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Thrombectomy in acute ischemic stroke 2015 in Lund: a retrospective comparison of outcomes and assessment of times

Retrospektiv uppföljning av trombektomi vid akut ischemisk stroke i Lund 2015: jämförelse av patientutfall och sammanställning av tidsintervall

Master thesis

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Abbreviations

AIS – Acute Ischemic Stroke

CT – Computed Tomography

CTA – Computed Tomography Angiography

FDA – Food and Drug Administration

IVT – Intravenous fibrinolytic Therapy

mRS – modified Rankin Scale

NIHSS – National Institutes of Health Stroke Scale

PACS – Pictures and Archiving Communications System

RIS – Radiology Information Systems

TICI – Thrombolysis In Cerebral Infarction

Abstract

Background and purpose: Stroke is one of the world's most common diseases and the second leading cause of death worldwide. From 1996 to 2006 the treatment of acute ischemic stroke (AIS) was limited to intravenous fibrinolytic therapy; a treatment often associated with risk and insufficiency. In 2006, treating AIS by mechanical clot removal, known as thrombectomy, was approved by the U.S. Food and Drug Administration (FDA). It did not garner much attention until 2015 when five major studies showed that outcomes dramatically improved. Today, thrombectomy is rapidly expanding and to ensure that it is correctly applied, quality must be continually evaluated. The primary purpose of this project is to evaluate thrombectomies performed in Lund between Jan 1, 2015 and Dec 31, 2015 by comparing patient outcomes with the corresponding data in the largest study. The secondary purpose is to summarise time intervals from ictus to thrombectomy as shorter times are always desirable.

Methods: All data was collected from Picture and Archiving Communication Systems (PACS), Radiology Information System (RIS), and electronical medical charts. Patient outcomes were measured by autonomy according to the modified Rankin Scale (mRS) 90 days after thrombectomy and mortality.

Results: mRS score was acquired for 49 of 74 patients of which 80 % were ≤ 2. Mortality was 18 %. The longest median interval was between first imaging and arrival to angio suite. The percentage of patients with mRS ≤ 2 was higher than the largest study compared, and if those with an unknown mRS would all be mRS ≥ 3, results would still be on par.

Conclusion: It can thus be concluded that Lund in general has satisfactory outcomes. The interval between imaging and arrival to angio suite can be expected to be the longest, but it also

holds the largest potential for improvement. As knowledge and experience of thrombectomy increases, more patients might successfully be treated.

Populärvetenskaplig sammanfattning på svenska

Blodpropp i hjärnan, ofta benämnt som stroke, är en av de vanligaste sjukdomarna i världen och drabbar årligen 32 000 i Sverige. Utfallet av stroke kan variera från inga kvarstående symptom, till förlamning, bortfallen talförmåga, blindhet eller död.

Behandlingen för stroke har utöver rehabilitering i många år varit begränsad till trombolys, en läkemedelsbehandling i akutskedet som syftar till att lösa upp proppen. Trombolys är dock förenat med risker och många bitar måste falla på plats för en framgångsrik behandling. Ett decennium efter att trombolys introducerades godkändes en ny behandling för stroke av det amerikanska läkemedelsverket FDA. Denna behandling går under namnet trombektomi och innebär att blodproppen i hjärnan mekaniskt avlägsnas under röntgengenomlysning. Ett genombrott för teknologin skedde i början av 2015 då fem stora studier visade överväldigande positiva resultat för behandlingen.

Då behandlingen idag betraktas som ny och snabbt expanderande krävs det kontinuerlig kontroll och utvärdering. Detta projekt syftar till att vara en del i denna process genom att kontrollera hur det gick för patienter som genomgått trombektomi i Lund 2015. Detta jämförs sedan med andra studier av trombektomi. Ett annat syfte med det här projektet var att titta på hur lång tid det tar från ett insjuknande till trombektomi då snabbare behandlingar tydligt innebär bättre resultat. Genom att samla in uppgifter från journalsystem kunde patientutfallen och tidpunkter från insjuknande till behandling sammanställas.

Av de överlevande patienter där det gick att fastställa ett utfall, hade 80 % inga eller endast lätta handikapp. Av alla patienter avled totalt 18 %, likvärdigt med jämförda studier. Procentuellt var det betydligt fler som hade inga eller endast lätta handikapp i Lund än i den största jämförda

studien. Det var dock ett stort antal patienter i Lund där utfallet inte gick att fastställa, och om alla dessa antogs ha ett måttligt eller större handikapp skulle resultatet fortfarande vara likvärdigt. Den process som oftast tog längst tid var den mellan röntgenundersökning och ankomsten till röntgenunderstödd behandling i Lund. Att detta var den längsta processen har ett flertal förklaringar, men samtidigt också de bästa förutsättningarna för att minskas.

För att i framtiden kunna göra välgrundade ställningstagande för att undvika över- och underbehandling, behövs det mer kunskap om vilka patienter som är lämpade alternativt olämpliga för trombektomi.

Background

Stroke is a commonly used umbrella term for acute ischemic stroke (AIS), intracerebral haemorrhagic stroke and subarachnoid haemorrhagic stroke, of which AIS is the most common (87 %)[1]. Worldwide, stroke accounts for 11.3 % of global mortality and the second most Disability-Adjusted Life Years, both numbers only surpassed by ischaemic heart disease[2]. The global incidence 2013 was 6.9 million[3] and the annual incidence in Sweden is around 32 000[4].

Since 1996, the treatment of AIS in the acute setting has mainly been limited to the usage of a tissue plasminogen activator; a treatment known as intravenous fibrinolytic therapy (IVT) which aims at dissolving the occluding clot. IVT has been shown to improve patient recovery if administered within 4.5 h of symptoms onset, with a diminishing effect the longer the delay before administration[5, 6]. The treatment with IVT is however associated with plenty of complex factors the treating physician must consider. As an example there are absolute contraindications such as ongoing usage of anticoagulants, significantly elevated blood pressure, and stroke in previous 3 months[7]. Considering these factors, including the aspect of time, far from all patients are well suited for IVT or able to receive it. Only 13 % of patients (age 18-80) with stroke in Sweden 2014 received IVT[8].

In 1998, two years after the U.S Food and Drug Administration's (FDA) approval of IVT, treating AIS by mechanical retrieval of an intracranial embolus was described for the first time by Swedish radiologist G. Wikholm in a case report[9]. Six years later, in 2004, the MERCI trial showed that patients with AIS who were ineligible for IVT had improved outcomes if they were treated with endovascular thrombectomy[10]. This led to the FDA's approval of the first device for cerebral clot retrieval, the Merci Retriever (Concentric® Medical, Inc. California, USA), which

in turn was followed by the approval of another thrombectomy device in 2008, the Penumbra System (Penumbra®, Inc. California, USA).

Today, 5 major studies have been conducted on thrombectomy with stent retrievers: MR CLEAN[11], EXTEND IA[12], ESCAPE[13], REVASCAT[14], and SWIFT PRIME[15]. These were all randomized, multicentre, prospective studies comparing endovascular therapy in patients with AIS of the anterior circulation with a control group, measuring patient autonomy 90 days after thrombectomy according to the very well-established and validated modified Rankin Scale[16]. These five studies all showed favourable outcomes of endovascular therapy when compared to their respective control groups and MR CLEAN was the only study which was carried out for the entire planned duration. The remaining four were all halted early due to efficacy following the publication of MR CLEAN, January 2015.

Out of these five studies MR CLEAN is the most representative of clinical practice as its only requirements for inclusion were a verified occlusion in the anterior circulation, National Institutes of Health Stroke Scale (NIHSS) score ≥ 2, and the intraarterial treatment (delivery of a thrombolytic agent and/or mechanical thrombectomy: decision made by the local interventionist) had to be initiated within 6 hours after ictus. It is also the largest study of these five with a total of 500 patients. The remaining four studies had smaller patient groups and varying specific inclusion criteria such as IVT required (EXTEND IA, SWIFT PRIME) or a remaining occlusion after IVT/ineligible for IVT (REVASCAT), or moderate-to-good collateral circulation (ESCAPE).

As mentioned above, the good outcomes of IVT diminishes as time from onset to administration increases and the same could be expected for thrombectomy. This is verified by a meta-analysis

of the five studies of thrombectomy above, which showed time to be an equally important factor where an increased time between onset to groin puncture, and onset to reperfusion show a clear correlation. Treatment effect became nonsignificant if groin puncture was performed later than 7.3 hours after onset[17].

Aim

The primary aim of this project is to summarise and evaluate the outcomes of those who underwent thrombectomy in Lund 2015 in regard to mortality and patient autonomy 90 days after thrombectomy, and to compare the results with those of the largest and most representative study of routine thrombectomy, the MR CLEAN study.

The secondary aim of this project is to collect time points of critical moments from ictus to recanalization and summarise the intervals between these steps.

Issue

Endovascular therapy in AIS is a relatively new and a very expanding technology with major papers published as recently as 2015 showing improved outcomes. As any other healthcare practice, thrombectomy requires continuous evaluation and validation as a part of quality assurance, not only in large multicentre trials, but also as local and regional quality controls.

As time from AIS onset to thrombectomy is a critical factor for outcome, where shorter times have better outcomes, all delays should be identified and reduced if possible.

Material & Method

Patients referred for thrombectomy in Lund between Jan 1, 2015 and Dec 31, 2015 were identified by referral-code and date. Written data was obtained from referral, postinterventional

results and charts from Picture Archiving And Communications System, the electronic health systems (PACS), Radiology Information System (RIS), and the regional medical charting system Melior.

Written data was sought for the following parameters:

- First registered NIHSS score
- Occluded vessel on Computed Tomography Angiography (CTA).
    - If CTA was not available or occluded vessel was not determinable by CTA, occluded vessel was determined either by identification of hyperdense artery sign on Computed Tomography (CT) or by digital subtraction angiography.
- Thrombolysis In Cerebral Infarction (TICI) after thrombectomy; a scale describing the perfusion past an occlusion on angiography ranging from 0 – 3, where 0: no perfusion, 1: penetration with minimal perfusion, 2A: partial filling of distal vascular territory, 2B: complete but slower filling of the expected territory, and 3: a complete perfusion[18].
- Score on the modified Rankin scale (mRS); a scale describing patient autonomy after AIS ranging from 0 (no symptoms) to 5 (severe disability)[19] and 6 (dead) according to follow-up 90 days after thrombectomy.
    - mRS was primarily acquired as a written number in medical charts
    - If no written number was available, an interpretation was made from available charting if possible
    - If there was no data available after initial discharge but patient did not appear as dead in the electronical medical health system, the patient was registered as alive but with unknown mRS
- If death was related to AIS or treatment or neither

- Time point of ictus, first imaging, arrival to angio suite, groin puncture, and recanalization.
    - If ictus occurred within a known interval, the earliest time was chosen as AIS onset.
    - First imaging was always performed out at the local hospital before transportation to Lund

SPSS Statistics 24 and Microsoft Excel 2016 were used for data input, chart, and table creation. mRS outcomes and mortality 90 days after thrombectomy were collected from the five studies of thrombectomy. The percental distribution of mRS 0-5 in these five studies was calculated by removing the portion of mRS 6 and setting the remaining mRS 0-5 as 100 %. Data of mRS outcomes and mortality were compared between Lund and these five studies by a bar chart and by a table. Intervals between time points in Lund were calculated accordingly.

Ethics

We did not apply for ethical vetting for this project. As this is a student project and mainly a quality assurance, applying for ethical vetting is not only unrequired but also actively discouraged by the regional ethical vetting board. Nonetheless, ethical aspects should still be taken into consideration. This project requires obtaining of information which contains sensitive health data, a procedure which is a breach of integrity. This breach of integrity must be weighed towards the issue of ensuring good quality in all aspects of a powerful procedure, and the results might require a re-evaluation, termination or expansion of the procedure. As results are acquired, ethical principles should be applied to discuss what constitutes sufficient quality in terms of cost-

effectiveness, availability at the cost of quality, the principle of doing no harm and the strife of minimising any suffering.

Quality assurance is not only an ethical obligation, but also mandated by the Swedish laws regulating healthcare which state that the quality of operations shall systematically and continuously be developed and secured[20] and that health- and hospital staff are mandated to contribute to maintaining a high degree of patient security[21].

Results

96 patients were referred to thrombectomy in Lund 2015. 80 underwent thrombectomy and 74 of these had an occlusion in the anterior circulation (Figure 1). The baseline characteristics of these patients are displayed in Table 1. Of the 74 with an occlusion in the anterior circulation who underwent thrombectomy, 23 had an onset which could not be completely determined. Five of these did not have any known interval of onset: one due to very fluctuating symptoms and four due to data missing. TICI score was acquired for all patients, of which 57 (77 %) had a score of 2b or 3 after thrombectomy. mRS 90 days after thrombectomy was obtained for 49 patients, of which 36 were alive (Figure 2). Ten patients in the county of Skåne had no documented follow-up in the regional medical charting system and one had restricted access to their charts. Medical charts of potential follow-ups were unavailable for 14 from outside the county of Skåne. Of these 25 patients for which follow-up could not be obtained, none were registered as dead in the electronic health system.

Of the deceased patients (Table 2), eight had a cause of death related to AIS (aspiration pneumonia, cerebral herniation or cerebral bleeding), four had a cause of death that was not

secondary to stroke (all cardiac failures) and one patient did not have any obtainable data regarding cause of death.

The median times between gathered time points in this project are displayed as a box plot (Figure 3).

Discussion

The collected data suggests that patients who underwent thrombectomy in Lund 2015 have an outcome which is on par or better than MR CLEAN concerning autonomy 90 days after thrombectomy. As Lund had a mortality of 18 % which was 3 percentage points lower than MR CLEAN, mortality should be considered to be on par with literature. The other four studies of thrombectomy are not further discussed as their inclusion criteria or treatment requirements are not representative of clinical routine thrombectomy.

While mRS 0-5 outcomes in Lund may seem superior to MR CLEAN (Figure 1), it must be noted that this project had a large portion of surviving patients with a missing value at 90 days in comparison to MR CLEAN which had no missing corresponding values. This makes our results of functional outcome according mRS 0-5 at 90 days somewhat uncertain. It is possible that the missing data from patients from outside region Skåne have influenced the results in a favourable manner as these patients in general come from hospitals further away and therefore have a longer transportation time. The longer transportation times may have increased the entire time from ictus to groin puncture, which is a factor affecting outcome negatively[17]. However, presuming a worst-case scenario where all 25 patients with an unknown mRS value would have an mRS score 3-5, the percentage of patients with an mRS between 3-5 would be 63 %. This would still be on par to MR CLEAN (with no missing data) for which the corresponding group accounted for 59 %. Such

a worst-case scenario is however not likely, given the larger number of patients with a good reperfusion (TICI 2B or 3) in Lund (77 %) when compared to MR CLEAN (59 %). The comparison of mortality is more reliable as the number of patients are greater and there are no missing data regarding alive or dead. We could not compare if the numbers of stroke-related cause of death was similar in MR CLEAN as it did not list causes of death. With these statements, it can be concluded that Lund so far has performed at least on par with the largest study of thrombectomy despite the missing data.

The collected time points show that the longest interval is most often between first imaging and the arrival to angio suite. This is expected as patients undergoing thrombectomy are frequently transported from other hospitals from as far as 200 km away. Even though this interval contains the unaffectable factor of geographical distance, it has great potential to be reduced by several means. The first possible improvement that should be addressed is the early identification of patients suited for thrombectomy, where not only patients with contraindications to IVT should be quickly referred, but also those with lower chances of successful IVT. Examples of factors decreasing the chance of successful IVT treatment are thrombus length, where a thrombus ≥ 8 mm has nearly no chance of dissolving[22], and site of occlusion, where distal occlusions of the cerebral middle artery have the greatest chance of recanalizing and terminal occlusions of the internal carotid artery have the lowest[23]. The rapid identification of these patients is linked to the second possible improvement which is the implementation of bridging; a concept where referral and transportation to a neuroendovascular centre are initiated simultaneously as IVT, instead of first passively awaiting a potential improvement from IVT. Lastly, logistical organisation and transportation from local hospital to the endovascular centre can be improved by streamlining

decisions, implementation and improvement of routines, usage of aerial transport when suitable, constant re-evaluation and adaption.

The time between ictus to first imaging could be divided into pre-hospital and in-hospital time of which the pre-hospital time is most likely the longest according to a large review article of pre-hospital and in-hospital delays in AIS[24]. The pre-hospital time could in turn be divided into patient's delay and logistical time. Reducing the interval between ictus to first imaging could be achieved by targeting these three parts. Patient's delay has a large potential to improve given the Swedish public's quite low awareness of stroke and intent to call 112[25]. Logistical delay of first response by emergency medical services is unbeknownst to the author and may vary locally, but given the relatively small geographical area of Skåne and neighbouring counties, transportation from the scene of ictus to the local hospital is unlikely to decrease. It should also be noted that time between ictus and first imaging in our results is most likely slightly longer than reality as the earliest possible time of ictus was chosen 18 patients where ictus was only known as an interval.

Time between arrival to angio suite and groin puncture had a median of 25 minutes. This interval is potentially reduced by streamlining the procedure, implementation of routines, increased experience of involved personnel and constant re-evaluation.

Time from groin puncture to recanalization is expected to decrease as neurointerventional teams acquire more experience with an increasing number of thrombectomies performed and with the constant development of devices for thrombectomy.

In addition to the data described in the METHOD and RESULTS section additional data was collected regarding first hospital of arrival, IVT given, significant collateral flow on CTA, thrombus length measured by hyperdense artery sign on CT, blood pressure before and after

thrombectomy, general anaesthesia or not, attempts of recanalization, cancelled thrombectomy, and source of embolus. These data were originally intended for subgroup analysis, but in retrospect no such analysis was performed. This is due to neither MR CLEAN, ESCAPE, REVASCAT, nor SWIFT PRIME being able to find any significant difference between such subgroups despite having more than twice as many patients with a known outcome. These data may however be used for further similar projects of thrombectomy in Lund as the number of thrombectomies increase.

Strengths in this project lies primarily within its simplicity; as a retrospective project with low resource cost and the complete usage of only quantitative data when comparing to other studies allows for easy reproduction, comparison and expansion. The largest weakness of this project is the large portion of patients with a missing value of mRS at 90 days (34 %). The number may seem astonishing at first, but this portion of missing data should be put in proportion to another study utilising the Swedish stroke register (Riksstroke) which found that 23,7 % of patients hospitalized for ischemic or haemorrhagic stroke in southern Sweden Jan 2008 - Dec 2010 did not have a physician's follow-up[26]. With these numbers as a comparison, lacking information of follow-up for 34 % is a reasonable loss considering this study was retrospective and without access to any register or any medical charting from outside the county. The loss has potential to be decreased if access was available to Riksstroke and medical charts from outside the county. This would however require ethical vetting. Another weakness is that this project did not record which thrombectomy device was used. As different devices have different outcomes in large studies[27-29] it is possible that varying usage of different devices between Lund and the compared studies might have affected the results. However, given the small number of patients in Lund, a subgroup analysis for this factor would probably not be feasible. Another desirable subgroup

discrimination that was deemed not feasible for the same reason, was by premorbid autonomy or known risk factors for a poor outcome such as high age, sex, prestroke disability, hypertension, atrial fibrillation and stroke severity[30]. The premorbid status could affect outcomes unrelated to AIS, i.e. a previously autonomous but parparetic patient might make a great neurological recovery but still be unable to walk and thus receive mRS score of 3-4. This factor did not affect the comparison of Lund to MR CLEAN as neither selected nor adjusted for premorbid status, and the exclusion criteria in MR CLEAN were basically the same as in routine clinical practice.

Using first imaging as the initial time point recorded after ictus was chosen over arrival to the local hospital as time of imaging are easily and reliably obtainable via PACS. As patients with a suspected AIS intended for acute treatment must undergo imaging, a recorded time exists for almost every patient. This is in difference to the time of arrival to the local hospital which is not regularly recorded in the medical charts.

The results can be used as a basis for an ethical discussion regarding thrombectomies in Lund. Assuming the worst-case scenario above, where all patients missing mRS-outcome are presumed to be mRS 3-5, Lund is still on par with MR CLEAN. While this might sound satisfactory, it should be discussed if such percental outcomes are desirable when they are far better in the other studies of thrombectomy. The discussion should focus on whether thrombectomy should be performed more selectively, improving percental outcomes, or if it should be used more liberally, treating more patients at the risk of over-treating. Hopefully, as knowledge and proven experience of thrombectomy increases on all scales, more patients can be effectively identified if they are suited for thrombectomy or not: maximizing favourable outcomes while still minimizing unfavourable without an overly defensive selection of patients. The expanding treatment of thrombectomy is reflected by the increasing number of patients referred for thrombectomy in

Lund. In the year of 2016, 149 patients were referred: an increase of 59 % from the entirety of 2015.

Conclusion

Patients undergoing thrombectomy in Lund 2015 have an outcome which is at least on par with MR CLEAN, the largest published study of thrombectomy, concerning mortality and patient autonomy.

The largest interval was between first imaging and arrival to angio suite, which also has the largest potential of improvement.

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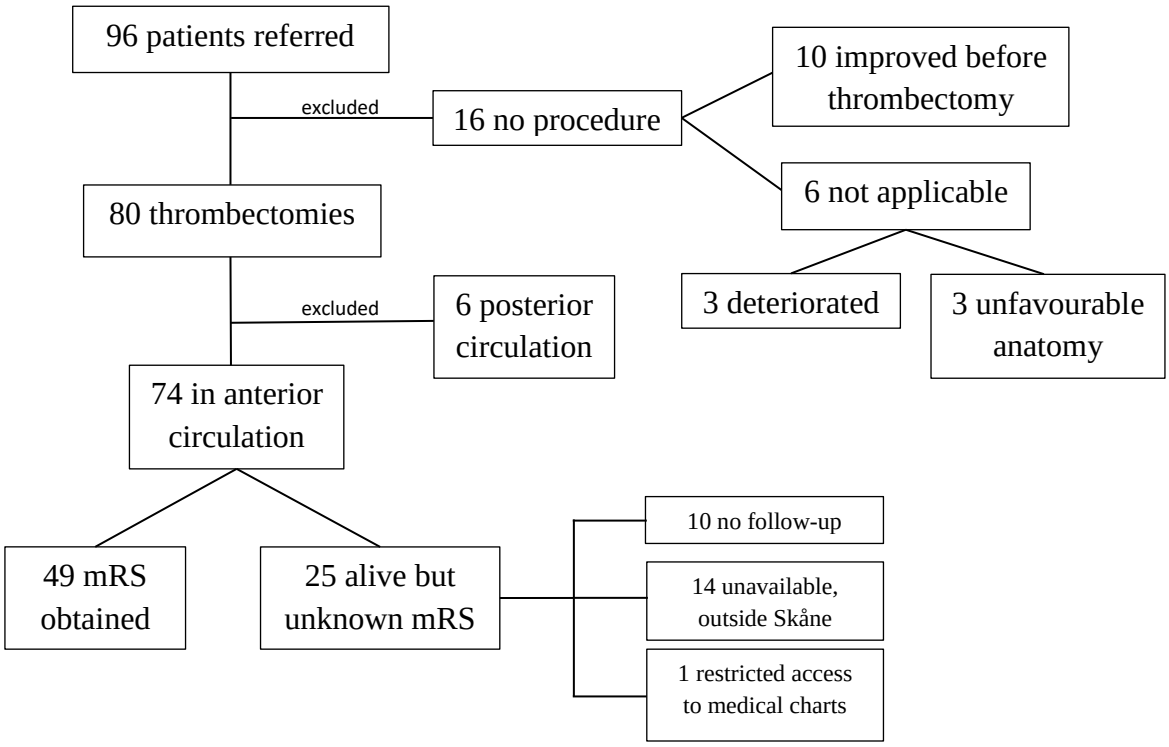

Figure 1. The flow chart above describes the patient material.

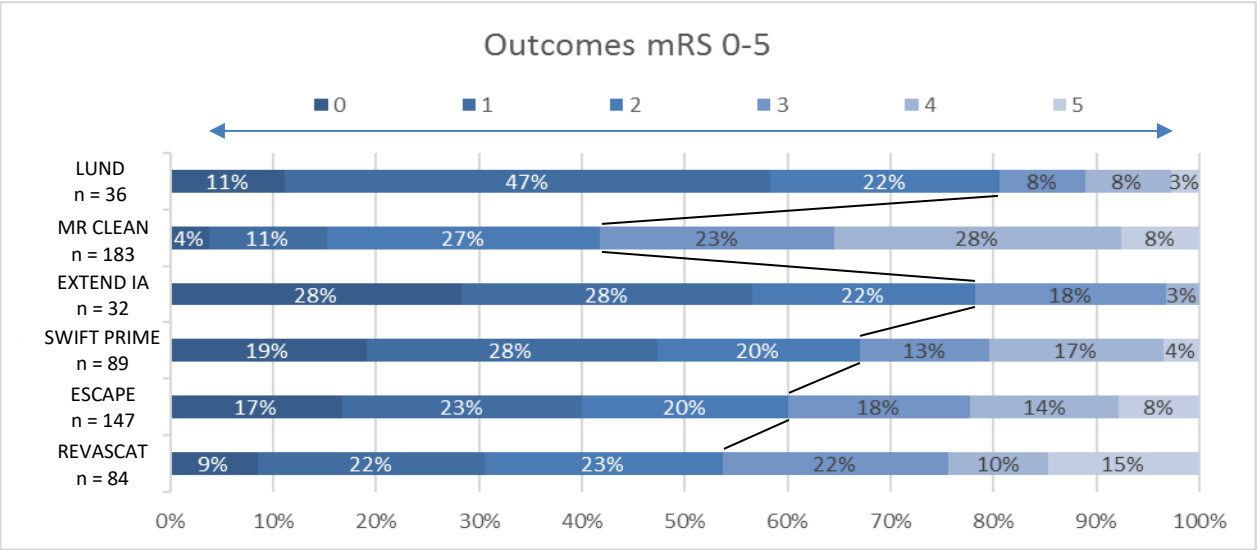

Figure 2. The bar chart above displays the percental distribution of outcomes between mRS 0-5 90 days after thrombectomy in Lund and the five studies of thrombectomy.

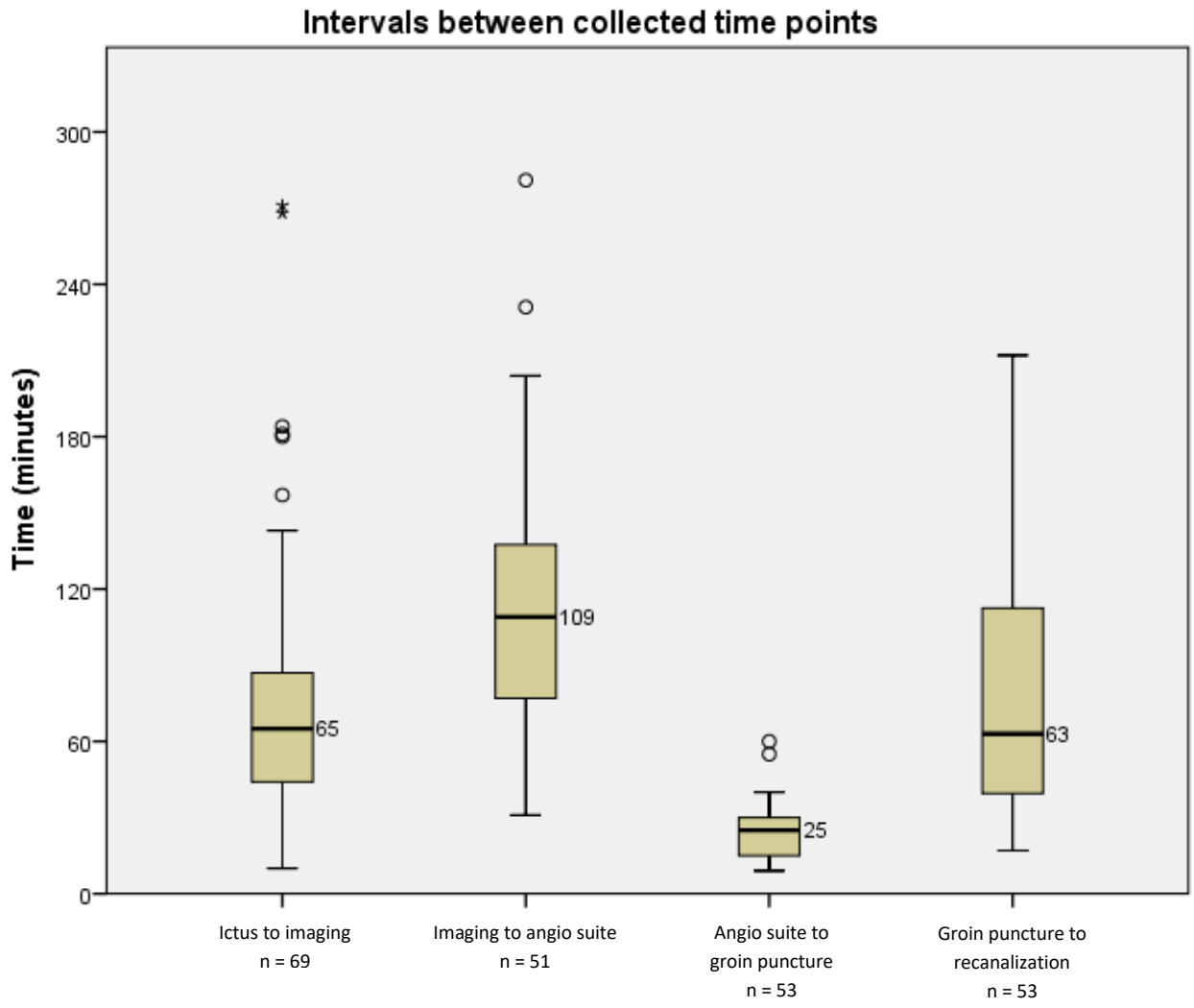

Figure 3. The chart above is a box plot of the median times between each named procedural moments. If ictus was a known interval, the earliest time was used. Numbers in respective boxes vary due to some patients having no recorded time of ictus (n=4), first imaging being performed at unknown time (n=2), no time of arrival to angio suite recorded (n=21), or thrombectomy cancelled (n=11). One patient had neither a recorded time of ictus nor a known time of first imaging. Arrival to angio suite was not regularly recorded until mid-spring 2015.

Table 1. Baseline characteristics of patients.

Characteristic (n = 74)	
Male sex (%)	42
Age	
Range	17 - 89
Median	71
Interquartile range	65 - 78
NIHSS score	
Range	3 - 29
Median	16
Interquartile range	13 - 20

Table 2. The table below shows the mortality in Lund and the five studies of thrombectomy.

	LUND	**MR CLEAN**	**ESCAPE**	**EXTEND IA**	**REVASCAT**	**SWIFT PRIME**
No. of patients	74	232	164	35	103	98
Alive 90 days after ictus	82 %	79 %	90 %	92 %	82 %	91%
Dead 90 days after ictus	18 %	21 %	10 %	9 %	18 %	9%