NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of inducing and maintaining normothermia using temperature modulation devices to improve outcomes after stroke or subarachnoid haemorrhage

When blood flow to the brain is suddenly interrupted by a blockage (ischaemia) or bleeding (haemorrhage), brain cells are damaged. This may result in a high body temperature, which can further damage brain cells. In this procedure, a temperature modulation device cools the body using pads placed on the skin or tubes put into the body. This gradually brings the body temperature within a normal range (normothermia) and keeps it there. The aim is to reduce brain damage and improve neurological outcomes.

Contents

Abbreviations

Word or phrase	Abbreviation
Adverse event	AE
Anterior communicating aneurysm	ACOM
Area under the temperature curve	AUC
Bedside shivering assessment scale	BSAS
Confidence interval	CI
Conventional fever management	CFM
Deep vein thrombosis	DVT
Glasgow coma scale	GCS
Glasgow outcome scale	GOS
Internal carotid artery	ICA
Intracerebral haemorrhage	ICH
Intracranial pressure	ICP
Major adverse event	MAE
National Institutes of Health Stroke Scale	NIHSS
Neurological intensive care unit	NICU
Odds ratio	OR
Posterior communicating aneurysm	PCOM
Subarachnoid haemorrhage	SAH
Standard deviation	SD
Targeted temperature management	TTM
Temperature modulation device	TMD

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional

procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in August 2020 and updated in March 2021.

Procedure name

- Inducing and maintaining normothermia using temperature modulation devices to improve outcomes after stroke or subarachnoid intracranial hemorrhage

Professional societies

- The British Association of Stroke Physicians
- The Royal College of Anaesthetists
- The Intensive Care Society

Description of the procedure

Indications and current treatment

Stroke (ischaemic stroke and intracerebral haemorrhage [ICH]) is an acute neurological event presumed to be vascular in origin and causing cerebral ischaemia, cerebral infarction or cerebral haemorrhage. Subarachnoid haemorrhage (SAH) is a haemorrhage from a cerebral blood vessel, aneurysm or vascular malformation into the subarachnoid space. Both conditions can interrupt blood flow to the brain, damage brain cells and cause abnormalities of thermoregulation and an abnormally high body temperature (neurogenic fever). The abnormally high temperature may result in secondary neurological injury and is associated with worse outcomes, greater morbidity and mortality.

Diagnosis and initial management of stroke is described in NICE's guideline on stroke and transient ischaemic attack in over 16s. Current treatments for managing fever after stroke or SAH include identifying and treating a cause, antipyretic medications and standard physical methods of cooling such as fans and cooling blankets to lower body temperature.

What the procedure involves

In this procedure, a temperature modulation device is used to maintain the patient's core temperature within normal limits (37.0±0.5°C). Either surface techniques (such as heat exchange cooling pads) or internal techniques (such as an endovascular cooling device) may be used. Heat is exchanged between the patient and the device to allow the body temperature to be controlled to a pre-set point determined by the clinician.

This procedure aims to reduce brain injury and improve neurological outcomes following stroke or SAH by maintaining normothermia with precise temperature control.

Outcome measures

The Glasgow Coma Scale (GCS) describes the extent of impaired consciousness in brain injured patients. The GCS measures the functions of eye opening, verbal response and motor response. Brain injury can be classified as severe (GCS 8 or less), moderate (GCS 9 to 12) and mild (GCS 13 to 15).

The Glasgow Outcome Scale (GOS) is a global scale to assess functional outcome of patients with brain injuries. There are 5 categories: dead (GOS 1), vegetative state (GOS 2), severe disability (GOS 3), moderate disability (GOS 4) and good recovery (GOS 5).

The Modified Rankin Score (mRS) measures the degree of disability or dependence in the daily activities of people with stroke or other causes of neurological disability. It is a 6-point disability scale, ranging from 0 (the patient has no residual symptoms) to 5 (the patient has severe disability; bedridden, incontinent, requires continuous care). A separate category of 6 is usually added for patients who died.

Fever burden is a calculation measuring the combined effect of temperature and duration of fever. It is usually defined as the maximum temperature minus 100.0°F (37.8°C), multiplied by the number of days with a fever. Fever burden (in degree-days) is categorised as low (0.1 to 2.0), medium (2.1 to 4.0), or high (more than 4.0).

Efficacy summary

Fever burden

In a randomised controlled trial of 102 patients with cerebrovascular disease, overall median total fever burden was statistically significantly lower in patients who had normothermic treatment using intravascular cooling (0.0°C hour; mean 1.5°C hours) compared with patients who had conventional fever management (CFM) (4.3°C hours; mean 9.3°C hours) during the course of treatment ($p<0.0001$) (Broessner 2009). In the same study, post hoc analyses of fever burden by disease type showed that median fever burden between the 2 groups was 0.0°C hour compared with 7.5°C hours for SAH ($p<0.0001$, prophylactic normothermia maintained for 336 hours), 3.0°C hours compared with 0.8°C hours for cerebral infarction ($p=0.59$, prophylactic normothermia maintained for 168 hours), and 0.0°C hour compared with 4.6°C hours for ICH ($p<0.0001$, prophylactic normothermia maintained for 168 hours).

In a non-randomised comparative study of 120 patients with SAH, there was a statistically significant difference in mean daily fever burden between the normothermic treatment using surface cooling group and the CFM group during the first 2 weeks after SAH (0.9°C x hours compared with 0.2°C x hours, $p<0.001$) (Badjatia 2010).

In a non-randomised comparative study of 32 patients with SAH or ICH, no statistically significant difference was found in fever burden between the normothermic treatment using oesophageal cooling group and the group using other temperature modulation devices (TMDs) (above 37.5°C: 0.05 x hours compared with -0.15 x hours, $p=0.09$; above 38°C: -0.44 x hours compared with -0.53 x hours, $p=0.47$) (Khan 2018).

Induction and maintenance of normothermia

In the non-randomised comparative study of 32 patients with SAH or ICH, mean time to achieve target temperature of 37.5°C was 5.4 hours (SD=3.7) for patients who had oesophageal cooling (baseline temperature 38.7°C) and 2.9 hours (SD=3.2) for patients who had other TMDs (baseline temperature 38.5°C, $p=0.07$) (Khan 2018).

In a case series of 9 patients with SAH, target temperature of 36.5±0.2°C was achieved in 78% (7/9) of patients with a median intravascular cooling time of 2 hours from baseline (≥38.3°C) (Badjatia 2004). In the same study, maintenance of temperature at 37.5°C or below at 24 hours and 72 hours after the completion

of temperature management was reported in 67% (6/9) and 22% (2/9) of patients respectively.

In a case series of 18 patients with acute ischaemic or haemorrhagic stroke, mean time to achieve target temperature of 36°C to 37°C from baseline (mean 37.6°C) was 4.2 hours using surface cooling (Knoll 2002). In the same study, at the end of 24-hour cooling, mean body core temperature reduced to 36.6°C but increased to 37.1°C at 26 hours (Knoll 2002).

In a case series of 10 patients with acute ischaemic stroke or ICH, mean time to achieve target temperature of 36.0°C to 37.5°C from baseline (mean 38.5°C) was 2.6 hours using transnasal cooling (SD=1.9 hours; range 0.5 to 5.5 hours) (Badjatia 2020). At 4 hours and 8 hours after cooling started, mean core temperature reduced to 37.3±0.7°C and 37.1±0.7°C. Fever reduction was statistically significant for both comparisons between baseline and 4 hours and 8 hours after cooling started ($p<0.01$). Within 24 hours post-cooling, 60% (6/10) of patients became febrile again and needed continued temperature management.

Neurological outcomes

In the randomised controlled trial of 102 patients with cerebrovascular disease, GOS scores of 4 or 5 were reported in 33% (17/51) of patients who had normothermic treatment using intravascular cooling compared with 41% (21/51) of patients who had CFM at 6-month follow up ($p=0.41$) (Broessner 2009). In the same study, modified Rankin Scale (mRS) scores of 0 to 2 were reported in 27% (14/51) and 29% (15/51) of patients respectively ($p=0.51$) at 6-month follow up.

In a non-randomised comparative study of 80 patients with ICH, there was no statistically significant difference in mRS scores at discharge between the normothermic treatment using surface cooling group and the CFM group (mRS 0 to 3: 0% compared with 5%; mRS 4 to 5: 65% in both groups, $p=0.3$) (Lord 2014). In the same study, median 14-day GCS change from admission was 0 (range -2 to 3) for the normothermic treatment group and 2 (range -2 to 5) for the CFM group ($p=0.1$) and median discharge GCS change from admission was 2 (range -2 to 6) for each group.

In the non-randomised comparative study of 120 patients with SAH, there was no statistically significant difference in the proportion of patients with a mRS score of 4 or higher at 14-day and 3-month follow up between the normothermic treatment using surface cooling group and the CFM group (14 days: 83% compared with 85%, $p=0.7$; 3 months: 44% compared with 60%, $p=0.1$) (Badjatia 2010). The difference was statistically significant at 12 months (21% compared with 46%, $p=0.03$).

In the case series of 18 patients with acute ischaemic or haemorrhagic stroke, median mRS was 3 and median Barthel Index was 75 at 3-month follow up after normothermic treatment using surface cooling (Knoll 2002).

Haemodynamic and intracranial pressure

In the case series of 10 patients with acute ischaemic stroke or ICH, there was no statistically significant change in the systolic blood pressure (132±15.8 mm Hg compared with 130.8±12.2 mm Hg, p=0.74) and ICP (8.9±3.8 cm H_2O compared with 8.6±3.6 cm H_2O, p=0.59) during 8-hour normothermic treatment using transnasal cooling (Badjatia 2020).

Length of stay

In the randomised controlled trial of 102 patients with cerebrovascular disease, mean duration of stay in the neurological intensive care unit (NICU) was 29.5 days (SD=25.8) for patients who had normothermic treatment using intravascular cooling compared with 24.2 days (SD=18.4) for patients who had CFM (p=0.24) (Broessner 2009).

In the non-randomised comparative study of 80 patients with ICH, median length of NICU stay was statistically significantly longer for patients who had normothermic treatment using surface cooling (15 days; IQR 11 to 18) compared with patients who had CFM (10 days; IQR 6 to 17, p=0.003) (Lord 2014). There was also a statistically significant difference in median length of hospital stay (23 days [IQR 15 to 36] compared with 18 days [IQR 9 to 34], p=0.009).

In the non-randomised comparative study of 120 patients with SAH, mean length of NICU stay was statistically significantly longer for patients in the normothermic treatment using surface cooling group (19 days, SD=7) compared with patients in the CFM group (14 days, SD=8, p=0.001) (Badjatia 2010). In the same study, mean length of hospital stay was 28 days for both groups.

Mortality

In the randomised controlled trial of 102 patients with cerebrovascular disease, mortality was 35% (18/51) of patients who had normothermic treatment using intravascular cooling compared with 27% (14/51) of patients who had CFM at 6-month follow up (p=0.52) (Broessner 2009). No death was considered to be related to the treatment, and no death before discharge was considered to be caused by infection.

In the non-randomised comparative study of 80 patients with ICH, mortality (mRS 6) at discharge was 35% of patients who had normothermic treatment

using surface cooling group compared with 30% of patients who had CFM (p=0.3) (Lord 2014).

In the case series of 18 patients with acute ischaemic or haemorrhagic stroke, mortality was 12% (2/18) of patients who had normothermic treatment using surface cooling at 3-month follow up (Knoll 2002).

In the non-randomised comparative study of 120 patients, mortality (mRS 6) within the first 14 days after SAH was 10% (4/40) of patients who had normothermic treatment using surface cooling and 13% (10/80) of patients who had CFM (Badjatia 2010).

Safety summary

Cerebrovascular complications

Malignant cerebral oedema was reported in 1 patient who had normothermic treatment using intravascular cooling and no patients who had CFM (p=1.00) at NICU discharge, 30-day and 6-month follow up in the randomised controlled trial of 102 patients with cerebrovascular disease (Broessner 2009). Malignant cerebral oedema was observed in 1 patient in the case series of 18 patients with acute ischaemic or haemorrhagic stroke and the patient had a surgical hemicraniectomy shortly after surface cooling (Knoll 2002).

Cerebral infarction (new onset) was reported in 25% (10/40) of patients who had normothermic treatment using surface cooling compared with 21% (17/80) of patients who had CFM (p=0.6) in the non-randomised comparative study of 120 patients with SAH (Badjatia 2010).

Haemorrhagic transformation (symptomatic) of cerebral infarcts was described in 2 patients who had normothermic treatment using surface cooling in the case series of 18 patients with acute ischaemic or haemorrhagic stroke (Knoll 2002). None of these patients had intravenous rt-PA or intravenous heparin or had pathologic coagulation parameters.

Symptomatic vasospasm was reported in 35% (14/40) of patients who had normothermic treatment using surface cooling compared with 31% (25/80) of patients who had CFM (p=1.0) in the non-randomised comparative study of 120 patients with SAH (Badjatia 2010).

Cardiovascular complications

Congestive heart failure was reported in 20% (8/40) of patients who had normothermic treatment using surface cooling compared with 19% (15/80) of patients who had CFM (p=1.0) in the non-randomised comparative study of 120 patients with SAH (Badjatia 2010).

Myocardial infarction was reported in 5% (2/40) of patients who had normothermic treatment using surface cooling compared with 11% (9/80) of patients who had CFM (p=0.3) in the non-randomised comparative study of 120 patients with SAH (Badjatia 2010).

Arrhythmia was reported in a statistically significantly higher proportion in patients who had normothermic treatment using surface cooling (43% [17/40]) than in patients who had CFM (20% [16/80], p=0.02) in the non-randomised comparative study of 120 patients with SAH (Badjatia 2010).

Sinus bradycardia was reported in 1 patient who had normothermic treatment using surface cooling in the case series of 18 patients with acute ischaemic or haemorrhagic stroke (Knoll 2002). This event was not accompanied by a drop in blood pressure.

Infectious complications

At least 1 infectious adverse event was reported in 96% (49/51) of patients who had normothermic treatment using intravascular cooling compared with 80% (41/51) of patients who had CFM (p=0.03) during 6-month follow up in the randomised controlled trial of 102 patients with cerebrovascular disease (Broessner 2009). All these events were considered either mild or moderate and resolved with no sequelae.

Bacteraemia was reported in 6% (3/51) of patients in the normothermic treatment using intravascular cooling group compared with 10% (5/51) of patients in the CFM group (p=0.72) during 6-month follow up in the randomised controlled trial of 102 patients with cerebrovascular disease (Broessner 2009).

Meningitis was reported in 18% (7/40) of patients who had normothermic treatment using surface cooling compared with 16% (13/80) of patient who had CFM (p=0.9) in the non-randomised comparative study of 120 patients with SAH (Badjatia 2010).

Pneumonia was reported in 58% (23/40) of patients who had normothermic treatment using surface cooling compared with 51% (41/80) of patients who had CFM (p=0.8) in the non-randomised comparative study of 120 patients with SAH

(Badjatia 2010). Development of pneumonia was statistically significantly associated with a poor outcome at 12 months after SAH (OR 3.1, 95% CI 1.2 to 7.7, p=0.02).

Pneumonia was reported in 2 patients who had normothermic treatment using surface cooling in the case series of 18 patients with acute ischaemic or haemorrhagic stroke (Knoll 2002). These 2 patients did not develop major respiratory insufficiency.

Pneumonia (ventilator-associated) was reported in 48% (19/40) of patients who had normothermic treatment using surface cooling compared with 35% (14/40) of patients who had CFM (p=0.3) in the non-randomised comparative study of 80 patients with ICH (Lord 2014).

Urinary tract infection was reported in 20% (8/40) of patients who had normothermic treatment using surface cooling compared with 19% (15/80) of patient who had CFM (p=0.9) in the non-randomised comparative study of 120 patients with SAH (Badjatia 2010).

Respiratory complications

Pulmonary oedema was reported in 45% (18/40) of patients who had normothermic treatment using surface cooling compared with 38% (30/80) of patients who had CFM (p=0.6) in the non-randomised comparative study of 120 patients with SAH (Badjatia 2010).

Pneumothorax was reported in 8% (4/51) of patients who had normothermic treatment using intravascular cooling compared with 4% (2/51) of patients who had CFM at both NICU discharge and 30-day follow up (p=0.68) in the randomised controlled trial of 102 patients with cerebrovascular disease (Broessner 2009). At 6-month follow up, pneumothorax occurred in 10% (5/51) compared with 4% (2/51, p=0.44) of patients.

Shivering

Device-related shivering was reported in 4 patients during 8-hour transnasal cooling in the case series of 10 patients with acute ischaemic stroke or ICH and this was treated with medication (Demerol) (Badjatia 2020).

Median shivering interventions per patient per day were statistically significantly lower in patients who had normothermic treatment using oesophageal cooling (3, range 0 to 14) compared with patients who had other TMDs (5, range 0 to 21; p=0.03) in the non-randomised comparative study of 32 patients with SAH or ICH (Khan 2018). This statistically significant difference was also found in the total

shivering interventions per patient (14 [range 5 to 35] compared with 30 [range 8 to 46], p=0.02).

Deep vein thrombosis

DVT was reported in 15% (6/40) of patients who had normothermic treatment using surface cooling and 8% (3/40) of patients who had CFM (p=0.3) in the non-randomised comparative study of 80 patients with ICH (Lord 2014).

DVT was reported in 2 patients who had normothermic treatment using intravascular cooling in the case series of 9 patients with SAH (Badjatia 2004). These were not associated with clinical sequelae and inferior vena cava filters were placed.

Kidney injury or failure

Renal failure was reported in 5% (2/40) of patients who had normothermic treatment using surface cooling compared with 8% (6/80) of patients who had CFM (p=0.7) in the non-randomised comparative study of 120 patients with SAH (Badjatia 2010).

Acute kidney injury was reported in 38% (15/40) of patients who had normothermic treatment using surface cooling and 40% (16/40) of patients who had CFM (p=0.8) in the non-randomised comparative study of 80 patients with ICH (Lord 2014).

Hyperglycaemia

Hyperglycaemia was reported in a statistically significantly higher proportion of patients who had normothermic treatment using surface cooling (93% [37/40]) compared with patients who had CFM (60% [24/40], p=0.001) in the non-randomised comparative study of 80 patients with ICH (Lord 2014).

Hyperglycaemia was reported in a statistically significantly higher proportion of patients who had normothermic treatment using surface cooling (95% [38/40]) compared with patients who had CFM (65% [52/80], p<0.01) in the non-randomised comparative study of 120 patients with SAH (Badjatia 2010).

Anecdotal and theoretical adverse events

No professional expert questionnaires for inducing and maintaining normothermia using temperature modulation devices to improve outcomes after stroke or SAH were submitted. Therefore, in addition to safety outcomes reported in the literature, there was no information about anecdotal adverse events (events

which professional experts have heard about) and theoretical adverse events (events which professional experts think might possibly occur, even if they have never happened).

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to inducing and maintaining normothermia using temperature modulation devices to improve outcomes after stroke or SAH. The following databases were searched, covering the period from their start to 8 March 2021: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria shown in the following table were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with stroke or SAH.
Intervention/test	Inducing and maintaining normothermia using temperature modulation devices.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 371 patients from 1 randomised controlled trial, 3 non-randomised comparative studies and 3 case series.

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on inducing and maintaining normothermia using temperature modulation devices to improve outcomes after stroke or SAH

Study 1 Broessner G (2009)

Study details

Study type	**Randomised controlled trial**
Country	Austria and Germany (2 centres)
Recruitment period	2003 to 2006
Study population and number	**n=102 (51 normothermic treatment using intravascular cooling group compared with 51 conventional fever management)** Patients with cerebrovascular disease (SAH, cerebral infarction & ICH)
Age and sex	Normothermia: mean 59 years; 41% (21/51) male Conventional fever management: mean 59 years; 49% (25/51) male
Patient selection criteria	Inclusion criteria: patients with spontaneous SAH with Hunt and Hess grade 3 to 5, spontaneous ICH with a GCS score ≤10, or CI with a NIHSS score ≥15 requiring ICU management (i.e. basilar artery occlusion, large territorial middle cerebral artery infarction). A central venous line was needed. Exclusion criteria: age <18 years, active sepsis syndrome, history of heparin-induced thrombocytopenia, moribund status, contraindication for the placement of a central venous line catheter, thrombolytic treatment within the past 12 hours, spontaneous hypothermia <35.5°C at enrolment, active cardiac dysrhythmia resulting in haemodynamic instability, impossibility of measuring the urinary bladder temperature, and pregnancy.
Technique	Normothermia: an intravascular device (CoolGard 3000 and CoolLine devices; Alsius Corp, Irvine, Calif) was inserted into the subclavian vein. Target temperature was set at 36.5°C to maintain normothermia, and endovascular treatment was strictly adhered to for the respective period. When the device was insufficient for maintaining normothermia and patient temperature was >37.9°C, conventional fever management was added. Conventional fever management: prophylactic administration of fever management - acetaminophen, ibuprofen, pethidine, surface cooling blanket (Blanketrol, Cincinnati Sub-Zero).
Follow-up	**6 months**

Conflict of interest/source of funding	Conflict of interest: none Funding: This study was partly supported by an unrestricted research grant from Alsius Corp, Irvine, Calif. Alsius Corp was neither involved in study design, collection, analysis, and interpretation of data nor writing of the reports. Alsius did not suppress any data or outcome analysis carried out as predefined in the study protocol. Audit of source data and statistical analyses were conducted by independent institutes.

Analysis

Follow-up issues: This paper states that losses to follow-up at 6 months were 7 patients in the normothermic treatment using an intravascular device group and 4 patients in the CFM group. For patients in either the ICH group or the severe cerebral infarction group, fever burden was assessed between randomisation and day 7 (168 hours) or until neuro-ICU discharge, whichever was earlier. Fever burden for patients with SAH was assessed until day 14 (336 hours) or neuro-ICU discharge, whichever was earlier.

Study design issues: This prospective, pilot trial (not registered) investigated the efficacy and safety of prophylactic long-term normothermia (i.e., maintaining body core temperature at 36.5 °C) with an intravascular device compared with a strict escalating, conventional fever management protocol in patients with life threatening cerebrovascular disease. The primary efficacy end point was fever burden, as defined by the area under the temperature curve (AUC) when body temperature exceeded the fever threshold of 37.9°C (bladder temperature). The primary analysis compared the median AUC (fever burden) between the 2 treatment groups. Safety outcomes included adverse events and major adverse events. A major adverse event was defined as bacteraemia, malignant cerebral oedema, pneumothorax, sepsis or death.

The sample size for this trial of 50 patients in each group (100 total) provides 99% power to detect a difference in mean fever burden of 25°C hours (SD=5.6°C hours). Even if 1 assumes a dropout rate as high as 30%, 50 patients in each group still provides 95% power to detect a smaller difference of 5°C hours (SD=5.6°C hours) between the 2 groups. One hundred two patients were randomised in a 1:1 ratio based on a permuted blocked randomisation list to provide an approximate balance between treatment groups. The randomisation list was stratified by site. Randomisation was done by opening sealed allocation envelopes.

Study population issues: Baseline demographics were evenly distributed across both treatment groups. Fifty-one patients (55% normothermia with an intravascular device, 45% conventional fever management) were enrolled with spontaneous SAH with a median Hunt and Hess score of 3, 41 patients (37% normothermia with an intravascular device, 43% conventional fever management) had spontaneous ICH with a median GCS of 4, and 10 patients (8% normothermia with an intravascular device, 12% conventional fever management) had complicated CI. Median NIHSS score in patients with complicated ischaemic stroke was 28.

Key efficacy findings

Number of patients analysed: 102 (51 normothermic treatment using intravascular cooling compared with 51 conventional fever management)

Duration of normothermia:

- SAH: prophylactic normothermia maintained for 336 hours
- Cerebral infarction and ICH: prophylactic normothermia maintained for 168 hours

Body core temperature at baseline, mean±SD:

- Normothermia using intravascular cooling compared with conventional fever management: 36.3±0.82˚C compared with 36.2±0.94°C, p=0.50

Fever burden

Disease category	Total fever burden in hours			Fever burden per patient per day		
	Normothermia (n=51)	CFM (n=51)	p value	Normothermia (n=51)	CFM (n=51)	p value
Overall			<0.0001			<0.0001
No.	51	51		51	51	
Mean±SD	1.5±3.3	9.3±14.5		0.18±0.38	1.27±2.63	
Median	0.0	4.3		0.0	0.54	
SAH			<0.0001			<0.0001
No.	28	23		28	23	
Mean±SD	1.5±3.3	10.9±13.9		0.14±0.26	1.40±3.16	
Median	0.0	7.5		0.0	0.54	
Non-SAH (cerebral infarction and ICH)			0.0005			0.0004
No.	23	28		23	28	
Mean±SD	1.5±3.4	8.0±15.1		0.23±0.50	1.17±2.15	
Median	0.0	3.9		0.0	0.55	
Cerebral infarction			0.59			0.75
No.	4	6		4	6	
Mean±SD	5.4±7.3	2.1±2.8		0.81±1.03	0.33±0.39	
Median	3.0	0.8		0.49	0.21	
ICH			<0.0001			<0.0001
No.	19	22		19	22	
Mean±SD	0.7±1.2	9.6±16.7		0.10±0.18	1.40±2.38	
Median	0.0	4.6		0.0	0.66	

Neurologic function

	Discharge		Day 30		Month 6	
	Normothermia (n=51)	CFM (n=51)	Normothermia (n=51)	CFM (n=51)	Normothermia (n=51)	CFM (n=51)
GOS						

Death	18% (n=9)	16% (n=8)	24% (n=12)	20% (n=10)	35% (n=18)	27% (n=14)
Persistent vegetative state	12% (n=6)	14% (n=7)	6% (n=3)	8% (n=4)	0	6% (n=3)
Severe disability	49% (n=25)	47% (n=24)	41% (n=21)	41% (n=21)	18% (n=9)	18% (n=9)
Moderate disability	16% (n=8)	14% (n=7)	14% (n=7)	12% (n=6)	16% (n=8)	18% (n=9)
Good recovery	6% (n=3)	10% (n=5)	4% (n=2)	10% (n=5)	18% (n=9)	24% (n=12)
Intubated	0	0	6% (n=3)	2% (n=1)	0	0
Lost to follow-up	0	0	4% (n=2)	2% (n=1)	14% (n=7)	8% (n=4)
Missing	0	0	2% (n=1)	6% (n=3)	0	0
P value	0.81		0.55		0.41	
MRS						
No symptoms	0	0	2% (n=1)	2% (n=1)	6% (n=3)	8% (n=4)
No significant disability	6% (n=3)	10% (n=5)	4% (n=2)	8% (n=4)	12% (n=6)	16% (n=8)
Slight disability	4% (n=2)	6% (n=3)	2% (n=1)	6% (n=3)	10% (n=5)	6% (n=3)
Moderate disability	16% (n=8)	6% (n=3)	16% (n=8)	6% (n=3)	6% (n=3)	8% (n=4)
Moderately severe disability	18% (n=9)	14% (n=7)	16% (n=8)	14% (n=7)	12% (n=6)	14% (n=7)
Severe disability	39% (n=20)	49% (n=25)	25% (n=13)	35% (n=18)	6% (n=3)	14% (n=7)
Death	18% (n=9)	16% (n=8)	24% (n=12)	20% (n=10)	35% (n=18)	27% (n=14)
Intubated	0	0	6% (n=3)	2% (n=1)	0	0
Lost to follow-up	0	0	4% (n=2)	2% (n=1)	14% (n=7)	8% (n=4)
Missing	0	0	2% (n=1)	6% (n=3)	0	0
P value	0.78		0.92		0.51	

Duration of stay in Neuro-ICU between the normothermic treatment using intravascular cooling group and the CFM group, days:

- Mean: 29.5±25.8 days compared with 24.2±18.4 days (p=0.24)
- Median: 22 days compared with 21 days

Within the first 30 days of the study, 31 patients in the normothermic treatment using intravascular cooling group and 39 patients in the CFM group had been discharged from NICU.

Key safety findings

Any adverse events by infection status: normothermia with an intravascular device n=51 compared with conventional fever management n=51

Event type	Through NICU discharge			Through day 30			Through month 6		
	Normothermia (n=51)	CFM (n=51)	p	Normothermia (n=51)	CFM (n=51)	p	Normothermia (n=51)	CFM (n=51)	p
Overall	94% (n=48)	84% (n=43)	0.20	96% (n=49)	86% (n=44)	0.16	96% (n=49)	86% (n=44)	0.16
Infectious	94% (n=48)	78% (n=40)	0.04	96% (n=49)	80% (n=41)	0.03	96% (n=49)	80% (n=41)	0.03
Non-infectious	37% (n=19)	39% (n=20)	1.00	37% (n=19)	39% (n=20)	1.00	37% (n=19)	39% (n=20)	1.00

Patients who experienced >1 event of a given infection type or >1 event overall were counted only once for that infection type and overall infection type.

The most frequent adverse events experienced at least once during the study across both treatment groups were pneumonia (70%) and urinary tract infections (33%). Three patients in the normothermia with an intravascular device group experienced adverse events that were considered by the investigators to be at least remotely related to the study procedure (1 patient had 2 instances of a positive blood culture for coagulase-negative staphylococci, 1 patient had a positive blood culture for bacteraemia, and 1 patient had an episode of shivering); all events resolved with no permanent sequelae.

Major adverse events (MAE)

Event type	Adverse event term	Through NICU discharge			Through day 30			Through month 6		
		Normothermia (n=51)	CFM (n=51)	p	Normothermia (n=51)	CFM (n=51)	p	Normothermia (n=51)	CFM (n=51)	p
Overall	Any MAE	31% (n=16)	31% (n=16)	1.00	35% (n=18)	33% (n=17)	1.00	49% (n=25)	39% (n=20)	0.43

	Death	20% (n=10)	16% (n=8)	0.80	24% (n=12)	20% (n=10)	0.82	35% (n=18)	27% (n=14)	0.52
Infectious	Any MAE	6% (n=3)	12% (n=6)	0.49	8% (n=4)	12% (n=6)	0.74	8% (n=4)	16% (n=8)	0.36
	Bacteraemia	6% (n=3)	10% (n=5)	0.72	6% (n=3)	10% (n=5)	0.72	6% (n=3)	10% (n=5)	0.72
	Death	0	0		2% (n=1)	0	1.00	2% (n=1)	4% (n=2)	1.00
	Sepsis	0	2% (n=1)	1.00	0	2% (n=1)	1.00	0	2% (n=1)	1.00
Non-infectious	Any MAE	24% (n=12)	20% (n=10)	0.81	25% (n=13)	22% (n=11)	0.82	33% (n=17)	22% (n=11)	0.27
	Cerebral oedema	2% (n=1)	0	1.00	2% (n=1)	0	1.00	2% (n=1)	0	1.00
	Death	18% (n=9)	16% (n=16)	1.00	20% (n=10)	18% (n=9)	1.00	25% (n=13)	18% (n=9)	0.47
	Pneumothorax	8% (n=4)	4% (n=2)	0.68	8% (n=4)	4% (n=2)	0.68	10% (n=5)	4% (n=2)	0.44
Unknown	Death	2% (n=1)	0	1.00	2% (n=1)	2% (n=1)	1.00	8% (n=4)	6% (n=3)	1.00

Patients who experienced >1 event of a given infection type or >1 event overall were counted only once for that infection type and overall infection type.
All reported pneumothoraces were detected during the study period.
No death was considered to be related to the study treatment, and no death before discharge was considered due to infection.

Study 2 Lord AS (2014)

Study details

Study type	**Non-randomised comparative study**
Country	US (single centre)
Recruitment period	Normothermia: 2006 to 2010 Conventional fever management: 2001 to 2004
Study population and number	**n=80 (40 normothermic treatment using surface cooling compared with 40 conventional fever management)** Patients with fever after spontaneous ICH
Age and sex	Normothermia : mean 60 years; 62% (25/40) male Conventional fever management: mean 59 years; 45% (18/40) male
Patient selection criteria	Inclusion criteria for normothermia using a surface TTM device: admission to Columbia NICU with diagnosis of ICH visualised by non-contrast head CT; consecutive fevers ≥38.3°C over 2 hours despite the use of acetaminophen; and TTM utilised for fever control with goal temperature of 37°C. Exclusion criteria for normothermia using a surface TTM device: TTM to goal temperature other than 37°C, death or withdrawal of care within 72 hours of admission, and ICH due to trauma, tumour, aneurysm, haemorrhagic conversion of ischaemic infarct, or venous thrombosis.
Technique	For fever management, all patients with fever ≥38.3°C had acetaminophen (650 mg every 4 to 6 hours orally) and a water-circulating blanket (Blanketrol II). Normothermia was used only in patients who, after treatment described above, had a persistent fever for at least 2 hours. TTM was initiated with a surface TTM device (Arctic Sun; Medivance, Inc., Louisville, CO, USA) with target temperature of 37°C.
Follow-up	**14 days**
Conflict of interest/source of funding	Conflict of interest: none. Funding: SM has received consulting fees from Acetlion, Biogen Idec, CSL Behring, Haemonetics, Medivance/CR Bard, Neuroptics, Orsan Technologies, Pfizer, Sage Therapeutics, Sanofi-Aventis, Stryker and Edge Therapeutics; Stock/Stock Options in Orsan Technologies.

Analysis

Study design issues: This case control study, comparing a consecutive cohort to a historical cohort in ICH patients with fever, determined the impact of TTM (normothermic treatment using surface cooling) on fever burden and its association with hospital complications and discharge outcomes. A post hoc power analysis demonstrated an ability to detect an absolute difference in good outcome (mRS 0 to 3) of 30% given 40 patients in each group.

ICH size was calculated in a blinded manner using the ABC/2 method on the Columbia NICU admission CT scan. Outcome data for all patients were interpreted from written examinations from neurologist or physical therapy notes by an author trained in evaluation of mRS.

Study population issues: Patients were selected from the Columbia TTM database, a prospectively collected database of all patients treated with a TTM device in the Columbia NICU. Controls were selected from the retrospective portion of the Columbia ICH project, a database of all patients with spontaneous ICH admitted to the Columbia NICU. Therefore, the retrospective collection of controls made all findings less robust than a prospective study.

Baseline characteristics were evenly matched between the 2 groups, even though baseline GCS trended slightly lower in the normothermic treatment group compared with the CFM group (6 compared with 8, p=0.08) and there were less non-white patients (60% compared with 80%, p=0.05). Admission temperatures were not different between the normothermic treatment group and the CFM group (37.1°C compared with 37.7°C, p=0.07).

Key efficacy findings

Number of patients analysed: 80 (40 in the normothermic treatment using surface cooling group compared with 40 in the CFM group)

Normothermic treatment was started on a median bleed day of 2.5 (IQR 1 to 4.5) after ICH onset and median days of TTM was 6 (IQR 3 to 9).

Median core temperatures and percentage of patients febrile (Tmax >38.3°C) by group

	Bleed day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Normothermia	43%	35%	30%	25%	28%	41%	31%	24%	38%	28%	6%	22%	20%	33%
Conventional fever management	43%	63%	65%	73%	68%	68%	64%	59%	44%	45%	41%	46%	39%	35%

For the 21 patients with at least 1 recorded Bedside Shivering Assessment Scale (BSAS), the average BSAS was 0.8 and 50% of values 1 or higher (shivering present). It was unclear whether the shivering was related to the normothermic treatment.

Outcomes

	Normothermia (n=40)	CFM (n=40)	P value
Discharge modified Rankin score			0.3
0 to 3	0 (0)	5% (n=2)	
4 to 5	65% (n=26)	65% (n=26)	
6 (mortality)	35% (n=14)	30% (n=12)	

IP overview: Inducing and maintaining normothermia using temperature modulation devices to improve outcomes after stroke or subarachnoid haemorrhage

Transition to comfort measures	20% (n=8)	25% (n=10)	0.6
14-day GCS change from admission, median (IQR)	0 (-2 to 3)	2 (-2 to 5)	0.1
GCS on discharge, median (IQR)	9 (3 to 11)	11 (3 to 15)	0.06
Discharge GCS change from admission, median (IQR)	2 (-2 to 6)	2 (-2 to 6)	0.5
Length of stay			
NICU length of stay (days), median (IQR)	15 (11 to 18)	10 (6 to 17)	0.003
Hospital length of stay (days), median (IQR)	23 (15 to 36)	18 (9 to 34)	0.09

Key safety findings

Hospital complications

	Normothermia (n=40)	**CFM (n=40)**	**P value**
Neurological complications			
External ventricular drains	63% (n=25)	63% (n=25)	0.1
Craniotomy for haematoma evacuation	5% (n=2)	3% (n=1)	1.0
Emergent hemicraniectomy	18% (n=7)	20% (n=8)	0.8
Hypertonic solution	80% (n=32)	63% (n=25)	0.08
Medical complications			
Intubated	100% (n=40)	88% (n=35)	0.03
Sedation days, median (IQR)	8 (5 to 11)	1 (0 to 3)	<0.001
% of first 14 ICU days on sedation, median (IQR)	71 (45 to 93)	10 (0 to 32)	<0.001
Ventilator-associated pneumonia	48% (n=19)	35% (n=14)	0.3
Days of mechanical ventilation, median (IQR)	14 (8 to 21)	6 (2 to 16)	0.003
Tracheostomy	55% (n=22)	26% (n=9)	0.010
DVT	15% (n=6)	8 (n=3)	0.3
Acute kidney injury	38% (n=15)	40 (n=16)	0.8
Troponin >0.4	25% (n=10)	38% (n=15)	0.2
Peak glucose >180	93% (n=37)	60% (n=24)	0.001

Risk factors for tracheostomy placement:

Categorical variables associated with tracheostomy placement included receiving normothermic treatment (p=0.01), receiving hemicraniectomy (p=0.03), presence of hydrocephalus on admission scan (p=0.04), peak glucose >180 (p=0.005), and more than 6 days of normothermic treatment (0.05). When placed into a binomial logistic regression model for tracheostomy placement, normothermic treatment for more than 6 days (OR 6.1, 95% CI 1.7 to 21.7), hemicraniectomy (OR 5.1, 95% CI 1.3 to 20.0) and hydrocephalus on admission (OR 3.3, 95% CI 1.1 to 10.1) were associated with tracheostomy.

Study 3 Badjatia N (2010)

Study details

Study type	**Non-randomised comparative study**
Country	US (single centre)
Recruitment period	Normothermia (39 with a surface TTM device and 1 with intravascular and surface cooling): 2003 Conventional fever management: 1996 to 2003
Study population and number	**n=120 (40 normothermic treatment using surface [and intravascular] cooling and 80 conventional fever management)** Patients with fever after SAH
Age and sex	Mean 58 years in each group: gender was not reported
Patient selection criteria	Survival past 1-week post bleed was 1 inclusion criterion but other criteria were not reported.
Technique	For fever management (≥38.3°C), all patients were treated with acetaminophen, 650 mg every 4 to 6 hours orally, with or without the use of a water-circulating cooling blanket (Blanketrol II; Cincinnati Sub-Zero, Cincinnati, OH). Normothermic treatment was used only in patients who, after treatment described above, had a persistent fever for at least 2 hours. A surface (Arctic Sun;Medivance, Inc, Louisville, CO) or intravascular (RapidBlue; InnerCool Therapies, Inc, San Diego, CA) temperature modulating device was initiated to target normothermia (37°C).
Follow-up	**12 months**
Conflict of interest/source of funding	SAM received research and unrestricted educational grant support, speaking honoraria, consulting fees, and stock options from Medivance, Inc, and unrestricted educational grant support from InnerCool Therapies and Alsius, Inc. There was no involvement of industry in any stages of planning, execution, or analysis of this study. NB received funding for this study from a K 12 Career Development Award (grant no. KL2 RR024157) from the National Centre for Research Resources. The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

Analysis

Follow-up issues: The paper states that 3 and 12 months after SAH, each patient or his or her proxy was asked to complete a 45-minute telephone or in-person interview. No patients were lost to follow-up between 14 days and 3 months; however, 3 patients were lost to follow-up between 3 months and 12 months after SAH. Two patients were in the CFM group and 1 was in the normothermic treatment group. For all 3 patients, the 3-month outcome was carried forward to 12 months.

Study design issues: This case control study investigated whether the application of normothermia with a temperature-modulating device had an impact on fever burden, the rate of complications, and outcome after SAH by comparing a consecutive cohort of SAH patients controlled to normothermia to a historical cohort of

SAH patients who underwent conventional fever management with acetaminophen and a water-circulating blanket.

Study population issues: There was no difference in age, Hunt and Hess score and SAH sum score at baseline between the therapeutic normothermia and CFM groups. The cohorts were not concurrent, and the controls (CFM group) were historical. Also, the number of patients was small. The sample size of 40 patients who had normothermic treatment and 80 CFM patients did not adequately power the difference in the proportion of good outcome at 12 months.

Key efficacy findings

Number of patients analysed: 120 (40 normothermic treatment and 80 CFM)

Normothermic treatment was begun on median post bleed day 3 (range, 0 to 6 days) and continued for 7 days (range, 1 to 13 days).

Mean admission temperatures were not different between the 2 groups (36.7±1.4°C compared with 36.7 ±1.5° C, p=0.8).

Devices used in the normothermic treatment group: 39 patients used a surface cooling device and 1 initially used an intravascular cooling device for 36 hours and then switched over to a surface cooling device for the subsequent 96 hours. The change from intravascular to surface cooling was based on concern for DVT, although follow-up testing failed to demonstrate DVT.

Mean daily fever burden for the first 2 weeks after SAH:

- Normothermic treatment, 0.9±0.5°C x hours compared with CFM, 0.2±0.7 ^{0}C x hours, p<0.001

On a generalised estimating equation analysis, the daily temperature burden was statistically significantly lower for patients who had normothermic treatment compared with patients who had CFM during the first 14 days after SAH (p<0.001).

Outcome measurements

	Normothermia (n=40)	**CFM (n=80)**	**P value**
modified Rankin Score			
>3 at 14 days	83%	85%	0.7
6 at 14 days	10% (n=4)	13% (n=10)	
>3 at 3 months	44%	60%	0.1
>3 at 12 months	21%	46%	0.03
Length of stay			
NICU length of stay (days)	19±7	14±8	0.001
Hospital length of stay (days)	28±13	28±21	0.9

On univariate analysis, age (61±13 years compared with 54±14 years, p=0.01), admission Hunt and Hess score (χ^2 =13.0, p=0.01), pneumonia (71% compared with 42%, p=0.001), arrhythmia (36% compared with

17%, p=0.02), and anaemia (67% compared with 51%, p=0.08) were all found to be associated with poor outcome at 12 months.

Predictors of 12-month outcome after SAH

Predictor	OR	95% CI	P value
Advanced fever control	0.2	0.1 to 0.6	0.004
Hunt and Hess grade	1.6	1.03 to 2.4	0.04
Pneumonia	3.1	1.2 to 7.7	0.02
Arrhythmia	2.6	0.9 to 8.1	0.1
Anaemia	2.1	0.9 to 5.3	0.1
Age	1.2	0.9 to 1.4	0.2

When entered into a multivariable linear regression model adjusting for age, CFM was associated with improved outcome at 12 months after SAH, whereas admission Hunt and Hess grade and development of pneumonia were significantly associated with a poor outcome at 12 months after SAH.

Key safety findings

Hospital complications

Complications	Normothermia (n=40)	CFM (n=80)	P value
Medical			
Hyperglycemia	95% (n=38)	65% (n=52)	<0.01
Anaemia	58% (n=23)	63% (n=50)	0.7
Renal failure	5% (n=2)	8% (n=6)	0.7
Arrhythmia	43% (n=17)	20% (n=16)	0.02
Pulmonary oedema	45% (n=18)	38% (n=30)	0.6
Congestive heart failure	20% (n=8)	19% (n=15)	1.0
Myocardial infarction	5% (n=2)	11% (n=9)	0.3
Tracheostomy	60%	41%	0.05
Mechanical ventilation	98%	89%	0.1
Intravenous sedation	100%	71%	<0.001
Infectious			
Pneumonia	58% (n=23)	51% (n=41)	0.8
Urinary tract infection	20% (n=8)	19% (n=15)	0.9
Meningitis	18% (n=7)	16% (n=13)	0.9
Neurologic			
Symptomatic vasospasm	35% (n=14)	31% (n=25)	1.0
Cerebral infarction	25% (n=10)	21% (n=17)	0.6

Study 4 Khan I (2018)

Study details

Study type	**Non-randomised comparative study**
Country	US (single centre)
Recruitment period	2015 to 2016
Study population and number	**n=32 (8 normothermic treatment using oesophageal cooling and 24 other surface or intravascular TMDs)** Patients with refractory fever after aneurysmal SAH or spontaneous ICH
Age and sex	Normothermia: mean 52 years; 27% (3/8) male Other TMDs: mean 53 years; 50% (12/24) male
Patient selection criteria	Inclusion criteria: adults patients with aneurysmal SAH or spontaneous ICH with refractory fever (defined as a febrile episode, temperature ≥38.3°C, that remained >38°C at least 2 hours after the administration of acetaminophen 650 mg enterally), endotracheal intubation and haemodynamic stability. Exclusion criteria: anticipated extubation, surgery, or withdrawal of support within 24 hours; anticipated TTM for ≤72 hours; active or recent upper gastrointestinal bleeding; history of oesophageal varices; history of oral, oesophageal, or gastric surgery or cancer; history of hiatal hernia; and any contraindication to orogastric tube placement.
Technique	Oesophageal cooling: The EnsoETM (Attune Medical, Chicago, IL) was placed orogastrically using standard bedside technique. A continuous temperature probe was placed in the bladder or rectum. The EnsoETM was connected to the Medi-Therm III temperature management system. For the first 2 patients, the Medi-Therm III was then set to AUTO, RAPID cooling mode with set point 37°C. All subsequent patients were initially set on MANUAL, set point 4 ^{0}C. Once the patients' temperature reached <37.5°C, the Medi-Therm III was set to AUTO, RAPID, 36°C. Other surface or intravascular TMDs: TTM was done using Arctic Sun, Stryker Rapr.Round, and/or Zoll intravascular cooling catheter.
Follow-up	**Not reported**
Conflict of interest/source of funding	NB reports research support from C.R. Bard, Inc. and from the Maryland Industrial Partnerships Program (MIPS 6021) outside the submitted work. NB is also cochair for the TTM Guideline Committee for the Neurocritical Care Society. JH reports grants from Maryland Industrial Partnerships Program (MIPS 6021) outside the submitted work. No other authors report any conflicts of interest.

Analysis

Follow-up issues: Ten patients had normothermic treatment using oesophageal cooling and 2 were excluded from analysis (1 patient due to duration of normothermia less than 48 hours and the other due to early removal of the device to secure gastric access).

Study design issues: This study investigated the ability of the EnsoETM to treat refractory fever after nontraumatic brain haemorrhage and hypothesised that it would achieve normothermia with less shivering than currently available surface or intravascular TMDs. Efficacy of temperature management with the EnsoETM was identified as the time taken to achieve normothermia and time spent above normothermia during TTM. Fever burden (time spent above normothermia range) was calculated for >37.5°C and >38.0°C x time in hours.

Multiple controls per case (3:1 ratio) was used to increase both power and precision. The final sample of 32 was assessed using a non-centrality parameter t-statistic using a power assumption of 80% (β=0.2) and significance of 5% (α=0.05). This analysis demonstrated adequate power was achieved with a total sample of 31. However, the overall sample size was small.

Study population issues: No differences were found in baseline characteristics between the 2 groups, including age, sex, body surface area, body mass index, GCS at initiation of therapy, diagnosis, or presence of intraventricular haemorrhage. Non-consecutive patients were selected to match the oesophageal cooling group across variables associated with shivering; this might have introduced bias into the results.

Key efficacy findings

Number of patients analysed: 32 (8 normothermic treatment using oesophageal cooling and 24 other cooling TMDs)

Maintenance of normothermia: up to 120 hours.

Targeted temperature management characteristic and outcomes

	Normothermia (n=8)	**Other TMDs (n=24)**	**P**
Temperature at initiation (˚C), mean±SD	38.7±0.4	38.5±0.5	0.4
Time to target (hours), mean±SD	5.4±3.7	2.9±3.2	0.07
Maintenance fever burden (˚C x hours), mean±SD			
Above 37.5	0.05±0.25	-0.15±0.28	0.09
Above 38	-0.44±0.25	-0.53±0.31	0.47
Shivering interventions per patients, median(range)			
Total	14 (5 to 35)	30 (8 to 46)	0.02
Per day	3 (0 to 14)	5 (0 to 21)	0.03

Key safety findings

No device-related adverse events were reported in patients who had the normothermic treatment using oesophageal cooling or other TMDs.

Study 5 Badjatia N (2004)

Study details

Study type	**Case series**
Country	US (single centre)
Recruitment period	2001 to 2002
Study population and number	**n=9** Patients with fever after SAH
Age and sex	mean 50 years; 33% (3/9) male
Patient selection criteria	Inclusion criteria: age between 18 and 80 years old; presence of fever, refractory to acetaminophen (650 mg) after 1 hour; signed informed consent from patient or legal substitute; no current and history of DVT; aneurysmal SAH within 7 days; and ability to obtain 72-hour follow-up. Exclusion criteria: contraindications to hypothermia, such as patients with known haematological dyscrasias that affect thrombosis, (cryoglobulinemia, sickle cell disease, and serum cold agglutinins) or vasospastic disorders (such as Raynaud disease or thromboangiitis obliterans); contraindication for central venous catheter placement or femoral vein access to IVC; significant cardiac disease or myocardial infarction within 90 days of procedure; patients who are allergic to acetaminophen; patients with insulin dependent diabetes before current illness; patients with a diagnosis of unstable renal failure, defined as a serum creatinine level >1.6; and patients with severe peripheral vascular disease, as assessed by a clinician.
Technique	Normothermia was restored using intravascular cooling catheter (Celsius Control™ system, Innercool Therapies, San Diego, CA). The goal of the temperature management was to reduce patient temperature to 36.5±0.2°C and then maintain it in that range for the remaining 24-hour period. Adjunctive cooling methods (lavages, intravascular solutions, and water mattress, and so on) were not allowed during the time the investigational device was used.
Follow-up	**3 days**
Conflict of interest/source of funding	This project was supported by Innercool Therapies, Inc.

Analysis

Follow-up issues: Patients were assessed during the course of enrolment into the study through their follow-up examinations 72 hours after the completion of temperature management (or before discharge from the ICU).

Study design issues: This prospective, single-arm, feasibility trial assessed the safety and performance of a novel femoral intravascular cooling device to restore normothermia in the patients with an acute cerebrovascular injury and refractory fever. Developed fever within 7 days of SAH. Fever was defined as a core temperature (assessed by bladder temperature probe) more than 38.3°C.

Efficacy of invasive temperature management with the intravascular cooling catheter was identified as the ability to achieve and maintain normothermia, defined as 36.5±0.2°C for 24 hours. The amount of time spent above target temperature of 36.5±0.2°C was calculated and represented as a fever burden (°C × time in minutes).

Study population issues: As part of the anti-shivering protocol, all patients also received surface warming with forced convective air warming blankets.

Key efficacy findings

Number of patients analysed: 9

Once patients reached the target temperature (36.5°C) and then maintained within 0.2°C of that target for 24 hours.

Clinical characteristics and outcomes

Case	Location aneurysm	Size (mm)	Hunt and Hess grade	Fisher's group	GCS (pretreatment)	Infectious source	Discharge ranking scale	Discharge GCS
1	(R) ICA	8	1	3	15	None	1	15
2	(R) PCOM	8	3	3	12	None	4	9
3	ACOM	6	1	1	15	None	0	15
4	ACOM	8	1	3	15	Urine	1	15
5	(L)ICA	8	3	3	11T	None	3	15
6	(L)ICA	2	4	3	8T	No fever w/u	6	N/A
7	Basilar	10	4	3	10T	No fever w/u	6	N/A
8	(R) PCOM	4	3	4	10T	None	6	N/A
9	ACA	5	1	3	15	None	4	14

During temperature management:

- Mechanical ventilation: n=3
- Sedation: n=3 (sedation was initiated before study enrolment to treat agitation from the underlying SAH)
- Intravascular cooling interruption for diagnostic procedures: n=5 (During these interrupted periods, all had elevations in their core body temperature)
- Anti-shivering treatment: n=9

Cumulative fever burden and postcooling temperatures

case	Catheter size (F)	Fever burden (ºC x hours)			Posttreatment temperature (ºC)	
		Temperature >36.7ºC	Temperature >37.5ºC	Temperature >38.0ºC	24 hours	72 hours
1[a]	9	N/A	N/A	N/A	38.4	37.6
2[a]	9	26.8	8	0.6	38.5	38.5
3	14	10.9	0.8	0	37.3	N/A
4	14	0.7	0.3	0.1	37.3	36.7
5[c]	9	2.4	0.5	0.2	37	38.6
6[c]	9	3.4	0.3	0	37.7	37
7[b,c]	9	12.8	1.9	0	37.3	38.1
8[c]	14	0.4	0.1	0	38	38.4
9[c]	14	0.6	0.1	0	36.7	39.4

[a]Inadequately treated for shivering
[b]Cooling console malfunction. Replaced at hour 16.
[c]Temperature management was interrupted for 45 to 60 minutes for diagnostic procedures.

No. of patients achieving target normothermic temperature: n=7

Time to reach target cooling: median 2 hours - 2 to 22.5 hours for the 9F catheter and was less than 1 hour in all but 1 patient that received the 14F catheter.

Control of shivering was associated with achieving and maintaining cooling for patients receiving both the 14F catheter and the 9F catheter.

Key safety findings

DVT: n=2, diagnosis by ultrasound and possibly related to use of the catheter. Both cases were not associated with clinical sequelae and IVC filters were placed.

Study 6 Knoll T (2002)

Study details

Study type	**Case series**
Country	Germany (single centre)
Recruitment period	Not reported
Study population and number	**n=18** Patients with acute ischaemic or haemorrhagic stroke
Age and gender	Mean 69.9 years; 56% (10/18) male
Patient selection criteria	Inclusion criteria: patients were admitted to the acute stroke unit (study site) with a clinical and computed tomography-based diagnosis of acute ischaemic or haemorrhagic stroke, a moderate or severe neurologic deficit (NIHSSS ≥8), a body core temperature >37°C, and informed consent. Exclusion criteria: stupor or coma (a score of >1 on the level of consciousness section of the NIHSS), respiratory dysfunction, seizures, coagulation disorders and alcohol abuse.
Technique	Patients were kept on a water-perfused cooling mattress for 24 hours (HICO Variotherm 541, Hirtz & Co., Cologne, Germany) to keep the body temperature between 36 and 37°C, without the use of antipyretic drugs.
Follow-up	**3 months**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Patients were assessed every 2 hours during the cooling period, at the end and at 2 and 4 hours after cooling. After 3 months, Barthel Index and mRS were administered by telephone interview. One patient was lost to follow up after 3 months (follow-up rate 94.5%).

Study design issues: This feasibility study established the feasibility and safety of continuous body surface cooling towards low normothermic temperatures in non-comatose, nonventilated stroke unit patients without muscle relaxation and ventilation. There was a learning curve in temperature management and incidence of adverse events due to improved adjustment of mattress temperature and infusion rates with nearly no problems in the last 5 patients.

Study population issues: of the 18 patients, 15 had ischemic infarct and 3 haemorrhage. All infarcts and haemorrhages were located in the anterior cerebral circulation. At baseline, median NIHSSS was 15.5 (mean 15.4; range 8 to 24). Patients were not treated with muscle relaxation and ventilation.

Key efficacy findings

Number of patients analysed: 18

Cooling initiation: a mean of 26 hours after stroke onset (median 21.5, range 8 to 60).

Cooling parameters

Parameter	Mean	Median	Minimum	maximum
Baseline temperature (°C)	37.6	37.5	37.1	38.3
Time to reach temperature below 37°C (hours)	4.2	3.3	1	12
Lowest temperature (°C)	36.3	36.4	35.1	36.9
Highest temperature (°C)	36.9	36.9	36.6	37.3

Cooling was performed for 24 hours in all but 1 patient. This patient developed an increase in central venous pressure and cooling was stopped after 4 hours because of security concerns.

Mean temperature values over the 24-hour cooling period

- 3 hours: 37.0°C
- 5 hours: 36.8°C
- 10 hours: 36.5°C
- 12 hours: 36.6°C
- 18 hours 36.6°C
- 24 hours: 36.6°C
- 26 hours: 37.1°C

Clinical outcomes after 3 months (n=17):

- Median mRS score: 3 (score of 0 to 1: 6%; score of 2 to 3: 47%; score of 4 to 5: 35%; score of 6: 12%)
- Median Barthel Index score: 75 (score of 95 to 100: 18%; score of 55 to 90: 41%; score of 0 to 50: 29%; score of 0: 12%)

Key safety findings

Adverse events

Event	**No. of events**	**No. of patients**
Procedure-related adverse events	14	11
Vomiting	2[a]	8
Drop in mean arterial blood pressure >20%	2[b] (maximum 27%)	
Increased central venous pressure (>20 cm H_2O)	3[c] (maximum 30 cm H_2O)	
Pneumonia (within 3 days)	2[d]	
Bradycardia (<60/min)	1[e] (55/min)	

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Platelets (<150.000/µL)	2 (minimum 140.000)	
Potassium (<3.5 mmol/L)	2 (minimum 2.7 mmol/L)	
Stupor/coma	0	
Respiratory dysfunction (oxygen saturation <95% or pCO_2 >40 mm Hg)	0	
Renal or pancreatic dysfunction	0	
Sodium or glucose deviation	0	
Further adverse events		
Haemorrhagic transformation (symptomatic)	2[f]	
Critically increased ICP (hemicraniectomy)	1[g]	
Mortality		
First week	0	
3 months	2 (12%)	

[a]Vomiting could be treated by injection of metoclopramide and this was a side effect of pethidine or a symptom of increased ICP and not a result of decreased body temperature.
[b]A drop in mean ABP occurred in the first 2 patients to whom DHT was given as a bolus injection initially. By changing the protocol to continuous infusion of DHT, this side effect could not be seen further.
[c]Increased CVP, probably due to a too-low infusion rate of DHT resulting in centralisation, could successfully be treated by increasing the infusion rate of DHT in 2 patients. In another patient, the cooling procedure was stopped due to an increase of CVP from initially 20 to 30 cm H_2O after 5 hours.
[d]The 2 patients with pneumonia did not develop major respiratory insufficiency.
[e]Sinus bradycardia in 1 patient was not accompanied by a drop in blood pressure.
[f]one immediately, the second 13 hours after the end of cooling. None of these patients was treated with intravenous rt-PA or intravenous heparin or had pathologic coagulation parameters.
[g]The patients developed malignant brain oedema and had a surgical hemicraniectomy shortly after the cooling period.

Study 7 Badjatia N (2020)

Study details

Study type	**Case series**
Country	US (single centre)
Recruitment period	2018 to 2019
Study population and number	**n=10** Patients with refractory fever after acute ischemic stroke or ICH
Age and sex	Mean 57.1 years; 60% (6/10) male
Patient selection criteria	Inclusion criteria: patients were admitted to the NICU with an ischemic or haemorrhagic stroke; febrile with an oral temperature ≥37.5°C or a core temperature ≥38.0°C, despite standard treatment with antipyretics for at least 1 hour, and is clinically indicated for normothermia treatment; and must have informed consent from the patient or the legally authorised representative making decisions for the patient. Exclusion criteria: age <18 years or >70 years; recent skull base fracture, facial fractures in the region of the nasal airflow, or any clinically significant craniofacial abnormality; on anticoagulation therapy or with a coagulopathy; fever due to significant ongoing systemic infection or sepsis; Haemodynamic instability (such as systolic blood pressure <90 mm Hg or heart rate <50 beats/min during 3 serial measurements during the 30-min period before initiating treatment); SaO_2 of <90% or FiO_2 of >40%; not intubated and sedated; existing head or nasal bleeding; currently exhibiting symptoms of an infectious disease capable of being transmitted through airborne pathogens; history of cryoglobulinemia, sickle cell disease, serum cold agglutinin disease or epistaxis; known or suspected pregnancy; participation in another ongoing investigational study; and prisoners and/or patients for whom no legally authorised representative is available.
Technique	Transnasal cooling device was used when patients had refractory fever. The temperature input to the device for this study was a core temperature from either an oesophageal or bladder probe. The lower target temperature was set on the device to 36.5°C. Patients were continued on their current medications, including scheduled doses of antipyretic agents.
Follow-up	24 hours
Conflict of interest/source of funding	Funding: This study was funded by the Maryland Industrial Partnerships program. Conflict of interest: HT is the founder of CoolTech LLC, which is developing a transnasal device for hypothermia. The other authors report no conflict of interests.

Analysis

Study design issues: This non-randomised, non-blinded clinical trial (NCT03360656) evaluated the safety and performance of the CoolStat transnasal thermal regulating device in reducing and maintaining normothermia (36.0 to 37.5°C) in febrile patients following ischaemic and haemorrhagic stroke. Refractory fever was defined

as a febrile episode with a core temperature ≥38.3°C at least 2 hours after the administration of acetaminophen 650 mg. Primary endpoint of the study was the ability to induce normothermia during the study period. The therapy was considered effective if more than 75% of patients achieved normothermia.

Study population issues: Diagnosis included ICH (n=8) and acute ischemic stroke (n=2). Mean GCS was 7 (range 4 to 10) and mean temperature was 38.5°C at baseline. Median post-injury duration was 4 days (range 1 to 7). In 3 patients, fever was partially attributed to either pneumonia (n=2) or urinary tract infection (n=1). In the other 7 patients, there were no alternative sources of fever identified, with refractory fever thought to be centrally mediated.

The cooling device was used in endotracheally intubated patients only, therefore limiting the overall population of febrile patients that may benefit. Throughout the cooling period, 4 patients received continuous infusions of sedatives and/or analgesics; 2 received a fentanyl infusion; 1 received concomitant dexmedetomidine (0.4 to 0.7 mcg/kg/h) and fentanyl (25 to 50 mcg/h); and 1 received propofol (30 mcg/kg/min) and fentanyl (25 mcg/h).

Key efficacy findings

Number of patients analysed: 10

Cooling duration: 8 hours

Targeted temperature management data during study period

Variables	n=10	P value
Goal temperature ≤37.5°C		
Achieved goal	80% (n=8)	N/A
Time achieved, median (range)	2.6 (0.5 to 5.5)	N/A
Time achieved, mean (SD)	2.6 (1.9)	N/A
Core temperature (°C)		
Baseline temperature, mean (SD)	38.5 (0.1)	-
4-hour temperature, mean (SD)	37.3 (0.7)	<0.001
8-hour temperature, mean (SD)	37.2 (0.7)	0.001
Lowest temperature	37.1 (0.7)	0.001
Tympanic temperature (°C)		
Baseline temperature	37.4 (0.6)	-
4-hour temperature, mean (SD)	36.9 (0.8)	0.001
8-hour temperature, mean (SD)	36.7 (0.7)	0.001
Lowest temperature, mean (SD)	36.1 (1.0)	0.001
Temperature source		
Oesophageal	70% (n=7)	N/A
Bladder	30% (n=3)	N/A
SpotOn	0	N/A
Shivering		

BSAS, median (range)	0 (0 to 1)	N/A
Mederidine (mg)	50 (27.2)	N/A
Interventions/subject, median (range)	1 (0 to 2)	N/A

8-hour cooling was done in 80% (8/10) of patients. One patient was cooled for 5 hours and another for 7 hours. One patient did not achieve normothermia until 5.5 h, and 1 failed to ever achieve normothermia.

Post cooling therapy: 6 patients became febrile again, necessitating continued TTM.

Haemodynamic and intracranial pressure changes during the intervention period:

- Systolic blood pressure: 132±15.8 mm Hg compared with 130.8±12.2 mm Hg, p=0.74
- ICP: 8.9±3.8 H_2O compared with 8.6±3.6 cm H_2O, p=0.59

Key safety findings

Adverse events: n=8

- Device-related shivering: n=4, these events happened during the cooling and were graded with a BSAS score of 1. These was treated with medication (Demerol).
- Mild epistaxis: n=1, this happened 14 hours after cooling therapy ended and was declared not directly related to the device by the otolaryngologist.
- Insufficient cooling: n=1, this was not related to device but CoolStat was suspended.
- Adverse effects on systolic blood pressure: n=2, one was not related to device and clavidipine infusion dose was increased. The other was unlikely caused by device but there might be a possible relationship; this was treated with medication (Labetalol).

Validity and generalisability of the studies

- The total sample of 371 was small and there was only 1 randomised controlled trial (Broessner 2009).
- Of the 7 studies, 5 were conducted in US and 2 in Germany (and Australia). There were no UK data.
- Where reported, only 1 study (Badjatia 2010) had a follow-up period of 12 months and others ranged from 1 day to 6 months.
- Between studies there was variation in time to initiate normothermic treatment, temperature at initiation, sources of fever (infectious fever, n=4), the targeted temperature, devices used for cooling, cooling activity and the procedure duration (both induction and maintenance of normothermia). All of these might affect safety and efficacy profiles.
- In some studies, patients were sedated and mechanically ventilated during the normothermic treatment.
- Some patients had additional treatments such as antishivering interventions, tracheostomy (associated with normothermic treatment as shown in Lord [2014]), craniotomy and external ventricular drains.

Existing assessments of this procedure

The Neurocritical Care Society guideline (2017) on the implementation of targeted temperature management could not recommend 'any specific timing of TTM initiation (prophylactic or symptom-based), due to equivocal evidence about its impact on length of stay, ICP burden and neurologic outcome'. However, the guideline recommended 'using controlled normothermia to reduce fever burden in patients with fever refractory to conventional therapy' (strong recommendation, moderate-quality evidence). This recommendation was based on 4 studies (2 RCTs, 1 cohort study and 1 case-control study) and the population included patients with SAH, ICH, ischemic stroke and (severe) TBI.

The American Heart Association/American Stroke Association guideline (2012) on the management of aneurysmal subarachnoid haemorrhage recommended that 'aggressive control of fever to a target of normothermia by use of standard or advanced temperature modulating systems is reasonable in the acute phase of

aSAH' (Class IIa; Level of Evidence B). This recommendation was based on limited evidence, with 1 case-control study specifically relating to the procedure.

The Neurocritical Care Society developed recommendations for the critical care management of patients following acute SAH (Diringer 2011). For managing pyrexia, it recommended that:

- surface cooling or intravascular devices are more effective and should be employed when antipyretics fail in cases where fever control is highly desirable (High quality evidence - strong recommendation)
- use of these devices should be accompanied by monitoring for skin injury and venous thrombosis (Weak quality evidence - strong recommendation).

Of the studies supporting these recommendations, 4 studies were relevant to the procedure.

For the use of non-pharmacological TTM in patients with ICH, SAH or acute ischaemic stroke with non-infectious fever (assumed neurogenic fever), 9 experts in the management of neurogenic fever recommended that:

- TTMnorm is appropriate for the management of neurogenic fever in adult patients with ICH, SAH, or AIS. TTM should be initiated if the patient temperature increases to ≥37.5ºC and infection is excluded
- TTM should be initiated as rapidly as possible once fever is detected if pharmacological treatment has not controlled temperature within 1 hour of administration
- the target temperature for patients with ICH, SAH, or acute ischaemic stroke who develop neurogenic fever is 37.0±0.5ºC
- TTM should be maintained for as long as there is potential for secondary brain damage
- the use of an advanced TTM method enabling precise temperature control is required to maintain temperature effectively.

Of the studies supporting these recommendations, 1 study specifically related to the procedure.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Therapeutic hypothermia for acute ischaemic stroke. NICE interventional procedures guidance 647 (2019). Available from https://www.nice.org.uk/guidance/ipg647

NICE guidelines

- Stroke and transient ischaemic attack in over 16s: diagnosis and initial management. NICE guideline 128 (2019). Available from https://www.nice.org.uk/guidance/ng128

Additional information considered by IPAC

Professional experts' opinions

No professional expert questionnaires for inducing and maintaining normothermia using temperature modulation devices to improve outcomes after stroke or SAH were submitted.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

References

1. Broessner G, Lackner P, Fischer M et al. (209) Prophylactic, endovascularly based, long-term normothermia In ICU patients with severe cerebrovascular disease: bicentre prospective, randomised trial. Stroke: e657-e665
2. Lord AS, Karinja S, Lantigua H et al. (2014) Therapeutic temperature modulation for fever after intracerebral hemorrhage. Neurocritical care 21(2): 200-6
3. Badjatia N, Fernandez L, Schmidt JM et al. (2010) Impact of induced normothermia on outcome after subarachnoid hemorrhage: a case-control study. Neurosurgery 66(4): 696-1
4. Khan I, Haymore J, Barnaba B et al. (2018) Esophageal cooling device versus other temperature modulation devices for therapeutic normothermia in subarachnoid and intracranial hemorrhage. Therapeutic hypothermia and temperature management 8(1): 53-8
5. Badjatia N, O'Donnell J, Baker J R et al. (2004) Achieving normothermia in patients with febrile subarachnoid hemorrhage: feasibility and safety of a novel intravascular cooling catheter. Neurocritical care 1(2): 145-56
6. Knoll T, Wimmer MLJ, Gumpinger F et al. (2002) The low normothermia concept - maintaining a core body temperature between 36 and 37 degrees C in acute stroke unit patients. Journal of neurosurgical anesthesiology 14(4): 304-8
7. Badjatia N, Gupta N, Sanchez S. et al. (2020) Safety and feasibility of a novel transnasal cooling device to induce normothermia in febrile cerebrovascular patients. Neurocritical Care
8. Madden LK, Hill M, May TL et al. (2017) The implementation of targeted temperature management: an evidence-based guideline from the Neurocritical Care Society. Neurocritical care 27(3): 468-87
9. Connolly ES, Rabinstein AA, Ricardo Carhuapoma J et al. (2012) Guidelines for the management of aneurysmal subarachnoid haemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 43: 1711-37
10. Diringer MN, Bleck TP, Claude Hemphill III J et al. (2011) Critical care management of patients following aneurysmal subarachnoid haemorrhage: recommendations from the Neruocritical Care Society's multidisciplinary consensus conference. Neurocrit Care 15: 211-40
11. Andrews PJD, Verma V, Healy M et al. (2018) Targeted temperature management in patients with intracerebral haemorrhage, subarachnoid

haemorrhage, or acute ischaemic stroke: consensus recommendations. British Journal of Anaesthesia 121(4): 768-75

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	08/03/2021	Issue 3 of 12, March 2021
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	08/03/2021	Issue 3 of 12, March 2021
International HTA database (INAHTA)	08/03/2021	n/a
MEDLINE (Ovid)	08/03/2021	1946 to March 05, 2021
MEDLINE In-Process (Ovid)	08/03/2021	1946 to March 05, 2021
MEDLINE Epubs ahead of print (Ovid)	08/03/2021	March 05, 2021
EMBASE (Ovid)	08/03/2021	1974 to 2021 March 05

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

Literature search strategy

Number	Search term

1	stroke/
2	Cerebral Infarction/ or Brain Ischemia/ or *Arterial Occlusive Diseases/
3	(stroke or strokes).tw.
4	((brain or cerebral*) adj2 (isch?emi* or infarct*)).tw.
5	(arter* adj2 occlusi*).tw.
6	apoplexy.tw.
7	((cerebrovascular* or vascular*) adj2 accident*).tw.
8	(CVA or CVAS).tw.
9	cerebral hemorrhage/ or intracranial hemorrhages/ or subarachnoid hemorrhage/
10	Hematoma, Subdural/ or Hematoma, Epidural, Cranial/
11	((brain or cerebrum or cerebral or intracerebral or cranial or intracranial or extradural or epidural or subdural or subarachnoid or 'posterior fossa') adj2 h?emorrhage*).tw.
12	((cranial or subdural or epidural) adj2 h?ematoma*).tw.
13	(SAH or SAHs).tw.
14	or/1-13
15	Body Temperature Regulation/
16	(temperature adj2 (target* or modulat* or regulat* or manag* or normal)).tw.
17	normothermi*.tw.
18	(fever adj1 reduc*).tw.
19	or/15-18
20	14 and 19
21	animals/ not humans/
22	20 not 21
23	('Arctic Sun' or arcticsun* or AS5000 or Blanketrol or CoolGard or 'Esophageal Cooling Device').tw.
24	22 or 23
25	limit 24 to English language

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Aujla GS, Nattanmai P, Premkumar K et al. (2017) Comparison of Two Surface Cooling Devices for Temperature Management in a Neurocritical Care Unit. Therapeutic hypothermia and temperature management 7(3): 147-151	Non-randomised comparative study n=21 (11 Gaymar compared with 10 Arctic Sun)	Arctic Sun surface cooling device was more efficient in attaining the target temperature, had less incidence of rebound hyperthermia, and was able to maintain normothermia better than Gaymar cooling wraps. The incidence of shivering tended to be more common in the Arctic Sun group.	Diagnosis included aSAH/AVM, ICH, status epilepticus, ischemic stroke, becterial meningitis, TBI and sepsis. Outcomes were not reported separately.
Badjatia N (2009) Hyperthermia and fever control in brain injury. Critical care medicine 37(7suppl): 250-7	Review	New, advanced temperature-modulating devices make it possible to treat fever and maintain normothermia for prolonged periods. However, prolonged fever control with these devices has not been prospectively studied in terms of outcome, and like any new therapy, therapeutic normothermia is presenting new, unforeseen challenges, such as shivering and infection surveillance,	Review article

		that may impair its long-term benefit.	
Badjatia N. (2006) Therapeutic temperature modulation in neurocritical care. Current Neurology and Neuroscience Reports 6(6): 509-517	Review	Therapeutic temperature modulation is an attainable goal for neurocritical care patients. However, the physiologic impact of manipulating an endogenous temperature set point remains unknown. Studies focusing on these consequences will help determine the timing, depth, and duration of therapeutic temperature modulation that can best impact positively on patient outcomes.	Review article
Broessner G, Lackner P, Fischer M et al. (2010) Influence of prophylactic, endovascularly based normothermia on inflammation in patients with severe cerebrovascular disease: a prospective, randomised trial. Stroke 41(12): 2969-72	Randomised controlled trial n=102 (51 in the CoolGard group compared with 51 in the control group)	The proinflammatory cytokines C-reactive protein and interleukin-6 were significantly elevated in patients receiving prophylactic endovascularly based long-term normothermia. Nonsteroidal anti-inflammatory drugs significantly affected the course of proinflammatory parameters; thus, future trials should investigate the role of nonsteroidal anti-inflammatory drugs in severe cerebrovascular disease patients and their interaction with temperature management.	This study was an additional analysis of the data from Broessner (2009).

Bohman L-E and Levine JM (2014) Fever and therapeutic normothermia in severe brain injury: An update. Current Opinion in Critical Care 20(2): 182-188	Review	The value of therapeutic normothermia in the neurocritical care unit is increasingly accepted, yet prospective trials that demonstrate a functional benefit to patients are lacking.	Review article
Burns JD, Green DM, Metivier K et al. (2012) Intensive care management of acute ischemic stroke. Emergency medicine clinics of North America 30(3): 713-44	Review	Given induced normothermia (IN) complexity, labour-intensive nature, potentially narrow therapeutic index with shivering, and unknown benefits, the authors do not take IN beyond environmental measures and acetaminophen in the emergency department.	Review article
Burns JD, Fisher JL and Cervantes-Arslanian AM (2017) Recent Advances in the Acute Management of Intracerebral Haemorrhage. Neurologic Clinics 35(4): 737-749	Review	Whether TTM with physical cooling in ICH provides net benefit, harm, or neither remains unanswered.	Review article
Carhuapoma JR, Gupta K, Coplin WM et al. (2003) Treatment of refractory fever in the neurosciences critical care unit using a novel, water-circulating cooling device. A single-centre pilot experience. Journal of neurosurgical	Case series n=6	Use of the water-circulating cooling device is safe, rapidly effective, and able to maintain sustained normothermia following fever in a cohort of critically ill neurologic/ neurosurgical patients.	The sample was small. Diagnosis included SAH, sever TBI, status epilepticus and intracerebral/intraventricular haemorrhage.

anesthesiology 15(4): 313-8			
Cormio M, Citerio G, Portella G et al. (2003) Treatment of fever in neurosurgical patients. Minerva anestesiologica 69(4): 214-22	Review	Maintenance of normothermia appears to be a desirable therapeutic goal in managing the patients with damaged or at-risk brain tissue. Evidence on the use of temperature management devices is limited.	Review article
Corry JJ (2012) Use of hypothermia in the intensive care unit. World journal of critical care medicine 1: 106-122	Review	Currently, the strongest evidence for the use of TTM, in adults, is for HT in OHCA for VT/VF, ICP control, and for normothermia in the neurocritical care population. In sum, though intuitively appealing, TTM remains enigmatic in the ICU.	Review article
Diringer MN (2004) Treatment of fever in the neurologic intensive care unit with a catheter-based heat exchange system. Critical care medicine 32(2): 559-564	Randomised controlled trial n=296 (154 Catheter compared with 142 controls)	The addition of this catheter-based cooling system to conventional management significantly improves fever reduction in neurologic intensive care unit patients.	Diagnosis included ICH, SAH, CI and TBI. Outcomes for non-TBI were not reported separately.
Fischer M, Dietmann A, Lackner P et al. (2012) Endovascular cooling and endothelial activation in hemorrhagic stroke patients. Neurocritical care 17(2): 224-30	Randomised controlled trial n=63 (37 with spontaneous SAH and 26 with spontaneous ICH)	Endovascular long-term temperature management did not alter Ang-1 and -2 levels compared to the control group indicating that the endovascular cooling technique itself does not lead to additional endothelial impairment. However, application of NSAIDs	The sample and clinical outcomes (efficacy and safety) were included in Broessner (2009)

		led to lower Ang-2 serum concentrations in the endovascular group.	
Fischer M, Katan M, Morgenthaler NG et al. (2014) The prognostic value of midregional proatrial natriuretic peptide in patients with hemorrhagic stroke. Cerebrovascular diseases (Basel, Switzerland) 37(2): 128-33	Randomised controlled trial n=46	Increased levels of MR-proANP are independently associated with poor functional outcome and increased mortality after 180 days in patients with haemorrhagic stroke. Endovascular temperature control had no significant influence on MR-proANP levels.	The sample was included in Broessner (2009) and limited efficacy data were reported.
Fischer M, Lackner P, Beer R et al. (2015) Cooling activity is associated with neurological outcome in patients with severe cerebrovascular disease undergoing endovascular temperature control. Neurocritical care 23(2): 205-9	Case series n=47	High cooling activity of an endovascular feedback device is associated with favourable outcome in patients with severe cerebrovascular disease	The sample was included in Broessner (2009)
Fischer M, Schiefecker A, Lackner P et al. (2017) Targeted Temperature Management in Spontaneous Intracerebral Haemorrhage: A Systematic Review. Current drug targets 18(12): 1430-1440	Systematic review	Active, controlled TTM shows promising preliminary results in animal and human studies with neuroprotective properties regarding oedema control and hematoma growth. To date, there are no findings from an RCT investigating the effect of TTM on functional outcome after spontaneous ICH.	Limited efficacy data were reported.

Ginsberg MD and Busto R (1998) Combating hyperthermia in acute stroke: a significant clinical concern. Stroke 29(2): 529-34	Review	Authors suggest that body temperature be maintained in a safe normothermic range (eg, 36.7°C to 37.0°C [98.0°F to 98.6°F]) for at least the first several days after acute stroke or head injury.	Review article
Gowda R, Jaffa M and Badjatia N (2018) Thermoregulation in brain injury. Handbook of clinical neurology 157: 789-797	Review	Early optimism about TTM's role in brain injury has been tempered by the failure of successive clinical trials to show improved patient outcomes. However, given the deleterious effects of fever, aggressive fever management is still warranted in the critically ill neurologic patient.	Review article
Hinz J, Rosmus M, Popov A et al. (2007) Effectiveness of an intravascular cooling method compared with a conventional cooling technique in neurologic patients. Journal of neurosurgical anesthesiology 19(2): 130-5	Non-randomised comparative study n=26 (13 in the CoolGard group and 13 in the conventional group)	The effectiveness of the intravascular cooling catheter is excellent compared with conventional cooling therapies.	Smaller sample
Hoedemaekers CW, Ezzahti M, Gerritsen A et al. (2007) Comparison of cooling methods to induce and maintain normo- and hypothermia in intensive care unit patients: a prospective intervention study.	Randomised controlled trial n=50	Cooling with water-circulating blankets, gel-pads and intravascular cooling is more efficient compared to conventional cooling and air-circulating blankets. The intravascular cooling system is most reliable	Diagnosis included SAH, TBI, post-anoxic, ICH, OHA, IHA and cardiac origin. Outcomes for non-TBI were not reported separately.

Critical care (London, England) 11(4): r91		to maintain a stable temperature.	
Griffiths SA, Ahmad J, Francoeur CL et al. (2019) The EMCOOLs surface cooling system for fever control in neurocritical care patients: A pilot study. Clinical Neurology and Neurosurgery 184: 105412	Case series n=12	The EMCOOLs system is a well-tolerated, safe and effective short-term intervention for control of fever (normothermia) in neurological patients. Future studies are needed to compare efficacy of the EMCOOLs to other devices and interventions.	The sample was small. Diagnosis included ICH, subdural hematoma, altered mental status and benign neoplasm.
Marehbian J and Greer DM (2017) Normothermia and stroke. Current Treatment Options in Neurology 19(1): 4	Review	Normothermia also has the advantage of allowing for more rapid clearance of sedating medications and less confounding of neuroprognostication. More difficult to quantify is the increased nursing and patient care complexity associated with moderate hypothermia compared to normothermia.	Review article
Marion DW (2004) Controlled normothermia in neurologic intensive care. Critical care medicine 32(2suppl): 43-5	Review	For controlled normothermia, intravascular temperature modulation has been shown to be more effective for preventing fever than conventional methods, such as antipyretic medications or surface-cooling techniques.	Review article
Mayer SA, Commichau C, Scarmeas N et al. (2001) Clinical trial of an air-circulating cooling blanket for fever control in	Randomised controlled trial n=220 (113 acetaminophen plus air blanket	Treatment with an air-circulating cooling blanket did not effectively reduce body temperature in febrile neuro-ICU patients treated with	Diagnosis included SAH, ICH, TBI, CNS neoplasm, CI and seizures. Outcomes were not reported

critically ill neurologic patients. Neurology, 56(3): 292-298	compared with 107 acetaminophen)	acetaminophen. More effective interventions are needed to maintain normothermia in patients at risk for fever-related brain damage.	separately for stroke and SAH.
Mayer SA, Kowalski RG, Presciutti M et al. (2004) Clinical trial of a novel surface cooling system for fever control in neurocritical care patients. Critical care medicine 32(12): 2508-15	Randomised controlled trial n=49 (23 Arctic Sun compared with 24 SubZero)	The Arctic Sun Temperature Management System is superior to conventional cooling-blanket therapy for controlling fever in critically ill neurologic patients.	Diagnosis included SAH, CI, ICH, TBI and respiratory arrest. Outcomes were not reported separately for stroke and SAH.
McGinniss J, Marshall P and Honiden S (2015) Novel uses of targeted temperature management. Clinics in chest medicine 36(3): 385-400	Review	Maintaining normothermia may be as effective as deeper cooling in TTM. TTM is safe to use in a highly monitored setting in an experienced centre. There seems to be an increased risk of pneumonia with TTM use, but no increased risk of bleeding or arrhythmia.	Review article
Oddo M, Frangos S, Maloney-Wilensky E et al. (2010) Effect of shivering on brain tissue oxygenation during induced normothermia in patients with severe brain injury. Neurocritical care 12(1): 10-6	Case series n=15	In patients with severe brain injury treated with induced normothermia, shivering was associated with a significant decrease of PbtO2, which correlated with the intensity of cooling. Monitoring of therapeutic cooling with computerised thermoregulatory systems may help prevent shivering and optimise the	The sample was small. Diagnosis included severe TBI and aneurysmal SAH.

		management of induced normothermia.	
Oddo M, Frangos S, Milby A et al. (2009) Induced normothermia attenuates cerebral metabolic distress in patients with aneurysmal subarachnoid haemorrhage and refractory Fever. Stroke 40(5): 1913-6	Case series n=18	Fever control is associated with reduced cerebral metabolic distress in patients with SAH, irrespective of ICP.	The sample was smaller. Limited efficacy data were reported.
Pegoli M, Zurlo Z and Bilotta F (2020) Temperature management in acute brain injury: a systematic review of clinical evidence. Clinical neurology and neurosurgery 197: 106165	Systematic review n=63 studies	Hyperthermia in acute brain injury patients is associated with worse functional outcome and higher mortality. The use of normothermic targeted temperature management has an established indication only in traumatic brain injury; further studies are needed to define the role and the indications of normothermic targeted temperature management in acute brain injury patients.	Of the 4 cited studies relating to this procedure, 3 were included in the key evidence summary and 1 in the appendix. Limited efficacy and safety outcomes relating to this procedure were reported.
Rincon F (2017) Targeted temperature management in brain injured patients. Neurologic Clinics 35(4): 665-694	Review	Clinical trials have explored the potential role of maintaining normothermia and treating fever in critically ill patients with brain injury. Maintenance of normothermia and fever prevention after brain injury is generally considered a standard therapy in the ICU	Review article

Scaravilli V, Tinchero G and Citerio G (2011) Fever management in SAH. Neurocritical Care 15(2): 287-294	Review	Antipyretic medications, surface cooling, and intravascular cooling may all reduce temperatures in patients with subarachnoid haemorrhage; however, benefits from cooling may be offset by negative consequences from shivering.	Review article
Schmutzhard E, Engelhardt K, Beer R et al. (2002) Safety and efficacy of a novel intravascular cooling device to control body temperature in neurologic intensive care patients: a prospective pilot study. Critical care medicine 30(11): 2481-8	Case series n=51	This novel intravascular cooling device (Cool Line catheter and Cool Gard cooling device) was highly efficacious in prophylactically controlling the body temperature of neurologic intensive care patients with very severe intracranial disease (median GCS score, 3 to 15). Morbidity and mortality rates were consistent with the ranges reported in the literature for such neurologic intensive patients.	Diagnosis included SAH, ICH, TRI, supratentorial brain infarction, basilar artery thrombosis, brain abscess, hypoxic encephalopathy, herpes simplex encephalitis and craniopharynge oma with obstructive hydrocephalus. Outcomes were not reported separately for ICH and SAH.
Springborg JB, Springborg KK and Romner B (2013) First clinical experience with intranasal cooling for hyperthermia in brain-injured patients. Neurocrit care 18: 400-405	Case series n=9	In brain-injured patients with hyperthermia, cooling with a prototype intranasal balloon system was clinically inadequate as the effect was delayed and not brain selective.	The sample was small. Diagnosis included TBI, SAH, intraventricular haemorrhage and bilateral thalamic infarction.
Wartenberg KE and Mayer SA (2008) Use of induced hypothermia for neuroprotection:	Review	More experience and controlled trials are required for management of side effects and shivering in	Review article

Indications and application. Future Neurology 3(3): 325-361		order to prevent any complication with a negative impact on the efficacy of hypo- or normothermia and outcome.	
Wrotek SE, Kozak WE, Hess DC et al. (2011) Treatment of fever after stroke: conflicting evidence. Pharmacotherapy 31(11): 1085-91	Review	Nonpharmacologic approaches to cooling have been more effective in achieving normothermia, but whether stroke outcomes can be improved remains unclear.	Review article
Zawadzka M, Szmuda M and Mazurkiewicz-Beldzinska M (2017) Thermoregulation disorders of central origin - how to diagnose and treat. Anaesthesiology intensive therapy 49(3): 227-234	Review	Further randomised clinical trials are needed to evaluate the indications for treatment of hyperthermia.	Review article
Ziai WC, Shah D, Assis FR et al. (2019) Feasibility and safety of transnasal high flow air to reduce core body temperature in febrile neurocritical care patients: a pilot study. Neurocrit care 31: 280-287	Case series n=7	High flow transnasal air in a unidirectional fashion lowers core body temperature in febrile patients in the NCCU setting. No adverse events were seen, and the process showed no signs of shivering or any other serious side effects during short-term exposure. This pilot study should inform further investigation.	The sample was small. Diagnosis included intracerebral or intraventricular haemorrhage, transverse myelitis, and anoxic brain injury due to a cardiac arrest.