# DEcompressive surgery Plus hypoTHermia for Space-Occupying Stroke (DEPTH-SOS): a protocol of a multicenter randomized controlled clinical trial and a literature review

Hermann Neugebauer[1,2]*, Rainer Kollmar[3], Wolf-Dirk Niesen[4], Julian Bösel[5], Hauke Schneider[6], Carsten Hobohm[7], Klaus Zweckberger[8], Peter U. Heuschmann[9], Peter D. Schellinger[10], and Eric Jüttler[1,2] for the DEPTH-SOS Study Group and the IGNITE Study Group

***Rationale*** **Although decompressive hemicraniectomy clearly reduces mortality in severe space-occupying middle cerebral artery infarction (so-called malignant middle cerebral artery infarction), every fifth patient still dies in the acute phase and every third patient is left with moderate to severe disability. Therapeutic hypothermia is a neuroprotective and antiedematous treatment option that has shown promising effects in severe stroke. A combination of both treatment strategies may have the potential to further reduce mortality and morbidity in malignant middle cerebral artery infarction, but needs evaluation of its efficacy within the setting of a randomized clinical trial.**

***Aims*** **The DEcompressive surgery Plus hypoTHermia for Space-Occupying Stroke (DEPTH-SOS) trial aims to investigate safety and feasibility of moderate therapeutic hypothermia (33°C ± 1) over at least 72 h in addition to early decompressive hemicraniectomy (≤48 hours after symptom onset) in patients with malignant middle cerebral artery infarction.**

***Design*** **The DEcompressive surgery Plus hypoTHermia for Space-Occupying Stroke is a prospective, multicenter, open, two-arm (1:1) comparative, randomized, controlled trial.**

***Study outcomes*** **The primary end-point is mortality at day 14. The secondary end-points include functional outcome at day 14 and at 12 months follow-up, and complications related to hypothermia.**

***Discussion*** **The results of this trial will provide data on safety and feasibility of moderate hypothermia in addition to decompressive hemicraniectomy in malignant middle cerebral artery infarction. Furthermore, efficacy data on early mortality and long-term functional outcome will be obtained, forming the basis of subsequent trials.**

Correspondence: Hermann Neugebauer*, Department of Neurology, University Hospital of Ulm, Oberer Eselsberg 45, 89081 Ulm, Germany. E-mail: hermann.neugebauer@charite.de
[1]Center for Stroke Research Berlin (CSB), Charité – Universitätsmedizin, Berlin, Germany
[2]Department of Neurology, University Hospital, Ulm, Germany
[3]Department of Neurology, University Hospital, Erlangen, Germany
[4]Department of Neurology, University Hospital, Freiburg, Germany
[5]Department of Neurology, University Hospital, Heidelberg, Germany
[6]Department of Neurology, Dresden University of Technology, Germany
[7]Department of Neurology, University Hospital, Leipzig, Germany
[8]Department of Neurosurgery, University Hospital, Heidelberg, Germany
[9]Institute for Clinical Epidemiology and Biometry, Center for Clinical Studies, and Comprehensive Heart Failure Center, University of Wurzburg, Wurzburg, Germany
[10]Department of Neurology, Johannes Wesling Hospital, Minden, Germany

Conflicts of interest: The authors declare no potential conflict of interest.

DOI: 10.1111/ijs.12086

Key words: decompressive surgery, hemicraniectomy, hypothermia, ischaemic stroke, malignant MCA infarct, randomized trial

## Introduction and rationale

Severe space-occupying middle cerebral artery (MCA) infarction, so-called malignant MCA infarction, is a devastating disease with a high-case fatality of up to 80% under palliative care and about 70% even under maximum conservative treatment (1–5). Early decompressive hemicraniectomy (DHC) has been proven effective in reducing mortality and improving functional outcome in randomized controlled trials in patients aged 18 to 60 years (2–5). Despite this clear and marked treatment effect, every 5th patient still dies in the acute phase mostly due to edema-induced brain tissue shift and every 3rd patient survives but is moderately to severely disabled. In other words, there is still room for improvement in the treatment of patients with malignant MCA infarctions.

Therapeutic hypothermia (TH) is a neuroprotective and antiedematous therapy with proven efficacy in animal models and clinical trials after global ischemia, albeit proof of efficacy is still lacking for focal cerebral ischemia (6–8).

### Review of the literature on hypothermia for malignant MCA infarction

There is high interest among clinicians to use TH in patients with malignant MCA infarction. This is foremost reflected by a large number of review articles published on this subject (30 as of March 2012) and the fact that TH is already being applied as a standard therapy within local treatment protocols for severe stroke in several centers throughout Germany, either alone or combined with DHC. In contrast, there are only comparably few numbers of studies in stroke patients, 9 case reports and 19 observational studies as of March 2012 (for references and search strategy, see Supporting Information Table S1).

Quality and amount of reliable data on patients treated with TH decrease even further when reviewing the original articles: The study by Krieger and colleagues is often cited in this context (9). However, only 9 of the 19 patients in this study fulfilled the imaging criteria of a large MCA infarction as used in recent randomized trials (2–4). The work by Jian S and Su J (who are both Jian Su) and co-workers (*Int J Dev Neurosci* 2003;**21**:353–6 meanwhile retracted and *Chin J Traumatol* 2003;**6**:318–20) are one to one plagiarisms of the article published by Schwab and co-workers in 1998 (10). In several articles (9–13), a study by

Naritomi H, Shimizu T and colleagues is cited with different orders of authors and citations, which cannot be tracked on PubMed (Mild hypothermia in acute embolic stroke: a pilot study. *J Stroke Cerebrovasc Dis* 1996;**6**:193–6; Mild hypothermia is effective for the treatment of acute embolic stroke if induced within 24 hours after onset but not the later phase. *J Stroke Cerebrovasc Dis* 1996;**6**(suppl 1):193–6; Mild hypothermia is effective for the treatment of acute embolic stroke if induced within 24 hours after onset but not in the later phase. *J Cereb Blood Flow Metab* 1997;17:42). Most of the remaining studies had no control groups and TH was often used in patients who were thought ineligible for DHC (i.e., patients with infarctions of the dominant hemisphere), at a time before data on DHC were available from randomized controlled trials. When reviewing these articles, it seems that several of them reported on patients who have already been reported in previous studies, thereby indicating at least partial repeated publication (Supporting Information Table S1).

Nevertheless, the available data allow estimating a potential treatment effect of hypothermia in malignant MCA infarction (Supporting Information Table S2): Although less effective than DHC, moderate TH (32–33°C) seems to reduce mortality to about 40% in observational studies, a treatment effect that was broadly similar across different studies, settings, and duration of hypothermia (1 to 22 days). In addition, clinical outcome of survivors seems to be better than after DHC (Supporting Information Tables S1 and S2). Most deaths under TH occurred due to rebound edema in the rewarming phase (10,14), before slow rewarming was demanded in subsequent protocols (15). Frequent complications of hypothermia include an increased risk of pneumonia, cardiac arrhythmias, and coagulation disorders (10,14,16,17). However, the latest Cochrane Review did not find significant differences in complications between TH and conventional treatment (18).

There are three studies reporting data on the combined approach of DHC plus TH (19–21). Only one of these studies reported outcome data comparing DHC plus mild TH (35°C) for two-days with DHC alone in a prospective, randomized, controlled fashion. The study included 25 patients and might therefore not be capable to demonstrate a moderate benefit in the treatment group. However, a trend toward improved functional outcome without an increased risk of severe side-effects and complications could be observed in patients undergoing additional TH (21).

Available data suggest that because of its promising effects, and its acceptable rate of side-effects, which are usually controllable in the intensive care setting, a combined approach of TH with DHC could further reduce morbidity and mortality in patients with malignant MCA infarction. To test this hypothesis, the DEcompressive surgery Plus hypoTHermia for Space-Occupying Stroke (DEPTH-SOS) Study Group decided to conduct a multicenter, randomized controlled trial to create the best possible evidence for this approach.

## Methods

### Design

The DEPTH-SOS is a prospective, multicenter, open, two-armed, comparative, randomized controlled trial (Fig. 1). The trial was approved by the leading ethics committee of the Friedrich-Alexander University, Erlangen, Germany (Reference Number: 4349, date of approval: February 24, 2011) and the local ethics committees of the participating centers. The study is performed in accordance with the Declaration of Helsinki and its subsequent amendments and the guidelines of Good Clinical Practice. The study is registered in the German Clinical Trial Register (DRKS) and the International Clinical Trials Registry Platform (http://www.drks.de/DRKS00000623). As of March 2012, six centers are participating.

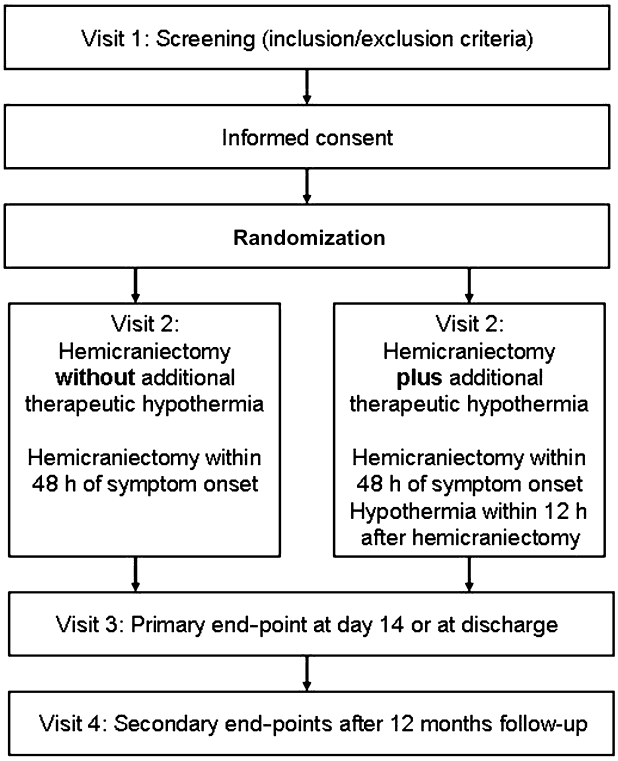


**Fig. 1** Study flowchart of the DEPTH-SOS trial.

### Patient population

All subjects with space-occupying MCA infarction planned for early DHC within 48 h of symptom onset independent of the trial are eligible for participation if the following inclusion criteria are met:

- age between 18 and 60 years
- clinical signs of unilateral MCA infarction
- severe stroke as determined by the National Institute of Health Stroke Scale (NIHSS) score ≥15 if the nondominant hemisphere is affected or ≥20 if the dominant hemisphere is affected
- reduced level of consciousness as determined by NIHSS item 1a (≥1)
- unilateral ischemia of at least 2/3 of the MCA territory confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). The basal ganglia must be at least partially involved. Additional involvement of the anterior and/or posterior cerebral artery territories may be present
- decision to proceed to DHC by the treating physicians
- possibility to start DHC within 48 h after symptom onset
- possibility to start TH within 12 hours after DHC, and

• written informed consent by the subject himself/herself, his/her legal representative, adjudication of a legally competent judge, or an independent physician according to the respective local conditions.

Subjects are not eligible for participation and will be excluded from the trial if any of the following criteria is fulfilled:

• premorbid mRS score ≥2 and/or Barthel Index <95
• simultaneous other brain lesion, for example, traumatic brain injury, infarction contralateral or infratentorial in addition to the index-infarction
• clinical signs of transtentorial herniation
• deep coma as determined by a Glasgow Coma Scale (GCS) score <6 (does not apply to intubated patients)
• secondary hemorrhage in the area of infarction with space-occupying effect (PH2)
• known systemic bleeding or coagulation disorders
• known contraindications for TH, for example, vasospastic disease, hematological disease with increased risk of thrombosis, paramyotonia congenita, severe preexisting cardiac, liver or kidney disease
• known indications for TH, for example, after cardiopulmonary resuscitation
• pregnancy
• life expectancy of less than three-years
• sepsis
• end-stage malignant disease, and
• participation in any other interventional trial

## Randomization

After written informed consent, subjects are randomly assigned to DHC alone (standard treatment) or DHC plus moderate hypothermia using a web-based system (http://www.randomizer.at). Randomization is stratified for center and allocates patients 1:1 to one of the two treatment arms.

## Treatment

All participating centers must have adequate experience in the management of acute ischemic stroke, intensive care treatment of patients with severe stroke and increased intracranial pressure (ICP), including DHC and TH, and access to neurosurgical facilities on a 24-h/day basis.

### Decompressive hemicraniectomy and conservative treatment

All patients included in the trial receive standard medical care on a dedicated neurointensive care unit and DHC within 48 h, in accordance with the recommendations of current guidelines (22). DHC technique and intensive care treatment are in line with protocols used in recent trials on DHC and are described elsewhere (23). It has to be emphasized that temperature must not be lowered below 36·5°C to reach normothermia in the control group.

### Therapeutic hypothermia

Patients allocated to TH receive additional cooling to achieve a core body temperature of 33°C as measured using a urinary bladder catheter. TH is started as soon as possible after randomization and may be started before hemicraniectomy and maintained during surgery, but must be initiated within 12 h post surgery, that is, within 60 h after symptom onset. Centers may use endovascular or surface cooling devices allowing controlled cooling and rewarming. Ice-cold saline infusions, cool-packs, or cooling-blankets may be used in addition for induction of hypothermia. Warming blankets and pharmacological measures are recommended to avoid shivering. TH must be maintained for a minimum of 72 h, but may be continued depending on the decision of the treating physician. In case of longer cooling periods with endovascular devices, repeated screening for deep venous thrombosis and changing the catheter every fourth day is advised. Blood testing for coagulation should be performed routinely. TH is terminated by controlled, slow rewarming by 0·05 to 0·1°C per hour. In case of clinical deterioration due to rebound brain edema during the rewarming phase, TH may be prolonged until the patient is in a stable condition and rewarming is considered safe.

## Primary outcome

The aim of the trial is to investigate safety and feasibility of moderate TH in addition to early DHC in malignant MCA infarction. The primary outcome measure is mortality at day 14.

## Secondary outcome

Safety and feasibility measures include: (1) any severe adverse event (SAE) and any adverse event (AE) either related to TH (i.e., procedure related, bleeding events, thrombotic events, infections, electrolyte derangement, liver or renal dysfunction), related to DHC (i.e., surgery-related hemorrhages, impaired surgical wound healing and wound infections, liquor fistula, hygroma), or related to general or intensive care treatment (i.e. epileptic seizures, and anaesthesia- or sedation-related incidents); (2) treatment parameters (i.e., time to DHC, time to target temperature, duration of TH, total time of ventilation, rate of tracheostomy, total time on the intensive care unit, medication (i.e., use of cathecholamines, muscle relaxants, sedatives, osmotherapeutics, and ICP-lowering drugs), use of therapeutic hyperventilation, number of head CT and MRI scans during hospital stay, and rate of cooling-catheter replacements in case of endovascular treatment. Other secondary outcome measures include: (1) stroke severity as determined by the NIHSS at day 14; (2) GCS at day 14; (3) functional outcome as determined by the mRS and the Barthel Index at discharge and at 12 months; (4) retrospective consent to treatment at 12 months. Follow-up at 12 months is done using a structured telephone interview.

## Data safety and monitoring board

AEs and SAEs will be collected from the moment of informed consent up to the completion of the follow-up examination. All AEs and SAEs are reported to the monitor of the Center for Stroke Research Berlin (CSB), and the local institutional review board in accordance with local guidelines. Interim analyses of all SAEs and the primary end-point will be conducted after every 10th patient. Based on the interim analyses, an independent Data Safety and Monitoring Board that consists of three physicians not involved in the planning or conduction of the trial recommends to continue or to stop the trial.

## Statistical methods and sample size calculation

The primary end-point is survival at day 14. Mortality under DHC alone is estimated following the results of the pooled

analysis on DHC for malignant MCA infarction (20%) (5). Mortality in patients treated by additional TH is estimated following the trial by Els and coworkers (8%) (21). However, data on treatment effect of hypothermia are weak because they derive from one small observational study which included 25 patients only. For safety and ethical reasons, we plan an interim analysis after 50 patients using the concept of group-sequential tests for two proportions with two repeated significance tests. Because it is important to react early on possible considerable differences in mortality between the two treatment arms, the alpha-spending function by Pocock is applied. Then sample sizes of 162 for each treatment group (324 in total) ensure an 80% power to detect a difference of 0·20–0·08 = 0·12 in proportions of dead patients at day 14 at a significance level of 0·05 (Fisher's exact test). Statistical analysis will be performed as intention to treat. Summary statistics will be used for descriptive analysis. In addition *P* values for group comparisons and corresponding 95% confidence intervals will be calculated using two-sample *t*-testing, the Mann–Whitney *U*-test, or $\chi 2$ testing as applicable.

### Duration

Based on the number of patients treated in the participating centers and the one -year for follow-up period, the total duration of the trial is estimated to be four-years.

### Study organization and funding

The steering committee consists of the two project leaders, R. Kollmar (Erlangen) and E. Jüttler (Berlin), and principle investigators of the participating centers. The Institute of Clinical Epidemiology and Biometry of the University of Wurzburg will support data management. There is no external funding. The study is exclusively driven by internal means of the CSB, the Institute for Clinical Epidemiology and Biometry, University of Wurzburg, and the participating centers.

## Discussion

Treatment procedures were designed according to already existing protocols of the participating centers and after reviewing the available literature: Concerning the optimal target temperature, animal data show that there may be a U-shaped curve of effectiveness of TH in ischemic stroke with 33 to 34°C showing the best results (8,13,24). The best clinical experience exists with target temperatures of 32–33°C as the majority of clinical studies on TH in malignant MCA infarction used these values (see Table S1). Side-effects of hypothermia, for example, platelet dysfunction, coagulation disorders, cardiac arrhythmias, are directly related to the temperature achieved (25). Based on these findings and considerations, and established protocols, a target temperature of 33°C was chosen.

With respect to the duration of cooling, animal experiments reported a larger benefit with longer treatment durations, whereas the optimal duration of TH was never systematically investigated in clinical studies in stroke patients (8,26–28). Most patients in the available studies used TH over a period of one to three-days (10,14,16,17), only two smaller studies allowed longer cooling duration with a maximum of 22 days in some cases (20,29). Although these studies do not allow to conclude on an optimal cooling duration, TH was found to be safe and feasible when used up to three-days and in most cases even if applied over longer periods, when slow rewarming was done (15–17,19–21,29). As the maximum infarct swelling in malignant MCA infarction is present between the second and the fifth day (1), a cooling duration of at least 72 h was determined for the DEPTH-SOS trial. The decision to apply TH for longer periods if edema formation is ongoing is left to the discretion of the treating physician.

Similarly to the uncertainties concerning target temperature and duration of cooling, data on the time window for starting TH are also insufficient. Animal data and pathophysiological considerations suggest a greater benefit with early treatment (7,8). This is why DEPTH-SOS TH should be started as soon as possible after randomization. The combined approach of DHC and TH, however, could raise practical problems in applying hypothermia, as it may not be possible to start cooling before or maintain it throughout surgery in some centers. As surgery must be performed within 48 h, we set a time frame to start treatment 12 h postsurgery at the latest.

We believe that the results of the DEPTH-SOS trial will provide reliable data on safety and feasibility of moderate TH in addition to DHC in malignant MCA infarction as well as efficacy data on mortality and outcome, thereby forming the basis for a subsequent future studies on this subject.

## Summary

Early DHC within 48 h of symptom onset is the recommended treatment of patients with malignant MCA infarction. TH is a promising treatment option that could be of benefit as an additional therapy to further reduce mortality and morbidity in these patients. The scarcity of data on hypothermia in malignant MCA infarction, derived mainly from observational studies of insufficient level of evidence, does not currently allow to routinely apply TH outside of clinical trials. DEPTH-SOS is a phase II, prospective, randomized, controlled, clinical, multicenter trial on the combined approach of DHC and TH. Primary outcome measure is mortality at day 14. Secondary outcome measures include safety parameters and functional outcome at one-year.

Details on the principal investigators, steering committee, local principal investigators, search strategy, and tables on available studies on TH and outcome data can be found in the supporting information.

## References

1 Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. *Arch Neurol* 1996; **53:**309–15.
2 Hofmeijer J, Kapelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB, for the HAMLET investigators. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial (HAMLET]): a multicentre, open, randomised trial. *Lancet Neurol* 2009; **8:**326–33.
3 Jüttler E, Schwab S, Schmiedek P *et al.* Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomised, controlled trial. *Stroke* 2007; **38:**2518–25.

4 Vahedi K, Vicaut E, Mateo J *et al*. Sequential-design, multicenter, randomised, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). *Stroke* 2007; **38:**2506–17.
5 Vahedi K, Hofmeijer J, Juettler E *et al*. Early decompressive surgery in malignant middle cerebral artery infarction: a pooled analysis of three randomised controlled trials. *Lancet Neurol* 2007; **6:**215–22.
6 Bernard SA, Gray TW, Buist MD *et al*. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; **346:**557–63.
7 van der Worp HB, Macleod MR, Kollmar R, European Stroke Research Network for Hypothermia (EuroHYP). Therapeutic hypothermia for acute ischemic stroke: ready to start large randomised trials? *J Cereb Blood Flow Metab* 2010; **30:**1079–93.
8 van der Worp HB, Sena ES, Donnan GA, Howells DW, Macleod MR. Hypothermia in animal models of acute ischaemic stroke: a systematic review and meta-analysis. *Brain* 2007; **130:**3063–74.
9 Krieger DW, De Georgia MA, Abou-Chebl A *et al*. Cooling for acute ischemic brain damage (cool aid): an open pilot study of induced hypothermia in acute ischemic stroke. *Stroke* 2001; **32:**1847–54.
10 Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. *Stroke* 1998; **29:**2461–6.
11 Abou-Chebl A, DeGeorgia MA, Andrefsky JC, Krieger DW. Technical refinements and drawbacks of a surface cooling technique for the treatment of severe acute ischemic stroke. *Neurocrit Care* 2004; **1:**131–43.
12 Schwab S. Therapy of severe ischemic stroke: breaking the conventional thinking. *Cerebrovasc Dis* 2005; **20**(Suppl. 2)**:**169–78.
13 Kollmar R, Schwab S. Hypothermia in focal ischemia: implications of experiments and experience. *J Neurotrauma* 2009; **26:**377–86.
14 Schwab S, Georgiadis D, Berrouschot J, Schellinger PD, Graffagnino C, Mayer SA. Feasibility and safety of moderate hypothermia after massive hemispheric infarction. *Stroke* 2001; **32:**2033–5.
15 Steiner T, Friede T, Aschoff A, Schellinger PD, Schwab S, Hacke W. Effect and feasibility of controlled rewarming after moderate hypothermia in stroke patients with malignant infarction of the middle cerebral artery. *Stroke* 2001; **32:**2833–5.
16 Georgiadis D, Schwarz S, Kollmar R, Schwab S. Endovascular cooling for moderate hypothermia in patients with acute stroke: first results of a novel approach. *Stroke* 2001; **32:**2550–3.
17 Georgiadis D, Schwarz S, Aschoff A, Schwab S. Hemicraniectomy and moderate hypothermia in patients with severe ischemic stroke. *Stroke* 2002; **33:**1584–8.
18 Den Hertog HM, van der Worp HB, Tseng MC, Dippel DW. Cooling therapy for acute stroke. *Cochrane Database Syst Rev* 2009; (1):CD001247.
19 Poca MA, Benejam B, Sahuquillo J *et al*. Monitoring intracranial pressure in patients with malignant middle cerebral artery infarction: is it useful? *J Neurosurg* 2010; **112:**648–57.
20 Mourand I, Escuret E, Héroum C *et al*. Feasibility of hypothermia beyond 3 weeks in severe ischemic stroke: an open pilot study using gamma-hydroxybutyrate. *J Neurol Sci* 2012; **316:**104–7. [Epub ahead of print].
21 Els T, Oehm E, Voigt S, Klisch J, Hetzel A, Kassubek J. Safety and therapeutical benefit of hemicraniectomy combined with mild hypothermia in comparison with hemicraniectomy alone in patients with malignant ischemic stroke. *Cerebrovasc Dis* 2006; **21:**79–85.
22 European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; **25:**457–507.
23 Jüttler E, Bösel J, Amiri H *et al*. DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY II. *Int J Stroke* 2011; **6:**79–86.
24 Kollmar R, Blank T, Han JL, Georgiadis D, Schwab S. Different degrees of hypothermia after experimental stroke: short- and long-term outcome. *Stroke* 2007; **38:**1585–9.
25 Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. *Crit Care Med* 2009; **37:**1101–20.
26 Yanamoto H, Nagata I, Niitsu Y *et al*. Prolonged mild hypothermia therapy protects the brain against permanent focal ischemia. *Stroke* 2001; **32:**232–9.
27 Clark DL, Penner M, Orellana-Jordan IM, Colbourne F. Comparison of 12, 24 and 48 h of systemic hypothermia on outcome after permanent focal ischemia in rat. *Exp Neurol* 2008; **212:**386–92.
28 Maier CM, Ahern K, Cheng ML, Lee JE, Yenari MA, Steinberg GK. Optimal depth and duration of mild hypothermia in a focal model of transient cerebral ischemia: effects on neurologic outcome, infarct size, apoptosis, and inflammation. *Stroke* 1998; **29:**2171–80.
29 Milhaud D, Thouvenot E, Heroum C, Escuret E. Prolonged moderate hypothermia in massive hemispheric infarction: clinical experience. *J Neurosurg Anesthesiol* 2005; **17:**49–53.


## Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Table S1** Studies on TH in malignant MCA infarction. [a]Number of patients refer to patients actually treated with hypothermia. [b]Hours are rounded up to the next highest number. *Studies supposed of at least partial repeated publication. TH, therapeutic hypothermia; n.k., not known.

**Table S2** Outcome in malignant MCA infarction with respect to the different treatment modalities. Definition of clinical outcome: no disability corresponds to mRS 0–1, mild-moderate disability corresponds to mRS 2–3, and severe disability corresponds to mRS 4–5.

**Appendix S1**. Details on the steering commitee, DEPTH-SOS Study Group, and IGNITE Study Group.