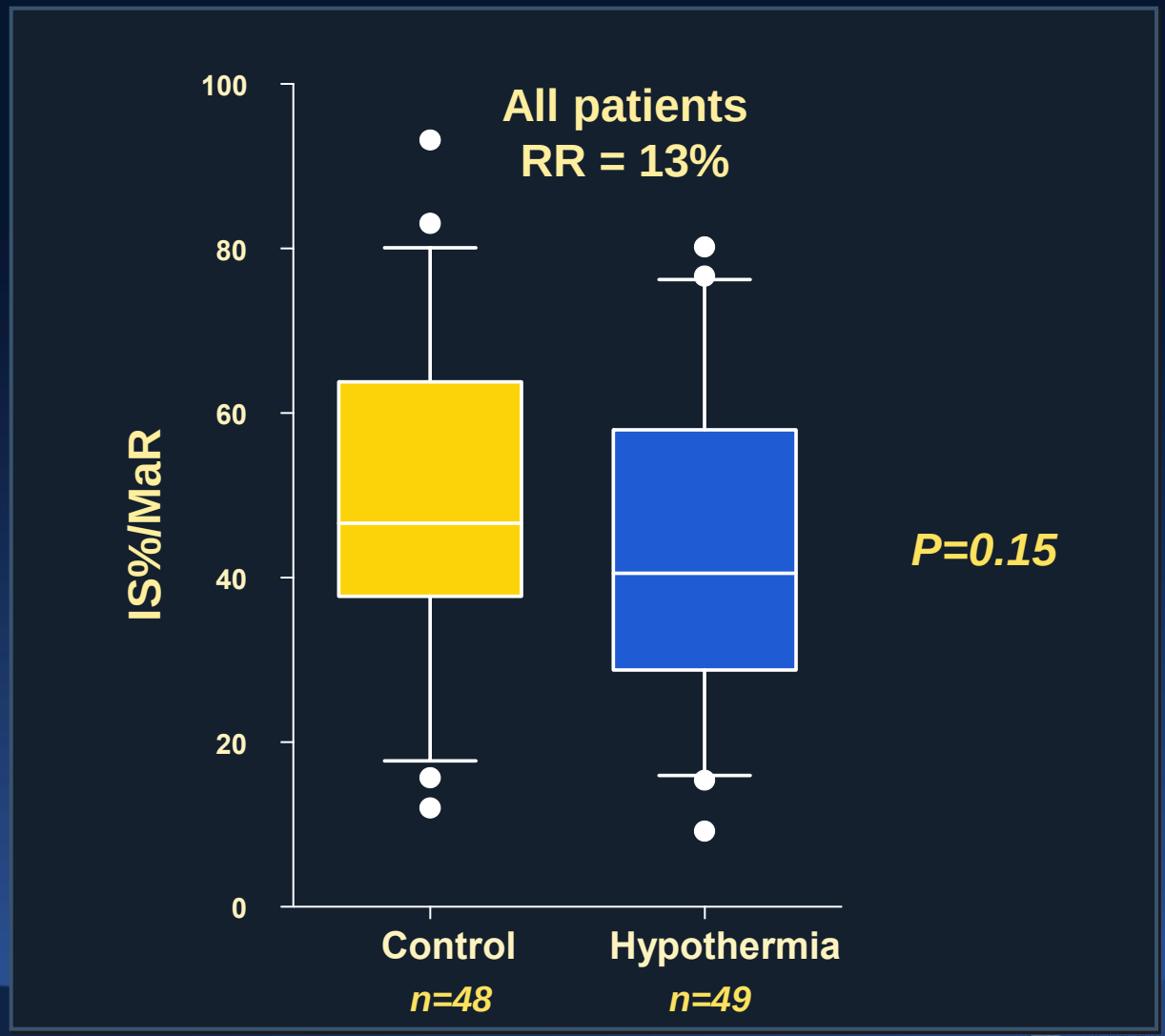
# CHILL-MI: Cardiac MRI

- MRI was evaluated at core lab in evaluator blinded fashion
- Area at risk (AAR) was similar between groups
- MRI was performed at day 4±2 in 81% of patients
- MRI drop out similar between groups

| Reason for no MRI-result at day 4±2 | |
|---|---|
| Claustrophobia | 6 |
| Patient not willing | 6 |
| MRI not available/Technical quality unsatisfactory | 6 |
| MRI aborted on patients decision (e.g. lumbago) | 3 |
| Incorrectly randomised | 1 |
| Costa fracture after CPR | 1 |

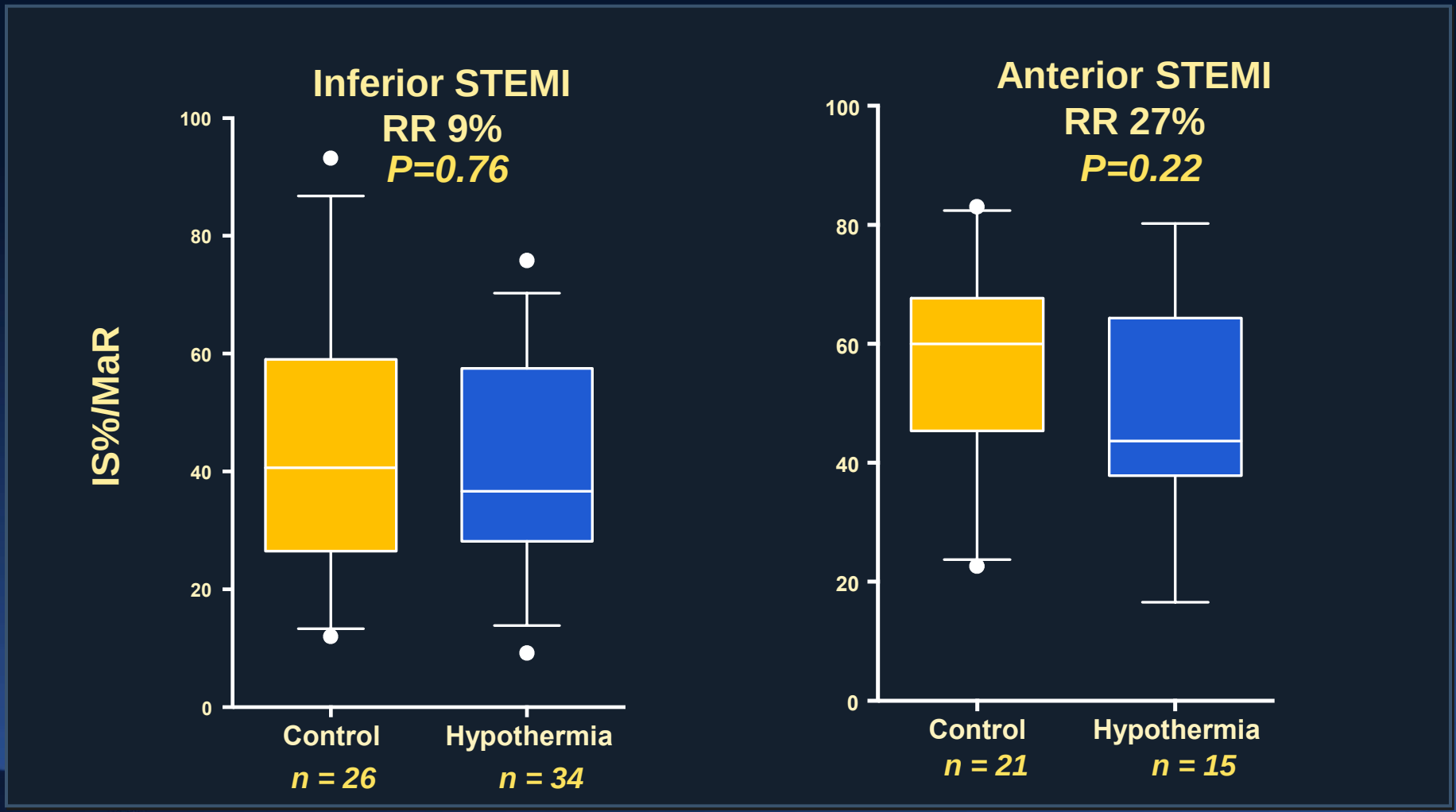
# CHILL-MI: Primary endpoint

Infarct Size/Myocardium at Risk at 4±2 days



# CHILL-MI: Secondary endpoint

Infarct size by location at 4±2 days

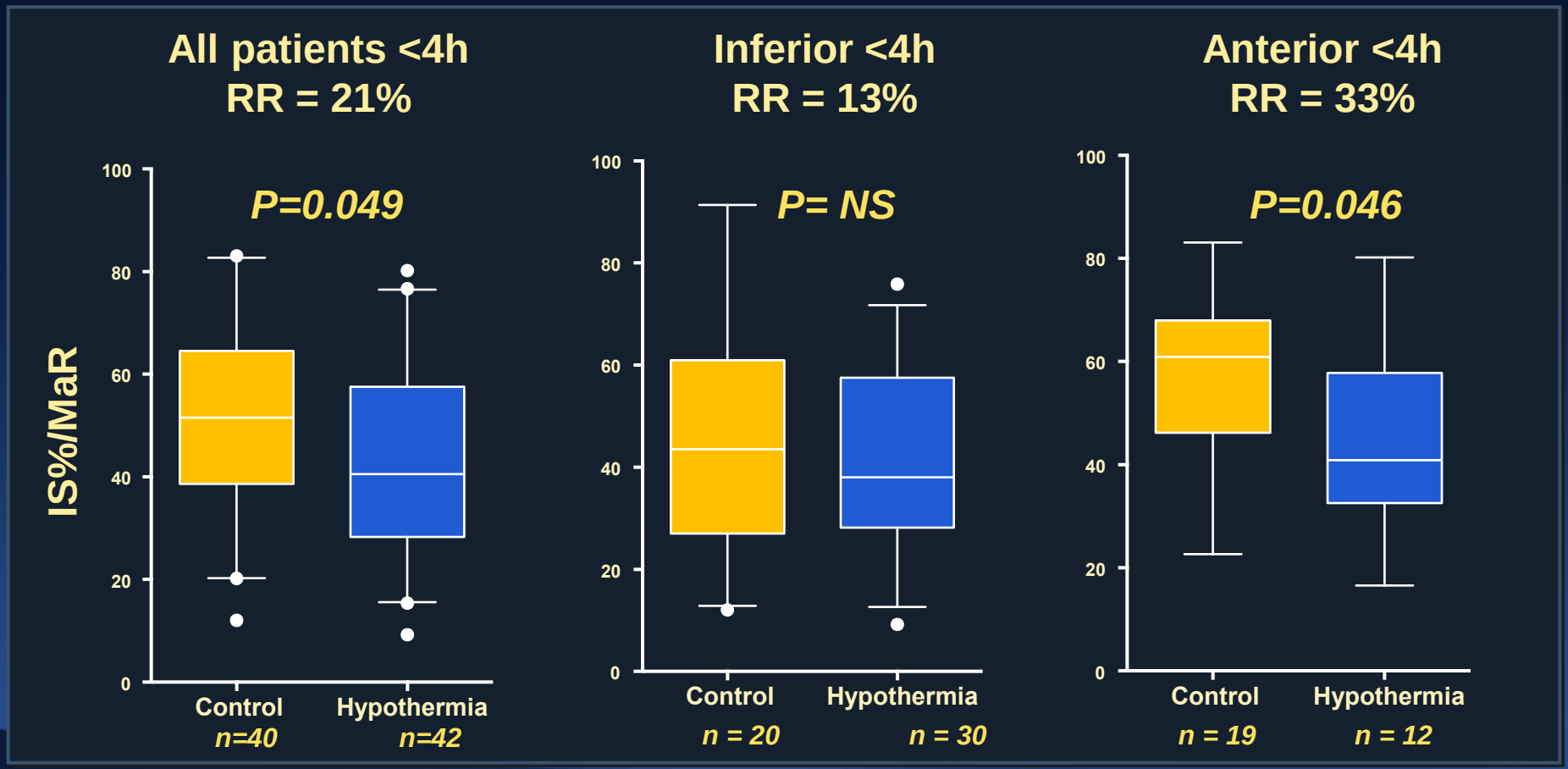



Median (IQR)

# CHILL-MI: Infarct size by location

## Symptom onset to PCI of 0-4 hrs

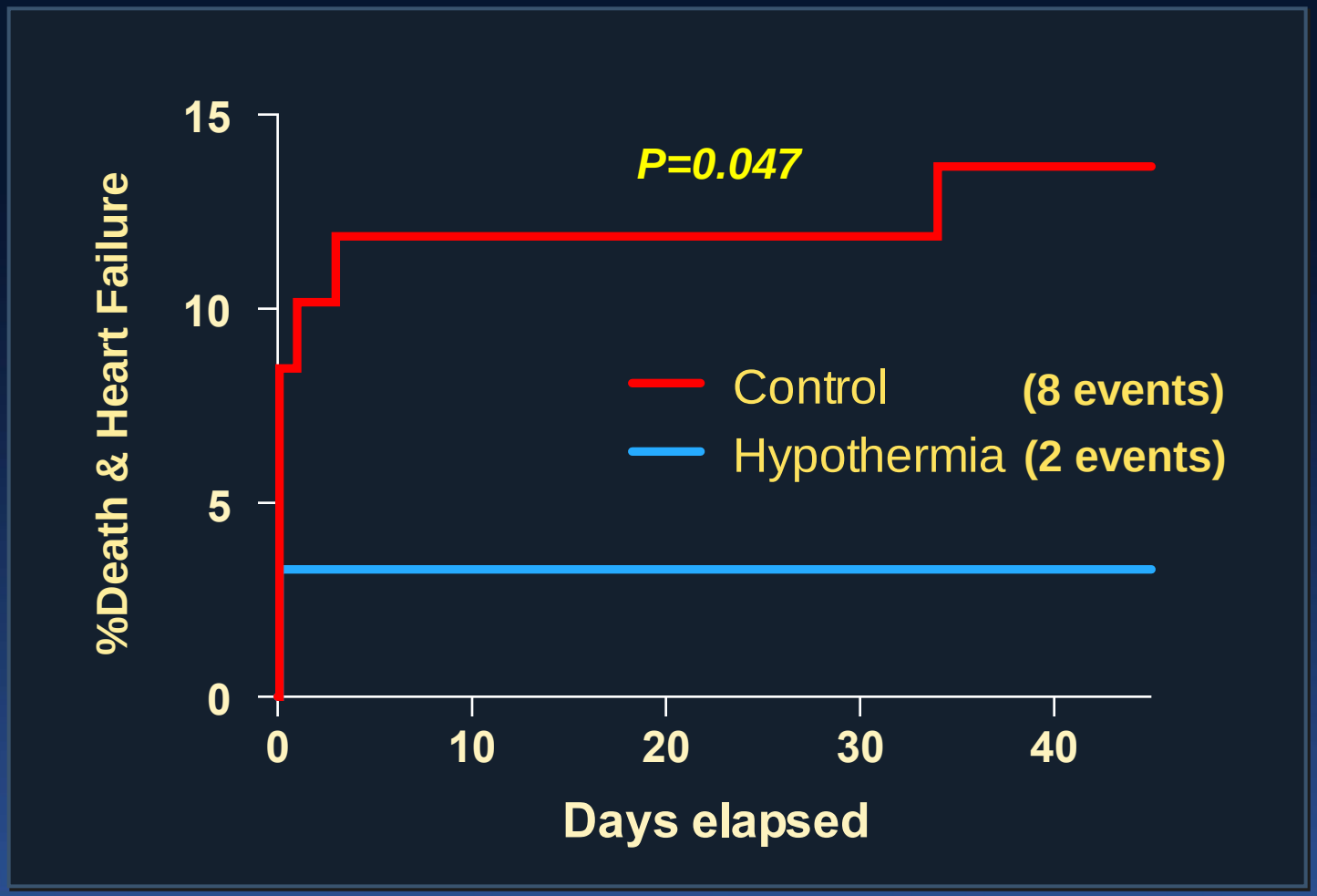
### *Exploratory analysis*




Median (IQR)

# CHILL-MI: Adjudicated Death & Heart failure

## Main Clinical endpoint




No mortality; HF in anterior patients only

# CHILL-MI: Clinical events

| Variable at 45 days | Hypothermia (n=61) | Control (n=59) |
|---|---|---|
| Mortality | 0 | 0 |
| Heart failure | 2 (3%)* | 8 (14%) |
| Re-infarction | 1 (2%) | 0 (0%) |
| VT/VF | 5 (8%) | 2 (3%) |
| Atrial fibrillation/flutter | 4 (6%) | 4 (7%) |
| Stroke | 0 | 0 |
| Pneumonia | 3 (5%) | 1 (2%) |
| Pulmonary edema | 1 (2%) | 2 (3%) |
| Major bleeding | 0 (0%) | 1 (2%) |
| Bradycardia | 2 (3%) | 1 (2%) |

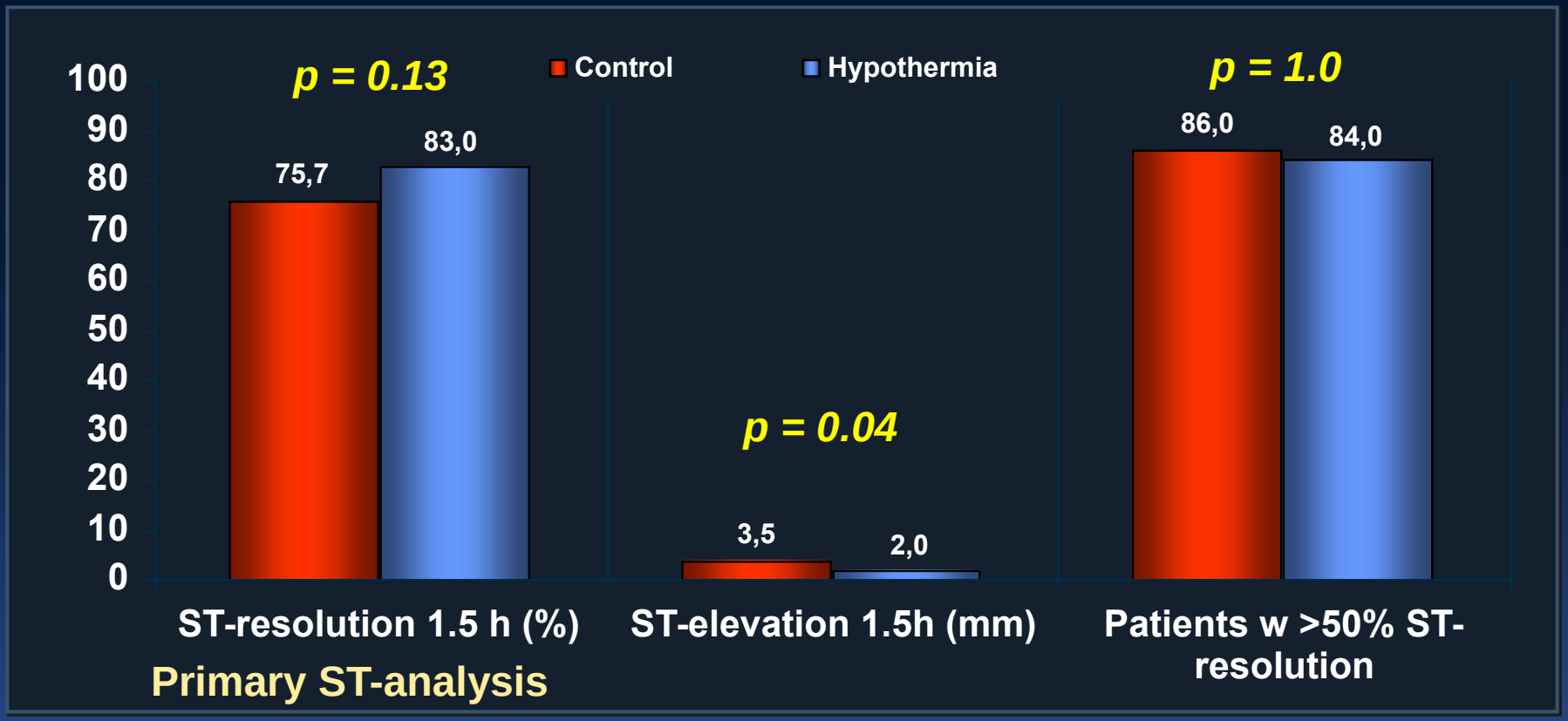
* $p < 0.05$, for other comparisons p = NS

# CHILL-MI: Additional Results

| Outcome | Hypothermia | Control | P-value |
|---|---|---|---|
| Microvascular obstruction size at 4±2 days (% of LV), Median (IQR) | 0.26 (0; 9.35) | 0.12 (0, 5.25) | 0.79 |
| Left ventricular ejection fraction at 4±2 days (%), Median (IQR) | 48 (42; 53) | 51 (43; 56) | 0.39 |
| Hs-Troponin-T, 48 hour AUC (arbitrary unit), mean (%CV) | 137626 (158) | 137468 (123) | 0.96 |
| CKMB, 48 hour AUC (arbitrary unit), mean (%CV) | 4281 (107) | 3877 (99) | 0.59 |
| NT-proBNP at 4±2 days (ng/L), mean (%CV) | 834.2 (115) | 637.9 (153) | 0.21 |

# CHILL-MI: ST-resolution

## *1.5 h post PCI*



# CHILL-MI: Conclusions

- Did not achieve primary endpoint of IS/MaR in total study population (RR 13%)
- Exploratory analysis indicates reduced IS/MaR in early, anterior hypothermia patients (RR 33%)
- Heart failure events were reduced in hypothermia group
- Patients were rapidly cooled to ≤35˚ C prior to PCI with minimal increase in door-to-balloon time
- Protocol was safe, easy to administer and well tolerated by patients
- Current findings in conjunction with the strategy of recently published studies, support a future RCT focused on early (0-4 hr), anterior STEMI patients [1,2]



*1* Stone et al. *JAMA,* 2012, "Infuse AMI"
*2* Chakrabarti et al. *Am. Heart Journal,* 2013, "Embrace STEMI"