UiT The Arctic University of Norway

Faculty of Health Sciences

# A population-based registry study of outcome after decompressive hemicraniectomy in patients with malignant cerebral infarction in Norway

**Pablo Anke**

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Supervisor: Tor Ingebrigtsen (IKM)
Co-supervisors: Ellisiv B. Mathiesen (IKM) and Lars K. Pedersen (UNN)

# Preface

This study is written as a fifth year master's thesis in medicine at the University of Tromsø (UiT).

In the process of finding the right project for my master's thesis, I contacted the Brain and Circulation Research Group at UiT to hear if they had any topic ideas as this is a research field that I find very interesting. I was thereafter introduced to the idea of performing a population-based study with data from the Norwegian Stroke Registry (NSR) on the topic of decompressive craniectomy.

A solid thank you goes to supervisor Tor Ingebrigtsen for good follow up and guidance throughout the work process. Further thank you goes to co-supervisors Ellisiv B. Mathiesen and Lars K. Pedersen for additional guidance and feedback.

**Pablo Anke**
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# Abstract

**Background and purpose:** In a small group of stroke patients, middle cerebral artery (MCA) thrombosis cause a large infarction, that can develop to become of space-occupying character, and eventually cause progressive neurological deterioration, cerebral herniation and death. Eight prospective randomized trials (RCTs) show that surgical treatment with decompressive hemicraniectomy (DHC) reduces both the mortality and the risk of a poor outcome if performed within 48 hours after symptom onset. Clinical quality registers are important for evaluation of the external validity of RCTs and the quality of recommendations based on the RCTs in clinical guidelines. Treatment data for DHC has been registered in the Norwegian Stroke Registry (NSR) since 2017, creating a unique opportunity to perform a descriptive study of the usage and outcomes after DHC and to compare these outcomes with those reported from the RCTs.

**Methods:** The study population was all stroke patients who had been treated with DHC in the Norwegian health care system and are registered in the NSR in the years of 2017-19. Variables were divided into the following three main categories; patient demographic data, treatment data, and outcome data after 3 months. The primary outcome measure was the modified Rankin scale (mRS) score measured at 3 months after surgery, dichotomized as favorable (mRS ≤ 3), and unfavorable (mRS > 3). Secondary outcome measures were mortality and residence.

**Results:** 68 (17 (25 %) women) patients with median age 57,5 (IQR 48,3-66,0) years underwent a DHC. The crude surgical rate was 0,43 per 100 000 population per year, with variation (range 0,29 – 1,40) between the four health regions. The proportion transferred from a local hospital to a university hospital for the operation was lower (50 %) than expected (68 %) based on the geographic distribution of residency. Median time from onset of symptoms to DHC was 34,3 (IQR 40,9) hours and the median NIHSS score on admission was 14,0 (IQR 11,0). The proportion with a favorable outcome (mRS score ≤3) after 3 months was 29,4%. Eight (11,8 %) patients died.

**Conclusion:** The low proportion of females, the geographic variation in surgical rates and the low proportion of inter-hospital transfers indicate inequalities in access to DHC. For patients who received the operation, the use was in accordance with recommendations in clinical guidelines, and the outcome was comparable with those reported from the RCTs.

# Abbreviations

MCA = Middle cerebral artery

DHC = Decompressive hemicraniectomy

NSR = Norwegian Stroke Registry (Norsk hjerneslagregister)

RCT = Randomized controlled trial

mRS = Modified Rankin scale

NICE = National Institute for Health and Care Excellence

AHA/ASA = American Heart Association/American Stroke Association

CT = Computer tomography

MRI = Magnetic resonance imaging

UNN = University Hospital of North Norway

REC = Regional Committee for Medical and Health Research Ethics

NIHSS = National Institutes of Health

# Background

The severe condition of stroke is the cause of 10 000-11 000 hospital admissions in Norway every year. It is a frequent cause of death, and it is the dominating cause of serious disability among the population (1).

In 85% of the patients the stroke is caused by thrombosis (1), most frequently of the middle cerebral artery (MCA). In a small patient group, the acute severity of the MCA infarction will further develop for it to become of space-occupying character, also referred to as a malignant MCA infarction. Progressive edema, raised intracranial pressure, and eventually cerebral herniation provides a high risk for neurological deterioration and death. For these patients, decompressive hemicraniectomy (DHC) is an alternative for treatment (2).

Evidence based recommendations for the use of treatments such as DHC can be found in clinical guidelines. Specific data about the actual practice is registered in clinical quality registries. Such registries are important for evaluating both the quality of clinical guidelines, and the external validity of the clinical studies on which the guidelines are based.

This thesis presents a population-based registry study of the use of DHC on stroke patients registered in the Norwegian Stroke Registry (NSR) in the years of 2017-2019.

**DHC as a treatment for malignant infarction**

Since the 1950s, DHC as we understand it today, has been studied as a treatment option in modern medicine for patients with hemispheric stroke of space-occupying character (2). The surgical technique itself is based on the principle that the skull is a non-expandable structure, no matter the degree of raised intracranial pressure. By removing a bone-flap of the skull accompanied by a duroplasty, an opening is made, causing decompression. The typical operation performed is a fronto-temporo-parietal DHC at the side of the infarction (2). The mortality of malignant infarction is around 80% without surgical intervention (3).

In 1974, Ivamoto and co-workers published a case report that included a review of DHC in 17 cases of cerebral infarction (4). In spite of their conclusion being that extensive ischemic stroke can cause significant cerebral edema and thus severe pressure effects, the authors highlighted that in the absence of a controlled trial, the benefits of DHC for cerebral infarctions are not conclusive. It was not before the 2000s that the first randomized controlled trials (RCTs) on DHC for anterior circulation stroke were finally conducted (2).

**Randomized controlled trials on DHC**

The patient outcome after DHC as treatment for MCA infarction has been studied in a total of eight RCTs. They collectively show that DHC performed within 48 h of stroke onset reduces both the mortality and the risk of a poor outcome (modified Rankin scale score of 4-6) compared to conservative (non-invasive) treatment, in patients with malignant MCA infarction. There is no evidence that DHC improves functional outcome when performed after 48 h, however the mortality is still reduced. Further, age ≤ 60 years is an independent predictor of favorable outcome (5, 6, 7, 8, 9, 10, 11, 12).

**Treatment recommendations on DHC in clinical guidelines**

The knowledge that is obtained from RCTs is important in the development of evidence-based treatment recommendations in clinical guidelines. The two most extensive clinical guidelines for acute stroke management of today, respectively from the National Institute for Health and Care Excellence (NICE) and the American Heart Association/American Stroke Association (AHA/ASA), still have a certain discrepancy when it comes to the criteria for the use of DHC as treatment for acute stroke (14, 15). The NICE-guidelines recommend that DHC is done within 48h of symptom onset, whereas the AHA/ASA-guidelines recommend it within 48h from brain swelling. The NICE-guidelines consider the following factors important in order to recommend DHC; infarction-location in the territory of the MCA, decreased level of consciousness, and significant infarction volume on radiology (14). The equivalent factors in the AHA/ASA-guidelines are; neurological deterioration despite medical therapy, decreased level of consciousness, patient age ≤60 years, and MCA infarction of unilateral character (15). However, both guidelines recommend, and emphasizes the relevance of, discussing the risks and benefits of the treatment in terms of outcome with the patient (if possible) or their family members. In Norway the national guidelines for stroke management recommends that DHC is offered within 48h of symptom onset for patients with acute cerebral infarction and risk of developing malignant edema (16).

**The relevance of external validity**

Patients included in randomized controlled trials are strictly and selectively recruited in accordance to narrow inclusion criteria. When the results of the studies are developed into recommendations for treatment in clinical guidelines, and thereafter routinely used in a “real world” practice, there is often a greater variation in who receives the treatment. Clinical quality registries are therefore necessary to assess whether the knowledge obtained from the

RCTs has sufficient external validity, and whether the same results can be achieved in a less selective, and routinely based, practice.

**The Norwegian Stroke Registry**

Clinical quality registries are databases that systematically collect information on patients within a health care system, with the purpose of monitoring outcomes and report on the quality of care. They are therefore key in projects for clinical quality improvement. In Norway, the NSR is the national quality registry for the treatment of stroke. It is mandatory by law to register all patients with acute stroke that are treated in Norwegian hospitals (1). All hospitals (100 %) report to the registry. The data coverage rate at the individual level is 87 %, and the case completeness rate at follow up after 3 months is 77 % (17). The registry data accounts for patient demographic data, treatment data, and outcome data in the acute phase and after 3 months.

# Purpose

Treatment with DHC is controversial, since most of the patients who survive obtain a degree of disability. There is still uncertainty about the treatment's effect on the risk of a poor functional outcome, but the timing of treatment seems to be of importance (18). The decision of performing DHC is therefore a difficult one.

Because of this, it will be valuable to study how DHC as a treatment of malignant infarction is used in Norway, and how the functional outcome is in these selected patients, especially considering that this includes all cases in the country where DHC is performed, and not only patients selected by the criteria of the prospective randomized trials. There is a unique opportunity to perform such a descriptive study because all cases of DHC in the country have been registered in the NSR since 2017.

The main aim of this study is to describe the use of DHC in Norway, including characteristics of the patients, the acute phase, and the treatment. Secondary aims are to describe the outcome in these patients treated with DHC, and to compare the outcomes with those achieved in the prospective randomized trials.

# Material and methods

**Registry data**

For a condition to be included in the NSR as a diagnosed stroke, it has to meet one of the three following criteria (19):

1. Acute focal deficits > 24 hours with positive radiology diagnostics. Admitted to hospital within 28 days from onset of symptoms.
2. Acute focal deficits > 24 hours without positive radiology diagnostics. Admitted to hospital within 28 days from onset of symptoms.
3. Acute focal deficits < 24 hours with positive radiology diagnostics.

For conditions included, there are three categories of stroke diagnoses in the NSR (13);

1. I 61 / Cerebral hemorrhage: Computer tomography (CT)/magnetic resonance imaging (MRI) or autopsy has shown bleeding.
2. I 63 / Cerebral infarction: CT/MRI or autopsy has shown no currently relevant pathology or has shown a currently relevant infarction. For thrombolysis with no following sequela or radiology findings, the code is still given as I 63. Hemorrhagic infarction shall be coded as I 63.
3. I 64 / Unspecified: I 64 should only be used in cases where CT/MRI or autopsy is not done.

**Data sources**

The total data that is stored in the NSR is originally collected through the usage of three standardized data forms; the Acute Form (appendix 1), the Follow-up Form (appendix 2) and the Voluntary Complement Form for Transient deficits. The latter form only applies for conditions meeting criterium 3 of the NSR's three criteria for stroke diagnosis (19).

Every registering hospital has both contact- and register-responsible persons for the NSR. They are employed by the departments that are treating acute stroke.

Data information for the Acute Form is collected from the patient record. For the Follow-up Form the data information is collected after 3 months, either during visits at the outpatient clinic, as phone interviews, or by mail (17).

Data on the population sizes in Norway were retrieved from Statistics Norway for calculation of crude surgical rates.

**Study population**

The study population was all stroke patients who had been treated with DHC in the Norwegian health care system and were registered in the NSR in the years of 2017, 2018 and 2019.

The following inclusion criteria applied; Acute stroke that is classified by the NSR as a cerebral infarction (I 63), and that is treated with DHC during the primary hospitalization. Stroke that was categorized as cerebral hemorrhage (I 61) or as unspecified (I 64) by the NSR, was excluded from the study.

The data material was individual and it was collected from the NSR, sent in digital form from the registry controller that is the National Institute of Public Health (Folkehelseinstituttet). The criteria for inclusion and exclusion were taken into account upon application, and the final data collectively comprised 68 cases.

**Data storage**

Register data was stored at a password protected safe research server at the University Hospital of North Norway (UNN), and available only to the four participants in the project group. Data management was in accordance with standardized requirements approved by the Data protection officer (personvernombudet) at the UNN. It was applied for and granted approval of the project from both the Data protection officer (case number 02593) and the Regional Committee for Medical and Health Research Ethics (REC) North (case number 184357).

**Variables**

Variables were selected from the Acute Form and the Follow-up Form of the NSR. We applied for and received access to a total of 51 specific variables, divided into the following three main categories: patient demographic data, treatment data, and outcome data after 3 months.

**Outcome measures**

The primary outcome measure was the mRS score measured at 3 months after surgery. Secondary outcome measures were mortality and residence.

The mRS is a scale from 0 to 6 used for measuring the degree of disability in patients who have suffered a stroke, where 0 means no symptoms and 6 means that the patient is dead.

The precursor for the mRS, the Rankin scale, originally introduced by dr. John Rankin in 1957 (20), was modified to its current form by Charles Warlow and others as part of the United Kingdom Transient Ischemic Attack (UK-TIA) trial in the 1980s (21). The mRS is today the primary functional outcome scale for acute stroke trials (22).

The six scores of the mRS are as follows:

0: No symptoms at all.
1: No significant disability and able to carry out all duties.
2: Slight disability. Unable to carry out some previous activities, but able to look after own affairs without assistance.
3: Moderate disability. Requiring some help, but able to walk without assistance.
4: Moderately severe disability. Unable to walk without assistance and unable to attend to own bodily needs without assistance.
5: Severe disability. Bedridden, incontinent and requiring constant nursing care and attention.
6: Dead.

Strokes scoring from 0 to 2 were originally counted as “non-disabling” and those scoring from 3 to 5 were counted as “disabling” (20).

In the eight randomized trials, mRS 0 to 3 was defines as “favorable” outcomes and mRS 4 to 6 as “unfavorable”. Because of the planned comparison of the results from this study with those of the RCTs, this dichotomization has been used here as well.

**Statistics**

Statistical data analyses was done in the Statistical Package for the Social Sciences (SPSS; version 27, IBM Corp). Distribution of continuous variables was depicted with histograms and normality plots, and analyzed with the Kolmogorov-Smirnov test. Most continuous data were not normally distributed, and it is therefore reported medians and inter quartile ranges (IQR).

The distribution of categorical variables is reported as proportions in percentages. All valid patient cases were included in analyzes of proportions. This concerns analyzes within the

three groups “total, n”, “favorable outcome” and “unfavorable outcome”, with respectively 68, 20, and 32 valid patient cases.

Crude surgical rates per 100 000 population per year were calculated by dividing the annual mean number of DHC by the mean population size for the years 2017-2019.

Differences between groups were compared with the Mann-Whitney U-test for continuous variables, and the chi square test or Fisher’s exact test (when $n < 5$ in one or more cells) for categorical variables. Patient cases with missing values were excluded from analyzes estimating the p-value. The level of statistical significance was defined as $p < 0,05$.

**Comparison with clinical trials**

A systematic literature search in the databases Embase and Medline was performed 19.08.20 to identify RCTs that have compared DHC to conservative treatment in stroke. The search retrieved relevant publications from a total of eight RCTs.

The results from this study have been compared with those reported from the RCTs. The comparison included; age, time to surgery from onset of symptoms, sex, mRS score before the stroke, NIHSS score, and proportion with mRS $\leq 3$ after 3 months.

# Results

## Regional numbers and surgical rates

NSR registered 68 patients treated with DHC during the three-year study period 2017-2019. These were distributed amongst the four health regions of the country with 38.2 % of the cases located in the South-East, 29.4 % in the North, 17.7 % in the West, and 11,8% in the Mid-Norway health region. The crude surgical rate was 0.43 per 100 000 population per year. The regional surgical rates were 1.40 in the North, 0.37 in the Mid-Norway, 0.36 in the West and 0.29 per 100 000 population per year in the South-East health region. Table 1 shows the predicted and the actual proportional distribution amongst the health regions.

In 50 % of the cases, the patient was transferred from a local hospital to a hospital with neurosurgical capabilities. This wase the case for 35 % of cases in the North, 25 % in the Mid-Norway, 25 % in the West, and 77 % in the South-East health region.

Table 1: **Distribution of proportions amongst health regions**

| Health region | Predicted proportions based on coverage in the general population | Actual proportions of DHC performed | Regional surgical rate (cases per 100 000 population per year) |
|---|---|---|---|
| South-East | 56.23 % | 38.2 % | 0.29 |
| North | 9.2 % | 29.4 % | 1.40 |
| West | 20.9 % | 17.7 % | 0.36 |
| Mid-Norway | 13.7 % | 11.8 % | 0.37 |

## Patient characteristics

Table 2 shows the patients' baseline characteristics. 17 (25 %) were women and 41 (75 %) men, with median age 59.0 (49.5-63.0) years and 56.0 (48.0-68.0) years. Most were highly functional before stroke-onset, with 66 (97.1 %) living in their own residency without any need of assistance, and 67 (98.5 %) without any problems in activities of daily living (movement, toilet visitation, dressing). Prior to the stroke, 54 (79.4 %) were without symptoms at all (mRS 0), 8 (11.7 %) had some symptoms without any significant disability (mRS 1) and 4 (5.9 %) had a slight disability (mRS 2). There were no patients registered with mRS 3-6 before stroke onset. At this point, 18 (26.5 %) were registered as not working.

Table 2: **Baseline characteristics**

| | Missing values, n (%) | All n=68 | Favorable outcome (mRS 0-3) n=20 | Unfavorable outcome (mRS 4-6) n=32 | p-value* |
|---|---|---|---|---|---|
| Age, median (IQR) | | 57.5 (48.3-66.0) | | | |
| Age women, median (IQR) | | 59.0 (49.5-63.0) | | | |
| Age men, median (IQR) | | 56.0 (48.0-68.0) | | | |
| Women, n (%) | | 17 (25 %) | | | |
| Residency before stroke, n (%) | 1 (1.5 %) | | | | 1.000 |
| Own residence without assistance | | 66 (97.1 %) | 20 (100 %) | 31 (96.9 %) | |
| Own residence with assistance | | 1 (1.5 %) | 0 | 1 (3.1 %) | |
| Mobility before stroke, n (%) | 0 | | | | n.a. |
| Alone – outdoors and indoors. | | 67 (98.5 %) | 20 (100 %) | 32 (100 %) | |
| Alone – indoors | | 1 (1.5 %) | 0 | 0 | |
| Manages toilet visits alone, n (%) | 1 (1.5 %) | 67 (98.5 %) | 20 (100 %) | 32 (100 %) | n.a. |
| Manages dressing alone, n (%) | 1 (1.5 %) | 67 (98.5 %) | 20 (100 %) | 32 (100 %) | n.a. |
| Employed before stroke, n (%) | 21 (31.0 %) | | | | 0.763 |
| Yes | | 29 (42.6 %) | 11 (55 %) | 18 (56.2 %) | |
| No | | 18 (26.5 %) | 8 (40 %) | 10 (31.3 %) | |
| Driver's license before stroke, n (%) | 29 (42.6 %) | - | | | 0.504 |
| Yes | | 44 (64.7 %) | 19 (95 %) | 25 (78.1 %) | |
| No | | 2 (2.9 %) | 0 | 2 (6.2 %) | |
| mRS before stroke-onset (0-6), n (%) | 2 (2.9 %) | | | | 0.241 |
| 0: No symptoms | | 54 (79.4 %) | 19 (95 %) | 24 (75 %) | |
| 1: No significant disability | | 8 (11.8 %) | 1 (5 %) | 4 (12.5 %) | |
| 2: Slight disability | | 4 (5.9 %) | 0 | 3 (9.4 %) | |

*p-value for differences between patients with favorable and unfavorable outcome. mRS=modified Rankin Scale, IQR=interquartile range

## Acute phase characteristics

Table 3 shows the patients' conditions, the use of imaging diagnostics and the proportion with large vessel occlusion diagnosed on admission. 35 (51.4 %) of the patients were awake, 20 (29.4 %) were drowsy with adequate response to light stimulation, and 9 (13.3 %) were either non-responsive or only responsive to strong/repetitive stimulation. The median NIHSS score on admission was 14.0 (IQR 11.0). Side-location of the strokes was distributed as 35.3 % right-sided and 51.5 % left-sided. 14 % of the patients had woken up with stroke symptoms, and 64.7 % had occlusion of large-branch vessels. CT examination only was used in 21 (30.9 %), MRI only in 1 (1.5 %), and both in 45 (66.2 %) cases.

Table 3: **Acute phase characteristics**

| | **Missing values, n (%)** | **All n=68** | **Favorable outcome (mRS 0-3) n=20** | **Unfavorable outcome (mRS 4-6) n=32** | **p-value*** |
|---|---|---|---|---|---|
| Level of consciousness on admission, n (%) | 4 (5.9 %) | | | | 0.120 |
| Awake | | 35 (51.4 %) | 17 (85 %) | 15 (46.9 %) | |
| Drowsy, responds adequate to light stimulation | | 20 (29.4 %) | 2 (10 %) | 8 (25 %) | |
| Drowsy, responds only to strong/repetitive stimulation. | | 4 (5.9 %) | 1 (5 %) | 3 (9.4 %) | |
| Non-responsive or responds only with indeterminant movement | | 5 (7.4 %) | | 3 (9.4 %) | |
| Facialis/facial palsy, n (%) | 8 (11.7 %) | | | | 0.352 |
| Yes | | 40 (58.8 %) | 8 (40 %) | 19 (59.4 %) | |
| No | | 20 (29.4 %) | 9 (45 %) | 10 (31.3 %) | |
| Arm palsy, n (%) | 3 (0.4 %) | | | | **0.013** |
| Yes | | 50 (73.5 %) | 10 (50 %) | 26 (81.3 %) | |
| No | | 15 (22.1 %) | 10 (50 %) | 5 (15.6 %) | |
| Leg palsy, n (%) | 3 (4.4 %) | | | | **0.009** |
| Yes | | 51 (75.0 %) | 10 (50 %) | 27 (84.4 %) | |
| No | | 14 (20.6 %) | 10 (50 %) | 4 (12.5 %) | |
| Language difficulties, n (%) | 7 (10.3 %) | | | | 0.232 |
| Yes | | 35 (51.5 %) | 9 (45 %) | 18 (56.3 %) | |
| No | | 26 (38.2 %) | 11 (55 %) | 9 (28.1 %) | |
| Other focal symptoms, n (%) | 23 (33.8 %) | | | | 0.552 |
| Yes | | 55 (80.9 %) | 16 (80 %) | 27 (84.4 %) | |
| No | | 4 (5.9 %) | 2 (10 %) | 1 (3.1 %) | |
| **NIHSS on admission** | 14 (20.6 %) | | | | **0.064** |
| Mean (95% CI) | | 12.7 (10.5-15.0) | 10.2 (6.7-13.7) | 14.3 (11.4-17.2) | |
| Median (IQR) | | 14.0 (11.0) | 12.0 (13.0) | 15.0 (9.0) | |
| Side location of stroke | 9 (13.2 %) | | | | 0.517 |
| Right | | 24 (35.3 %) | 7 (35 %) | 10 (31.3 %) | |
| Left | | 35 (51.5 %) | 8 (40 %) | 20 (62.5 %) | |
| Awoke with symptoms, n (%) | 10 | | | | 0.303 |
| Yes | | 14 (20.6 %) | 3 (15 %) | 9 (28.1 %) | |
| No | | 44 (64.7 %) | 15 (75 %) | 17 (53.1 %) | |
| Radiology diagnostics of stroke, n (%) | 0 | | | | 0.358 |
| None | | 1 (1.5 %) | 1 (5 %) | | |
| CT | | 21 (30.9 %) | 5 (25 %) | 11 (34.4 %) | |
| MRI | | 1 (1.5 %) | 1 (5 %) | | |
| Both CT and MRI | | 45 (66.2 %) | 13 (65 %) | 21 (65.6 %) | |
| Large vessel occlusion, n (%) | 4 (5.9 %) | | | | 0.767 |
| Yes | | 44 (64.7 %) | 12 (60 %) | 21 (65.6 %) | |
| No | | 20 (29.4 %) | 7 (35 %) | 10 (31.3 %) | |

*p-value for differences between patients with favorable and unfavorable outcome. mRS=modified Rankin Scale, CI=confidence interval, IQR=interquartile range

## Treatment characteristics

Table 4 shows treatment characteristics. The median time from onset of symptoms to hospital admission was 91.0 (IQR 250) minutes, and the time from onset of symptoms to DHC was 34.3 (IQR 40.9) hours. Thrombolysis was performed in 32 (47.1 %) of the cases, and thrombectomy in 31 (45.6 %).

Table 4: **Treatment characteristics**

| | **Missing values, n (%)** | **All n=68** | **Favorable outcome (mRS 0-3) n=20** | **Unfavorable outcome (mRS 4-6) n=32** | **p-value*** |
|---|---|---|---|---|---|
| **Minutes from onset of symptoms to admission** | 5 (73.5 %) | | | | 0.347 |
| Mean (95 % CI) | | 262.0 (139.8-384.1) | 348.3 (84.3-612.3) | 208.4 (84.9-331.9) | |
| Median (IQR) | | 91.0 (250) | 166,0 (320) | 90.0 (147.0) | |
| **Hours from onset of symptoms to DHC** | 16 (23.5 %) | | | | 0.855 |
| Mean (95 % CI) | | 44.3 (33.6-55.0) | 45.4 (24.4-66.3) | 43.5 (31.0-56.0) | |
| Median (IQR) | | 34.3 (40.9) | 34.2 (43.7) | 34.3 (39.8) | |
| Thrombolysis, n (%) | 0 | | | | **0.004** |
| Yes | | 32 (47.1 %) | 4 (20 %) | 20 (62.5 %) | |
| No | | 36 (52.9 %) | 16 (80 %) | 12 (37.5 %) | |
| Thrombectomy, n (%) | 0 | | | | 0.393 |
| Yes | | 31 (45.6 %) | 12 (60 %) | 14 (43.8 %) | |
| No | | 37 (54.4 %) | 8 (40 %) | 18 (56.3 %) | |

*p-value for differences between patients with favorable and unfavorable outcome. mRS=modified Rankin Scale, CI=confidence interval, IQR=interquartile range

## Outcome

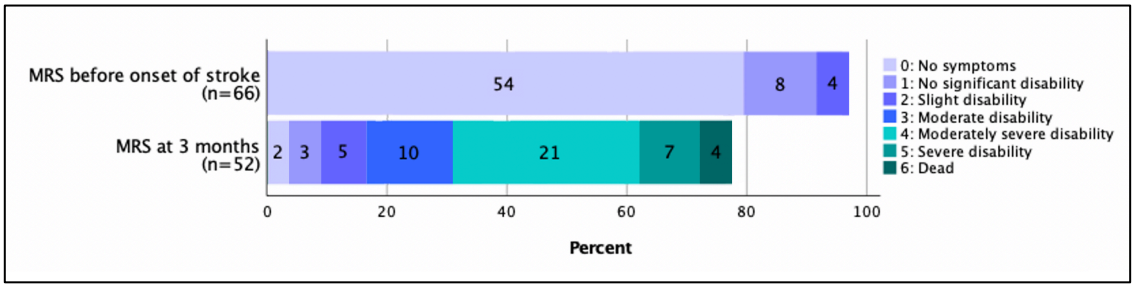
Figure 1 and table 5 show the patients outcomes at the three-month follow-up. The outcome data were collected within a median time of 106.0 (45.0) days from the onset of symptoms.

A favorable outcome (mRS score ≤ 3) was achieved for 20 (29.4 %) of the patients, while 32 (47.1 %) experienced an unfavorable outcome (mRS score > 3). 8 (11.8 %) patients were dead. Median time to death (n=6) was 25.5 (IQR 317.0) days.

At follow-up, 20 (29.4 %) patients were living in their own residency, of which 13 (19.1 %) without any need of assistance. Nine (13.2 %) were in nursery homes, and 14 (20.6 %) were still in rehabilitation facilities. The patients had an overall increased demand for assistance in activities of daily living, including movement (39.7 %), toilet visits (46.6 %), and dressing (47.1 %). Having trouble reading and writing, was reported by 30 (44.1 %), trouble swallowing by 11 (16.2 %), trouble with language/speech by 25 (36.8 %), and vision problems by 18 (26.5 %).

At the follow-up 41 (60.3 %) of the patients reported that they had not recovered from the stroke since discharge. 46 (67.6 %) were now reported as not working, and 1 (1.5 %) patient had retained their driver's license.

Figure 1: **MRS before onset of stroke and at 3 months**




*Stacked-bar chart showing modified Rankin Scale (mRS) score before onset of stroke and at follow up after three months. Numbers on the bars show the number of patients in each outcome category. The differences between the lengths of the bars and the full scale (0-100 %) is caused by missing data.*

Table 5: **Outcome characteristics at 3 months**

| | Missing values, n (%) | All n=68 | Favorable outcome (mRS 0-3) n=20 | Unfavorable outcome (mRS 4-6) n=32 | p-value* |
|---|---|---|---|---|---|
| **Days from onset of symptoms to follow-up** | 20 (29.4 %) | | | | 0.137 |
| Mean (95 % CI) | | 123.0 (109.0-136.9) | 130.6 (107.2-154.0) | 117.5 (99.3-135.7) | |
| Median (IQR) | | 106.0 (45.0) | 128.0 (52.0) | 98.5 (31.0) | |
| **Days from onset of symptoms to death (n=6)** | | | | | |
| Mean (95 % CI) | | 165.5 | 0 | 165.5 | |
| Median (IQR) | | 25.5 (317.0) | 0 | 25.5 (317.0) | |

| | | | | | |
|---|---|---|---|---|---|
| Residency at 3 months, n (%) | 23 (33.8 %) | | | | **< 0.001** |
| Own residence without assistance | | 13 (19.1 %) | 13 (65 %) | 0 | |
| Own residence with assistance | | 7 (10.3 %) | 4 (20 %) | 3 (9.4 %) | |
| Sheltered housing with continuous day and night service | | 2 (2.9 %) | 0 | 2 (6.3 %) | |
| Nursing home | | 9 (13.2 %) | 1 (5 %) | 8 (25 %) | |
| Still in residency of rehabilitation | | 14 (20.6 %) | 2 (10 %) | 12 (37.5 %) | |
| Mobility at 3 months, n (%) | 20 (29.4 %) | | | | **< 0.001** |
| Alone – outdoors and indoors | | 13 (19.1 %) | 13 (65 %) | | |
| Alone – indoors | | 8 (11.8 %) | 5 (25 %) | 3 (9.4 %) | |
| With assistance | | 27 (39.7 %) | 2(10 %) | 25 (78.1 %) | |
| Manage toilet visits at 3 months, n (%) | 20 (29.4 %) | | | | **< 0.001** |
| Alone | | 19 (27.9 %) | 17 (85 %) | 2 (6.3 %) | |
| With assistance | | 29 (46.6 %) | 3 (15 %) | 26 (81.3 %) | |
| Manages dressing at 3 months, n (%) | 20 (29.4 %) | | | | **< 0.001** |
| Alone | | 16 (23.5 %) | 14 (70 %) | 2 (6.3 %) | |
| With assistance | | 32 (47.1 %) | 6 (30 %) | 26 (81.3 %) | |
| Reading or writing difficulties at 3 months, n (%) | 25 (36.8 %) | | | | 0.332 |
| Yes | | 30 (44.1 %) | 11 (55 %) | 19 (59.4 %) | |
| No | | 13 (19.1 %) | 7 (35 %) | 6 (18.8 %) | |
| Swallowing problems at 3 months, n (%) | 20 (29.4 %) | | | | **0.016** |
| Yes | | 11 (16.2 %) | 1 (5 %) | 10 (31.3 %) | |
| No | | 37 (54.4 %) | 19 (95 %) | 18 (56.3 %) | |
| Language/speech problems at 3 months, n (%) | 21 (30.9 %) | | | | 0.386 |
| Yes | | 25 (36.8 %) | 9 (45 %) | 16 (50 %) | |
| No | | 22 (32.4 %) | 11 (55 %) | 11 (34.4 %) | |
| Vision problems at 3 months, n (%) | 30 (44.1 %) | | | | 0.058 |
| Yes | | 18 (26.5 %) | 5 (25 %) | 13 (40.6 %) | |
| No | | 20 (29.4 %) | 12 (60 %) | 8 (25 %) | |
| Recovery after stroke, n (%) | 22 (32.4 %) | | | | 0.069 |
| Yes | | 5 (7.4 %) | 4 (20 %) | 1 (3.1 %) | |
| No | | 41 (60.3 %) | 14 (70 %) | 27 (84.4 %) | |
| Employed at 3 months, n (%) | 21 (30.9 %) | | | | 0.426 |
| Yes | | 1 (1.5 %) | 1 (5 %) | | |
| No | | 46 (67.6 %) | 19 (95 %) | 27 (84.4 %) | |
| Driver's license at 3 months, n (%) | 30 (44.1 %) | | | | 0.180 |
| Still valid license | | 1 (1.5 %) | 1 (5 %) | | |
| Suspended license | | 6 (8.8 %) | 1 (5 %) | 5 (15.6 %) | |
| Still temporary prohibition | | 31 (45.6 %) | 17 (85 %) | 14 (43.8 %) | |
| mRS at 3 months, n (%) | 16 (23.5 %) | | | | n.a. |
| 0: No symptoms | | 2 (2.9 %) | 2 (10 %) | 0 | |
| 1: No significant disability | | 3 (4.4 %) | 3 (15 %) | 0 | |
| 2: Slight diasability | | 5 (7.4 %) | 5 (25 %) | 0 | |
| 3: Moderate disability | | 10 (14.7 %) | 10 (50 %) | 0 | |
| 4: Moderately severe disability | | 21 (30.9 %) | 0 | 21 (65.6 %) | |
| 5: Severe disability | | 7 (10.3 %) | 0 | 7 (21.9 %) | |
| 6: Dead | | 4 (5.9 %) | 0 | 4 (12.5 %) | |
| mRS *favorable* (mRS 0-3) at 3 months | | 20 (29.4 %) | 20 (100 %) | | n.a. |
| mRS *unfavorable* (mRS 4-6) at 3 months | | 32 (47.1 %) | | 32 (100 %) | n.a. |

*p-value for differences between patients with favorable and unfavorable outcome. mRS=modified Rankin Scale, CI=confidence interval, IQR=interquartile range

**Comparison of the dichotomic groups.**

Tables 2-5 also show comparisons between patients with favorable outcome (mRS ≤ 3) and unfavorable outcomes (mRS > 3). On admission, the group with an unfavorable outcome had a higher median NIHSS score (15.0, IQR 9.0) than the group with a favorable outcome (12.0, IQR 13.0). This difference was near statistic significance (p = 0.064). For arm paralysis, there was a significant (p = 0.013) difference, as this was seen in 50 % of the patients who had a favorable outcome, compared to 81.3 % in the unfavorable outcome group. The same was found for leg paralysis where the corresponding proportions was 50 % and 84.4 % (p = 0.009).

There was a significant (p = 0.004) difference between the groups in the proportion who received thrombolysis treatment. In the group with a favorable outcome (mRS ≤ 3) 20 % received the treatment, compared to 62.5 % in the group with an unfavorable outcome.

**Comparison with the clinical trials**

Table 6 summarizes the main findings from the eight published RCTs, and the corresponding data from the NSR between 2017-19.

In total, the RCTs included 376 (range 26 – 112) cases. The mean/median age ranged from 43.4 to 70.0 years. Females were under-represented in five of the eight studies, with a proportion ranging from 13.8 to 53.1 %. The mean/median NIHSS score was reported by seven studies and varied little (range 20.0 – 23.0). In six out of eight studies, the NIHSS score was registered upon randomization, and in one study on admission. Five studies reported mean/median time from onset of symptoms to DHC, which ranged from 20.5 to 36.6 hours.

Median age and time from onset of symptoms to DHC in the present study is comparable to the RCT's, while the proportion of females (25 %) is in the lower range, and the median NIHSS score (14.0) is clearly lower than in the RCT's.

The outcomes in the RCTs were assessed after varying length of follow-up (3 to 12 months), and the proportion achieving a favorable outcome (mRS ≤ 3) ranged from 25 to 47 %. The proportion of 29.4 % with a favorable outcome at the follow-up in the present study was within this range.

**Table 6:** Main findings from the RCTs on DHC

| Study | n, DHC and total | Age | Gender, % female | Time from onset of symptoms to DHC | NIHSS, surgery group | Time point for registering NIHSS score | Favorable outcome (mRS ≤ 3) |
|---|---|---|---|---|---|---|---|
| HeMMi Trial. Chua, 2015refnr! | 29 (16 DHC) | 50.2 yrs (mean). | 4:20 (13.8 %) | 36.6 h (mean, SD 19.7) | 22.8 (mean, SD 4.7) | Upon randomization | 4 (25 %) (at 6 months) |
| HeADDFIRST trial. Frank, 2014. | 26 (15 DHC) | 55.1 yrs (median) | 8:15 (30.8 %) | 53.8 h (median, IQR 27.7–80.4)† | 23.0 (median, IQR 20.5–27.5) | Upon randomization | 29 % (at 3 months) |
| HAMLET trial. Hofmeijer, 2009. | 64 (32 DHC) | 48.7 yrs (mean). | 26:38 (40.6 %) | 41 h (median, IQR 29-50)† | 23 (median, IQR 17-34) | Upon randomization | 8 (25 %) (at 12 months) |
| DESTINY trial. Juttler, 2007. | 32 (17 DHC) | 44.6 yrs (mean) | 17:15 (53.1 %) | 24 h (median) | 21 (median) | On admission | 47 % (at 6 months) |
| DECIMAL trial. Vahedi, 2007. | 38 (20 DHC) | 43.4 yrs (mean) | 20:18 (52.6 %) | 20.5 h (mean, SD 8.3) | 22.5 (mean, SD 5.4) | Upon randomization | 5 (25 %) (at 6 months) |
| DESTINY II trial, Juttler, 2014. | 112 (49 DHC) | 70 yrs (median) | 56:56 (50 %) | 28 h (median) | 20 (median) | Upon randomization | 7 (14 %) (at 6 months) |
| Slezins, 2012. | 28 (11 DHC) | 61.5 yrs (mean) | 12:16 (42.9%) | 21 h (mean) | 21.2 (mean) | Upon randomization | 5 (45 %) (at 12 months) |
| Zhao, 2012. | 47 (24 DHC) | 64 yrs (median) | 13:34 (27.7 %) | 23.6 h (mean, SD 6.4)† | n.a. | n.a. | 5 (21 %) (at 6 months) |
| Data from the NSR between 2017-2019 | 68 DHC | 57.5 (median) | 17:51 (25 %) | 34.3 (median, IQR 40.9) | 14,0 (median, IQR 11.0) | | 20 (29.4 %) (at 3 months) |

† from onset of symptoms to randomization

# Discussion

**Main findings**

The main findings in this population-based cohort was that patients operated with DHC at Norwegian hospitals were comparable to those included in the RCTs with respect to age and timing of the operation, but the proportion of women was low, and the NIHSS score was lower than the scores reported in the RCTs. In addition, there was a noticeable variation in the regional surgical rate, with the highest rate observed in the North health region.

Only one previous Norwegian study of DHC has been published. This was an observational study of outcomes in a single institution cohort of 45 patients recruited between 1998 and 2010 (23, 24). This study also registered NIHSS score on admission, and the score was comparable (15 versus 14) to that observed in the present study. However, the patients were younger (48.1 versus 57.1 years) and the proportion of women higher (42 versus 25 %), and the proportion reaching a favorable outcome (mRS ≤ 3) higher (46 versus 29 %). The authors reported an association between lower age and survival. Two prospective observational cohort studies from China and India included 219 and 36 patients, respectively (25, 26). The patients' median? NIHSS-scores were 21 and 19, but the time points for registration were not reported. Otherwise, both patient- and treatment characteristics and the outcomes (mRS score ≤ 3 32 and 20 %) were comparable to the present study.

The proportion of women treated with a DHC was low both in this study (25 %) and in five of the eight RCTs (13.8 – 42.9 %). According to data from the NHR for the years 2017-19, women constituted 45 % of the stroke cases in Norway (17, 27, 28). This could indicate that men were considered more eligible for treatment with DHC than women. The inequality in sex category representation is not explained nor discussed in the publications from the RCTs. In general, healthcare inequality in women's disfavor is a concern (29). This is therefore an undisclosed topic that should be investigated in further research based on data from the NSR.

The lower NIHSS score in this study could have indicated that Norwegian hospitals had a lower threshold for performing DHC than that necessary for inclusion in the RCTs. However, the clinical course of a stroke patient is dynamic, and the NIHSS score increase after admission in patients who deteriorate. Six of the 8 RCTs reported that the NIHSS score was registered at the time of randomization. This is contrary to the NSR, where the NIHSS score is registered at the time of admission to hospital. Accordingly, deterioration between

admission and the time point for randomization in the RCTS could explain the difference between the NIHSS scores reported from the RCTs and the present study. This may also explain why lower NIHSS score for patients in the NHR did not correspond with a higher proportion with a favorable outcome.

The dichotomization in terms of primary outcome (mRS) showed a statistically significant lower proportion of patients with arm- and leg palsy, and a nearly significant lower NIHSS score on admission among patients with a favorable outcome. Both arm and leg paralysis are amongst the variables that are used in the calculation of NIHSS, This is in accordance with the apparent difference in NIHSS score between the two groups with the respective medians of 12.0 (IQR 13.0) and 15.0 (IQR 9.0).

The proportion of patients with a *favorable* outcome (mRS score ≤ 3 at 3 months) was 29.4 %. On the other hand, 47.1 % experienced an unfavorable outcome, with most (41.2 %) being either moderately severe or severely disabled (mRS score 4-5). According to a pooled analysis of the three European RCTs HAMLET, DESTINY and DECIMAL (7, 8, 9) published by Lancet in 2007, DHC increased the probability of surviving in a condition with moderately severe disability (mRS score 4) more than ten times compared to no surgical intervention (30). The same analysis showed that the probability of surviving with moderate disability (mRS score 3) was doubled and with severe disability (mRS score 5) was unchanged. It is therefore fair to assume that most of the patients with an unfavorable outcome in this study probably would have died if left unoperated.

Eight (11.8 %) patients in total were registered as dead at the 3 months follow-up, 4 in whom were registered as having an mRS score of 6 (dead) and 4 others in whom had gotten registered “death” as the cause for lack of follow-up. 6 of these had registered days from onset of symptoms to death.

There was an unwarranted geographic variation in the use of DHC between the four health regions. The discrepancy between the observed and predicted proportion of DHCs performed was largest for the South-East (low surgical rate) and the North (high surgical rate) regions. Comparison of the data from NHR on the registered number of stroke cases of stroke per health region (17, 27, 28) with regional population data from Statistics Norway for 2017-19 does not show any higher incidence in the north region to justify the higher surgical rates.

The data on hospital transfers shows that patients within the coverage area of a local hospital that performs DHC (no need of hospital transfer), are more likely to receive this type of treatment. The five hospitals (Oslo University Hospital, Stavanger University Hospital, Haukeland University Hospital, and The University Hospital of North Norway) that offers DHC covers in total 32 % of the population, thus 68 % of the population does not have a local hospital that offers DHC and would have to be transferred if they needed this type of surgery. The data from the NSR showed that only 50 % of the patients who underwent DHC had been transferred from another hospital. This means that the remaining 50 % were patients with residency covered by either one of five hospitals that offers DHC, i.e. considerably more than the expected number of 32 %.

**Strengths and limitations**

The major strength with the study is that it is register-based and therefore includes an unselected patient group that is representative for routine clinical practice in Norwegian hospitals. The data coverage rate at the individual level in the NSR is high (87 %). This is likely to give reliable data about the use of and outcomes from DHC.

The selected baseline- and outcome measures are well validated with a low risk of information bias.

DHC is recommended for a small proportion of patients with acute stroke, and the e number of patients included in this study is therefore limited, despite nationwide data catchment. This implies a risk of power problems which can cause type I errors (rejected true null-hypothesis) and type II errors (accepted false null-hypothesis) in the between-groups comparisons. Further, the low number of cases and high number of possible predictors for the outcome precluded any meaningful prediction analysis. This suggests the advantage of repeating the investigations of the present study at a time when more data is available (e.g. after 10 years).

The NSR collects outcome data only at three months follow-up. This is a limitation when comparing to some of the RCTs, that collected data also at 6 to 12 months follow-ups.

In extension of the present study, the complete dataset in the NSR could possibly be used to identify all registered cases that fulfil the criteria for DHC recommended by the national guidelines for stroke management. This might entail a possibility to identify the proportion of cases eligible for the procedure, and perform a comparison between those who received it

with those who did not. Such analysis would yield a better understanding of the degree of guideline adherence. A between groups comparison (operated versus not operated) with propensity score matching could be used to analyze whether the benefit (e.g. in terms of outcome or survival) from the operation in a non-selected population-based cohort is comparable to that achieved in the RCTs. This would eliminate the possible selection-bias introduced by inclusion only of the operated cases, as in this study. Unfortunately, the lack of repeated NIHSS-score registrations in patients who deteriorate after admission is an obstacle.

# Conclusion

This study shows that 68 patients were treated with DHC for a malignant MCA infarction in Norway in the years of 2017-2019. The crude surgical rate was 0.43 per 100 000 population per year. The proportions of patients with male gender (75 %), residency within the local hospital coverage area of a university hospital, and residency in the North health region were higher than expected based on their representation in the general population. The survival rate was 88 % and the proportion achieving a favorable outcome (mRS score ≤ 3) at follow-up 3 months after surgery was 29.4 %. There are gender- and geographically based inequality in access to the procedure. Data on patients' characteristics, time of the operation and the outcomes were comparable to those reported from the RCTs. This indicates that patient selection for DHC is in accordance with recommendations in evidence based guidelines for those who undergo the operation.

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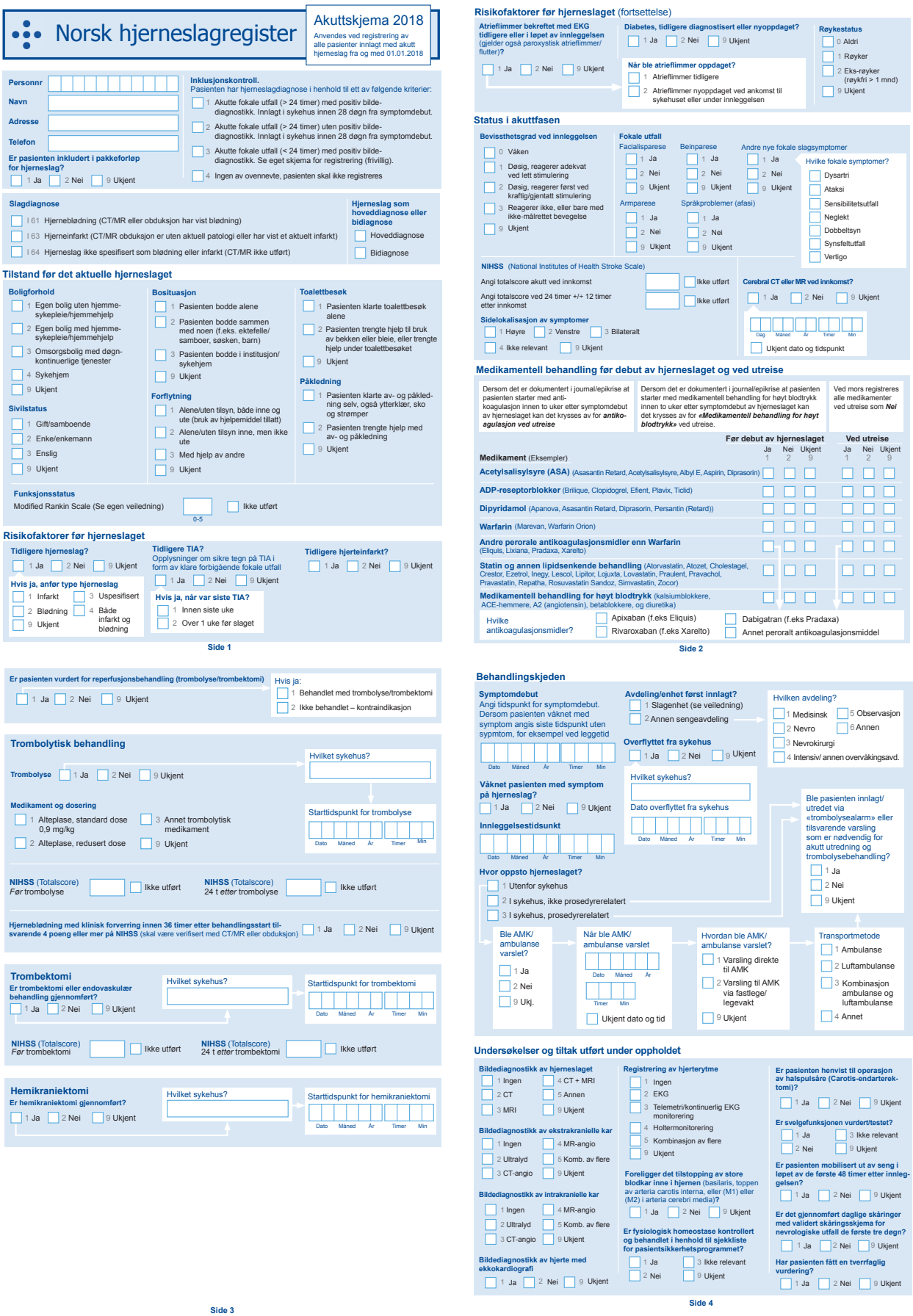
# Appendix

## Appendix 1: NSR Acute form 2018



Norsk hjerneslagregister

Akuttskjema 2018

Anvendes ved registrering av alle pasienter innlagt med akutt hjerneslag fra og med 01.01.2018

Personnr

Navn

Adresse

Telefon

Er pasienten inkludert i pakkeforløp for hjerneslag? 1 Ja 2 Nei 9 Ukjent

Inklusjonskontroll.
Pasienten har hjerneslagdiagnose i henhold til ett av følgende kriterier:

1 Akutte fokale utfall (> 24 timer) med positiv bilde-diagnostikk. Innlagt i sykehus innen 28 døgn fra symptomdebut.

2 Akutte fokale utfall (> 24 timer) uten positiv bilde-diagnostikk. Innlagt i sykehus innen 28 døgn fra symptomdebut.

3 Akutte fokale utfall (< 24 timer) med positiv bilde-diagnostikk. Se eget skjema for registrering (frivillig).

4 Ingen av ovennevte, pasienten skal ikke registreres

Slagdiagnose

I 61 Hjerneblødning (CT/MR eller obduksjon har vist blødning)

I 63 Hjerneinfarkt (CT/MR obduksjon er uten aktuell patologi eller har vist et aktuelt infarkt)

I 64 Hjerneslag ikke spesifisert som blødning eller infarkt (CT/MR ikke utført)

Hjerneslag som hoveddiagnose eller bidiagnose

Hoveddiagnose

Bidiagnose

Tilstand før det aktuelle hjerneslaget

Boligforhold

1 Egen bolig uten hjemme-sykepleie/hjemmehjelp

2 Egen bolig med hjemme-sykepleie/hjemmehjelp

3 Omsorgsbolig med døgn-kontinuerlige tjenester

4 Sykehjem

9 Ukjent

Sivilstatus

1 Gift/samboende

2 Enke/enkemann

3 Enslig

9 Ukjent

Bosituasjon

1 Pasienten bodde alene

2 Pasienten bodde sammen med noen (f.eks. ektefelle/samboer, søsken, barn)

3 Pasienten bodde i institusjon/sykehjem

9 Ukjent

Forflytning

1 Alene/uten tilsyn, både inne og ute (bruk av hjelpemiddel tillatt)

2 Alene/uten tilsyn inne, men ikke ute

3 Med hjelp av andre

9 Ukjent

Toalettbesøk

1 Pasienten klarte toalettbesøk alene

2 Pasienten trengte hjelp til bruk av bekken eller bleie, eller trengte hjelp under toalettbesøket

9 Ukjent

Påkledning

1 Pasienten klarte av- og påkledning selv, også ytterklær, sko og strømper

2 Pasienten trengte hjelp med av- og påkledning

9 Ukjent

Funksjonsstatus

Modified Rankin Scale (Se egen veiledning) 0-5 Ikke utført

Risikofaktorer før hjerneslaget

Tidligere hjerneslag? 1 Ja 2 Nei 9 Ukjent

Hvis ja, anfør type hjerneslag

1 Infarkt 3 Uspesifisert

2 Blødning 4 Både infarkt og blødning

9 Ukjent

Tidligere TIA?
Opplysninger om sikre tegn på TIA i form av klare forbigående fokale utfall 1 Ja 2 Nei 9 Ukjent

Hvis ja, når var siste TIA?

1 Innen siste uke

2 Over 1 uke før slaget

Tidligere hjerteinfarkt? 1 Ja 2 Nei 9 Ukjent

Side 1

Er pasienten vurdert for reperfusjonsbehandling (trombolyse/trombektomi) 1 Ja 2 Nei 9 Ukjent

Hvis ja:

1 Behandlet med trombolyse/trombektomi

2 Ikke behandlet – kontraindikasjon

Trombolytisk behandling

Trombolyse 1 Ja 2 Nei 9 Ukjent

Hvilket sykehus?

Medikament og dosering

1 Alteplase, standard dose 0,9 mg/kg

2 Alteplase, redusert dose

3 Annet trombolytisk medikament

9 Ukjent

Starttidspunkt for trombolyse Dato Måned År Timer Min

NIHSS (Totalscore) *Før* trombolyse Ikke utført

NIHSS (Totalscore) 24 t *etter* trombolyse Ikke utført

Hjerneblødning med klinisk forverring innen 36 timer etter behandlingsstart tilsvarende 4 poeng eller mer på NIHSS (skal være verifisert med CT/MR eller obduksjon) 1 Ja 2 Nei 9 Ukjent

Trombektomi

Er trombektomi eller endovaskulær behandling gjennomført? 1 Ja 2 Nei 9 Ukjent

Hvilket sykehus?

Starttidspunkt for trombektomi Dato Måned År Timer Min

NIHSS (Totalscore) *Før* trombektomi Ikke utført

NIHSS (Totalscore) 24 t *etter* trombektomi Ikke utført

Hemikraniektomi

Er hemikraniektomi gjennomført? 1 Ja 2 Nei 9 Ukjent

Hvilket sykehus?

Starttidspunkt for hemikraniektomi Dato Måned År Timer Min

Side 3

Risikofaktorer før hjerneslaget (fortsettelse)

Atrieflimmer bekreftet med EKG tidligere eller i løpet av innleggelsen (gjelder også paroxystisk atrieflimmer/flutter)? 1 Ja 2 Nei 9 Ukjent

Når ble atrieflimmer oppdaget?

1 Atrieflimmer tidligere

2 Atrieflimmer nyoppdaget ved ankomst til sykehuset eller under innleggelsen

Diabetes, tidligere diagnostisert eller nyoppdaget? 1 Ja 2 Nei 9 Ukjent

Røykestatus

0 Aldri

1 Røyker

2 Eks-røyker (røykfri > 1 mnd)

9 Ukjent

Status i akuttfasen

Bevissthetsgrad ved innleggelsen

0 Våken

1 Døsig, reagerer adekvat ved lett stimulering

2 Døsig, reagerer først ved kraftig/gjentatt stimulering

3 Reagerer ikke, eller bare med ikke-målrettet bevegelse

9 Ukjent

Fokale utfall

Facialisparese 1 Ja 2 Nei 9 Ukjent

Beinparese 1 Ja 2 Nei 9 Ukjent

Andre nye fokale slagsymptomer 1 Ja 2 Nei 9 Ukjent

Armparese 1 Ja 2 Nei 9 Ukjent

Språkproblemer (afasi) 1 Ja 2 Nei 9 Ukjent

Hvilke fokale symptomer?

Dysartri

Ataksi

Sensibilitetsutfall

Neglekt

Dobbeltsyn

Synsfeltutfall

Vertigo

NIHSS (National Institutes of Health Stroke Scale)

Angi totalscore akutt ved innkomst Ikke utført

Angi totalscore ved 24 timer +/- 12 timer etter innkomst Ikke utført

Sidelokalisasjon av symptomer

1 Høyre 2 Venstre 3 Bilateralt

4 Ikke relevant 9 Ukjent

Cerebral CT eller MR ved innkomst? 1 Ja 2 Nei 9 Ukjent

Dag Måned År Timer Min

Ukjent dato og tidspunkt

Medikamentell behandling før debut av hjerneslaget og ved utreise

Dersom det er dokumentert i journal/epikrise at pasienten starter med anti-koagulasjon innen to uker etter symptomdebut av hjerneslaget kan det krysses av for ***antiko-agulasjon ved utreise***

Dersom det er dokumentert i journal/epikrise at pasienten starter med medikamentell behandling for høyt blodtrykk innen to uker etter symptomdebut av hjerneslaget kan det krysses av for ***«Medikamentell behandling for høyt blodtrykk»*** ved utreise.

Ved mors registreres alle medikamenter ved utreise som ***Nei***

| Medikament (Eksempler) | Før debut av hjerneslaget: Ja 1 | Nei 2 | Ukjent 9 | Ved utreise: Ja 1 | Nei 2 | Ukjent 9 |
|---|---|---|---|---|---|---|
| **Acetylsalisylsyre (ASA)** (Asasantin Retard, Acetylsalisylsyre, Albyl E, Aspirin, Diprasorin) | | | | | | |
| **ADP-reseptorblokker** (Brilique, Clopidogrel, Efient, Plavix, Ticlid) | | | | | | |
| **Dipyridamol** (Apanova, Asasantin Retard, Diprasorin, Persantin (Retard)) | | | | | | |
| **Warfarin** (Marevan, Warfarin Orion) | | | | | | |
| **Andre perorale antikoagulasjonsmidler enn Warfarin** (Eliquis, Lixiana, Pradaxa, Xarelto) | | | | | | |
| **Statin og annen lipidsenkende behandling** (Atorvastatin, Atozet, Cholestagel, Crestor, Ezetrol, Inegy, Lescol, Lipitor, Lojuxta, Lovastatin, Praulent, Pravachol, Pravastatin, Repatha, Rosuvastatin Sandoz, Simvastatin, Zocor) | | | | | | |
| **Medikamentell behandling for høyt blodtrykk** (kalsiumblokkere, ACE-hemmere, A2 (angiotensin), betablokkere, og diuretika) | | | | | | |

Hvilke antikoagulasjonsmidler? Apixaban (f.eks Eliquis) Rivaroxaban (f.eks Xarelto) Dabigatran (f.eks Pradaxa) Annet peroralt antikoagulasjonsmiddel

Side 2

Behandlingskjeden

Symptomdebut
Angi tidspunkt for symptomdebut. Dersom pasienten våknet med symptom angis siste tidspunkt uten sypmtom, for eksempel ved leggetid
Dato Måned År Timer Min

Våknet pasienten med symptom på hjerneslag? 1 Ja 2 Nei 9 Ukjent

Innleggelsestidsunkt
Dato Måned År Timer Min

Hvor oppsto hjerneslaget?

1 Utenfor sykehus

2 I sykehus, ikke prosedyrerelatert

3 I sykehus, prosedyrerelatert

Avdeling/enhet først innlagt?

1 Slagenhet (se veiledning)

2 Annen sengeavdeling

Overflyttet fra sykehus 1 Ja 2 Nei 9 Ukjent

Hvilket sykehus?

Dato overflyttet fra sykehus
Dato Måned År Timer Min

Hvilken avdeling?

1 Medisinsk 5 Observasjon

2 Nevro 6 Annen

3 Nevrokirurgi

4 Intensiv/ annen overvåkingsavd.

Ble pasienten innlagt/ utredet via «trombolysealarm» eller tilsvarende varsling som er nødvendig for akutt utredning og trombolysebehandling? 1 Ja 2 Nei 9 Ukjent

Ble AMK/ ambulanse varslet? 1 Ja 2 Nei 9 Ukj.

Når ble AMK/ ambulanse varslet
Dato Måned År Timer Min
Ukjent dato og tid

Hvordan ble AMK/ ambulanse varslet? 1 Varsling direkte til AMK 2 Varsling til AMK via fastlege/ legevakt 9 Ukjent

Transportmetode 1 Ambulanse 2 Luftambulanse 3 Kombinasjon ambulanse og luftambulanse 4 Annet

Undersøkelser og tiltak utført under oppholdet

Bildediagnostikk av hjerneslaget 1 Ingen 2 CT 3 MRI 4 CT + MRI 5 Annen 9 Ukjent

Bildediagnostikk av ekstrakranielle kar 1 Ingen 2 Ultralyd 3 CT-angio 4 MR-angio 5 Komb. av flere 9 Ukjent

Bildediagnostikk av intrakranielle kar 1 Ingen 2 Ultralyd 3 CT-angio 4 MR-angio 5 Komb. av flere 9 Ukjent

Bildediagnostikk av hjerte med ekkokardiografi 1 Ja 2 Nei 9 Ukjent

Registrering av hjerterytme 1 Ingen 2 EKG 3 Telemetri/kontinuerlig EKG monitorering 4 Holtermonitorering 5 Kombinasjon av flere 9 Ukjent

Foreligger det tilstopping av store blodkar inne i hjernen (basilaris, toppen av arteria carotis interna, eller (M1) eller (M2) i arteria cerebri media)? 1 Ja 2 Nei 9 Ukjent

Er fysiologisk homeostase kontrollert og behandlet i henhold til sjekkliste for pasientsikkerhetsprogrammet? 1 Ja 2 Nei 3 Ikke relevant 9 Ukjent

Er pasienten henvist til operasjon av halspulsåre (Carotis-endarterek-tomi)? 1 Ja 2 Nei 9 Ukjent

Er svelgefunksjonen vurdert/testet? 1 Ja 2 Nei 3 Ikke relevant 9 Ukjent

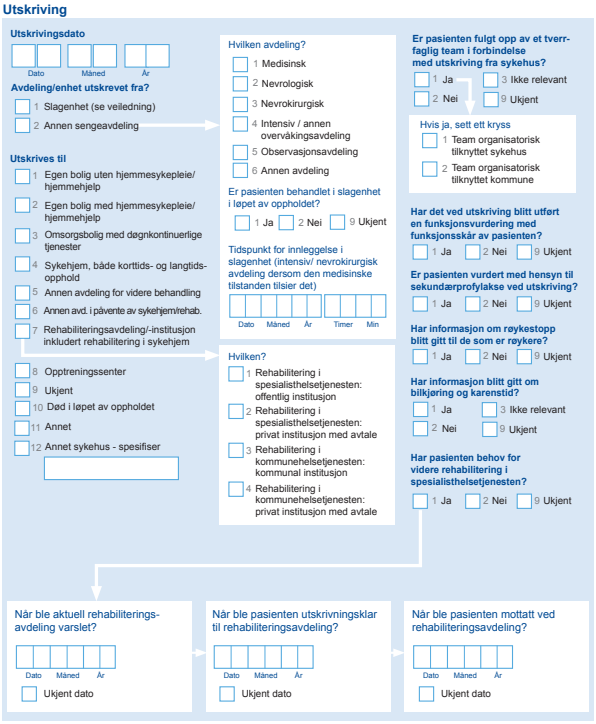
Er pasienten mobilisert ut av seng i løpet av de første 48 timer etter innleggelsen? 1 Ja 2 Nei 9 Ukjent

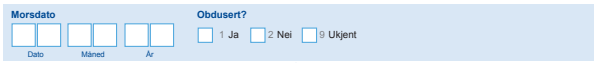
Er det gjennomført daglige skåringer med validert skåringsskjema for nevrologiske utfall de første tre døgn? 1 Ja 2 Nei 9 Ukjent

Har pasienten fått en tverrfaglig vurdering? 1 Ja 2 Nei 9 Ukjent

Side 4

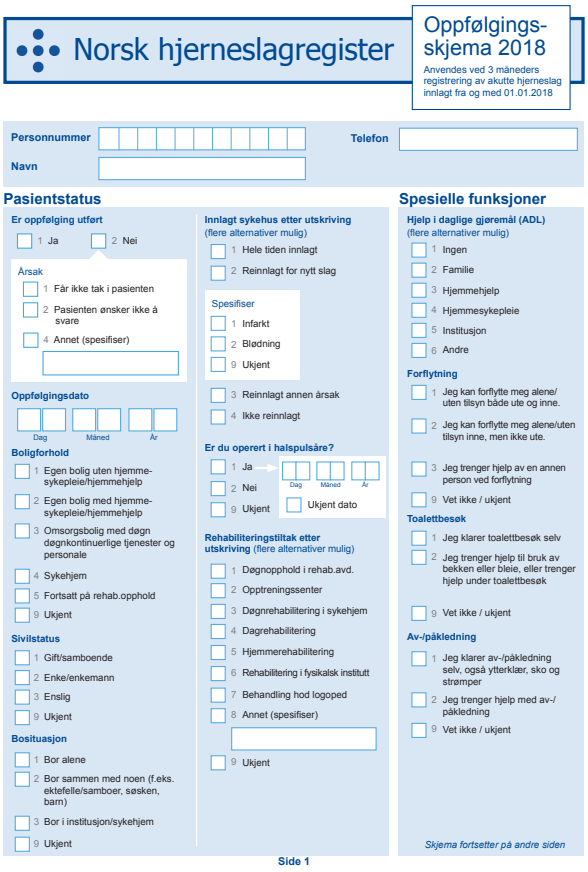
## Utskriving




Side 5

# Appendix 2: NSR Follow-up form 2018



Norsk hjerneslagregister

Oppfølgings-skjema 2018

Anvendes ved 3 måneders registrering av akutte hjerneslag innlagt fra og med 01.01.2018

Personnummer

Telefon

Navn

## Pasientstatus

**Er oppfølging utført**
1 Ja 2 Nei

Årsak
1 Får ikke tak i pasienten
2 Pasienten ønsker ikke å svare
4 Annet (spesifiser)

**Oppfølgingsdato**
Dag Måned År

**Boligforhold**
1 Egen bolig uten hjemme-sykepleie/hjemmehjelp
2 Egen bolig med hjemme-sykepleie/hjemmehjelp
3 Omsorgsbolig med døgn døgnkontinuerlige tjenester og personale
4 Sykehjem
5 Fortsatt på rehab.opphold
9 Ukjent

**Sivilstatus**
1 Gift/samboende
2 Enke/enkemann
3 Enslig
9 Ukjent

**Bosituasjon**
1 Bor alene
2 Bor sammen med noen (f.eks. ektefelle/samboer, søsken, barn)
3 Bor i institusjon/sykehjem
9 Ukjent

**Innlagt sykehus etter utskriving** (flere alternativer mulig)
1 Hele tiden innlagt
2 Reinnlagt for nytt slag

Spesifiser
1 Infarkt
2 Blødning
9 Ukjent

3 Reinnlagt annen årsak
4 Ikke reinnlagt

**Er du operert i halspulsåre?**
1 Ja → Dag Måned År
2 Nei
9 Ukjent
Ukjent dato

**Rehabiliteringstiltak etter utskriving** (flere alternativer mulig)
1 Døgnopphold i rehab.avd.
2 Opptreningssenter
3 Døgnrehabilitering i sykehjem
4 Dagrehabilitering
5 Hjemmerehabilitering
6 Rehabilitering i fysikalsk institutt
7 Behandling hod logoped
8 Annet (spesifiser)
9 Ukjent

## Spesielle funksjoner

**Hjelp i daglige gjøremål (ADL)** (flere alternativer mulig)
1 Ingen
2 Familie
3 Hjemmehjelp
4 Hjemmesykepleie
5 Institusjon
6 Andre

**Forflytning**
1 Jeg kan forflytte meg alene/ uten tilsyn både ute og inne.
2 Jeg kan forflytte meg alene/uten tilsyn inne, men ikke ute.
3 Jeg trenger hjelp av en annen person ved forflytning
9 Vet ikke / ukjent

**Toalettbesøk**
1 Jeg klarer toalettbesøk selv
2 Jeg trenger hjelp til bruk av bekken eller bleie, eller trenger hjelp under toalettbesøk
9 Vet ikke / ukjent

**Av-/påkledning**
1 Jeg klarer av-/påkledning selv, også ytterklær, sko og strømper
2 Jeg trenger hjelp med av-/påkledning
9 Vet ikke / ukjent

*Skjema fortsetter på andre siden*

Side 1

## Oppfølging og livskvalitet

**Har du problemer med å lese eller skrive (som ikke var tilstede før hjerneslaget)?**
1 Ja
2 Nei
9 Vet ikke / ukjent

**Har du problemer med å svelge (som ikke var tilstede før hjerneslaget)?**
1 Ja
2 Nei
9 Vet ikke / ukjent

**Har du problemer med å snakke (som ikke var tilstede før hjerneslaget)?**
1 Ja
2 Nei
9 Vet ikke / ukjent

**Har du synsproblemer (som ikke var tilstede før hjerneslaget)?**
1 Ja
2 Nei
9 Vet ikke / ukjent

**Har du kommet deg helt etter hjerneslaget?**
1 Ja
2 Nei
9 Vet ikke / ukjent

**Har du fått tilstrekkelig hjelp etter hjerneslaget?**
1 Ja
2 Nei
3 Har ikke behov
9 Vet ikke / ukjent

**Har du fått så mye trening som du ønsker etter hjerneslaget?**
1 Ja
2 Nei
3 Har ikke behov
9 Vet ikke / ukjent

**Har du vært til legekontroll etter hjerneslaget?**
1 Ja
2 Nei
9 Vet ikke / ukjent

Kontroll for hjerneslaget i sykehus?
1 Ja → Dag Måned År
2 Nei
9 Vet ikke/ ukjent
Ukjent dato

**Er du like fornøyd med tilværelsen etter hjerneslaget som før hjerneslaget?**
1 Ja
2 Nei
9 Vet ikke / ukjent

**Tar du medisin mot høyt blodtrykk?**
1 Ja
2 Nei
9 Vet ikke / ukjent

**Tar du blodfortynnende medisin mot blodpropp?**
1 Ja
2 Nei
9 Vet ikke / ukjent

**Tar du medisin mot høyt kolesterol?**
1 Ja
2 Nei
9 Vet ikke / ukjent

**Røykestatus**
0 Aldri
1 Røyker
2 Eks-røyker (røykfri > 1 mnd)
9 Ukjent

**Var du yrkesaktiv da du fikk hjerneslag?**
1 Ja
2 Nei
9 Vet ikke / ukjent

**Er du yrkesaktiv nå?**
1 Ja
2 Nei
9 Vet ikke / ukjent

**Hadde du førerkort før du fikk hjerneslag?**
1 Ja
2 Nei
9 Vet ikke/ukjent

Hvis ja, hva er førerkortstatus nå?
1 Fortsatt gyldig førerkort
2 Inndratt førerkort
3 Fortsatt gyldig førerkort, men midlertidig kjøreforbud
9 Ukjent

**Hvis fortsatt gyldig førerkort, kjører du bil nå?**
1 Ja
2 Nei
9 Vet ikke / ukjent

**Funksjonsstatus** (Modified Rankin Scale) Sett kun ett kryss ved svaralternativet som best beskriver ditt funksjonsnivå

0 Ingen symtomer
1 Ingen betydningsfull funksjonssvikt til tross for symptomer, klarer å utføre alle oppgaver og aktivi-teter som før
2 Lett funksjonssvikt; klarer ikke å utføre alle aktiviteter som før, men klarer sine daglige gjøremål
3 Moderat funksjonssvikt; trenger noe hjelp, men går uten hjelp
4 Alvorlig funksjonssvikt; klarer ikke å gå uten hjelp og klarer ikke å ivareta sine grunnleggende behov uten hjelp
5 Svært alvorlig funksjonssvikt; sengeliggende og trenger konstant tilsyn og hjelp

**Besvart av** (flere alternativer mulig)
1 Pasient
2 Familie
3 Helsepersonell
4 Andre → Spesifiser

**Hvordan ble oppfølgingsskjema etter 3 måneder registrert?**
1 Per telefon
2 Per brev
3 Ved besøk på poliklinikk
4 Annet

Side 2

# Appendix 3: Complete list of variables

**Data fra «Akuttskjema»:**

| Variabel | Beskrivelse |
|---|---|
| Pasient nr. (Individ) | 1-68 |
| Årstall | 1. 2017<br>2. 2018<br>3. 2019 |
| I: PREHOSPITALT OG STATUS AKUTTFASE | |
| Inklusjonskriterier | |
| Kriterium som pasienten har hjerneslagdiagnose i henhold til | 1. Vedvarende akutte fokale utfall (> 24 timer) med positiv bildediagnostikk. Innlagt i sykehus innen 28 døgn fra symptomdebut<br>2. Vedvarende akutte fokale utfall (> 24 timer) uten positiv bildediagnostikk. Innlagt i sykehus innen 28 døgn fra symptomdebut<br>3. Forbigående akutte fokale utfall (< 24 timer) med positiv bildediagnostikk<br>4. Ingen av overnevnte |
| Slagdiagnose | 1. I 61 = Hjernebløding<br>2. I 63 = Hjerneinfarkt<br>3. I 64 = Uspesifisert |
| Hjerneslag som hoveddiagnose eller bidiagnose? | 1. Hoveddiagnose<br>2. Bidiagnose |
| Tilstand før det aktuelle hjerneslaget | |
| Boligforhold | 1. Egen bolig uten hjemmesykepleie/hjemmehjelp<br>2. Egen bolig med hjemmesykepleie/hjemmehjelp<br>3. Omsorgsbolig med døgnkontinuerlige tjenester<br>4. Sykehjem<br>9. Ukjent |
| Bosituasjon | 1. Pasienten bodde alene<br>2. Pasienten bodde sammen med noen<br>3. Pasienten bodde i institusjon/sykehjem<br>9. Ukjent |
| Forflytning | 1. Alene - ute og inne<br>2. Alene - inne<br>3. Med hjelp<br>9. Ukjent |
| Toalettbesøk | 1. Alene<br>2. Med hjelp<br>9. Ukjent |
| Påkledning | 1. Alene<br>2. Med hjelp<br>9. Ukjent |
| Funksjonsstatus: Modified Rankin Scale | 1. 0: Ingen symptomer<br>2. 1: Ikke betydelig funksjonssvikt<br>3. 2: Lett funksjonssvikt<br>4. 3: Moderat funksjonssvikt<br>5. 4: Alvorlig funksjonssvikt<br>6. 5: Svært alvorlig funksjonssvikt<br>7. 6: Død |
| Risikofaktorer før hjerneslaget | |
| Tidligere hjerneslag? | 1. Ja<br>2. Nei<br>9. Ukjent |
| Anfør type | 1. Infarkt<br>2. Blødning<br>3. Uspesifisert<br>4. Både infarkt og blødning<br>9. Ukjent |
| Gjennomgått store hjerte- eller karintervensjoner | 1. Ja<br>2. Nei<br>9. Ukjent |
| Når | 1. Innen siste uke<br>2. 1-4 uker før slaget<br>3. 4-12 uker før slaget<br>4. Over 12 uker |
| Atrieflimmer bekreftet med EKG tidligere eller i løpet av innleggelsen (gjelder også paroxystisk atrieflimmer/flutter)? | 1. Ja<br>2. Nei<br>9. Ukjent |
| Når ble atrieflimmer oppdaget? | 1. Atrieflimmer tidligere |

| | |
|---|---|
| | 2. Atrieflimmer nyoppdaget ved ankomst til sykehuset eller under innleggelsen |
| **Status i akuttfasen** | |
| Bevissthetsgrad ved innleggelsen | 0. Våken<br>1. Døsig, reagerer adekvat ved lett stimulering<br>2. Døsig, reagerer først ved kraftig/gjentatt stimulering<br>3. Reagerer ikke, eller bare med ikke-målrettet bevegelse<br>9: Ukjent |
| Facialisparese | 1. Ja<br>2. Nei<br>9. Ukjent |
| Armparese | 1. Ja<br>2. Nei<br>9. Ukjent |
| Beinparese | 1. Ja<br>2. Nei<br>9. Ukjent |
| Språkproblemer (afasi) | 1. Ja<br>2. Nei<br>9. Ukjent |
| Andre nye fokale slagsymptomer | 1. Ja<br>2. Nei<br>9. Ukjent |
| *Hvis ja, angi fokale slagsymptomer* | • Dysartri<br>• Ataksi<br>• Sensibilitetsutfall<br>• Neglekt<br>• Dobbeltsyn<br>• Synsfeltutfall<br>• Vertigo |
| NIHSS - angi totalscore akutt ved innkomst | 0-42 |
| NIHSS – angi totalscore ved 24 timer +/÷ 12 timer etter innkomst | 0-42 |
| Sidelokalisasjon av symptomer | 1. Høyre<br>2. Venstre<br>3. Bilateralt<br>4. Ikke relevant<br>9. Ukjent |
| Cerebral CT eller MR ved innkomst (innen 12 timer) | 1. Ja<br>2. Nei<br>9. Ukjent |
| **II: MEDIKAMENTER OG PROSEDYRER** | |
| **Reperfusjonsbehandling** | |
| Er pasienten vurdert for reperfusjonsbehandling (trombolyse/trombektomi)? | 1. Ja<br>2. Nei<br>9. Ukjent |
| Hvis Ja, vurdert: | 1. Behandlet med trombolyse/trombektomi<br>2. Ikke behandlet - kontraindikasjon |
| **Trombolytisk behandling** | |
| Trombolytisk behandling | 1. Ja<br>2. Nei<br>3. Inklusjon i studie<br>9. Ukjent |
| Dersom ja, ved hvilket sykehus | Ett blant alle norske sykehus (totalt 67) |
| Starttidspunkt trombolyse | Dato og klokkeslett |
| Medikament og dosering | 1. Alteplase, standard dose 0,9 mg/kg<br>2. Alteplase, redusert dose<br>3. Annet trombolytisk medikament<br>9. Ukjent |
| Hjerneblødning innen 36 timer etter behandlingsstart | 1. Ja<br>2. Nei<br>9. Ukjent |
| Er trombektomi eller annen endovaskulær behandling gjennomført? | 1. Ja<br>2. Nei<br>3. Inklusjon i studie<br>9. Ukjent |
| Dersom ja, ved hvilket sykehus | Ett blant alle norske sykehus |
| **Hemikraniektomi** | |
| Er hemikraniektomi gjennomført? | 1. Ja |

| | |
|---|---|
| | 2. Nei<br>3. Inklusjon i studie<br>9. Ukjent |
| Dersom ja, ved hvilket sykehus | Ett blant alle norske sykehus |
| Starttidspunkt hemikraniektomi | Dato og klokkeslett |
| **III: BEHANDLINGSKJEDE OG UTSKRIVING** | |
| **Behandlingskjeden** | |
| Symptomdebut | Dato og klokkeslett |
| Våknet pasienten med symptom på hjerneslag? | 1. Ja<br>2. Nei<br>9. Ukjent |
| Innleggelsestidspunkt | Dato og klokkeslett |
| Timer fra symptomdebut til innleggelse | 1. 0-3 timer før innleggelse<br>2. 3-4,5 timer før innleggelse<br>3. 4,5-6 timer før innleggelse<br>4. 6-12 timer før innleggelse<br>5. 12-24 timer før innleggelse<br>6. 24 timer – 7 dager før innleggelse<br>7. Mer enn 7 døgn før innleggelse |
| Mindre enn fire timer fra symptomdebut til innleggelse | 1. Ja<br>2. Nei<br>9. Ukjent |
| Hvor oppsto hjerneslaget | 1. Utenfor sykehus<br>2. I sykehus, ikke prosedyrerelatert<br>3. I sykehus, prosedyrerelatert |
| Hvis utenfor sykehus; ble AMK/ambulanse varslet | 1. Ja<br>2. Nei<br>9. Ukjent |
| Transportmetode | 1. Ambulanse<br>2. Luftambulanse<br>3. Kombinasjon av ambulanse og luftambulanse<br>4. Annet |
| Ble pasienten innlagt/utredet via «trombolysealarm» eller tilsvarende varsling som er nødvendig for akutt utredning og trombolysebehandling | 1. Ja<br>2. Nei<br>9. Ukjent |
| Avdeling/enhet først innlagt | 1. Slagenhet<br>2. Annen sengeavdeling |
| Annen avdeling først innlagt, hvilken | 1. Medisinsk<br>2. Nevrologisk<br>3. Nevrokirurgisk<br>4. Intensivavdeling<br>5. Observasjonsavdeling<br>6. Annen Avdeling |
| Overflyttet fra sykehus | 1. Ja<br>2. Nei<br>9. Ukjent |
| Hvis overflyttet, fra hvilket sykehus | Ett blant alle norske sykehus |
| **Hvilke undersøkelser og tiltak er utført/bestilt under oppholdet?** | |
| Bildediagnostikk av hjerneslaget | 1. Ingen<br>2. CT<br>3. MRI<br>4. Både CT og MRI<br>5. Annen<br>9. Ukjent |
| Bildediagnostikk av ekstrakranielle kar | 1. Ingen<br>2. Ultralyd<br>3. CT-angio<br>4. MR-angio<br>5. Kombinasjon av flere<br>9. Ukjent |
| Bildediagnostikk av intrakranielle kar | 1. Ingen<br>2. Ultralyd<br>3. CT-angio<br>4. MR-angio<br>5. Kombinasjon av flere<br>9. Ukjent |
| Foreligger det tilstopping av store blodkar inne i hjernen (toppen av arteria carotis | 1. Ja<br>2. Nei |

| | |
|---|---|
| interna, eller (M1) eller (M2) i arteria cerebri media)? | 9. Ukjent |
| Har pasienten fått en tverrfaglig vurdering | 1. Ja<br>2. Nei<br>9. Ukjent |
| Utskrivingsdato | Dato og klokkeslett |
| Avdeling utskrevet fra | 1. Slagenhet<br>2. Annen sengeavdeling |
| Hvis annen avdeling, hvilken? | 1. Medisinsk<br>2. Nevrologisk<br>3. Nevrokirurgisk<br>4. Intensivavdeling<br>5. Observasjonsavdeling<br>6. Annen avdeling |
| Er pasienten behandlet i slagenhet i løpet av oppholdet? | 1. Ja<br>2. Nei<br>9. Ukjent |
| Utskrives til | 1. Egen bolig uten hjemmesykepleie/hjemmehjelp<br>2. Egen bolig med hjemmesykepleie/hjemmehjelp<br>3. Omsorgsbolig med døgnkontinuerlige tjenester<br>4. Sykehjem, både korttids- og langtidsopphold<br>5. Annen avdeling for videre behandling<br>6. Annen avdeling i påvente av sykehjem/rehabilitering<br>7. Rehabiliteringsavdeling/-institusjon – inkludert rehabilitering i sykehjem<br>8. Opptreningssenter<br>9. Ukjent<br>10. Død i løpet av oppholdet<br>11. Annet<br>12. Annet sykehus |
| Rehabiliteringsinstitusjon | 1. Rehabilitering i spesialisthelsetjenesten – offentlig institusjon<br>2. Rehabilitering i spesialisthelsetjenesten – privat institusjon med avtale<br>3. Rehabilitering i kommunehelsetjenesten – kommunal institusjon<br>4. Rehabilitering i kommunehelsetjenesten – privat institusjon med avtale |
| Antall dager innlagt | Antall dager |
| Oppfølging av et tverrfaglig team i forbindelse med utskriving fra sykehus | 1. Ja<br>2. Nei<br>3. Ikke relevant<br>9. Ukjent |
| Har det ved utskriving blitt utført en funksjonsvurdering med funksjonsskår av pasienten? | 1. Ja<br>2. Nei<br>9. Ukjent |
| Morsdato | Dato og klokkeslett |

**Data fra «Oppfølgingsskjema»:**

| **Variabel** | **Beskrivelse** |
|---|---|
| Pasient nr. (Individ) | 1-150(?) |
| Årstall | 1. 2017<br>2. 2018<br>3. 2019<br>4. 2020 |
| **Oppfølging utført** | |
| Er oppfølging utført | 1. Ja<br>2. Nei |
| Årsak | 1. Får ikke tak i pasienten<br>2. Pasienten ønsker ikke å svare<br>3. Død<br>4. Annet |
| Dødsdato | Dato og klokkeslett |
| Annet spesifisert | Fri eller kodet tekst. |
| Oppfølgingsdato | Dato og klokkeslett |
| Antall dager mellom innleggelse og oppfølging | Antall |
| Antall dager mellom innleggelse og død | Antall |
| **Status** | |
| Boligforhold | 1. Egen bolig uten hjemmesykepleie/hjemmehjelp<br>2. Egen bolig med hjemmesykepleie/hjemmehjelp<br>3. Omsorgsbolig med døgnkontinuerlige tjenester<br>4. Sykehjem<br>9. Ukjent |
| Bosituasjon | 1. Pasienten bodde alene |

| | |
|---|---|
| | 2. Pasienten bodde sammen med noen<br>3. Pasienten bodde i institusjon/sykehjem<br>9. Ukjent |
| **Reinnleggelse og rehabilitering** | |
| Innlagt sykehus etter utskriving | 1. Hele tiden<br>2. Reinnlagt for nytt slag<br>3. Reinnlagt annen årsak<br>4. Ikke reinnlagt |
| Hvis reinnlagt for nytt hjerneslag, hvilken type hjerneslag? | 1. Infarkt<br>2. Blødning<br>9. Ukjent |
| Er du operert i halspulsåre? | 1. Ja<br>2. Nei<br>9. Ukjent |
| *Reinnleggelse og rehabilitering etter utskriving (flere alternativer mulig)* | • Hjemmerehabilitering<br>• Opptreningssenter<br>• Dagrehabilitering<br>• Døgnopphold i rehab. avd<br>• Døgnrehabilitering i sykehjem<br>• Rehabilitering i fysikalsk institutt<br>• Behandling hos logoped<br>• Ukjent<br>• Annet (Spesifiser under)<br>- Spesifiser: Fri eller kodet tekst |
| *Hjelp i daglige gjøremål (ADL)* | • Ingen<br>• Familie<br>• Hjemmehjelp<br>• Hjemmesykepleien<br>• Institusjon<br>• Andre |
| **Hjelp i daglige gjøremål** | |
| Forflytning | 1. Alene - ute og inne<br>2. Alene – inne<br>3. Med hjelp<br>9. Ukjent |
| Toalettbesøk | 1. Alene<br>2. Med hjelp<br>9. Ukjent |
| Påkledning | 1. Alene<br>2. Med hjelp<br>9. Ukjent |
| **Vurdering av oppfølging og livskvalitet etter hjerneslaget** | |
| Har du problemer med å lese og skrive (som ikke var tilstede før hjerneslaget)? | 1. Ja<br>2. Nei<br>9. Vet ikke/Ukjent |
| Har du problemer med å svelge (som ikke var tilstede før hjerneslaget)? | 1. Ja<br>2. Nei<br>9. Vet ikke/Ukjent |
| Har du problemer med å snakke (som ikke var tilstede før hjerneslaget)? | 1. Ja<br>2. Nei<br>9. Vet ikke/Ukjent |
| Har du synsproblemer (som ikke var tilstede før hjerneslaget)? | 1. Ja<br>2. Nei<br>9. Ukjent |
| Har du kommet deg helt etter hjerneslaget? | 1. Ja<br>2. Nei<br>9. Vet ikke/Ukjent |
| Har du fått tilstrekkelig hjelp etter hjerneslaget? | 1. Ja<br>2. Nei<br>3. Har ikke behov<br>9. Vet ikke/Ukjent |
| Har du fått så mye trening som du ønsker etter hjerneslaget? | 1. Ja<br>2. Nei<br>3. Har ikke behov<br>9. Vet ikke/Ukjent |
| Har du vært til legekontroll etter hjerneslaget? | 1. Ja<br>2. Nei<br>9. Vet ikke/Ukjent |

| | |
|---|---|
| Er du like fornøyd med tilværelsen etter hjerneslaget som før hjerneslaget? | 1. Ja<br>2. Nei<br>9. Vet ikke/Ukjent |
| Tar du blodfortynnende medisin mot blodpropp? | 1. Ja<br>2. Nei<br>9. Vet ikke/Ukjent |
| Var du yrkesaktiv da du fikk hjerneslaget? | 1. Ja<br>2. Nei<br>9. Ukjent |
| Er du yrkesaktiv nå? | 1. Ja<br>2. Nei<br>9. Ukjent |
| Hadde du førerkort før du fikk hjerneslag? | 1. Ja<br>2. Nei<br>9. Ukjent |
| Førerkortstatus nå? | 1. Fortsatt gyldig førerkort<br>2. Inndratt førerkort<br>3. Fortsatt midlertidig kjøreforbud<br>9. Ukjent |
| Kjører du bil nå? | 1. Ja<br>2. Nei<br>9. Ukjent |
| Modified Rankin Scale | 1. 0: Ingen symptomer<br>2. 1: Ikke betydelig funksjonssvikt<br>3. 2: Lett funksjonssvikt<br>4. 3: Moderat funksjonssvikt<br>5. 4: Alvorlig funksjonssvikt<br>6. 5: Svært alvorlig funksjonssvikt<br>7. 6: Død |

# Summary of evidence quality/certainty grading

| **Reference:** Chua AE, Buckley BS, Lapitan MC, Jamora, RD. Hemicraniectomy for Malignant Middle cerebral Infarction (HeMMI): A randomised controlled clinical trial of decompressive surgery with standardized medical care versus standardized medical care alone. Acta medica Philippina [electronic article]. 2015 [cited 2021-05-24];49(1):28-33. doi: . | **Design:** RCT |
|---|---|
| | |
| | GRADE Low/moderate |

| **Purpose/goal** | **Material and methods** | **Results** | **Discussion/comments** |
|---|---|---|---|
| To compare decompressive hemicraniectomy combined with standard medical care with standard medical care alone at the Philippine General Hospital.<br><br>**Conclusion**<br><br>The HeMMi trial identified no statistically significant differences between either treatment and functional outcomes or mortality.<br><br>**Country**<br><br>Philippines.<br><br>**Year of data collection**<br><br>January 2002 - December 2009. | **Recruitment of participants:**<br>All patients were recruited from a single centre, the Philippine General Hospital.<br>**Inclusion criteria:**<br>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.<br>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.<br>**Exclusion criteria:**<br>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.<br>**Data:**<br>Undisclosed. Results for primary and secondary outcome measures are reported by intention-to-treat (ITT) and per-treatment.<br>**Outcome:**<br>Mortality at 6 months and functional outcomes (mRS 0-3 and 4-6) at 6 months.<br>“Primary outcome: functional status (mRS) at 6 months.<br>Secondary outcome: mortality/death.”<br>**Important confounding factors:** n.a.<br>**Statistical methods:**<br>Results for primary and secondary outcome measures are reported by intention-to-treat (ITT) and per-treatment. Distributions of baseline characteristics and dichotomized outcomes were compared between groups using t-tests and chi-squared tests as appropriate and distributions of the whole spectrum of functional outcome scores using Wilcoxon-Mann-Whitney U tests. Risk difference (absolute risk reduction) and 95% confidence intervals were calculated for all outcomes. | **Main findings:**<br>No statistically significant differences in either functional status outcome or mortality were observed in either functional status outcome or mortality were observed in either intention-to-treat or per-treatment analysis.<br><br>**Other findings:**<br>No statistically significant differences in baseline characteristics were observed between the two groups | **Checklist:**<br>**Is the purpose of the study well formulated?** No.<br>**Were the groups alike from the start?** No statistically significant differences in baseline characteristics were observed between the two groups.<br>**Randomization technique:** Randomization was computer-generated, with each treatment assignment enclosed in sealed sequentially numbered envelopes. After confirming eligibility and obtaining informed consent, the envelope with the lowest number was opened upon patient enrollment. Treatment allocation sequence was concealed from study staff and the patient until the envelope was opened.<br>**Were all participants documented at the end of the study?**<br>5 participants lost to follow up<br>**Were the participants/staff blinded?** Undisclosed.<br>**Were the groups treated the same, except for «intervension»?** Undisclosed.<br>**What are the results?** Comparison (in terms of statistical significance) of decompressive hemicraniectomy combined with standard medical care, with standard medical care alone.<br>**Are the results transferable to practice?:** Uncertain. High risk of bias due to incompletely disclosed method of blinding. The study is a single-center study, which can affect generalizability.<br>**Were all outcomes evaluated?** Yes.<br>**Does the pros outweigh the cons?** Not discussed<br>**What does the authours discuss about:**<br>**Strength:** The trial design allowed the crossover of medical group patients who deteriorated to surgery,<br>**Weakness:** This was a single-center study, which can affect generalizability.<br>**Does the authors refer to other literature to strengthen/weaken the results?**Yes, the detection of no statistically significant association between treatment and functional status (mRS) at 6 months are in line with previous meta-analyses of 1-year outcomes of three European trials (Hamlet, DESTINY, and DECIMAL).<br>The detection of no association between surgery and improved survival, is not in line with the three European trials, but these results are similar to those in the study HeADDFIRST conducted in the U.S.<br>**Does the results have plausible explanations?**<br>Yes, that no improved survival was seen in HeMMI’s surgical group may reflect a lower capacity to recover from major surgery as a result of the relatively older age of the trial’s patients compared to those in the European trials, in which a survival benefit was observed. This may also be related to the effect of poorer general health status on capacity to recover. |

**Reference:** Frank JI, Schumm LP, Wroblewski K, Chyatte D, Rosengart AJ, et al. Hemicraniectomy and durotomy upon deterioration from infarction-related swelling trial (HeADDFIRST): randomized pilot clinical trial. Stroke [electronic article]. 2014 [cited 2021-05-24];45(3):781-787. doi:10.1161/STROKEAHA.113.003200.

**Design: RCT**

GRADE: moderate

| Purpose/goal | Material and methods | Results | Discussion/comments |
|---|---|---|---|
| To evaluate the benefit of surgical decompression for brain swelling from large supratentorial cerebral hemispheric infarction.<br><br>**Conclusion**<br><br>HeADDFIRST randomization criteria effectively distinguished low from high risk of death from large supratentorial cerebral hemispheric infarction. Lower mortality in the medical treatment only group than in other published trials suggests a possible benefit to standardizing medical management<br><br>**Country**<br><br>United Kingdom<br><br>**Year of data collection** | **Recruitment of participants:**<br>All patients with ischemic stroke admitted to each participating centre were screened. Twenty centers in North America participated in HeADDFIRST, each with its own neurologist investigator.<br>**Inclusion criteria:**<br>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.<br>**Exclusion criteria:**<br>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.<br>**Outcome:**<br>The primary end point was survival at 21 days after stroke onset. Secondary end points included the following: Modified Rankin Scale, NIHSS, Glasgow Outcome Scale, and Barthel Index Score. .<br>**Important confounding factors:** n.a.<br>**Statistical methods:**<br>Descriptive statistics (median, 25th and 75th percentiles, or frequency counts) were used to summarize the demographics, comorbidities, and disease characteristics of the study groups. Fisher exact test was used to evaluate differences in categorical measures between groups. Confidence intervals (CI) for mortality rates in each treat- ment group were calculated using exact binomial methods, and a confidence interval for the difference in mortality rates was calcu- lated using the normal approximation. Statistical significance was defined as P<0.05. Analyses and data management were performed using Stata. | **Main findings:**<br>Mortality at 21 and 180 days was 40% (4/10) in the medical treatment only and 21% (3/14) and 36% (5/14) in the medical treatment plus surgery arms, respectively. | **Checklist:**<br>**Is the purpose of the study well formulated?** Yes.<br>**Were the groups alike from the start?** The MTO group had more risk factors in baseline characteristics (e.g. age, hypertension, arrhytmias, diabetes).<br>**Randomization technique:**<br>Randomization was performed in blocks of size 4 within each cen- ter and separately by hemispheric side (left or right). In addition, as- signments were further restricted to guarantee that both treatments would be assigned within the first 3 patients enrolled at each center.<br>To ensure that registration and randomization could be performed quickly and efficiently, the Data Coordinating Center designed a Web-based registration and randomization system.<br>**Were all participants documented at the end of the study?**<br>- Mortality at 6 mo: 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<br>- MRS at 90 days: 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.<br>- MRS 0-2 at 90 days: 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<br>- MRS 0-3 at 90 days: 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<br>- MRS 0-4 at 90 days: 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.<br>**Were the participants/staff blinded? ?** During the examination, patients wore a specially designed cap intended to mask any signs of surgery, and family and caregivers were instructed not to discuss the patient's acute management with the examiner. After the examination, the examiner completed a questionnaire in which he or she was asked to guess the patient's treatment assignment and to re- port on any conversation or other factors that might have revealed the patient's treatment assignment.<br>**Were the groups treated the same, except for «intervension»?**<br>One center had a single major violation in one patient that involved the use of mannitol off protocol in an MTO patient on 1 occasion thereby triggering a warning and planned site visit for the next registered patient which never occurred. Seven patients at 4 centers had minor violations related to for- mulary differences at the respective centers.<br>**What are the results?** Higher mortality in patients receiving medical treatment only, compared to DHC<br>**Are the results transferable to practice?** Uncertain. The study is a multi-center study, which is in favour of generalizability.<br>**Were all outcomes evaluated?**No. Mortality, NIHSS and functional outcome (mRS) was evaluated.<br>**Does the pros outweigh the cons? ?** Not discussed.<br>**What does the authours discuss about:**<br>**Streangth: N**ot discussed<br>**Weakness:** Not discussed<br>**Does the results have plausible explanations?**<br>The lower mortality of the HeADDFIRST conservatively treated patients may be related to the fact that HeADDFIRST inclusion criteria allowed older patients than the randomized European trials (DECIMAL, DESTINY, HAMLET). Older patients have more brain atrophy and are well recognized to tolerate their brain swelling better than younger patients. |

| **Reference:** Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB. 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 [electronic article]. 2009 [cited 2020-03-24];8(4):326-33. doi: 10.1016/S1474-4422(09)70047-X. | **Design: RCT** |
|---|---|
| | |
| | GRADE Moderate |

| Purpose/goal | Material and methods | Results | Discussion/comments |
|---|---|---|---|
| To assess the effect of decompressive surgery within 4 days of the onset of symptoms in patients with space-occupying hemispheric infarction.<br><br>**Conclusion**<br><br>Surgical decompression reduces case fatality and poor outcome in patients with space-occupying infarctions who are treated within 48 h of stroke onset. There is no evidence that this operation improves functional outcome when it is delayed for up to 96 h after stroke onset.<br><br>**Country**<br><br>Netherlands<br><br>**Year of data collection**<br><br>November, 2002 - October, 2007 | **Recruitment of participants:**<br>Patients were enrolled at six centres in the Netherlands, according to a previously published protocol.Setting: Stroke unit, intensive care unit<br>**Inclusion criteria:**<br>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.<br>**Exclusion criteria:**<br>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.<br>**Outcome:**<br>Mortality at 1 year and functional outcome (mRS 0-3) at 1 year. Both for surgery within and after 48h.<br>**Important confounding factors:** n.a.<br>**Statistical methods:**<br>To assess the effect of surgical treatment, absolute risk reductions (ARR) and corresponding 95% CIs were calculated. Analyses were by intention to treat. To assess the effect of imbalances in age and time to randomisation at baseline, we also calculated adjusted effect estimates. | **Main findings:**<br>Surgical decompression had no effect on the primary outcome measure (absolute risk reduction [ARR] 0%, 95% CI –21 to 21) but did reduce case fatality (ARR 38%, 15 to 60). | **Checklist:**<br>**Is the purpose of the study well formulated?** Yes.<br>**Were the groups alike from the start?**<br>The patients who were treated surgically were slightly older, and those who were treated medically waited slightly longer for randomisation.<br>**Randomization technique:**<br>Patients were randomly assigned to surgical decompression or best medical treatment by use of a computerised randomisation service that was available 24 h a day. Randomisation was based on a published algorithm designed to prevent imbalance between treatment groups.<br>**Were all participants documented at the end of the study?**<br>**-** Mortality at 1 year: Group 1 Number missing: 0; Group 2 Number missing: 0.<br>- MRS 0-3 at 1 year: Group 1 Number missing: 0; Group 2 Number missing: 0<br>**Ble gruppene behandlet likt?**<br>Because all but three of the patients who were treated surgically were admitted to an intensive care unit, more of the patients in this group were ventilated, whereas more patients who were medically treated received osmotherapy.<br>**Were the participants/staff blinded?**<br>To prevent observer bias, patients' scores on the mRS were decided independently by three blinded investigators on the basis of a narrative written by an unblinded and independent study nurse who had visited each patient and their relatives.<br>**Were the groups treated the same, except for «intervension»?** To adjust for any potential benefits of treatment in an intensive care unit over treatment at a stroke unit, the authors aimed to study the effect of decompressive surgery in all patients who had received treatment in an intensive care unit and in a group of patients for whom the standard therapy was care at a stroke unit. For this reason, randomisation was stratified according to the intended mode of best medical treatment (ie, intensive care unit or stroke unit).<br>**What are the results?**<br>Surgical decompression had no effect on the primary outcome measure, but did reduce case fatality<br>**Are the results transferable to practice?** Uncertain. The study is a multi-center study, which is in favour of generalizability.<br>**Were all outcomes evaluated?**Yes.<br>**Does the pros outweigh the cons?** Not discussed.<br>**What does the authours discuss about:**<br>**Strength:** Not discussed.<br>**Weakness:** Information on quality of life and symptoms of depression in survivors is misleading in a study of this kind. The 59% absolute reduction in case fatality after surgical decompression in patients randomised within 48 h came at the expense of an almost equivalent increase in the number of patients with moderately severe or severe disability (mRS score of 4 or 5). Post of the patients were referred from general hospitals. The small number of patients with aphasia suggests that there was some selection in the referral of patients for inclusion in this trial.<br>**Does the results have plausible explanations?**<br>One reason for a smaller benefit of surgical decompression in HAMLET could be that the average time until randomisation was longer than it was in DECIMAL and DESTINY, even for the patients who were randomised within 48 h of symptom onset |

| **Reference:** Jüttler 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 [electronic article]. 2007 [cited 2020-03-24];38(9):2518–25. doi: 10.1161/STROKEAHA.107.485649. | **Design: RCT** |
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| | GRADE: Moderate |

| Purpose/goal | Material and methods | Results | Discussion/comments |
|---|---|---|---|
| To assess the effect of decompressive surgery in terms of 30-day mortality and 6- and 12-month functional outcomes.<br><br>**Conclusion**<br><br>Hemicraniectomy reduces mortality in large hemispheric stroke. With 32 patients included, the primary end point failed to demonstrate statistical superiority of hemicraniectomy,<br><br>**Country**<br><br>Germany<br><br>**Year of data collection**<br><br>February 2004 - October 2005 | **Recruitment of participants:**<br>DESTINY is a prospective, oligocenter, randomized, controlled, clinical trial based on a sequential design and registered in the Current Controlled Trials registry<br>**Inclusion criteria:**<br>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<br>**Exclusion criteria:**<br>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<br>**Outcome:**<br>Mortality at 30 days and 1 year. Functional outcome (mRS 0-3) at 30 days and 1 year.<br>**Important confounding factors:** n.a.<br>**Statistical methods:**<br>For analysis of the primary end point, a 2-sided test with an error level of 0.05 was defined. Thereafter, depending on the observed difference in functional outcome, the final sample size was recalculated for a second exploratory trial stage. | **Main findings:**<br>A statistically significant reduction in mortality was reached after 32 patients had been included: 15 of 17 (88%) patients randomized to hemicraniectomy versus 7 of 15 (47%) patients randomized to conservative therapy survived after 30 days (P=0.02). After 6 and 12 months, 47% of patients in the surgical arm versus 27% of patients in the conservative treatment arm had a modified Rankin Scale score of 0 to 3 (P=0.23). | **Sjekkliste:**<br>**Is the purpose of the study well formulated?** Nei<br>**Were the groups alike from the start?** No. There were some imbalances in characteristics, such as a higher median National Institutes of Health Stroke Scale score in the conservative treatment arm (24, versus 21 in the surgical treatment arm), which was due to a statistically nonsignificant higher proportion of patients with infarction of the dominant hemisphere in the conservative treatment arm.<br>**Randomization technique:**<br>Blocked randomization codes, stratified for each center, were provided by an institute in sealed envelopes. Conservative treatment and decompressive surgery were conducted according to a consensus protocol of all participating neurologic, neurosurgical, and intensive care physicians<br>**Were all participants documented at the end of the study?**<br>- Mortality at 30 days: Group 1 Number missing: 0; Group 2 Number missing: 0.<br>- Mortality at 1 year: Group 1 Number missing: 0; Group 2 Number missing: 0<br>- mRS 0-3 at 30 days: Group 1 Number missing: 0; Group 2 Number missing: 0<br>- mRS 0-3 at 1 year: Group 1 Number missing: 0; Group 2 Number missing: 0<br>**Were the participants/staff blinded?**<br>Six-month and 1-year follow-ups were conducted by 1 single investigator, who was not involved in screening, randomization, or patient care. No blinding was applied.<br>**Were the groups treated the same, except for «intervension»?** Yes. All patients were ventilated and treated on an intensive care unit.<br>**What are the results?**<br>A statistically significant reduction in mortality with DHC compared to medical treatment only. Improvement in functional outcome with DHC, although not significant.<br>**Are the results transferable to practice?** Uncertain. The study is a oligo-center study, which is not optimal for generalizability.<br>**Were all outcomes evaluated?**Yes.<br>**Does the pros outweigh the cons?** Not discussed.<br>**What does the authours discuss about:**<br>**Strength:** Not discussed.<br>**Weakness:** 81% of patients originated from 2 centers only. As a matter of fact, this makes DESTINY an oligocenter rather than a multicenter trial. Blinded evaluation of clinical outcome was not possible, which may have introduced bias for the outcome assessment. There were 2 major protocol violations, which were included in the ITT analysis.<br>**Does the authors refer to other literature to strengthen/weaken the results? No** |

| **Reference:** Vahedi K, Vicaut E, Mateo J, Kurtz A, Orabi M, Guichard JP, et. al. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). Stroke [electronic article]. 2007 [cited 2020-03-24];38(9):2506-17. doi: 10.1161/STROKEAHA.107.485235. | **Design: RCT** |
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| Purpose/goal | Material and methods | Results | Discussion/comments |
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| To assess the efficacy of early decompressive craniectomy in patients with malignant MCA infarction.<br><br>**Conclusion**<br><br>Early decompressive craniectomy increased by more than half the number of patients with moderate disability and very significantly reduced (by more than half) the mortality rate compared with that after medical therapy.<br><br>**Country**<br><br>France<br><br>**Year of data collection**<br><br>December 2001 - November 2005 | **Recruitment of participants:**<br>13 selected stroke centers (including a stroke unit and a neurosurgery department in France)<br>**Inclusion criteria:**<br>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.<br>**Exclusion criteria:**<br>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.<br>**Outcome:**<br>Mortality and mRS at 6 months and 1 year.<br>**Important confounding factors:** n.a.<br>**Statistical methods:**<br>Because of ethical considerations (especially the possibility of early termination of the trial in case of a high benefit of craniectomy), it was used a sequential design based on a triangular test (allows early study termination).<br>The frequency of qualitative parameters or categories of mRS scores were compared between the 2 groups by an exact probability test. Comparison of outcomes according to nondichotomized scores on the mRS was made with the Mann-Whitney test.<br>Correlations were done only for exploratory purposes with Spearman‘s nonpara- metric correlation coefficient. For DWI infarct volumes, interrater reliability between the local investigators and the validation committee was tested with an intraclass correlation coefficient. | **Main findings:**<br>Among the 38 patients randomized, the proportion of patients with a modified Rankin scale score 0-3 at the 6-month and 1-year follow-up was 25% and 50%, respectively, in the surgery group compared with 5.6% and 22.2%, respectively, in the no-surgery group (P=0.18 and P=0.10, respectively). There was a 52.8% absolute reduction of death after craniectomy compared with medical therapy only (P=0.0001). | **Sjekkliste:**<br>**Is the purpose of the study well formulated?** Yes<br>**Were the groups alike from the start?** Yes.<br>**Randomization technique:** Undisclosed.<br>**Were all participants documented at the end of the study?**<br>- Mortality at 6 mo and 1 year: Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A<br>- mRS 0-3 at 6 mo: Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A:<br>- mRS 0-3 at 1 year: Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A<br>**Were the participants/staff blinded?**<br>At all visits after the 12-week visit, a neurologist blinded to the therapeutic arm assignment of the patient assessed the mRS (primary outcome). To keep the investi- gator neurologist blinded to therapeutic assignment, the head of each patient (in both groups) was covered with a surgical cap.<br>**Were the groups treated the same, except for «intervension»?** Yes<br>**What are the results?**<br>The proportion of patients with a modified Rankin scale score 0-3 at the 6-month and 1-year were both higher in the surgery group, but not significant. There was a 52.8% significant absolute reduction of death after craniectomy compared with medical therapy only.<br>**Are the results transferable to practice?** Uncertain. The study is a multi-center study, which is in favour of generalizability.<br>**Were all outcomes evaluated?**Yes.<br>**Does the pros outweigh the cons?** Not discussed.<br>**What does the authours discuss about:**<br>**Strength:** Not discussed<br>**Weakness:** Not discussed.<br>**Does the authors refer to other literature to strengthen/weaken the results? No** |