NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of therapeutic hypothermia for acute ischaemic stroke

An ischaemic stroke happens when a blood clot stops the flow of blood to the brain. Brain tissue is then damaged because it does not get enough oxygen. In this procedure, a cooling device is used to reduce the body's temperature by 2ºC to 4°C (creating hypothermia) for several hours immediately after a stroke. When the brain is cooler it needs less oxygen from the blood. The aim is to limit the damage to brain cells caused by the stroke.

Contents

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 specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in August 2018 and updated in February 2019.

Procedure name

- Therapeutic hypothermia for acute ischaemic stroke.

Specialist societies

- Royal College of Physicians
- British Association of Stroke Physicians (BASP)
- Faculty of Intensive Care Medicine
- Association of British Neurologists.

Description of the procedure

Indications and current treatment

Acute ischaemic stroke is characterised by the sudden loss of blood circulation to an area of the brain and a corresponding loss of neurological function. This may lead to symptoms such as numbness or weakness of the face, arm or leg on 1 side of the body, and often problems with speech and swallowing. Stroke severity can be measured using scales such as the National Institutes of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (mRS). Broadly, strokes are classified as either haemorrhagic or ischaemic. Acute ischaemic stroke refers to stroke caused by an arterial thrombosis or embolism. It is more common than haemorrhagic stroke.

Patients suspected to be having an acute ischaemic stroke should have rapid assessment and early intervention with specialist care according to NICE's guideline on stroke and transient ischaemic attack in over 16s: diagnosis and initial management. Recanalisation strategies, such as thrombolysis, attempt to re-establish blood flow so that cells starved of oxygen can be rescued before they are irreversibly damaged. Effective stroke care also includes specialised supportive care and rehabilitation when appropriate.

What the procedure involves

Evidence suggests that reducing central body temperature decreases cerebral metabolism, neurotransmitter production, inflammation, free radical generation and oedema, and disrupts cellular apoptotic pathways. These factors are all believed to aggravate neurological outcome after cerebral hypoxia or ischaemia. The timing, duration and degree of therapeutic hypothermia in trials has varied. Typically, however, cooling has been attempted as close to stroke onset as possible (usually within 6 hours) and continued for at least 12 to 24 hours with body temperature maintained at 33°C to 36°C. This overview only refers to the use of therapeutic hypothermia and not to other targeted temperature management approaches that treat or prevent pyrexia.

Before the procedure, the patient's temperature is measured and further temperature monitoring is done continuously with an internal (intravesical, rectal or oesophageal) probe connected to the cooling device. Cooling devices can be surface (ice-cold saline, surface cooling, cooling helmets and nasal cooling) or endovascular. After cooling, the body is slowly rewarmed, at a rate of 0.25°C to 0.5ºC every hour. Rewarming takes about 8 hours. During cooling, patients need close cardiovascular monitoring in an intensive care environment, and may also need intubation and sedation. Drugs, including neuromuscular blockers, may be used to manage shivering. The procedure may be used with thrombolysis (intravenous alteplase), mechanical thrombectomy or other vascular reperfusion techniques. The aim of the procedure is to reduce the risk of secondary brain damage.

Outcome measures

The NIHSS

This is used to measure the severity of a stroke. It scores areas such as level of consciousness, vision, sensation, movement, speech and language. A maximum of 42 points represents the most severe symptoms.

The levels of stroke severity on the NIHSS are categorised as:

- 0: no stroke
- 1–4: minor stroke
- 5–15: moderate stroke
- 16–20: moderate/severe stroke
- 21–42: severe stroke.

mRS

This is a functional assessment scale that measures the degree of disability or dependence of people who have suffered a stroke.

The scale runs from perfect health without symptoms to death:

- 0: no symptoms
- 1: no significant disability; able to carry out all usual activities, despite some symptoms
- 2: slight disability; able to look after own affairs without assistance, but unable to carry out all previous activities
- 3: moderate disability. Needs some help, but able to walk unassisted
- 4: moderately severe disability; unable to attend to own bodily needs without assistance, and unable to walk unassisted
- 5: severe disability; needs constant nursing care and attention, bedridden, incontinent
- 6: dead.

Efficacy summary

Neurological outcome

In a systematic review of 252 patients (6 randomised controlled trials [RCTs]), the risk ratio for a favourable outcome (defined as an mRS score of 0 or 1) after therapeutic hypothermia (endovascular or surface-based cooling) was 0.85 (95% confidence interval [CI] 0.56 to 1.29; p=0.46, I^2=0%, 5 studies). The risk ratio for a poor outcome (defined as an mRS score of 3 to 6) was 1.20 (95% CI 0.88 to 1.64; p=0.24, I^2=0%; 3 studies).[1]

In an RCT of 120 patients who had endovascular therapeutic hypothermia or standard care, the mRS was 0 in 33% of patients and 1 in 38% of patients at 90-day follow-up (odds ratio 0.81, 95% CI 0.36 to 1.85). The NIHSS score at 7 days was similar in the 2 groups (10.4±10.3 compared with 10.6±11.3).[2]

In an RCT of 33 patients who had endovascular therapeutic hypothermia or standard care, at 6 months, a good neurological outcome (an mRS score of 0 to 3) was reported in 88% (7/8) and 40% (4/10) of surviving patients respectively (p=0.066).[3]

In a non-randomised comparative study of 75 patients, 37 patients who had therapeutic hypothermia with endovascular cooling and 2 who had surface cooling were compared with 36 patients who had standard care (controls). At 3-month follow-up, there was a statistically significantly higher proportion of patients with an mRS score of 0 to 1 in the hypothermia group compared with the control group (31% [12/39] versus 8% [3/36], p=0.015) or an mRS score of 0 to 2 (49% [19/39] versus 22% [8/36], p=0.017). The proportion of patients with an mRS score of 0 to 3 at 3-month follow-up was higher in the hypothermia group but the difference was not statistically significant (56% [22/39] versus 39% [14/36], p=0.129).[4]

In a non-randomised comparative study of 111 patients who had hemicraniectomy after suspected middle cranial artery infarction (with or without surface or endovascular therapeutic hypothermia), 25% (13/53) of patients who had therapeutic hypothermia and 41% (24/58) of controls had an mRS score of 0 to 3 at 12 months (risk ratio 0.59, 95% CI 0.34 to 1.04).[7]

In a case series of 50 patients who had therapeutic hypothermia with surface cooling, the mean NIHSS score was 29 at 4 weeks and the mRS score was 2.9 (range 2 to 5) at 3-month follow-up.[5]

In a case series of 19 patients who had an extended period of therapeutic hypothermia (surface cooling), the mean NIHSS score was 8.3±2.7 at 12-month follow-up and the mean mRS was 3.2±0.9.[6]

Mortality

In the systematic review of 252 patients, the risk ratio for mortality from all causes after therapeutic hypothermia was 1.12 (95% CI 0.62 to 2.05; p=0.70, I^2=0%, 6 studies). Mortality in the hypothermia group in the individual studies was 28%, 21%, 12%, 0%, 8%, and 13% (pretreatment mean NIHSS score was 15.2, 14.3, 8.0 [median], 12.0, 18.0 and 11.4 respectively). None of the deaths were considered to be related to hypothermia.[1]

In the RCT of 120 patients, mortality was 16% with endovascular therapeutic hypothermia and 9% with standard care (odds ratio 1.95, 95% CI 0.56 to 7.79).[2]

In the RCT of 33 patients, mortality was 50% (8/16) with endovascular therapeutic hypothermia and 41% (7/17) with standard care at 6 months (p=0.732).[3]

In the non-randomised comparative study of 75 patients, mortality at 1 month was similar in the 2 groups (15% [6/39] with endovascular or surface cooling compared with 14% [5/36] with standard care, p=0.855).[4]

In the non-randomised comparative study of 111 patients, survival at 12 months was 49% (26/53) in the hypothermia group (surface or endovascular cooling) and 79% (46/58) in the control group (risk ratio 0.62, 95% CI 0.46 to 0.84).[7]

In a non-randomised comparative study of 47 patients who had hemicraniectomy following suspected middle cranial artery infarction with or without hypothermia (surface cooling), in-hospital mortality was 15% in the hypothermia group and 41% in the control group (p=0.056). Hypothermia was identified as the strongest factor that affected survival in the multivariable analysis (odds ratio 6.21, 95% CI 1.04 to 37.05; p=0.045). Mortality at 1-year follow-up was 28% (5/18) in the hypothermia group and 52% (13/25) in the control group (p=0.112).[8]

Cerebral oedema

In the non-randomised comparative study of 75 patients, 54% (21/39) of patients who had therapeutic hypothermia had no cerebral oedema compared with 17% (6/36) of patients in the control group (p=0.001). Absence of cerebral oedema was an independent predictor of a good outcome (odds ratio 5.4, 95% CI 1.6 to 18.2).[4]

Stroke recurrence

Stroke recurrence was reported in 26% (5/19) of patients in the case series of 19 patients who had surface cooling (4 happened during the cooling period and 1 at 5 days after rewarming); 3 patients had severe clinical deterioration and died, and 2 survived (1 of whom had a hemicraniectomy).[6]

Safety summary

Pneumonia

Pneumonia was reported at a statistically significantly higher rate in patients who had therapeutic hypothermia (endovascular, intravenous or surface-based) in the systematic review of 252 patients (risk ratio 3.30, 95% CI 1.48 to 7.34; p=0.003, I^2=0%).[1]

It was reported in 19% of patients who had endovascular therapeutic hypothermia and 11% of patients in the control group in the RCT of 120 patients (odds ratio 1.99, 95% CI 0.63 to 6.98).[2]

It was reported in a similar proportion of patients in each group in the RCT of 33 patients (44% [7/16] endovascular hypothermia and 47% [8/17] standard care, p=1.00).[3]

It was reported at a statistically significantly lower rate in patients who had therapeutic hypothermia in the non-randomised comparative study of 75 patients (5% [2/39] compared with 31% [11/36], p=0.004) of patients in the control group.[4]

It was reported in 48% (24/50) and 42% (8/19) of patients respectively in the case series of 50 and 19 patients who had therapeutic hypothermia with surface cooling.[5,6]

Pneumonia was the most common adverse event in patients in intensive care in the non-randomised comparative study of 47 patients, but there was no statistically significant difference between the groups (25% [5/20] in the hypothermia group compared with 19% [5/27] in the control group, p=0.723).[8]

Intracerebral haemorrhage

In the non-randomised comparative study of 75 patients, 39% (15/39) of patients who had therapeutic hypothermia had no haemorrhagic transformation compared with 14% (5/36) of patients in the control group (p=0.016).[4]

In the non-randomised comparative study of 47 patients, haemorrhagic transformation after hemicraniectomy was reported in 35% (7/20) of patients who had therapeutic hypothermia compared with 26% (7/27) of patients in the control group (p=0.501).[8]

Symptomatic intracerebral haemorrhage was reported in 2% of patients who had endovascular hypothermia and 4% of patients in the control group in the RCT of 120 patients (odds ratio 0.45, 95% CI 0.01 to 8.80).[2]

Cardiac arrhythmia or bradycardia

Bradycardia was reported in 44% (7/16) of patients who had endovascular hypothermia and 12% (2/17) of patients in the control group (p=0.057) in the RCT of 33 patients.[3]

Bradycardia was reported in 8% (3/39) of patients who had therapeutic hypothermia and 3% (1/36) of patients in the control group in the non-randomised comparative study of 75 patients (p value not reported).[4]

Cardiac arrhythmia or bradycardia was reported in 62% (31/50) of patients in the case series of 50 patients who had surface cooling.[5]

All patients had bradycardia during the hypothermia procedure, without arrhythmia, in the case series of 19 patients who had surface cooling.[6]

Cardiac arrhythmia was reported in 28% (15/53) of patients who had therapeutic hypothermia with surface or endovascular cooling and 10% (2/20) of patients

who had surface cooling in the non-randomised comparative studies of 111 and 47 patients respectively.[7,8]

Electrolyte disorder

Electrolyte disorder was reported in 100% (16/16) of patients who had endovascular hypothermia and 53% (9/17) of patients in the control group (p=0.003) in the RCT of 33 patients.[3]

Hypoalbuminaemia

Hypoalbuminaemia was reported in 69% (11/16) of patients who had endovascular hypothermia and 41% (7/17) of patients in the control group (p=0.166) in the RCT of 33 patients.[3]

Stress hyperglycaemia

Stress hyperglycaemia was reported in 38% (6/16) of patients who had endovascular hypothermia and 6% (1/17) of patients in the control group (p=0.039) in the RCT of 33 patients.[3]

Hypotension

Severe hypotension (mean arterial pressure less than 50 mmHg) was reported in 4% (2/50) of patients in the case series of 50 patients who had therapeutic hypothermia with surface cooling.[5]

Hypotension was reported in 38% (6/16) of patients who had endovascular hypothermia and 18% (3/17) of patients in the control group (p=0.259) in the RCT of 33 patients.[3]

All patients had hypotension, which needed continuous infusion of norepinephrine, during the hypothermia procedure (surface cooling) in the case series of 19 patients.[6]

Coagulation dysfunction

Severe coagulopathy was reported in 4% (2/50) of patients in the case series of 50 patients who had therapeutic hypothermia with surface cooling. This was fatal in 1 patient.[5]

Coagulation dysfunction was reported in 88% (14/16) of patients who had endovascular hypothermia and 88% (15/17) of patients in the control group (p=1.00) in the RCT of 33 patients.[3]

Sepsis

Severe sepsis was reported in 11% (6/53) of patients who had therapeutic hypothermia (surface or endovascular cooling) in the non-randomised comparative study of 111 patients. It was the cause of death in 1 patient.[7]

Sepsis was reported in 1 patient who had therapeutic hypothermia (surface cooling) in the non-randomised comparative study of 47 patients. The hypothermia treatment was stopped.[8]

Gastrointestinal bleeding

Gastrointestinal bleeding was reported in 50% (8/16) of patients who had endovascular hypothermia and 12% (2/17) of patients in the control group (p=0.026) in the RCT of 33 patients.[3]

Gastric retention

Gastric retention was reported in 94% (15/16) of patients who had endovascular hypothermia and 41% (7/17) of patients in the control group (p=0.002) in the RCT of 33 patients.[3]

Deep venous thrombosis

Deep venous thrombosis was reported in 9% (5/53) of patients who had therapeutic hypothermia (surface or endovascular cooling) in the non-randomised comparative study of 111 patients.[7]

Lower extremity deep venous thrombosis was reported in 25% (4/16) of patients who had endovascular hypothermia and 12% (2/17) of patients in the control group (p=0.398) in the RCT of 33 patients.[3]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers did not list any additional anecdotal or theoretical adverse events.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to therapeutic hypothermia for acute ischaemic stroke. The following databases were searched, covering the period from their start to 14 December 2018: 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 following selection criteria (table 1) 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.

Table 1 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 if no clinical outcomes were reported, or if 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 ischaemic stroke
Intervention/test	Therapeutic hypothermia
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 overview

This overview is based on about 800 patients from 1 systematic review, 3 RCTs (1 of which was a conference abstract and included for safety data only), 3 non-randomised comparative studies and 2 case series.[1–9]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on therapeutic hypothermia for acute ischaemic stroke

Study 1 Wan Y-H (2014)

Details

Study type	**Systematic review and meta-analysis**
Country	Study countries not reported
Recruitment period	Trials that were completed and published by February 2014 were included.
Study population and number	**n=252** (6 randomised controlled trials) Patients with acute ischaemic stroke
Age and sex	Mean age varied from 49 to 69 years; 50% (126/252) male
Patient selection criteria	Patients older than 18 years with acute ischaemic stroke, and cerebral haemorrhage had been excluded as the cause of the symptoms based on CT or MRI. The intervention of interest was therapeutic hypothermia including thrombolytic therapy if indicated. Information about the depth, duration, and rewarming speed had to be available for the study to be included.
Technique	Studies used endovascular, intravenous or surface-based cooling. One of the 6 studies used hemicraniectomy as the control, the other studies used standard treatment, including thrombolytic therapy.
Follow-up	**Range 1 to 6 months**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Complete outcome data were reported in 4 trials. It was unclear whether data were complete in the other 2 trials.

Study design issues: Systematic review and meta-analysis complying with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. The Cochrane risk of bias tool was used to assess the risk of bias in the included studies and the Grading of Recommendations, Assessment, Development, and Evaluation system was used to grade the quality of evidence for the outcomes. A sensitivity analysis was done by sequentially removing each study.

Adequate methods of random sequence generation were used in 4 trials, 1 was inadequate and 1 did not report the methods of random sequence generation. Four trials used allocation concealment, whereas the description was unclear in the other 2 trials. Patients and staff were blinded in only 1 trial. The assessors of outcomes were blinded in 2 trials, but the other 4 trials did not provide information on the blinding of outcome assessment.

The evidence quality for each outcome was low or very low.

Characteristics of included studies (6 randomised controlled trials)

Author	Patients	Hypothermia treatment	Control treatment	Follow-up
De Georgia et al., 2004	n=40 (18 versus 22) Patients with acute circulation ischaemic stroke ≤12 hours of symptom onset	Endovascular cooling: mean time from stroke onset to cooling 9.0 hours; depth 33°C, duration 24 hours, rewarming speed 0.2°C/hour	Standard medical treatment, including thrombolytic therapy if indicated	1 month

		Oesophageal temperature monitoring		
Els et al., 2006	n=25 (12 versus 13) Patients with severe supratentorial ischaemic stroke	10 intravenous cooling, 2 external cooling Depth 35°C, duration 48 hours, rewarming speed 0.04°C/hour Continuous oesophageal temperature monitoring	Hemicraniectomy	6 months
Hemmen et al., 2010	n=58 (28 versus 30) Patients with acute ischaemic stroke ≤6 hours of symptom onset	Intravenous cooling Time from stroke onset to cooling start (median): 5.9 hours; depth 33°C, duration 24 hours, rewarming speed 0.3°C/hour	Standard treatment, including thrombolytic therapy.	3 months
Krieger, 2013	n=31 (17 versus 14) Patients with acute ischaemic stroke ≤24 hours of symptom onset	7 endovascular cooling, 10 surface-based cooling Mean time from stroke onset to cooling start 12.2 hours; depth 33°C, duration 24 hours, rewarming speed 0.25°C/hour to 0.5°C/hour Temperatures measured by bladder thermistor probe.	Standard treatment, including thrombolytic therapy if indicated.	3 months
Piironen et al., 2014	n=36 (18 versus 18) Patients with acute ischaemic stroke after intravenous thrombolysis	Surface-based cooling and saline infusions Time from stroke onset to cooling start (median) 6 hours; depth 34.5°C to 35.5°C; duration 10.5 hours, rewarming speed 0.2°C/hour to 0.5°C/hour Continuous bladder temperature monitoring	Treatment according to in-house guidelines	3 months
Tong, 2011	n=62 (31 versus 31) Patients with acute ischaemic stroke ≤6 hours of symptom onset	Surface-based cooling Mean time from stroke onset to cooling start 3.9 hours; depth 32°C to 34°C; duration 24 hours, Continuous rectal temperature monitoring	Thrombolytic therapy	3 months

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **252** **Favourable neurological outcome (modified Rankin Scale score 0 to 1)** 5 studies reported data on favourable neurological outcome. RR=0.85 (95% CI 0.56 to 1.29, p=0.46, I^2=0%) None of the subanalyses (32°C to 33.9°C versus 34°C to 35.9°C, duration ≤24 hours, rewarming speed ≤12 hours versus >12 hours) were statistically significant. **Poor neurological outcome (modified Rankin Scale score 3 to 6)** 3 studies reported data on poor neurological outcome. RR=1.20 (95% CI 0.88 to 1.64, p=0.24, I^2=0%) None of the subanalyses (32°C to 33.9°C versus 34°C to 35.9°C, duration ≤24 hours, rewarming speed ≤12 hours versus >12 hours) were statistically significant. **Mortality** 6 studies reported mortality from all causes. RR=1.12 (95% CI 0.62 to 2.05, p=0.70, I^2=0%) None of the subanalyses (32°C to 33.9°C versus 34°C to 35.9°C, duration ≤24 hours, rewarming speed ≤12 hours versus >12 hours) were statistically significant. Mortality in the hypothermia group in the individual studies were 27.8%, 21.4%, 11.8%, 0%, 8.3%, and 12.9% (pretreatment mean National Institutes of Health Stroke Scale score was 15.2, 14.3, 8.0 (median), 12.0, 18.0, and 11.4 respectively). None of the deaths were considered to be related to hypothermia.	**Complications** • Pneumonia: RR=3.30, 95% CI 1.48 to 7.34, p=0.003, I^2=0% • Symptomatic intracranial haemorrhage: RR=1.07, 95% CI 0.37 to 3.04, p=0.90, I^2=0% • Fatal intracranial haemorrhage: RR=1.40, 95% CI 0.33 to 5.99, p=0.65, I^2=0% • Deep vein thrombosis: RR=2.25, 95% CI 0.68 to 7.44, p=0.18, I^2=12% • Atrial fibrillation: RR=1.14, 95% CI 0.40 to 3.25, p=0.80, I^2=0%
Abbreviations used: CI, confidence interval; RR, risk ratio	

Study 2 Lyden P (2016)

Details

Study type	**Randomised controlled trial (ICTus 2)**
Country	US
Recruitment period	Recruitment was suspended in December 2014 and final follow-up visits were completed by May 2015
Study population and number	**n=120 (63 hypothermia, 57 normothermia)** Patients with acute ischaemic stroke.
Age and sex	Hypothermia: mean age 66 years; 54% male Normothermia: mean age 68 years; 61% male
Patient selection criteria	Patients with ischaemic stroke had treatment within 3 hours of symptom onset with intravenous recombinant tissue-type plasminogen activator (r-tPA); NIHSS ≥7 and ≤20 (left brain stroke) or ≤24 (right brain stroke); age 22 to 82 years. Intra-arterial recanalisation procedures were disallowed.
Technique	Patients randomised to hypothermia immediately had 2 litres of normal saline (4°C) as fast as possible; patients in the normothermia group had the same volume of room temperature saline. Hypothermia technique: target temperature 33°C, intravascular cooling device (Celsius Catheter, Innercool, Carlsbad) for 24 hours, followed by controlled rewarming for 12 hours. Anti-shivering measures (meperidine, buspirone, and skin warming) were used for all 36 hours. If shivering could not be controlled without respiratory compromise, the target temperature was raised in 0.5°C increments until shivering stopped (permissive hypothermia). Time from arrival to r-tPA treatment=60 minutes; mean time from symptom onset to cooling=287.6±65.8 minutes.
Follow-up	**90 days**
Conflict of interest/source of funding	Study was part of an NINDS (National Institute of Neurological Disorders and Stroke) funded SPOTRIAS (Specialized Program of Translational Research in Acute Stroke), a collaboration among the NINDS, University of California and University of Texas. The first author serves on the data safety monitoring board for an industry sponsored trial of therapeutic hypothermia for cardiac arrest.

Analysis

Follow-up issues: One patient in each group was lost to follow-up; 90-day outcome data were missing for 2 patients in the normothermia group.

Study design issues: Prospective, randomised, single-blind, multicentre study. The study was planned to have 2 stages: a phase 2 study to assess safety and feasibility of various protocol changes and a phase 3 efficacy study. Phase 2 was intended to have 400 patients who would have been included in the total 1600 patient phase 3 study. During the application to renew funding for the trial, several publications established the efficacy of intra-arterial neurothrombectomy for selected patients. The Steering Committee decided to stop the trial, examine the data and redesign the trial to include neurothrombectomy. No statistically significant primary results were expected. A per-protocol and intention-to-treat analysis was done. The primary endpoint was favourable outcome, defined as a 90-day mRS score of 0 or 1.

Study population issues: The baseline demographics were similar between the 2 groups.

Other issues: Of the 120 enrolled patients, 16 (13%) showed a rapid reversal of their deficit before the study procedures were started, making them 'early responders' (9 hypothermia and 7 normothermia). These patients were included in the intention-to-treat population but not the per-protocol analysis.

The authors noted that the efficacy results in this small study reflect the effect of mild (<35°C) hypothermia.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **120 (63 versus 57)** **mRS score of 0 or 1 at 90 days (primary outcome)** *ITT population* • Hypothermia=33% • Normothermia=38%, OR 0.81, 95% CI 0.36 to 1.85 *PP population* • Hypothermia=24% • Normothermia=38%, OR 0.50, 95% CI 0.19 to 1.30 Using severity-adjusted outcomes based on initial NIHSS, the ITT-adjusted OR for a good outcome was 1.37 (0.60 to 3.19). The PP-adjusted OR was 0.89 (0.34 to 2.30). ITT OR for mRS score of 2 to 6 in the hypothermia group was 1.03 (0.55 to 1.95). The PP OR was 1.39 (0.69 to 2.80). **Multivariable analysis** (using age, baseline NIHSS, diabetes mellitus history, admission glucose, and time from stroke onset to start of r-tPA) *OR for a good outcome in the hypothermia group* • ITT population=0.62 (95% CI 0.26 to 1.51) • PP population=0.29 (95% CI 0.10 to 0.85), p<0.05 Time to reach target temperature did not seem to change outcome. In the 33 patients with core body temperature <35°C within 6 hours of cooling onset, the proportion with 90-day mRS score of 0 or 1 was 24% (OR 0.52, 95% CI 0.16 to 1.52). **NIHSS score at 7 days** • Hypothermia=10.4±10.3 (n=58) • Normothermia=10.6±11.3 (n=55) There was no statistically significant difference between the groups with regard to the Barthel index at 90 days and the mRS score at 60 days. A >7-point decrease in the NIHSS at 7 days after stroke significantly correlated with 90-day mRS score.	**Serious adverse events (ITT population)** • Hypothermia=41% • Normothermia=35% (OR 1.30, 95% CI 0.58 to 2.92) **Mortality** • Hypothermia=15.9% • Normothermia=8.8% (OR 1.95, 95% CI 0.56 to 7.79) **Pneumonia** • Hypothermia=19% • Normothermia=10.5% (OR 1.99, 95% CI 0.63 to 6.98) **Fluid overload** • Hypothermia=4.8% (3/63) • Normothermia=12.3% (7/57) **Symptomatic intracerebral haemorrhage** • Hypothermia=1.6% • Normothermia=3.5% (OR 0.45, 95% CI 0.01 to 8.80) There were no adverse events related to the intravascular cooling catheter, such as haematoma or arterial injury.
Abbreviations used: CI, confidence interval; ITT, intention to treat; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PP, per-protocol; r-tPA, recombinant tissue-type plasminogen activator.	

Study 3 Su Y (2016)

Details

Study type	**Randomised controlled trial**
Country	China
Recruitment period	2010 to 2013
Study population and number	**n=33 (16 hypothermia, 17 standard medical treatment)** Patients with massive cerebral hemispheric infarction
Age and sex	Hypothermia: mean age 60 years (range 46 to 75); 94% male Control: mean age 69 years (range 53 to 79); 59% male
Patient selection criteria	Patients aged 18 to 80 years; acute unilateral ischaemic stroke <48 hours ago; infarction involving at least two thirds of the middle cerebral artery territory on cranial CT or MRI; a National Institute of Health Stroke Scale (NIHSS) score ≥15 if the non-dominant hemisphere was affected or ≥20 if the dominant hemisphere was affected; a reduced level of consciousness indicated by an NIHSS item 1a score ≥1; unable to have decompressive craniectomy because of the premorbid use of antiplatelet or anticoagulant drugs or because the patient declined the procedure. Patients were excluded if they met any of the following criteria: premorbid modified Rankin Scale score >2; secondary haemorrhage involving more than a third of the infarction territory with a space-occupying effect; Glasgow Coma Scale without a verbal response item score <6; rapidly improving symptoms; both pupils fixed and dilated; simultaneous other brain lesion, including tumours and contralateral or infratentorial infarctions; platelet count <75,000/mm^3, severe coagulopathy or cardiac, liver or kidney disease; vasospastic disease, haematological disease with increased risk of thrombosis, or paramyotonia congenita; sepsis; premorbid treatment with a monoamine oxidase inhibitor or an allergy to pethidine; inferior vena cava fistula or a filter in its place, a mass near the inferior vena cava, or a height of <1.5 m; pregnancy; life expectancy <6 months.
Technique	The temperature of the patients in the control group was sustained between 36.5°C and 37.5°C to maintain normothermia. Patients randomised to the hypothermia group had endovascular hypothermia treatment using a mobile temperature management device (CoolGard, Alsius Corporation). A Foley temperature catheter was used to monitor the bladder temperature and was also connected to the temperature management system. The device adjusted the saline temperature according to the patient's temperature and the target temperature. Hypothermia was started as soon as possible after admission. The target bladder temperature was 33°C or 34°C. Hypothermia was maintained for a minimum of 24 hours and could be prolonged to 72 hours if necessary. Shivering was suppressed with gloves, socks and a quilt. Patients also had oral buspirone, intravenous (IV) pethidine, IV midazolam, and an IV muscle relaxant. The IV infusion drugs started from the minimum doses and were adjusted according to the severity of shivering. Intracranial pressure was invasively and continuously monitored with a transducer-tipped pressure-temperature monitoring catheter.
Follow-up	**6 months**
Conflict of interest/source of funding	Study was supported by a grant from the National Key Department of Neurology funded by the National Health and Family Planning Commission of the People's Republic of China and the National Key Department of Critical Care Medicine funded by the National Health and Family Planning Commission of the People's Republic of China.

Analysis

Follow-up issues: There were no losses to follow-up.

Study design issues: Prospective, single-centre randomised controlled trial. Randomisation was done by using sealed envelopes, with odd numbers being assigned to the hypothermia group and even numbers to the control group. The envelopes were opened by an investigator who was not involved in patient screening, treatment, data collection or analysis. The primary outcomes were mortality and the modified Rankin Scale score at 6 months. The sample size was calculated to be 168, which was not achieved because of slow recruitment.

Study population issues: Patients in the hypothermia group were younger than those in the control group (p=0.006) and there was a higher proportion of males in the hypothermia group (p=0.039). An additional 2 patients were randomised to the hypothermia group, but the catheter could not be inserted because of severe bleeding at the puncture site or lumen malfunction. These patients were excluded from the analysis.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **33 (16 versus 17)**

Good neurological outcome (modified Rankin Scale score of 0 to 3) in surviving patients at 6 months

- Hypothermia=87.5% (7/8)
- Control=40.0% (4/10), p=0.066

OR=10.5, 95% CI 0.9 to 121.4

Adjusted OR=4.8, 95% CI 0.3 to 71.1

Mortality at 6 months

- Hypothermia=50.0% (8/16)
- Control=41.2% (7/17), p=0.732

7 patients in the hypothermia group and 6 patients in the control group died of herniation.

Intracranial pressure

10 patients in the hypothermia group had intracranial pressure monitoring; 5 developed transtentorial herniation. In these 5 patients, the intracranial pressure was 18.7±5.5 mmHg at the start of cooling and decreased to 12.4±6.0 mmHg when the target temperature was reached. During the maintenance period, it increased, reaching 18.8±7.4 mmHg at the start of rewarming. The pressure increased significantly during the rewarming period, reaching 39.4±9.6 mmHg at the end of rewarming. All 5 patients died from herniation.

Safety

Complications

Of the 33 patients, only 1 patient in the control group did not have a complication.

Complications	Hypothermia group n=16	Control group n=17	p value
Recurrent infarction	0	2	0.485
Haemorrhagic transformation	1	2	1.00
Bradycardia	7	2	0.057
Tachycardia	9	10	1.00
Arrhythmia	1	3	0.601
Hypotension	6	3	0.259
Pneumonia	7	8	1.00
Lower extremity deep venous thrombosis	4	2	0.398
Electrolyte disorder	16	9	0.003
Coagulation dysfunction	14	15	1.00
Gastrointestinal bleeding	8	2	0.026
Gastric retention	15	7	0.002
Stress hyperglycaemia	6	1	0.039
Hypoalbuminaemia	11	7	0.166
Acute liver injury	2	1	0.601
Acute kidney injury	2	0	0.227
Total	**109**	**74**	**0.001**

Abbreviations used: CI, confidence interval; OR, odds ratio

Study 4 Hong JM (2014)

Details

Study type	**Non-randomised comparative study**
Country	South Korea (2 tertiary referral stroke centres)
Recruitment period	2010 to 2012
Study population and number	**n=75 (39 hypothermia, 36 control)** Patients with acute ischaemic stroke in the anterior circulation, who had successful recanalisation
Age and sex	Hypothermia: mean age 65 years; 59% (23/39) male Control: mean age 68 years; 50% (18/36) male
Patient selection criteria	Inclusion criteria: ischaemic stroke involving the anterior circulation (National Institute of Health Stroke Scale [NIHSS] ≥10); acute infarction with diffusion-weighted imaging confirmation; endovascular recanalisation (thrombolysis in cerebral ischaemia, grade ≥2b) within 6 hours after symptom onset, or spontaneous recanalisation.
Technique	Hypothermia: patients were cooled with either an endovascular cooling catheter (Alsius) placed in the inferior vena cava (n=37) or a surface cooling device (Arctic Sun, n=2). All cooled patients were mechanically ventilated, midazolam was used for sedation and vecuronium for neuromuscular blockade. The target temperature was 34.5°C. Core body temperatures were plotted with an oesophageal temperature probe. Hypothermia therapy was maintained for 48 hours, and rewarming was done under sedation at a rate of 0.5°C per every 12 hours. Antipyretic and anti-shivering agents other than paralytics were not used during hypothermia. All patients had treatment according to international guidelines for stroke care. Surgical hemicraniectomy was done when necessary.
Follow-up	**90 days**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: No losses to follow-up were described.

Study design issues: Prospective cohort study at 2 tertiary referral stroke centres. All patients in 1 centre had mild hypothermia treatment and patients in the other centre had standard treatment without hypothermia. Neurological deficit was assessed by serial NIHSS scores by certificated stroke nurses or stroke neurologists at least every 4 hours. Neurological scales were checked daily until discharge and every 3 months thereafter. The clinical outcome was primarily dichotomised into good (0 to 2 points) and poor (3 to 6 points) groups using a mRS score at 90 days.

Study population issues: Baseline characteristics, stroke risk factors, and initial laboratory findings were similar between the 2 groups.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **75 (39 versus 36)**

Radiological and clinical outcomes

	Hypothermia n=39	Control n=36	p value
HT			
None	15 (38.5)	5 (13.9)	0.016
HT type 1	8 (20.5)	9 (25.0)	
HT type 2	1 (2.6)	7 (19.4)	
PH type 1	8 (20.5)	8 (22.2)	
PH type 2	7 (17.9)	7 (19.4)	
Cerebral oedema			
None	21 (53.8)	6 (16.7)	0.001
Mild	9 (23.1)	14 (38.9)	
Midline shift	9 (23.1)	16 (44.4)	
Clinical outcomes			
mRS 0 to 1 at 3 months	12 (30.8)	3 (8.3)	0.015
mRS 0 to 2 at 3 months	19 (48.7)	8 (22.2)	0.017
mRS 0 to 3 at 3 months	22 (56.4)	14 (38.9)	0.129
Mortality at 1 month	6 (15.4)	5 (13.9)	0.855
Hemicraniectomy	4 (10.3)	5 (13.9)	0.629

HT type 1 was defined as small petechiae along the margins of the infarct; type 2 was defined as confluent petechiae within the infarcted area but without a space-occupying effect.

PH type 1 was defined as haematoma in <30% of the infarcted area with some space-occupying effect; type 2 was defined as haematoma in >30% of the infarcted area with a substantial space-occupying effect.

After adjustment for potential confounders, therapeutic hypothermia (OR 3.0, 95% CI 1.0 to 8.9, p=0.047) and distal occlusion (OR 7.3, 95% CI 1.3 to 40.3, p=0.022) were independent predictors for a good outcome. Absence of cerebral oedema (OR 5.4, 95% CI 1.6 to 18.2, p=0.006) and no medical complications (OR 9.3, 95% CI 2.2 to 39.9, p=0.003) were also independent predictors for good outcome during the treatment.

Safety

Medical complications

	Hypothermia n=39	Control n=36	p value
Patients with 1 or more medical complication	11 (28.2)	17 (47.2)	0.089
Bradycardia	3 (7.7)	1 (2.8)	-
Elevated creatine kinase	2 (5.1)	2 (5.6)	-
Cardiac events (T-wave inversion, non-STEMI)	1 (2.6)	0 (0)	-
Hypokalaemia	2 (5.1)	0 (0)	-
Pulmonary oedema	2 (5.1)	1 (2.8)	-
Decreased blood pressure	1 (2.6)	0 (0)	-
Pneumonia	2 (5.1)	11 (30.6)	0.004*
Urinary tract infection	0 (0)	2 (5.6)	-
Deep vein thrombosis	0 (0)	0 (0)	-
Gastrointestinal bleeding	0 (0)	1 (2.8)	-

* this p value is given in the body of the text, which states the rate of pneumonia was 8% in the hypothermia group rather than 5% that was quoted in the table.

Abbreviations used: CI, confidence interval; HT, haemorrhagic transformation; mRS, modified Rankin Scale; OR, odds ratio; PH, parenchymal haematoma; STEMI, ST-segment-elevation myocardial infarction

Study 5 Schwab S (2001)

Details

Study type	**Case series**
Country	Germany (4 neurocritical care units)
Recruitment period	Not reported
Study population and number	**n=50** Patients with acute ischaemic cerebral infarction, involving at least the complete territory of the middle cerebral artery
Age and sex	Mean 57 years; 70% (35/50) male
Patient selection criteria	Patients with acute ischaemic cerebral infarction, involving at least the complete territory of the middle cerebral artery. Patients with history of disabling neurological disease, terminal illness, or severe cardiac failure (New York Heart Association class III or IV) were excluded.
Technique	None of the patients had thrombolytic therapy. The timing of hypothermia treatment was based on individual decision making; some patients had treatment immediately after initial CT scan and some had treatment only after clinical or radiological signs of midline shift became evident (mean interval between onset of symptoms and start of hypothermia was 22±9 hours [range 4 to 75 hours]). Hypothermia was induced by cooling blankets and alcohol and ice bags. Target temperature: 32°C to 33°C (moderate hypothermia) for 24 to 72 hours. After this period, passive rewarming over 24 hours to normal temperature was allowed; the pace of rewarming was decided by the local physician. All patients were sedated with midazolam or propofol; morphine or fentanyl was used for analgesia. All patients had neuromuscular blockade before the start of moderate hypothermia, continued until rewarming at 36°C was achieved.
Follow-up	**3 months**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: 6% (3/50) of patients were lost to follow-up.

Study design issues: Prospective observational study, consecutive patients. Initial patient status and patient status at 4 weeks were assessed with the NIHSS. Clinical outcome was assessed with the Rankin Scale and the 100-point Barthel Index at 3-month follow-up. The study aimed to assess the feasibility and safety of the procedure.

Study population issues: The mean NIHSS on admission was 25 (range 15 to 32). All patients had complete middle cerebral artery stroke; 5 patients had an additional anterior or posterior artery territory infarction.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 50

Intracranial pressure
Mean ICP before start of hypothermia=19.8±14.2 mmHg (range 4 to 36)

When steady state of hypothermia was reached, ICP reduced to 12.4±5.3 mmHg (p<0.05)

A rise in ICP was seen in all patients during rewarming, to mean values of 23.4±8.7 mmHg (range 17 to 71)

A shorter (<16 hours) rewarming period was associated with a more pronounced rise in ICP (15±10% versus 26±15%, p=not significant).

Neurological outcomes
• NIHSS score at 4 weeks=29
• Mean Barthel Index at 3 months=65 (range 10 to 85)
• Mean Rankin Scale score at 3 months=2.9 (range 2 to 5)</td><td>Complications
<table><tr><th>Variable</th><th>Number of patients (%)</th></tr><tr><td>Platelet count <100,000/nanolitre</td><td>35 (70%)</td></tr><tr><td>Cardiac arrhythmia/bradycardia</td><td>31 (62%)</td></tr><tr><td>Pneumonia</td><td>24 (48%)</td></tr><tr><td>Pancreatitis</td><td>3 (6%)</td></tr><tr><td>Severe hypotension (mean arterial pressure <50 mmHg)</td><td>2 (4%)</td></tr><tr><td>Severe coagulopathy</td><td>2 (4%)</td></tr><tr><td>Cardiac failure</td><td>1 (2%)</td></tr></table>NB: the figures above are as reported in the table of the study publication, but there are some discrepancies between the text and the table. The body of the text states that 3 patients had severe arterial hypotension. This was refractory under high doses of vasopressor agents in 1 patient and the other 2 patients finally died of cardiac failure. It also states that 3 patients had severe coagulopathy, which was fatal in 1 patient.

The pancreatitis was treated conservatively.

The prevalence of pneumonia increased with longer duration of hypothermia.

Mortality=38% (19/50)
2 patients died of cardiac failure, 1 patient died of severe coagulopathy, 1 patient died of herniation on day 3 while still under moderate hypothermia, and 15 patients died after hypothermia was stopped and were caused by an extensive increase in ICP.</td></tr>
<tr><td colspan="2">Abbreviations used: ICP, intracranial pressure; NIHSS, National Institutes of Health Stroke Scale</td></tr>
</table>

Study 6 Mourand I (2012)

Details

Study type	**Case series**
Country	France
Recruitment period	Not reported
Study population and number	**n=19** Patients with severe acute ischaemic stroke
Age and sex	Mean 53 years (range 27 to 65); 68% male
Patient selection criteria	Inclusion criteria: age between 18 and 65 years; large middle cerebral artery infarction involving more than two-thirds of the area; an NIHSS score of ≥20 for left-hemispheric stroke and ≥17 for right-hemispheric stroke, with an item level of consciousness of 1 (drowsy, but arousable by minor stimulation); starting moderate hypothermia within 24 hours of symptom onset; not eligible for intravenous thrombolysis. Exclusion criteria: sepsis within the 72 hours before stroke onset; any previous disabling neurological disease or terminal illness that gave a life expectancy of <6 months.
Technique	Hypothermia was induced as soon as possible, but always within the first 24 hours. A cooling blanket was used (Blanketrol II, Cincinnati Sub-Zero) and adjusted to maintain a rectal temperature of between 32°C and 33°C. Hypothermia was stopped when the midline shift was <5 mm without major lateral-ventricle compression. Rewarming was induced at a rate of <1.5°C/24 hours. All patients were mechanically ventilated, and paralysed for the first 72 hours to avoid shivering. Sedation was induced by high-dose gamma hydroxybutyrate and low-dose midazolam and fentanyl. Norepinephrine was continually infused. A hemicraniectomy was done when necessary. An intracranial pressure probe was not used. Mean duration of hypothermia=22.6±4.9 days.
Follow-up	**12 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: No losses to follow-up were described.

Study design issues: Single-centre, prospective observational study with consecutive patients. The aim of the study was to assess the feasibility and safety of very prolonged moderate hypothermia for severe acute ischaemic stroke.

Study population issues: The Alberta Stroke Program Early CT Score for all patients was ≤4 at study entry and was 0 for 50% of patients. The mean NIHSS was 20.9±2.0 and Glasgow Coma Score was 11.7±1.8.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **19** **Neurological outcomes** The 10 patients who survived were discharged to rehabilitation programmes. All were living at home 12 months after the stroke. • Mean NIHSS score at 12 months=8.3±2.7 • Mean Barthel Index at 12 months=67±18 • Mean modified Rankin Scale score at 12 months=3.2±0.9 **Stroke recurrence=26% (5/19)** (4 happened during the cooling period and 1 at 5 days after rewarming; 3 patients had severe clinical deterioration and died, and 2 survived [1 of whom had a hemicraniectomy]). Uncontrolled intracranial pressure with cerebral herniation=31.6% (6/19) (5 patients had a hemicraniectomy within the first 9 days of the hypothermia period; 4 patients survived after the hemicraniectomy).	**Complications** During the hypothermia procedure, all patients had hypotension, which needed continuous infusion of norepinephrine, and bradycardia of between 35 and 50 pulses per minute, without arrhythmia. Bacterial pneumonia=42% (8/19) (treated with antibiotics; 1 patient died) Platelet counts continuously and slowly decreased in all patients; a preventive platelet transfusion was needed in 8 patients between days 15 and 20). **In-hospital and 90-day mortality=47% (9/19)** (4 deaths were during the hypothermia treatment between days 1 and 11 [1 cardiac arrest caused by a myocardial infarct present in the acute phase, 1 multiple organ failure, and 2 uncontrolled intracranial hypotension], 3 patients died during the rewarming phase between days 15 and 27 [1 nosocomial pneumonia, 2 uncontrolled intracranial hypertension] and 2 deaths were after rewarming [both caused by stroke recurrence]. There was a significant difference in the mean duration to reach target temperature between patients who survived [8.1±5.5 hours] and those who died [14.0±7 hours], p=0.031). Comparisons between survivors and deceased patients showed that only haematocrit was statistically different by day 8 between the 2 groups (34.8% versus 42.5%, p=0.038).
Abbreviations used: NIHSS, National Institute of Health Stroke Scale	

Study 7 Schneider H (2017)

Details

Study type	**Non-randomised comparative study**
Country	Germany
Recruitment period	2001 to 2010
Study population and number	**n=111 (53 hemicraniectomy and hypothermia versus 58 hemicraniectomy alone)** Patients with space-occupying cerebral infarction
Age and sex	Mean age 48 years; 58% (64/111) male
Patient selection criteria	Inclusion criteria for hypothermia group: age 18 to 60 years; clinical deficits suggestive of large infarction in the territory of the middle cerebral artery; decrease of consciousness (score of 1 or greater on item 1a of the NIHSS); signs on CT or MRI of an infarct of at least 50% of the middle cerebral artery territory, with or without additional infarction in the territory of the ipsilateral anterior or posterior cerebral artery; hemicraniectomy within 48 hours after onset of symptoms; no fixed pupils before hemicraniectomy; no contralateral ischaemia or other brain lesion that could affect outcome; hypothermia treatment. Inclusion criteria for control group were comparable and included age 18 to 60 years and time from symptom onset to hemicraniectomy 48 hours.
Technique	All patients had a hemicraniectomy (median 23.5 hours after symptom onset). In the hypothermia group, hypothermia was induced immediately after surgery and patients were transferred to the neurocritical care unit. An intracranial pressure probe was inserted ipsilaterally in the affected brain tissue. The target temperature was 33°C to 34°C, except in patients with known cardiac arrhythmia or coagulopathy when the target was 35°C. The target temperature was maintained for at least 96 hours with a rewarming phase in steps of 1°/day to normothermia (36.5°C). From 2001 to 2004, cooling mats were used for surface cooling (Blanketrol, CSZ, Cincinnati) and from 2004 to 2010, surface cooling or endovascular temperature management were used (Arctic Sun, Medivance Inc. US; CoolGard, Alsius, US). No specific anti-shivering medication or methods were needed because patients were deeply sedated and showed no shivering. Core body temperature was measured with a urinary bladder catheter.
Follow-up	**12 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: No losses to follow-up were described.

Study design issues: Retrospective observational study. Patients in the hypothermia group all had treatment at a single centre. The comparison group consisted of patients who had early hemicraniectomy from 3 randomised controlled trials. The primary outcome measure was the functional outcome, determined by the mRS score at 12 months, dichotomised 0 to 3 versus 4 to 6.

Study population issues: In the hypothermia group, mean age was higher than in the control group (50 versus 46 years) and there were more males (64% versus 52%). Cardiovascular risk factors were more frequent in the hypothermia group than in the control group (diabetes: 23% versus 9%; arterial hypertension: 67% versus 37%). Baseline stroke severity was similar in the 2 groups according to NIHSS scores, but the dominant hemisphere was more often affected in the hypothermia group (60% versus 52%). Body temperature on admission was higher in the control group (37.2°C versus 36.3°C).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **111 (53 versus 58)** **mRS score of 0 to 3 at 12 months** • Hypothermia=25% (13/53) • Control=41% (24/58) RR=0.59, 95% CI 0.34 to 1.04 RR adjusted for age and NIHSS score at baseline=0.66, 95% CI 0.38 to 1.13 Adjustment for a propensity score based on age, hours to surgery, and hypertension: RR 0.71, 95% CI 0.40 to 1.24 **mRS score of 0 to 4 at 12 months** • Hypothermia=40% (21/53) • Control=72% (42/58) RR=0.54, 95% CI 0.38 to 0.79 **Survival after 12 months** • Hypothermia=49% (26/53) • Control=79% (46/58) RR=0.62, 95% CI 0.46 to 0.84 The results for mRS score of 0 to 4 and survival at 12 months did not change significantly after adjusting for various factors.	Events reported in the hypothermia group during the intensive care unit stay: • Severe sepsis=11% (6/53) • Tracheobronchitis or pneumonia=74% (39/53) • Deep venous thrombosis=9% (5/53) • Cardiac arrhythmia=28% (15/53) **Mortality in hypothermia group** 20 patients died during the first 14 days after symptom onset; 18 deaths were caused by intracranial herniation, 1 was caused by severe sepsis and 1 was caused by malignant cardiac arrhythmia.
Abbreviations used: CI, confidence interval; mRS, modified Rankin Scale; NIHSS, National Institutes for Health Stroke Scale; RR, risk ratio	

Study 8 Park HS (2018)

Details

Study type	**Non-randomised comparative study**
Country	Korea
Recruitment period	2012 to 2016
Study population and number	**n=47** (20 hypothermia and hemicraniectomy, 27 hemicraniectomy alone) Patients with malignant middle cerebral artery infarction
Age and sex	Hypothermia group: mean age 62 years; 60% (12/20) male Control group: mean age 59 years; 63% (17/27) male
Patient selection criteria	Inclusion criteria: acute cerebral infarction involving more than two-thirds of middle cerebral artery territory and a mental status decrease to stupor or worse (a Glasgow coma scale score <11) with midline shift >10 mm or a transtentorial herniation sign (a fixed and dilated pupil).
Technique	Hypothermia was induced immediately after hemicraniectomy or after the decision of hypothermia during postoperative care. Hypothermia was achieved by a cooling blanket (Blanketrol III, Cincinnati Sub-Zero, USA) set to maintain the rectal temperature at 34°C. The duration of hypothermia was determined according to the findings on CT scans, done every 2 to 3 days, as well as the condition of the patient. Active rewarming was done at a rate of 0.2°C/hour. Patients were sedated with midazolam and vecuronium and ventilated. Hypothermia was maintained for 4±2 days (range 1 to 7). All patients had a decompressive hemicraniectomy. Intracranial pressure monitoring was not used.
Follow-up	**1 year**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: 18 of the 20 patients in the hypothermia group and 25 of the 27 patients in the control group were followed up to 1 year.

Study design issues: Retrospective analysis of prospectively maintained stroke registry. Patients in the hypothermia group had treatment between 2012 and 2016. Control group patients had treatment between 2010 and 2012; patients who met the inclusion criteria for hypothermia were selected. The primary outcome of the study was defined as either death or survival within the hospital.

Study population issues: In the hypothermia group, 35% (7/20) of patients showed a transtentorial herniation sign (a fixed and dilated pupil) before hypothermia. There were no statistically significant differences between the groups with regard to age, preoperative infarct volume, Glasgow Coma score, National Institutes of Health Stroke Scale score before surgery, maximal degree of midline shift, and time interval between symptom onset and hemicraniectomy.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **47 (20 versus 27)** **In-hospital mortality** • Hypothermia=15.0% • Control=40.7%, p=0.056 The causes of death in the hypothermia group were transtentorial herniation (n=2) and cardiac failure (n=1). In the control group, the causes of death were transtentorial herniation (n=7), pneumonia (n=2), pulmonary thromboembolism (n=1), and acute kidney injury (n=1). Hypothermia was identified as the strongest factor that affected survival in the multivariable analysis (odds ratio 6.21, 95% confidence interval 1.04 to 37.05, p=0.045). **Mortality at 1 year** • Hypothermia=27.8% (5/18) • Control=52.0% (13/25), p=0.112 Functional outcomes at 1-year follow-up were not statistically significantly different between the 2 groups.	**Hypothermia-related complications and serious adverse events in the intensive care unit** • Arrhythmia=10% (2/20) • Sepsis=5% (1/20) • Pneumonia=5% (1/20) • Hypotension=5% (1/20) In 3 patients, hypothermia was stopped because of these side-effects (1 patient with sepsis, 1 with hypotension and 1 with bradycardia). Of all the adverse events during the stay in the intensive care unit, pneumonia was the most common (n=5, 25%), but there were no statistically significant differences compared with the control group (n=5, 18.5%, p=0.723). **Haemorrhagic transformation after hemicraniectomy** • Hypothermia=35.0% (7/20) • Control=25.9% (7/27), p=0.501 Only 1 patient in the control group had revision surgery for removal of intracerebral haemorrhage in the basal ganglia.

Study 9 Petersson J on behalf of the EuroHYP-1 investigators (October 2018) – conference presentation (included for safety data only)

Data have been redacted

Validity and generalisability of the studies

- There are different techniques and devices used for cooling, which may have different safety and efficacy profiles.
- The target temperature and the duration of hypothermia varied between the studies.
- Induction time and rewarming speed varied between the studies.
- Different methods of temperature monitoring were used.
- In some studies, patients were sedated and mechanically ventilated during the hypothermia treatment.
- Some patients had additional treatments, such as thrombolysis and hemicraniectomy, as well as therapeutic hypothermia.

Existing assessments of this procedure

The European Stroke Organisation published guidelines for the management of temperature in patients with acute ischaemic stroke in 2015.[10] With regard to induction of hypothermia, the recommendation states:

> 'In patients with acute ischemic stroke, we do not recommend induction of hypothermia as a means to improve functional outcome and/or survival.'

The quality of evidence was graded as very low and the strength of the recommendation was defined as weak, according to the GRADE methodology. The report strongly encouraged recruitment of eligible patients to ongoing RCTs.

Recent guidelines from a French expert panel stated:

> 'We suggest considering targeted temperature management (TTM) at normothermia during the early phase of severe ischaemic stroke. (Expert opinion)
>
> Rationale: Hyperthermia or fever is a frequent complication (>50%) in patients at the acute phase of stroke and is correlated with poor functional outcome. However, the efficacy of therapeutic hypothermia has not yet been shown, according to 6 randomized trials that tested hypothermia (33–35 °C) in stroke patients. There were few patients and methodological biases were numerous. A single study investigated patients with severe stroke (NIHSS >15). Two randomized studies are ongoing: EuroHYP-1

explores the value of 24 h; 34–35°C hypothermia following recent stroke, and the recent ICTuS 2/3 trial. In that later study, intravascular therapeutic hypothermia was found safe and feasible in patients treated with recombinant tissue-type plasminogen activator.'[11]

Related NICE guidance

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

Interventional procedures

- Therapeutic hypothermia following cardiac arrest. NICE interventional procedures guidance 368 (2011). Available from https://www.nice.org.uk/guidance/ipg386

- Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury. NICE interventional procedures guidance 347 (2011). Available from https://www.nice.org.uk/guidance/ipg347

- Mechanical clot retrieval for treating acute ischaemic stroke. NICE interventional procedures guidance 548 (2016). Available from https://www.nice.org.uk/guidance/ipg548

Technology appraisals

- Alteplase for treating acute ischaemic stroke. NICE technology appraisal 264 (2012). Available from http://www.nice.org.uk/guidance/TA264

NICE guidelines

- Stroke and transient ischaemic attack in over 16s: diagnosis and initial management. NICE clinical guideline 68 (2008). Available from http://www.nice.org.uk/guidance/CG68 [update in development]

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. One Specialist Adviser Questionnaire for therapeutic hypothermia for acute ischaemic stroke were submitted and can be found on the NICE website.

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 5 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.

Issues for consideration by IPAC

- Ongoing trials:
  - Mild Hypothermia After Endovascular Treatment in Acute Ischemic Stroke (HELMET) (NCT02985060); RCT; Korea; estimated enrolment 40; estimated study completion date November 2017.
  - Cooling Plus Best Medical Treatment Versus Best Medical Treatment Alone for Acute Ischaemic Stroke (EuroHYP-1) (NCT01833312); RCT; Germany; estimated enrolment 800; estimated completion date December 2020.

- Evidence on reducing the temperature to normal in patients with fever after ischaemic stroke has not been included.

References

1. Wan Y-H, Nie C, Wang H-L et al. (2014) Therapeutic hypothermia (different depths, durations, and rewarming speeds) for acute ischemic stroke: a meta-analysis. Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association 23: 2736–47
2. Lyden P, Hemmen T, Grotta J et al. (2016) Results of the ICTuS 2 Trial (Intravascular Cooling in the Treatment of Stroke 2). Stroke 47: 2888–95
3. Su Y, Fan L, Zhang Y et al. (2016) Improved Neurological Outcome With Mild Hypothermia in Surviving Patients With Massive Cerebral Hemispheric Infarction. Stroke 47: 457–63
4. Hong JM, Lee JS, Song H-J et al. (2014) Therapeutic hypothermia after recanalization in patients with acute ischemic stroke. Stroke 45: 134–40
5. Schwab S, Georgiadis D, Berrouschot J et al. (2001) Feasibility and safety of moderate hypothermia after massive hemispheric infarction. Stroke 32: 2033–5
6. Mourand I, Escuret E, Heroum C et al. (2012) Feasibility of hypothermia beyond 3 weeks in severe ischemic stroke: an open pilot study using gamma-hydroxybutyrate. Journal of the neurological sciences 316: 104–7
7. Schneider H, Kruger P, Algra A et al. (2017) No benefits of hypothermia in patients treated with hemicraniectomy for large ischemic stroke. International journal of stroke: official journal of the International Stroke Society 12: 732–40
8. Park H-S, Choi J-H (2018) Safety and Efficacy of Hypothermia (34°C) after Hemicraniectomy for Malignant MCA Infarction. Journal of Korean Neurosurgical Society 61: 267–76
9. Petersson J on behalf of the EuroHYP-1 investigators (2018) Therapeutic Hypothermia in Acute Ischemic Stroke - Main Results. Presented at the World Stroke Congress, Montreal, 17 to 20 October 2018.
10. Ntaios G, Dziedzic T, Michel P et al. (2015) European Stroke Organisation (ESO) guidelines for the management of temperature in patients with acute ischemic stroke. International journal of stroke: official journal of the International Stroke Society 10: 941–9
11. Cariou A, Payen J-F, Asehnoune K et al. (2017) Targeted temperature management in the ICU: guidelines from a French expert panel. Annals of Intensive Care 7:70

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	14/12/2018	Issue 12 of 12, December 2018
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	14/12/2018	Issue 12 of 12, December 2018
HTA database (CRD website)	14/12/2018	n/a
MEDLINE (Ovid)	14/12/2018	1946 to December 13, 2018
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	14/12/2018	December 13, 2018
MEDLINE Epubs ahead of print (Ovid)	14/12/2018	December 13, 2018
EMBASE (Ovid)	14/12/2018	1974 to 2018 December 13

Trial sources searched 20th February 2018

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

Websites searched 20th February 2018

- 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)
- EuroScan
- 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.

1	Stroke/
2	Cerebral Infarction/ or Brain Ischemia/ or *Arterial Occlusive Diseases/
3	((acute or isch?emi* or thrombotic or embolic) adj3 stroke).tw.
4	((brain or cerebral*) adj2 (isch?emi* or infarct*)).tw.
5	(arter* adj2 occlusi*).tw.
6	((cerebrovascular* or vascular*) adj2 accident*).tw.

7	CVA.tw.
8	or/1-7
9	((surface or endovascular or circulat* or therap* or neuroprotect* or device* or induc*) adj4 (cool* or chill* or hypotherm*)).tw.
10	Hypothermia, Induced/
11	(temperature adj4 (manag* or target*) adj4 (cool* or chill* or reduc* or low*)).tw.
12	or/9-11
13	8 and 12
14	(iqool or braincool).tw.
15	13 or 14
16	animals/ not humans/
17	15 not 16
18	limit 17 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 main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies. Case reports have been excluded, unless they report a unique safety event.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Abou-Chebl A, DeGeorgia, MA, Andrefsky JC et al. (2004) Technical refinements and drawbacks of a surface cooling technique for the treatment of severe acute ischemic stroke. Neurocritical care 1: 131-43	Case series n=18	Surface cooling for the treatment of acute ischemic stroke can be performed rapidly with early neuromuscular paralysis. Advanced age and prolonged hypothermia may be associated with an increased risk of complications.	Larger or more recent studies are included.
Abou-Chebl A, Sung G, Barbut D et al. (2011) Local brain temperature reduction through intranasal cooling with the RhinoChill device: preliminary safety data in brain-injured patients. Stroke 42: 2164-9	Case series n=15	Intranasal cooling with the RhinoChill device appears safe and effectively lowers brain and core temperatures. Further study is warranted to assess the efficacy of hypothermia through intranasal cooling for brain-injured patients.	Small case series, with mixed indications.
Bi M, Ma Q, Zhang S et al. (2011) Local mild hypothermia with thrombolysis for acute ischemic stroke within a 6-h window. Clinical neurology and neurosurgery 113: 768-73	RCT n=93 (31 versus 31 versus 31) FU=90 days	There was no benefit of combined local hypothermia/IV rtPA treatment compared to IV rtPA alone.	Trial is included in systematic review by Wan YH et al., 2014 (study 1), cited as Tong, 2011.
Chen J, Liu L, Zhang H et al. (2016) Endovascular Hypothermia in Acute Ischemic Stroke: Pilot Study of Selective Intra-Arterial Cold Saline Infusion. Stroke 47: 1933-5	Case series n=26	Selective brain cooling by intra-arterial infusion of cold saline combined with endovascular recanalisation therapy in acute ischemic stroke seems feasible and safe.	Larger or more recent studies are included.
De Georgia MA, Krieger DW, Abou-Chebl A et al. (2004) Cooling for Acute Ischemic Brain Damage (COOL AID): a feasibility trial of endovascular cooling. Neurology 63: 312-7	RCT n=40 (18 versus 22) FU=1 month	Induced moderate hypothermia is feasible using an endovascular cooling device in most patients with acute ischemic stroke. Further studies are needed to determine if hypothermia improves outcome.	Study is included in systematic review by Wan YH et al., 2014 (study 1).
Den Hertog HM, van der Worp HB, Tseng MC et al. (2009) Cooling therapy for acute stroke. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD001247. DOI: 10.1002/14651858.CD001247.pub2.	Systematic review n=132 (3 studies on physical cooling)	There was no statistically significant effect of pharmacological or physical temperature-lowering therapy in reducing the risk of death or dependency (odds ratio (OR) 0.9, 95% confidence interval (CI) 0.6 to 1.4) or death (OR 0.9, 95% CI 0.5 to 1.5). Both interventions were associated with a non-	A more recent systematic review is included. All the relevant studies identified are included in table 2 or the

		significant increase in the occurrence of infections.	appendix of this overview.
Els T, Oehm E, Voigt S et al. (2006) Safety and therapeutical benefit of hemicraniectomy combined with mild hypothermia in comparison with hemicraniectomy alone in patients with malignant ischemic stroke. Cerebrovascular diseases 21: 79-85	RCT n=25 (12 versus 13) FU=6 months	The present study suggests that a combined therapy of mild hypothermia and hemicraniectomy in malignant brain infarction does not imply additional risks by side effects and improves functional outcome as compared with hemicraniectomy alone.	Study is included in systematic review by Wan YH et al., 2014 (study 1).
Froehler MT, Ovbiagele B (2010) Therapeutic hypothermia for acute ischemic stroke. Expert review of cardiovascular therapy 8: 593-603	review	Rapid induction of hypothermia is key and is best accomplished with a combination of ice-cold saline infusion and the use of endovascular cooling devices. Shivering can be overcome with aggressive anti-shivering protocols including meperidine, buspirone and surface warming. If proven efficacious, hypothermia would be a welcome complement to established reperfusion therapies for ischaemic stroke patients.	A more recent systematic review is included.
Georgiadis D, Schwarz S, Kollmar R et al. (2001) Endovascular cooling for moderate hypothermia in patients with acute stroke: first results of a novel approach. Stroke 32: 2550–3	Case series n=6	Induction and maintenance of hypothermia with an intravenous cooling device are feasible. The safety of this approach remains to be evaluated.	Larger or more recent studies are included.
Georgiadis D, Schwarz, S, Aschoff A et al. (2002) Hemicraniectomy and moderate hypothermia in patients with severe ischemic stroke. Stroke 33: 1584-8	Non-randomised comparative study n=36	In patients with severe ischaemic stroke, hemicraniectomy results in lower mortality and lower complication rates compared with moderate hypothermia. Both treatment modalities, however, are associated with intensive medical treatment and a prolonged stay in the neurological intensive care unit.	Larger or more recent studies are included.
Georgiadis D, Schwarz S, Evans DH et al. (2002) Cerebral autoregulation under moderate hypothermia in patients with acute stroke. Stroke 33: 3026–9	Case series n=14	Static cerebral autoregulation appears intact under moderate hypothermia with the use of alpha-stat for pH maintenance.	Larger or more recent studies are included.
Geurts M, Petersson J, Brizzi M et al. (2017) COOLIST (Cooling for Ischemic Stroke Trial) A multicentre, open, randomized, phase II, clinical trial. Stroke 48: 219–21	RCT n=22 FU=3 months	In awake patients with acute ischaemic stroke, surface cooling is feasible to 35°C but not to 34.5°C and 34°C. Cooling is associated with an increased risk of pneumonia.	Small study, which assessed feasibility and safety of cooling to different target temperatures.
Guluma KZ, Hemmen TM, Olsen SE et al. (2006) A trial of therapeutic hypothermia via	Case series n=10	The procedure was well tolerated, with minimal shivering and no rebound hyperthermia.	Larger or more recent studies are included.

endovascular approach in awake patients with acute ischemic stroke: methodology. Academic emergency medicine: official journal of the Society for Academic Emergency Medicine 13: 820-7			
Guluma KZ, Oh H, Yu SW et al. (2008) Effect of endovascular hypothermia on acute ischemic edema: morphometric analysis of the ICTuS trial. Neurocritical care 8: 42-7	Case series n=18 FU=30 days	Endovascular hypothermia decreases acute post-ischemic cerebral oedema. A larger trial is warranted to determine if it affects final infarct volume and outcome in stroke.	Larger or more recent studies are included.
Guluma KZ, Liu L, Hemmen TM et al. (2010) Therapeutic hypothermia is associated with a decrease in urine output in acute stroke patients. Resuscitation 81: 1642-7	Case series n=11	Urine output decreased 5.1 ml/hour for every 1°C decrease in body temperature (p=0.001), with no associated serious adverse events.	Larger or more recent studies are included.
Harris B, Andrews PJD, Murray GD et al. (2012) Systematic review of head cooling in adults after traumatic brain injury and stroke. Health Technology Assessment 16 (45)	Systematic review	Out of 46 head-cooling studies in TBI and stroke, there were no RCTs of suitable quality for formal outcome analysis. Some methods of head cooling can reduce intracranial temperature, which is an important first step in determining effectiveness, but there is insufficient evidence to recommend its use outside of research trials.	Review focuses on head cooling. A more recent systematic review is included.
Hemmen TM, Raman R, Guluma KZ et al. (2010) Intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke (ICTuS-L): final results. Stroke 41: 2265-70	RCT n=58 (28 versus 30) FU=90 days	This study demonstrates the feasibility and preliminary safety of combining endovascular hypothermia after stroke with intravenous thrombolysis. Pneumonia was more frequent after hypothermia, but further studies are needed to determine its effect on patient outcome and whether it can be prevented.	Study is included in systematic review by Wan YH et al., 2014 (study 1).
Horn CM, Sun CHJ, Nogueira RG et al. (2014) Endovascular Reperfusion and Cooling in Cerebral Acute Ischemia (ReCCLAIM I). Journal of neurointerventional surgery 6: 91–5	Case series n=20 FU=90 days	Hypothermia can be safely performed after definitive intra-arterial reperfusion therapy in patients with large pretreatment core infarcts. A phase II study randomising patients to hypothermia or normothermia is needed to properly assess the efficacy of hypothermia as a neuroprotectant for reperfusion injury.	Larger or more recent studies are included.
Horstmann S, Koziol JA, Martinez-Torres F et al. (2009) Sonographic monitoring of mass effect in stroke patients treated with hypothermia. Correlation	Non-randomised comparative study n=30	Hypothermia reduces matrix metalloproteinase 9 activity as well as midline shift. Transcranial duplex sonography may reduce	Larger or more recent studies are included.

with intracranial pressure and matrix metalloproteinase 2 and 9 expression. Journal of the neurological sciences 276: 75-8		the need for repetitive CT scans in neurological critically ill patients.	
Hwang YH, Jeon JS, Kim YW et al. (2017) Impact of immediate post-reperfusion cooling on outcome in patients with acute stroke and substantial ischemic changes. Journal of neurointerventional surgery 9: 21-25	Case series n=18 FU=3 months	Favourable outcome (modified Rankin Scale <=2) at 3 months was observed in 10 (56%) patients. Symptomatic intracranial haemorrhage, malignant brain oedema, and pneumonia were observed in 2, 6, and 8 patients, respectively.	Small case series with short term follow-up.
Jaramillo A, Illanes S, Diaz V (2008) Is hypothermia useful in malignant ischemic stroke? Current status and future perspectives. Journal of the neurological sciences 266: 1-8	Review n=196 (11 studies)	Moderate hypothermia ameliorates ischemic injury by multiple mechanisms. Treatment of acute ischemic stroke patients is feasible, and additional studies, including randomised clinical trials, are warranted.	A more recent systematic review with meta-analysis is included (study 1).
Kammersgaard LP, Rasmussen BH, Jorgensen HS et al. (2000) Feasibility and safety of inducing modest hypothermia in awake patients with acute stroke through surface cooling: A case-control study: the Copenhagen Stroke Study. Stroke 31: 2251–6	Non-randomised comparative study n=73 (17 versus 56) FU=6 months	Modest hypothermia can be achieved in awake patients with acute stroke by surface cooling with the "forced air" method, in combination with pethidine to treat shivering. It was not associated with a poor outcome.	Larger or more recent studies are included.
Kim JY, Yenari MA (2015) Hypothermia for treatment of stroke. Brain Circulation 1:14-25	Review	Animal models and the method of cooling used in the laboratory are quite different from those employed clinically. Thus, an effort to simulate the clinical condition more precisely might provide solutions for better and wider application of therapeutic hypothermia in human patients. Second, there are few investigations into overcoming the complications of systemic hypothermia such as shivering, infection, and coagulopathies. Though these complications are largely ignored in the laboratory, they are significant at the clinical level and will need to be addressed.	No meta-analysis. The relevant cited studies are included.
Kollmar R, Schellinger PD, Steigleder T et al. (2009) Ice-cold saline for the induction of mild hypothermia in patients with acute ischemic stroke: a pilot study. Stroke 40: 1907–9	Case series n=10	This pilot study suggests that rapid ice-cold saline infusions in combination with pethidine and buspirone lower the body temperature significantly without major side effects.	Larger or more recent studies are included.
Krieger DW, De Georgia MA., Abou-Chebl A et al. (2001) Cooling for acute ischemic brain damage (cool aid): an open pilot	Non-randomised comparative study	Induced hypothermia appears feasible and safe in patients with acute ischemic stroke even after thrombolysis. Refinements of the	Larger or more recent studies are included.

study of induced hypothermia in acute ischemic stroke. Stroke 32: 1847-54	n=19 (10 versus 9)	cooling process, optimal target temperature, duration of therapy, and, most important, clinical efficacy, need further study.	
Lakhan SE, Pamplona F (2012) Application of mild therapeutic hypothermia on stroke: a systematic review and meta-analysis. Stroke research and treatment 295906	Systematic review and meta-analysis n=288 (7 trials)	Hypothermia does not significantly improve stroke severity; however, this finding should be taken with caution due to the high heterogeneity and limited number of included studies. No impact on mortality was observed.	A more recent systematic review is included.
Lyden PD, Allgren RL, Ng K et al. (2005) Intravascular Cooling in the Treatment of Stroke (ICTuS): early clinical experience. Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association 14: 107-14	Case series n=18	Endovascular cooling with a proactive anti-shivering regimen can be accomplished in awake stroke patients. Further studies are needed to establish the safety and efficacy of this approach.	Larger or more recent studies are included.
Lyden PD, Krieger D, Yenari M et al. (2006) Therapeutic hypothermia for acute stroke. International journal of stroke: official journal of the International Stroke Society 1: 9-19	Review	Therapeutic hypothermia is promising, but further Phase 1 and Phase 2 development efforts are needed to ensure that cooling of stroke patients is safe, before definitive efficacy trials.	A more recent systematic review is included.
Martin-Schild S, Hallevi H, Shaltoni H et al. (2009) Combined Neuroprotective Modalities Coupled with Thrombolysis in Acute Ischemic Stroke: A Pilot Study of Caffeinol and Mild Hypothermia. Journal of Stroke and Cerebrovascular Diseases 18: 86-96	Case series n=20	Combining caffeinol with hypothermia in patients with acute stroke who have IV t-PA is feasible. A prospective placebo-controlled randomised study is needed to further assess safety and to test the efficacy of caffeinol, hypothermia, or both	Larger or more recent studies are included.
Meijer RJ, Visser H, Koudstaal PJ et al. (2001) Lowering body temperature in acute ischemic stroke without artificial ventilation and heavy sedation: a feasibility study. Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association 10: 157-60	Case series n=8	The study suggests that mild hypothermia in non-comatose stroke patients during a period of 24 hours after the ictus may be accomplished with a cooling blanket and light sedation with midazolam in a well-equipped stroke unit.	Larger or more recent studies are included.
Milhaud D, Thouvenot E, Heroum C et al. (2005) Prolonged moderate hypothermia in massive hemispheric infarction: clinical experience. Journal of neurosurgical anesthesiology 17: 49–53	Case series n=12 FU=6 months	Prolonged hypothermia with gamma-hydroxybutyrate can be used to treat malignant cerebral infarction patients, with a fairly good clinical outcome for survivors.	Larger or more recent studies are included.
Ovesen C, Brizzi M, Pott FC et al. (2013) Feasibility of endovascular and surface cooling strategies in acute	RCT n=31 (17 versus 14) FU=30 days	Therapeutic hypothermia with general anaesthesia is feasible in stroke patients. There were increased rates of pneumonia,	Trial is included in systematic review by Wan YH et al., 2014

stroke. Acta neurologica Scandinavica 127: 399-405		while the length of hospital stay remained comparable. The endovascular cooling strategy provides a faster induction period than surface cooling.	(study 1), cited as Krieger, 2013.
Piironen K, Tiainen M, Mustanoja S et al. (2014) Mild hypothermia after intravenous thrombolysis in patients with acute stroke: a randomized controlled trial. Stroke 45: 486-91	RCT n=36 (18 versus 18) FU=3 months	Mild hypothermia with a surface-cooling device in an acute stroke unit is safe and feasible in thrombolysed, spontaneously breathing patients with stroke, despite the adverse events.	Study is included in systematic review by Wan YH et al., 2014 (study 1).
Poli S, Purrucker J, Priglinger M et al. (2013) Induction of cooling with a passive head and neck cooling device: effects on brain temperature after stroke. Stroke 44: 708-13	Case series n=11	Although the decrease of brain temperature after cooling device application was statistically significant, we doubt clinical relevance of this rather limited effect (-0.36°C). Moreover, the transient increases of blood pressure and ICP warrant caution.	Larger or more recent studies are included.
Poli S, Purrucker J, Priglinger M et al. (2014) Rapid Induction of COOLing in Stroke Patients (iCOOL1): a randomised pilot study comparing cold infusions with nasopharyngeal cooling. Critical care 18: 582	RCT n=20	In intubated stroke patients, brain cooling is faster during cold infusions (CI) than during nasopharyngeal cooling (NPC). Importantly, contrary to previous expectations, brain cooling stopped soon after CI cessation. Oesophageal but neither bladder nor rectal temperature is suited as surrogate for brain temperature during CI and NPC. Several severe adverse events demand further studying of safety.	Small RCT, comparing 2 different cooling methods.
Poli S, Purrucker J, Priglinger M et al. (2014) Safety evaluation of nasopharyngeal cooling (RhinoChill) in stroke patients: an observational study. Neurocritical care 20: 98-105	Case series n=10 FU=6 months	The RhinoChill system cools the brain efficiently. However, steep increases in blood pressure raise serious concerns regarding the safety of its use in stroke patients.	Larger or more recent studies are included.
Schwab S, Schwarz S, Spranger M et al. (1998) Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. Stroke 29: 2461-6	Case series n=25 FU=3 months	Moderate hypothermia in the treatment of severe cerebral ischemia is not associated with severe side effects. Moderate hypothermia can help to control critically elevated ICP values in severe space-occupying oedema after MCA stroke and may improve clinical outcome in these patients.	Larger or more recent studies are included.
Tahir RA, Pabaney AH (2016) Therapeutic hypothermia and ischemic stroke: A literature review. Surgical neurology international 7: S381-6	review	Although hypothermia has been used for various purposes over several decades, its efficacy in the treatment of ischemic stroke is debatable. Several trials have proven its safety and feasibility; however, more robust, randomised clinical trials with large volumes of patients are	A systematic review with a meta-analysis is included (study 1).

		needed to fully establish its utility in the clinical setting.	
Wang H, Olivero W, Lanzino G et al. (2004) Rapid and selective cerebral hypothermia achieved using a cooling helmet. Journal of neurosurgery 100: 272-7	RCT n=14 (8 versus 6)	The helmet delivers initial rapid and selective brain cooling and maintains a significant temperature gradient between the core and brain temperatures throughout the hypothermic period to provide enough regional hypothermia yet minimise systemic complications.	Small RCT with mixed indications (severe stroke or head injury).