National Guideline Centre

Draft for consultation

Stroke (update)

Evidence review H: Decompressive Hemicraniectomy

NICE guideline

Intervention evidence review

November 2018

Draft for consultation

This evidence review was developed by the National Guideline Centre

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1 Decompressive hemicraniectomy

1.1 Review question: Which patients should be referred for decompressive hemicraniectomy?

1.2 Introduction

In 2-8% of patients with anterior circulation ischaemic stroke (due to occlusion of the internal carotid, middle cerebral artery, anterior cerebral artery, or a combination of these) large-volume brain infarction causes space-occupying brain swelling ("malignant middle cerebral artery syndrome") which, untreated, has a mortality of about 80%. Hemicraniectomy (neurosurgical removal of part of the skull to reduce intracerebral pressure) is life-saving. The previous NICE guideline CG68 (2008) recommends referring patients under the age of 60 with a severe stroke syndrome, reduced level of consciousness and a CT-defined infarct of at least 50% of the middle cerebral artery territory, for consideration of hemicraniectomy.

There remains uncertainty about the net clinical benefit of hemicraniectomy, especially in people with stroke over the age of 60, because it might increases the number of stroke survivors with serious disability to a greater extent than in younger people. Since the last guideline was published, the DESTINY-II randomised trial has reported the effect of hemicraniectomy in patients over the age of 60 years. This review therefore aimed to establish which patients should be referred for decompressive hemicraniectomy, with a focus on patient age.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People with large volume acute anterior circulation ischaemic stroke with complicating space-occupying brain oedema (sometimes described as malignant middle cerebral artery infarction), evident on cerebral computed tomography or magnetic resonance imaging.
Intervention	Decompressive surgery plus best medical treatment (icp monitoring, ventilation, mannitol, other diuretics, corticosteroids, hyperventilation, barbiturates, etc.)
Comparison	Best medical therapy (ICP monitoring, ventilation, mannitol, other diuretics, corticosteroids, hyperventilation, barbiturates, etc.)
Outcomes	Critical Mortality 6 months Mortality 1 year Functional outcome (degree of disability or dependence in daily activities) at 6 months and 1 year: Modified Rankin scale (mRS) score of 0-3 or ordinal shift analysis Important Quality of life (both health- and social-related)
Study design	Randomised controlled trials Systematic reviews and meta-analyses of the above

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[7] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

Eight studies were included in the review; [6, 12, 17, 21, 22, 40, 46, 51] these are summarised in Table 2 and Table 3) below. Evidence from these studies is summarised in the clinical evidence summary below (Table 4).

All the studies are open labelled randomised controlled trials (RCTs), with some having a blinded outcome evaluation (HAMLET[17], HeADDFIRST[12], Zhao[51]). It is noted that although open labelled RCTs are the highest quality of study design suitable for these trials, outcomes have been downgraded due to no blinding of patient or care giver and the outcome assessor not being blinded to interventions or the key confounders.

The studies were stratified according to mean or median age, with three being included in the strata for aged over 60 years. The trial by Slezins[40] was downgraded for indirectness due to the age range being 49 to 81 years and not having subgroup analysis of those aged over 60. This review extracted just the subgroup analysis results of those aged over 60 from the trial by Zhao[51], as the median overall age for the population was over 60.

A Cochrane review[8] was identified and all the relevant references have been checked and included where appropriate.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix H.

1.5.2 Excluded studies

See the excluded studies list in appendix H.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review for those aged under 60 years

Study	Intervention and comparison	Population	Outcomes
Chua, 2015[6] HeMMi Trial	Decompressive surgery plus medical therapy (n=16) Vs Medical therapy (n=13)	Adults aged 18 to 65 years (mean=50.2 yrs, SD=8.3yrs) Philippines	• Mortality at 6 months • mRS at 6 months
Frank, 2014[12] HeADDFIRST trial	Decompressive surgery plus medical treatment (n=15) Vs Medical treatment (n=10)	Adults aged 18 to 75 years (median=55.1 yrs, IQR=45.45 to 62.4yrs) United Kingdom	• Mortality at 6 months • mRS at 6 months

Study	Intervention and comparison	Population	Outcomes
Hofmeijer, 2009[17] HAMLET trial	Decompressive surgery (n=32) Vs Medical treatment (n=32)	Adults aged 18 to 60 years (mean=48.7 yrs, SD=9.05yrs) Netherlands	• Mortality at 1 year • mRS at 1 year • Quality of life at 1 year
Juttler, 2007[21] DESTINY trial	Decompressive surgery plus conservative treatment (n=17) Vs Conservative treatment (n=15)	Adults aged 18 to 60 years (mean=44.6 yrs, SD=9.1yrs) Germany	• Mortality at 30 days and 1 year • mRS at 6 months and 1 year
Vahedi, 2007[46] DECIMAL trial	Decompressive surgery plus standard medical therapy (n=20) Vs Standard medical therapy (n=18)	Adults aged 18 to 55 years (mean=43.4 yrs, SD=8.4yrs) France	• Mortality at 6 months and 1 year • mRS at 6 months and 1 year

Table 3: Summary of studies included in the evidence review for those aged over 60 years

Study	Intervention and comparison	Population	Outcomes
Juttler, 2014[22] DESTINY II trial	Decompressive surgery (n=49) Vs Conservative treatment (n=63)	Adults aged 61 and above (median=70, range=61 to 82yrs) Germany	• Mortality at 1 year • mRS at 6 months and 1 year • Quality of life at 1 year
Slezins, 2012[40]	Decompressive surgery plus medical management (n=11) Vs Medical management (n=13)	Adults aged 49 to 81 years (mean=61.5 yrs, range=49 to 81yrs) Latvia	• Mortality at 1 year • mRS at 6 months and 1 year
Zhao, 2012[51]	Decompressive surgery plus standard medical treatment (n=16) Vs Standard medical treatment (n=13)	Adults aged 61 to 80 years (median=69.25 yrs) China	• Mortality at 6 months and 1 year • mRS at 6 months and 1 year

See appendix D for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 4: Clinical evidence summary: Decompressive hemicraniectomy compared to medical treatment for those aged under 60 years

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical Treatment	Risk difference with DHC (95% CI)
Mortality at 30 days	32 (1 study) 30 days	⊕⊕⊕⊖ MODERATE1 due to imprecision	RR 0.22 (0.06 to 0.88)	533 per 1000	416 fewer per 1000 (from 64 fewer to 501 fewer)
Mortality at 6 months	86 (3 studies) 6 months	⊕⊕⊕⊖ MODERATE1 due to imprecision	RR 0.52 (0.32 to 0.86)	545 per 1000	262 fewer per 1000 (from 76 fewer to 371 fewer)
Mortality at 1 year	134 (3 studies) 1 year	⊕⊕⊕⊕ HIGH	RR 0.34 (0.21 to 0.56)	594 per 1000	392 fewer per 1000 (from 261 fewer to 469 fewer)
Functional outcomes at 6 months Score of 0-3 on mRS scale (range: 0-6, high is poor outcome)	118 (4 studies) 6 months	⊕⊕⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.39 (0.76 to 2.56)	283 per 1000	110 more per 1000 (from 68 fewer to 441 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical Treatment	Risk difference with DHC (95% CI)
Functional outcomes at 1 year Score of 0-3 on mRS scale (range: 0-6, high is poor outcome)	134 (3 studies) 1 year	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 1.52 (0.90 to 2.57)	250 per 1000	130 more per 1000 (from 25 fewer to 392 more)
Quality of life, 1 year, SF-36 mental summary (range: 0-100, high is good outcome)	35 (1 study) 1 year	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean SF-36 mental summary in the control groups was 53	The mean SF-36 mental summary in the intervention groups was 2 higher (5.92 lower to 9.92 higher)
Quality of life, 1 year, SF-36 physical summary (range: 0-100, high is good outcome)	35 (1 study) 1 year	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean SF-36 physical summary in the control groups was 36	The mean SF-36 physical summary in the intervention groups was 7 lower (13.85 to 0.15 lower)
Quality of life, 1 year, VAS (range: 0-100, high is good outcome)	32 (1 study) 1 year	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean VAS in the control groups was 62	The mean VAS in the intervention groups was 7 lower (27.49 lower to 13.49 higher)
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. 2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.					

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2 **Table 5: Clinical evidence summary: Decompressive hemicraniectomy compared to medical treatment for those over 60 years**

Outcomes	No of Participant	Quality of the evidence	Relative effect	Anticipated absolute effects

	s (studies) Follow up	(GRADE)	(95% CI)	Risk with Medical Treatment	Risk difference with Decompressive Hemicraniectomy (95% CI)
Mortality, 6 months	29 (1 study) 6 months	⨁⨁⨁⨀ MODERATE1 due to imprecision	RR 0.20 (0.05 to 0.8)	609 per 1000	487 fewer per 1000 (from 122 fewer to 579 fewer)
Mortality, 1 year	162 (3 studies) 1 years	⨁⨁⨁⨀ MODERATE2 due to indirectness	RR 0.52 (0.39 to 0.7)	758 per 1000	364 fewer per 1000 (from 227 fewer to 462 fewer)
Functional outcomes, 6 months Score of 0-3 on mRS scale (range: 0-6, high is poor outcome)	141 (2 studies) 6 months	⨁⨀⨀⨀ VERY LOW1,3 due to risk of bias, imprecision	RR 2.45 (0.55 to 10.91)	16 per 1000	23 more per 1000 (from 7 fewer to 159 more)
Functional outcomes, 1 year Score of 0-3 on mRS scale (range: 0-6, high is poor outcome)	165 (3 studies) 1 year	⨁⨀⨀⨀ VERY LOW1,3 due to risk of bias, imprecision	RR 3.18 (1.03 to 9.83)	34 per 1000	100 more per 1000 (from 10 more to 180 more)4
Quality of life, 1 year EQ-5D scale (range: -0.205 “dead” to 1.0 “perfect health”)	100 (1 study) 1 years	⨁⨁⨀⨀ LOW1,3 due to risk of bias, imprecision		The mean quality of life, EQ-5D in the control groups was -0.1	The EQ-5D in the intervention groups was 0.10 higher (0 to 0.2 higher)
Quality of life, 1 year EQ-5D, visual analogue scale (range 0-100; high is good outcome)	99 (1 study) 1 years	⨁⨁⨀⨀ LOW1,3 due to risk of bias, imprecision		The mean EQ-5D VAS in the control groups was 7.6	The mean EQ-5D VAS in the intervention groups was 16.40 higher (6.54 to 26.26 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical Treatment	Risk difference with Decompressive Hemicraniectomy (95% CI)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
2 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively.
3 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
4 Calculated from risk difference.

1 See appendix F for full GRADE tables.

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1.6 Economic evidence

1.6.1 Included studies

One health economic study was identified with the relevant comparison and has been included in this review. [18] This is summarised in the health economic evidence profile below (Table 6) and the health economic evidence table in appendix I.

1.6.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.6.3 Summary of studies included in the economic evidence review

Table 6: Health economic evidence profile: surgical decompression versus best medical treatment

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Hofmeijer, 2013 [18] (The Netherlands, health system perspective)	Partially applicable[(a)]	Potentially serious limitations [(b)]	Within-trial analysis (RCT) with Markov model post-trial extrapolation. HAMLET RCT included in clinical review [14]. Markov model simulating a lifetime time horizon.	£206,742[(c)]	4.2 QALYs	ICER: £49,224 per QALY gained (da)	NR

Abbreviations: da: deterministic analysis; ICER: incremental cost-effectiveness ratio; NR: not reported; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) Within-trial analysis with post-trial extrapolation, from Dutch societal perspective

(b) Treatment effects derived from HAMLET trial only, which reported less favourable outcomes for decompressive surgery compared with other trials. Discounting of costs and outcomes not reported for post-trial Markov model, sensitivity analysis not undertaken for lifetime horizon. Outpatient department and general practitioner resource use obtained retrospectively. Recurrent stroke not modelled. Cycle lengths of Markov model not reported.

(c) Converted using 2009 purchasing power parities[35]

1.6.4 Unit costs

Table 7: UK costs of non-elective long stay decompressive hemicraniectomy

Currency Description	Unit Cost	Average length of stay
AA52D – AA52A Very Major Intracerebral Procedures, 19 years and over, inclusive of excess bed days, with CC Score 0-3 to CC Score 12+; as recorded for Non-Elective Long Stay	£9,174 - £15,386	8.54 – 22.60 days
AA52B Very Major Intracerebral Procedures, 19 years and over, weighted for complications and co-morbidities for HRG codes: AA52A, AA52B, AA52C and AA52D; as recorded for Non-Elective Long Stay	£10,721	12.17 days

Source: NHS Reference Costs, 2016-2017

1.7 Resource costs

The committee has made a recommendation based on this review (see section 1.9) that decompressive hemicraniectomy should be 'considered'. The recommendation is not expected to have a substantial impact on resources to the NHS in England.

The committee noted that where this recommendation is implemented there would be additional costs relating to the increase in the population eligible for decompressive hemicraniectomy compared to current practice. However, the committee agreed that this would not necessarily lead to significantly more people undergoing surgery compared with current practice; not all people eligible for decompressive hemicraneictomy ultimately go on to have surgery following discussions between carers and physicians. The committee noted that more informed discussion of the outcomes following surgery might reduce the uptake of surgery. In addition, the recommendation on endovascular therapy made elsewhere as part of this guideline update (see evidence review D) will increase the population eligible for and provision of endovascular therapy. This is likely to decrease the population referred for decompressive hemicraniectomy.

1.8 Evidence statements

1.8.1 Clinical evidence statements

1.8.1.1 Aged under 60 years

- There was a clinically important benefit of surgery compared to standard care for reduced mortality at 30 days (1 study; n=32; Moderate quality), 6 months (3 studies; n=86; Moderate quality) and 1 year (3 studies; n=134; High quality) and for achieving mRS 0-3 at 6 months (4 studies; n=118; Very Low quality) and 1 year (3 studies; n=134; Low quality).
- There was no clinically important difference for the SF-36 mental summary score or VAS but a clinically important harm of surgery for the SF-36 physical summary scale (1 study; n=35; Very Low and Low quality).

1.8.1.2 Aged over 60 years

- There was a clinically important benefit of surgery compared to standard care for reduced mortality at 6 months (1 study; n=29; Moderate quality) and 1 year (3 studies; n=162; Moderate quality) and for achieving mRS 0-3 at 1 year (3 studies;

n=165; Very Low quality) but the benefit did not reach clinical significance at 6 months (2 studies; n=141; Very Low quality).

- Evidence from 1 study in 100 people showed a clinically important benefit of surgery for quality of life at 1 year as measured by the EQ-5D index scale and VAS score (Low quality).

1.8.2 Health economic evidence statements

- One cost-utility analysis found that decompressive surgery was not cost effective compared with best medical treatment (ICER: £49,224 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.

1.9 Recommendations

H1. Consider decompressive hemicraniectomy (which should be performed within 48 hours of symptom onset) for people with acute stroke who meet all of the following criteria:

- clinical deficits that suggest infarction in the territory of the middle cerebral artery, with a score above 15 on the National Institutes of Health Stroke Scales (NIHSS)
- decreased level of consciousness, with a score of 1 or more on item 1a of the NIHSS
- signs on CT of an infarct of at least 50% of the middle cerebral artery territory:
    - with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side, or
    - with infarct greater than 145cm^3, as shown on diffusion-weighted MRI scan. [2019]

H2. Discuss the risks and benefits of decompressive hemicraniectomy with people or their family members or carers (as appropriate), taking into account their functional status before the stroke, and their wishes and preferences. [2019]

1.10 Rationale and impact

1.10.1 Why the committee made the recommendations

The evidence showed that surgery improved mortality rates and, to a lesser extent, functional outcomes as measured by the modified Rankin Score (mRS). The benefit on mortality was seen in all age groups considered, although the benefit for functional outcome was smaller in people aged over 60 years compared with people under 60 years. Based on this and to ensure that people over 60 have similar opportunities for the surgery as younger people, the committee removed the previous age cut-off for considering surgery. The committee also acknowledged that although surgery results in more people surviving and better functional outcome than without surgery, many still have overall poor functional outcome and their quality of life may be low. The acceptability of this trade-off was agreed to be a very individual judgement. Some people may choose not to have surgery if there is a risk of severe disability, whereas others may wish to go ahead based on mortality benefit alone. Therefore the committee highlighted the need for careful discussion about risks and benefits between clinicians and family members or carers. They noted that patients would not be able to be involved at the time because of the severity of the stroke, so the family members or carers would be responsible for making the decision. In deciding whether to opt for surgery considerations should include pre-stroke functional status, because surgery would not be appropriate for people with severe disability before stroke.

The committee noted that although some of the trials included people who had surgery as long as 96 hours after symptom onset, the benefits in terms of reduced mortality and improved functional outcome were largely driven by studies that only allowed surgery up to a maximum of 48 hours after onset. Therefore, they agreed to retain the the reference to surgery being performed within 48 hours of onset from the original recommendations. The committee also reviewed the criteria used to determine eligibility for hemicraniectomy from the stroke guideline published in 2008. It was agreed that these were still appropriate and reflect the populations included in the studies used to inform the new recommendations.

The committee agreed that although the cost effectiveness of decompressive hemicraniectomy remains uncertain, it should be considered for some people because of the clear mortality benefit and the improved functional outcomes. Shared decision making between physicians, surgeons, families and carers is important given the high likelihood of residual moderate or severe disability after surgery.

1.10.2 Impact of the recommendations on practice

In current practice, around 5% of people on the stroke unit are referred for decompressive hemicraniectomy. Decompressive hemicraniectomy is currently considered for those aged under 60.

This recommendation will require a change from current practice by all providers. The guidance will also require healthcare professionals to take into account people's pre-stroke functional status and to have a discussion about the risks and benefits.

The committee believed that including people over 60 years would not necessarily lead to significantly more people undergoing surgery because informed discussion of the outcomes might reduce its uptake in this population. In addition, increasing the population eligible for endovascular therapy and its provision is likely to decrease the population referred for decompressive hemicraniectomy. The committee therefore did not anticipate a substantial resource impact to result from this recommendation.

1.11 The committee's discussion of the evidence

1.11.1 Interpreting the evidence

1.11.1.1 The outcomes that matter most

The critical outcomes identified for this review were functional outcome (modified Rankin Scale) and mortality at 90 days and 1 year. Both outcomes were considered to be crucial in decision making. Important outcomes included health and social related quality of life (EQ-5D).

Note that for this review a good functional outcome was defined as a score of 0, 1, 2 or 3 on the mRS because in this population of very severe stroke cases achieving an mRS 3 was agreed to be likely to represent a 'good' outcome compared to the expected clinical outcome without surgery.

1.11.1.2 The quality of the evidence

Eight RCTs were included in this review, five being categorised into the under 60 years and three in the over 60 years age category. Trials were categorised according to the age range used for their inclusion criteria, where possible, or using the median age and IQR to determine whether the majority of participants were over or less than 60 years of age. Some outcomes were only reported by one trial with few participants for each age category, resulting in imprecise effect estimates. Therefore, the committee were not confident that the outcome reflected the true effect. The trials were all open labelled, which meant patients, care givers and outcome assessors were not blinded to the intervention. Three studies however, had a blinded outcome evaluation. As a result, subjective outcomes (mRS and quality of life) were downgraded for risk of bias. Some results for these outcomes were downgraded further if they showed imprecision through estimates of effect having wide confidence intervals. Additionally one study in the over 60 category was further downgraded for an indirect population.

Evidence ranged from very low to high quality, with the majority of evidence rated as low and moderate quality. The mortality evidence was of high and moderate quality, while the functional outcome data were low and very low quality.

A published cost utility analysis with a Dutch societal perspective was included in the health economic review and was assessed as partially applicable with potentially serious limitations.

1.11.1.3 Benefits and harms

The evidence showed a clear mortality benefit in the short and longer term in those aged both over and under 60 years when decompressive hemicraniectomy is performed compared to medical treatment alone.

Also, there was a clinically important benefit of surgery for functional outcome (defined as mRS score 0-3) at 6 months and 1 year in those aged under 60 years. However, the committee noted that the benefit was questionable because overall functional outcome was poor. When surgery is performed it results in more patients surviving, but many have poor functional outcomes. To some extent, there is a trade off between reduced mortality but at the expense of overall poor functional outcome. This may be acceptable to a significant proportion of patients. In those aged over 60 years this benefit in the number achieving a 'good' functional outcome of 0-3 on the mRS scale was not seen at 6 months follow-up, although a modest clinical benefit was reported at 1 year.

Quality of life (EQ-5D and SF-36) data were not widely reported and ranged from showing a clinically important benefit of surgery in 1 study of the over 60s, to a clinically important harm of surgery for the physical component score but no clinical difference for the mental summary score or the overall visual analogue score in 1 study in the under 60s. Hemicraniectomy inevitably leads to more people surviving with disability, whereby survivors may have a low quality of life. The committee noted that judging quality of life is variable, subjective and emotionally charged, and perspectives might differ greatly between patients and carers.

Overall there is good clinical evidence for the benefit of surgery in regards to mortality, with some supporting evidence of improved functional outcomes and variability in the reported impact on quality of life, which was low in both the treated and untreated groups.

The committee noted that although some of the trials in those aged under 60 years included people who had surgery as long as 96 hours after symptom onset, the benefits in terms of reduced mortality and improved functional outcome appeared to be largely driven by studies which only allowed surgery up to a maximum of 48 hours after onset. Therefore, it was agreed that the reference to surgery being performed within 48 hours of onset should be retained from the original recommendations.

The committee also reviewed the criteria used to determine eligibility for hemicraniectomy from CG68. It was agreed that these were still appropriate and reflect the populations included in the studies used to inform the new recommendations.

The decision to have surgery is very individual and some patients may choose not to have surgery if there is a risk of severe disability, whereas others may wish to go ahead based on mortality benefit alone. For this reason the committee chose to leave the recommendation as a 'consider' so that it remained an option for management following discussion with suitable patients and their carers. They also recommended discussion about the risks and benefits of surgery. The committee noted that patients would not be able to be involved at the time because of the severity of the stroke, so the family members or carers would be responsible for making the decision. In deciding whether to opt for surgery considerations should include individual wishes and preferences and the pre-stroke functional status, as surgery would not be appropriate for people with severe disability before stroke. The high likelihood of residual moderate or severe disability after surgery should be made clear.

1.11.2 Cost effectiveness and resource use

The results of a published cost utility analysis with a Dutch societal perspective found that decompressive surgery is not cost effective compared with best medical treatment in adults aged 60 or younger with space-occupying hemispheric infarction. [18] The study estimated the lifetime incremental cost effectiveness ratio to be £49,224 per quality adjusted life year gained. At three years, decompressive surgery had a 2% likelihood of being cost effective at an £66,961 (€80,000) per QALY gained willingness to pay threshold. Although this economic evidence did not support decompressive hemicraniectomy the committee was not confident that it was sufficiently robust to make a strong recommendation not to offer decompressive hemicraniectomy, due to its partial applicability and potentially serious limitations.

To aid the committee's discussion of the economic evidence, the most appropriate UK NHS reference costs corresponding to the unit costs used in the study were combined with the resource usage over three years reported for the within-trial phase of the study. This allowed calculation of a three-year incremental cost for surgical decompression over best medical treatment of £90,886. The study reported an incremental QALY difference of 1.0 QALYs over the three year within-trial period. Using the estimate of UK incremental costs, the three year ICER generated is £90,886 per QALY gained. The lifetime incremental QALY difference reported in the study was 4.2 QALYs. At a £20,000 per QALY gained willingness to pay threshold, the lifetime incremental cost of surgical decompression would need to be <£84,000 to be considered cost effective. As this value is less than the three year

incremental cost, this scenario is highly unlikely as there are additional continuing incremental costs after three years. However,the committee expressed concerns about some of the resource usage reported in the study. Zero days in the nursing home were reported in the 'best medical treatment' arm, which the committee considered highly unlikely to be representative of this population and therefore of very limited applicability to the UK setting. Higher nursing home resource usage in the 'best medical treatment' arm would increase the total cost of 'best medical treatment' and reduce the incremental cost difference between 'best medical treatment' and 'decompressive hemicraniectomy'. This would result in a lower incremental cost effectiveness ratio. Although there still remains uncertainty regarding the cost effectiveness of decompressive hemicraniectomy, undertaking a *de novo* analysis from a UK perspective was not considered likely to reduce this uncertainty, as the resource use reported in the identified study still remains the only published resource use data, therefore a new model would be based on tenuous assumptions.

In addition, the committee noted that in the under 60 population, the only quality of life data available were from the HAMLET trial, on which the Dutch societal cost utility analysis was based. For the outcome 'functional outcome score 0-3 mRS at 1 year', the HAMLET trial has a much smaller effect size than in the DESTINY and DECIMAL trials, which show a trend towards benefit of decompressive hemicraniectomy. Quality of life reported by the HAMLET trial might therefore be expected to be lower than in the other trials. If quality of life data were available from all the trials, the ICER might be improved. Overall, the clinical evidence identified a modest improvement in functional outcome which the committee deemed was clinically important. Despite this slight improvement, functional outcome is poor in this population.Regardless of the limited applicability of the one identified economic study, decompressive hemicraniectomy significantly reduces mortality, while most of the survivors have significant neurological impairment and disability which limits their functional ability. Many people will need ongoing and costly long term nursing care. The committee agreed that considerations other than cost effectiveness were relevant to this issue. The clear mortality benefit of decompressive hemicraniectomy was expected to be important to many people with stroke, their families, and carers, irrespective of the poor functional outcomes of surgery. The committee discussed that the decision to undergo surgery warrants careful discussion between stroke physicians, surgeons, people with stroke and their families and carers. These shared decisions should be made on a case by case basis.

No health economic evidence was identified that considered the cost effectiveness of decompressive hemicraniectomy in people aged over 60. In the over 60 population, quality of life measured on the EQ-5D index and visual analogue scales was reported at 1 year by the DESTINY II trial. Both measures showed an improved quality of life for people undergoing decompressive hemicraniectomy compared with best medical treatment, though baseline quality of life was low. The clinical evidence did not show a differential effect between the over 60 and under 60 population and so, for equity reasons, the restriction of the population eligible for decompressive hemicraniectomy to those under 60 years of age is not supported. Due to the poor, though slightly improved functional outcomes after the surgery, the decision regarding whether a person should have a decompressive hemicraniectomy is a shared decision, to be made in conjunction with individuals, families and carers. In current practice, around 5% of people with stroke undergo decompressive hemicraniectomy. The committee acknowledged that extending the population eligible for surgery is a change to current practice, noting that people aged over 60 will generally take longer to recover from surgery and may therefore accrue higher rehabilitation costs. Without an age cut off, other factors will still be taken into consideration when determining whether a person is suitable for surgery. The committee agreed that increasing the population eligible for decompressive hemicraniectomy would not necessarily lead to significantly more people undergoing surgery; not all people eligible for decompressive hemicraneictomy ultimately go on to have surgery following discussions between carers and physicians. The committee noted that more informed discussion of the outcomes following surgery might reduce the uptake of surgery. In addition, the recommendation on endovascular therapy made elsewhere as part of this guideline update (see evidence review D) will increase the population eligible for

endovascuar therapy and increase provision of endovascular therapy. This is likely to decrease the population referred for decompressive hemicraniectomy. The committee therefore does not expect this recommendation to have a substantial resource impact on the NHS in England.

In conclusion, the committee thought that the cost effectiveness of decompressive hemicraniectomy remains uncertain. The committee recommended that decompressive hemicraniectomy be considered for some patients, following shared decision making between physicians, surgeons, families and carers. This recommendation was made based on consideration of the clear mortality benefit of decompressive hemicraniectomy, which the committee thought would be important to a significant proportion of the population, irrespective of the overall limited improvement in functional outcome following surgery.

1.11.13.2 Other factors the committee took into account

The evidence did not support the use of an age cut-off for surgery and therefore the age cut-off had been removed from the recommendation. The committee considered that the patients' pre-morbid state was much more relevant than age as a marker of potential outcome with and without surgery that would help decision making.

The committee discussed that, aside from removing the age cut-off, the weight of evidence was not strong enough either way to change the recommendation from consider.

It was noted that deciding to have surgery is a very difficult decision and patients should be provided with data of functional outcomes to guide their decision. The committee decided that patients or their carers should be given specific information on the risks and benefits in terms of their functional outcomes and risk of mortality. The decision should be made between the patient, their carers and medical or surgical team.

The committee took into account that the definition of a 'good' functional outcome will vary on an individual patient basis, as while one person might prefer to be alive with a functional score of 5, another might think this is an unacceptable state, potentially worse than death.

The committee were also aware of some limited evidence that decompressive hemicraniectomy may be performed beyond 48 hours.

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1 Appendices

2 Appendix A: Review protocols

3 **Table 7: Review protocol: Decompressive hemicraniectomy**

Field	Content
Review question	Which patients should be referred for decompressive hemicraniectomy?
Type of review question	Intervention A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To examine the effects of decompressive surgery in people with acute ischaemic stroke with cerebral oedema, and to determine if decompressive surgery is effective in improving survival or reducing the risk of disability.
Eligibility criteria – population / disease / condition / issue / domain	People aged over 16 with large volume acute anterior circulation ischaemic stroke with or without complicating space-occupying brain oedema (sometimes described as malignant middle cerebral artery infarction), evident on cerebral computed tomography or magnetic resonance imaging
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Decompressive surgery plus medical treatment (mannitol, other diuretics, corticosteroids, hyperventilation, barbiturates, etc)
Eligibility criteria – comparator(s) / control or reference (gold) standard	Medical treatment alone
Outcomes and prioritisation	Critical Mortality 90 days Mortality 1 year Functional outcome (degree of disability or dependence in daily activities) at 90 days and 1 year: • Modified Rankin Score (mRS) of 3 and 4 – 5 Important Quality of life (both health- and social-related)
Eligibility criteria – study design	Randomised controlled intervention trials
Other inclusion exclusion criteria	Inclusion Language: Restrict to English only Setting: Emergency department, High dependency or intensive care units, Hyperacute or acute stroke units, Other hospital settings
Proposed sensitivity / subgroup analysis, or meta-regression	Strata Age older than 60 years Subgroups Surgery within 24h, 48h, 72h of stroke onset Dominant/non-dominant hemisphere
Selection process – duplicate screening /	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria

selection / analysis	specified in this protocol.
Data management (software)	• EndNote will be used for reference management, sifting, citations and bibliographies. • EviBASE will be used for data extraction and quality assessment for clinical studies. • Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	Databases: Medline, Embase, Cochrane Library Language: Restrict to English only Date restriction: 2007 Key papers 1. Gupta R, Connolly ES, Mayer S et al. Hemicraniectomy for massive middle cerebral artery territory infarction: a systematic review. Stroke 2004;35(2):539–543. 2. Vahedi K, Hofmeijer J, Juettler E et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurology 2007;6(3): 215–222. 3. Hofmeijer J, Kappelle LJ, Algra A et al. (2009) 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 Neurology 8:326-333. 4. Juttler E, Schwab S, Schmiedek P et al. (2007) Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial. Stroke 38:2518-2525. 5. Cruz-Flores S, Berge E, and Whittle IR. (2012) Surgical decompression for cerebral oedema in acute ischaemic stroke. [Review][Update of Cochrane Database Syst Rev. 2002;(3):CD003435; PMID: 12137695]. Cochrane Database of Systematic Reviews 1:CD003435.
Identify if an update	Yes 2 papers included in CG68, date cut off 2007 Question in CG68: Which patients should be referred for decompressive hemicraniectomy? Recommendations from CG68 1.9.2.1 People with middle cerebral artery infarction who meet all of the criteria below should be considered for decompressive hemicraniectomy. They should be referred within 24 hours of onset of symptoms and treated within a maximum of 48 hours. • Aged 60 years or under. • Clinical deficits suggestive of infarction in the territory of the middle cerebral artery, with a score on the National Institutes of Health Stroke Scale (NIHSS) of above 15. • Decrease in the level of consciousness to give a score of 1 or more on item 1a of the NIHSS. • Signs on CT of an infarct of at least 50% of the middle cerebral artery territory, with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side, or infarct volume greater than 145 cm3 as shown on diffusion weighted MRI. 1.9.2.2 People who are referred for decompressive hemicraniectomy should be monitored by appropriately trained professionals skilled in

	neurological
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10071
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Jason Kendall in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

1

2 **Table 8: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B2 of reviews. For questions being updated, the search will be run from 2007, which was the cut-off date for the searches conducted for NICE guideline CG68. For the new review question on endovascular therapy, the search will be run from 2007 as studies published before 2007 are not likely to be relevant.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2002 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[32] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the

	committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded health economic studies in appendix H. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2002 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review. [Add cross reference]

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

1 **Table 9: Database date parameters and filters used**

Database	Dates searched	Search filter used
Medline (OVID)	01 January 2018 – 22 June 2018	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	01 January 2018 – 22 June 2018	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 6 of 12 CENTRAL to 2018 Issue 5 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

2

3 **Medline (Ovid) search terms**

1.	exp Stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststoke*1).ti,ab.
5.	exp Intracranial Hemorrhages/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	exp Brain infarction/
9.	exp Carotid Artery Thrombosis/
10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	exp Brain Ischemia/
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	Ischemic Attack, Transient/
14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.
16.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 (oedema* or edema* or swell* or swollen or enlarg*)).ti,ab.
17.	or/1-16
18.	letter/
19.	editorial/
20.	news/

21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/
31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	decompression, surgical/ or neurosurgical procedures/ or craniotomy/ or trephining/
38.	(decompress* or craniectom* or craniotom* or hemi-craniect* or hemicraniect* or trepa* or treph*).ti,ab.
39.	(hippocampectom* or lobectom* or strokectom*).ti,ab.
40.	37 or 38 or 39
41.	36 and 40
42.	randomized controlled trial.pt.
43.	controlled clinical trial.pt.
44.	randomi#ed.ti,ab.
45.	placebo.ab.
46.	randomly.ti,ab.
47.	Clinical Trials as topic.sh.
48.	trial.ti.
49.	or/42-48
50.	Meta-Analysis/
51.	exp Meta-Analysis as Topic/
52.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
53.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
54.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
55.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
56.	(search* adj4 literature).ab.
57.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
58.	cochrane.jw.
59.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
60.	or/50-59
61.	49 or 60
62.	41 and 61

63.	limit 62 to English language

1 **Embase (Ovid) search terms**

1.	*cerebrovascular accident/ or cardioembolic stroke/ or exp experimental stroke/ or lacunar stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	*brain hemorrhage/ or *brain ventricle hemorrhage/ or *cerebellum hemorrhage/ or *subarachnoid hemorrhage/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	*brain infarction/ or *brain infarction size/ or *brain stem infarction/ or *cerebellum infarction/
9.	*Carotid Artery Thrombosis/
10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	*brain ischemia/ or *hypoxic ischemic encephalopathy/
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	*Transient ischemic attack/
14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.
16.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 (oedema* or edema* or swell* or swollen or enlarg*)).ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	case report/ or case study/
22.	(letter or comment*).ti.
23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental Animal/
30.	animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice).ti.
33.	or/25-32

34.	17 not 33
35.	limit 34 to English language
36.	braint decompression/ or decompression surgery/ or decompression/
37.	skull surgery/ or craniectomy/ or cranioplasty/ or craniotomy/ or neurosurgery/
38.	(decompress* or craniectom* or craniotom* or hemi-craniect* or hemicraniect* or trepa* or treph*).ti,ab.
39.	(hippocampectom* or lobectom* or strokectom*).ti,ab.
40.	or/36-39
41.	35 and 40
42.	random*.ti,ab.
43.	factorial*.ti,ab.
44.	(crossover* or cross over*).ti,ab.
45.	((doubl* or singl*) adj blind*).ti,ab.
46.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
47.	crossover procedure/
48.	single blind procedure/
49.	randomized controlled trial/
50.	double blind procedure/
51.	or/42-50
52.	systematic review/
53.	meta-analysis/
54.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
55.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
56.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
57.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
58.	(search* adj4 literature).ab.
59.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
60.	cochrane.jw.
61.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
62.	or/52-61
63.	51 or 62

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Stroke] explode all trees
#2.	(stroke or strokes):ti,ab
#3.	((cerebro* or cerebral*) near/2 (accident* or apoplexy)):ti,ab
#4.	(CVA or poststroke or poststrokes):ti,ab
#5.	MeSH descriptor: [Intracranial Hemorrhages] explode all trees
#6.	(brain near/2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)):ti,ab
#7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) near/3 (hemorrhag* or haemorrhag* or bleed*)):ti,ab
#8.	MeSH descriptor: [Brain Infarction] explode all trees
#9.	MeSH descriptor: [Carotid Artery Thrombosis] explode all trees

#10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) near/3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab
#11.	MeSH descriptor: [Brain Ischemia] explode all trees
#12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) near/3 isch?emi*):ti,ab
#13.	MeSH descriptor: [Ischemic Attack, Transient] this term only
#14.	(isch?emi* near/2 attack*):ti,ab
#15.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) near/3 (oedema* or edema* or swell* or swollen or enlarg*)):ti,ab
#16.	TIA:ti,ab
#17.	(or #1-#16)
#18.	MeSH descriptor: [Decompression, Surgical] this term only
#19.	MeSH descriptor: [Neurosurgical Procedures] this term only
#20.	MeSH descriptor: [Craniotomy] this term only
#21.	MeSH descriptor: [Trephining] explode all trees
#22.	(decompress* or craniectom* or craniotom* or hemi-craniect* or hemicraniect* or trepa* or treph*):ti,ab
#23.	(hippocampectom* or lobectom* or strokectom*):ti,ab
#24.	(or #18-#23)
#25.	#17 and #24

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the stroke population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics.

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2007 – 06 August 2018	Exclusions Health economics studies
Embase	01 January 2007 – 06 August 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 01 January 2007 – 10 November 2017 NHSEED - 01 January 2007 – March 2015	None

Medline (Ovid) search terms

1.	exp Stroke/

2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	exp Intracranial Hemorrhages/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	exp Brain infarction/
9.	exp Carotid Artery Thrombosis/
10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	exp Brain Ischemia/
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	Ischemic Attack, Transient/
14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.
16.	or/1-15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language
37.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
38.	36 not 37
39.	economics/

40.	value of life/
41.	exp "costs and cost analysis"/
42.	exp Economics, Hospital/
43.	exp Economics, medical/
44.	Economics, nursing/
45.	economics, pharmaceutical/
46.	exp "Fees and Charges"/
47.	exp budgets/
48.	budget*.ti,ab.
49.	cost*.ti.
50.	(economic* or pharmaco?economic*).ti.
51.	(price* or pricing*).ti,ab.
52.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
53.	(financ* or fee or fees).ti,ab.
54.	(value adj2 (money or monetary)).ti,ab.
55.	or/39-54
56.	38 and 55

1 **Embase (Ovid) search terms**

1.	*cerebrovascular accident/ or cardioembolic stroke/ or exp experimental stroke/ or lacunar stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	*brain hemorrhage/ or *brain ventricle hemorrhage/ or *cerebellum hemorrhage/ or *subarachnoid hemorrhage/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	*brain infarction/ or *brain infarction size/ or *brain stem infarction/ or *cerebellum infarction/
9.	*Carotid Artery Thrombosis/
10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	*brain ischemia/ or *hypoxic ischemic encephalopathy/
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	*Transient ischemic attack/
14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.
16.	or/1-15
17.	letter.pt. or letter/
18.	note.pt.

19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	or/17-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice).ti.
32.	or/24-31
33.	16 not 32
34.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
35.	33 not 34
36.	health economics/
37.	exp economic evaluation/
38.	exp health care cost/
39.	exp fee/
40.	budget/
41.	funding/
42.	budget*.ti,ab.
43.	cost*.ti.
44.	(economic* or pharmaco?economic*).ti.
45.	(price* or pricing*).ti,ab.
46.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
47.	(finance* or fee or fees).ti,ab.
48.	(value adj2 (money or monetary)).ti,ab.
49.	or/36-48
50.	35 and 49

1 **NHS EED and HTA (CRD) search terms**

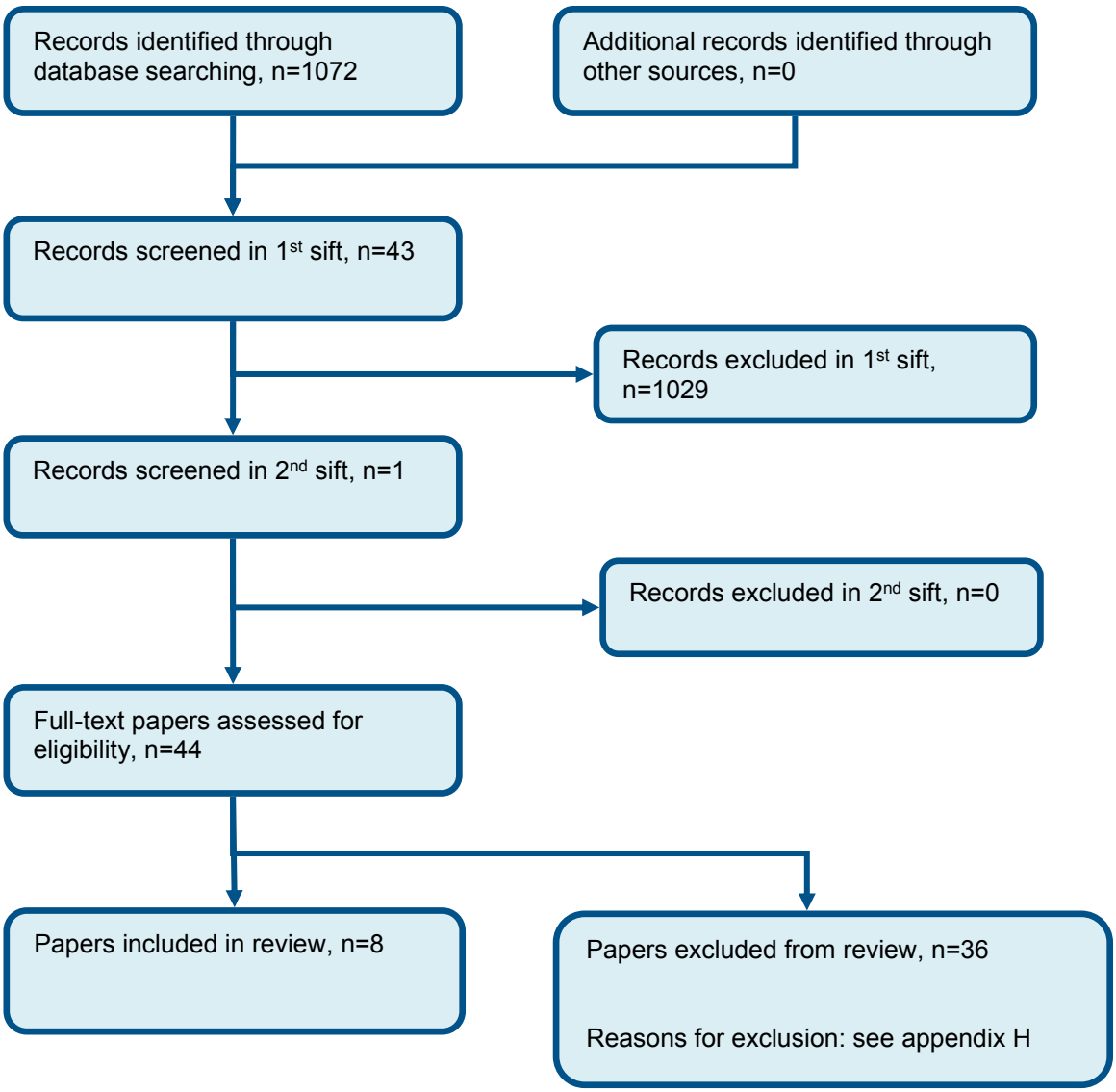
#1.	MeSH DESCRIPTOR Stroke EXPLODE 1 2
#2.	((stroke or strokes))
#3.	(((cerebro* or cerebral*) adj2 (accident* or apoplexy)))
#4.	((CVA or poststroke or poststrokes))
#5.	MeSH DESCRIPTOR Intracranial Hemorrhages EXPLODE ALL TREES
#6.	((brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)))
#7.	(((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or

	haemorrhag* or bleed*)))
#8.	MeSH DESCRIPTOR Brain Infarction EXPLODE ALL TREES
#9.	MeSH DESCRIPTOR Carotid Artery Thrombosis EXPLODE ALL TREES
#10.	(((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)))
#11.	MeSH DESCRIPTOR Brain Ischemia EXPLODE ALL TREES
#12.	(((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*))
#13.	MeSH DESCRIPTOR Ischemic Attack, Transient EXPLODE ALL TREES
#14.	((isch?emi* adj2 attack*))
#15.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

1 .
2

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of decompressive hemicraniectomy



Appendix D: Clinical evidence tables

Study	DECIMAL trial: Vahedi 2007[46]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in France; Setting: Conducted in 13 selected stroke centers (including a stroke unit and a neurosurgery department in France)
Line of therapy	1st line
Duration of study	Intervention + follow up: upto 30hrs after symptoms + 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients between 18 and 55 years of age were included within 24 hours of a malignant middle cerebral artery (MCA) infarction defined by the association of 3 criteria: a National Institutes of Health Stroke Scale score >16, including a score >1for item 1a (level of consciousness); brain computed tomography ischemic signs involving >50% of the MCA territory; and a diffusion-weighted imaging (DWI) infarct volume >145 cm3.
Exclusion criteria	Exclusion criteria included pre-existing significant disability defined by a modified Rankin Scale (mRS) score >2, a significant contralateral infarction, a severe secondary haemorrhagic infarction involving >50% of the MCA territory, any known coagulopathy (including use of recombinant tissue-type plasminogen activator), life expectancy <3 years or any serious illness that could confound treatment assessment, pregnancy, and any magnetic resonance imaging (MRI) contraindication.
Age, gender and ethnicity	Age - Mean (SD): overall - 43.4 (8.4), surgery - 43.5 (9.7), control - 43.3 (7.1). Gender (M:F): 18 male, 20 female. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Decompressive surgery - External or internal. Decompressive surgery consisted of a large hemicraniectomy that removed, ipsilateral to the stroke, a bone flap as large as possible including temporal, frontal, parietal, and some occipital bones. The dura had to be open, and duraplasty was left to the discretion of the neurosurgeon. Duration 180 days. Concurrent medication/care: In both groups of patients,

Study	DECIMAL trial: Vahedi 2007[46]
	standard medical therapy was based on published guidelines for the early management of patients with ischemic stroke. . Indirectness: No indirectness Further details: 1. Surgery within 48hrs: Surgery within 48hrs (Surgery had to be done within 30hrs of onset of symptoms). (n=18) Intervention 2: Medical treatment - Mannitol, other diuretics, corticosteroids, hyperventilation, barbiturates, etc. Standard medical treatment - In both groups of patients, standard medical therapy was based on published guidelines for the early management of patients with ischemic stroke. . Duration 180 days. Concurrent medication/care: In both groups of patients, standard medical therapy was based on published guidelines for the early management of patients with ischemic stroke. . Indirectness: No indirectness Further details: 1. Surgery within 48hrs:
Funding	Academic or government funding (French Ministry of Health and the Assistance Publique–Ho ˆpitauxde Paris (Programme Hospitalier de Recherche Clinique AOM 00148, P001004).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL OR INTERNAL versus MANNITOL, OTHER DIURETICS, CORTICOSTEROIDS, HYPERVENTILATION, BARBITURATES, ETC

Protocol outcome 1: Mortality at 6 months or 1 year
- Actual outcome for Surgery within 48hrs: Mortality at 6 months; Group 1: 5/20, Group 2: 14/18; Comments: Same as 12 months outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score surgery group - 22.5, medical group - 23.4; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A
- Actual outcome for Surgery within 48hrs: Mortality at 1 year; Group 1: 5/20, Group 2: 14/18
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score surgery group - 22.5, medical group - 23.4; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 2: Functional outcomes at 90 days
- Actual outcome for Surgery within 48hrs: 0-3 at 6 months at 6 months; Group 1: 5/20, Group 2: 1/18
Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score surgery group - 22.5, medical group - 23.4; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A
- Actual outcome for Surgery within 48hrs: 0-3 at 1 year at 1 year; Group 1: 10/20, Group 2: 4/18
Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study	DECIMAL trial: Vahedi 2007[46]
Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score surgery group - 22.5, medical group - 23.4; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Degree of disability/dependence in daily activities at Define; Quality of life (questionnaire only completed by a minority of patients)

1

2

Study	DESTINY II trial: Juttler 2014[22]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=112)
Countries and setting	Conducted in Germany; Setting: Intensive care unit
Line of therapy	1st line
Duration of study	Intervention + follow up: Treatment was initiated within 48 hours after the onset of symptoms and not later than 6 hours after randomization. 6 and 12 month follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	>60 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were eligible for inclusion in the study if they were 61 years of age or older, had clinical symptoms of acute unilateral middle-cerebral- artery infarction with an onset of symptoms less than 48 hours before the initiation of treatment, and had scores higher than 14 (in patients with an infarction in the non-dominant hemisphere) or higher than 19 (in patients with an infarction in the dominant hemisphere) with reduced levels of consciousness on the National Institutes of Health Stroke Scale (NIHSS) (total scores on the NIHSS range from 0 to 42, with higher scores indicating more severe stroke). An additional criterion for inclusion was ischemic infarction of at least two thirds of the middle-cerebral-artery territory, including the basal ganglia, on brain imaging.
Exclusion criteria	Exclusion criteria were a preexisting score of more than 1 on the modified Rankin scale (on a scale of 0 to 6, with 0 indicating no symptoms and 6 indicating death) or a preexisting score of less than 95 on the Barthel index of functional levels in activities of daily living (on a scale ranging from 0 [complete dependence] to 100 [independence] in increments of 5). Additional exclusion criteria were the absence of pupillary reflexes, a

Study	DESTINY II trial: Juttler 2014[22]
	score of less than 6 on the Glasgow Coma Scale (on which scores range from 3 to 15, with lower scores indicating reduced levels of consciousness), hemorrhages or other associated brain lesions, contraindications to surgery, or an estimated life expectancy of less than 3 years.
Age, gender and ethnicity	Age - Median (range): overrall - 70 (61-82), surgery - 70 (62-82), control - 70 (61-80). Gender (M:F): 56 male, 56 female. Ethnicity: N/A
Further population details	
Indirectness of population	No indirectness
Interventions	(n=49) Intervention 1: Decompressive surgery - External or internal. Decompressive hemicraniectomy - Treatment was initiated within 48 hours after the onset of symptoms and not later than 6 hours after randomization. Surgical treatment consisted of a large hemicraniectomy (with a diameter of at least 12 cm) and duroplasty. The surgical standards and the conservative treatment protocol are detailed in the study protocol.. Duration 12 months. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Surgery within 48hrs: (n=63) Intervention 2: Medical treatment - Mannitol, other diuretics, corticosteroids, hyperventilation, barbiturates, etc. Conservative treatment options, based on a consensus protocol used by all participating centers, included basic therapy in the ICU for stroke; osmotherapy with the use of mannitol, glycerol, or hypertonic hydroxyethyl starch; sedation; intubation and mechanical ventilation; hyperventilation; and administration of buffer solutions.. Duration 1 year. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Surgery within 48hrs:
Funding	Academic or government funding (German Research Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL OR INTERNAL versus MANNITOL, OTHER DIURETICS, CORTICOSTEROIDS, HYPERVENTILATION, BARBITURATES, ETC

Protocol outcome 1: Mortality at Define
- Actual outcome for >60 years : Mortality on mRS scale at 12months at 12 months; Group 1: 20/47, Group 2: 47/62
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS median score surgery - 20, control - 21 ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Functional outcomes at 90 days
- Actual outcome for >60 years : Functional outcomes of 0-3 on mRS at 6months at 6 months; Group 1: 3/49, Group 2: 2/63
Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study	DESTINY II trial: Juttler 2014[22]
Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS median score surgery - 20, control - 21 ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for >60 years : Functional outcomes of 0-3 on mRS at 1 year at 1 year; Group 1: 3/49, Group 2: 3/63 Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS median score surgery - 20, control - 21 ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Quality of life at Define - Actual outcome for >60 years : QoL measured on EQ-5D visual analogue scale at 12months at 12 months; Group 1: mean 25.2 (SD 29.2); n=34, Group 2: mean 8.1 (SD 19.2); n=39 Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS median score surgery - 20, control - 21 ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for >60 years : QoL measured on EQ-5D index scale at 12months at 12 months; Group 1: mean 0.2 (SD 0.3); n=22, Group 2: mean 0.3 (SD 0.3); n=11 Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS median score surgery - 20, control - 21 ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for >60 years : QoL measured on EQ-5D visual analogue scale at 12 months; Group 1: mean 24 (SD 28.6); n=42, Group 2: mean 7.6 (SD 18.2); n=57 Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS median score surgery - 20, control - 21 ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for >60 years : QoL measured on EQ-5D index scale at 12months, Group 1: mean 0 (SD 0.3); n=42, Group 2: mean -0.1 (SD 0.2); n=58 Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS median score surgery - 20, control - 21 ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Degree of disability/dependence in daily activities at Define; Cost effectiveness at Define

1

Study	DESTINY trial: Juttler 2007[21]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=32)
Countries and setting	Conducted in Germany
Line of therapy	1st line
Duration of study	Follow up (post intervention): 6 month and 1 year follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18–60 years, Clinical signs of infarction of the MCA territory with an NIHSS score >18 for lesions of the non-dominant hemisphere and >20 for lesions of the dominant hemisphere, Decrease in the level of consciousness to a score of >1 on item 1a of the NIHSS Computed tomography–documented unilateral MCA infarction, including at least 2/3 of the territory and including at least part of the basal ganglia, with or without additional ipsilateral infarction of the anterior or posterior cerebral artery, Onset of symptoms >12 and <36 hours before a possible surgical intervention, Possibility to start treatment/surgery within 6 hours after randomization, Written, informed consent by the patient or legal representative
Exclusion criteria	Prestroke mRS score >2, Prestroke score on the Barthel Index <95, Score on the Glasgow Coma Scale <6, Both pupils fixed and dilated, Any other coincidental brain lesion that might affect outcome, Space-occupying haemorrhagic transformation of the infarct, Life expectancy <3 years, Other serious illness that might affect outcome, Known coagulopathy or systemic bleeding disorder, Contraindication for anaesthesia, Pregnancy
Age, gender and ethnicity	Age - Mean (SD): overall - 44.6 (9.1), surgery - 43.2 (9.7), medical - 46.1 (8.4). Gender (M:F): 15 male, 17 female. Ethnicity: N/A
Further population details	
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Decompressive surgery - External or internal. Decompressive surgery - Large (reversed) question mark–shaped skin incision based at the ear. Removal of a bone flap (diameter >12 cm, including the frontal, parietal, temporal, and parts of the occipital squama). Removal of additional temporal bone so that the floor of the middle cerebral fossa can be explored. Opening of the dura and insertion of an augmented dural patch consisting of either homologous periost and/or temporal fascia. No resection of infarcted brain tissue. Fixation of the dura at the margin of the craniotomy. Reapproximation and securing of the temporal muscle and skin flap. Insertion of a sensor for registration of intracranial pressure. Cranioplasty in surviving patients after 6–8 weeks, with the stored bone flap or artificial bone flap. Duration 1 year. Concurrent medication/care: Conservative treatment. Indirectness: No

	indirectness Further details: 1. Surgery within 48hrs: (n=15) Intervention 2: Medical treatment - Mannitol, other diuretics, corticosteroids, hyperventilation, barbiturates, etc. Conservative treatment - Osmotherapy: Indication—Any clinical or neuroradiologic signs of space-occupying brain edema. Mannitol (0.5 g/kg 4x /day, every 4 to 6 hours; maximum daily dose, 2.5 g/kg), glycerol (250 mL, 10% solution, 4x /day), or hydroxyethyl starch (6% hetastarch in 0.9% NaCl injection, 100–250 mL every 8 hours; maximum daily dose, 750 mL); target serum osmolality=315 to 320 mOsm, Intubation and mechanical ventilation: Indication—Glasgow Coma Scale score <8, any signs of respiratory insufficiency (PO_2 <60 mm Hg, PCO_2 >48 mm Hg), or compromised airway. Ventilation mode left at discretion of the treating physician. Target parameters = PO_2 ≥75 mm Hg, PCO_2 36–44 mm Hg. In case of raised intracranial pressure, target parameters = PO_2 >100 mm Hg, PCO_2 35–40 mm Hg, tidal volume 8–10 mL/kg, 10–12 breaths per minute, minimum of 5 cm H_2O of positive end-expiratory pressure, Hyperventilation: Ultimate ratio in case of further neurologic deterioration and/or uncontrolled increase in intracranial pressure. Target PCO_2 28–32 mm Hg. Venous oxygenation (jugular bulb oxymetry, saturation >50%), Intracranial pressure monitoring: Invasive measurement in the ipsilateral hemisphere, Sedation: Mode including use of muscle relaxants left at the discretion of the treating physician. Propofol recommended. Use of barbiturates discouraged, Blood pressure: Target parameters in formerly hypertensive patients=180/100–105 mm Hg, in formerly normotensive patients=160–180/90–100 mm Hg. Target parameters during the first 8 hours after decompressive surgery=140–160 mm Hg, Positioning: Plane head positioning, elevation of 15°-30° recommended in case of severely increased intracranial pressure, depending on cerebral perfusion pressure, or in patients at high risk of infection, Body core temperature: Target=normothermia. Treatment started at >37.5°C. Use of antipyretics, external or intravasal cooling left at the discretion of the treating physician, Blood glucose level: Target parameters=80–110 mg/dL. Treatment started at >140 mg/dL with insulin. Hypoglycemia treated with 10% or 20% glucose, Fluid management: Target=normovolemia; avoid hyponatremia, Prophylaxis of deep venous thrombosis: Weight-adjusted low-molecular-weight heparin, No seizure prophylaxis. Duration 1 year. Concurrent medication/care: Conservative treatment. Indirectness: No indirectness Further details: 1. Surgery within 48hrs:
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL OR INTERNAL versus MANNITOL, OTHER DIURETICS, CORTICOSTEROIDS, HYPERVENTILATION, BARBITURATES, ETC

Protocol outcome 1: Mortality at 6 months or 1 year
- Actual outcome: Mortality after 30 days at 30 days; Group 1: 2/17, Group 2: 8/15
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score median surgery - 21, medication - 24; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Mortality after 1 year at 1 year ; Group 1: 3/17, Group 2: 8/15 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score median surgery - 21, medication - 24; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Functional outcomes at 90 days - Actual outcome: 0-3 at 6 months at 6 months; Group 1: 8/17, Group 2: 4/15 Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score median surgery - 21, medication - 24; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: 0-3 at 1 year at 1 year; Group 1: 8/17, Group 2: 4/15 Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score median surgery - 21, medication - 24; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Degree of disability/dependence in daily activities at Define; Quality of life at Define

Study	HAMLET trial: Hofmeijer 2009[17]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in Netherlands; Setting: Stroke unit, intensive care unit
Line of therapy	First line
Duration of study	Intervention + follow up: Treatment occurred within 3hrs of randomization plus 1 year follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified
Inclusion criteria	Diagnosis of acute ischaemic stroke in the territory of the middle cerebral artery, with onset within 96 h of the start of the trial treatment. Score on the National Institutes of Health stroke scale (NIHSS) of ≥16 for right-sided lesions or ≥21 for left-sided lesions. Gradual decrease in consciousness to a score of ≤13 on the Glasgow coma scale for right-sided lesions or an eye and motor score of ≤9 for left-sided lesions. Ischaemic changes on CT that affect two-thirds or more of the territory of the middle cerebral artery and the formation of space-occupying oedema; displacement of midline structures on CT was not required. Age 18–60 years. Able to start trial treatment within 3 h of randomization. Written, informed consent given by a legal representative of the patient.
Exclusion criteria	Ischaemic stroke of the whole cerebral hemisphere (anterior, middle, and posterior cerebral artery territories). Decrease in consciousness partially because of causes other than the formation of oedema, such as metabolic disturbances or medication. Both pupils fixed and dilated. Alteplase in the 12 h before randomization. Known systemic bleeding disorder. Pre Stroke score on the modified Rankin scale of greater than 1 or less than 95 on the Barthel index. Life expectancy is less than 3 years. Other serious illness that might confound treatment assessment.
Recruitment/selection of patients	Patients were enrolled between November, 2002, and October, 2007, at six centres in the Netherlands, according to a previously published protocol.
Age, gender and ethnicity	Age - Mean (SD): overall - 48.7 (9.05), surgery - 50 (8.3), medical - 47.4 (9.8). Gender (M:F): 38 male, 26 female. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Decompressive surgery - External or internal. Treatment had to be started within 3 h of randomization. Surgical decompression consisted of removal of a flap of bone of at least 12 cm diameter and including parts of the frontal, parietal, temporal, and occipital squama. If necessary, more temporal bone

	was removed so that the floor of the middle cerebral fossa could be assessed. The dura was opened, and an augmented dural patch was inserted. The position of the temporalis muscle and skin flap was then approximated and they were secured. Infarcted brain tissue was not resected. A sensor to measure intracranial pressure could be left in situ, if required. After the operation, patients were transferred to an intensive care unit. Drugs to prevent oedema were given at the discretion of the treating physician. . Duration within 3 hrs of randomisation. Concurrent medication/care: Because no mode of medical treatment has been shown as superior, best medical treatment was given at the discretion of the treating physician and could consist of treatment at an intensive care unit or at a stroke unit. To improve the consistency of treatment between centres, recommendations were made for treatment in the intensive care unit. . Indirectness: No indirectness Further details: 1. Surgery within 48hrs: (n=32) Intervention 2: Medical treatment - Mannitol, other diuretics, corticosteroids, hyperventilation, barbiturates, etc. Best medical treatment. . Duration 1 year. Concurrent medication/care: Because no mode of medical treatment has been shown as superior, best medical treatment was given at the discretion of the treating physician and could consist of treatment at an intensive care unit or at a stroke unit. To improve the consistency of treatment between centres, recommendations were made for treatment in the intensive care unit. . Indirectness: No indirectness Further details: 1. Surgery within 48hrs:
Funding	Study funded by industry (Netherlands Heart Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL OR INTERNAL versus MANNITOL, OTHER DIURETICS, CORTICOSTEROIDS, HYPERVENTILATION, BARBITURATES, ETC

Protocol outcome 1: Mortality at 6 months or 1 year
- Actual outcome: Mortality - Modified Rankin Scale at 1 year; Group 1: 7/32, Group 2: 19/32; Comments: Absolute risk reduction (95% CI) - 38% (15 to 60)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score surgery - 23 (17-34), medical - 24 (20 -36); Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Surgery within 48 hrs: Mortality - mRS at 1 year; Group 1: 4/21, Group 2: 14/18; Comments: ARR (95 % CI) - 59% (33 to 84)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score surgery - 23 (17-34), medical - 24 (20 -36); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Functional outcomes at 90 days
- Actual outcome: 0-3 on Modified Rankin Scale at 1 year; Group 1: 6/32, Group 2: 6/32; Comments: ARR (95% CI) - 0% (-21 to 21)

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score surgery - 23 (17-34), medical - 24 (20 -36); Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Surgery within 48hrs: mRS of 0-3 <48hrs at 1 year; Group 1: 5/21, Group 2: 4/18; Comments: ARR (95% CI) - 2% (-25 to 28) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score surgery - 23 (17-34), medical - 24 (20 -36); Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Quality of life at 6 months or 1 year - Actual outcome: SF-36 questionnaire - physical summary at 1 year; Group 1: mean 29 (SD 7); n=32, Group 2: mean 36 (SD 11); n=32; Comments: MD (95% CI) = -8 (-14 to -1) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score surgery - 23 (17-34), medical - 24 (20 -36); Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: SF-36 questionnaire -mental summary at 1 year; Group 1: mean 55 (SD 12); n=32, Group 2: mean 53 (SD 11); n=32; Comments: MD (95% CI) = 3 (-6 to 10) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score surgery - 23 (17-34), medical - 24 (20 -36); Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Degree of disability/dependence in daily activities at Define

Study	HeADDFIRST trial: Frank 2014[12]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=26)
Countries and setting	Conducted in United Kingdom; Setting: A specialized neuromonitoring unit (intermediate or intensive care)
Line of therapy	1st line
Duration of study	Intervention + follow up: surgery within 4hrsrs + 180 days Follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified: <48 hrs, 60+years,
Inclusion criteria	All patients with ischemic stroke admitted to each participating centre were screened for 4 criteria: unilateral middle cerebral artery (MCA) stroke, 18 to 75 years old, National Institutes of Health Stroke Scale (NIHSS) score of ≥18, and responsive to minor stimulation (NIHSS Item 1a<2). Those who met these 4 criteria satisfied the neuroimaging criterion of either hypodensity involving ≥50% of the MCA territory on a CT performed<5 hours after the stroke onset6 or hypodensity involving the complete MCA territory on a CT performed <48 hours after stroke onset, 1 and those who metno exclusion criteria (Table 1) were deemed eligible, and those patients (or their surrogates) were approached for consent.
Exclusion criteria	Deterioration to randomisable condition before admission to the participating hospital, Confluent parenchymal hematoma, Subdural hematoma, Subarachnoid haemorrhage, PTT>40 s, INR>1.4, Platelet count<100 k/μL before correction with blood products, Pre-existing illness limiting life expectancy to <6 mo, Pre-existing disability with modified Rankin>2, Pre-existing or concurrent brain injury with associated deficits in addition to principal stroke, Current participation in another clinical trial
Recruitment/selection of patients	All patients with ischemic stroke admitted to each participating centre were screened
Age, gender and ethnicity	Age - Median (IQR): Overall - 55.1 (45.45-62.4), MTO - 57.9 (45.4-65.8), MTS - 52.3 (45.5-59.0). Gender (M:F): 15 male, 8 female. Ethnicity: N/A
Further population details	
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Decompressive surgery - External or internal. Surgical decompression carried out within 96 hours from symptom onset. In patients who were randomized to surgical treatment, the standardized hemicraniectomy and durotomy required rapid initiation of surgery, with a target of ≤4 hours from meeting criteria for randomization, in addition to continued compliance with the SMMP. All patients underwent a durotomy (circumferential or cruciate) with dural grafting recommended but not required. No brain amputation was allowed in any case. Perioperative antibiotics (unspecified) were required for the first

	24 hours after surgery. Postoperative dressings were non-compressive.Ventricular drains could not be used. All randomized patients required anipsilateral parenchymal ICP monitor, frontally located. All neurosurgeons participated in an investigator training session and demonstrated detailed knowledge of the medical and surgical protocols and agreement to adhere to them even when there were personal variances in usual practice outside of the study setting. Duration < 4hrs. Concurrent medication/care: Medical treatment - All registered patients were cared for in a specialized neuromonitoring unit (intermediate or intensive care) with a consensus developed SMMP with the formal agreement of all investigators for required adherence to the protocol (not simply recommended) after in-person training and an examination that assessed an understanding of the protocols and required adherence. A comprehensive protocol specified detailed procedures for airway management, ventilator settings, blood pressure control and agents, fluid and electrolyte management, gastrointestinal and nutritional management, hematologic monitoring and management, ICP monitoring, sedation, use of mannitol, anticonvulsants, prophylaxis against deep-vein thrombosis, and rehabilitation.. Indirectness: No indirectness Further details: 1. Surgery within 48hrs: (n=10) Intervention 2: Medical treatment - Mannitol, other diuretics, corticosteroids, hyperventilation, barbiturates, etc. Medical treatment - All registered patients were cared for in a specialized neuromonitoring unit (intermediate or intensive care) with a consensus developed SMMP with the formal agreement of all investigators for required adherence to the protocol (not simply recommended) after in-person training and an examination that assessed an understanding of the protocols and required adherence. A comprehensive protocol specified detailed procedures for airway management, ventilator settings, blood pressure control and agents, fluid and electrolyte management, gastrointestinal and nutritional management, hematologic monitoring and management, ICP monitoring, sedation, use of mannitol, anticonvulsants, prophylaxis against deep-vein thrombosis, and rehabilitation.. Duration N/A. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Surgery within 48hrs:
Funding	Academic or government funding (This study was funded by a grant from National Institute of Neurological Disorders and Stroke (R01 NS40229, Dr Frank, PI).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL OR INTERNAL versus MANNITOL, OTHER DIURETICS, CORTICOSTEROIDS, HYPERVENTILATION, BARBITURATES, ETC

Protocol outcome 1: Mortality at 6 months or 1 year
- Actual outcome: Mortality at 90 days at 90 days; Group 1: 5/14, Group 2: 4/10
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score MTO - 218, MTS - 341; Group 1 Number missing: 1,

Reason: 1 withdrew after being randomized and 1 withdrew before being randomized to a group; Group 2 Number missing: 0, Reason: 1 withdrew before being randomized to a group Protocol outcome 2: Functional outcomes at 90 days - Actual outcome: Functional outcomes at 90 days at 90 days; Group 1: mean 4.4 (SD 1.16); n=14, Group 2: mean 4.7 (SD 0.44); n=10 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score MTO - 218, MTS - 341; Group 1 Number missing: 1, Reason: 1 withdrew after being randomized and 1 withdrew before being randomized to a group; Group 2 Number missing: 0, Reason: 1 withdrew before being randomized to a group - Actual outcome: 0-2 at 90 days at 90 days; Group 1: 1/14, Group 2: 0/10 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score MTO - 218, MTS - 341; Group 1 Number missing: 1, Reason: 1 withdrew after being randomized and 1 withdrew before being randomized to a group; Group 2 Number missing: 0, Reason: 1 withdrew before being randomized to a group - Actual outcome: 0-3 at 90 days at 90 days; Group 1: 4/14, Group 2: 1/10 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score MTO - 218, MTS - 341; Group 1 Number missing: 1, Reason: 1 withdrew after being randomized and 1 withdrew before being randomized to a group; Group 2 Number missing: 0, Reason: 1 withdrew before being randomized to a group - Actual outcome: 0-4 at 90 days at 90 days; Group 1: 8/14, Group 2: 6/10 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score MTO - 218, MTS - 341; Group 1 Number missing: 1, Reason: 1 withdrew after being randomized and 1 withdrew before being randomized to a group; Group 2 Number missing: 0, Reason: 1 withdrew before being randomized to a group	
Protocol outcomes not reported by the study	Degree of disability/dependence in daily activities at Define; Quality of life at Define

Study	HeMMI trial trial: Chua 2015[6]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=29)
Countries and setting	Conducted in Philippines; Setting: Hospital
Line of therapy	First line
Duration of study	Intervention + follow up: 6 month follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients between 18 and 65 years old who presented with clinical signs of infarction of the MCA territory and who arrived at the hospital within 72 hours of symptom onset were potentially eligible for inclusion. Other inclusion criteria included a Glasgow coma score (GCS) of 6 to14 in patients with right MCA infarction or GCS 5 to 9 in patients with left MCA infarction (adjusted to account for effect on speech deficit on GCS scores), or GCS of 15 on arrival but subsequent neurological deterioration defined by a score of ≥1 on the level of consciousness item of the National Institutes of Health Stroke Scale (NIHSS); computed tomography (CT) scan showing ischemic changes of more than 50% of the MCA territory with or without involvement of other vascular territories; and written informed consent from the patient or a legal representative.
Exclusion criteria	Exclusion criteria were previous disabling neurological disease, estimated premorbid modified Rankin Scale (mRS) score >2; terminal illness; presence of serious medical comorbidities like end-stage renal failure and cardiac disease with severe hemodynamic compromise; infarction due to surgical complications or vasospasm; primary intracranial haemorrhage; coagulopathies; and high risk for surgery upon assessment by the medical team.
Recruitment/selection of patients	All patients were recruited from a single centre, the Philippine General Hospital.
Age, gender and ethnicity	Age - Mean (SD): 50.2 (8.3). Gender (M:F): 20 male, 4 female. Ethnicity: N/A
Further population details	
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Decompressive surgery - External or internal. Decompressive hemicraniectomy involved removal of a large bone flap at least 12 cm in diameter, including parts of the frontal, temporal, parietal and occipital bones, with further craniectomy to the floor of the temporal fossa. The dura was opened widely and duraplasty performed using periosteum and temporalis fascia. The bone flap was either stored in a subcutaneous pocket in the abdomen or placed in the bone bank. Cranioplasty was performed on an

	elective basis not earlier than 6 months from the initial surgery.. Duration 6 months. Concurrent medication/care: Medical therapy. All patients enrolled in either arm of the study received standardized medical therapy in an intensive care unit (ICU), which included elevation of the head of bed at 30° to promote venous drainage without compromising cerebral blood flow, intermittent hyperventilation administered when necessary to acutely address signs of increased intracranial pressure refractory to other measures, and intravenous mannitol to achieve a serum osmolarity of 300 to 320 mOsm while keeping patients euvolemic. Mean arterial pressure was maintained above 90 mmHg. Hemoglobin concentration was maintained above 90 g/L. Hyperglycemia, hyperthermia and hypotension were avoided or corrected when present. Patients randomized to the medical group who deteriorated further while under treatment were offered decompressive hemicraniectomy for ethical and compassionate reasons.. Indirectness: No indirectness Further details: 1. Surgery within 48hrs: (n=13) Intervention 2: Medical treatment - Mannitol, other diuretics, corticosteroids, hyperventilation, barbiturates, etc. Standard medical therapy. All patients enrolled in either arm of the study received standardized medical therapy in an intensive care unit (ICU), which included elevation of the head of bed at 30° to promote venous drainage without compromising cerebral blood flow, intermittent hyperventilation administered when necessary to acutely address signs of increased intracranial pressure refractory to other measures, and intravenous mannitol to achieve a serum osmolarity of 300 to 320 mOsm while keeping patients euvolemic. Mean arterial pressure was maintained above 90 mmHg. Haemoglobin concentration was maintained above 90 g/L. Hyperglycemia, hyperthermia and hypotension were avoided or corrected when present. Patients randomized to the medical group who deteriorated further while under treatment were offered decompressive hemicraniectomy for ethical and compassionate reasons.. Duration 6 months. Concurrent medication/care: All patients enrolled in either arm of the study received standardized medical therapy in an intensive care unit (ICU), which included elevation of the head of bed at 30° to promote venous drainage without compromising cerebral blood flow, intermittent hyperventilation administered when necessary to acutely address signs of increased intracranial pressure refractory to other measures, and intravenous mannitol to achieve a serum osmolarity of 300 to 320 mOsm while keeping patients euvolemic. Mean arterial pressure was maintained above 90 mmHg. Hemoglobin concentration was maintained above 90 g/L. Hyperglycemia, hyperthermia and hypotension were avoided or corrected when present. Patients randomized to the medical group who deteriorated further while under treatment were offered decompressive hemicraniectomy for ethical and compassionate reasons.. Indirectness: No indirectness Further details: 1. Surgery within 48hrs:
Funding	Academic or government funding (The work of trial staff was supported by the University of the Philippines and Philippine General Hospital. No other funding was received.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL OR INTERNAL versus MANNITOL, OTHER DIURETICS,

CORTICOSTEROIDS, HYPERVENTILATION, BARBITURATES, ETC Protocol outcome 1: Mortality at 6 months or 1 year - Actual outcome: Mortality at 6 months at 6 months; Group 1: 5/13, Group 2: 6/11 Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS mean score surgery - 22.8, control - 22.5; Group 1 Number missing: 3, Reason: 3 lost to follow up; Group 2 Number missing: 2, Reason: 2 lost to follow up Protocol outcome 2: Functional outcomes at 90 days - Actual outcome: Functional outcomes measured by mRS scale of 0-3 at 6 months at 6 months; Group 1: 3/13, Group 2: 4/11 Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS mean score surgery - 22.8, control - 22.5; Group 1 Number missing: 3, Reason: 3 lost to follow up; Group 2 Number missing: 2, Reason: 2 lost to follow up - Actual outcome: Functional outcomes measured by mRS scale of 0-4 at 6 months at 6 months; Group 1: 6/13, Group 2: 5/11 Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS mean score surgery - 22.8, control - 22.5; Group 1 Number missing: 3, Reason: 3 lost to follow up; Group 2 Number missing: 2, Reason: 2 lost to follow up	
Protocol outcomes not reported by the study	Degree of disability/dependence in daily activities at Define; Quality of life at Define

Study	Slezins 2012[40]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=28)
Countries and setting	Conducted in Latvia; Setting: A stroke unit or an intensive care unit
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 year follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	>60 years
Subgroup analysis within study	Not applicable
Inclusion criteria	The inclusion criteria into the study were as follows: age of at least 18 years of both sexes, major space-occupying cerebral infarction of at least 50% of the MCA territory as defined by computed tomography (CT) and/or magnetic resonance imaging (MRI) with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side, or cerebral infarct volume (CIV) of >145 cm3, with an acute onset of corresponding clinical signs and symptoms (NIHHS score, >15), and no absolute contraindications to perform DCE, and possibility to start surgery within 48 hours from onset.
Exclusion criteria	The exclusion criteria were as follows: the mRS score of 2 or more before stroke and other serious pre stroke conditions that could affect a clinical course, GCS score of 5 or less, 2 fixed dilated pupils, known coagulopathy or systemic bleeding disorder, and contraindication for anaesthesia.
Age, gender and ethnicity	Age - Mean (range): 61.5 (49 to 81). Gender (M:F): 12 female, 16 male. Ethnicity: N/A
Further population details	
Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: Decompressive surgery - External or internal. Decompressive Craniectomy - DCE of at least 12 cm in diameter was done by removing the parts of the frontal, parietal, temporal, and occipital squama with removal of additional temporal bone so that the floor of the middle cerebral fossa could be reached. The wide durotomy was performed, and a dural patch was placed into the incision to enlarge the intradural space. The skin flap was then sutured. The infarcted brain tissue was not resected. Duration 1 year. Concurrent medication/care: Medical management was conducted in either a stroke unit or an intensive care unit (ICU) setting. Indirectness: No indirectness Further details: 1. Surgery within 48hrs: (n=13) Intervention 2: Medical treatment - Mannitol, other diuretics, corticosteroids, hyperventilation, barbiturates, etc. Medical management was conducted in either a stroke unit or an intensive care unit (ICU)

	setting. Duration 1 year. Concurrent medication/care: Medical management was conducted in either a stroke unit or an intensive care unit (ICU) setting. Indirectness: No indirectness Further details: 1. Surgery within 48hrs:
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL OR INTERNAL versus MANNITOL, OTHER DIURETICS, CORTICOSTEROIDS, HYPERVENTILATION, BARBITURATES, ETC Protocol outcome 1: Mortality at 6 months or 1 year - Actual outcome for >60 years : Mortality at 1 year at 12 months ; Group 1: 6/11, Group 2: 12/13 Risk of bias: All domain - High, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: mean NIHHS scores surgery - 21.2, control - 20.8; Group 1 Number missing: 4, Reason: 3 underwent surgery but were not included due to time frame violation, 1 had a parenchymal ICP monitoring gauge implanted but did not receive surgery ; Group 2 Number missing: 0 Protocol outcome 2: Functional outcomes at 90 days - Actual outcome for >60 years : mRS of 0-3 at 1year at 12 months ; Group 1: 5/11, Group 2: 0/13 Risk of bias: All domain - High, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: mean NIHHS scores surgery - 21.2, control - 20.8; Group 1 Number missing: 4, Reason: 3 underwent surgery but were not included due to time frame violation, 1 had a parenchymal ICP monitoring gauge implanted but did not receive surgery ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Degree of disability/dependence in daily activities at Define; Quality of life at Define

Study	Zhao 2012[51]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=47)
Countries and setting	Conducted in China; Setting: Carried out in 4 medical institutions from four provinces in mainland China. All recruited patients were admitted to the neurological intensive care units (NICUs) immediately after randomisation, and standard medical therapies were initiated as soon as possible.
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months and 12 months FU
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	>60 years
Subgroup analysis within study	Not stratified but pre-specified
Inclusion criteria	18-80yrs, inclusion and able to start DHC within 48hrs of stroke onset, decrease in consciousness to an eye and motor score of <9 on the GCS, ischemic signs on subsequent CCT involving at least 2/3 of the MCA territory with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side and the development of space occupying edema and written, informed consent given by the closest relatives of patients.
Exclusion criteria	Prestroke score on the mRS >2, diminished consciousness due to other causes such as metabolic disturbances or medication, rather than the formation of space occupying edema, a GCS score without the verbal response item <6, a dilated and fixed pupil ipsilateral to the infarct side, or both pupils fixed and dilated, a concomitant contralateral infarction or a secondary space occupying hemorrhage in the area of infarction, any other coincidental brain lesion or serious illness that might affect the outcome, life expectancy less than 3 years, and contraindications for anesthesia or surgery, including known coagulopathy, systemic bleeding disorder or pregnancy etc.
Age, gender and ethnicity	Age - Median (range): 64 yrs (29 - 80). Gender (M:F): 13 female, 34 male. Ethnicity: N/A
Further population details	
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: Decompressive surgery - External or internal. Decompressive hemicraniectomy - consisted of a large hemicraniectomy and a duraplasty. The surgical procedure was performed as follows: 1) a large skin incision ipsilateral to the stroke, in the shape of a reversed question mark based at the ear, was made. 2) a bone flap with a diameter of at least 12cm (including temporal, frontal, parietal and some occipital bones) was removed. 3) more temporal bone was resected so that the floor of the middle cerebral fossa could be explored. 4) the dura was opened and a dural patch, made of a dura substitute was placed into the incision and secured. 5) the dura had to be fixed at the edge of the craniotomy to prevent epidural bleeding.

	6) the temporal muscle and the skin flap were then reapproximated and sutured. The timing of cranioplasty for each individual varied and depended on the discretion of the neurosurgeons. . Duration 1 year. Concurrent medication/care: Standard medical treatment - administered in accordance with a consensus protocol of all participating centers. The therapeutic measurements in the protocol were mainly derived from the mode of medical treatment shown in DESTINYand HAMLET trials. All recruited patients were admitted to the neurological intensive care units (NICUs) immediately after randomisation, and standard medical therapies were initiated as soon as possible. . Indirectness: No indirectness Further details: 1. Surgery within 48hrs: (n=23) Intervention 2: Medical treatment - Mannitol, other diuretics, corticosteroids, hyperventilation, barbiturates, etc. Standard medical treatment - administered in accordance with a consensus protocol of all participating centers. The protocol included positioning, osmotherapy, fluid management, pulmonary function and airway protection, cardiac care, BP management, body temperature control, blood glucose management, sedation, prevention of DVT and PE, length of stay on the NICU. The therapeutic measurements in the protocol were mainly derived from the mode of medical treatment shown in DESTINYand HAMLET trials. All recruited patients were admitted to the neurological intensive care units (NICUs) immediately after randomisation, and standard medical therapies were initiated as soon as possible. . Duration 1 year. Concurrent medication/care: Standard medical treatment - administered in accordance with a consensus protocol of all participating centers. The therapeutic measurements in the protocol were mainly derived from the mode of medical treatment shown in DESTINYand HAMLET trials. All recruited patients were admitted to the neurological intensive care units (NICUs) immediately after randomisation, and standard medical therapies were initiated as soon as possible. Indirectness: No indirectness Further details: 1. Surgery within 48hrs:
Funding	Study funded by industry (Supported by Capital Medical Development Foundation (no. 2007 - 1043))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL OR INTERNAL versus MANNITOL, OTHER DIURETICS, CORTICOSTEROIDS, HYPERVENTILATION, BARBITURATES, ETC

Protocol outcome 1: Mortality at Define
- Actual outcome for >60 years : Mortality at 6 months at 6 months; Group 1: 2/16, Group 2: 8/13; Comments: ARR (CI) - 49 (18 to 80.1)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: pre existing mRS scores median (range) - surgery - 0 (0-2), control - 0 (0-2); Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for >60 years : Mortality at 12 months at 12 months; Group 1: 3/16, Group 2: 9/13; Comments: ARR (CI) - 50.5 (18.9 to 82.0)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: pre existing mRS scores median (range) - surgery - 0 (0-2), control - 0 (0-2); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Functional outcomes at 90 days - Actual outcome for >60 years : Functional outcomes, mRS 0-3 at 6 months at 6 months; Group 1: 2/16, Group 2: 0/13 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: pre existing mRS scores median (range) - surgery - 0 (0-2), control - 0 (0-2); Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for >60 years : Functional outcomes, mRS 0-3 at 12 months at 12 months; Group 1: 2/16, Group 2: 0/13 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: pre existing mRS scores median (range) - surgery - 0 (0-2), control - 0 (0-2); Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Degree of disability/dependence in daily activities at Define; Quality of life at Define; Cost effectiveness at Define

Appendix E: Forest plots and ordinal shift graphs

E.1 Decompressive hemicraniectomy vs medical treatment in those under 60 years

Figure 1: Mortality at 30 days

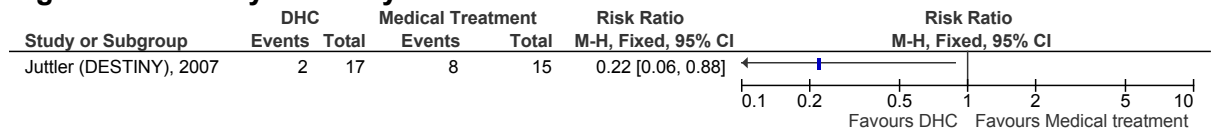


Figure 2: Mortality at 6 months

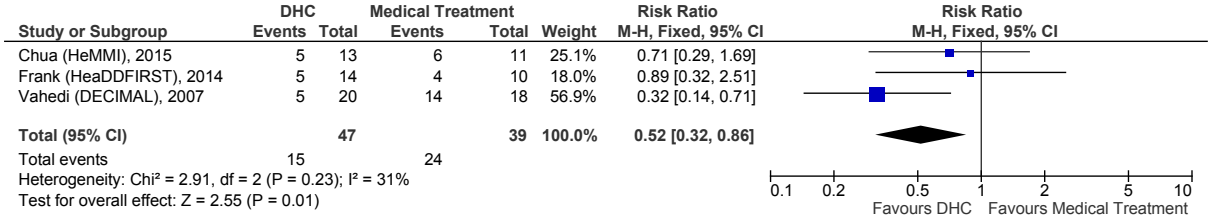


Figure 3: Mortality at 1 year

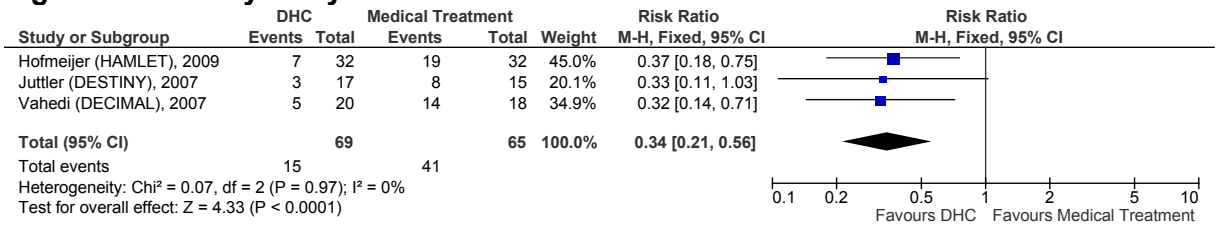


Figure 4: Functional outcomes, score of 0-3 on mRS scale at 6 months

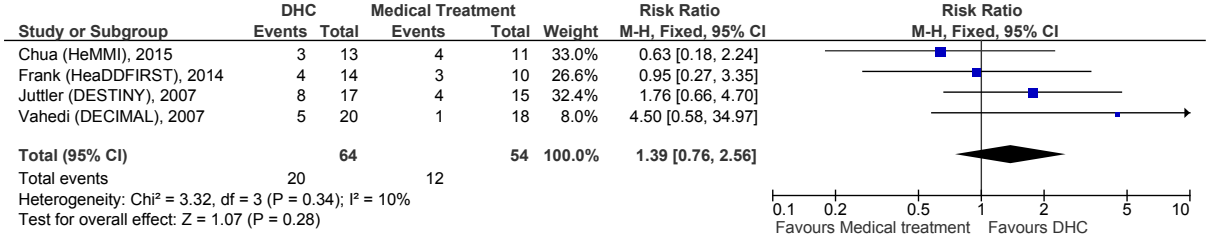


Figure 5: Functional outcomes, score of 0-3 on mRS scale at 1 year

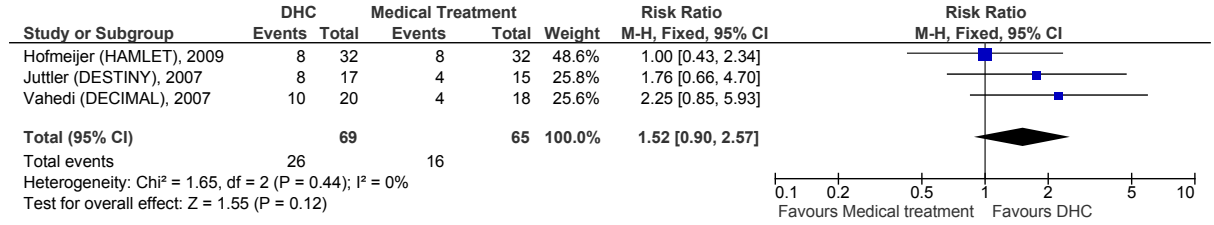
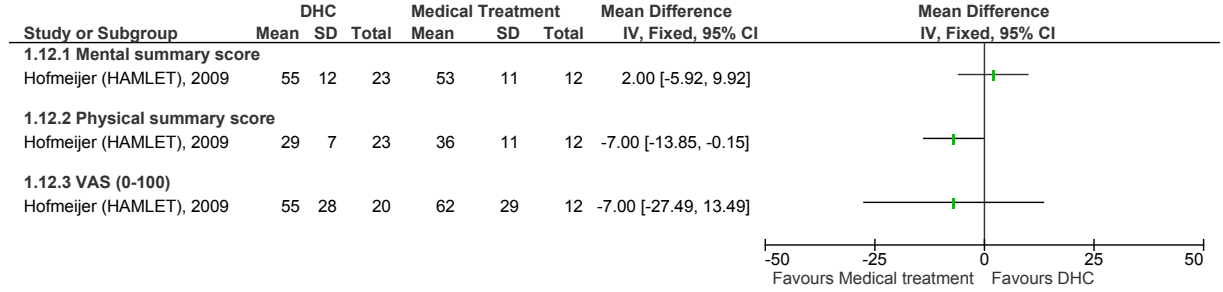


Figure 6: Quality of life, SF-36 at 1 year



E.2 Decompressive hemicraniectomy vs medical treatment in those over 60 years

Figure 7: Mortality, 6 months

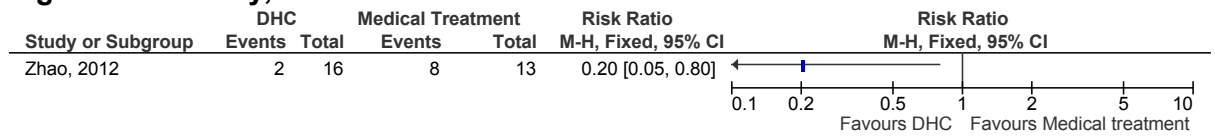


Figure 8: Mortality, 1 year

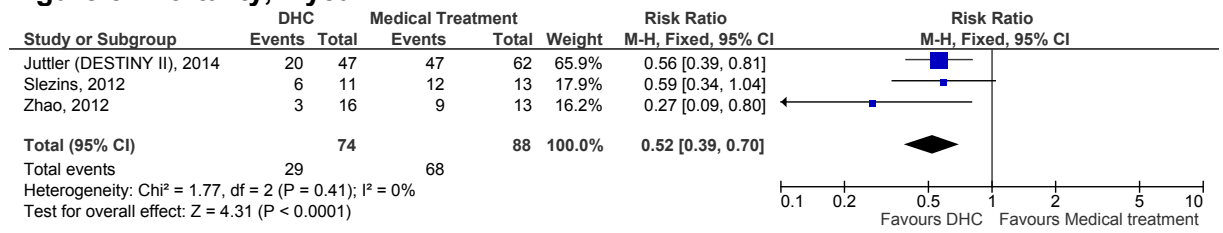
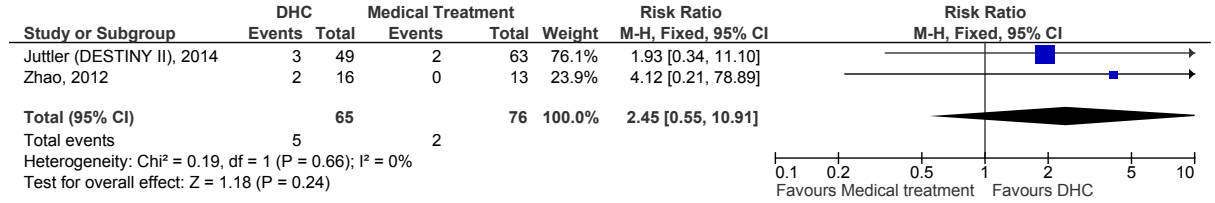
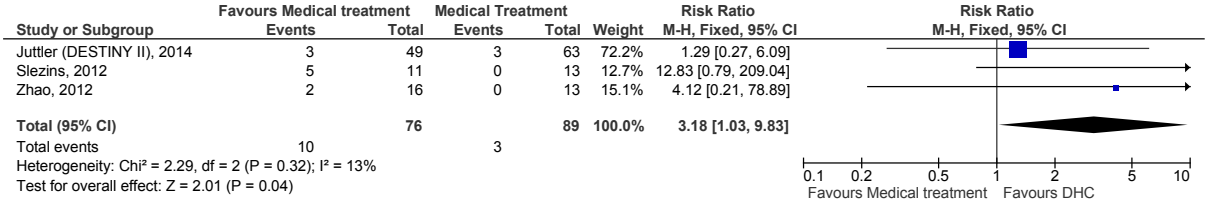


Figure 9: Functional outcomes, mRS 0-3 at 6 months



1

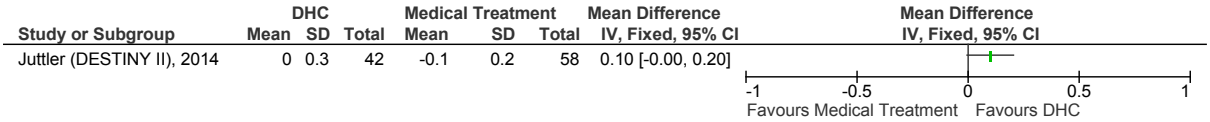
Figure 10: Functional outcomes, mRS 0-3, 1 year



2

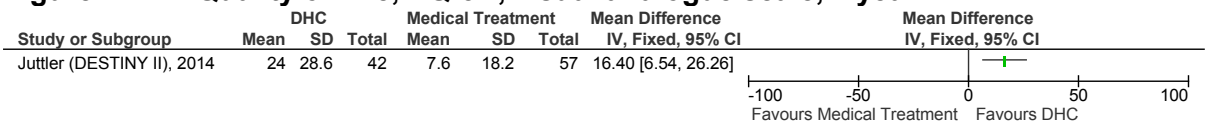
3

Figure 11: Quality of life, EQ-5D, index scale, 1 year



4

Figure 12: Quality of Life, EQ-5D, visual analogue scale, 1 year



5

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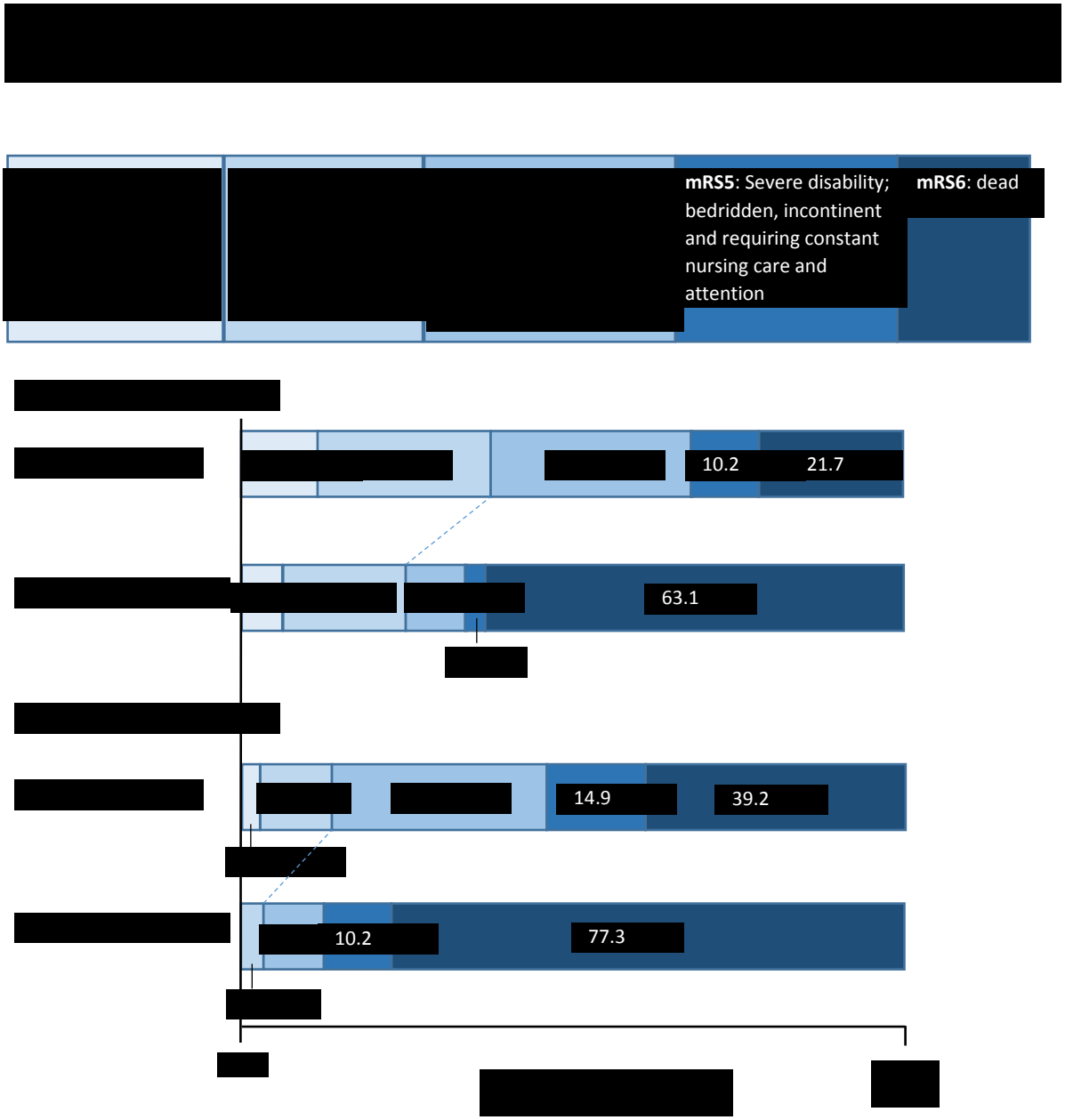
E.3 Ordinal shift analysis for decompressive hemicraniectomy vs medical treatment

Figure 13: mRS distribution at 6 months

Figure 14: mRS distribution at 1 year



1

2

1 Appendix F: GRADE tables

2 **Table 11: Clinical evidence profile: Decompressive hemicraniectomy vs medical treatment for those under 60yrs**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DHC	Medical Treatment	Relative (95% CI)	Absolute		
Mortality at 30 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	2/17 (11.8%)	53.3%	RR 0.22 (0.06 to 0.88)	416 fewer per 1000 (from 64 fewer to 501 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Mortality at 6 months												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	15/47 (31.9%)	54.54%	RR 0.52 (0.32 to 0.86)	262 fewer per 1000 (from 76 fewer to 371 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Mortality at 1 year												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/69 (21.7%)	59.38%	RR 0.34 (0.21 to 0.56)	392 fewer per 1000 (from 261 fewer to 469 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Functional outcomes at 6 months, score of 0-3 on mRS scale (range: 0-6, high is poor outcome)												
4	randomised trials	Very serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	20/64 (31.3%)	28.3%	RR 1.39 (0.76 to 2.56)	110 more per 1000 (from 68 fewer to 441 more)	⊕OOO VERY LOW	CRITICAL
Functional outcomes at 1 year, score of 0-3 on mRS scale (range: 0-6, high is poor outcome)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	126/69 (37.7%)	25%	RR 1.52 (0.9 to 2.57)	130 more per 1000 (from 25 fewer to 392 more)	⊕⊕OO LOW	CRITICAL

Quality of Life, SF-36 mental summary (0-100), high is good outcome (follow-up 1 years)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	23	12	-	MD 2 higher (5.92 lower to 9.92 higher)	⊕OOO VERY LOW	IMPORTANT
Quality of Life, SF-36 physical summary (0-100), high is good outcome (follow-up 1 years)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	23	12	-	MD 7 lower (13.85 to 0.15 lower)	⊕⊕OO LOW	IMPORTANT
Quality of Life, SF-36 VAS (0-100), high is good outcome (follow-up 1 years)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	20	12	-	MD 7 lower (27.49 lower to 13.49 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[3]Control arm had zero events.

Table 12: Clinical evidence profile: Decompressive hemicraniectomy vs medical treatment for those over 60yrs

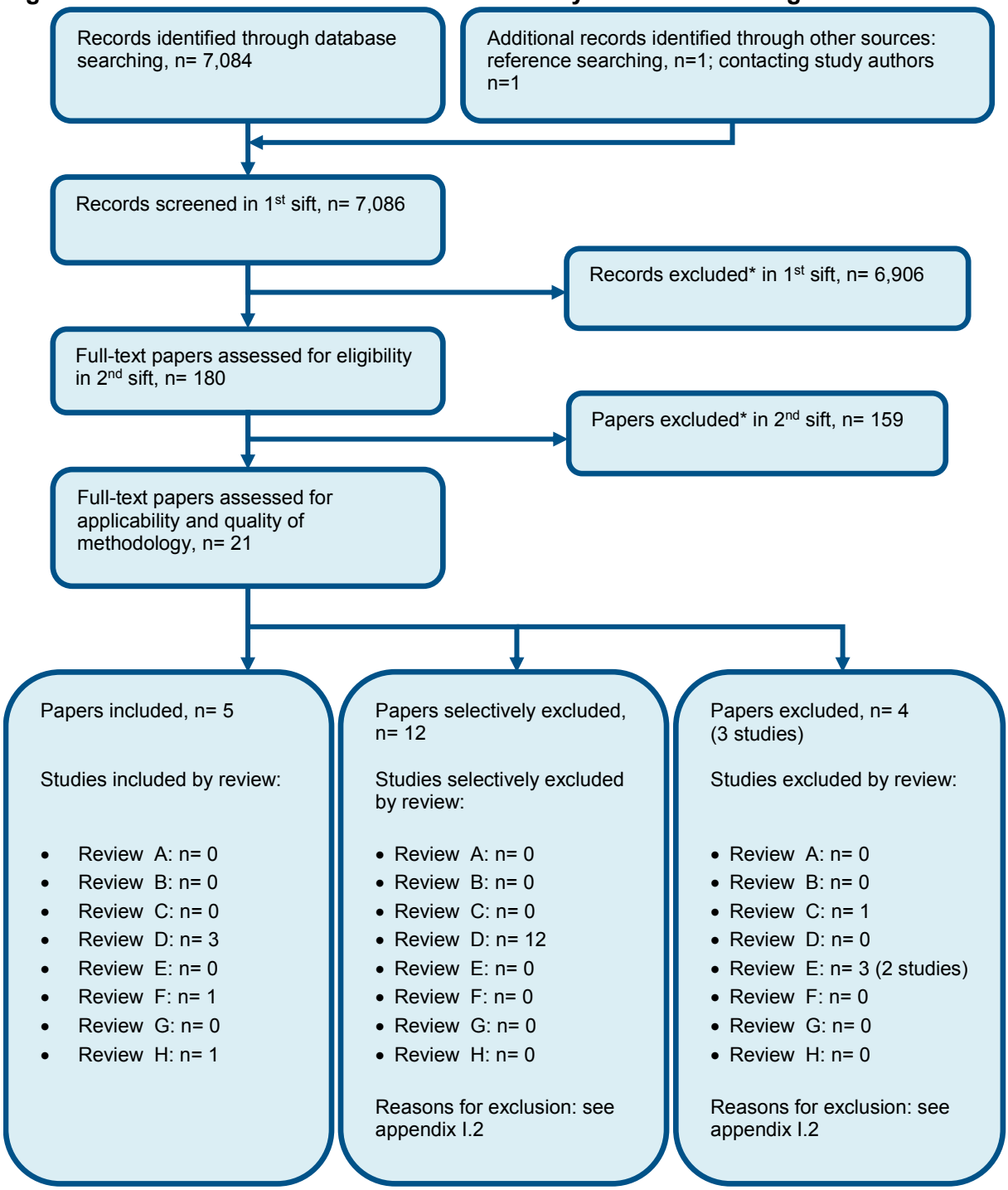
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Decompressive Hemicraniectomy**	**Medical Treatment**	**Relative (95% CI)**	**Absolute**		
Mortality, 6 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	2/16 (12.5%)	60.9%	RR 0.20 (0.05 to 0.8)	487 fewer per 1000 (from 122 fewer to 579 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Mortality, 1 year												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	29/74 (39.2%)	75.8%	RR 0.52 (0.39 to 0.7)	364 fewer per 1000 (from 227 fewer to 462 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Functional outcomes, 6 months, score of 0-3 on mRS scale (range: 0-6, high is poor outcome)												

2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[1]	none	5/65 (7.7%)	2/76 (2.6%)	RR 2.45 (0.55 to 10.91)	23 more per 1000 (from 7 fewer to 159 more)	⊕OOO VERY LOW	CRITICAL
Functional outcomes, 1 year, score of 0-3 on mRS scale (range: 0-6, high is poor outcome)												
3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	10/76 (13.2%)	3/89 (3.4%)	RR 3.18 (1.03 to 9.83)	100 more per 1000 (from 10 more to 180 more)[4]	⊕⊕OO LOW	CRITICAL
Quality of Life, 1 year, EQ-5D (Better indicated by higher values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	42	58	-	MD 0.10 higher (0 to 0.2 higher)	⊕⊕OO LOW	IMPORTANT
Quality of Life, 1 year, EQ-5D, visual analogue scale (Better indicated by higher values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	42	57	-	MD 16.40 higher (6.54 to 26.26 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively.
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[4] Calculated from risk difference.

Appendix G: Health economic evidence selection

Figure 15: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 13: Studies excluded from the clinical review

Study	Exclusion reason
Alexander 2016[1]	Incorrect study design. Systematic review with references checked.
Ayling 2018[2]	Incorrect study design. Systematic review with no RCTs.
Back 2015[3]	Meta-analysis with references checked.
Cho 2003[5]	Incorrect comparison.
Delgado-López 2004[9]	Not in English.
Dhand 2014[10]	Inappropriate comparison. Incorrect interventions. Correspondence.
Elsawaf 2018[11]	Incorrect comparison
Georgiadis 2002[13]	Incorrect interventions
Geurts 2013[14]	Follow up study
Gupta 2004[15]	Incorrect interventions. Inappropriate comparison. Systematic review: study designs inappropriate.
Hofmeijer 2008[16]	Abstract only
Inamasu 2013[19]	Incorrect study design. Retrospective.
Juttler 2011[20]	Incomplete study. Awaiting their results.
Kamran 2017[23]	Incorrect study design. Retrospective.
Khoozestan 2012[24]	Incorrect study design. Protocol.
Li 2017[25]	Incorrect study design. Systematic review.
Lin 2016[26]	Incorrect study design. NRS.
Lu 2014[27]	Incorrect study design. Systematic Review.
Lucas 2012[28]	Incorrect study design. Observational.
Macleod 2006[29]	Incorrect study design. Protocol.
McKenna 2012[30]	Inappropriate comparison.
Mohan Rajwani 2017[31]	Incorrect study design. Systematic review
Neugebauer 2012[33]	Incorrect study design. Protocol.
Omay 2013[34]	Incorrect study design. RCTs obtained.
Pledl 2016[36]	Incorrect study design. Retrospective.
Schwab 1995[38]	Not in English.
Sengeze 2014[39]	Incorrect study design. NRS.
Streib 2016[41]	Meta-analysis with references checked.
Vahedi 2004[43]	Incorrect study design. Trial record
Vahedi 2005[45]	Incorrect study design. Abstract
Vahedi 2007[44]	Meta-analysis with references checked.
Vahedi 2009[42]	Incorrect study design. Review
Van Middelaar 2015[47]	Incorrect study design. Systematic review with not solely RCTs.
Vibbert 2010[48]	Incorrect study design. Review
Worp 2006[49]	Incorrect study design. Protocol
Yang 2015[50]	Systematic review with references checked.

1

Appendix I: Health economic evidence tables

Study	Hofmeijer, 2013 [18]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Within-trial analysis (RCT) with Markov model post-trial extrapolation **Approach to analysis:** Within-trial analysis: For utility values, SF-6D was used, with linear interpolation used to calculate area under the curve. Resource use was based on case record files and outpatient department and general practitioner visits were obtained retrospectively. Post-trial extrapolation: Patients enter the Markov model in one of seven health states based on their mRS score at 3 years (mRS 0,1,2,3,4,5 and death) and remain in health	**Population:** Adult patients ≤60 years with space-occupying hemispheric infarction, within 48 hours of stroke onset **Cohort settings:** n: 39 (best medical treatment: n=18, surgical decompression: n=21) Start age: best medical treatment:47 (SD 11), surgical decompression: 52 (SD 6) Male: 54% (best medical treatment: 44%, surgical decompression: 62%) **Intervention 1:** Best medical treatment **Intervention 2:** Surgical decompression	**Three year total costs (mean per patient):** Intervention 1: £14,062 Intervention 2: £120,530 Incremental (2−1): £106,468 (95% CI: £61,186-£151,499; p=NR) **Lifetime total costs (mean per patient):** Intervention 1: £16,740 Intervention 2: £223,482 Incremental (2−1): £206,742 (95% CI: NR; p=NR) **Currency & cost year:** 2009 euros (presented here as 2009 UK pounds[(b)]) **Cost components incorporated:** Surgical decompression. Inpatient care: (high-care unit, stroke unit (academic	**Three year QALYs (mean per patient):** Intervention 1: 0.3 Intervention 2: 1.3 Incremental (2−1): 1.0 (95% CI: 0.6-1.4; p=NR) **Lifetime QALYs (mean per patient):** Intervention 1: 3.2 Intervention 2: 7.4 Incremental (2−1): 4.2 (95% CI: NR; p=NR)	**Three year ICER (Intervention 2 versus Intervention 1):** £106,468 per QALY gained (da) 95% CI: NR **Lifetime ICER (Intervention 2 versus Intervention 1):** £49,224 per QALY gained (da) 95% CI: NR **Analysis of uncertainty:** Bootstrapping generated 2000 replications of the three-year ICER. Surgical decompression was found to be cost effective at an 80,000 euro per QALY gained cost effectiveness threshold in 2% of estimates. No other sensitivity analyses reported.

state at 3 years until death. Cycle lengths NR. Hazard ratios for mortality after stroke for each mRS score are applied to age and sex specific death rates. No recurrent stroke. **Perspective:** Dutch societal perspective **Time horizon/Follow-up]:** 3 years (within-trial analysis) and lifetime (post-trial extrapolation) **Treatment effect duration:**(a) 3 years **Discounting:** Costs: NR; Outcomes: NR		or general), rehabilitation centre, nursing home. Consultations/visits: outpatient department, general practitioner, home visit by general practitioner		
Data sources				
Health outcomes: Treatment effects and baseline risks from HAMLET RCT. [14] **Quality-of-life weights:** SF-6D derived from SF-36 used for each patient up to year 3. For lifetime, HAMLET data used to year 3, then utility weights for health states mRS 0-3 and 4-5 were derived from a systematic review. [37] **Cost sources:** 2009 Dutch Diagnosis-Treatment-Combination prices, Dutch Manual for Costing Research. For lifetime, costs obtained from the literature. [4]				
Comments				
Source of funding: HAMLET trial funded by Dutch Heart Foundation. **Limitations:** Treatment effects derived from HAMLET trial only, which reported less favourable outcomes for decompressive surgery compared to other trials. Outpatient department and general practitioner resource use obtained retrospectively. Within-trial utilities elicited using SF-6D. Discounting of costs and outcomes NR for post-trial Markov model. Recurrent stroke not modelled. Cycle lengths of Markov model NR. Sensitivity analysis not reported for lifetime ICER. **Other:**				
Overall applicability: Partially applicable(c) **Overall quality:** Potentially serious limitations(d)				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost–utility analysis; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; NR: not reported; mRS: modified Rankin Scale; QALYs: quality-adjusted life years; RCT: randomised controlled trial; SD: standard deviation; SF-36: short-form health survey 36-item; SF-6D: medical outcomes study 36-item short-form health survey- 6 dimension.

(a) A Markov model is used to extrapolate the treatment effect beyond the treatment effect duration (3 years) to the lifetime horizon.

(b) Converted using 2009 purchasing power parities[35]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

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