Improving logistics for acute ischaemic stroke treatment:

Reducing system delay before revascularisation therapy by reorganisation of the prehospital visitation and centralization of stroke care

Research Year Report

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Preface

Early in my medical studies at Aarhus University in 2010, I was introduced to clinical neurology by Neurologist Trine Tandrup, who introduced me to Professor Grethe Andersen to whom I expressed my interest in vascular neurology. Eventually this lead to the planning of my research year project about stroke in a collaboration between neurology and clinical epidemiology.

I want to express my deep appreciation to my main supervisor, Professor Grethe Andersen, for the opportunity, help and support she has offered me on this project. Without her help, I doubt I would have been able to complete the project in such a proficient manner. I consider myself very fortunate for getting the chance to work with an expert of her caliber. I credit her for the success of this project as well as for my own professional growth. She has truly inspired me to work with hard work and dedication.

I would like to thank my co-supervisor, Associate Professor Søren Paaske Johnson, for all the knowledge and wisdom in epidemiology he has imparted upon me during my research year. He has been an excellent teacher, mentor and a great inspiration to me. I really look forward to the day I can do the same for someone else.

My special thanks is extended to collaborator and Neurologist Claus Z. Simonsen. I really value the knowledge and insight he has in neurology, and his willingness to share it with me. I feel very grateful to him for taking time out of his busy schedule to answer my many questions – sometimes even beyond the subject of the project. I consider him a valuable mentor.

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Thanks to colleagues and staff at Department of Neurology, Aarhus and “DCE” for the warm welcome I got at the departments, and for the help I have received during the year.

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Abbreviations

AIS	Acute ischemic stroke
r-tPA	Recombinant tissue Plasminogen Activator
EVT	Endovascular therapy
EMS	Emergency Medical Service
DSR	Danish Stroke Registry
EMSCs	Emergency Medical Service Centres
mRS	modified Rankin Scale
OR	Odds ratio
NIHSS	National Institute of Health Stroke Scale
ACS	Acute Coronary Syndrome
FR	Flow Restoration

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Introduction

Timely reperfusion therapy is of critical importance in patients with acute ischemic stroke (AIS) as it is estimated that occlusion of one of the brains large vessels leads to destruction of 1.9 mio. of neurons and 12 km of nerve fibres pr. minute(1). In 2013 the proportion of patients having received revascularization with the use of r-tPA therapy within the narrow 4.5 hour therapeutic window in Denmark was 15% (https://www.sundhed.dk/content/cms/69/4669_dansk-apopleksi-register_aarsrapport_2013_kommenteret-_off_28042014.pdf. Accessed Marts 3 2015). Endovascular therapy (EVT) is another recently evidence-based reperfusion therapy in acute stroke patients with large vessel occlusion in the central arteries of the anterior or posterior circulation (2-4). Treatment with r-tPA and EVT can be combined or EVT can be performed alone when r-tPA is contraindicated. In Denmark EVT has been recommended as an experimental treatment since 2011 guided by a national clinical guideline. EVT is less frequently being used in comparison with r-tPA since only about 25% of acute strokes are major strokes. In order to ensure that more patients receive revascularization therapy within the narrow therapeutic window, and as EVT is only available in 3 highly specialized centres in Denmark it is necessary to reconfigure stroke organization.(5-10) Pre-hospital selection of patients suspected of major stroke to direct transport to and treatment without any delay at one of the 3 EVT centres will be a topic for future research.

Identification of stroke symptoms by patients, bystanders and Emergency Medical Service (EMS) dispatcher staff is not trivial, and symptoms related to the posterior circulation can be particularly difficult to recognize. In addition as many as 20% of the presumed stroke symptoms in patients are caused by other diseases so-called stroke mimics such as migraine, seizure, intracranial processes and more. The reported proportion of strokes correctly identified by EMS dispatchers varies between 30% and 83%, (11-

13) a finding that suggests that additional efforts are warranted in order to improve pre-hospital visitation of patients with acute stroke. Furthermore, continued efforts are needed to ensure effective in-hospital logistics to avoid unnecessary delays after the patients have been admitted.(14,15)

Total delay and patient delay is based on information regarding symptom onset, which may be prone to recall bias and thus uncertain. Moreover, it is often impossible to establish the exact time of stroke onset, and for this reason it would be more relevant to study the effect of health care interventions on system delay, i.e., the time from first contact with the health care system to revascularization. System delay is not hampered by recall bias and less prone to selection bias, and confounding (16). In the present study it was examined whether it was possible to reduce system delay by optimizing the pre-hospital visitation through educating medical dispatch staff and ambulance paramedics in selection, referral and transportation of patients with suspected major stroke symptoms for direct admission at a dedicated stroke centre, and by centralization of in-hospital stroke care.

Methods

Setting and Design: The study was a population-based before-and-after study within Central Denmark Region among patients with AIS admitted for revascularization therapy with thrombolysis and/or endovascular therapy (EVT). The study period was divided into a pre- (June 1 2011-March 31, 2012) and a post-interventional period (April 1, 2012-September 30, 2013) reflecting the timing of the education campaign of the EMS dispatch staff and the centralization of the in-hospital stroke care.

The Danish National Health Service provides tax-supported health care for all inhabitants, guaranteeing access to treatment at general practitioners and hospitals, including EMS transportation. The study was based on data obtained from the Danish Stroke Registry (DSR) and the EMS. The DSR is a clinical registry, which holds data on patient characteristics and care including thrombolysis and EVT on all acute stroke patients in Denmark. The EMS holds pre-hospital data from all operating agencies.

The EMS system in the Central Denmark Region is organized as a partially 1-level and partially 2-level system with initial dispatcher triage. All emergencies deemed in need of an ambulance result in the dispatch of a primary unit manned with two EMS personnel trained in basic life support. Subject to availability and determined by either dispatcher triage or evaluation by the primary unit a physician-manned ambulance or a unit manned with a paramedic also attend the scene.

Prior to the campaign, education in recognizing symptoms of major stroke was undertaken by experienced doctors instructing medical dispatch staff: medical dispatch nurses from the Emergency Medical Service Centres (EMSCs) and ambulance paramedics, in the Central Denmark Region. The medical dispatch staff uses a criteria-based dispatch protocol, namely the Danish Index for Emergency Care (17) (http://www.rm.dk/files/Sundhed/Pr%C3%A6hospital%20og%20Beredskab/Sundhedsberedskab%20-%20og%20pr%C3%A6hospital%20udvalg/Dansk%20Indeks%20version%201.2.pdf. Accessed October 6 2014.) dividing patients into five emergency groups and into 37 chief complaint groups. Assessment is based on systematic questioning of the callers according to the Danish Index for Emergency Care.

Patients with AIS in Central Denmark Region were in the pre-interventional period treated at 6 different hospitals with varying specialization in AIS treatment. In the post-interventional period, all patients were admitted to one of two high volume specialized units: one local thrombolysis centre at Holstebro Hospital and one highly specialized centre providing both thrombolysis and EVT treatment at Aarhus University Hospital.

Unambiguous individual-level linkage between the databases used in this study was possible using the civil registration number, a unique 10-digit personal identification number assigned to every Danish citizen at birth. The study was approved by the Danish Data Protection Agency (J. No. 1-16-02-440-13).(18,19)

Study population: Self-presenters and patients without EMS data were excluded, as were AIS patients not treated with revascularization therapy with either thrombolysis and/or EVT. A flow chart of the identification of the study population is presented in Figure 1. We identified a total of 473 patients who received revascularization therapy including 152 patients in the pre-interventional period and 321 in the post-interventional period.

Data on the size of the total population in Central Denmark Region during the study period was obtained from Statistics Denmark (http://www.statistikbanken.dk/statbank5a/default.asp?w=1280. Accessed December 11 2014). EMS data were not available for patients who were foreign citizens (n=6), living outside the Central Denmark region (n=22) or selfpresenters (n=1).

Thrombolysis has been the recommended treatment for AIS in Denmark since 2002 after the publication of the American National Institute of Neurological Disorders and Stroke (20) (NINDS) trial and the European Cooporative Acute Stroke Study (ECASS) 1(21) and 2(22). Patients were considered potentially eligible for thrombolysis if treatment could be performed within a maximum of 4,5 hours after debut of symptoms (21-23), and after exclusion of intracranial bleeding using MRI or CT. EVT was recommended in addition to r-tPA treatment when the latter was not sufficient or alone when r-tPA treatment was contraindicated.

Outcomes:

1. **Proportion** of revascularized AIS patients.
2. **Time delay**: The estimates of various delays to the initiation of reperfusion therapy were based on prehospital data registered by the EMS providers (Falck A/S and Responce A/S, Aarhus, Denmark) and data registered in the DSR. Figure 2 illustrates delays from symptom onset to revascularization therapy in patients with AIS transported by the Emergency Medical Service:
    - **Treatment delay** was used for the sum of patient, pre- and inhospital delay, i.e. the time from symptom onset to revascularization therapy:
        a. **Patient delay** was defined as the time from symptom onset to EMS call.

        Symptom onset was registered in the DAP and an EVT-database registered by a neurologist at Holstebro or Aarhus University Hospital, respectively. Time of EMS call was registered by a time stamp at the dispatch centre.

b. **System delay** was defined as the sum of pre- and inhospital delay, i.e. the time from contact with the EMS to start of r-tPA infusion or time of groin puncture during EVT:

   i. **Pre-hospital delay** was defined as the time from contact with the EMS to arrival at the revascularizing hospital. Time of arrival on scene, departure from scene, arrival at the local hospital, departure from the local hospital, and arrival at the thrombolysis centre were registered electronically in the ambulance by the EMS personnel by pressing a radio button.

   ii. **In-hospital delay** was defined as the time from arrival at the revascularizing hospital to r-tPA infusion or time of groin puncture during EVT. Symptom onset, time of r-tPA infusion and time of reperfusion during EVT were also registered in the DAP and an EVT-database registered by a neurologist at Holstebro or Aarhus University Hospital, respectively.

   iii. **EVT procedure delay** comprised a part of the inhospital delay in patients treated with EVT, and was defined as the time from groin puncture (guiding-catheter insertion) to time of reperfusion. If time of reperfusion was not available the time of end of EVT procedure was used instead. The use of time of reperfusion during EVT as a surrogate for time of revascularization was made possible using CT-imaging.

3. **Modified Rankin Scale (mRS)** is a measure of functional outcome (FIGURE 3) and was assessed three months after admission in both the pre-interventional and post-interventional group.

Covariates: Baseline characteristics and other covariates (TABLE 1) were derived from the DSR-, EMS- and EVT-databases. In addition time of year and time of transportation variables were created.

Statistical Analysis: Dichotomous data were presented as percentages. Continuous variables were presented as medians with corresponding interquartile ranges. We used a chi-squared test with 1 degree of freedom and a P-value of 0.05 to examine whether there was a difference between the proportions of patients revascularized in the post- and pre-intervention. Treatment was stratified according to whether the patients had received revascularization regardless of reperfusion method, with r-tPA and EVT alone or in combination with r-tPA. Patients were stratified according to whether they belonged to the group of patients being EMS-transported in the pre- or post-interventional period. Time of year and time of transportation were stratified because these were considered as possible confounders to transportation time delay. Time delays were compared using multivariable linear regression. A log transformation of the time delays was made in order to obtain normal distribution. Logistic regression was used to calculate crude and adjusted odds ratios (OR) of field-triage directly to the revascularization centre, and for a three months mRS score of ≤1, ≤2 and ≤3, respectively, when comparing the post-interventional group with the pre-interventional group. mRS was dichotomized into one group defined as good outcome with mRS ≤ 2 and another as poorer outcome with mRS > 2. The same was done for mRS scores of ≤ 1 and ≤ 3. In addition a multivariate ordinal logistic regression was used to estimate the crude and adjusted OR of any improvement in mRS when comparing the post-interventional with the pre-interventional group.

Adjustment was made for the following plausible confounders: EVT procedure delay, distance from pick-address to the nearest revascularization centre or local hospital, type of revascularization therapy, quarter (season) of year, hours stratified into four groups: 1: 24.00-05.59, 2: 06.00-11.59, 3: 12.00-17.59 and 4: 18.00-23.59, gender, age at admission, total National Institute of Health Stroke Scale (NIHSS) score before revascularization therapy. All statistical analyses were performed using Stata 13.0 (StataCorp, College Station, Texas).

Results

During the entire study period, including both the pre- and post-interventional periods, a total of 4237 patients with confirmed AIS were admitted to hospital. The incidence rate of AIS for the pre-interventional period was 15 per 10,000 person years compared with 20 per 10,000 person years in the post-interventional period. A total of 584 (corresponding to 13.8% of all AIS patients) patients received revascularization therapy in the study period. In the pre-interventional period 186 of 1212 (15.4%) patients received revascularization therapy, including 147 (12.1%) who only received r-tPA, 9 (0.7%) who only received EVT and 30 (2.5%) who received both r-tPA and EVT vs. a total of 398 of 3025 (13.2%) patients in the post-interventional period (P>0.05), including 322 (10.6%) who only received r-tPA, 18 (0.6%) who only received EVT and 30 (1.9%) received both r-tPA and EVT. During the study period a total of 24 patients were transported to the admission hospital by the acute-doctor-assisted helicopter.

The median delay times (TABLE 2) from EMS call to revascularization (treatment delay), regardless of revascularisation method, in the pre- and post-interventional groups were 202 (IQR: 145-262) minutes and 192 (IQR: 144-251) minutes, respectively. The delay from arrival at the revascularization centre to start of revascularization therapy were 66 (IQR: 52-111) minutes and 51 (IQR: 42-71) minutes, respectively, whereas the delay from EMS call to start of revascularization therapy were 127 (IQR: 101-175) minutes and 119 (IQR: 98-156) minutes, respectively. Median treatment delay times for those treated with either EVT alone or with both r-tPA and EVT were 272 (IQR: 214-423) minutes and 232 (IQR: 177-322) minutes, respectively, and from arrival at revascularization centre to revascularization therapy were 174 (IQR: 119-227) minutes and 115 (IQR: 90-165) minutes, respectively; and from EMS call to revascularization therapy were 234 (IQR: 184-282) minutes and 185 (IQR: 141-226) minutes, respectively.

Adjusted relative time delays using the pre-interventional group as reference are presented in Table 3. The relative delays were 1.08 (95%CI: 0.90-1.30) for overall revascularization treatment, 1.17 (95%CI: 0.94-1.45) for r-tPA alone, 0.73 (95%CI: 0.55-0.97) for either EVT alone or r-tPA and EVT combined.

The proportion of patients field-triaged directly to the revascularization centre was 314 of 321 (97.8%) in the post-interventional group compared with 146 out of 152 (96.1%) in the pre-interventional group. This corresponded to an adjusted OR of 1.15 (95% CI: 0.34-3.92) using the pre-interventional group as reference.

Regardless of the type of revascularization therapy, 68.2% (n=101 of 148) patients in the pre-interventional group had a three months mRS outcome ≤ 2 (TABLE 4), compared to 73.0% (n=230 of 315) in the post-interventional group. The corresponding adjusted OR was 1.46 (95% CI: 0.84-2.52) again using the pre-interventional group as reference.

For patients treated with EVT a total of 44.1% (n=15 of 34) had a three months mRS outcome ≤ 2 in the preinterventional group, compared to 65.0% (n=39 of 60) in the post-interventional group. The corresponding OR (including adjustment for EVT procedure delay) was 3.58 (95% CI: 1.14-11.25) using the pre-interventional group as a reference.

For patients only treated with r-tPA 75.4% (n=86 of 114) had a three months mRS outcome ≤ 2 in the preinterventional group, compared to 74.9% (n=191 of 255) in the post-interventional group. The corresponding adjusted OR was 1.03 (95% CI: 0.53-2.02) again using the pre-interventional group as reference.

There was a non-significant difference (FIGURE 3, 4 & 5) between the post-interventional and the pre-interventional group in the overall and in the EVT treatment distribution of mRS scores in an analysis using multivariate ordinal logistic regression, crude common OR 1.17 (95% CI: 0,82-1.66) and 1.82 (95% CI: 0,85-3.90), respectively (TABLE 5), as well as after adjustment of the mRS score for: EVT procedure delay, distance from pick-address to the nearest revascularization centre or local hospital, type of revascularization therapy, quarter (season) of year, hours stratified into four groups, gender, age at admission, total National Institute of Health Stroke Scale (NIHSS) score before revascularization therapy in an analysis with ordinal multivariable logistic regression adjusted common OR, 1.20 (95% CI: 0.84-1.71) and 1.75 (95% CI: 0,79-3.86).

Comment

In this population-based study, no differences in overall use of revascularization therapy or system delay among patients with AIS was found following an education campaign focused on medical dispatch staff and ambulance paramedics and centralization of in-hospital stroke care. However, significant improvements in system delay were found for AIS patients treated with EVT. In addition, a significant increase in the proportion of patients reaching a mRS score of ≤ 2 after three months was observed among the EVT treated patients when comparing patients in the post-interventional period with patients in the pre-interventional period.

An important aspect of this study was the focus on correct selection and visitation of patients with suspected major stroke to Aarhus University Hospital for EVT treatment. This could have overshadowed the group of patients only needing treatment with r-tPA which then possibly would lead to a longer transportation distance if these AIS patients had a shorter distance to the nearest revascularization hospital for r-tPA treatment. However this was not the case in the current study.

In a study from the United Kingdom and Ireland (24) median time between symptom onset and arrival to the hospital was 123 minutes for those calling the EMS, compared with 432 minutes for patients who first saw their general practitioner. Furthermore in comparable studies reported by Chang et al (25) and Faiz et al (26), decision delay accounted for 45% and 62.3% of the prehospital delay, respectively. This indicates that about half of the preadmission delay may be related to hesitation in seeking medical assistance after symptom onset. These studies support the “time is brain” paradigm and the fact that treatment delay is a critical factor in stroke treatment, and furthermore suggest the need for educative campaigns raising public awareness of stroke symptoms. However patient delay and thus treatment delay are subject to confounding, selection bias and recall bias and it seems reasonable to focus on reducing system delay which is less prone to confounding and bias as an effective way of reducing the total treatment delay.

Theoretically treatment and patient delays are applicable to all patients however these delays are only available in the selected cohort of patients surviving until the contact with the health care system and only if the patient is able to recall the exact time of symptom onset or instead the "last seen well"-concept is employed, i.e. the time at which the patient last was seen well. Furthermore whereas pain is the main symptom in the majority of patients with acute coronary syndrome (ACS), it is rarely associated with stroke. Patients with stroke often have different distribution of symptoms such as aphasia, reduced consciousness, or cognitive impairment, preventing them from seeking help and thereby increasing the patient delay. The apparent lack of a significant overall association between reorganisation of the prehospital visitation and inhospital stroke care and treatment and patient delay may thus be explained by confounding, selection bias, recall bias and measurement bias, but these factors are unlikely to account for the lack of association with prehospital, inhospital and system delay. However neither this observation nor the lack of any long-lasting effect of campaigns on patient or treatment delays should discourage patients to seek medical help as soon as possible after the onset of symptoms (27-29).

Studying the system delay can be done in all patients contacting the health care system, and it is not affected by selection bias from the time of survival of stroke since it by definition only is defined in patients surviving until contact with the hospital, and it is neither prone to recall bias due to its objective parameter. In a study of treatment delay reduction in patients with STEMI, minimizing system delay by optimizing prehospital and inhospital triage seemed to be the only risk factor modifiable in the acute phase, which is very much applicable in the effort to reduce treatment delay in stroke patients (30,31) Furthermore Fonarow et al (32) found a significant association between a national quality improvement initiative and substantial improvement in the timeliness of r-tPA administration with the proportion of patients with door-to-needle times of 60 minutes or less increasing from 29.6% to 53.3%, lower inhospital mortality, symptomatic intracranial haemorrhage, and overall r-tPA complications with an increase in the percentage of AIS patients able to be discharged to home. All findings that also reinforce the importance and clinical benefits of more rapid administration of intravenous r-tPA, and thus the significance of reducing system delay.

Since data on patients with primary contact to the general practitioners in the acute phase were not available, a limitation of this study would be that the system delay could potentially have been underestimated in some patients. In a study on system delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention by Terkelsen CJ et al(29) they found that 6% of the EMS-transported patients were not in the EMS registry which is another limitation that possibly is to be rediscovered in the current study, and possibly resulting in a minor underestimation of the number of EMS-transported patients, however we have no reason to think that there is a difference in the distribution of this number of EMS-transported patients in the pre- and postinterventional period.

A newly published study by Berkhemer et al (2) with 500 patients with acute stroke treatable within 6 hours from symptom onset and randomized to either EVT or best medical treatment found an adjusted common OR of 1.67 (95% CI: 1.21-2.30) of falling into a better category on the 90 days mRS, and an OR of 2.16 of having a mRS $\leq$ 2. There was an absolute difference of 13.5 percentage points (95% CI, 5.9 to 21.2) in the rate of functional independence (mRS $\leq$ 2) in favor of the intervention (32.6% vs. 19.1%). The numbers needed to treat (NNT) in order for 1 to be self-reliant (mRS $\leq$ 2) was 7.4. In another study by Goyal et al (4) 316 patients with acute stroke were randomly selected using CT-angiography and an evaluation of collateral circulation status to receive standard care (control group) or standard care plus endovascular treatment (intervention group). Their goal was to treat the patients within 12 hours after symptom onset. 75% were given r-tPA before EVT. They found an increase in the rate of functional independence (90-day mRS $\leq$ 2) favoring the intervention (53.0%, vs. 29.3% in the control group; $P<0.001$), and a common OR of 2.6 favoring the intervention as a measure of the likelihood that the intervention would lead to lower scores on the mRS than would the control care (shift analysis). Furthermore the NNT for functional independence was estimated to 4, and the intervention was associated with reduced mortality (10.4%, vs. 19.0% in the control group; $P=0.04$). In a third study by Campbell et al (3) 70 patients with ischemic stroke were randomly assigned to receive either alteplase alone or an amount of alteplase and then undergo EVT with the Solitaire FR (Flow Restoration). They found an improved functional outcome at 90 days, with more patients achieving functional independence (mRS score ≤ 2) with an absolute risk reduction of 31% (71% vs. 40%; P=0.01), and the NNT was 3.2. Both the ESCAPE and the EXTEND-IA trials were stopped early because of efficacy. Our findings further complement the three above-mentioned studies which have contributed to the fact that EVT recently was approved as an evidence-based degree 1A treatment of major ischemic stroke, and is in addition internationally considered as "standard care"-treatment. We found that our intervention significantly improved the functional outcome at 90 days for ischemic stroke patients treated with EVT alone or EVT plus r-tPA, with more of these patients achieving functional independence (mRS ≤ 2) in favor of the postinterventional group. Furthermore we found significant results on reduction of both treatment and system delay for patients treated with EVT alone or EVT in combination with r-tPA. The findings of these studies all suggest that the time factor be essential in gaining a better prognosis measured using mRS score at 90 days, and in continuation hereof reducing the pre- and inhospital delays in order for these patients to get the relevant treatment as early as possible.

Nonetheless there must be a much wider focus on the total health care system delay on a national perspective in order to optimize triage of patients with stroke, and minimize the pre- and inhospital delay due to the already narrow therapeutic revascularization window. A future nationwide study on system delay is needed.

Conclusion

We conclude that the proportion of patients revascularized was unchanged during the study period. There was an increase in the proportion of patients triaged directly to the revascularization centre, and an increase in the adjusted three months mRS score of ≤ 2 OR in the post-interventional period for patients treated with either EVT alone or EVT plus r-tPA. Moreover, there was a significant association between reorganisation of the pre-hospital visitation and in-hospital stroke care, and reduction in EVT treatment delay, system delay, and inhospital delay. However there were no significant associations between overall system delay or r-tPA system delay, and the intervention.

Dansk resumé

Introduktion: Behovet for at rekonfigurere apopleksi håndteringen, for at sikre at mere end 15% ((95% CI: 14-16), fra 2013) af patienter med akut iskæmisk apopleksi (AIA) i Danmark kan revaskulariseres med r-tPA behandling indenfor det snævre tids vindue (5-10) og/eller endovaskulær terapi (EVT), er fortsat en udfordring i behandlingen af apopleksi patienter.

Metoder: Studiet var et populationsbaseret før-og-efter studie i Region Midt Danmark blandt patienter indlagt til revaskulariserende behandling med r-tPA og/eller EVT. Studieperioden blev inddelt i en præ-(June 1 2011-March 31, 2012) og post-interventions (April 1, 2012-September 30, 2013) periode, som afspejler tidsaspektet af uddannelse af Akut Medicinsk Koordination (AMK)-vagtcentralens dispatch medarbejdere og centralisering af den in-hospitale apopleksi behandling. Vi identificerede i alt 473 patienter, som havde fået revaskularisering. Vores outcomes var andelen af revaskulariserede AIA patienter, tid "delays" fra symptom debut til revaskularisering og modified Rankin Scale (mRS) score tre måneder efter indlæggelse blev benyttet som udtryk for det funktionelle outcome spændende sig fra 0 (ingen symptomer) til 6 (død). Desuden anvendte vi en multivariate ordinal logistisk regression til at estimere den justerede odds ratio (OR) af en forbedring i mRS scorerne ved sammenligning af den post-interventionelle gruppe med den pre-interventionelle gruppe (shift analyse).

Resultater: Andelen af alle AIA patienter som modtog r-tPA i den post-interventionelle periode var 13,2% versus 15,4% i den præ-interventionelle periode (P>0,05). De relative forsinkelser var 1.08 (95%CI: 0.90-1.30) for "overall" revaskulariserende behandling, 1.17 (95%CI: 0.94-1.45) for r-tPA alene, 0.73 (95%CI: 0.55-0.97) for EVT alene eller r-tPA kombineret med EVT. For patienter behandlet med EVT (alene eller kombineret med r-tPA) opnåede flere patienter "selvhjulpenhed" (mRS ≤ 2) i den post-interventionelle periode (63.9% vs. 44.1%). Den tilsvarende OR (efter justering for bl.a. EVT procedure forsinkelse) var 3.58 (95% CI: 1.14-11.25), hvor den præ-interventionelle gruppe blev brugt som reference. Der var en ikkesignifikant forskel mellem de post- og præ-interventionelle grupper i "overall" og EVT behandlings fordelingen af mRS scorer i en analyse med ordinal multivariable logistic regression justret common OR på hhv. 1.20 (95% CI: 0.84-1.71) og 1.75 (95% CI: 0,79-3.86).

Konklusion: Vi konkluderer, at andelen af revaskulariserede patienter var uændret under studieperioden. Der var en stigning i den justerede tre måneders mRS score ≤ 2 OR i den post-interventionelle periode for patienter behandlet med EVT. Desuden var der en signifikant association mellem reorganisering af den præ-hospitale visitation og in-hospitale apopleksi behandling og en reduction i EVT "delays". Der var ingen signifikant association mellem "overall" eller r-tPA "delays" og interventionen. (Sponsoreret af TrygFonden Danmark og godkendt af Datatilsynet (J. No. 1-16-02-440-13).)

English summary

Background: The necessity to reconfigure stroke management in order to ensure that more than 15% ((95% CI: 14-16), in 2013) stroke patients in Denmark receive revascularization therapy with the use of r-tPA therapy (15% (95% CI: 14-16) in 2013) within the narrow therapeutic window (5-10) and/or endovascular therapy (EVT) is an ongoing challenge in the care of stroke patients.

Methods: The study was a population-based before-and-after study within Central Denmark Region among patients with acute ischaemic stroke (AIS) admitted for revascularization therapy with thrombolysis (r-tPA) and/or endovascular therapy (EVT). The study period was divided into a pre- (June 1 2011-March 31, 2012) and a post-interventional period (April 1, 2012-September 30, 2013) reflecting the timing of the education campaign of the EMS dispatch staff and the centralization of the in-hospital stroke care. We identified a total of 473 patients, who received revascularization. The outcomes were proportion of revascularized AIS patients, time delays from onset of symptoms to revascularization, and modified Rankin Scale (mRS) score three months after admission used to measure the functional outcome and ranging from 0 (no symptoms) to 6 (death). In addition a multivariate ordinal logistic regression was used to estimate the adjusted odds ratio (OR) of any improvement in mRS scores when comparing the post-interventional with the pre-interventional group (shift analysis).

Results: The proportion of AIS patients who received r-tPA in the post-interventional period was 13.2% vs. 15.4% in the pre-interventional period (P>0.05). The relative delays were 1.08 (95%CI: 0.90-1.30) for overall revascularization treatment, 1.17 (95%CI: 0.94-1.45) for r-tPA alone, 0.73 (95%CI: 0.55-0.97) for either EVT alone or r-tPA and EVT combined. For patients treated with EVT (alone or combined with r-tPA) more patients achieved functional independence (mRS ≤ 2) in the post-interventional period (63.9% vs. 44.1%). The corresponding OR (including adjustment for EVT procedure delay) was 3.58 (95% CI: 1.14-11.25) using the preinterventional group as a reference. There was a non-significant difference between the post- and pre-interventional groups in the overall and in the EVT treatment distribution of mRS scores in an analysis with ordinal multivariable logistic regression adjusted common OR, 1.20 (95% CI: 0.84-1.71) and 1.75 (95% CI: 0,79-3.86), respectively.

Conclusions: We conclude that the proportion of patients revascularized was unchanged during the study period. There was an increase in the adjusted three months mRS scores of ≤ 2 OR in the post-interventional period for patients treated with EVT. Moreover, there was a significant association between reorganisation of the prehospital visitation and inhospital stroke care, and reduction in EVT delay. However there were no significant associations between overall or r-tPA delays, and the intervention. (Funded by TrygFonden Denmark, and approved by the Danish Data Protection Agency (J. No. 1-16-02-440-13).)

Supplementary information

Introduction

Revascularization and the time factor

Thrombolysis with r-tPA and EVT administered within a therapeutic window provides an effective therapy for AIS. Nevertheless, only 15% of patients with stroke obtain treatment with r-tPA in Denmark (6,17) mainly because of prehospital delay.(8,17) Continuous public awareness campaigns, education of medical service personnel, the use of standardized and validated scales for recognition of stroke symptoms and for triaging to the appropriate institution, and advance notification of the receiving hospital are all measures for improvement and thus links in the prehospital stroke rescue chain recommended be optimized in order that more than a small minority of patients can profit from time-sensitive AIS therapy.

Previous studies have shown that only 15-60% of patients with stroke arrived at hospital within 3 hours after onset of symptoms, and only 14-48% arrived within 2 hours. (8-10,24,33-37) The aim of this study is to further elucidate the necessity of the emergency priority of stroke in a similar way as for acute myocardial infarction or trauma due to the great benefit of patients from direct transfer to a hospital with stroke expertise and the option for thrombolytic (38-42) therapy and EVT. In a recent randomized control clinical trial involving 942 patients in Sweden (43), having the EMS dispatch office establish an increased priority level for patients with stroke reduced time to arrival at the stroke centre, and increased the rates of alteplase use from 10% to 24% ($p<0.001$) without negatively affecting other medical emergencies.

The correct identification of stroke symptoms by doctors as well as dispatcher staff is not trivial in that symptoms related to the posterior circulation can be difficult to recognize and furthermore as many as 20% of presumed stroke symptoms are caused by completely different diseases – so-called stroke mimics such as migraine, seizure, intracranial processes and more. The reported proportion of strokes correctly identified by EMS dispatchers varies between 30% and 83%,(11-13) a finding that suggests the need for the present type of campaign that aims to improve logistics for AIS treatment by reorganisation of the prehospital visitation and inhospital stroke care and thus reduce system delay.(14,15)

Methods

<u>Before-and-after study</u>

The goal of the study was to examine the effect of exposure i.e. reorganization of pre-hospital and in-hospital care on the outcome, i.e. reduction of system delay.

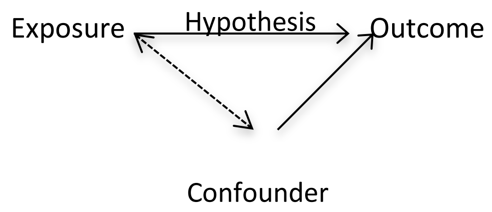
In order to examine a given association between the intervention and system delay, it was beneficial to do a non-randomized controlled before-and-after study. A follow up study was not needed because we did not have an outcome that needed long-term follow up. If our outcome were modified Rankin Scale scores then a follow up study would be to prefer rather than a before-and-after study.

In the present study we had the pre-interventional group consisting of stroke patients being transported to the nearest revascularization centre in a period prior to the intervention on the pre-hospital visitation and inhospital stroke care, and similarly the post-interventional group being stroke patients transported for revacularization in a period after the implementation of the abovementioned campaign. As described by Hauer (1997) there are different approaches to before-and-after studies, and they are commonly used in traffic and safety studies. There is the naïve before-and-after study, the before-and-after study with yoked comparison, the before-and-after study with comparison, and the before-and-after study with Emperical Bayes. The latter is used in the present study. In order to compare the system delay in the pre- and post-interventional groups, they have to be under the same circumstances. This means we have to control for all possible confounders that presumably can result in bias. If we were to examine the system delay of stroke patient transportation in the winter period, it would be expected that the time from the pickup of the AIS patient to arrival at the revascularization centre would be longer than in the summer period due to the risk of different weather conditions in the two seasons. This would then be a possible confounder to the time delay if the distribution of transportation between the two groups of stroke patients in the current study were different. Furthermore if we were to compare it to the system delay in the post-interventional group in the summer period, where a quicker arrival to the destination is expected, the reduction in system delay would be confounded due to the weather conditions which could explain our findings. More correctly we cannot separate the effect of the intervention. This is known as regression-to-mean bias, which is avoided in the before-and-after study with Emperical Bayes. This method is a statistical approach to determine the appropriate weighting to place on each relevant factor such as for instance time of year when estimating the outcome(s). In the present study we accounted for regression-to-mean bias by stratifying the "year"-variable into 4 quarters each representing a time of the year followed by the use of multivariable regression. The advantage of multivariable regression is that we can control for several confounders all at once. Some of the confounders included in this study are distance from pickup destination to revascularization centre, sex, age and NIHSS before treatment, season and time of day during transportation. The latter is a similar example of a possible confounder, which we also adjusted for in the comparison of the pre- and post-interventional groups in our study.

Confounding and effect modification

Confounding is defined by confusion of causes, which results in misinterpretation of data. In the present study our exposure was the implementation of a pre-hospital visitation and in-hospital stroke care campaign, and the outcome was among others the time delay specifically system delay. In order to examine the relationship between the exposure and the outcome we had to adjust for several possible confounders one of which was the preadmission assessment of the neurologic impairment of the stroke patients by using the famous NIHSS. A high NIHSS score indicates severe stroke. Using the figure below we would easily understand that NIHSS is a possible extraneous variable that either directly or inversely correlates with both the exposure and the outcome as illustrated below.

The following figure shows the interplay of confounding with a hypothesis.



In this figure the arrows illustrate hypothetical or real causal relations while the dotted arrow illustrates an association that can be causal or not causal. However if a factor is part of the chain of events from exposure to outcome it is not a confounding variable. Therefore a confounder has to be assessed in relation to a specific hypothesis. A confounder must fulfil the following criteria, with exposure “E”, confounder “C” and outcome “O”:

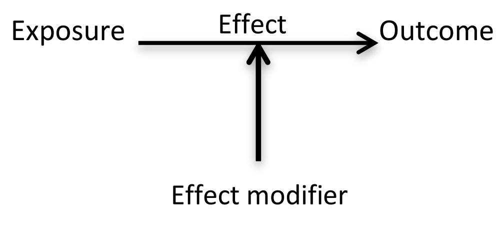
i. C is associated (inversely or directly) with O.
ii. C is associated with O, independent of E.
iii. C is associated (inversely or directly) with E.
iv. C is not in the causal pathway of E to O (C is not a direct consequence of E, and thus not a way by which E produces O).

Since our exposure involves improvement of inhospital stroke care this would be correlated with a lower NIHSS score (i) and furthermore lower NIHSS indicates less disability and thus better cooperation of the stroke patient with the personnel at admission which hypothetically could implicate a shorter inhospital time delay (i and ii). Finally the exposure is not dependent of the NIHSS score variable in its pathway to the outcome and so the NIHSS variable seems to fulfil the abovementioned criteria.

Confounding can be prevented by the study design (follow-up study, case-control studies), restrictions and randomization. In reality it is not possible to completely prevent confounding and for this reason the confounders are controlled for by stratified analysis instead. Residual confounding however occurs when imprecise information or rough classifications of the confounder/exposure are made. This leads to incomplete adjustment, and so it is necessary to classify properly and give precise information on the confounder/exposure even if there has been made a stratified analysis. If there were a big difference between the adjusted and non-adjusted estimates, and if the information about the confounder/exposure has been imprecise it could be a sign of residual confounding.

A second example of stratification in the current study would be the time of day during transportation of the patient to the hospital in order to adjust for a possible effect of degree of crowdedness in the traffic during the prehospital transportation of the patient on the time delay.

Another way to control for confounding is by standardization, which can be made directly or indirectly. Both stratified analysis and standardization have limitations when we need to control for different confounders at once. Regression analysis makes it possible to look at the same effect of several factors. There are nevertheless two main problems with regression analysis. Firstly it is important to be aware of the interactions (effect modification) e.g. treatments or exposures work differently on different people or groups. For instance the distance from the pick up place of the patient and to the hospital could be a possible effect modifier do to the difference of both the route and the distance of for instance a patient living near a revascularization centre and another living 80 km from the nearest revascularization centre. This can be illustrated by the following figure, here given in a hypothetical situation:



Secondly with modern computer programs it is very easy to make many regression analyses, which sometimes can result in superficial academic researching. Finally it is important to realize that the effect of an effect modifier on the effect of the exposure on the outcome can easily be dependent on the association parameter used in the analysis.

Selection bias

Our study is a comparative study and the composition of the study population is similar to that of a follow-up study in that it doesn't necessarily reflect any existing population; the aim is to achieve a maximal exposure contrast by comparing transportation delay of stroke patients prior to the intervention, which isn't therefore prone to the exposure, with transportation delay of stroke patients after the implementation of the intervention in our study. Since our study is comparative, selection bias has other consequences than those applying to descriptive studies. Selection bias is a dropout of a patient in the study that can be correlated to the exposure, the outcome or both the exposure and outcome. Generally dropout in comparative studies can result in bias if it were correlated to both the exposure and the outcome (double biased). If it were only correlated to the exposure or the outcome it does not necessarily lead to bias in the association estimate – it depends on which association goals are used. However the problem with dropout is that information about the exposure and/or the outcome is missing and therefore the nature of the dropout cannot be determined. Nonetheless our aim was to study the effect of the implementation of an improvement campaign of the pre-hospital visitation and in-hospital stroke care by examining its effect on the system delay. Studying system delay can be done in all patients contacting the health care system, and it is not affected by any of the abovementioned selection bias from the time of survival of stroke or/and inclusion in the study since it by definition only is defined in patients surviving until contact with the hospital. It is neither prone to recall bias due to its objective parameter.

Ethical considerations

Registry data used in the project and the study was approved by the Danish Data Protection Agency (J. No. 1-16-02-440-13).

Conclusions

Future studies

There is a need for further studies examining the association between the current campaign and specifically the system delay. This could be done by expanding this study by designing a nationwide study investigating the correlation between the current campaign and for instance outcomes such as prehospital, inhospital, system delay and three months mRS score. A nationwide study compared to our study which only involved the middle Denmark Region would have more volume and power presumably giving more applicable and significant result. We have a firm belief that the three months mRS is associated with the time delay before revascularization, and increased focus on the total health care system delay may optimize triage of patients with AIS and may be the key to further improving the individual functioning level of these patients.

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Table Contents

Table 1. Characteristics of Patients with AIS Transported by Emergency Medical Service and treated with revascularization therapy (n=473).

Characteristic	Pre-interventional, Percentage of total, N=161	Post-interventional, Percentage of total, N=347
Demographics Age, median (IQR), y	68(59-77)	71(62-79)
Women	38.2	38.2
Admission NIHSS, mean	7 (3-13)	6 (3-12)
Comorbid conditions		
Hypertension	59.2	62.1
Diabetes	14.6	13.7
Atrial Fibrillation	23.7	23.9
Previous stroke	12.5	17.7
Delays and transportation Delay, median (IQR), min		
Treatment*	202 (145-262)	192 (144-251)
Patient	36 (14-101)	48 (16-103)
Prehospital	55 (39-70)	56 (43-69)
Inhospital	66 (52-111)	51 (42-71)
System**	127 (101-175)	119 (98-156)
Transportation of stroke patients field-triaged to revascularization centre, median(IQR), km	36 (13-50)	39 (19-49)
Clinical characteristics, median(IQR)		
Body mass index	26 (24-30)	26 (23-29)
Systolic, mmHg	151 (140-170)	155 (136-170)
Diastolic, mmHg	84 (78-93)	80 (74-90)
Life style factors		
Active or previous smoker	60.5	62.7
Alcohol	86.8	82.0

* Time delay from symptom onset to revascularization.

** Time delay from EMS call to revascularization.

Table 2. Medians of Stratified Time Delays.

Time delays	Overall revascularization treatment				r-tPA alone				EVT*			
	Preinterventional		Postinterventional		Preinterventional		Postinterventional		Preinterventional		Postinterventional	
	n	Median (IQR), min	n	Median (IQR), min	n	Median (IQR), min	n	Median (IQR), min	n	Median (IQR), min	n	Median (IQR), min
Treatment delay	129	202 (145-262)	273	192 (144-251)	100	176 (138-229)	222	178 (137-242)	29	272 (214-423)	51	232 (177-322)
Patient delay	129	36 (14-101)	273	48 (16-103)	100	37 (17-111)	222	51 (17-109)	29	22 (9-59)	51	36 (9-79)
Prehospital delay	151	55 (39-70)	322	56 (43-69)	117	53 (38-68)	259	56 (43-69)	34	62 (45-74)	63	57 (42-75)
Inhospital delay	151	66 (52-111)	322	51 (42-71)	117	59 (50-73)	259	51 (42-71)	34	174 (119-227)	63	115 (90-165)
EVT procedure delay**	–	–	–	–	–	–	–	–	34	51 (35-80)	63	57 (31-97)
System delay	151	127 (101-175)	322	119 (98-156)	117	119 (96-143)	259	112 (92-140)	34	234 (184-282)	63	185 (141-226)

* Time of groin puncture for EVT is used, and among these a small group only received EVT while the larger group received both r-tPA and EVT
** Time from groin puncture to either reperfusion or end of EVT procedure

Table 3. Crude and adjusted Relative Risks (RR)* of Stratified Time Delays with 95% confidence intervals.

	Overall revascularization treatment				r-tPA alone				EVT **			
Time delays	n	Crude RR postinter-ventionally	n	Adjusted RR postinter-ventionally	n	Crude RR postinter-ventionally	n	Adjusted RR postinter-ventionally	n	Crude RR postinter-ventionally	n	Adjusted RR postinter-ventionally
Treatment delay	401	1.04 (0.86-1.25)	402	1.08 (0.90-1.29)	322	1.15 (0.92-1.42)	322	1.17 (0.94-1.45)	80	0.76 (0.57-1.00)	79	0.73 (0.55-0.97)
Patient delay	401	1.14 (0.81-1.59)	402	1.18 (0.84-1.66)	322	1.17 (0.80-1.72)	322	1.21 (0.83-1.78)	80	0.95 (0.46-1.94)	79	0.83 (0.40-1.72)
Prehospital delay	472	0.99 (0.91-1.08)	473	0.96 (0.89-1.04)	376	1.02 (0.93-1.12)	376	1.00 (0.92-1.08)	97	0.88 (0.71-1.10)	95	0.83 (0.69-1.01)
Inhospital delay	472	0.90 (0.78-1.01)	473	0.93 (0.84-1.02)	376	0.97 (0.87-1.08)	376	0.97 (0.87-1.08)	97	0.78 (0.63-0.96)	92	0.77 (0.62-0.96)
EVT procedure delay***	–	–	–	–	–	–	–	–	96	1.03 (0.72-1.46)	95	0.96 (0.67-1.38)
System delay	472	0.94 (0.86-1.02)	473	0.95 (0.88-1.02)	376	1.00 (0.93-1.08)	376	0.99 (0.92-1.07)	97	0.80 (0.68-0.95)	92	0.79 (0.66-0.94)

* Adjustment was made for the following plausible confounders: distance from pick-up address to the nearest revascularization centre or local hospital, type of revascularization therapy, quarter (season) of year, hours stratified into four groups, gender, age at admission, total National Institute of Health Stroke Scale (NIHSS) score before revascularization therapy.
** Time of groin puncture for EVT is used, and among these a small group only received EVT while the larger group received both r-tPA and EVT
*** Time from groin puncture to either reperfusion or end of EVT procedure

Table 4. Crude and adjusted odds ratio (OR)* with 95% confidence intervals (95% CI) for three months modified Rankin Scale (mRS) outcome ≤1, ≤2 and ≤3 comparing the postinterventional group with the preinterventional group in regards to type of revascularization treatment.

Type of treatment	**mRS≤1**				**mRS≤2**				**mRS≤3**			
	n	Crude OR postinter-ventionally	n	Adjusted OR postinter-ventionally	n	Crude OR postinter-ventionally	n	Adjusted OR postinter-ventionally	n	Crude OR postinter-ventionally	n	Adjusted OR postinter-ventionally
Regardless of type of revascula-rization therapy	463	1.20 (0.81-1.77)	462	1.17 (0.74-1.86)	463	1.26 (0.82-1.93)	462	1.46 (0.84-2.52)	463	1.29 (0.78-2.12)	462	1.41 (0.72-2.73)
r-tPA	368	1.11 (0.71-1.73)	368	1.05 (0.62-1.77)	368	0.99 (0.59-1.65)	368	1.03 (0.53-2.02)	368	0.93 (0.49-1.74)	368	0.77 (0.31-1.95)
EVT	95	1.46 (0.61-3.46)	94	1.51 (0.55-4.14)	95	2.25 (0.95-5.28)	94	3.67 (1.19-11.36)	95	2.35 (0.95-5.82)	94	2.96 (0.96-9.17)
EVT**	95	1.46 (0.61-3.46)	94	1.48 (0.52-4.22)	95	2.25 (0.95-5.28)	94	3.58 (1.14-11.25)	95	2.35 (0.95-5.82)	94	2.86 (0.91-8.99)

* Adjustment was made for the following plausible confounders: distance from pick-address to the nearest revascularization centre or local hospital, type of revascularization therapy, quarter (season) of year, hours stratified into four groups, gender, age at admission, total National Institute of Health Stroke Scale (NIHSS) score before revascularization therapy.
** Besides the above-mentioned adjustments, in addition adjustment for EVT procedure delay was made.

Table 5. Crude and adjusted common odds ratio (OR)* with 95% confidence intervals (95% CI) for three months modified Rankin Scale (mRS) outcome comparing the postinterventional group with the preinterventional group in regards to type of revascularization treatment.

	mRS			
Type of treatment	n	Crude common OR in the postinterventional period	n	Adjusted common OR in the postinterventional period
Regardless of type of revascularization therapy	463	1.17 (0.82-1.66)	462	1.20 (0.84-1.71)
r-tPA	368	1.03 (0.69-1.53)	368	1.03 (0.69-1.54)
EVT	95	1.82 (0.85-3.90)	94	1.78 (0.81-3.93)
EVT**	95	1.82 (0.85-3.90)	94	1.75 (0.79-3.86)

* Adjustment was made for the following plausible confounders: distance from pick-address to the nearest revascularization centre or local hospital, type of revascularization therapy, quarter (season) of year, hours stratified into four groups, gender, age at admission, total National Institute of Health Stroke Scale (NIHSS) score before revascularization therapy.
** Besides the above-mentioned adjustments, adjustment was also made for EVT procedure delay.

Figures

Figure 1: *Flow Chart of Patient Inclusion Into Study.*

Figure 2: *Delays From Symptom Onset to Revascularization Therapy in Patients with Acute Ischaemic Stroke Transported by Emergency Medical Service.*

Figure 3: *Modified Rankin Scale (mRS) Scores at 3 moths, Pre- and Postinterventional, for patients treated with revascularization regardless of type of revascularization therapy.*

Figure 4: *Modified Rankin Scale (mRS) Scores at 3 moths, Pre- and Postinterventional, for patients only treated with r-tPA.*

Figure 5: *Modified Rankin Scale (mRS) Scores at 3 moths, Pre- and Postinterventional, for patients only treated with EVT.*

Figure 1. Flow chart of patient inclusion into study.

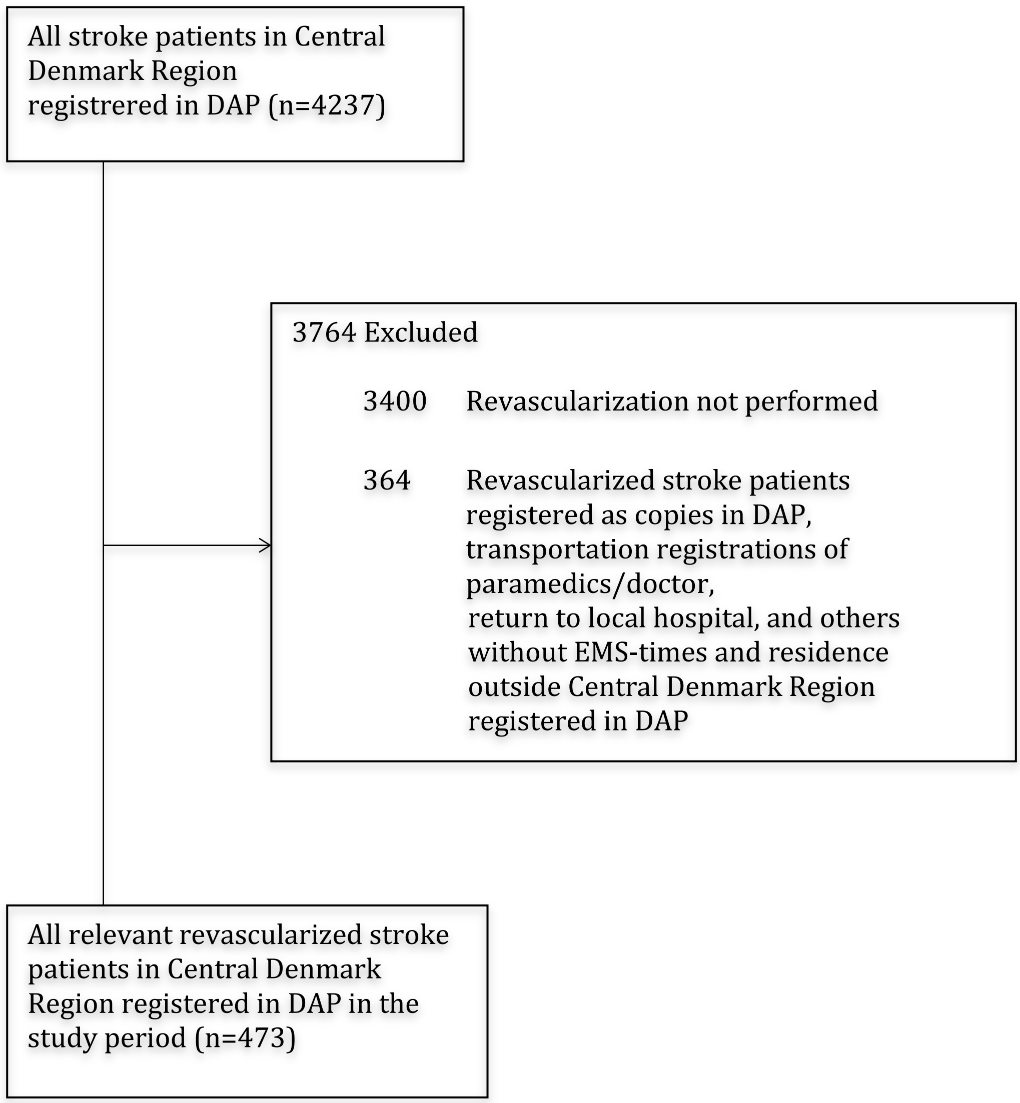
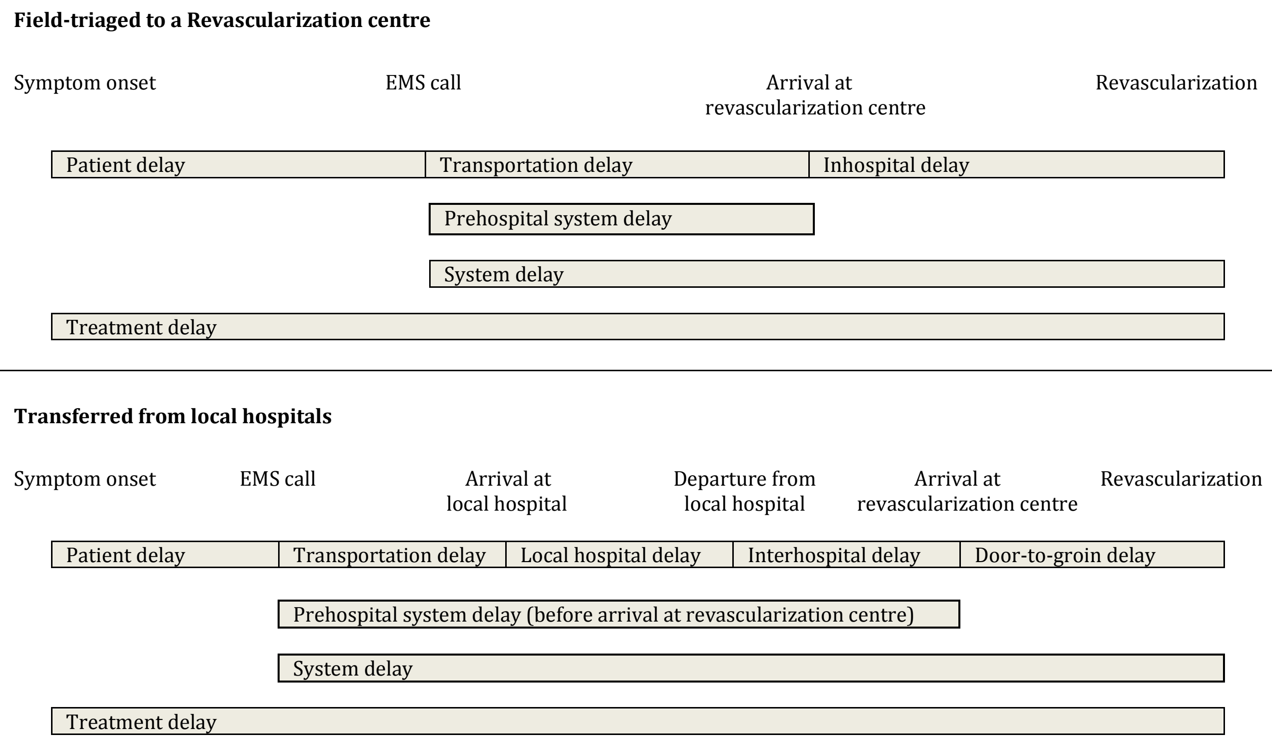
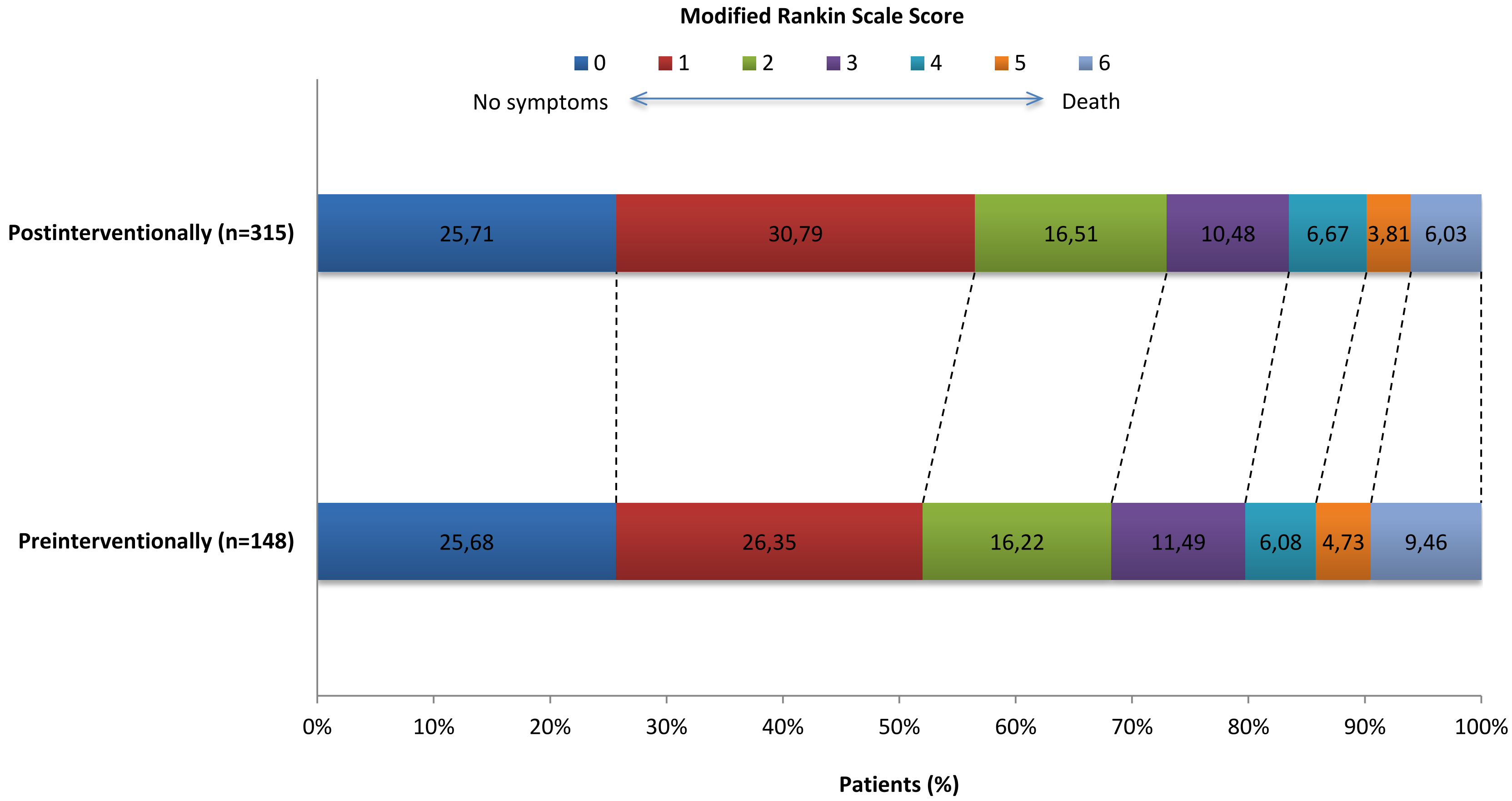


Figure 2. Delays from symptom onset to revascularization therapy in patients with acute ischaemic stroke transported by Emergency Medical Service (EMS).



For explanation of the figure see text on p.4.

Figure 3. Modified Rankin Scale (mRS)* Scores at 3 moths, Pre- and Postinterventional, for patients treated with revascularization regardless of type of revascularization therapy.

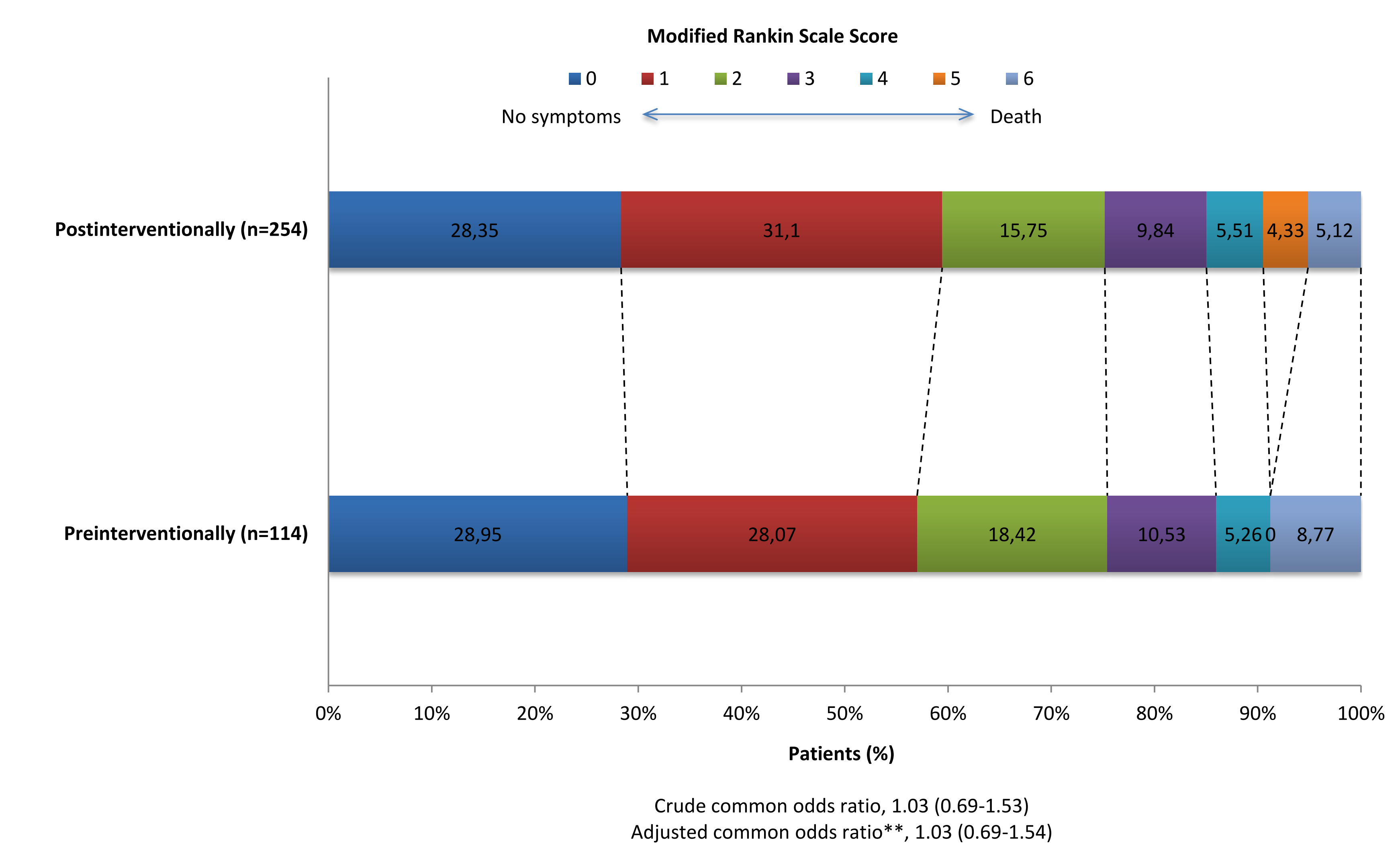


Crude common odds ratio, 1.17 (0.82-1.66)
Adjusted common odds ratio**, 1.20 (0.84-1.71)

* The scale runs from 0-6, running from perfect health without symptoms to death: 0 - No symptoms, 1 - No significant disability, 2 – Slight disability, 3 - Moderate disability, 4 - Moderately severe disability, 5 - Severe disability, 6 - Dead. (33)

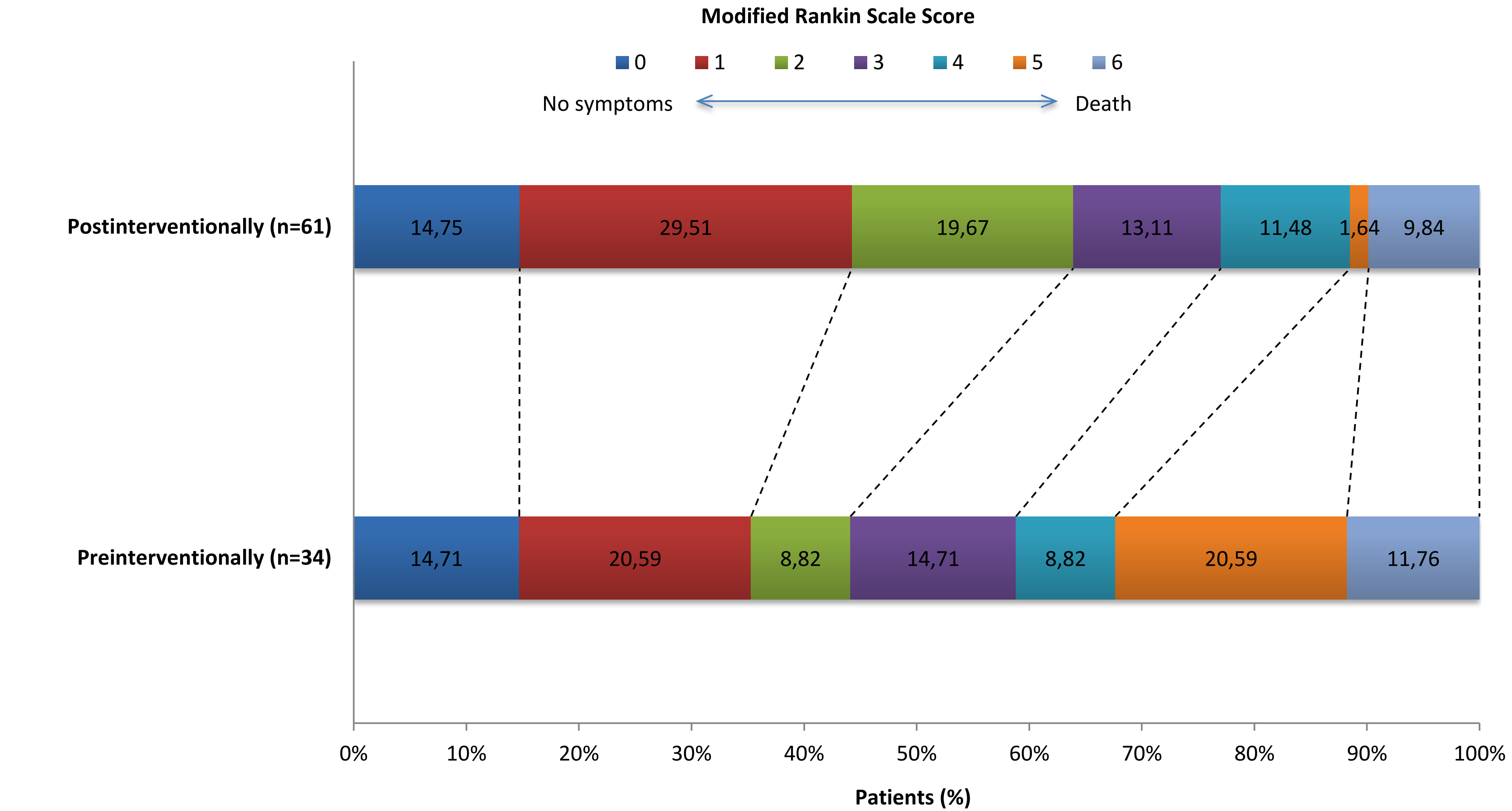
** Adjustment was made for the following plausible confounders: distance from pick-address to the nearest revascularization centre or local hospital, type of revascularization therapy, quarter (season) of year, hours stratified into four groups, gender, age at admission, total National Inst itute of Health Stroke Scale (NIHSS) score before revascularization therapy.

Figure 4. Modified Rankin Scale (mRS)* Scores at 3 moths, Pre- and Postinterventional, for patients only treated with r-tPA.



* The scale runs from 0-6, running from perfect health without symptoms to death: 0 - No symptoms, 1 - No significant disability, 2 – Slight disability, 3 - Moderate disability, 4 - Moderately severe disability, 5 - Severe disability, 6 - Dead. (44)
** Adjustment was made for the following plausible confounders: distance from pick-address to the nearest revascularization centre or local hospital, type of revascularization therapy, quarter (season) of year, hours stratified into four groups, gender, age at admission, total National Institute of Health Stroke Scale (NIHSS) score before revascularization therapy.
*** In the preinterventional group no patients had a modified Rankin score of 5.

Figure 5. Modified Rankin Scale (mRS)* Scores at 3 moths, Pre- and Postinterventional, for patients only treated with EVT.



Crude common odds ratio, 1.82 (0.85-3.90)
Adjusted common odds ratio**, 1,75 (0.79-3,86)

* The scale runs from 0-6, running from perfect health without symptoms to death: 0 - No symptoms, 1 - No significant disability, 2 – Slight disability, 3 - Moderate disability, 4 - Moderately severe disability, 5 - Severe disability, 6 - Dead. (44)
** Adjustment was made for the following plausible confounders: distance from pick-address to the nearest revascularization centre or local hospital, type of revascularization therapy, quarter (season) of year, hours stratified into four groups, gender,age at admission, total National Institute of Health Stroke Scale (NIHSS) score before revascularization therapy. Besides the above-mentioned adjustments, in addition adjustment for EVT procedure delay was made.

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