**A multicentre, prospective, randomized controlled trial to assess the safety and effectiveness of cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction: the COOL AMI EU Pivotal Trial**

**Short title:** COOL AMI EU Pivotal Trial

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**Abstract**

Background: Despite primary PCI (PPCI), STEMI can still result in large infarct size (IS). New technology with rapid intravascular cooling showed positive signal for reduction in IS in anterior STEMI.

Aims: We investigated the effectiveness and safety of rapid systemic intravascular hypothermia as an adjunct to primary PCI (PPCI) in conscious patients with anterior ST-elevation myocardial infarction (STEMI) without cardiac arrest.

Methods: Hypothermia was induced using ZOLL® Proteus™ Intravascular Cooling System. After randomization of 111 patients, 58 to hypothermia and 53 to control groups, the study was prematurely discontinued by the sponsor due to inconsistent patient logistics between the groups resulting in significantly longer total ischemic delay in hypothermia group (232 vs 188 minutes; p <0.001).

Results: There were no differences in angiographic features and PPCI result between the groups. Intravascular temperature at wire crossing was 33.3+0.9°C. Infarct size/left ventricular mass (IS/LV) by cardiac magnetic resonance (CMR) at day 4-6 was 21.3% in hypothermia group and 20.0% in control group (p=0.540). Major adverse cardiac events (MACE) at 30 days were non significantly increased in hypothermia group (8.6% vs 1.9%; p=0.117) while cardiogenic shock (10.3% vs 0%; p=0.028) and paroxysmal atrial fibrillation (43.1% vs 3.8%; p<0.001) were significantly more frequent in hypothermia group.

Conclusion: Intravascular ZOLL TM Proteus Cooling System reduced temperature to 33.3oC before PPCI in patients with anterior STEMI. Due to inconsistent patient logistics between the groups, this hypothermia protocol resulted in longer ischemic delay, did not reduce IS/LV mass and was associated with increased adverse events.

**Keywords:** STEMI, Femoral, Other technique

**Condensed abstract**

Intravascular ZOLL TM Proteus Cooling System reduced temperature to 33.3oC before PPCI in patients with anterior STEMI. Due to inconsistent patient logistics between the groups, this hypothermia protocol resulted in longer symptom onset to balloon delay (232 vs 188 minutes; p <0.001), did not reduce IS/LV mass at day 4-6 (21.3% vs 20.0%; p=0.540) and was associated with increased adverse events.

**Abbreviations**

BSAS=Bedside shivering assessment scale

CE-SSFP= contrast-enhanced steady state free precession

CMR=Cardiac magnetic resonance imaging

DMC=Data monitoring committee

EF=Ejection fraction

IS=Infarct size

LV=Left ventricle

LGE=Late gadolinium enhancement

MACE=Major adverse cardiac events

NSAE =Non-serious adverse event

PPCI=Primary percutaneous coronary intervention

STEMI=ST-elevation myocardial infarction

SAE= serious adverse event

**Introduction**

Experimental studies in different animal species have consistently shown that mild hypothermia, induced prior to reperfusion of acute coronary occlusion, reduces infarct size (IS) (1-6). Cooling before reperfusion therefore appeared as a promising adjunct to primary percutaneous coronary intervention (PPCI) in ST-elevation myocardial infarction (STEMI) (7-8). Several randomized clinical trials (7-11) showed mixed results although intravascular cooling appeared to be safe and well tolerated. Subsequent combined analysis of RAPID MI-ICE and CHILL MI (12) revealed significant reduction in IS in a subgroup of early presenters with anterior STEMI who were cooled below 35 °C prior to reperfusion. A similar favourable signal was also observed in COOL AMI Pilot randomized trial, which enrolled 50 patients with anterior STEMI (13). With up to 1000 ml of intravenous infusion of cold saline and ZOLL® Proteus™ Intravascular Cooling System, patients were safely cooled to 33.6°C at the time of coronary guidewire crossing which resulted in numerical reduction in IS from 23.8% to 16.7% (p=0.31). We therefore performed the COOL AMI EU Pivotal trial powered to demonstrate a clinically meaningful reduction in IS using rapid intravascular systemic hypothermia prior to PPCI compared to standard treatment with PPCI only.

**Methods**

COOL AMI EU Pivotal trial **(NCT03173313)** was a multicentre, prospective, interventional, randomized controlled two-arm pivotal trial performed at 24 sites in 11 countries. Each center had to perform up to 4 successful roll-in patients before starting to randomize. All procedures were in accordance with the Declaration of Helsinki and the local /national ethics committees approved the study protocol. All patients gave written informed consent prior to inclusion in the study. An independent Clinical Event Committee (Icahn School of Medicine at Mount Sinai, New York, USA) adjudicated major adverse cardiac events (MACE). An independent Data Monitoring Committee (DMC), consisting of three physicians and one statistician independent of the trial sponsor and operational leadership, monitored the safety of the study based on access to unblinded data. An Advisory board comprised of the study principal investigator and the most experienced study investigators.

The study enrolled conscious patients >18 years of age with < 4.5 hours duration of symptoms presenting with an anterior STEMI with persistent ST-segment elevation of > 0.2mV in two contiguous leads. Patients with resuscitated cardiac arrest, previous acute myocardial infarction, PCI or coronary artery bypass grafting, Killip class II-IV, atrial fibrillation, end stage kidney disease, hepatic failure, recent stroke, coagulopathy and pregnancy were excluded. Eligible patients were randomized 1:1 using a computer-generated system to hypothermia (hypothermia + PPCI + standard care) or to control (PPCI + standard care) groups. All patients received acetylsalicylic acid, heparin and a P2Y12 inhibitor. Glycoprotein IIb/IIIa inhibitors were administered at the discretion of the treating physician.

Patients assigned to hypothermia initially received 60 mg of oral Buspirone and Pethidine (Meperidine) as an intravenous loading dose of 1 mg/kg (maximum 100 mg) or 0.5 mg/kg if the patient had already received morphine. After 15 minutes, an additional dose of 0.5 mg/kg Pethidine was given and continued as infusion at 25mg/hour (<80 kg body weight) or 35 mg/hour (>80 kg body weight) for the duration of the device deployment. Patients were placed on Bair Hugger® which covered catheterization table for skin counter-warming. Continuous verbal contact with the patient was maintained. Respiratory rate and pulse oximetry were monitored with targets of >10 breaths/minute and arterial oxygen saturation of >90%. Hypothermia was initiated with a forced intravenous infusion of up to 1L of cold saline (4°C) using pressure bags and continued by intravascular cooling with the ZOLL® Proteus™ Cooling System **(Figure 1).** Cooling catheter was inserted via femoral vein into the inferior vena cava with the tip positioned at the level of the diaphragm. Proteus temperature probe was put through the catheter lumen into the right atrium for continuous measurement of blood temperature. Console temperature was set to 32.0°C and cooling at maximum power started. An interval of 18 minutes of endovascular cooling from catheter activation to coronary guidewire passing across the acute occlusion was advised. Following placement and activation of the cooling catheter, arterial puncture, coronary angiography, administration of anticoagulation/antiplatelet therapy and PPCI were performed. Cooling was maintained up to 3 hours followed by active rewarming at the rate of 1.0 °C / hour to attain 36.0 °C. The catheter was then removed.

Shivering was continuously assessed by bedside shivering assessment scale (BSAS) with following categories:

0 - No shivering on palpation of the masseter, neck or chest wall

1 - Shivering localized to the neck and/or thorax only

2 - Shivering with gross movement of the neck, thorax and upper extremities

3 - Shivering involves gross movements of the trunk, upper and lower extremities

If BSAS was >2, additional boluses of pethidine (25 mg) were used and infusion increased to a maximum of 35 mg/hour. If shivering persisted, device target temperature was stepwise raised by 0.5°C until shivering disappeared.

After 4-6 days, patients underwent cardiac magnetic resonance imaging (CMR) in the supine position. After initial scout images to locate the heart and the standard imaging planes, 0.2 mmol/kg of body weight of an extracellular gadolinium-based contrast agent was administered. For evaluation of left ventricular (LV) function, early contrast-enhanced steady state free precession (CE-SSFP) cine images were obtained approximately 5 minutes after contrast injection (slice thickness 8 mm with no slice gap, temporal resolution 20 to 30 frames per cardiac cycle, in-plane resolution 1.5 mm x 1.5 mm). For infarct visualisation, late gadolinium enhancement (LGE) images were acquired 15-20 minutes after administration of the contrast agent using an inversion-recovery gradient-echo sequence (slice thickness 8 mm with no slice gap, in-plane resolution 1.5 mm x 1.5 mm). Inversion time was manually adjusted to null the signal from viable myocardium, typically 200-300 milliseconds. Cine and LGE images were acquired in the short-axis view, from base to apex, and in the three standard long-axis views (two-chamber, four-chamber and left ventricular outflow tract views). Analyses of CMR images were performed by an independent core lab (Imacor AB, Lund, Sweden) using post-processing software (Segment EWA) (14). IS divided by LV mass (IS/LV mass) and LV ejection fraction EF) were measured. Microvascular obstruction was quantified from LGE images using EWA algorithm with manual adjustments when needed and expressed as percentage of LV mass (14). For visualization of the area at risk, early contrast-enhanced steady state free precession cine images were obtained approximately 5 minutes after contrast injection as previously described (15).

The trial was considered to have met the primary effectiveness endpoint if the hypothermia arm demonstrated a statistically significant reduction in IS/LV mass (IS/LV%) measured by CMR on day 4-6 compared to the control arm. The primary safety endpoint was a non-inferiority comparison with a 6% non inferiority margin of MACE at day 30 day defined as cardiac death, myocardial reinfarction and clinically-driven target lesion revascularization. Additional secondary safety endpoints included stent thrombosis, cardiogenic shock, pulmonary oedema, arrhythmias, deep venous thrombosis, pulmonary embolism, vascular complications requiring intervention and infections. Adverse events were collected and described as serious adverse event (SAE) and non-serious adverse event (NSAE) based on hospital charts reviewed by independent monitors.

Based on assumed standard deviation of 12% and two-sided alpha of 0.044, the required total sample size to detect 20% relative reduction in IS/LV% with 80% power was 384 subjects. Because of expected drop out of 24% due to missing CMR data, the planned total sample size was increased to 500 patients (250 patients per group).

Continuous data were reported as mean +/- standard deviation or median with interquartile ranges. Categorical data were shown as frequencies and proportions. For continuous variables, Wilcoxon rank-sum and t-test were used for comparison between the two treatment groups as appropriate. For comparison of categorical variables, Fisher’s exact test or Chi-square test were used. No imputation was done for missing data. The data are presented as intention-to-treat except for primary effectiveness endpoint for which also per-protocol analysis was performed. The p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

**Results**

From April 2016 to August 2018, among 1815 screened patients, 166 fulfilled inclusion criteria. Fifty-five patients were included into the roll-in group and 111 patients were randomized to either hypothermia (n=58) or control (n=53) groups. Follow up was 98% and 100% at 4-6 days and 90% and 96% at 30 days in hypothermia and control groups, respectively. On August 18, 2018 the trial was prematurely discontinued by the sponsor with support of the DMC due to operational issues related to different patient pathways through the hospital between the hypothermia and control arms resulting in significant difference in ischemic delay to reperfusion.

Hypothermia and control groups were comparable in terms of age, gender, body mass index and risk factors for coronary disease **(Table 1).** Mean delay from symptom onset to the balloon was 232 minutes in the hypothermia group and 188 minutes in the control group (p<0.001). Observed increase in total ischemic time in hypothermia group was caused by both, numerically increased delay from symptoms onset to randomization (175 minutes versus 157 minutes; p=0.125) and significantly longer delay from randomization to balloon (61 minutes versus 32 minutes; p<0.001). There were no differences in angiographic features, primary PCI result and periprocedural medication between the groups.

Among 58 patients randomized to hypothermia, 55 were cooled (95%). Anti-shivering medication administered before and during the cooling included Buspirone and Pethidine **(Table 2)**. Mean total volume of infused cold saline was 1028 ml and interval between cooling catheter activation and coronary guidewire crossing was 20 minutes. At this point, mean intravascular temperature reached 33.3°C. Uncontrolled shivering was documented in 12 patients (20.7%).

As shown in **Table 3**, mean IS/LV% by CMR at day 4-6 was comparable between hypothermia and control groups using intention-to-treat (21.3% vs 20.0%; p=0.540) and per-protocol analyses (21.6% vs 20.9%; p=0.680) **(Figure 2)**. Additional CMR measurements including IS/Area at risk (46.9% vs 42.8%; p=0.356), myocardial salvage index (0.5 vs 0.6; p=0.356), microvascular obstruction (3.3% vs 3.0%; p=0.598) and left ventricular ejection fraction (41% vs 43%; p=0.592) were also comparable between hypothermia and control groups.

MACE at 30 days was non significantly increased in hypothermia group (8.6% vs 1.9%; p=0.117) while cardiogenic shock (10.3% vs 0%; p=0.028) and paroxysmal atrial fibrillation (43.1% vs 3.8%; p<0.001) were significantly more frequent in hypothermia group **(Table 4)**. Paroxysmal atrial fibrillation resolved spontaneously in all patients during the rewarming phase and did not result in increased stroke rate at 30 days. No significant increase in stent thrombosis, malignant ventricular arrhythmia or infections were observed in hypothermia group. There were no cooling catheter-related complications.

**Discussion**

The present study using 1L intravenous infusion of cold saline and intravascular ZOLL TM Proteus Cooling System showed that rapid cooling to 33.3oC did not reduce IS in patients with anterior STEMI undergoing primary PCI. Cooled subjects had longer ischemic times and an excess of SAE and NSAE. Longer ischemic times caused in part by different patient pathways led to the early discontinuation of the study and confounded the results. These results contrast with a successful pilot trial (13), and several lessons can be learned for future hypothermia STEMI trials.

The key reason that reassuring animal data on IS reduction were not reproduced in this study may be related to the 44 minute increase in total ischemic delay in hypothermia group which was predominantly due to workflow logistics that resulted in significantly longer delay from randomization to passing of the guidewire across the occlusion. Comparable IS between the groups despite unacceptable cooling-related delay may indirectly indicate that detrimental effect of increased ischemic time on IS may be nullified when subjects are treated with hypothermia. This is in accordance with recent experimental study in pigs in which 48 minute increase in ischemic delay did not translate into a larger IS/Area at risk if intravascular cooling was implemented before reperfusion (16).However, for clinically meaningful reduction in IS, cooling-related delay must be minimized by improved logistics and rapid and organized team approach in the catheterization laboratory. This includes simultaneous and co-ordinated implementation of anti-shivering protocol and priming of the cooling console. At the same time, the interventional team should be drapping a patient and inserting a cooling catheter. After cooling catheter activation, the interventional cardiologist has 18 minutes to obtain arterial access, perform coronary angiography, administer anticoagulation/antiplatelet agents, place guiding catheter and advance guidewire up to occlusion without crossing. Since these procedures are usually done faster than in 18 minutes, further technological development should focus on more powerful intravascular cooling systems enabling shorter intravascular cooling and elimination of the need for concomitant cold saline infusion. It is also important to keep in mind that cooling prior to reperfusion is probably more likely to reduce IS in early STEMI presenters. Total ischemic time in our cooled patients (232 minutes) was longer than in other trials including CHILL MI (132 minutes) (10), VELOCITY (172 minutes) (11), RAPID MI ICE (174 minutes) (7) and COOL MI (205 minutes) (8). All these tasks might be best achieved in mature high volume STEMI networks with direct transfer of patients to the catheterization laboratory.

As described, there was an excess of SAE and NSAE in our study. Significantly increased rate of peri-procedural self terminating paroxysmal atrial fibrillation, which did not increase stroke rate, was observed. Such signal has been documented already in the pilot trial but not in other studies with less rapid cooling. We documented also a non-significant increase in ventricular fibrillation/tachycardia also not evident in the pilot trial. Observed arrythmias might have been related to more rapid and profound cooling and this possible association should be rigorously addressed in future trials. Both, atrial and ventricular arrythmias together with numerically increased rate of acute and subacute stent thrombosis may also explain significantly greater incidence of cardiogenic shock in the hypothermia group.

An excess of stent thrombosis was not reported in the pilot study and also not in any of the previous intravascular cooling trials (7-10). Striking and rapid decrease in core temperature of 1.4 °C more than in previous studies together with a 3-hour extension of hypothermia after reperfusion may have facilitated platelet aggregation by increasing ADP levels (17,18) which have been demonstrated in vitro (19) and in healthy volunteers (20). In this setting, also absorption and onset of P2Y12 inhibition may be delayed even with novel agents such as ticagrelor, as demonstrated in comatose survivors of cardiac arrest undergoing hypothermia between 32-34°C for 24 hours (21). In these patients, an almost a 3-hour “P2Y12 inhibition gap” was documented following administration of crushed ticagrelor tablets via nasogastric tube. Furthermore, concomitant pethidine administration as a part of our anti-shivering protocol is likely to further impair gastrointestinal mobility and P2Y12 absorption. A new intravenous P2Y12 inhibitor cangrelor, with immediate onset of platelet inhibition and up to 4-hour infusion, might therefore represent an effective bridging for future cooling studies. Since rapid intravascular cooling may create more prothrombotic environment favoring stent thrombosis, achievement of optimal angiographic result may be of even greater importance. We advise culprit only PCI in the acute setting, selection of least thrombogenic and contemporary drug eluting stent with adequate sizing/expansion using intravascular imaging if necessary, and avoiding unnecessary complex and long non culprit lesion stenting.

**Limitations**

Importantly, our study was stopped prematurely due to site-specific issues, which limits the power of our results to detect significant difference in IS/LV at 4-6 days following procedure. Overwhelmingly, the greatest study limitations were the large disparities observed in door-to-balloon and total ischemic times between the study groups which ultimately precluded meaningful group comparisons. We also acknowledge that measurements of blood temperature in the control group at the time of reperfusion would add additional scientific merit to our study protocol.

**Conclusion**

The present study using 1L intravenous infusion of cold saline and intravascular ZOLL TM Proteus Cooling System reduced temperature in patients with anterior STEMI to 33.3oC before reperfusion. Due to inconsistent patient logistics between the groups, this hypothermia protocol resulted in longer ischemic delay in cooled subjects, did not reduce IS/LV mass and was associated with increased adverse events. Future hypothermia studies should therefore focus on reduction of cooling related delay. Because such delay is likely to counterbalance potential myocardial salvage and increase adverse events, we advise to implement a predefined stopping rule not only for hypothermia but also for other trials investigating myocardial salvage beyond PPCI.

**Impact of daily practice**

Cooling as an adjunct to primary PCI in STEMI remains experimental. Lessons learned from this, prematurely discontinued trial, should be implemented in the protocols of possible future trials.

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**Conflict of interest statement**

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**References**

1.Dae MW, Gao DW, Sessler DI, Chair K, Stillson CA. Effect of endovascular cooling on

myocardial temperature, infarct size, and cardiac output in human-sized pigs. Am J Physiol

Heart Circ Physiol 2002;282:H1584-91.

2. Duncker DJ, Klassen CL, Ishibashi Y, Herrlinger SH, Pavek TJ, Bache RJ. Effect of

temperature on myocardial infarction in swine. Am J Physiol 1996;270:H1189-99.

3. Hale SL, Dave RH, Kloner RA. Regional hypothermia reduces myocardial necrosis even

when instituted after the onset of ischemia. Basic Res Cardiol 1997;92:351-7.

4. Hale SL, Kloner RA. Ischemic preconditioning and myocardial hypothermia in rabbits with prolonged coronary artery occlusion. Am J Physiol 1999;276:H2029-34.

5. Gotberg M, Olivecrona GK, Engblom H, Ugander M, van der Pals J, Heinberg E, Arheden

H, Erlinge D. Rapid short-duration hypothermia with cold saline and endovascular cooling

before reperfusion reduces microvascular obstruction and myocardial infarct size. BMC

Cardiovascular Disorders 2008;8:7.

6. Erlinge D. A Review of mild hypothermia as an adjunctive treatment for ST-elevation

myocardial infarction. Ther Hypothermia Manag 2011;1:129-141.

7. Gotberg M, Olivecrona GK, Koul S, Carlsson M, Engblom H, Ugander M, van der Pals J, Algotsson L, Hakan A, Erlinge D. A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. Circ Cardiovasc Interv 2010;3:400-7.

8. Dixon SR, Whitbourn RJ, Dae MW, Grube E, Sherman W, Schaer GL, Jenkins JS, Baim

DS, Gibbons RJ, Kuntz RE, Pompa JJ, Nguyen TT, O’Neill WW. Induction of mild systemic

hypothermia with endovascular cooling during primary percutaneous coronary interventionfor

acute myocardial infarction. J Am Coll Cardiol 2002;40:1928-34.

9. Grines CL, on behalf of the ICE-IT Investigators. Intravascular cooling adjunctive to percutaneous coronary intervention for acute myocardial infarction. Presented at 16th annual Transcatheter Cardiovascular Therapeutics, Washington DC, USA, September 2004. In: O’Neill WW, Dixon SR, Grines CL: The year in interventional cardiology. J Am Coll Cardiol 2005;45:1117-34.

10. Erlinge D, Gotberg M, Lang I, Holzer M, Noc M, Clemmensen P, Jensen U, Metzler B, James S, Botker HE, Omerovic E, Engblom H, Cardlsson M, Arheden H, Ostlund O, Wallentin L, Harnek J, Olivecrona GK. Rapid endovascular catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial Infarction (the CHILL MI Trial). J Am Coll Cardiol 2014;63:1857–65

11. Nichol G, Stricklands W, Shavelle D, Maehara A, Ben-Yehuda O, Genereux P, Dressler O, Parvataneni R, Nichols M, McPherson J, Barbeau G, Laddu A, Elrod JA, Tully GW, Ivanhoe R, Stone GW; fort he VELOCITY investigators. Prospectice, multicenter, randomized controlled pilot trial of peritoneal hypothermiain patients with ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv 2015;8:e001965.

12. Erlinge D, Gotberg M, Noc M, Lang I, Holzer M, Clemmensen P, Jensen U, Metzler B, James S, Botker HE, Omerovic E, Koul S, Engblom H, Carlsson M, Arheden H, Ostlund O,

Wallentin L, Klos B, Harnek J, Olivecrona GK. Therapeutic hypothermia for the treatment of

acute myocardial infarction-combined analysis of the RAPID MI-ICE and the CHILL-MI

trials. Ther Hypothermia Manag 2015;5:77-84.

13. Noc M, Erlinge D, Neskovic AN, Kafedzic S, Merkely B, Zima E, Fister M, Petrović M,

Čanković M, Veress G, Laanmets P, Pern T, Vukcevic V, Dedovic V, Średniawa B,

Świątkowski A, Keeble TR, Davies JR, Warenits AM, Olivecrona G, Peruga JZ, Ciszewski

M, Horvath I, Edes I, Nagy GG, Aradi D, Holzer M. COOL AMI EU Pilot Trial: A

Multicenter, Prospective, Randomized Controlled Trial to Assess Cooling as an Adjunctive

Therapy to Percutaneous Intervention in Patients with Acute Myocardial Infarction.

Eurointervention 2017;13(5):e531-e535.

14. Engblom H, Tufvesson J, Jablonsowski R, Carlsson M, Aletras A, Hoffmann P, Jacquier A, Kober F, Metzler B, Erlinge D, Atar D, Arheden H, Heiberg E. A new automatic algorithm for quantification of myocardial infarction by late gadolinium enhancement cardiovascular magnetic resonance: experimental validation and comparison to expert delineations in multi-center, multi-vendor patient data. J Cardiovasc Magnetic Resonance 2016,18:27-40.

15. Ubachs JF, Sorensson P, Engblom H, Carlsson M, Jovinge S, Pernow J, Arheden H. Myocardium at risk by magnetic resonance imaging: head-to-head comparison of T2-weighted imaging and contrast-enhanced steady-state free precession. European heart journal cardiovascular Imaging. 2012;13(12):1008-15.

16. [Shanmugasundaram M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Shanmugasundaram%20M%5BAuthor%5D&cauthor=true&cauthor_uid=32155385), [Truong HT](https://www.ncbi.nlm.nih.gov/pubmed/?term=Truong%20HT%5BAuthor%5D&cauthor=true&cauthor_uid=32155385), [Harhash A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Harhash%20A%5BAuthor%5D&cauthor=true&cauthor_uid=32155385), [Ho D](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ho%20D%5BAuthor%5D&cauthor=true&cauthor_uid=32155385), [Tran A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Tran%20A%5BAuthor%5D&cauthor=true&cauthor_uid=32155385), [Smith N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Smith%20N%5BAuthor%5D&cauthor=true&cauthor_uid=32155385), [Ciurlino B](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ciurlino%20B%5BAuthor%5D&cauthor=true&cauthor_uid=32155385), [Noc M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Noc%20M%5BAuthor%5D&cauthor=true&cauthor_uid=32155385),[Hsu P](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hsu%20P%5BAuthor%5D&cauthor=true&cauthor_uid=32155385), [Kern KB](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kern%20KB%5BAuthor%5D&cauthor=true&cauthor_uid=32155385). Extending time to reperfusion with mild therapeutic hypothermia: A new

paradigm for providing primary percutaneous coronary intervention to remote ST segment

elevation myocardial infarction patients. [Ther Hypothermia Temp Manag.](https://www.ncbi.nlm.nih.gov/pubmed/32155385) 2020 Mar 9. doi:

10.1089/ther.2019.0039. [Epub ahead of print]

17. Straub A, Krajewski S, Hohmann JD, Westein E, Jia F, Bassler N, Selan C, Kurz J, Wendel HP, Dezfouli S, Yuan Y, Nandurkar H, Jackson S, Hickey MJ, Peter K. Evidence of platelet activation at medically used hypothermia and mechanistic data indicating ADP as a key mediator and therapeutic target. *Arterioscler Thromb Vasc Biol*. 2011;31(7):1607-16.

18. Krajewski S, Kurz J, Geisler T, Peter K, Wendel HP, Straub A. Combined blockade of ADP receptors and PI3-kinase p110β fully prevents platelet and leukocyte activation during hypothermic extracorporeal circulation. *PLoS One*. 2012;7(6):e38455.

19. Scharbert G, Kalb ML, Essmeister R, Kozek-Langenecker SA. Mild and moderate hypothermia increases platelet aggregation induced by various agonists: a whole blood in vitro study. *Platelets*. 2010;21(1):44-8.

20. Högberg C, Erlinge D, Braun OO. Mild hypothermia does not attenuate platelet aggregation and may even increase ADP-stimulated platelet aggregation after clopidogrel treatment. *Thromb J*. 2009;7:2.

21. Steblovnik K, Blinc A, Miljovski M, Fister M, Mikuz U, Noc M. Ticagrelor versus

clopidogrel in comatose survivors of out-of-hospital cardiac arrest undergoing percutaneous

coronary intervention and hypothermia: A randomized study. Circulation 2016;134:2128-30.

**Figure legends**

**Figure 1.** ZOLL® Proteus™ Intravascular Cooling System

**Figure 2.** Infarct size by left ventricular mass (IS/LV %) measured by cardiac magnetic resonance (CMR) in hypothermia and control groups at day 4-6 shown as intention-to-treat and per -protocol analyses.