Canadian Stroke Best Practices

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Acute Stroke Management Evidence Tables

Early Management of Patients Considered for Hemicraniectomy

Jean-Martin Boulanger and Kenneth Butcher (Writing Group Chairs)
on Behalf of the Canadian Stroke Best Practice Recommendations
ACUTE STROKE MANAGEMENT Writing Group

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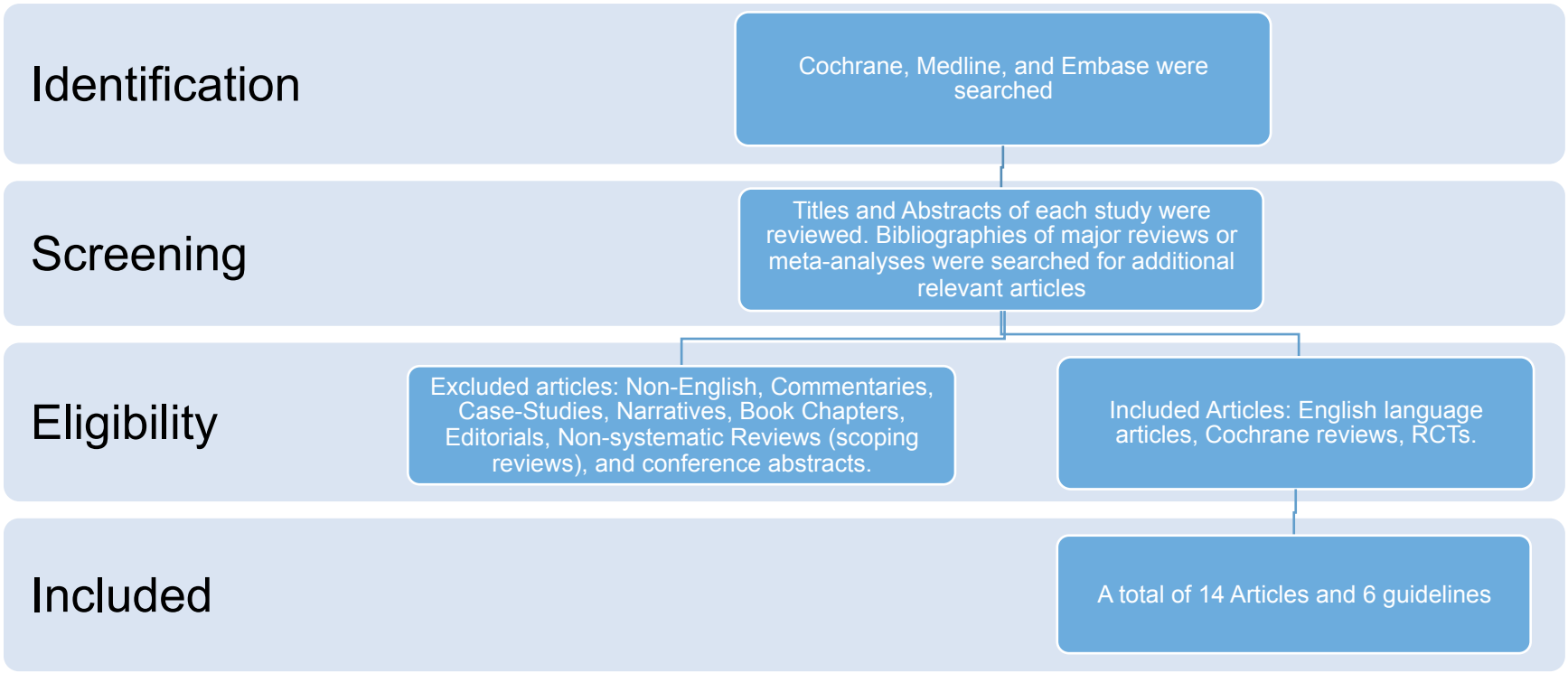
Search Strategy



Cochrane, Medline, and Embase were searched using the terms (“stroke” and “hemicraniectomy”). The title and abstract of each article was reviewed for relevance. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review. A total of 14 articles and 6 guidelines were included and were separated into categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL; on behalf of the American Heart Association Stroke Council. **2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke.* 2018; Mar;49(3):e46-e110** **(selected)**	5.1. Cerebellar and Cerebral Edema 4. Patients with large territorial supratentorial infarctions are at high risk for complicating brain edema and increased intracranial pressure. Discussion of care options and possible outcomes should take place quickly with patients (if possible) and caregivers. Medical professionals and caregivers should ascertain and include patient-centered preferences in shared decision making, especially during prognosis formation and considering interventions or limitations in care. Class I; LOE C-EO. 5. Patients with major infarctions are at high risk for complicating brain edema. Measures to lessen the risk of edema and close monitoring of the patient for signs of neurological worsening during the first days after stroke are recommended. Early transfer of patients at risk for malignant brain edema to an institution with neurosurgical expertise should be considered. Class I; LOE C-LD. 6. In patients ≤60 years of age with unilateral MCA infarctions who deteriorate neurologically within 48 hours despite medical therapy, decompressive craniectomy with dural expansion is reasonable because it reduces mortality by close to 50%, with 55% of the surgical survivors achieving moderate disability (able to walk) or better (mRS score 2 or 3) and 18% achieving independence (mRS score 2) at 12 months. Class IIa; LOE A. 7. In patients >60 years of age with unilateral MCA infarctions who deteriorate neurologically within 48 hours despite medical therapy, decompressive craniectomy with dural expansion may be considered because it reduces mortality by close to 50%, with 11% of the surgical survivors achieving moderate disability (able to walk [mRS score 3]) and none achieving independence (mRS score ≤2) at 12 months. Class IIb; LOE B-R. 8. Although the optimal trigger for decompressive craniectomy is unknown, it is reasonable to use a decrease in level of consciousness attributed to brain swelling as selection criteria. Class IIa; LOE A.
Stroke Foundation. Clinical Guidelines for Stroke Management 2017. Melbourne Australia. (Part 3)	Strong recommendation Selected patients aged 60 years and under with malignant middle cerebral artery territory infarction should undergo urgent neurosurgical assessment for consideration of decompressive hemicraniectomy. When undertaken, hemicraniectomy should ideally be performed within 48 hours of stroke onset. Weak recommendation New Decompressive hemicraniectomy may be considered in highly selected stroke patients over the age of 60 years, after careful consideration of the pre-morbid functional status and patient preferences. Weak recommendation AGAINST Corticosteroids are not recommended for management of stroke patients with brain oedema and raised intracranial pressure.
Intercollegiate Stroke Working Party. Royal College of Physicians. National Clinical guidelines for stroke. 5th Edition 2016, Edinburgh,	Patients with middle cerebral artery (MCA) infarction who meet the criteria below should be considered for decompressive hemicraniectomy. Patients should be referred to neurosurgery within 24 hours of stroke onset and treated within 48 hours of stroke onset: − pre-stroke modified Rankin Scale score of less than 2;

Guideline	Recommendations
Scotland	− clinical deficits indicating infarction in the territory of the MCA; − National Institutes of Health Stroke Scale (NIHSS) score of more than 15; − a decrease in the level of consciousness to a score of 1 or more on item 1a of the NIHSS; − signs on CT of an infarct of at least 50% of the MCA 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 cubic centimetres on diffusion-weighted MRI.
Kim DH, Ko SB, Cha JK, et al. **Updated Korean Clinical Practice Guidelines on Decompressive Surgery for Malignant Middle Cerebral Artery Territory Infarction.** ***Journal of Stroke* 2015;17(3):369-376.**	Revised Recommendation of the Korean Clinical Practice Guidelines for Stroke 1. Decompressive hemicraniectomy within 48 hours of stroke onset is recommended in patients with malignant MCA infarction who are 60 years or younger (level of evidence Ia, grade of recommendation A) or older than 60 years (level of evidence Ib, grade of recommendation A) and meet all of the following criteria: (1) clinical symptoms and signs of infarction in the MCA territory, (2) NIHSS score of 16 points or more, (3) decrease in level of consciousness as defined by an NIHSS item 1a score of 1 point or more, and (4) infarction affecting more than 50% of the total MCA territory on CT or an infarct volume greater than 145 cm3 on diffusion-weighted MRI. 2. The physician should inform the patient's family or guardian(s) of the potential outcome of survival with severe disability and lack of evidence of the benefit of surgery on the quality of life (grade of recommendation GPP).
Wijdicks EFM, Sheth KN, Carter BS, Greer DM, Kasner SE, Kimberly WT, Schwab S, Smith EE, Tamargo RJ, Wintermark M; on behalf of the American Heart Association Stroke Council. **Recommendations for the management of cerebral and cerebellar infarction with swelling: a statement for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke 2014*;45(4):1222-38.**	In patients <60 years of age with unilateral MCA infarctions that deteriorate neurologically within 48 hours despite medical therapy, decompressive craniectomy with dural expansion is effective. The effect of later decompression is not known, but it should be strongly considered (Class I; Level of Evidence B). Although the optimal trigger for decompressive craniectomy is unknown, it is reasonable to use a decrease in level of consciousness and its attribution to brain swelling as selection criteria (Class IIa; Level of Evidence A). 3. The efficacy of decompressive craniectomy in patients >60 years of age and the optimal timing of surgery are uncertain (Class IIb; Level of Evidence C). 4. Suboccipital craniectomy with dural expansion should be performed in patients with cerebellar infarctions who deteriorate neurologically despite maximal medical therapy (Class I; Level of Evidence B).
Institute for Clinical Systems Improvement (ICSI). Diagnosis and treatment of ischemic stroke. **Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2010 Jun. 70 p. [190 references]**	Early Treatment of Ischemic Brain Edema Although ischemic brain swelling typically peaks between three and five days after stroke onset, marked early swelling (in the first 24 to 48 hours) causing mass effect and tissue shift can occur in the most severe cases ("malignant" ischemic brain edema). Low attenuation changes exceeding two-thirds of the middle cerebral artery territory and large areas of hypoperfusion on perfusion scans (CT perfusion or magnetic resonance perfusion) on initial radiological evaluation are associated with high risk of developing malignant brain edema. Patients with these features should be strictly monitored with serial neurological examinations, ideally in a stroke unit. Repeating CT scan of the brain to evaluate for progression of regional mass effect is indicated if the patient develops any signs of neurological deterioration. The value of serial CT scans of the brain in the

Guideline	Recommendations
	absence of clinical changes remains to be established. Decompressive hemicraniectomy with durotomy improves survival and functional outcome [M]. The optimal timing of the procedure is not well established, but most experts recommend early intervention. Improvement in functional outcome has been shown only for patients 60 years old or younger. Osmotherapy (mannitol 20% or hypertonic saline) may be used to treat ischemic brain edema, but there is very limited data supporting its value [R]. Mannitol 20% is usually administered as a bolus of 1 to 2 g/kg of body weight followed by repeated boluses as needed for neurological decline or scheduled doses of 0.25 to 0.5 g/kg every four to six hours. In patients with established signs of herniation, a rescue dose of 23.4% of saline solution (30 cc) may be useful [D]. Hyperventilation should be avoided except for mild to moderate hyperventilation (target pCO2 30 to 34 mm Hg) for brief periods of time because of the risk of exacerbating ischemia by causing vasoconstriction.

Evidence Table

Decompressive Hemicraniectomy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic Reviews & Meta-analyses					
Qureshi et al. 2016 **USA** **Meta-analysis**	NA	7 RCTs (n=341) that included patients with ischemic stroke randomized to hemicraniectomy within 7 days of symptom onset. Mean/median age ranged from 43.2 to 70 years. Patients were randomized within 72 hours of symptom onset in 5 trials.	Studies compared decompressive surgery plus medical treatment to medical treatment only.	**Primary outcome:** Favourable outcome (mRS 0-3) at 6-12 months' post randomization **Secondary outcomes:** mRS scores of 0-4, and survival at 6-12 months	The odds of a favourable outcome were increased significantly for the hemicraniectomy patients (OR=2.04, 95% CI 1.03-4.02, p=0.04) The odds of survival were increased significantly for the hemicraniectomy patients (OR=5.56, 95% CI 3.40-9.08, p<0.001). The odds of a mRS score of 0-4 were increased significantly for the hemicraniectomy patients (OR=3.78, 95% CI 2.33-6.11, p<0.001)
Cruz-Flores et al. 2012 **UK** **Cochrane Review**	NA	3 RCTs (n=134) including patients ≤60 years with acute ischemic stroke and complicating cerebral edema evident on cerebral computed tomography and magnetic resonance imaging. Time window for intervention from stroke onset was 30 -36 hours in two trials (DECIMAL, DESTINY 1) and 96 hours in 1 trial (HAMLET). All 3 RCTs were stopped early.	Studies compared decompressive surgery plus medical treatment to medical treatment only.	**Primary Outcomes:** Death at the end of follow-up. **Secondary outcome:** Death or moderately severe disability (mRS > 3) at 6 and 2 months, death or severe disability (mRS > 4) at 12 months, Survival with severe disability (mRS 4 or 5) at 12 months.	Surgical decompression reduced the odds of death at the end of follow-up (OR=0.19, 95% CI 0.09 to 0.37, p<0.05). There were no significant differences between groups in the odds of death or moderately severe disability at the end of follow-up (OR=0.56, 95% CI 0.27 to 1.15). Surgical compression was associated with a significant reduction in the odds of death of severe disability at 12 months (OR=0.26, 95% CI 0.13 to 0.51). Surgical decompression was associated with a non-significant trend to survival with severe disability (OR=2.45, 95% CI 0.92 to 6.55, p<0.05).
Mc Kenna et al. 2012 **UK**	NA	Data representing 276 patients was obtained from 17 case series that used valid and reliable	Data was extracted and equally weighted and pooled. Comparisons were made with respect	Outcomes were dichotomized as 'good' vs. 'poor' (poor outcome= BI <60, mRS>3, GOS <4,	**Time 1:** Results from 14 studies (n=89) included. Higher mortality was observed for patients > 60 years of age (62.5%) compared to younger patients (35.1%; p<0.05, OR=3.0, 95% CI 1.3-7.6).

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Systematic Review		objective measures of functional outcome.	to 3 temporal post-stroke periods: 1. Outcome within 1-month post stroke (T1); 2. between 1 month and 6 months post-stroke (T2) and; 3. more than 6 months post stroke (T3).	death, or placement in an institution).	No other comparisons were significant. **Time 2:** Results from 14 studies (n=139) included. Higher mortality was observed for patients >60 years of age compared to younger patients (31.8% vs. 8.4%; p<0.001, OR=5.0, 95% CI 1.9 to 13.3). Patients >60 years of age were less likely to achieve a good outcome compared to younger patients (9.1% vs. 49.5%; p<0.001, OR=9.8, 95% CI 3.3 to 29.4). **Time 3:** Results from 10 trials (n=115) included. Higher mortality was observed for patients >60 years of age compared to younger patients (13.3% vs. 2.4%; p<0.05, OR=6.0, 95% CI 1.1 to 36.9). Patients >60 years of age were less likely to achieve a good outcome compared to younger patients (20% vs. 64.7%%; p<0.05, OR=7.0, 95% CI 2.7 to 20.0). The odds of having a poor outcome were 2.5 times higher for female as compared to male patients (95% CI 1.0 to 6.1).
Vahedi et al. 2007a **France** **Meta-analysis**	NA	3 RCTs (n=93) comparing decompressive surgery plus medical management (n=51) and medical management only (n=42) within 48 hours of symptom onset. Included patients were 18-60 years of age with acute ischemic stroke and complicating cerebral edema.	Absolute risk reductions and the number needed to treat (NNT) were calculated. Individual patient data from the DECIMAL, DESTINY, and the ongoing HAMLET trails were pooled. Protocol for the pooled analysis was designed prospectively whilst the HAMLET trial was still recruiting patients.	**Primary Outcome**: Score on the modified Rankin Scale (mRS) at 1 year, (favourable=0-4 vs. unfavourable=5-6). **Secondary Outcomes**: Death at 1 year, mRS at 1 year (mRS=0-3 vs. 4-6). Subgroup analyses were conducted according to the following predefined subgroups: Age (<50 vs. ≥50 years of age), time to randomization (<24 vs. ≥24 hours), presence of aphasia.	**Primary outcome:** 75% (38/51) of patients in the surgical arm vs. 24% (10/42) in the control group had a favourable outcome at 1-year. ARR=51%, 95% CI 34 to 69%. **Secondary outcomes:** 22% (11/51) of patients in the surgical arm vs. 71% (30/42) in the medical arm died within 1-year. ARR=50.3%, 95% CI 33 to 67%. mRS at 1 year: 43% (22/51) of patients in the surgical arm vs. 21% (9/42) in the control arm had a mRS=0-3 at 1-year. ARR=23%, 95% CI 5 to 41. **Numbers Needed to treat (NNT):** Survival (mRS ≤4): NNT=2 (95% CI 1.5 to 3). Survival (mRS ≤3): NNT=4 (95%CI 2 to 22). Survival (all): NNT=2 (95% CI 1.5 to 3). Subgroup analyses showed non-significant subgroup-treatment effect interactions.

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Gupta et al. 2004 **US** **Systematic Review**	NA	12 studies were included, representing a total of 138 patients. Mean patient age was 50 years. Mean time to surgery = 59.3 hours (range: 8 to 456 hours).	The following data was required to be eligible for inclusion: Age, side of infarct, and functional outcome (BI, mRS, Glasgow Outcome Scale (GOS) or clinical description) at least 4 months following hemicraniectomy.	**Outcomes:** 1 = Functional independence (BI >90; mRS 0 to 1; or GOS 5), 2 = Mild to moderate disability (BI 60 to 85; mRS 2 to 3; or GOS 4), 3 = Severe disability (BI <60; mRS 4 or 5; or GOS 2 to 3), 4 = Death. Outcomes were also classified as 'good' (functional independence or mild to moderate disability) vs. 'poor' outcomes (severe disability or death).	Overall mortality was 24%. 58% (80/138) of patients had poor outcomes. **Age comparison:** 80% (60/75) of patients age >50 years had a poor outcome compared to 32% (20/63) of patients ≤50 years of age (p<0.001). **Other comparisons:** The timing of surgery, hemisphere involvement, presence of signs of herniation before surgery, and involvement of other vascular territories were not found to significantly impact outcomes.
Clinical Trials					
Juttler et al. 2014 **Germany** **RCT** ***Decompressive Surgery for the Treatment of Malignant Infarction of the MCA (DESTINY II)***	Concealed Allocation: ☒ Blinding: Patient:☒ Assessor ☑ ITT: ☑	112 patients from 13 sites, ≥61 years admitted with unilateral MCA infarction within 48 hours of symptom onset with NIHSS scores of >14 (infarction in non-dominant hemisphere) or 19 (dominant hemisphere), with good premorbid function (mRS score 0-1). Median age was 70 years, 50% were male. Median baseline NIHSS score was 20.	Patients were randomized to a conservative treatment group (n=63) or a surgical intervention group with hemicraniectomy (diameter ≥12 cm and duroplasty, n=49) within 6 hours of group assignment	**Primary outcome:** Survival without severe disability (mRS scores of 0-4) at 6 months **Secondary outcomes:** Survival, NIHSS score, mRS score, Quality of Life (SF-36), Hamilton Depression Rating Scale scores at 12 months	Patient recruitment ceased after 82 patients on the advice of the DSMB. A significantly higher proportion of patients in the surgical group were alive and living without severe disability at 6 months (38% vs.18%, OR=2.91, 95% CI 1.06-7.49, p=0.04). No patient in either group had mRS score of 0-2 at 6 or 12 months. A significantly higher percentage of patients in the surgical group had mRS scores of 3-4 (38% vs. 16%) and a significantly lower percentage had mRS scores of 5-6 (62% vs. 84%, p<0.001 ITT analysis). On ITT analysis patients in the surgical group fared significantly better on all secondary outcomes compared with those in the control group. There were no significant differences between groups when analyses were restricted to surviving patients. There was a total of 20 deaths in the surgical group and 47 in the control group. 77% of the control group deaths occurred within the first 14 days (vs. 25% in the surgical group). Sepsis (25%)

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					and herniation (20%) were the most common causes of death in patients in the surgery group.
Frank et al. 2014 **USA** **Pilot RCT** ***Hemicraniectomy and Durotomy Upon Deterioration From Infarction-Related Swelling Trial (HeADDFIRST)***	Concealed Allocation: ☒ Blinding: Patient ☒ Assessor ☑ ITT: ☒	25 patients aged 18-75 years, with ischemic stroke involving at least 50% of MCA territory on CT, with NIHSS score≥18, and responsive to motor stimuli. Mean age was 55 years, 62% were male.	Patients who deteriorated within 96 hours of stroke onset with mass effect, were randomized to hemicraniectomy (n=14) with duroplasty or standard medical treatment (n=10) groups	**Primary outcome:** Survival at 21 days **Secondary outcomes:** Death at 6-months and one-year, functional outcome at 12 months	21-day mortality was 21% (surgical group) vs. 40% (medical group). Mean difference=19%, 95% CI -13% to 50%). At 6 months, mortality was 36% (surgical group) and 40% (medical group).
Zhao et al. 2012 **China** **RCT**	Concealed Allocation: ☒ Blinding: Patient ☒ Assessor ☑ ITT: ☑	47 patients, aged 18–80 years, with ischemic signs on CT involving at least 2/3 of the MCA territory, with decreased LOC and motor score on GCS of ≤9, who could be randomized within 48 hours of stroke onset. Median age was 64 years, 72% were male. Median GCS scores were 8 and 8.5.	Patients were randomized to hemicraniectomy (n=24) with duroplasty or standard medical treatment (n=23) groups	**Primary outcome:** Favourable outcome (mRS 0-4) and poor outcome (mRS 5-6) at 6 months **Secondary outcomes:** 6 and 12-month mortality, favourable and poor outcome at 1 year	The trial was stopped prematurely after the 3rd interim analysis, demonstrating the superiority of DHC. 47 patients had been recruited of the 110, planned. A significantly lower proportion of surgical patients were dead at 6 and 12 months (12.5 vs. 60.9%, ARR=48.4%, 95% CI 24.4-72.3%, p=0.001, NNT=2; 16.7 vs. 69.6%, ARR=52.9%, 95% CI 28.9-76.9%, p<0.001, NNT=2, respectively) A significantly lower proportion of surgical patients had a poor outcome at 6 months and 12 (33.3 vs. 82.6%, ARR=49.3%, 95% CI 29.4-72.7%, p=0.001, NNT=2; 25.0 vs. 87.0%, ARR=25.0 vs. 87.0%, ARR=62.0, 95% CI 39.8-84.1%, p<0.001, NNT=2, respectively). The proportion of patients with an mRS score >3 at 6 and 12 months did not differ significantly between groups. The results of the primary and secondary outcomes were similar in the subgroup of 29 patients >60 years.
Hofmeijer et al. 2009	Concealed Allocation: ☑	64 patients 18-60 years of age, admitted with	Patients were randomized to receive	**Primary Outcome**: Functional outcome,	**Primary outcomes:** 75% (24/32) of patients in the surgical arm vs. 75%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Geurts et al. 2013 (3-year outcomes) **Multicenter, open RCT** **Netherlands** ***Hemicraniectomy After MCA infarction with Life-threatening Edema Trial (HAMLET)***	Blinding: Patient ☒ Assessor ☑ ITT: ☑	acute MCA ischemic stroke, with NIHSS score > 16 for right-sided lesions, or > 21 for left-sided lesions; with gradual decrease in consciousness GCS score <13 for right-sided lesions, or an eye and motor score of 9 or lower for left-sided lesions and hypodensity on CT involving ≥ 2/3 of MCA territory, and space-occupying edema formation.	surgical decompression (n=21) or best medical treatment (n=18) within 96 hours of stroke onset. This trial was terminated after recruitment of 64 patients and after 50 patients assessed at the 1-year follow-up due to futility.	assessed with the modified Rankin Scale (mRS=0-1 vs. 4-6) at 1 year. **Secondary Outcomes**: Mortality rate at 1-year, functional outcome (Barthel Index; mRS=0-4 and 5-6), depression symptoms (Montgomery and Asberg Depression Rating Scale), Quality of life (SF-36). Subgroup analyses were performed according to age, presence of aphasia and time from stroke onset to study randomization.	(24/32) in the medical arm obtained an mRS=4-6 (ARR=0%, 95% CI -21 to 21, p=1.00). **Secondary outcomes;** Mortality at 1 year: 22% (7/32) in surgical arm vs. 59% (19/32) in the medical arm (ARR=38%, 95% CI 15 to 60, p=0.002). Functional outcome: 41% (13/32) of patients in the surgical arm vs. 59% (19/32) in the medical arm obtained an mRS=5-6 (ARR=19%, 95% CI -5 to 43, p=0.13). Those who received decompressive hemicraniectomy had a significantly lower physical summary score on the SF-36 QoL scale compared with those who received medical care only (mean score= 29 [surgery] vs. 36 [medical treatment only]; mean difference = 8, 95% CI -14 to -1, p=0.02). No significance differences were found with respect to the Barthel Index, depression symptoms, or QOL at 1 year. **Subgroup analyses**: Patients randomized < 48 hrs after stroke onset showed benefit of surgical decompression. Functional outcome: 10/21 (48%) in surgical arm vs. 14/18 (78%) in medical arm had mRS scores of 5-6 (ARR=30%, 95% CI 1 to 59). Mortality: 4/21 (19%) in surgical arm vs. 14/18 (78%) in the medical arm died within 1 year (ARR=59%, 95% CI 33 to 84). For patients randomized >48 hrs after stroke onset, there was no effect of surgical decompression on any outcome measure. **3-year outcomes:** Mean duration of follow-up was 3.1 years. A significantly lower percentage of patients in the surgical group had died (26% vs. 63%, p=0.002).

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					There were no other significant differences between groups (functional outcome, SF-36 scores, symptoms of depression).
Juttler et al. 2007 **Germany** **RCT** ***Decompressive Surgery for the Treatment of Malignant Infarction of the MCA (DESTINY)***	Concealed Allocation: ☒ Blinding: Patient:☒ Assessor ☒ ITT: ☑	32 patients 18-60 years of age (recruited from 6 centers) with an onset of symptoms >12 and <36 hours before a possible surgical intervention. Malignant MCA infarction was defined as per the following criteria: NIHSS >18 for non-dominant and >20 for dominant hemisphere (including a score of 1 or greater for item 1a) and CT involvement of at least two-thirds of the MCA territory (including at least part of the basal ganglia).	Patients were randomized to either surgical plus medical treatment or to conservative medical treatment only. The trial was terminated after a significant between group difference, favouring the surgical group, was detected at 30-days.	**Primary Outcome**: Functional outcome (mRS=0-3 vs. 4-6) at 6 months. **Secondary Outcomes**: Mortality at 30 days, functional outcome (mRS=0-4 vs. 5-6) at 12 months, Quality of life (SF-36 and the Stroke Impact Scale), Aphasia recovery (Aachen Aphasia Test).	Functional outcome at 6 months: 47% of patients in the surgical arm versus 27% of patients in the conservative medical arm had mRS scores of 0-3 (*p*=0.23; OR=2.44, 95% CI 0.55 to 10.83). Mortality at 30 days: 88% (15/17) surgical arm vs. 47% (7/15) in the conservative medical treatment arm survived at 30 days (p=0.02; OR=6.4, 95% CI 1.35 to 29.2) Functional outcome at 12 months: 77% in the surgical arm versus 33% in the conservative medical treatment arm achieved an mRS = 0-4 (p=0.01; OR=6.50, 95%CI 1.38 to 30.68).
Vahedi et al. 2007b **France** **RCT** ***The DEcompressive Craniectomy In MALignant MCA Infarction (DECIMAL) Trial***	Concealed Allocation: ☒ Blinding: Patient:☒ Assessor ☑ ITT: ☑	38 patients 18-55 years of age from 7 stroke centers. All patients completed the study follow up. All patients underwent magnetic resonance diffusion weighted imaging MR DWI	Patients were randomized within 24 hours of a malignant MCA infarction to receive surgical decompression and medical treatment (n=20) or medical treatment only (n=18) The data safety monitoring committee terminated the trial due to a high difference in mortality and slow recruitment.	**Primary Outcomes**: Functional outcome (mRS=0-3 vs. 4-6) at 6 months. **Secondary Outcomes**: Survival at 12 months, functional outcome at 12 months (mRS≥3, BI> 85), National Institutes of Stroke Scale (NIHSS), QOL at 12 months (assessed by the French version of the Stroke Impact Scale 2.0) Correlation analyses were performed on subgroups: DWI infarct volume, age and hemispheric dominance	**Primary outcome:** Functional outcome: 25% (5/20) in surgical arm vs. 5.5% (1/18) in medical arm obtained an mRS = 0-3, p=0.18. *Non-dichotomized mRS score comparing surgical and medical arms*: At 6 months, p=0.011; At 12 months. p=0.002 **Secondary outcome:** Survival rate: 75% (15/20) in the surgical arm vs. 22.2% (4/18) in medical arm survived 12 months (ARR=52.8%, p<0.001). Functional outcome: 50% (10/20) in surgical arm vs. 22.2% (4/18) in medical arm obtained an mRS = 0-3 at 12 months, p=0.1. 65% (13/20) in surgical arm vs. 22% (4/18) in the

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					medical arm obtained an mRS = 0-4 at 6 months, p=0.001. 75% (15/20) in the surgical arm vs. 22.2% (4/18) in the medical arm obtained an mRS < 5 at 12 months; p=0.002. Barthel Index: 33.3% (5/15) in the surgical arm vs. 50% (2/4) in the medical arm achieved BI >85 at 12 months, p>0.05. **Subgroup correlation analyses:** DWI infarct volume and mRS at 6-months follow up: Spearman correlation coefficient R=0.38, p=0.09 (surgical arm); R=0.52, p=0.03 (medical arm). Younger age and mRS at 6-months: Spearman correlation coefficient R=0.64, p=0.002 (surgical arm); R=0.1, p=0.69 (medical arm).

Corticosteroids

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Sandercock & Soane 2011 **UK** **Cochrane Review**	NA	8 RCTs (n=466) that included patients with confirmed acute ischemic stroke. Mean age ranged from 66 to 75 years, 50% were men. Patients were randomized within 48 hours of symptom onset in 7 trials.	Patients were randomized to receive corticosteroid (intravenous, intra-muscular or oral) vs. control (placebo).	**Primary outcome:** Death during scheduled follow-up **Secondary outcomes:** Functional outcome, adverse events	Corticosteroids use was associated with a non-significant decrease in the odds of death within one year (OR=0.87, 95% CI 0.57-1.34, p=0.53) and one month (OR=0.97, 95% CI 0.63-1.47, p=0.87). Pooled analyses were not possible for any other outcomes.

Reference List

Cruz-Flores S, Berge E, Whittle IR. Surgical decompression for cerebral oedema in acute ischaemic stroke. *Cochrane Database Syst Rev* 2012, Issue 1. Art. No.: CD003435. DOI: 10.1002/14651858.CD003435.pub2.

Frank JI, Schumm LP, Wroblewski K, et al. Hemicraniectomy and durotomy upon deterioration from infarction-related swelling trial: randomized pilot clinical trial. *Stroke* 2014;45(3):781-787.

Geurts M, van der Worp HB, Kappelle LJ, Amelink GJ, Algra A, Hofmeijer J: Surgical decompression for space-occupying cerebral infarction: outcomes at 3 years in the randomized HAMLET trial. *Stroke* 2013;44:2506-2508.

Gupta, R., Connolly, E. S., Mayer, S., & Elkind, M. S. Hemicraniectomy for massive middle cerebral artery territory infarction: a systematic review. *Stroke* 2004;*35:* 539-543.

Hofmeijer, J., Kappelle, L. J., Algra, A., Amelink, G. J., van, G. J., & van der Worp, H. B. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. *Lancet Neurol* 2009*; 8:* 326-333.

Inamasu, J., Kaito, T., Watabe, T., Ganaha, T., Yamada, Y., Tanaka, T. et al. (2013). Decompressive Hemicraniectomy for Malignant Hemispheric Stroke in the Elderly: Comparison of Outcomes between Individuals 61-70 and >70 Years of Age. *J Stroke Cerebrovasc Dis* 2013*;*22(8):1350-4.

Juttler, E., Schwab, S., Schmiedek, P., Unterberg, A., Hennerici, M., Woitzik, J. et al. Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial. *Stroke* 2007; *38,* 2518-2525.

Juttler E, Unterberg A, Woitzik J, Bosel J, Amiri H, Sakowitz OW, Gondan M, Schiller P, Limprecht R, Luntz S, Schneider H, Pinzer T, Hobohm C, Meixensberger J, Hacke W: Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. *N Engl J Med* 2014;370:1091-1100.

McKenna, A., Wilson, C. F., Caldwell, S. B., & Curran, D. Functional outcomes of decompressive hemicraniectomy following malignant middle cerebral artery infarctions: a systematic review. *Br.J Neurosurg 2012; 26:* 310-315.

Qureshi AI, Ishfaq MF, Rahman HA, Thomas AP. H.Hemicraniectomy versus conservative treatment in large hemispheric ischemic stroke patients: A meta-analysis of randomized controlled trials. *J Stroke Cerebrovasc Dis 2016*;25(9):2209-2214.

Sandercock PAG, Soane T. Corticosteroids for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2011, Issue 9. Art. No.: CD000064. DOI: 10.1002/14651858.CD000064.pub2.

Vahedi, K., Hofmeijer, J., Juettler, E., Vicaut, E., George, B., Algra, A. et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol* 2007*a; 6:* 215-222.

Vahedi, K., Vicaut, E., Mateo, J., Kurtz, A., Orabi, M., Guichard, J. P. et al. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). *Stroke* 2007*b; 38:* 2506-2517.

Zhao, J., Su, Y. Y., Zhang, Y., Zhang, Y. Z., Zhao, R., Wang, L. et al. Decompressive hemicraniectomy in malignant middle cerebral artery infarct: a randomized controlled trial enrolling patients up to 80 years old. *Neurocrit Care* 2012*; 17:*161-171.