Therapeutic Hypothermia following Out-of-Hospital Cardiac Arrest – A randomized trial comparing mild and moderate therapeutic hypothermia

CAPITAL-CHILL

Principal Investigator: Michel Le May, M.D.

Address: **University of Ottawa Heart Institute**
40 Ruskin St.
Ottawa, Ontario, Canada

Telephone Number: **(613) 761- 4223**

Email Contact: **mlemay@ottawaheart.ca**

Co-Investigators:

Ronnen Maze, Benjamin M Hibbert, Derek Y So, George Wells, Alexander Dick, Christopher Glover, Michael Froeschl, J.F. Marquis, Shawn Marshall, Ali Pourdjabbar, Marino Labinaz

Research Coordinators: Christina Osborne
Melissa Blondeau

TABLE OF CONTENTS PAGE

1. GLOSSARY OF ABBREVIATIONS

AEs	Adverse Events
ARC	Academic Research Consortium
CABG	Coronary Artery Bypass Grafting
CCU	Coronary Care Unit
CHF	Congestive Heart Failure
CK	Creatinine Kinase
CRF	Case Report Form
DRS	Disability Ratings Scale
DSMC	Data and Safety Monitoring Committee
EAC	Event Adjudication Committee
ECG	Electrocardiogram
EEG	Electroencephalogram
ESF	Eligibility Screening Form
GCS	Glasgow Coma Score
IV	Intravenous
LV	Left Ventricular
mL	Millilitre
µmmol/L	Micromoles per litre
OHCA	Out-of-Hospital Cardiac Arrest
PCI	Percutaneous Coronary Intervention
ROSC	Return Of Spontaneous Circulation
SAE	Serious Adverse Event
STEMI	ST-Elevation Myocardial Infarction
TH	Therapeutic Hypothermia
UOHI	University of Ottawa Heart Institute

2. SYNOPSIS OF PROTOCOL

Title	Therapeutic Hypothermia following Out-of-Hospital Cardiac Arrest – A randomized trial comparing mild and moderate therapeutic hypothermia
Sponsors	None
Clinical phase	III
Indication	Therapeutic Hypothermia
Objectives	Cooling with moderate hypothermia to a goal temperature of 31°C will result in improved neurologic outcomes compared to mild hypothermia with a goal of 34°C in comatose survivors of OHCA.
Trial design	Single center, randomized, double blinded, parallel group design.
Number of subjects	340
Target population	Out-of-hospital cardiac arrest
Length of study	6 months
Investigational product(s)	None
Comparator "drug"	None
The primary outcome	Death or poor neurologic outcome at 6 months
Event adjudication committee	The following events will be adjudicated by a masked Event Adjudication Committee (EAC): neurologic outcome; death, stroke, and stent thrombosis
Data safety monitoring committee	The DSMC will give advice to the Steering Committee on the safety aspects of the study.

3. SYNOPSIS OF THE TRIAL

3.1 Primary Outcome

The primary outcome of the study will be death or poor neurologic outcome at six months. Neurologic outcome will be assessed using the Disability Ratings Scale (DRS), an 8-item ordinal scale that evaluates functional dependence (See Appendix 8).[1] Neurologic outcome will be assessed by a specialist in rehabilitation medicine at six months. Patients will be judged to have had a poor neurological outcome if the score on the DRS scale is >5 i.e. cannot live independently.

3.2 Inclusion Criteria

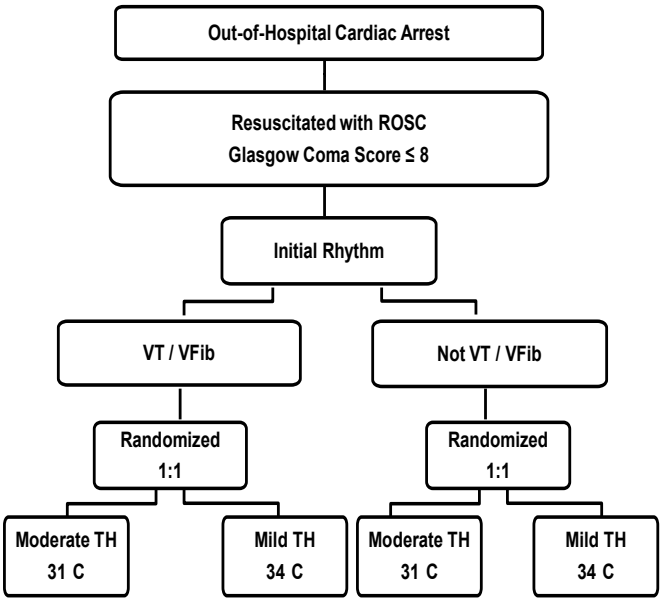
Any patient >18 years of age who is comatose (Glasgow Coma Score ≤8) following out-of-hospital cardiac arrest (OHCA) in whom the treatment plan includes therapeutic hypothermia (TH). The University of Ottawa Heart Institute Therapeutic Hypothermia protocol will guide in patient selection. However, patients will be recruited, irrespective of initial rhythm.

3.3 Exclusion Criteria

1. Patients residing in a Nursing Home or patients unable to reside independently,
2. Intracranial bleed responsible for the cardiac arrest,
3. Severe coagulopathy with clinical evidence of major bleeding,
4. Coma that is not attributable to cardiac arrest,
5. Pregnancy,
6. Life expectancy of < one year due to any cause unrelated to the cardiac arrest,
7. Known coagulation disorder (i.e. INR >2.0, platelets <100,000 / mm3),
8. Participation in a study with another investigational device or drug < four weeks,
9. The Endovascular cooling (ZOLL Thermogard XP) device is not available.

3.4 Study Design

CAPITAL CHILL



3.5 Summary

This is a single-center, randomized, double-blind investigator initiated prospective clinical trial to be performed at the University of Ottawa Heart Institute (UOHI). The patients for this study will be recruited amongst comatose survivors of OHCA who are admitted at the UOHI. The aim of this study is to determine whether neurologic outcomes at six months are improved with moderate (31°C) versus mild (34°C) TH following ROSC in patients suffering OHCA, with ROSC defined as the resumption of sustained perfusing cardiac activity.
The primary outcome will be the proportion of patients experiencing death or a poor neurologic outcome at six months after out of hospital cardiac arrest.

3.6 Statistical Analyses

3.6.1 Sample size

A total of 340 patients will be required to detect an absolute 15% risk reduction (30% relative risk reduction) in the primary outcome based on an anticipated event rate of 50% in the mild hypothermia group and of 35% in the moderate hypothermia group using a chi-square test for comparing proportions with alpha set of 0.05 and a power of 80%.

4. PROTOCOL

4.1 Background and Rationale

Despite many advances in cardiac care over the past decades, prognosis following out-of-hospital cardiac arrest (OHCA) remains poor. Patients are often left with severe neurologic dysfunction if they survive the index hospitalization.

Two pivotal trials published in the *New England Journal of Medicine* demonstrated improved neurologic outcomes in comatose survivors of OHCA who undergo therapeutic hypothermia (TH).[2, 3] Bernard and colleagues demonstrated an improvement in neurologic function at hospital discharge, while the Hypothermia After Cardiac Arrest group found both favourable neurologic outcomes and a significant improvement in survival at 6 months post-discharge.

Current American Heart Association/International Liaison Committee on Resuscitation guidelines incorporate TH as the standard of care for comatose survivors of OHCA.[4] Recently, the University of Ottawa Heart Institute published a paper in *Resuscitation* demonstrating a beneficial outcome in patients referred for primary percutaneous coronary intervention (PCI) and TH in patients with OHCA following ST-segment elevation myocardial infarction.[5] The use of TH (to a target temperature of 32-34 degrees) did not delay door-to-balloon times and neurologic benefit was seen despite the relatively slow cooling times in our retrospective cohort.

Therapeutic hypothermia functions to reduce cerebral metabolic demands, thereby reducing both the hypoxic insult and suppressing chemical reactions associated with reperfusion injury. These reactions include the production of free radicals, excitatory amino acid release and calcium shifts which can lead to apoptosis.[6] In the normal brain, hypothermia reduces cerebral metabolic rate for oxygen by 6% for every 1°C reduction in brain temperatures >28°C.[7]

Despite evidence that TH is beneficial following OHCA, there is a lack of evidence to guide the targeted temperature during TH. In the two aforementioned randomized controlled trials, Bernard et al targeted a core temperature of 33 degrees, while the HACA group set a target core temperature of 32-34 degrees. A recent retrospective review showed improved neurologic outcomes with mild hypothermia (32°C-34°C) compared to normothermia (<37.5°C).[8] Animal evidence suggests that even more aggressive cooling to a target temperature of 30°C may be associated with greater neuroprotection.[8, 9]

A recent pilot study by Lopez-de-Sa published in *Circulation* randomized 36 comatose survivors of OHCA to two distinct goal-cooling temperatures, 34°C or 32°C.[8, 10] The primary outcome was survival free from severe dependence (Barthel Index Score ≥ 60) at 6 months. They found no difference in the primary outcome between the two groups. Subgroup analysis found that in patients with an initial shockable rhythm, those randomized to 32°C had improved outcomes compared to those assigned to the 34°C target temperature. To date, this remains the first and only randomized controlled trial comparing two different goal-cooling temperatures in comatose survivors of OHCA. Cooling was achieved using the ZOLL endovascular cooling device (ZOLL Medical Corporation, Chelmsford, MA USA). This endovascular cooling device allows the treating physician to cool the patient rapidly to a target core body temperature with accuracy and efficiency. The device can be programmed to actively rewarm the patient after the cooling period is completed.

Despite advances in cooling mechanisms and comprehensive coronary care, patients surviving OHCA continue to experience poor outcomes from a neurologic perspective. The importance of TH is paramount in this high-risk population, and despite evidence of benefit with TH, the optimal goal temperature continues to remain unknown.

Our center is the single regional cardiac referral center for Eastern Ontario – servicing a population of approximately 1.2 million residents. In 2011, we established a CODE ROSC program to manage patients who suffer OHCA in a coordinated and timely fashion. All patients referred to the UOHI who are comatose following OHCA with no identifiable etiology are candidates for TH in our coronary care unit to preserve neurologic function.

Herein, we propose a randomized controlled trial to determine whether TH with cooling to a lower goal temperature is associated with improved outcomes. We hypothesize that cooling with moderate hypothermia to a goal temperature of 31°C will result in improved neurologic outcomes compared to mild hypothermia with a goal of 34°C in comatose survivors of OHCA.

Therapeutic hypothermia has been shown to improve neurologic outcomes and survival in comatose survivors of OHCA. Nevertheless, outcomes remain poor with as many as 60% of patients either dying or surviving with significant neurologic impairment. Despite many advances in cardiac care, these patients still suffer significant mortality and morbidity as a result of cardiac arrest. Our center has a particular interest in cardiac arrest and the use of TH to provide neuroprotection for these patients. In 2011, we established a "CODE ROSC" program in an attempt to streamline and centralize care for these patients (abstact at 2012 CCC in Toronto).

Commented [c1]: Reference?

Current American Heart Association/International Liaison Committee on Resuscitation guidelines incorporate TH as the standard of care for comatose survivors of OHCA. These guidelines recommend a target temperature of 32°C-34°C to provide neuroprotection following cardiac arrest. This degree of therapeutic hypothermia is an effective therapy (compared to placebo), improving neurologic outcomes at six months in comatose survivors of out-of-hospital cardiac arrest. However, the optimal goal temperature for therapeutic hypothermia in these patients has not been investigated in large randomized trial. It is possible that a further reduction in metabolic demand that is associated with cooler temperatures may lead to a clinically significant improvement in patient outcomes.

The proposed study is designed to test the hypothesis that more profound cooling by achieving moderate TH will result in improved neurologic outcomes. Our aim is to answer a clinically important question in a randomized, double-blinded fashion. The trial design respects evidence from previous trials and current international guidelines. We have chosen a design that is inclusive of all patients with cardiac arrest (unless attributable to a proven intracranial bleed) for whom the treating physician wishes to incorporate therapeutic hypothermia as part of the patient's treatment plan. While previous trials have excluded patients who presented with an initial rhythm of asystole or pulseless electrical activity, we have chosen to include these patients in our study as they are routinely treated with TH in most clinical settings. Although there is no data on the use of TH in patients with an initial rhythm of asystole, we believe that these patients should be offered TH and a randomized trial to address the utility of this strategy in these patients. Lastly, our protocol design allows for discontinuation of

cooling in patients in whom TH may be contributing to worsening clinical condition – however, data from our ROSC database and from the literature suggests this is an infrequent event[2, 4].

We believe that this randomized study will provide valuable clinical information for the physician and health care team treating comatose survivors of OHCA.

4.2. Study Design

4.2.1 Study Population

Our proposed study is a single-center, randomized, double-blind investigator initiated prospective clinical trial performed at the University of Ottawa Heart Institute (UOHI). The patients for this study will be recruited amongst comatose survivors of OHCA who are admitted at the UOHI. The aim of this study is to determine whether neurologic outcomes at six months are improved with moderate (31°C) versus mild (34°C) TH following ROSC in patients suffering OHCA, with return of spontaneous circulation (ROSC) defined as the resumption of sustained perfusing cardiac activity.

4.2.2 Inclusion Criteria

Inclusion criteria will be any patient >18 years of age who is comatose (Glasgow Coma Score [GCS] ≤8) following OHCA in whom the treatment plan includes TH. The UOHI and The Ottawa Hospital Therapeutic Hypothermia protocol (See Appendix 9) will guide in patient selection. However patients will be recruited, irrespective of initial rhythm found at the time of the cardiac arrest.

4.2.3 Exclusion Criteria

1. Patients residing in a Nursing Home or patients unable to reside independently,
2. Intracranial bleed responsible for the cardiac arrest,
3. Severe coagulopathy with clinical evidence of major bleeding,
4. Coma that is not attributable to cardiac arrest,
5. Pregnancy,
6. Life expectancy of < one year due to any cause unrelated to the cardiac arrest,
7. Known coagulation disorder (i.e. INR >2.0, platelets <100,000 / mm3),
8. Participation in a study with another investigational device or drug < four weeks,
9. The Endovascular cooling (ZOLL) device is not available.

4.2.4 Randomization

Randomization will be performed in a 1:1 fashion by sealed opaque envelopes and treatment assigned by random number generation done in blocks. Patients will be randomized immediately following insertion of the endovascular cooling catheter. Because patients with ventricular tachycardia (VT) or ventricular fibrillation (VF) have better survival than other rhythms[10] patients will be stratified based on their initial rhythm. Patients with an initial rhythm of either VT or VF will be randomized from a different series of envelopes than patients with an initial rhythm of asystole or pulseless electrical activity (PEA). The two different series of randomization

envelopes will be identifiable and differentiable by coding (ie. VT/VF randomization codes will begin by the number 1, while randomization codes for asystole/PEA will begin by the number 2). This will ensure balancing in the groups in this important prognostic factor.

4.2.5 Blinding

The treating physician and patient will be blinded to group allocation. The only member of the health care team who is not blinded will be the treating nurse as temperature adjustments on the cooling catheter will be performed by the nurse as per protocol. Nurses will chart temperature in a separate log, as per usual. This log, however, will be kept in the patient's room and will not be a part of the medical records that the physician has routine access to. Randomization documents will be collected by nurses and or the study coordinator to ensure blinding.

Outcomes will be adjudicated by an independent, blinded committee. Cardiologists performing the follow-up assessments will be blinded. Rehabilitation physicians performing the cognitive assessments will be blinded to group allocation.

4.2.6 Participation Consent

This study, complies with the Tri-Council Policy Statement 2 (TCPS 2) guidelines from Chapter 3, Sections 3.8, 3.9 and 3.10. for obtaining proper consent from the participants and or from their authorized third party.

4.3 Interventions

Eligible patients will be randomized to mild TH (goal cooling temperature of 34°C) *or* moderate TH (goal cooling temperature of 31°C). The rate of cooling to the signed temperature after randomization will be on the basis of as fast as technically feasible by the device. Cooling will be performed via an endovascular cooling device (ZOLL Medical Corporation, Chelmsford, MA) inserted via the femoral vein into the inferior vena cava either in the cardiac catheterization laboratory or in the coronary care unit. Our current practice is to target 33°C with the identical protocol. Paramedics and transferring facilities will be encouraged to initiate hypothermia with ice packs as soon as possible (prior to arrival at the University of Ottawa Heart Institute). This is done by placing ice packs to the neck, groin and axilla.

Upon presentation to the University of Ottawa Heart Institute, patients may be taken to the cardiac catheterization laboratory at the discretion of the treating team for coronary angiography and/or insertion of a mechanical support device (intra-aortic balloon pump).

All patients will be sedated, intubated and ventilated. The University of Ottawa Heart Institute standard cooling protocol will be used to implement sedation, analgesia and neuromuscular blockade. Paralytic agents will be used during the cooling process to inhibit shivering. All of these medications and monitoring are currently the standard of care. The temperature will be recorded via the ZOLL catheter. Patients will have nasopharyngeal and bladder temperature probes inserted to correlate with temperatures monitored intravascularly.

Patients who present to the Ottawa Heart Institute with body temperatures <34°C can still be randomized to one of the groups. The temperature will be adjusted with the endovascular cooling device according to the randomly assigned temperature. Note that the device is capable at cooling or warming to the set target temperature.

Patients will be maintained at their assigned cooling temperature for a duration of 24 hours after reaching target temperature. Following the mandated 24-hour cooling period, patients will be actively re-warmed at a rate of 0.25°C/hour until normothermia (36.5°C) is reached. Normothermia will be maintained for 48 hours from the time of initiation of re-warming with active management of the temperature via the ZOLL catheter. This is the current standard of practice at the University of Ottawa Heart Institute.

If, in the opinion of the blinded treating physician, cooling is contributing to intractable arrhythmia, or hypotension refractory to vasopressor use, then the treating physician may choose to abandon cooling. In this situation the temperature of the patient will be increased by 3°C (i.e. from 31°C to 34°C *or* from 34°C to 37°C). The treating physician will remain blinded to group allocation. If, despite the increased temperature, it is believed that cooling is still contributing to significant adverse events, the physician can request to raise the temperature again (34 to 37°C and if at 37°C then no change will be made). Blinding will be maintained.

The patient's dedicated nurse will perform all temperature changes on the ZOLL® machine. The nurse is the only member of the health care team that is unblinded to group allocation – for logistical reasons, blinding of the nurse is not feasible.

Aside from the difference in cooling temperatures, management in the coronary care unit and subsequently on the cardiology wards will be standard of care. Again, both the treating physicians and the patient will be blinded to treatment allocation to ensure assessment of outcomes remains unbiased.

4.4 Laboratory Assessments

Total creatinine kinase (CK) and troponins will be assessed on admission and q8h x 24 hrs. A complete blood count (CBC) will be obtained immediately upon admission and repeated daily x3, and thereafter as indicated. A CBC will be repeated anytime that there is evidence of overt bleeding. Initial blood work will include electrolytes and serum creatinine and repeated daily x3. An ECG will be done immediately after a PCI, and daily x3. An ejection fraction will be obtained within 1 week of admission and at 90 days. This can be obtained by echocardiography, radionuclear imaging (LV Gated scan) or by magnetic resonance imaging (MRI). The imaging at 90 days should be the same imaging modality as was used initially.

4.5 Discovery of Novel Biomarkers - Blood Samples

The purpose of the blood samples is to screen for potential biomarkers of prognosis in patients presenting with ROSC undergoing TH. To screen for identification of potential biomarkers 50 patients will be enrolled. Because of the need to process blood samples promptly, the first 50 patients presenting during regular working hours will be selected. Blood samples will be drawn at baseline, 12hrs, 24hrs, 48 hrs and 72hrs for a total of 5 samples. Each sample will be 5cc's and they will be drawn by the patient's nurse from the established cooling catheter thus requiring no additional venipuncture. Study co-investigators will be responsible for obtaining

blood samples from the nurses and processing the blood samples. In total, 25 cc's of blood will be drawn per patient. Therefore, a total of 1250 cc's of blood will be drawn in the context of this study.

Samples will be stored in the designated locked laboratory at the University of Ottawa Heart Institute for a period of one year at -80 degrees celsius. Samples will be de-identified by a number and linked to a password protected master list maintained on the University of Ottawa Heart Institute server and or secure network server.

Once samples from 50 patients have been collected we will screen for biomarkers of poor neurologic outcome (the primary outcome of the study) using unbiased screening technology. Specifically, we will screen serum levels of proteins using proteomics techniques which enable us to identify proteins with distinctly different levels between the groups. Secondarily, we will screen for levels of circulating microRNA which may predict poor neurologic outcome. No genetic testing will be performed on the samples.

The goal of these studies is to identify previously unidentified markers of poor prognosis in ROSC patients which are needed to prognosticate outcomes at an early stage of their presentation.

4.6 Follow-up

Patients will be assessed by a cardiologist at the following time intervals – 1, 3, 6 months after the cardiac arrest. Patients will be seen by the rehabilitation specialist at 6 months after the cardiac arrest. Current standard of care for follow-ups for this population is for patients to be seen by a cardiologist at 1 and 6 months. However, if deemed to be necessary the cardiologist may decide to see a patient at a higher frequency. Follow-up with the rehabilitation specialist is likely to be done at 6 months but is determined on a case by case basis.

4.7 Pre-specified subgroups

The following pre-specified subgroups will be analyzed at the end of the study:

1. Ventricular tachycardia or ventricular fibrillation as initial rhythm
2. ST segment elevation myocardial infarction as index event
3. Patients taken to the cardiac catheterization laboratory within 12 hrs of the cardiac arrest event
4. Patients undergoing percutaneous coronary intervention
5. Patients age >75yrs

5. STUDY OUTCOMES

5.1 Primary Outcome

The primary outcome of the study will be death or poor neurologic outcome at six months. Neurologic outcome will be assessed using the Disability Ratings Scale (DRS), an 8-item ordinal scale that evaluates functional dependence.[11] The DRS has both reliability and validity in the assessment of neurologic function following traumatic and acquired brain injury.[1, 8] Neurologic outcome will be assessed by a specialist in rehabilitation medicine. Patients will be judged to have had a poor neurologic outcome if the score on the DRS scale is >5.

5.2 Secondary Outcomes

1) Death during the initial hospitalization, at 30 days and at 6 months
2) Stroke during the initial hospitalization, and at 6 months
3) TIMI minor/major bleeding during first hospitalization (+7 days)
4) Length of stay in the unit
5) Length of stay in the hospital
6) Cardiogenic shock during the initial hospitalization
7) Repeat circulatory arrest requiring cardiopulmonary resuscitation (CPR)
8) Arrhythmia requiring anti-arrhythmic medication (aside from beta blocker)
9) Presence of seizures
10) Renal failure requiring renal replacement therapy
11) Ventilator associated pneumonia
12) LV function assessed by echo done on day 3 and at 90 days
13) CK release within first 48 hrs:
14) Frequency of Stent thrombosis
15) Discharged home.

All clinical events will be adjudicated by a committee utilizing the abovementioned definitions in a blinded manner. As noted, rehabilitation physicians performing the neurologic assessments will be blinded to group allocation.

6. DEFINITION OF STUDY OUTCOMES

6.1 Poor Neurological outcome

Defined as a DRS score > 5 (See Appendix 8).

6.2 Bleeding

Defined as TIMI minor or major (See Appendix 7).

6.3 Stroke

A neurologic injury occurring as a result of a disease process involving one or more of the blood vessels of the brain, i.e. atherosclerosis, dissection, thrombus, embolism, decreased perfusion pressure resulting in inadequate blood flow, vessel rupture associated with intracranial haemorrhage. Strokes will be classified as hemorrhagic or non-hemorrhagic with duration > 24 hrs.

6.4 Cardiogenic Shock

Systolic blood pressure < 80 mm Hg not responding to fluid expansion, and requiring the use of intravenous inotropic support or the use of intra-aortic balloon counterpulsation.

6.5 Stent Thrombosis According to Academic Research Consortium (ARC)

The Academic Research Consortium (ARC) of academic investigators, regulators, and industry representatives has proposed definitions to serve as standard criteria for stent thrombosis for the comparison of event rates across different trials and studies. [11]

Stent thrombosis was classified as:

1) Acute if it occurred within 24 hours after the index procedure,
2) Subacute if it occurred between 1 and 30 days after,
3) Late if it occurred between 31 days and 1 year after, and
4) Very late if it occurred more than 1 year after the procedure.

Stent thrombosis was then classified as definite, probable, or possible.

Definite stent thrombosis required the presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion.

Probable stent thrombosis included unexplained deaths within 30 days after the procedure or acute myocardial infarction involving the target-vessel territory without angiographic confirmation.

Possible stent thrombosis included all unexplained deaths occurring at least 30 days after the procedure.

Intervening target lesion revascularization was defined as any repeated percutaneous revascularization of the stented segment, including the 5-mm proximal and distal margins that preceded stent thrombosis.

6.6 PCI Procedural Success

PCI procedural success is defined as the achievement of TIMI grade 3 flow with < 30% residual stenosis by visual estimate.

7. STATISTICAL AND ANALYTICAL METHODS

All analyses on the primary outcome and its components will be performed on an intention-to-treat. The primary outcome will be compared between treatment arms using a significance level of 5% and a power of 80%. Secondary outcomes will be examined using parametric or non-parametric statistics as appropriate for the scale of measurement of the dependent variables. Analyses will be conducted using SAS.

7.1 Hypothesis Testing

Primary and secondary efficacy parameters will be evaluated for treatment-associated differences between the two groups. The null hypothesis states that there will be no between treatment difference. The

alternate hypothesis states that moderate TH will be significantly more effective than the mild TH at reducing the number of primary outcome events at six months.

7.2 Efficacy Analysis

All participants, who receive study treatment, will be included in the analyses according to their initial randomization group, i.e. intention to treat analysis. No interim analysis is planned.

7.3 Comparability of Patient Groups

Descriptive statistics will be used to evaluate the comparability of patients randomized to either group with respect to age, gender, cardiovascular history, functional capacity, medications and interventions administered in hospital, and course in hospital.

8. SAMPLE SIZE

8.1 Sample Size

Outcome measures for all randomized patients will be analyzed in an intention-to-treat analysis. The primary outcome of our study will be a composite of 1) death or 2) poor neurologic outcome, at 6 months. Based on our review of the literature and our own cardiac arrest database we estimate an event rate of 50% in the mild TH group. To detect a 30% relative risk reduction with 80% power and a type I error of 5% will require a sample size of 340 patients (170 per temperature group).

9. DATA QUALITY ASSURANCE

The DSMC will consist of one chairperson and two members, all external and not directly involved with the study. One member will be a qualified biostatistician/methodologist. The DSMC will review the data from the study at regular intervals and determine if it is safe to continue the study according to the protocol. The DSMC will have access to all available data from the study throughout the study duration. All Serious Adverse Events (SAEs), including deaths, will be reported immediately to the DSMC. The purpose of the DSMC will be primarily safety and no formal analysis will be done on major outcomes.

10. STUDY COMMITTEES

10.1 Steering Committee

The steering committee, chaired by the principal investigator, will have the responsibility of overseeing the scientific conduct of the study. Members are listed in Appendix 3.

10.2 Clinical Event Adjudication Committee

The adjudication committee will consist of a chairperson and two members. Members will not be investigators or co-investigators. The committee will adjudicate the following events on a regular basis: 1) death, 2) 6 month neurological outcome results according to the DRS, 3) stroke, and 4) stent thrombosis. Members will be provided with relevant physician and nurses' notes, ECGs and laboratory test results. The research

coordinator will mask the treatment group before providing documentation. The adjudication committee will perform the verification of clinical outcomes in a blinded manner and the statistician will perform a blinded analysis.

10.3 Data and Safety Monitoring Committee (DSMC)

The DSMC will consist of one chairperson and two members, all external and not directly involved with the study. One member will be a qualified biostatistician/methodologist. The DSMC will review the data from the study at regular intervals and determine if it is safe to continue the study according to the protocol. The DSMC will have access to all available data from the study throughout the study duration. All Serious Adverse Events (SAEs), including deaths, will be reported immediately to the DSMC. The purpose of the DSMC will be safety.

Commented [c2]: Specify

11. ANALYSIS OF DATA

Statistical analysis will be performed under the supervision of Dr. George Wells in the Methods Center at the University of Ottawa Heart Institute.

12. ASSESSMENT AND REPORTING OF ADVERSE EVENTS

12.1 Definition of an Adverse Event (AE)

An adverse event is any untoward medical occurrence or unfavourable and unintended sign in a subject administered a pharmaceutical product/biologic (at any dose), or medical device, whether or not considered related to the use of that product. Additionally, any event that is associated with or observed in conjunction with a product overdose (whether accidental or intentional) or a product abuse and/or withdrawal is also considered an adverse event.

12.2 Definition of Serious Adverse Events (SAE)

A serious adverse event is any adverse drug or biologic or device experience occurring at any dose that results in any of the following outcomes:

1) Death
2) life-threatening adverse event (i.e., one that places the subject, in the view of the initial reporter, at immediate risk of death from the adverse event as it occurs)
3) persistent or significant disability/incapacity
4) required in-patient hospitalization, or prolonged hospitalization
5) congenital anomaly or birth defect

12.3 Expedited Reporting of Serious Adverse Events

All serious adverse events, whether or not deemed drug-related or expected, must be reported by the principal investigator or designee to the Human Research Ethics Board and to the Data and Safety Monitoring Committee (DSMC) within 24 hours (one working day) of first becoming aware of the event. Serious adverse events that occur at any time after the inclusion of the subject in the study (defined as the time when the subject

signs the informed consent) up to 6 months after the subject completed or discontinued the study must be reported. The subject is considered to have completed the study either after the completion of the last visit or contact (e.g., phone contact with the investigator or designee), OR after the last dose of the study medication, whichever is later. The date of discontinuation is when a subject and/or investigator determines that the subject can no longer comply with the requirements for any further study visits or evaluations.

12.4 Reporting of Subject Death

The death of any subject during the study regardless of the cause will be reported to the Data and Safety Monitoring Committee (DSMC) within 24 hours of first becoming aware of the death.

13.1 APPENDIX 1: INVESTIGATORS

University of Ottawa Heart Institute

Principal Investigator
Michel Le May, MD

Co-Investigators
Ronnen Maze, MD
Benjamin M Hibbert, MD
Marino Labinaz, MD
Alexander Dick, M.D.
Jean-François Marquis, M.D.
Christopher Glover, MD
Michael Froeschl, MD
Derek So MD
Shawn Marshall, MD
Ali Pourdjabbar, MD
George Wells, Ph.D (Statistical Analyst)

Research Coordinator
Christina Osborne, B.Sc.

13.2 APPENDIX 2: ELIGIBILITY SCREENING FORM

SCREENING DATE: _____

ELIGIBILITY SCREENING FORM

Before entering a subject into the study, all of the following items must be completed. If any of the items are indicated "No", the subject is not eligible for enrolment.

INCLUSION CRITERIA

	Yes	No
Out of Hospital Cardiac Arrest,	[ ]	[ ]
and		
Glasgow Coma Score ≤ 8	[ ]	[ ]
and		
Return of Spontaneous Circulation	[ ]	[ ]

Before entering a subject into the study, all of the following items must be completed. If any of the items are indicated "Yes", the subject is not eligible for enrolment.

EXCLUSION CRITERIA	**YES**	**NO**
1. Age <18 years	[ ]	[ ]
2. Pregnancy	[ ]	[ ]
3. Patients residing in a Nursing Home or patients unable to reside independently	[ ]	[ ]
4. Intracranial bleed responsible for the cardiac arrest	[ ]	[ ]
5. Severe coagulopathy with clinical evidence of major bleeding	[ ]	[ ]
6. Coma that is not attributable to cardiac arrest	[ ]	[ ]
7. Life expectancy < one year due to cause unrelated to the cardiac arrest.	[ ]	[ ]
8. Known coagulation disorder (i.e. INR >2.0, platelets <100,000 / mm3)	[ ]	[ ]
9. Participation in a study with another investigational device or drug < four weeks	[ ]	[ ]
10. The Endovascular cooling (ZOLL) device is not available	[ ]	[ ]

Will the subject participate in this trial? Yes [ ] Randomization Number:
No [ ] Reason:

Investigator's Signature: Date: ____/____/____ (yr mo day)

13.3 APPENDIX 3: THE STEERING COMMITTEE

Michel Le May (Chairman)	University of Ottawa Heart Institute
George Wells	University of Ottawa Heart Institute
Ronnen Maze	University of Ottawa Heart Institute
Ben Hibbert	University of Ottawa Heart Institute
Shawn Marshall	Ottawa Hospital

13.4 APPENDIX 4: SAFETY AND LABORATORY TESTS

Adverse Events and Laboratory Abnormalities

Clinical Adverse Events

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An Adverse Event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions that worsen during a study are to be reported as Adverse Events.

All clinical adverse events (AEs) encountered during the clinical study will be reported on the AE page of the Case Report Form (CRF). Intensity of adverse events will be graded on a four -point scale (mild, moderate, severe, life-threatening) and reported as indicated on the CRF. Relationship of the adverse event to the treatment should also be assessed.

Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results pages of the CRF. Laboratory test value abnormalities as such should not be reported on the AE page of the CRF as adverse events unless they result in a clinically relevant condition.

Serious Adverse Events (SAE)

Please refer to Section 12 of the Protocol.

Treatment and Follow-up of Adverse Events

Adverse events will be followed up until they have returned to baseline status or stabilized.

13.5 APPENDIX 5: ETHICAL ASPECTS

Independent Ethics Committees/Institutional Review Board

Approval from the committee will be obtained before starting the study, and will be documented in a letter to the investigator specifying the date on which the committee met and granted the approval. Any modifications made to the protocol after receipt of the Independent Ethics Committee approval will also be submitted by the investigator to the Committee in accordance with local procedures and regulatory requirements.

Investigator's Files / Retention of Documents

For each patient enrolled, a CRF must be completed and signed by the principal investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the CRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome. The investigator should ensure the accuracy, completeness, legibility and timeliness of the data in the CRFs and in all required reports.

Documents will be kept for a period of 25 years after the study has been completed. This is in accordance to Health Canada. At the end of the retention period, all paper records will be disposed of in confidential waste or shredded, and all electronic records will be deleted.

Confidentiality of Trial Documents and Subject Records

Patients will be randomly assigned to treatment according to a prepared randomization schedule. The subject randomization numbers will be generated by the Investigator and will include balanced blocks for each study center. Sets of patient numbers and associated treatment(s) will be provided to the investigators in sealed opaque envelopes. The patient randomization numbers/envelopes are to be allocated sequentially in the order in which the subjects are enrolled.

13.6 APPENDIX 6: SCHEDULE OF ASSESSMENTS AND PROCEDURES

Boxes marked with an X show what will happen at each visit.

Visit	Screening/ Randomization Day 1	In-Hospital Day 2	In-Hospital Day 3	Cardiologist Visit 1 (1 month)	Cardiologist Visit 2 (3 month)	Cardiologist Visit 3 (6 month)	Rehabilitation Specialist (6 month)
Length of time needed	30 minutes	N/A	N/A	1 hour	1 hour	1 hour	1 hour
Written informed consent	x						
Medical History	x			x	x	x	x
Vital Signs	x			x	x	x	x
Physical examination	x			x	x	x	x
Routine Hematology	x	x	x				
Routine Blood Chemistry	x						
ECG	x	x	x				
LV Function Test			x		x		
Endovascular Cooling Device	x	x	x				
Study Blood Sample Collection	x	x	x				
Review of Medications	x			x	x	x	x
Neuro-Psychological Assessment (Disability Rating Scale)							x
Clinical Outcomes/ Endpoints				x	x	x	x

13.7 APPENDIX 7: TIMI BLEEDING DEFINITION

Types of TIMI Bleeding

1. Major:
   - Any intracranial bleeding or;
   - Clinically overt signs of hemorrhage associated with a drop in hemoglobin (Hgb) of ≥ 5 g/dL. (or, when Hgb is not available, an absolute drop in hematocrit (Hct) of ≥15%).
2. Minor:
   - Any clinically overt signs of hemorrhage (including imaging) that is associated with a fall in Hgb of 3 to < 5 g/dL (or, when Hgb is not available, a fall in Hct of 9 to b15%).
3. Needing medical attention
   - Any overt sign of hemorrhage that requires medical evaluation, medical treatment (including discontinuation of medications), or surgical treatment, and that does not meet criteria for a major or minor bleeding event, as defined above.
4. Minimal
   - Any overt bleeding event that does not meet the criteria above

NOTE: To account for transfusions, Hgb measurements will be adjusted for any packed red blood cells (PRBCs) or whole blood given between baseline and post-transfusion measurements. A transfusion of one unit of blood will be assumed to result in an increase by 1 gm/dL in Hgb. Thus, to calculate the true change in hemoglobin, if there has been an intervening transfusion between two blood measurements, the following calculations should be performed: Δ Hgb = [Baseline Hgb – Post transfusion Hgb] + [# transfused units].

TIMI Clinically Significant Bleeding:
The presence of either TIMI major or TIMI minor bleeding, or bleeding requiring medical attention.
For patients experiencing a hemorrhage that occurs as a result of CABG, the following criteria will be used:

5. Bleeding in the Setting of Coronary Artery Bypass Graft Surgery (CABG)
   Minor and minimal bleeding are not adjudicated in the setting of CABG
   As a drop in hemoglobin and transfusions are commonplace in routine CABG cases, one of the following criteria must be met to qualify for major bleeding in any of the preceding definitions:
   - Fatal bleeding (i.e., bleeding that directly results in death)
   - Perioperative intracranial bleeding*
   - Reoperation following closure of the sternotomy incision for the purpose of controlling bleeding
   - Transfusion of ≥ 5 units of packed red blood cells (PRBCs) or whole blood within a 48 hour period. Cell saver transfusion will not be counted in calculations of blood products
   - Chest tube output > 2 L within a 24 hour period

*In light of the increased sensitivity of brain imaging for microhemorrhages of uncertain clinical significance, brain imaging with an incidental finding of microhemorrage in the absence of associated clinical symptoms/ findings will not be considered to meet the protocol definition of intracranial hemorrhage.

Relationship of Bleeding to Death

Fatal Bleeding

Death in which a bleeding event directly led to death within 7 days. Examples of fatal bleeding events are an intracranial hemorrhage that led to herniation of the brain and death within 24 hours, and a massive gastrointestinal hemorrhage that results in shock, hemodynamic collapse, and death. If a bleeding event is considered fatal, then the cause of death must be either intracranial or non-intracranial bleeding.

Bleeding Contributed to Death

Death in which a bleeding event was part of a causal chain of medical events that ultimately led to death within 30 days of the bleed, but bleeding was not directly and/or immediately related to the subject's death. An example of bleeding contributing to death is a large retroperitoneal bleed that leads to surgical evacuation, development of a subsequent abscess in the area of bleeding that leads to sepsis, multiorgan failure, and death 10 days after the onset of bleeding. If bleeding has contributed to death (but the bleeding was not categorized as "fatal"), then the cause of death must be recorded as something other than intracranial / non-intracranial bleeding.

13.8 APPENDIX 8 – THE DISABILITY RATING SCALE (DRS)

TBI NATIONAL DATABASE COLLECTION FORM

Patient Name: _____ **Date of Rating:**_____

Name of Person Completing Form: _____

DISABILITY RATING SCALE:

Disability Rating Scale ratings to be completed within 72 hours after Rehab. Admission. And within 72 hours before Rehab. Discharge.

A. EYE OPENING:

- ☐ (0) Spontaneous
- ☐ (1) To Speech
- ☐ (2) To Pain
- ☐ (3) None

0-SPONTANEOUS: eyes open with sleep/wake rhythms indicating active arousal mechanisms, does not assume awareness.
1-TO SPEECH AND/OR SENSORY STIMULATION: a response to any verbal approach, whether spoken or shouted, not necessarily the command to open the eyes. Also, response to touch, mild pressure.
2-TO PAIN: tested by a painful stimulus.
3-NONE: no eye opening even to painful stimulation.

B. COMMUNICATION ABILITY:

- ☐ (0) Oriented
- ☐ (1) Confused
- ☐ (2) Inappropriate
- ☐ (3) Incomprehensible
- ☐ (4) None

0-ORIENTED: implies awareness of self and the environment. Patient able to tell you a) who he is; b) where he is; c) why he is there; d) year; e) season; f) month; g) day; h) time of day.
1-CONFUSED: attention can be held and patient responds to questions but responses are delayed and/or indicate varying degrees of disorientation and confusion.
2-INAPPROPRIATE: intelligible articulation but speech is used only in an exclamatory or random way (such as shouting and swearing); no sustained communication exchange is possible.
3-INCOMPREHENSIBLE: moaning, groaning or sounds without recognizable words, no consistent communication signs.
4-NONE: no sounds or communications signs from patient.

C. MOTOR RESPONSE:

- ☐ (0) Obeying
- ☐ (1) Localizing
- ☐ (2) Withdrawing
- ☐ (3) Flexing
- ☐ (4) Extending
- ☐ (5) None

0-OBEYING: obeying command to move finger on best side. If no response or not suitable try another command such as "move lips," "blink eyes," etc. Do not include grasp or other reflex responses.
1-LOCALIZING: a painful stimulus at more than one site causes limb to move (even slightly) in an attempt to remove it. It is a deliberate motor act to move away from or remove the source of noxious stimulation. If there is doubt as to whether withdrawal or localization has occurred after 3 or 4 painful stimulations, rate as localization.
2-WITHDRAWING: any generalized movement away from a noxious stimulus that is more than a simple reflex response
3-FLEXING: painful stimulation results in either flexion at the elbow, rapid withdrawal with abduction of the shoulder or a slow withdrawal with adduction of the shoulder. If there is confusion between flexing and withdrawing, then use pinprick on hands.
4-EXTENDING: painful stimulation results in extension of the limb.
5-NONE: no response can be elicited. Usually associated with hypotonia. Exclude spinal transection as an explanation of lack of response; be satisfied that an adequate stimulus has been applied.

D.FEEDING (COGNITIVE ABILITY ONLY)

- ☐ (0.0) Complete
- ☐ (1.0) Partial
- ☐ (2.0) Minimal
- ☐ (3.0) None

Does the patient show awareness of how and when to perform this activity? Ignore motor disabilities that interfere with carrying out this function. (This is rated under Level of Functioning described below.)
0-COMPLETE: continuously shows awareness that he knows how to feed and can convey unambiguous information that he knows when this activity should occur.
1-PARTIAL: intermittently shows awareness that he knows how to feed and/or can intermittently convey reasonably clearly information that he knows when the activity should occur.
2-MINIMAL: shows questionable or infrequent awareness that he knows in a primitive way how to feed and/or shows infrequently by certain signs, sounds, or activities that he is vaguely aware when the activity should occur.
3-NONE: shows virtually no awareness at any time that he knows how to feed and cannot convey information by signs, sounds, or activity that he knows when the activity should occur.

E.TOILETING (COGNITIVE ABILITY ONLY)

- ☐ (0.0) Complete
- ☐ (1.0) Partial
- ☐ (2.0) Minimal
- ☐ (3.0) None

Does the patient show awareness of how and when to perform this activity? Ignore motor disabilities that interfere with carrying out this function. (This is rated under Level of Functioning described below.) Rate best response for toileting based on bowel and bladder behavior
0-COMPLETE: continuously shows awareness that he knows how to toilet and can convey unambiguous information that he knows when this activity should occur.
1-PARTIAL: intermittently shows awareness that he knows how to toilet and/or can intermittently convey reasonably clearly information that he knows when the activity should occur.
2-MINIMAL: shows questionable or infrequent awareness that he knows in a primitive way how to toilet and/or shows infrequently by certain signs, sounds, or activities that he is vaguely aware when the activity should occur.
3-NONE: shows virtually no awareness at any time that he knows how to toilet and cannot convey information by signs, sounds, or activity that he knows when the activity should occur.

F.GROOMING (COGNITIVE ABILITY ONLY)

- ☐ (0.0) Complete
- ☐ (1.0) Partial
- ☐ (2.0) Minimal
- ☐ (3.0) None

Does the patient show awareness of how and when to perform this activity? Ignore motor disabilities that interfere with carrying out this function. (This is rated under Level of Functioning described below.) Grooming refers to bathing, washing, brushing of teeth, shaving, combing or brushing of hair and dressing.
0-COMPLETE: continuously shows awareness that he knows how to groom self and can convey unambiguous information that he knows when this activity should occur.
1-PARTIAL: intermittently shows awareness that he knows how to groom self and/or can intermittently convey reasonably clearly information that he knows when this activity should occur.
2-MINIMAL: shows questionable or infrequent awareness that he knows in a primitive way how to groom self and/or shows infrequently by certain signs, sounds, or activities that he is vaguely aware when the activity should occur.
3-NONE: shows virtually no awareness at any time that he knows how to groom self and cannot convey information by signs, sounds, or activity that he knows when the activity should occur.

G.LEVEL OF FUNCTIONING (PHYSICAL, MENTAL, EMOTIONAL OR SOCIAL FUNCTION))

- ☐ (0.0) Completely Independent
- ☐ (1.0) Independent in special environment
- ☐ (2.0) Mildly Dependent-Limited assistance (non-resid - helper)
- ☐ (3.0) Moderately Dependent moderate assist (person in home)
- ☐ (4.0) markedly Dependent-assist all major activities, all times
- ☐ (5.0) Totally Dependent-24 hour nursing care.

0-COMPLETELY INDEPENDENT: able to live as he wishes, requiring no restriction due to physical, mental, emotional or social problems.
1-INDEPENDENT IN SPECIAL ENVIRONMENT: capable of functioning independently when needed requirements are met (mechanical aids)
2-MILDLY DEPENDENT: able to care for most of own needs but requires limited assistance due to physical, cognitive and/or emotional problems (e.g., needs non-resident helper).
3-MODERATELY DEPENDENT: able to care for self partially but needs another person at all times. (person in home)
4-MARKEDLY DEPENDENT: needs help with all major activities and the assistance of another person at all times.
5-TOTALLY DEPENDENT: not able to assist in own care and requires 24-hour nursing care.

H."EMPLOYABILITY"(AS A FULL TIME WORKER, HOMEMAKER, OR STUDENT)

- ☐ (0.0) Not Restricted
- ☐ (1.0) Selected Jobs, competitive
- ☐ (2.0) Sheltered workshop, Non-competitive
- ☐ (3.0) Not Employable

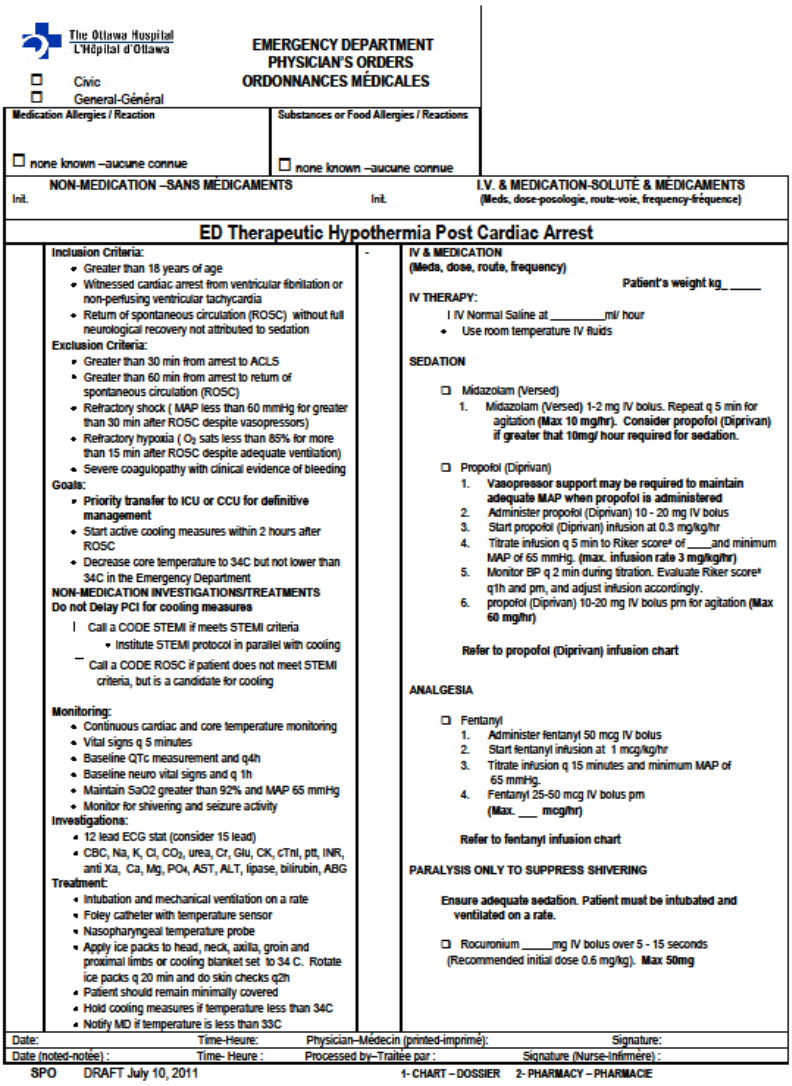
0-NOT RESTRICTED: can compete in the open market for a relatively wide range of jobs commensurate with existing skills or can initiate, plan execute and assume responsibilities associated with homemaking; or can understand and carry out most age relevant school assignments.
1-SELECTED JOBS, COMPETITIVE: can compete in a limited job market for a relatively narrow range of jobs because of limitations of the type described above and/or because of some physical limitations, or can initiate, plan, execute and assume many but not all responsibilities associated with homemaking, or can understand and carry out many but not all school assignments.
2-SHELTERED WORKSHOP, NON-COMPETITIVE: cannot compete successfully in a job market because of limitations described above and/or because of moderate or severe physical limitations; or cannot without major assistance initiate, plan, execute and assume responsibilities for homemaking; or cannot understand and carry out even relatively simple school assignments without assistance.
3-NOT EMPLOYABLE: completely unemployable because of extreme psychosocial limitations of the type described above, or completely unable to initiate, plan, execute and assume any responsibilities associated with homemaking; or cannot understand or carry out any school assignments

The psychosocial adaptability or "employability" item takes into account overall cognitive and physical ability to be an employee, homemaker or student.
This determination should take into account considerations such as the following:

1. Able to understand, remember and follow instructions.
2. Can plan and carry out tasks at least at the level of an office clerk or in simple routine, repetitive industrial situation or can do school assignments.
3. Ability to remain oriented, relevant and appropriate in work and other psychosocial situations.
4. Ability to get to and from work or shopping centers using private or public transportation effectively.
5. Ability to deal with number concepts.
6. Ability to make purchases and handle simple money exchange problems
7. Ability to keep track of time and appointments

Revised 03/2010

13.9 APPENDIX 9 – THE UNIVERSITY OF OTTAWA HEART INSTITUTE AND THE OTTAWA HOSPITAL THERAPEUTIC HYPOTHERMIA PROTOCOL



The Ottawa Hospital
L'Hôpital d'Ottawa

☐ Civic
☐ General-Général

EMERGENCY DEPARTMENT PHYSICIAN'S ORDERS
ORDONNANCES MÉDICALES

Medication Allergies / Reaction	Substances or Food Allergies / Reactions
☐ none known –aucune connue	☐ none known –aucune connue

NON-MEDICATION –SANS MÉDICAMENTS Init.

I.V. & MEDICATION-SOLUTÉ & MÉDICAMENTS Init.
(Meds, dose-posologie, route-voie, frequency-fréquence)

ED Therapeutic Hypothermia Post Cardiac Arrest

Inclusion Criteria:
- Greater than 18 years of age
- Witnessed cardiac arrest from ventricular fibrillation or non-perfusing ventricular tachycardia
- Return of spontaneous circulation (ROSC) without full neurological recovery not attributed to sedation

Exclusion Criteria:
- Greater than 30 min from arrest to ACLS
- Greater than 60 min from arrest to return of spontaneous circulation (ROSC)
- Refractory shock (MAP less than 60 mmHg for greater than 30 min after ROSC despite vasopressors)
- Refractory hypoxia (O_2 sats less than 85% for more than 15 min after ROSC despite adequate ventilation)
- Severe coagulopathy with clinical evidence of bleeding

Goals:
- **Priority transfer to ICU or CCU for definitive management**
- Start active cooling measures within 2 hours after ROSC
- Decrease core temperature to 34C but not lower than 34C in the Emergency Department

NON-MEDICATION INVESTIGATIONS/TREATMENTS
Do not Delay PCI for cooling measures

- Call a CODE STEMI if meets STEMI criteria
- Institute STEMI protocol in parallel with cooling
- Call a CODE ROSC if patient does not meet STEMI criteria, but is a candidate for cooling

Monitoring:
- Continuous cardiac and core temperature monitoring
- Vital signs q 5 minutes
- Baseline QTc measurement and q4h
- Baseline neuro vital signs and q 1h
- Maintain SaO2 greater than 92% and MAP 65 mmHg
- Monitor for shivering and seizure activity

Investigations:
- 12 lead ECG stat (consider 15 lead)
- CBC, Na, K, Cl, CO_2, urea, Cr, Glu, CK, cTnI, ptt, INR, anti Xa, Ca, Mg, PO_4, AST, ALT, lipase, bilirubin, ABG

Treatment:
- Intubation and mechanical ventilation on a rate
- Foley catheter with temperature sensor
- Nasopharyngeal temperature probe
- Apply ice packs to head, neck, axilla, groin and proximal limbs or cooling blanket set to 34 C. Rotate ice packs q 20 min and do skin checks q2h
- Patient should remain minimally covered
- Hold cooling measures if temperature less than 34C
- Notify MD if temperature is less than 33C

IV & MEDICATION
(Meds, dose, route, frequency)

Patient's weight kg_ _____

IV THERAPY:

- IV Normal Saline at _____ml/ hour
- Use room temperature IV fluids

SEDATION

☐ Midazolam (Versed)
1. Midazolam (Versed) 1-2 mg IV bolus. Repeat q 5 min for agitation **(Max 10 mg/hr). Consider propofol (Diprivan) if greater that 10mg/ hour required for sedation.**

☐ Propofol (Diprivan)
1. **Vasopressor support may be required to maintain adequate MAP when propofol is administered**
2. Administer propofol (Diprivan) 10 - 20 mg IV bolus
3. Start propofol (Diprivan) infusion at 0.3 mg/kg/hr
4. Titrate infusion q 5 min to Riker score[a] of ____and minimum MAP of 65 mmHg. **(max. infusion rate 3 mg/kg/hr)**
5. Monitor BP q 2 min during titration. Evaluate Riker score[a] q1h and prn, and adjust infusion accordingly.
6. propofol (Diprivan) 10-20 mg IV bolus prn for agitation **(Max 60 mg/hr)**

Refer to propofol (Diprivan) infusion chart

ANALGESIA

☐ Fentanyl
1. Administer fentanyl 50 mcg IV bolus
2. Start fentanyl infusion at 1 mcg/kg/hr
3. Titrate infusion q 15 minutes and minimum MAP of 65 mmHg.
4. Fentanyl 25-50 mcg IV bolus prn **(Max. ___ mcg/hr)**

Refer to fentanyl infusion chart

PARALYSIS ONLY TO SUPPRESS SHIVERING

Ensure adequate sedation. Patient must be intubated and ventilated on a rate.

☐ Rocuronium _____mg IV bolus over 5 - 15 seconds (Recommended initial dose 0.6 mg/kg). **Max 50mg**

Date:	Time-Heure:	Physician–Médecin (printed-imprimé):	Signature:
Date (noted-notée) :	Time- Heure :	Processed by–Traitée par :	Signature (Nurse-Infirmière) :

SPO DRAFT July 10, 2011 1- CHART – DOSSIER 2- PHARMACY – PHARMACIE

14. REFERENCES

(1) Gouvier WD, Blanton PD, LaPorte KK, Nepomuceno C. Reliability and validity of the Disability Rating Scale and the Levels of Cognitive Functioning Scale in monitoring recovery from severe head injury. *Arch Phys Med Rehabil* 1987 February;68(2):94-7.

(2) Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002 February 21;346(8):549-56.

(3) Bernard SA, Smith K, Cameron P et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. *Circulation* 2010 August 17;122(7):737-42.

(4) Peberdy MA, Callaway CW, Neumar RW et al. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010 November 2;122(18 Suppl 3):S768-S786.

(5) Maze R, Le May MR, Hibbert B et al. The impact of therapeutic hypothermia as adjunctive therapy in a regional primary PCI program. *Resuscitation* 2012 August 21.

(6) Colbourne F, Sutherland G, Corbett D. Postischemic hypothermia. A critical appraisal with implications for clinical treatment. *Mol Neurobiol* 1997 June;14(3):171-201.

(7) Steen PA, Newberg L, Milde JH, Michenfelder JD. Hypothermia and barbiturates: individual and combined effects on canine cerebral oxygen consumption. *Anesthesiology* 1983 June;58(6):527-32.

(8) Horburger D, Testori C, Sterz F et al. Mild therapeutic hypothermia improves outcomes compared with normothermia in cardiac-arrest patients--a retrospective chart review. *Crit Care Med* 2012 August;40(8):2315-9.

(9) Leonov Y, Sterz F, Safar P, Radovsky A. Moderate hypothermia after cardiac arrest of 17 minutes in dogs. Effect on cerebral and cardiac outcome. *Stroke* 1990 November;21(11):1600-6.

(10) Lopez-de-Sa E, Rey JR, Armada E et al. Hypothermia in comatose survivors from out-of-hospital cardiac arrest: pilot trial comparing 2 levels of target temperature. *Circulation* 2012 December 11;126(24):2826-33.

(11) Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007 March 8;356(10):1020-9.