NICE advice

Thermogard XP for therapeutic hypothermia after cardiac arrest

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Summary

The Thermogard XP temperature management system controls a patient's body temperature through central venous heat exchange. It can be used to induce and maintain therapeutic hypothermia in critically ill patients after cardiac arrest. One retrospective cohort study based on registry data found that Thermogard XP cooled the body more rapidly than surface-cooling devices with automatic temperature feedback systems. However, in this study, there was no statistically significant difference in neurological outcomes or in-hospital mortality. The per-patient consumable cost of Thermogard XP is between £500 and £900 depending on the type of catheter needed.

Product summary and likely place in therapy	Effectiveness and safety
• Thermogard XP controls a patient's body temperature through central venous heat exchange. It can be used for both cooling and warming clinical applications. This briefing focuses on its use for initiating and maintaining therapeutic hypothermia in critically ill adult patients after cardiac arrest. • Thermogard XP would be used in a hospital setting in place of standard interventions for the induction and maintenance of therapeutic cooling. • There is some uncertainty about the place in therapy of therapeutic hypothermia after cardiac arrest, compared with normothermia, and about the target temperature.	• Ten studies were identified that reported cooling efficiency outcomes in patients after cardiac arrest. One of these used the Thermogard XP device and 2 others used its immediate predecessor, the CoolGard 3000. The other 7 studies also used the CoolGard system but did not specify the version. • A retrospective cohort study based on registry data (n=803) reported no statistically significant difference in neurological outcomes or in-hospital mortality between the surface cooling and Thermogard XP groups. • One prospective case series using CoolGard 3000 (n=49) reported a time to target temperature of 33°C of 410 minutes. Faster cooling was associated with better neurological outcomes in this study. • One retrospective cohort study (n=1038) compared CoolGard 3000 against standard post-resuscitation therapy. The proportion of survivors with good neurological recovery was 53% in the CoolGard 3000 group and 34% in the standard care group.

Technical and patient factors	Cost and resource use
• The system circulates temperature-controlled saline within a closed-loop, multi-balloon intravascular catheter. The patient's blood is cooled or warmed as it passes over the saline-filled balloons. No fluid is infused into or removed from the patient. • The immediate predecessor to the Thermogard XP is the CoolGard 3000 system. The manufacturer states that the only notable difference between these 2 versions is that the Thermogard XP has increased cooling power output over the CoolGard 3000 (190 watts compared to 115 watts). • Using Thermogard requires the placement of a triple-lumen central venous catheter which provides saline inflow/outflow and standard central line ports for infusion, measuring central venous pressure and sampling. A temperature probe placed in the bladder is also needed.	• The list price of the Thermogard XP heat exchange control unit is £21,500. Single use intravascular catheters for use with the system range in price from £318.27 to £637.94. The single-use start-up kit is £235.87. A number of consumables, accessories and options are also available. • The UK supplier, Delta Surgical, may provide Thermogard XP control units free of charge to the NHS, based on commitment to purchase disposable components. • No published evidence on the resource consequences of Thermogard XP was identified.

Introduction

Cardiac arrest is caused by a loss of heart function. The heart stops pumping blood around the body, leading to loss of consciousness and death unless emergency resuscitation is given and the heart can be restarted to achieve the return of spontaneous circulation (ROSC). Post-cardiac arrest syndrome can occur after ROSC and involves multiple systems. It reflects a state of whole-body ischaemia (restricted blood supply) and subsequent reperfusion. Its severity depends on the duration and cause of cardiac arrest, often reflecting the underlying condition, pre-existing co-morbidities and other

complications of resuscitation. It can encompass post-cardiac arrest myocardial dysfunction and post-cardiac-arrest brain injury (Resuscitation Council (UK) 2010). Post-cardiac arrest brain injury can be manifested as any or all of the following: coma, seizures, involuntary muscle twitching, varying degrees of neurocognitive dysfunction and brain death. Cardiovascular instability can result in early mortality. Late mortality and morbidity can result from brain injury (the most common cause of death following ROSC), multi-organ failure and sepsis.

A recent analysis of the UK National Cardiac Arrest Audit database reported an overall incidence of adult in-hospital cardiac arrest of 1.6 per 1000 hospital admissions. Incidence varied seasonally, peaking in winter. Overall unadjusted survival to hospital discharge was 18.4%. The presenting rhythm was shockable (ventricular fibrillation or pulseless ventricular tachycardia) in 16.9% of cases and non-shockable (asystole or pulseless electrical activity) in 72.3%. The remaining 10.8% comprised non-shockable bradycardia, unknown rhythms (non-shockable and shockable) and some cases where the presenting rhythm was never determined or unknown. Rates of survival to hospital discharge associated with these rhythms were 49.0% and 10.5% respectively, but varied substantially across hospitals (Nolan 2014).

Published data for the out-of-hospital setting suggests that there are 38 all-rhythm cardiac arrests per 100,000 person-years in Europe that are attended by emergency medical services (EMS; Atwood 2005). In the NICE medical technologies innovation briefing on the RhinoChill intranasal cooling system for reducing temperature after cardiac arrest, these estimates were translated into 20,140 all-rhythm cardiac arrests occurring annually out-of-hospital and receiving emergency medical services care in England. A recent consensus paper from the British Heart Foundation, NHS England and Resuscitation Council UK (2014) highlights that the emergency medical services attempted to resuscitate approximately 28,000 cases of out-of-hospital cardiac arrest in England in 2013.

The impact of cardiac arrest on NHS resources in intensive care may be represented by the treatment of unconscious survivors, which accounts for 5.6% of the total UK adult general intensive care unit (ICU) bed days in the Intensive Care National Audit and Research Centre Case Mix Programme Database (ICNARC CMPD; Nolan 2007).

Therapeutic hypothermia (also called targeted temperature management) has gained support as a method to counteract the destructive mechanisms of cardiac arrest, although there is some uncertainty both about the benefits of this approach compared with

normothermia and about the optimal target temperature for hypothermia. A Cochrane Review (Arrich et al. 2012) of hypothermia for neuroprotection in adults after cardiopulmonary resuscitation concluded that conventional cooling methods to induce mild therapeutic hypothermia improved survival and neurological outcomes. A more recent review of clinical trial data concluded that mild hypothermia, defined as a reduction of core temperature to 32–34°C, is the only proven way to improve survival and neurological outcomes after sudden cardiac arrest (Weng 2012). Regarding the optimum target temperature for therapeutic hypothermia, 1 large, high quality randomised controlled trial concluded that, in unconscious survivors of out-of-hospital cardiac arrest of presumed cardiac cause, hypothermia at a target temperature of 33°C did not confer any benefit over maintaining a target temperature of normothermia at 36°C (Nielsen 2013). Updated guidelines from the UK Resuscitation Council on the place in management of therapeutic hypothermia are planned to publish during 2015.

This briefing focuses on the Thermogard XP temperature management system for achieving therapeutic hypothermia after cardiac arrest.

Technology overview

This briefing describes the regulated use of the technology for the indication specified, in the setting described, and with any other specific equipment referred to. It is the responsibility of healthcare professionals to check the regulatory status of any intended use of the technology in other indications and settings. Thermogard XP can also be used for therapeutic warming to prevent perioperative hypothermia, and therapeutic cooling to manage intracranial pressure and for fever and burns. These indications are beyond the scope of this briefing.

About the technology

Thermogard XP manages a patient's core body temperature through central venous heat exchange. The system circulates temperature-controlled saline in a closed-loop, multi-balloon intravascular catheter. The patient is cooled or warmed as venous blood passes over the balloons. No fluid is infused into or removed from the patient. The environmental operating temperature range for the system is 10–27°C. This briefing refers to the cooling application only.

Thermogard XP is the latest version of the intravascular temperature management system

from Zoll Medical Corporation. The first generation CoolGard 2050, originally manufactured by Alsius Corporation, became commercially available in 2000 and was replaced by the CoolGard 3000 in 2002. The current Thermogard XP was introduced in 2008 and the company has stated that it has an increased cooling power output of 190 watts compared with 115 watts for CoolGard 3000. Both Thermogard XP and CoolGard 3000 have the same user interface, use the same disposable accessories and are operated in the same way.

CE marking

The CoolGard 3000 heat exchange control unit (class IIb), start-up kit (sterile class I) and central venous heat exchange catheters (class III) were CE marked to Alsius Corporation in November 2003. An addendum for the current Thermogard XP heat exchange control unit (class IIb) was added in September 2009. The current certification for control unit, start-up kit and catheters was awarded to Zoll Circulation in January 2014, and is valid until December 2016.

Description

The system consists of 3 main components:

- The Thermogard XP heat exchange control unit, which is a moveable mains-powered console (114 cm high x 43 cm wide x 76 cm deep and weighing 52 kg), consisting of a chiller and heater with a range of 0.5°C to 42°C, a 2 litre coolant well and a coolant circulating pump. It is controlled using the push buttons and rotary control knob located under the colour display, which is mounted on the integrated stand. The display shows system status, menus, messages, alarms and patient temperature trend graphs.

- A sterile, single-use, heparin-coated intravascular catheter which is inserted as a central venous line and positioned in the inferior vena cava. The triple-lumen catheters provide saline inflow and outflow connectors, in addition to standard central line ports for infusion, measuring central venous pressure and sampling. Three catheter lengths are available, branded as Cool Line (22 cm long with 2 heat exchange balloons), Icy (38 cm long with 3 heat exchange balloons) and Quattro (45 cm long with 4 heat exchange balloons). Icy and Quattro are inserted via the femoral vein, whereas the shorter Cool Line can be inserted via the subclavical or internal jugular vein access site. The intravascular catheter is inserted by a trained clinician using the Seldinger technique and connected to the primed start-up kit via keyed Luer connectors.
- A sterile, single-use 'start-up kit' connecting the catheter to the control unit. The pre-assembled kit consists of a stainless steel heat exchange coil, an air trap to prevent air embolism in the patient, and interconnecting tubing with an inline flow indicator and a saline bag spike.

The start-up kit coil sits in the coolant well which is filled with an equal mixture of propylene glycol and distilled water. After placing the air trap in its holder, the tubing is routed through a peristaltic pump mounted on top of the Thermogard XP control unit. The start-up kit tubing is then primed using a standard 500 ml saline bag, which is placed inside an insulating jacket and hooked onto the integrated stand. A syringe is used to manually prime the intravascular catheter with sterile saline prior to patient insertion, which is then connected to the primed start-up kit. Therapy can be started immediately, although full cooling capacity is only reached after 20 minutes of operation.

There are 4 treatment modes:

- 'Max power' is used to cool the patient to the target temperature as quickly as possible. This can achieve cooling rates of up to 3.5°C per hour and will maintain the patient to within 0.2°C of the target temperature.
- 'Controlled rate' is used to programme a specific cooling or warming rate of between 0.1°C and 0.65°C per hour. The system reverts to 'max power' mode once target temperature is reached.
- 'Fever' is a cooling-only mode to maintain normothermia when the patient's temperature rises above the target temperature. High and low patient temperature safety alarms can be set.

- 'Warming' warms the patient when their temperature falls below the target temperature.

After setting the target patient temperature between 31°C and 38°C and selecting the treatment mode, therapy is started by changing the Thermogard XP from standby to run mode. The pump then circulates the temperature-controlled saline through the closed-loop start-up kit and intravascular catheter. The catheter balloons act as a heat exchange surface between the circulating saline and the patient's bloodstream.

As cooled blood circulates throughout the body, patient temperature is monitored by 1 or 2 temperature probes connected via an interface cable. A Foley catheter-type temperature probe placed in the bladder is recommended as the primary sensing probe. A secondary probe can be placed in the rectum or oesophagus to act as a back-up in the event of the primary sensor's failure. If this back-up is not used, the patient must be monitored by a separate temperature monitor. Coolant temperature is automatically adjusted to achieve and maintain operator-selected target patient temperature. Patient temperature trend graphs can be viewed at any point during therapy.

An optional interface accessory mounts to the rear panel of the main display, allowing the patient temperature (as measured using the primary probe) to be simultaneously displayed on an external patient monitor.

After treatment, patient temperature and system activity data must be either deleted or downloaded via the control unit serial interface to a PC installed with TempTrend software (supplied as standard) for viewing, before use on the next patient.

Setting and intended use

The Thermogard XP would be used in hospital settings including the operating theatre, recovery room and intensive care unit on critically ill adult patients with central line venous access. The system would be used by anaesthetists, theatre nurses and intensive care unit staff trained in central venous catheterisation who have appropriate training in using the system.

Current NHS options

The adult advanced life support chapter of the Resuscitation Council UK Guidelines 2010 states that therapeutic hypothermia can be used in post-resuscitation care, including in

comatose survivors of cardiac arrest associated with both shockable and non-shockable rhythms, although there is less evidence to support its use after cardiac arrest from non-shockable rhythms. NICE interventional procedures guidance on therapeutic hypothermia following cardiac arrest states that the evidence for the safety and efficacy of the procedure is adequate to support its use with normal arrangements for clinical governance, audit and consent.

The standard application of therapeutic hypothermia in current NHS practice is divided into 3 phases: induction, maintenance and rewarming.

External or internal cooling techniques can be used to induce cooling. Methods to induce or maintain hypothermia include the infusion of 4°C 0.9% sodium chloride or Hartmann's solution, simple ice packs or wet towels, cooling blankets or pads, water or air circulating blankets, water-circulating gel-coated pads, intravascular heat exchangers and cardiopulmonary bypass (Resuscitation Council UK 2010).

In the maintenance phase, the main goal is to avoid temperature fluctuations. This is best achieved with external or internal cooling devices that include continuous temperature feedback to achieve a set target temperature (Resuscitation Council UK 2010).

After cardiac arrest, comatose patients who have a return of spontaneous circulation can be cooled to a core temperature of 32–34°C to improve neurological outcomes. The patient's body is maintained at this temperature for 12–24 hours from the start of cooling and is monitored using a bladder temperature probe. In addition to cooling, patients generally also have standard critical care interventions, intravenous sedation and muscle relaxants (to prevent shivering). The guidance also recognises that prevention of rebound pyrexia is important for up to 72 hours from rewarming (Nielsen 2013).

NICE is not aware of any other CE-marked devices that have a similar mode of action to the Thermogard XP intravascular temperature management system.

Costs and use of the technology

Thermogard XP consists of 3 main components and a number of consumables, accessories and options. The UK supplier of the Thermogard XP, Delta Surgical, has provided the following list prices (excluding VAT):

- Thermogard XP heat exchange control unit: £21,500. Delta Surgical Limited may also provide Thermogard XP units free of charge in the UK, dependent upon committed volumes of consumable orders.
- Intravascular catheters (single use):
  - Cool Line £318.27
  - Icy £509.85
  - Quattro £637.94
- Start-up kit (model CG-500D, single use): £235.87
- Foley temperature probe (single use) £10.00
- Temperature probe interface cable: £89.00
- Propylene glycol coolant (1 gallon): £30.00
- Coolant well lid: £150.00
- Hospital monitor interface accessory option: £1759
- The optional secondary temperature probe would need to be supplied by the hospital at a cost of £1.54.

The Thermogard XP has an anticipated lifespan of approximately 10 years and comes with a 12-month warranty. The maximum continuous operating time is 7 days for the single use start-up kit. The Icy and Quattro catheters may be left in place for up to 4 days, whereas the Cool Line catheter may be used for up to 7 days. These components must be replaced if longer treatment is needed.

Depending on which catheter is used, the cost per patient treatment for single-use components ranges from £574.14 to £893.81 (excluding VAT).

Delta Surgical provides on-site training covering all aspects of the Thermogard XP system. Training is provided free of charge as part of the installation and includes indication-specific sessions, training aids and manuals. Training following system updates and refresher training is provided as part of ongoing support at no additional cost.

The Zoll Service Centre offers 3 maintenance contract options:

- on-demand for repairs and corrective maintenance
- annual preventative maintenance, which includes call out, labour, parts and all specified cleaning, checks and tests (including software and hardware upgrades)
- annual full protection, which combines the 2 other options and includes the use of a loan system if needed.

In addition, Delta Surgical provides a free-of-charge, biennial mini-service package across the lifespan of the system. This includes a coolant and filter change, flow rate test, and anonymised patient treatment data and event log download and analysis.

Likely place in therapy

The Thermogard XP system is used in a hospital setting for the induction, maintenance and rewarming phases of therapeutic hypothermia after cardiac arrest, in patients with ROSC. The system would replace current standard methods with little change to the overall care pathway.

Specialist commentator comments

One specialist commentator noted that a practical advantage of Thermogard XP is that it needs the least additional work from nursing staff compared with other cooling methods and cannot cause thermal injury to the skin of a patient. It does, however, carry the risks associated with central venous access devices, although because this patient group is likely to need such central access this is not necessarily an additional risk. The system has been in routine use for just over 1 year in their patient pathway following non-traumatic cardiac arrest with no adverse effects and an audit demonstrated effective targeted temperature management in this patient group.

A second specialist commentator stated that the problem of rebound pyrexia is clinically significant and the extended normothermia period is one explanation of the overall good outcomes reported in a large, high quality randomised controlled trial comparing various temperature management devices following ROSC (Nielsen et al. 2013). Rebound pyrexia can be difficult to prevent with surface cooling devices alone. The improved power of the Thermogard XP compared with the CoolGard 3000 suggests it will be more effective in preventing rebound pyrexia.

Regarding the optimum target temperature for therapeutic hypothermia, 3 specialist commentators concurred with the findings of Nielsen (2013), with 1 stating that this is currently the best quality evidence to inform the rationale and practice for cooling following out-of-hospital cardiac arrest. Another specialist commentator advised that maintaining normothermia will have fewer side effects than hypothermia and therefore, despite Nielsen (2013) being a single study, many intensive care units in the UK have adopted a normothermic approach. They also indicated that this has obvious financial implications since it is easier to achieve with cheaper equipment.

One specialist commentator noted that the forthcoming International Liaison Committee on Resuscitation and subsequent revised UK Resuscitation Council guidelines, both due in 2015, will reflect such new evidence, including a move to targeted temperature management at 36°C.

Equality considerations

NICE is committed to promoting equality and eliminating unlawful discrimination. In producing guidance, NICE aims to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women
- eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

The Thermogard XP system is indicated for use with adults only. Age is a protected characteristic under the 2010 Equality Act.

Evidence review

Clinical and technical evidence

Regulatory bodies

A search of the Medicines and Healthcare Products Regulatory Agency website revealed no manufacturer Field Safety Notices or Medical Device Alerts for this device.

Sixteen reports, relating to 14 separate adverse events, were identified from a search of the US Food and Drug Administration (FDA) database: Manufacturer and User Device Facility Experience (MAUDE). These reports were dated between November 2010 and March 2015. When investigated by the manufacturer, many of these reported events were either found to be non-system faults, irreproducible faults, or cases where the system in question was not returned to the manufacturer for investigation. Malfunctions confirmed by the manufacturer included:

- a defective lower controller board, which resulted in failure of the coolant to reduce in temperature
- a clogged cold well mesh, which resulted in the system failing to cool the patient
- leaking coolant, which resulted in the system failing to cool the patient
- a damaged temperature sensor and wire harness, which resulted in the system failing to cool.

One further event, dated 4 March 2015, does not yet appear to have been investigated by the manufacturer. This event reported a small hole in the catheter, resulting in the system alarm activating. The intravascular solution bag was found to be empty and the catheter had to be removed.

Clinical evidence

Ten studies reporting cooling efficiency outcomes following cardiac arrest were identified. Only 1 of these explicitly stated that the Thermogard XP device was used (Oh et al. 2015). Two others stated that its immediate predecessor, the CoolGard 3000, was used (Holzer et al. 2006; Wolff et al. 2009). The Thermogard XP has increased cooling power

output compared with the CoolGard 3000 (190 watts compared to 115 watts). These 3 studies were assessed in full in this briefing.

Although the other 7 studies stated that they used the CoolGard system, it was not clear which version was used. Because the earlier CoolGard 2050 system had a different operation and user interface to both the CoolGard 3000 and Thermogard XP, these other studies are included in summary form only (table 7).

The study by Oh et al. (2015) used the Thermogard XP. This retrospective cohort study analysed South Korean registry data from 24 hospitals collected between 2007 and 2012 to compare the neurological outcomes, efficacy and adverse events of various surface cooling techniques (with and without an automatic temperature feedback system), compared with Thermogard XP, following cardiac arrest. Results were reported for the whole cohort and further matching was done to adjust for the baseline characteristics in the Thermogard XP and surface cooling groups. The outcomes were then re-evaluated in the matched cohort.

Cooling efficacy was reported as induction time to target temperature in minutes. In the Thermogard XP group, target temperature was achieved in an average of 209.4±15.4 minutes, compared with 235.3±18.0 minutes for surface cooling devices (odds ratio 1.13, 95% confidence interval [CI] 0.79 to 1.62, p=0.51). There was no significant difference in neurological outcomes or hospital mortality between the surface cooling and Thermogard XP groups (p=0.31 and p=0.44, respectively). The rates of some adverse events were statistically significantly higher in the surface cooling group compared with the Thermogard XP cooling group including overcooling, rebound hyperthermia, rewarming-related hypoglycaemia and rewarming-related hypotension. These complications were not associated with surface cooling using hydrogel pads (which employ automatic temperature feedback regulation). An overview and summary of results from Oh et al. (2015) are included in appendix tables 1 and 2.

Holzer et al. (2006) investigated the effectiveness and safety of the CoolGard 3000 in 1038 people consecutively admitted following cardiac arrest by collating retrospective clinical data in a bespoke registry format. The hypothermia group consisted of 97 patients who had the CoolGard 3000 to achieve a target temperature of 33°C. patients who had standard post-resuscitation therapy, comprising analgesia and sedation, served as controls (941 patients). Patients who had initiation cooling through cold infusion as well as the CoolGard 3000 were excluded from analysis of cooling rate. This resulted in 56 of 97 CoolGard 3000 patients contributing to the analysis of cooling rate, which was reported as

1.2°C per hour, with an interquartile range of 0.7 to 1.5°C per hour. The primary reported outcome of survival at 30 days was 69% (67/97) in the CoolGard 3000 group and 50% (466/941) in the standard care group (odds ratio 2.28, 95% CI: 1.19 to 3.23, p=0.008). When neurological outcome was considered, the proportion of patients with good neurological recovery (defined as alert and with sufficient cerebral function to live independently and work part-time) was 53% (51/97) in the CoolGard 3000 group and 34% (320/941) in the standard care group (odds ratio 2.15, 95% CI: 1.57 to 4.17, p<0.001). The only statistically significant difference in adverse events between the 2 groups was transient bradycardia, with 15% (9/62) reported in the CoolGard 3000 group and 3% (2/104) in the standard care group (p=0.025). The authors concluded that treatment with the CoolGard 3000 after resuscitation following cardiac arrest reduced mortality and improved favourable neurological recovery at 30 days after cardiac arrest, or discharge (if sooner), compared with controls from a retrospective resuscitation database. An overview and summary of results from Holzer et al. (2006) are included in appendix tables 3 and 4.

Wolff et al. (2009) conducted a prospective case series of 49 patients with documented out-of-hospital or in-hospital cardiac arrest in a single tertiary hospital in Germany, with the hypothesis that the clinical benefit of mild therapeutic hypothermia (in the range of 32 to 34°C) is greater when more rapidly achieved. All of the patients were cooled using the CoolGard 3000, with a target temperature of 33°C. The median time to target temperature was 410 minutes (interquartile range 271 to 544 minutes). Based on the neurological outcome at discharge, the patient group was split into good outcomes (no/mild cerebral disability; cerebral performance categories 1 and 2) and poor outcomes (severe disability, coma, brain death; cerebral performance categories 3–5). The median time to target temperature for good outcome (28 patients) was 334 minutes (interquartile range 250 to 498 minutes) compared with 450 minutes (interquartile range 322 to 674 minutes) in the poor outcome group (21 patients; p=0.71). Mild therapeutic hypothermia was maintained adequately for 24 hours in all patients. The authors concluded that achieving mild therapeutic hypothermia early improves neurological outcomes and thus measures to speed up the initiation of cooling therapy after cardiac arrest appear warranted. An overview and summary of results from Wolff et al. (2009) are included in appendix tables 5 and 6.

The 7 additional studies investigated the cooling efficiency of unspecified models of the CoolGard system. Three studies compared CoolGard with surface cooling systems that have automatic temperature feedback control (de Waard et al. 2014; Pittl et al. 2013; Tømte et al. 2011), 2 compared it with surface cooling systems without automatic temperature feedback control (Knapik et al. 2011, Flemming et al. 2006), and 1 compared it

with both system types (Gillies et al. 2010). This briefing also includes a single non-comparative study (Pichon et al. 2007).

In the studies which compared CoolGard with surface cooling systems that have automatic temperature feedback control, CoolGard tended to have a similar cooling rate but better temperature control in the maintenance phase. As with the findings from Oh et al. (2015) regarding the Thermogard XP compared with hydrogel pads (a surface cooling system with automatic temperature feedback control), these 3 studies showed no significant differences in survival to hospital discharge and neurological outcomes. The study by de Waard et al. (2014) reported a measured cooling rate of 0.65°C per hour for CoolGard compared with the 1.2°C per hour reported for the CoolGard 3000 by Holzer et al. (2006). de Waard et al. also reported an improved Glasgow Coma Scale of 15 at discharge in the CoolGard group (interquartile range 3 to 15) compared with 10 in the surface cooling group (interquartile range 4 to 13; p=0.008.)

In the studies comparing CoolGard with surface cooling systems without automatic temperature feedback control, CoolGard tended to demonstrate both improved cooling rate and better temperature control.

In the final CoolGard study (Pichon et al. 2007), the authors reported an average time to the 33°C target temperature of 187 minutes (interquartile range 30 to 600 minutes), with hypothermia maintained in 91% of patients.

A summary of the results from these 7 additional studies is included in table 7.

Recent and ongoing studies

Two relevant ongoing or in-development trials of the Thermogard XP (or its predecessor devices) were identified in the preparation of this briefing:

- The COOL-ARREST pilot study, for witnessed out-of-hospital cardiac arrest (ClinicalTrials.gov identifier NCT01818388)
- Finding the Optimal Cooling Temperature After Out-of-Hospital Cardiac Arrest (FROSTI) for 3 different levels of hypothermia (32, 33 and 34°C), in comatose survivors from out-of-hospital cardiac arrest (ClinicalTrials.gov identifier NCT02035839).

Costs and resource consequences

The UK supplier, Delta Surgical, reported that as of April 2015, 56 hospitals across the UK were using the technology. Therapeutic hypothermia is accepted as routine clinical practice in the intensive care setting in the NHS according to NICE interventional procedure guidance on therapeutic hypothermia following cardiac arrest.

No published evidence on the resource consequences of Thermogard XP was identified.

One paper was identified which addressed key nursing aspects of implementing the CoolGard 3000 and surface cooling methods (Thermowrap and Arctic Sun, plus ice-water soaked towels) in critical care. Våga et al. (2008) surveyed intensive care nurses to subjectively evaluate ease of use, visual patient monitoring, workload, hygiene and noise level on a 4-point scale (1=worst, 4=best possible). There were some statistically significant differences in the results. For workload, all 3 commercial cooling devices scored significantly better than ice-water soaked towels ($p<0.05$). Only the CoolGard 3000 system scored significantly better than ice-water soaked towels for visual patient monitoring ($p<0.001$).

Strengths and limitations of the evidence

Although only 1 paper was found within the scope of this briefing that explicitly identified the Thermogard XP device for cooling following cardiac arrest (Oh et al. 2015), there is a large evidence base for its predecessor technology the CoolGard 3000. It was judged reasonable to assume that evidence for the CoolGard 3000 would be generalisable to the Thermogard XP, since both systems have the same user interface, use the same disposable accessories, and are operated the same. The only difference between the systems is the increased cooling power output of the Thermogard XP.

The retrospective and multicentre nature of the Oh et al. (2015) registry introduced the possibility of selection bias and reporting bias in the study. With regard to cooling efficiency, the target temperature was not reported. Because local clinical cooling protocols were likely to vary across the 24 hospitals recruited in the registry, the influence of target temperature on induction time to cooling could not be quantified. In addition, the authors highlighted that a number of confounding factors including cardiac interventions, haemodynamic status, time of endovascular catheter insertion following cardiac arrest and complications relating to vascular access were not recorded in the registry data fields. A lack of data on these confounders means that the reported cooling and adverse event

rates should be interpreted with caution. One strength of this study was the analysis carried out to adjust for differences in the baseline characteristics of each cohort. However, after the matching process was implemented, the final sample size was relatively small and comparisons had low statistical power, which was illustrated by the wide confidence intervals for the odds ratios in a number of the reported outcomes. It was also notable that this study was set in South Korea and therefore differences in the care pathways and population may limit generalisability to the NHS setting.

Similar to the study by Oh et al. (2015), Holzer et al. (2006) adopted a retrospective data analysis approach. In this instance, the authors compiled a bespoke registry from historical clinical data, which introduces the potential for selection bias and reporting bias. However, because these data are taken from a single institution in Austria, the study may be less susceptible to multicentre variations in clinical practice. Holzer et al. do not report cooling efficacy as a predefined outcome measure, but the authors present their cooling protocol in sufficient detail to obtain comparative data for the purposes of this briefing. Potential confounders, including variability in baseline characteristics, are robustly addressed in the data analysis and statistical treatment. However, the study was not blinded for the assessment of neurological outcome, which the authors state could have led to information bias. The primary end point of survival was objective and therefore robust. Disclosures by these authors make clear that the study was conducted with financial support from the manufacturer, although the company was not involved in key decisions around study design, data analysis and final manuscript content.

Wolff et al. (2009) was a non-comparative study with a sample size of 49 patients. Consecutive enrolment of eligible patients in this prospective case series minimised selection bias, but the post-hoc nature of stratification by neurological outcomes at discharge may be viewed as a weakness in the study design. The authors acknowledged the heterogeneous patient characteristics, including cardiac arrest occurring both in and out of hospital, with ventricular fibrillation/tachycardia and asystole. Although this may introduce potential confounders into the study, it is likely to be a realistic reflection of daily practice. A multivariate analysis was also done to adjust for differences in the baseline characteristics between good and poor outcomes. The authors reported that 11 of the 49 patients failed to reach the target temperature of 33°C, despite maximum cooling rates being applied. This may be explained by the inclusion of patients with potentially concurrent infection or neurogenic fever occurring as a result of severe anoxic brain injury. Each of these conditions would typically raise core body temperature, counteracting the cooling effect of the therapeutic hypothermia intervention.

Relevance to NICE guidance programmes

NICE has issued the following guidance:

- Therapeutic hypothermia following cardiac arrest (2011) NICE interventional procedures guidance 386
- The RhinoChill intranasal cooling system for reducing temperature after cardiac arrest (2014) NICE medtech innovation briefing 4

References

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Search strategy and evidence selection

Search strategy

The search strategy was designed to identify evidence on the clinical and cost effectiveness of Thermogard for therapeutic cooling in post-cardiac arrest.

The strategy was developed for MEDLINE (Ovid interface). The strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields. The search terms were identified through discussion within the research team, scanning background literature, browsing database thesauri and use of the PubMed PubReMiner tool. The strategy reflected the nature of the MIB assessments as rapid evidence reviews.

The main structure of the search strategy comprised 3 concepts:

- induced hypothermia
- key device characteristic – intravascular delivery
- cardiac arrest.

The search concepts were combined as follows: Induced hypothermia AND key device characteristic AND cardiac arrest.

Additional search lines included a search on manufacturer terms, a search on device brand name terms, and highly focused searches on invasive cooling, non-specific cooling systems and devices described as 'temperature modulation' therapies. These additional lines were designed to capture any records that may have been missed by the main 3-concept approach.

The strategy excluded non-English language publications. Animal studies were also excluded using a standard algorithm. No additional filters for study design were applied. Results were limited to studies published from 2000. This date reflected the year in which the device first became commercially available.

The final MEDLINE strategy was peer-reviewed by an independent information specialist. The MEDLINE strategy was translated appropriately for the other databases searched. The PubMed search was limited to records which were not fully indexed on MEDLINE. Conference-related records were excluded from the Embase search.

The following databases were searched:

- Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley)
- Cochrane Database of Systematic Reviews (Cochrane Library, Wiley)
- Database of Abstracts of Reviews of Effects (Cochrane Library, Wiley)
- Embase (Ovid SP)
- Health Technology Assessment Database (Cochrane Library, Wiley)
- MEDLINE and MEDLINE in Process (Ovid SP)
- NHS Economic Evaluation Database (Cochrane Library, Wiley)
- PubMed (online).

Evidence selection

A total of 997 records were retrieved from the literature search. After de-duplication, 594 records remained and were sifted against the inclusion criteria at title and abstract level.

Records were sifted independently by 2 researchers. Any disagreements were discussed

and agreement was reached in all cases, so a third independent arbiter was not required. The first sift removed 541 records based on the following exclusion criteria:

- articles of poor relevance against search terms
- publication types that were out of scope
- non-English language studies
- conference abstracts
- review articles.

Full articles were retrieved for the 53 remaining studies and a full text assessment was done independently by 2 researchers to identify relevant primary research addressing the key cooling efficiency outcomes of interest. One study explicitly investigated Thermogard XP and 2 additional studies explicitly stated that the intervention was the immediate predecessor CoolGard 3000 system. These 3 studies were included for full review.

A further 7 studies reporting relevant outcomes of interest stated that the intervention was the CoolGard system, but it could not be absolutely determined whether evidence from these 7 studies included cases using the earlier CoolGard 2050 system as the intervention.

Appendix

Contents

Table 6: Summary of results of Wolff et al. (2009)

Table 7: Summary of 7 additional studies on CoolGard

Table 1 Overview of the Oh et al. (2015) study

Study component	Description
Objectives/ hypotheses	To compare the neurological outcomes, effectiveness and adverse events of surface and endovascular cooling techniques in cardiac arrest patients.
Study design	Retrospective, observational cohort study with propensity-matched analysis.
Setting	24 teaching hospitals across South Korea contributing data to the Korean Hypothermia Network registry, from 2007 to 2012.
Inclusion/ exclusion criteria	Inclusion criteria: all adult cardiac arrest patients treated with therapeutic hypothermia using surface or endovascular cooling techniques. Exclusion criteria: traumatic cardiac arrest, patients receiving both surface and endovascular cooling techniques in combination. To adjust for differences in the baseline characteristics of patients undergoing each cooling method, 1 to 1 matching was performed using the propensity score.
Primary outcomes	Proportion of patients with poor neurological outcome at discharge, defined as Cerebral Performance Categories 3 to 5.

Statistical methods	Categorical variables were compared using the chi-square test or Fisher's exact test, where appropriate. The normality of the continuous variables was verified by the Shapiro–Wilk test. Thereafter, variables were expressed as the mean ± standard deviation and were compared using Student's t test, after confirming homogeneity of variance with Levene's test. For propensity score matching, multivariate logistic regression was used to model the dichotomous outcome of the surface or the endovascular cooling group for 803 patients in the study. The logistic model demonstrated a sufficient ability to differentiate between the two groups (c statistic=0.8). One-to-one matching with the propensity score used the Greedy-matching macro[a]. After propensity score matching, the success of the propensity score modelling was assessed by the standardised difference, and the balance of the two groups was evaluated using Student's t test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. After estimating the propensity scores, a logistic regression analysis was performed, to determine the prognosis factor (mortality, poor outcome). A probability value of $p<0.05$ was considered significant.
Patients included	803 patients were included in the analysis: 559 in the surface cooling group and 244 in the Thermogard XP cooling group. After propensity score matching, 379 patients were excluded from the surface cooling group and 64 patients were excluded from the Thermogard XP cooling group, leaving 180 in each arm for the matched analysis.

Results	With regard to the overall cohort patient baseline characteristics, the authors reported no differences in age, sex or underlying disease between the two study groups. After propensity score matching, there was no significant difference in neurological outcome or hospital mortality between the surface cooling and Thermogard XP groups (OR: 1.26, 95% CI: 0.81 to 1.96, p=0.31 and OR: 0.85, 95% CI: 0.55 to 1.30, p=0.44 respectively). With regard to cooling efficacy, both groups attained the target temperature in a similar amount of time. The rates of some adverse events were significantly increased in the surface cooling group compared with the Thermogard XP cooling group.
Conclusions	In the matched patient cohort, no significant differences in the rates of poor neurological outcomes and hospital mortality were observed between the surface cooling and Thermogard XP cooling groups. Overcooling, rebound hyperthermia, rewarming-related hypoglycaemia and rewarming-related hypotension were significantly increased in the surface cooling group compared with the Thermogard XP cooling group, although these complications were not associated with the surface cooling method using hydrogel pads (which employ automatic temperature feedback regulation).
Abbreviations: CI, confidence interval; n, number of patients; OR, odds ratio. [a] Parsons LS. (2001) Reducing bias in a propensity score matched-pair sample using Greedy matching techniques. Accessed 6 Jan 2015.	

Table 2 Summary of results from the Oh et al. (2015) study

	Thermogard XP	**Various surface cooling devices with automatic temperature feedback systems**	**Analysis**
Randomised	Not applicable	Not applicable	
Efficacy	n=180/244	n=180/559	

Primary outcome: Poor neurological outcome	65.0% (117/180)	70.0% (126/180)	OR 1.26 (95% CI 0.81 to 1.96) p=0.31
Selected secondary outcomes:			
Hospital mortality	38.3% (69/180)	34.4% (62/180)	OR 0.85 (95% CI 0.55 to 1.30) p=0.44
Induction time to target temperature (minutes)	209.4 ± 15.4	235.3 ± 18.0	OR 1.13 (95% CI 0.79 to 1.62) p=0.51
Safety: Overcooling	7.8% (14/180)	17.8% (32/180)	OR 2.56 (95% CI 1.32 to 4.99) p=0.01
Safety: Bradycardia	8.3% (15/180)	9.0% (16/180)	OR 1.09 (95% CI 0.52 to 2.27) p=0.83
Patients reporting serious adverse events:			
Sepsis in critical care	8.4% (15/180)	7.2% (13/180)	OR 0.85 (95% CI 0.39 to 1.84) p=0.68
Pneumonia in critical care	35.4% (63/180)	31.8% (57/180)	OR 0.85 (95% CI 0.55 to 1.32) p=0.48

Abbreviations: CI, confidence interval; n, number of patients; OR, odds ratio.

Table 3 Overview of the Holzer et al. (2006) study

Study component	Description
Objectives/ hypotheses	The aim of this study was to investigate the efficacy and safety of endovascular cooling in consecutively admitted survivors of cardiac arrest.
Study design	Retrospective, comparative cohort study with Bayesian approach.
Setting	Single tertiary teaching hospital in Austria. Retrospective clinical data from August 1991 to November 2004 were prospectively collated in a registry format.

Inclusion/ exclusion criteria	Eligibility criteria: • patients with witnessed cardiac arrest and successful restoration of spontaneous circulation. Exclusion criteria: • <18 years • cardiac arrest of traumatic or severe bleeding origin • terminal illness • pregnancy • pre-existing coagulopathy • tympanic membrane temperature below 30% on admission • received hypothermia with a method other than endovascular cooling • >240 minutes from restoration of spontaneous circulation until initiation of cooling • death within first 24 hours. The hypothermia group consisted of patients treated with CoolGard 3000 with the Icy catheter, with or without administration of infused cold fluids in the induction phase of hypothermia. All other patients served as controls. For the safety analysis, adverse events for the CoolGard 3000 group were predefined and recorded prospectively. Controls were selected by frequency matching. Matching criteria were witnessed out-of-hospital ventricular fibrillation cardiac arrest of presumed cardiac cause with duration of cardiac arrest longer than 1 minute. In the control group, a chart review was conducted to identify all adverse events. Arrhythmias and bleeding events were recorded between admission and 32 hours. Pneumonia, sepsis, acute renal failure and pancreatitis were recorded within the first 7 days.

Primary outcomes	Survival at 30 days after cardiac arrest. Neurological performance at 30 days using the cerebral performance category (CPC) score.
Statistical methods	Continuous variables were given as mean ± SD if they were normally distributed or as median and the range between the 25th and 75th quartile if they were not. Nominal data were given as counts and percentage of total number. Univariate comparisons between groups were conducted with a $\chi 2$ test or Fisher's exact test when indicated. For safety analyses, contingency tables and Fisher's exact tests were used.
Patients included	1038 patients met the inclusion criteria, 97 were treated with CoolGard 3000 and 941 served as controls. Of the 97 patients who were cooled with CoolGard 3000, 41 received additional cold Ringer's lactate during induction of hypothermia. As this might have influenced the calculated cooling rate of CoolGard 3000, the authors restricted the cooling efficacy analysis to patients who received endovascular cooling alone. Therefore, data from 56/97 CoolGard 3000 patients contributed to the analysis of cooling rate. In the matching process for the safety analysis, there were 62/97 patients in the CoolGard 3000 group and 104/941 in the control group.
Results	Regardless of treatment, 51% (533/1038) of patients survived for 30 days and 36% (371/1038) of patients survived for 30 days and had favourable neurological recovery (CPC 1 or 2). In the univariate analysis, patients in the CoolGard 3000 group had 2-fold increased odds of survival (67/97 patients versus 466/941 patients; odds ratio 2.28, 95% CI, 1.45 to 3.57; p<0.001). After adjustment for baseline imbalances in a multivariate model, the odds ratio was only slightly attenuated (odds ratio 1.96, 95% CI, 1.19 to 3.23; p=0.008). The model had an acceptable fit (Hosmer-Lemeshow $\chi 2$=7.39, df=8; p=0.495). When discounting the observational data in a Bayesian analysis by using a sceptical prior the posterior odds ratio was 1.61 (95% credible interval, 1.06 to 2.44).

Conclusions	Treatment of unselected patients after resuscitation from cardiac arrest with CoolGard 3000 significantly reduced mortality and improved favourable neurological recovery at 30 days or discharge as compared with controls from a retrospective resuscitation database. There was no statistically significant difference in adverse events between the CoolGard 3000 group and the control group, except for transient bradycardia. The cooling rate of 1.2°C/hour in this study was faster than external cooling with a water-filled cooling blanket or with cold air, based on previous studies in the literature.
Abbreviations: °C/h, degrees Centigrade per hour; CI, confidence interval; CPC, cerebral performance category score; df, degrees of freedom; n, number of patients; OR, odds ratio; SD, standard deviation; $\chi 2$, Chi-square test.	

Table 4 Summary of results from the Holzer et al. (2006) study

	CoolGard 3000 with Icy catheter	**Standard post-resuscitation therapy**	**Multivariate Analysis**
Randomised	Not applicable	Not applicable	
Efficacy	n=97 n=56/97[a]	n=941 n=466/941[b]	
Primary outcome: Survival to 30 days	69% (67/97)	50% (466/941)	OR 1.96 (95% CI 1.19 to 3.23) p=0.008
Selected secondary outcomes:			
Survival to 30 days, or until discharge, with Good Neurological Recovery[b]	53% (51/97)	34% (320/941)	OR 2.56 (95% CI 1.57 to 4.17) p<0.001
Cooling rate (°C/h) [Interquartile range, IQR]	1.2 [0.7–1.5]	Not applicable	-

Safety	n=62	n=104	-
Patients reporting serious adverse events			
Bradycardia	15% (9/62)	3% (2/104)	p=0.025

Abbreviations: °C/h, degrees Centigrade per hour; CI, confidence interval; CPC, cerebral performance category score; n, number of patients; OR, odds ratio; $\chi 2$, Chi-square test.

[a.] n=97 for reported primary clinical outcomes; n=56 for reported cooling rate.

[b.] Good neurological recovery in this study was defined as patients with a Cerebral Performance Category (CPC) score of 1 or 2 (the patient is at least alert and has sufficient cerebral function to live independently and work part-time).

Table 5 Overview of the Wolff et al. (2009) study

Study component	**Description**
Objectives/ hypotheses	The authors hypothesised that the clinical benefit of mild therapeutic hypothermia is greater when achieved more rapidly.
Study design	Prospective case series.
Setting	Single academic, regional, tertiary care hospital in Germany. Recruitment dates from June 2004 to February 2006.

Inclusion/ exclusion criteria	Eligibility criteria: • documented out-of-hospital or in-hospital cardiac arrest • successful CPR with return of a palpable arterial pulse >5 min • cardiac arrest for <20 min before the initiation of CPR attempts • restoration of spontaneous circulation within 60 min • comatose state after successful CPR (Glasgow Coma Scale ≤8). CA was defined as the absence of a palpable pulse and spontaneous respiration with ventricular fibrillation (VF), sustained pulseless ventricular tachycardia (VT) or asystole as the initial cardiac rhythm. Patients were excluded if they had malignancy or another terminal illness, pre-existing brain damage or a severe neurologic deficit (dementia, previous stroke, advanced/severe Parkinson's syndrome).
Primary outcomes	The primary endpoint was neurological outcome, based on defined 'cerebral performance categories:' Good outcomes related to no/mild cerebral disability (cerebral performance categories 1 and 2) and poor outcomes included severe disability, coma/vegetative state and brain death (cerebral performance categories 3–5). Association of the following time intervals from cardiac arrest to mild therapeutic hypothermia with neurological outcomes: • Time to cooling (time between onset of CA and initiation of cooling therapy) • Time to target temperature (TTT) (time between onset of CA and achievement of a body core T of 33°C) • Time to coldest temperature (TCT) (time between onset of CA and the coldest body core temperature recorded).

Statistical methods	Stepwise forward logistic regression with calculation of odds ratios (OR) to examine the effects of the cooling time variables on the primary endpoint (good neurological outcome). In addition, the following variables were included to control for potential confounding factors: • bystander CPR • asystole as initial cardiac rhythm • thrombolytic therapy • percutaneous coronary intervention • starting T (body core T before institution of cooling therapy) • body mass index (BMI) • location of cardiac arrest (in-hospital/out-of-hospital). Comparisons of continuous variables were made using the Mann–Whitney U-test. Categorical variables were compared by the use of a $\chi 2$ (Chi square) test or Fisher's exact test. All data are presented as median [interquartile range]. All tests are two-tailed. A probability value of $p<0.05$ was considered statistically significant.
Patients included	49 consecutive patients meeting the eligibility criteria were enrolled.

Results	Mild therapeutic hypothermia was maintained adequately for 24 hours in all patients. Complications such as sepsis, bleeding disorder, pneumonia, or thrombocytopenia did not occur in any patient during CoolGard 3000 cooling. There were no deaths during the CoolGard 3000 use. The time to cooling ranged between 35 minutes and 6 hours. Both time to target temperature (TTT) and time to coldest temperature (TCT) ranged between 2 hours 15 minutes and 23 hours 35 minutes. TCT was the only cooling variable with predictive value for the neurological outcome (OR for good outcome: 0.73, 95% CI 0.45–0.98; p=0.013). The target T of 33°C could not be achieved in 11 patients.
Conclusions	Early achievement of mild therapeutic hypothermia is a determinant of the final neurological outcome and thus measures to speed up the initiation of cooling therapy after cardiac arrest appear warranted.
Abbreviations: BMI, body mass index; CA, cardiac arrest; CI, confidence interval; CPR, cardiopulmonary resuscitation; n, number of patients; OR, odds ratio; T, temperature; TCT, time to coldest temperature; TTT, time to target temperature; VF, ventricular fibrillation; VT, ventricular tachycardia; $\chi 2$, Chi-square test. [a] Brain Resuscitation Clinical Trial I Study Group. (1986) A randomized clinical study of cardiopulmonary-cerebral resuscitation: design, methods and patient characteristics. American Journal of Emergency Medicine 4: 72–86.	

Table 6 Summary of results from the Wolff et al. (2009) study

	CoolGard 3000 **Good neurological outcome** **(No/mild cerebral disability)**	**CoolGard 3000** **Poor neurological outcome** **(Severe disability, coma/vegetative state, brain death)**	**Analysis**

Randomised	Not applicable	Not applicable	
Efficacy	n=28	n=21	
Primary outcome: Time to cooling [interquartile range] (minutes)	150 [114–199]	150 [98–198]	p=0.762
Primary outcome: Time to target temperature (TTT) [interquartile range] (minutes)	334 [250–498]	450 [322–674]	p=0.071
Primary outcome: Time to coldest temperature (TCT) [interquartile range] (minutes)	443 [280–543]	555 [425–985]	p=0.035
Selected secondary outcomes:			
Maximum serum neurone specific enolase (NSE) as a biochemical marker of brain damage [interquartile range] (µg/l)	18.7 [15.7–25.7]	58.8 [32.5–184.2]	p<0.001
Safety	Not applicable	Not applicable	-
Patients reporting serious adverse events	No events reported	No events reported	-
Abbreviations: n, number of patients; NSE, neurone specific enolase; TCT, time to coldest temperature; TTT, time to target temperature.			

Table 7 Summary of 7 additional studies on CoolGard

	CoolGard	**Various surface cooling techniques**	**Analysis**
Study 1 – Intravascular versus surface cooling speed and stability after cardiopulmonary resuscitation (de Waard et al. 2014)			

Design	Retrospective comparative study comparing the efficacy of CoolGard to non-invasive water-circulating body wraps (Medi-Therm, with automatic temperature feedback control)		
Randomised (if applicable)	Not applicable	Not applicable	
Efficacy	n=97	n=76	
Primary outcomes: Cooling efficacy			
Mean cooling speed [interquartile range] (°C/h)	0.65 [0.45–0.83]	0.7 [0.34–0.90]	p=0.95
Mean temperature (°C)	33.1 ± 0.3	32.5 ± 0.5	p<0.0001
Mean CV temperature [interquartile range] (%)	0.35 [0.18–0.60]	0.85 [0.50–1.29]	p<0.0001
Selected secondary outcomes:			
Glasgow Coma Scale at discharge from ICU	15 [3–15]	10 [4–13]	p=0.008
Length of stay (LOS) in ICU (hours)	144 [96–192]	172 [102–304]	p=0.08
Safety	n=97	n=76	–

Patients experiencing serious adverse events	None reported	None reported	–
Study 2 – Invasive versus non-invasive cooling after in- and out-of-hospital cardiac arrest: a randomized trial (Pittl et al. 2013)			
Design	Prospective, randomized, single centre study comparing the efficacy of CoolGard to the non-invasive ArcticSun surface cooling system (hydrogel pads with automatic temperature feedback control)		
Randomised	n=40	n=40	
Efficacy	n=39	n=39	
Primary outcomes: Neurological function			
Neurological outcome at 72 hours assessed by NSE values [interquartile range] (ng/ml)	19.0 [11.0–42.0]	16.5 [11.8–46.5]	p<0.0001
Survival with good neurological outcome during hospitalisation	35.9% (14/39)	35.9% (14/39)	p=0.99
Selected secondary outcomes: Cooling efficacy			

Cooling starting after sudden cardiac arrest [interquartile range] (mins)	242 [165–275]	180 [155–245]	p=0.13
Cooling rate [interquartile range] (°C/h)	1.3 [0.7–1.6]	1.0 [0.6–1.3]	p=0.29
Time to target temperature after the start of mild induced hypothermia (mins)	180 [150–330]	240 [180–390]	p=0.29
Target temperature maintenance (°C)	33.0 [32.9–33.0]	32.7 [32.4–32.9]	p<0.001
Safety	Not reported	Not reported	–
Patients experiencing serious adverse events	None reported	None reported	Other safety endpoints, such as infections or therapy requiring arrhythmia did not differ significantly.
Bleeding complication	17.9% (7/39)	43.6% (17/39)	p=0.03
Study 3 – Comparison of intravascular and conventional hypothermia after cardiac arrest (Knapik et al. 2011)			
Design	Prospective, non-randomised comparative study, comparing the efficacy of CoolGard with a traditional cooling using uncontrolled surface cooling, ice-cold intravenous fluids and ice-cold gastric lavage (without automatic temperature feedback control).		
Randomised	Not applicable	Not applicable	

Efficacy	n=20	n=21	
Primary outcomes: Cooling efficacy			
Urinary bladder temperature of <34°C reached	95.0% (19/20)	52.4% (11/21)	p=0.004
Mean time to achieve temperature of <34°C (hours)	4.0 ± 3.2	6.3 ± 4.3	Not significant
Stable temperature (32–34°C) during hypothermia reached	80% (16/20)	14.3% (3/20)	p<0.001
Selected secondary outcomes:			
Periods of inadequate cooling above 34°C	20% (6/20)	71.4% (15/21)	p=0.013
Periods of temperature overshoot below 32°C	0% (0/20)	19.1% (4/21)	Not significant
Safety	Not reported	Not reported	–
Patients experiencing serious adverse events	None reported	None reported	–

Study 4 – A comparison of intravascular and surface cooling techniques in comatose cardiac arrest survivors (Tømte et al. 2011)			
Design	Single centre observational comparative study, comparing the efficacy of CoolGard to the non-invasive ArcticSun surface cooling system (hydrogel pads with automatic temperature feedback control)		
Randomised	Not applicable	Not applicable	
Efficacy	n=75	n=92	
Primary outcomes: Cooling efficacy			
Median initiation of cooling to 34°C [interquartile range] (mins)	188 [86–256]	170 [83–240]	p=0.391
Median time for maintained hypothermia [interquartile range] (hours)	24 [24–24]	24 [24–24]	p=0.431
Selected secondary outcomes: Clinical outcomes			
Survival to final hospital discharge with good neurological function (CPC 1-2)	45% (34/75)	38% (34/90)	p=0.326

Median time in intensive care unit [interquartile range] (hours)	130 [74–213]	156 [74–213]	p=0.431
Safety	Not reported	Not reported	–
Patients experiencing serious adverse events			
Sustained hyperglycaemia (>8mmol/l) of >4 consecutive hours	48% (36/75)	70% (64/92)	p=0.005
Low serum magnesium (<0.7 mmol/l)	37% (27/74)	18% (16/87)	p=0.010
Study 5 – Therapeutic hypothermia after cardiac arrest: A retrospective comparison of surface and endovascular techniques (Gillies et al. 2010)			
Design	Retrospective comparative study comparing the efficacy of CoolGard to that of surface cooling systems including conventional ice packs, a cooling mattress and tent (Theracool, 2 patients, without automatic temperature feedback control), and a cold water recirculation system (CritiCool, 1 patient, with automatic temperature feedback control).		
Randomised	Not applicable	Not applicable	
Efficacy	n=42	n=41	
Primary outcomes: Cooling efficacy			

Mean time to target temperature (hours)	5.2 ± 3.3	6.1 ± 4.8	p=0.29
Mean time at target temperature (hours)	22.4 ± 6.1	17.5 ± 12.3	p=0.02
Average temperature fluctuation (°C) over 10–20 hours of maintenance phase	1.0 ± 0.8	1.7 ± 1.3	p=0.003
Selected secondary outcomes: Clinical outcomes			
ICU mortality	38.1% (16/42)	51.2% (21/41)	p=0.27
Poor neurological outcome	57.1% (24/42)	61.0% (25/41)	p=0.82
Safety	Not reported	Not reported	–
Patients experiencing serious adverse events	91% (38/42)	85% (35/41)	p=0.52
Overcooling	10% (4/42)	27% (11/41)	p=0.049
Target temperature not reached	7% (3/42)	24% (10/41)	p=0.04
Bleeding	14% (6/42)	2% (1/41)	p=0.11

Study 6 – Efficacy of and tolerance to mild induced hypothermia after out-of-hospital cardiac arrest using an endovascular cooling system (Pichon et al. 2007)			
Design	Prospective single-arm cohort study evaluating the efficacy of CoolGard.		
Randomised	Not applicable	Not applicable	
Efficacy	n=40	Not applicable	
Primary outcome: Cooling efficacy			
Time to target temperature of 33°C after initiation of MIH [interquartile range] (mins)	187 ± 119 [30–600]	Not applicable	–
Patients in which hypothermia was maintained	91% (31/34)*	Not applicable	*6 patients died during mild induced hypothermia
Selected secondary outcomes:			
Safety	Not reported	Not applicable	–
Patients experiencing serious adverse events	Not reported	Not applicable	–
Bleeding of any severity	8% (3/36)	Not applicable	–
Complication at catheter site	8% (3/36)	Not applicable	–

Nosocomial infection – septicaemia	13% (5/36)	Not applicable	–
Study 7 – Comparison of external and intravascular cooling to induce hypothermia in patients after CPR (Flemming et al. 2006)			
Design	Non-randomised comparative study comparing the efficacy of CoolGard to that of conventional cooling (Theracool, without automatic temperature feedback control, and additional use of cooling blankets and cold infusions when necessary).		
Randomised	Not applicable	Not applicable	
Efficacy	n=31	n=49	
Primary outcome: Cooling efficacy			
Achieved target temperature of 33°C	100% (31/31)	9% (4/49)	Not reported
Time to achieve target temperature (hours)	3.48 ± 0.6	9.2 ± 1.2*	Not reported * In this group a mean minimum temperature of 34.8°C was achieved after the onset of cooling
Selected secondary outcomes: Clinical outcomes			
Length of hospital stay (days)	13.7 ± 1.4	16.5 ± 1.6	p=0.17
Hospital mortality	26% (8/31)	22% (11/49)	p=0.2
Safety	Not reported	Not reported	–

Patients experiencing serious adverse events	None reported	None reported	–
Abbreviations: CPC, cerebral performance category; GCS, Glasgow Coma Scale; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MIH, mild induced hypothermia; mmol/l, millimole per litre; n, number of patients; ng/ml, nanogram per millilitre; NSE, neuron-specific enolase; °C/h, degrees Centigrade per hour.			

About this briefing

Medtech innovation briefings summarise the published evidence and information available for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers and procurement professionals.

Medtech innovation briefings aim to present information and critically review the strengths and weaknesses of the relevant evidence, but contain no recommendations and **are not formal NICE guidance**.

Changes after publication

September 2015: Minor maintenance.

Development of this briefing

This briefing was developed for NICE by Newcastle and York External Assessment Centre. The Interim process & methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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Specialist commentators

The following specialist commentators provided comments on a draft of this briefing:

- Dr John Andrzejowski, Consultant in Anaesthesia and Neurointensive care, Royal Hallamshire Hospital, Sheffield
- Dr Nick Fletcher, Consultant Anaesthetist for Cardiothoracic Surgery, St George's University Hospitals NHS Foundation Trust
- Dr Peter Isherwood, Consultant in Critical Care & Anaesthesia, University Hospitals Birmingham NHS Foundation Trust

Declarations of interest

- Nick Fletcher has been director of a course on the management of out-of-hospital cardiac arrest patients and the Thermogard technology is used in his trust.
- Peter Isherwood is the clinical lead for targeted temperature management in his trust which routinely uses the Thermogard technology as part of its pathway for comatose survivors of non-traumatic cardiac arrest.

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