Optimization of the Management and Triage of stroke patients in the acute phase

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2. Original research articles constituting the main body of the PhD thesis

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4. **Brehm A**, Nguyen Anh, Psychogios MN. Effective dose measurements of the latest generation angiographic system in acute stroke patients – a comparison to the newest multidetector CT generation

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3. Overview of PhD Thesis

Acute ischemic stroke (AIS) due to a large vessel occlusion (LVO) is a devastating disease associated with high rates of morbidity and mortality. Currently, the standard of care for patients presenting with a LVO is removal of the clot with specialized catheters (endovascular treatment). Although endovascular treatment has substantially improved the outcomes of AIS patients, still roughly 50% of patients suffer from severe disability or death. Due to the very high time dependency of the treatment effect, strategies to reduce time to treatment to a minimum are highly warranted. As of now no consensus exists on the best possible triage strategy for suspected AIS patients. One possible approach to reduce time delays within the hospital is to transport patients directly from the emergency room to the angiography room for diagnosis of a vessel occlusion and subsequent treatment (One-Stop management) instead of transporting the patient first to the CT room and after diagnosis of a vessel occlusion to the angiography room for treatment (traditional triage pathway). Imaging in the One-Stop management pathway is done with flat detector CT (FDCT) instead of traditional multidetector CT (MDCT). Many clinicians are still hesitant to use this triage pathway due to missing data and lower confidence in the quality of FDCT imaging. Therefore, several research gaps and challenges remain for the optimization of the management and triage of suspected stroke patients in the acute phase, of which we selected three aspects to focus on in the following topics that comprise this PhD thesis.

The **first topic** focusses on the radiation burden caused by alternative imaging modalities in AIS patients. While flat-detector CT (FDCT) imaging becomes more and more acknowledged as an alternative imaging modality for the diagnosis of an AIS and an LVO, the effective dose to patient of FDCT protocols was not evaluated systematically. For the widespread implementation of FDCT as an imaging modality it must be secured that no excess harm is caused due to a higher burden of radiation. We therefore measured the effective dose to patient and the eye lens dose on two angiography systems and compared it with measurements on the latest generation of commonly used MDCT systems.

The **second topic** focusses on the presentation of suspected AIS patients. As there is no high-level evidence for the implementation of a One Stop management approach, we are planning to conduct a randomized controlled trial. However, for the conduct of such a trial it is important to have reliable information of the expected patient cohort. We therefore analyzed all patients presenting to a tertiary university hospital in one year to give an estimate on the patient collectives expected for such a trial. The data can further be used to plan resources accordingly in times of expanding indications for endovascular treatment of AIS patients.

The **third and final topic** summarizes the available evidence regarding One-Stop management and direct to angiography approaches in a systematic review and meta-analysis. It gives an overview over the research conducted so far in this field and is the foundation for the planning of a randomized controlled trial evaluating a One-Stop management approach for suspected AIS patients.

4 Introduction

4.1 Acute Ischemic Stroke

Acute ischemic Stroke (AIS) is still one of the main causes of disability and loss of quality adjusted life years.[1, 2] Due to aging populations in Europe and Japan the burden of disability due to AIS will increase substantially over the next decades if no advances in the treatment of AIS - especially of AIS due to an occlusion of an intracranial vessel - are made.[2]

An AIS is caused by a blockage of an intracerebral artery. This blockage is caused by a thrombus (which is comprised of fibrin, erythrocytes, and thrombocytes), which could originate from different pathologies (for example arterial heart fibrillation, large artery atherosclerosis or a dissected artery).[3, 4] This blockage leads to an undersupply of the previously supplied brain tissue, which results in an ischemia of the tissue. This ischemia of tissue causes the typical focal symptoms of an AIS (for example hemiparesis or aphasia). If the blockage can be re-opened while the tissue has not undergone infarction it has the potential to regain its function. However, if the blockage persists the tissue might undergo infarction and become irreversible damaged, often leading to a prolonged or unrecoverable loss of the associated function of the brain tissue. In general, it can be said that after the blockage of an artery a subset of neurons undergoes infarction within minutes (the infarct core), while the surrounding tissue becomes severely oligemic (the penumbra) but is still viable.[5] If the blockage of the artery remains the penumbra becomes more and more ischemic and subsequently the neurons within this area become infarcted as well. It is therefore the goal of any reperfusion strategy to reopen the blockage as fast as possible to stop this process to rescue as much brain tissue as possible.[6]

4.2 Types of AIS

One possible classification system for AIS is to classify them according to the location of the occluded vessel. In general, three vessel locations are differentiated: a) proximal, large vessel occlusions (LVO), which are defined as an occlusion of either the internal carotid artery (ICA), the M1 or dominant M2 segment of the middle cerebral artery (MCA) or the basilar artery (BA), b) distal, medium vessel occlusions (MeVO), which are defined as an occlusion of the co- or non-dominant M2 segment, the M3 or M4 segment of the middle cerebral artery (MCA), the anterior cerebral artery (ACA) or the posterior cerebral artery (PCA)[7] and c) small vessel occlusions (SVO), which are occlusions of small perforator or very distal vessels. Overall, it can be said that LVO strokes have the most severe symptoms, although it must be noted that also SVO strokes can have devastating consequences if they affect an eloquent brain area.

4.3 Diagnosis of an AIS

The diagnosis of an AIS is based on a clinical examination of the patient and diagnostic imaging (either with Computer Tomography (CT) or Magnet Resonance Imaging (MRI)).[8] Most patients with a suspected AIS present first to the emergency room. In the emergency room these patients often undergo

a standardized examination based on which the National Institute of Health Stroke Scale (NIHSS) can be calculated. The NIHSS can give the physician a first overview over the symptoms and the severity of the stroke.[9, 10] Based on the occlusion location and the extend of the hypoperfused tissue, AIS patients often present with typical focal deficits. For example, the hallmark symptoms of a left-sided MCA occlusion are right-sided paresis of the arm and face and aphasia. In case of an ACA occlusion the weakness is often more prominent in the leg, while PCA occlusions often lead to visual field deficits. Basilar artery occlusions are harder to diagnosed clinically as they often present with unspecific symptoms such as fluctuating levels of consciousness or coma.[11]

However, the clinical examination is not sufficient to guide further treatment decisions for two reasons: a) the symptoms of an AIS can also be caused by a haemorrhagic stroke (i.e., an intracranial bleeding within a specific brain area) and b) it is impossible to deduct based on the clinical examination if a vessel occlusion is present. For this purpose, every suspected AIS patient undergoes neuroimaging either with CT or MRI. As in most hospitals in Europe and the United States of America CT is used for this purpose due to the wide availability, lower costs, and faster acquisition time, we will focus only on CT protocols in the next paragraph.

For the diagnosis of an AIS two CT protocols are mandatory, while the third can be done as an addon to receive further information. The first protocol is a non-contrast head CT, which is used to determine if the Stroke is caused by an intracranial haemorrhage (haemorrhagic stroke) or ischemia. It also gives the treating physician valuable information about the extent of the infarct. The second protocol is a CT angiography of the head and neck, which is used to determine if there is an occlusion present and in which location the occlusion is.[12] The third protocol is CT perfusion, which can give important information about how much brain tissue has already undergone infarction (infarct core) and how much can still be saved (penumbra).[13] It could also be used to detect medium vessel occlusions which are often not directly apparent on a CT angiography.[12]

4.4 Treatment of an AIS

For the treatment of an AIS two main reperfusion therapies with proven benefit exists: a) intravenous lysis and b) endovascular therapy (EVT). Intravenous lysis refers to the application of alteplase over one hour and it should dissolve the thrombus by enzymatic cleavage.[14] Endovascular therapy is a minimal invasive procedure in which the thrombus is extracted from the vessel mechanical by the utilization of a stent retriever or an aspiration catheter.[15]

Intravenous lysis was approved more than 20 years ago as a treatment for AIS.[14] In contrast to EVT it could be used in all types of AIS including SVOs in which no target occlusion can be identified. However, due to its various contraindications (mainly previous anticoagulant treatment) and its narrow time-window (up to 4.5 hours after stroke onset) only a small subset of AIS patients can profit from intravenous lysis.[16] Furthermore, the efficacy of intravenous lysis is low in LVO and MeVO strokes as

its recanalization rates are low with only 20 – 45% (depending on the localisation of the occlusion and length of the thrombus).[17, 18] Endovascular therapy on the other hand leads to very high recanalization rates (>80%) but can only be used in LVO and MeVO strokes since a target occlusion must be present.[19] In 2015 five randomized controlled trials showed the overwhelming efficacy of EVT for the prevention of disability in AIS due to an LVO.[20] For MeVO strokes no randomized controlled data is available but retrospective data suggest a good safety profile and acceptable efficacy.[21] Ongoing randomized clinical trials are evaluating the efficacy of LVO for the treatment of MeVO strokes.

4.5 Time dependency of the effectivity of AIS treatments

One of the most cited phrases regarding the treatment of AIS is "*Time is Brain"*, which refers to the pivotal importance of timely treatment in AIS patients. The importance of timing in stroke treatment could also be quantified as on average one minute delay in time to treatment causes the irreversible loss of 1.9 million neurons, 14 billion synapses and 12 km of myelinated fibers.[5] Especially the door to groin time (i.e., the time from hospital admission to start of endovascular therapy) is an independent variable for patient outcome as was shown in an analysis of 6,756 AIS patients with an LVO. Among every 1,000 patients treated, every 15-minute decrease in door-to-puncture time was associated with 21 (95%-CI 8 – 34) more patients discharged to home, 18 (95%-CI 4 – 31) more patients having freedom from disability and 22 (95%-CI 7 – 37) more patients having functional independence at discharge. It was further associated with 15 (95%-CI 4 – 26) fewer in-hospital deaths or patients being discharged to a hospice.[22] These results were further validated by other study groups. (8,21-22) Reducing time-delays in AIS patients has also important implications on a socioeconomic level as was recently shown by Kunz et al. They concluded based on the data of 7 large randomized controlled trials (RCTs) that every 10 minutes of earlier treatment result in an average gain of 39 days (95% prediction interval 23 – 53) of disability free life, translating to a reduction of $10,915 (95% prediction interval $5,928 - $15,365) of life-time healthcare costs.[23]

4.6 Strategies to reduce time from door to puncture

As there are still no reliable pre-hospital tests for the detection of an LVO or for the differentiation of ischemic or hemorrhagic stroke[24], the optimization of intra-hospital pathways is as of today one of the most promising research topics in stroke treatment.[25, 26] As of now, the optimized conventional workflow consists of a rapid clinical assessment of the patient, followed by diagnostic imaging with multi-detector CT and CT angiography (MDCT and MDCTA) in the CT room and MT of eligible patients in the angiography suite. This workflow leads in highly trained centers to a door-to-groin time of approx. 60-70 minutes.[27] Logistical circumstances such as patient positioning and transport to separate rooms hinder further time reductions.[10]

A potential solution to this problem is to do both imaging and subsequent MT in the angiography suite using flat-detector CT (FDCT) for the exclusion of intracranial hemorrhage and flat detector CT angiography (FDCTA) for diagnosis of LVO. This would omit the need for another stop in the MDCT

room and allow for direct transfer of the patient to the treatment room.[28] We and other workgroups were already able to show in large patient cohorts that this optimized "One Stop Management" workflow can reduce door to groin times to under 30 minutes.[29-31]

4.7 Current state of evidence for optimal triage strategies in AIS patients

Although there is promising data that One-Stop management can lead to reduced door to groin times and improved patient outcomes, there is no clear consensus on the best triage strategy for suspected AIS patients.

Current guidelines do not give specific recommendations for or against different triage pathways.[13, 32]

5 Aims and outline of the thesis

While the goal to shorten door to groin times to a minimum is unquestionable one of the most important targets in stroke therapy, optimal triage strategies for AIS patients are still a matter of debate. In this thesis, we will investigate different questions with regard to One Stop management to lay the foundation for further, planned investigations of this approach.

One important issue with flat-detector CT (FDCT) was the unknown burden of radiation to patients especially with newer angiography systems. To investigate the effective dose to patients, we performed phantom measurements of often used imaging protocols for the diagnosis of acute stroke patients on two different angiography systems (ARTIS Q and ARTIS Icono, both Siemens Healthineers GmbH, Erlangen, Germany). We further compared the effective dose to patients of the ARTIS Icono angiography system to a multi detector CT (SOMATOM Force, Siemens Healthineers GmbH, Erlangen, Germany) with the same setup to reliable measure potential differences between both systems. The **first topic** summarizes the results of these experiments.

To plan and conduct adequately powered trials in the field of stroke research and to foresee resources adequately it is of high importance to know the expected patient collectives and their characteristics. We therefore performed an analysis of all suspected stroke patients admitted to one German tertiary university hospital within one year. The acquired data and results are summarized in **the second topic.**

To give an overview over the currently available evidence regarding One Stop management and direct to angiography approaches we performed a systematic review and meta-analysis. This could be used as a basis for determining the direction of further research. The results of the systematic review and meta-analysis are summarized under the **last topic**.

Lastly, we discuss the implications of the findings of this thesis and provide directions for further research. We also give an overview of our next research projects and currently approved clinical trials.

6. First topic: Effective dose to patient measurements of the latest angiography systems in acute stroke patients

This topic includes the evaluation of the effective dose to patient of commonly used stroke protocols on the latest generation of angiography systems. We measured two different systems and compared the measurements to analogous protocols on the newest generation of multidetector CT systems.

6.1 Effective dose to patient measurements for flat-detector computed tomography protocols in acute stroke care

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Abstract

Objectives

The aim was to measure the effective dose of Flat-detector CT (FDCT) whole-brain imaging, biphasic FDCT-angiography (FDCT-A) and FDCT-perfusion (FDCT-P) protocols and compare it to previously reported effective dose values of multidetector CT (MDCT) applications.

Materials

We measured effective dose according to the IRCP 103 using an anthropomorphic phantom equipped with thermoluminescent dosimeters (TLDs). Placement was according to anatomical positions of each organ. In total 60 TLDs (≥4 TLDs/organ) were placed into and onto the phantom to account for all relevant organs. Organs within the primary beam were covered with more TLDs. Additionally, we measured dose to the eye lens with two TLDs per eye. Protocols which we routinely use in clinical practice were measured on a biplane angiography-system.

Results

The effective dose of the 20s-protocol/7s-protocol for whole-brain imaging was 2.6 mSv/2.4 mSv. The radiation dose to the eye lens was 24/23 mGy. For the biphasic high-/low-dose FDCT-A protocol the effective dose was 8.9/2.8 mSv respectively. The eye lens dose was 60/14 mGy. The contribution of bolus tracking to the effective dose was 0.66 mSv (assuming average duration of 14s). The multisweep FDCT-P protocol had an effective dose of 5.9 mSv and an eye lens dose of 46 mGy.

Conclusion

Except for the high-dose biphasic FDCT-A protocol, FDCT-applications used in neuroradiology have effective doses, which do not deviate more than one mSv from previously reported values for MDCT applications. However, the effective dose to the eye lens in commonly used stroke paradigms exceeds the recommended annual dose by two-folds.

Introduction

To reduce door-to-groin times in acute stroke patients, new triage paradigms have been developed, which incorporate stroke imaging in the angiography-suite with a flat-detector CT (FDCT) instead of a traditional multidetector CT (MDCT).[33] For this purpose, new imaging protocols have been developed enabling the physician to perform biphasic FDCT angiography and even perfusion in the angiography suite, omitting the need for additional patient transport.[34, 35] Furthermore, conventional whole-brain FDCT imaging can be used pre- and post-interventional to rule out intracranial hemorrhages.[36] Whole-brain FDCT imaging was done with a 20 second protocol in the past. Recently, a faster (seven second in older systems, six second in the latest generation) FDCT protocol was introduced, which might offer superior image quality due to a potential reduction of movement artefacts. Despite the growing use of these new FDCT protocols, effective dose to patient values have not been published. Furthermore, the radiation to the eye lens was never evaluated systematically and is not part of current standardized measurements of radiation exposure. However, in the light of recent publications regarding the connection between ionized radiation and cataract[37, 38], this should be of interest.

In the present study, our aim was to measure the effective dose to the patient and the eye lens dose using (1) FDCT whole-brain imaging with the 20 second protocol and compare it to the effective dose of the new faster protocol, (2) high-dose biphasic FDCT angiography (FDCT-A) and low-dose biphasic FDCT-A and (3) FDCT perfusion (FDCT-P). Effective dose values of analogous MDCT protocols reported previously in the literature were compared with our findings. All measurements have been performed in concordance with the guidelines of the International Commission on Radiological Protection (ICRP) publication 103.[39]

Materials and Methods

Phantom dose measurements

An Alderson-Rando phantom (Radiology Support Devices INC.) was used in all measurements. It consisted of natural bones embedded in a soft tissue equivalent material and has the dimensions of a standard male (175 cm, 73.5 kg). This ensured that the phantom absorption and scattering of X-ray are equivalent to human tissue. It is divided into transverse sections with a thickness of 2.5 cm. Each section included a grid of holes in the z-direction for the placement of thermoluminescent dosimeters (TLDs) at an angle of 90° with respect to the radiation beam. The TLDs were fit into holder pins (acrylic glass tubes) and then placed into the holes of the phantom. We used standard lithium-fluoride TLDs to achieve accurate results (type 100H, rod type, 1×1×6mm³, LiF:MgCuP, Thermo Fisher Scientific). TLDs are standardized measuring instruments for exact dose monitoring. They base on the ability to absorb and store energy of ionizing radiation. If they get heated subsequently, they emit the stored energy in the

form of electromagnetic radiation (light), which can be measured. The placement was according to the anatomical position of each organ tissue for the calculation of the effective dose. To account for all relevant organs (including the brain, thyroid, lung, red bone marrow, esophagus, breast, liver, stomach, colon, gonads and lenses) 60 TLDs were placed in and onto the phantom. Twelve TLDs were inserted into the head, while all other relevant organs (within and outside the primary beam) were covered with at least four TLDs. Organs near or in the primary beam (e.g. red bone marrow, thyroid, esophagus) were covered with even more TLDs. Dose to the eye lenses were measured with two TLDs per eye. Since the ICRP 103 doesn`t define the number and distribution of the TLDs within the phantom, these parameters have to be chosen by the investigator. The distribution and placement of the TLDs were identical in all measurements to ensure comparability of the results. The organ dose was defined according to the ICRP 103 as the mean of the TLDs at each organ point. In order to account for variation and to ensure that a dose above the minimal reliable detection level can be recorded, each acquisition was performed ten times. The phantom wasn`t moved during the different acquisition runs. Afterwards the absorbed dose recorded by the TLDs was divided by the number of acquisition runs, to calculate the average dose per run.

The effective dose to patient (E) was calculated according to the ICRP 103[39] using the following equation:

$$E = \sum_{T} W_T * H_T$$

W_T represent the weighting factor of the tissue, which is predefined by the ICRP 103 and its sum equals to one, while H_T is the equivalent dose of the individual organ measured by the TLDs in µGy. The unit of E is mSv.

To account for differences due to varying X-ray beam energies, we performed calibration measurements for 109 kV, 77 kV and 70 kV. An ionization chamber (Unidos E universal dosimeter, PTW Freiburg), which adheres to the guidelines of the German calibration service was used. This was necessary to prevent problems of energy and beam quality dependency of the TLDs. In our case the calibration factors were very close to 1, ranging from 0.976 to 0.997. Between each irradiation the complete information from previous irradiations was removed by heating the TLDs in an annihilation oven TLDO (Type 1301, PTW Freiburg). After the heating cycle (ϑ=240°C, t=20min) 60 TLDs were placed within the anthropomorphic phantom and the measurements were performed. To account for background radiation, we used 10 TLDs, which weren`t affected by any artificial radiation. 10 additional TLDs were each irradiated with a dose of 0.4 mGy to validate the measurement process (reference dosimeter). For reading out the information from the TLDs after the measurement an automatic thermoluminescence dosimetry reader 5500 (Thermo Fisher Scientific) was used. The dose was determined by calculating the area under the relevant part of the glow curve. Each dosimeter had its own calibration factor. This

was determined by irradiating each dosimeter with a 90Sr/90Y source. The source was calibrated in air KERMA with a calibration traceable to a secondary standard (Material Testing Institute Dortmund). To ensure the quality of the measurement the photomultiplier of the reader was checked by a light source of known intensity. To minimize tribo- and chemiluminescence effects the TLDs were heated with hot nitrogen (ϑ=250°C). Taking all errors into account, the accuracy of the measurement was estimated to be with ±10% range.

FDCT protocols

The examination of the phantom was performed on a biplane angiographic system (Artis Q, Siemens Healthineers AG). The placement of the phantom reassembled the placement of a typical patient.

For dose evaluation we used manufacturer-specified programs. The 20sDR-H program (DynaCT, 1.82 µGy/f, Siemens Healthineers AG) and the 7sDR-H program (1.82 µGy/f) were used to perform non-contrast whole-brain acquisition to evaluate brain parenchyma. The FDCT-A was performed using the mpFDCTA HD protocol (1.2 µGy/f), which included 2 rotations over 10 seconds each and using the mpFDCT low-dose protocol (0.36 µGy/f), which also included 2 rotations over 10 seconds each. The bolus tracking (3.0 µGy/f) was measured separately to calculate its contribution to the total dose of a FDCT-A. The protocol is described in detail elsewhere.[33] However, in brief 60 mL of contrast media (Imeron 400, Bracco Imaging GmbH) were injected with a power injector at a flow rate of 5 mL/s followed by 60 mL saline chaser at 5 mL/s. The acquisition of the arterial phase FDCT-A was manually started, when the bolus was visualized in the carotid siphon and the time-delay between the arterial and venous FDCT-A was 5 seconds. Whole-brain perfusion imaging was performed using the multisweep FDCT-P protocol (0.36 µGy/f), which included 10 rotations with a length of 5 seconds each. The used protocol was similar to the one described by Yang et al.[40] 60 ml contrast media (Imeron 400, Bracco Imaging GmbH) were injected over a power-injector at a flow rate of 5 mL/s) followed by 60 mL saline chaser at 5 mL/s. Figure 1 shows the position of the investigated area and the coverage length of each protocol.

Results

We summarized the effective dose to patient values for each protocol in table 1.

The difference of the effective dose between the two whole-brain FDCT protocols was well within the ±10% margin with 2.6 mSv for the 20s and 2.4 mSv for the 7s protocol. The FDCT-P protocol had an effective dose to patient of 5.9 mSv. With 8.9 mSv the high-dose biphasic FDCT-A protocol had the highest effective dose to patient. In comparison, the effective dose of the low-dose FDCT-A protocol was 2.8 mSv, resulting in a reduction of almost 70%. The contribution of the bolus tracking to the

effective dose of the whole FDCT-A protocol was relatively small with 0.047 mSv per second. As the average bolus tracking time in our institute was 14 seconds, the bolus tracking contributed on average 0.66 mSv to the effective dose of the FDCT-A protocol. This was less than 10% of the total effective dose in case of the high-dose FDCT-A protocol. However, in case of the low-dose protocol, it added almost 25% to the total effective dose.

The effective eye lens dose of the 20s and 7s whole-brain FDCT protocol was similar with 24.4 mGy (20s) and 22.7 mGy (7s). The highest eye lens dose was recorded for the high-dose mpFDCT-A with 60.4 mGy, while it was 13.8 mGy in case of the low-dose mpFDCT-A. Bolus-tracking had a lens dose rate of 251 μGy per second, which can be translated to 3.5 mGy per average scan. The eye lens dose of the FDCT-P was 45.6 mGy.

In all measurements at least 97% of the radiation was recorded in the brain, red bone marrow, esophagus and thyroid. The remaining organs received less than 3% of radiation, rendering them clinically unimportant. The eye lens dose was not used for the calculation of the effective dose, as it does not have a weighting factor.

Discussion

This study evaluated the effective doses of FDCT protocols, which are frequently used for the imaging of acute stroke patients in a modern angiography suite. It is the first study, which evaluates the new ultrafast whole-brain FDCT protocol for parenchymal imaging and the new multisweep FDCT-P protocol in a phantom according to ICRP publication 103. Furthermore, it is the first to evaluate the eye lens dose.

The highest quality for the evaluation of the brain parenchyma with FDCT has been achieved with the 20s DR-Head protocol.[41] Although image quality of this protocol is inferior to MDCT, previous work from our group showed that it was sufficient for delineating all relevant clinical questions in the acute or periinterventional setting.[36] Regarding the evaluation of early ischemic signs, using the Alberta Stroke Program Early CT Score, Maier et al. found no significant difference between FDCT and MDCT.[41] One major disadvantage of this protocol was, that it was susceptible to motion artefacts because of the long acquisition time. In order to surpass this technical limitation of current angiography systems and be able to acquire the same projection in faster times, a higher binning (4x4 instead of 2x2) has been chosen in a newly developed 7s protocol. Although this reduces spatial resolution, it should not affect contrast resolution which is far more relevant for parenchymal imaging. Our initial results (unpublished) with this new 7s protocol indicate a better overall contrast resolution, as the faster acquisition protocol could possible lead to a reduction of motion artefacts. Another difference was the used detector, since we used for the 7s protocol the Artis Q detector (Siemens Healthineers AG) as compared to the Artis AXIOM

detector (Siemens Healthineers AG) used in the study of Struffert et al.[42] If this affects image quality is a topic of ongoing investigation and still uncertain. Regarding the effective dose both protocols were equal as was shown in the results, which was not particularly surprising, since number of frames and dose per frame is roughly equal. This confirmed prior work from Struffert et al., which showed a similar effective dose for the 20s-protocol.[42] A recent evaluation by Lin et al. of modern MDCT brain parenchymal imaging protocols resulted in an effective dose of 1.72 mSv.[43] As the effective dose of the FDCT is less than 1 mSv higher, we advocate using the FDCT in the acute setting as the advantages of not having the patient transported can be seen as the dominant argument.

The applied multisweep FDCT-P with ten rotations is the first FDCT-P protocol, which allows the dynamic evaluation of brain parenchymal perfusion. It enables the calculation of the cerebral blood volume (CBV) map, but also time-resolved perfusion maps such as cerebral blood flow (CBF), time to drain (TTD) and mean transit time (MTT). Additionally, this FDCT-P protocol can be analyzed with the new RAPID-ANGIO software (iSchema View Inc.) for automatic evaluation of core and mismatch. These maps are indispensable for the triage of acute stroke patients especially in the late time-window. They can be used to estimate the size of the infarct core and of salvageable tissue. Therefore, the protocol cannot be compared to the NeuroPBV-8s protocol suggested by Struffert et al., as this protocol only allowed for calculating of the CBV maps.[42] Furthermore, the NeuroPBV-8s protocol can lead to an overestimation of the infarct core, which might cause wrong treatment decisions.[44] Another advantage of our protocol is that similar to MDCT perfusion and the NeuroPBV-8s protocol[34] the data set of the FDCT-P can be used for calculating an angiography in different phases, allowing the physician to evaluate collaterals and depict an intracranial occlusion.[45] Taken all the aforementioned points together, it should rather be compared to MDCT perfusion protocols. As existing literature on MDCT perfusion protocols reports an effective dose of ~5 mSv, the dose of our FDCT-P protocol is comparable, since with 5.9 mSv it is only 20 % higher.[46] This added radiation can be justified with the time-saving effect of performing comparative stroke imaging in the angiography suite, omitting the need of additional patient transport.[35] Furthermore, due to the high average age of stroke patients, radiation exposure should be a minor concern.

The effective dose of the high-dose FDCT-A (8.9 mSv) is notably above previously reported values for MDCT-A (3.3 mSv).[42] However, it has to be taken into account, that this is a biphasic protocol which incorporates two time points compared to only one time point in MDCT protocols. To reduce the dose of the FDCT-A protocol, we advocate the usage of our proposed low-dose FDCT-A protocol, with an effective dose of only 2.8 mSv. The lower dose per frame does not impose a problem for high-contrast imaging.[47] As mentioned above, the biphasic character of our proposed FDCT-A protocol is a clear advantage as it allows better evaluation of collaterals as a prognostic factor for stroke triage. According to Schlegel et al. it is of equal value for outcome prediction as CT perfusion, omitting the need of performing an additional FDCT-P.[48] Furthermore due to the isotropic nature of the FDCT images the

resolution of the FDCT-A is superior to MDCT-A.[47] An illustration of maximum intense projections (MIPs) reconstructed from FDCT-A and MDCT-A is shown in Figure 2. One important disadvantage of FDCT-A, which is still unsolved, is the limited coverage of the FDCT-A. It allows coverage of the intracranial vessels, the extracranial arteria carotid internal and partly the common carotid artery but not of the aortic arch. As mentioned above in our opinion the best strategy to reduce the effective dose would be to use a lower dose per frame, which can reduce the effective dose up to 70 %. Another strategy, which was proposed by Struffert et al., is the usage of colimitation in the second rotation.[42] However, in the setting of an acute stroke we think this approach is not practicable, since the information regarding the status of the proximal internal carotid is crucial in a tandem occlusion setting. A third strategy to reduce the effective dose would be to perform only one rotation. This would reduce the effective dose by 50 %. However, in this case the timing of the rotation would be of upmost importance as it is pivotal to acquire the angiography in the arterial phase. Since bolus tracking contributes only a fraction of the whole effective dose with 0.66 mSv for the average duration of 14 seconds, this can be an effective strategy to reduce the effective dose as well. However, we still advocate using the biphasic protocol, as it can provide important information on the collaterals in the venous phase.[48]

As epidemical evidence suggests, radiation-induced damage to the eye lens can lead to loss of clarity or clouding even several years after exposure.[49] This led the National Council on Radiation Protection and Measurements (NCRP) to limit the recommended absorbed eye dose to 50 mGy annually.[50, 51] As the normal work-up of an acute stroke patient includes one mpFDCT-A and up to two whole-brain FDCTs, this limit is already exceeded two-fold, without including the fluoroscopies in case of a thrombectomy. Therefore, counter-measurements such as lens protectors or altering the covered area should be evaluated in the future to limit the effective dose to the eye lens especially in younger patients.

Our study has some shortcomings. Although we tried to limit variations in the sensitivity of the TLDs by performing regular calibrations and tried to rule out measurement errors due to incomplete annihilation of the TLDs by putting multiple TLDs in each organ, the method was subjected to some inaccuracy. Therefore, the accuracy of the measurements was only ±10%. Furthermore, the IRCP 103 does not prescribe the placement of the TLDs within the phantom, limiting comparability of the results from different studies and workgroups. However, we tried to minimize this effect by placing multiple TLDs into each organ and the placement remained identical for all investigated protocols. Comparability between dose estimates from MDCT and FDCT pose another limitation, as there are important differences between both techniques. As todays C-arm devices typically use a 210° rotation compared to conventional MDCT with a 360° rotation, it has to be taken in account that this leads to a nonuniform dose distribution with the peak dose occurring in the central plane on the side of the phantom closest to the radiation source.[52] Furthermore, larger z-coverage of FDCT compared to MDCT renders traditional weighted CT dose index (CTDI) approaches unpractical.[53] On the other hand it has to be noted, that an approach utilizing TLDs addresses most of the issues mentioned above and leads to the closest

estimation possible within modern technical abilities. Regarding the measurement of the dose to the eye lens, it must be noted that the dose was measured directly above the eye, as we did not have the option of inserting a TLD at the level of the eye bulb. Therefor our results might overestimate the exposure, however the magnitude of this overestimation should not diminish the meaningfulness of the measured values.

The differences between MDCT and FDCT images are widely accepted, as FDCT has inferior soft-tissue visualization but higher spatial resolution for high-contrast structures (e.g. bones and vessels).[36, 41] The main advantage of the FDCT is to perform imaging directly in the angiography suite, which allows for periinterventional imaging of critical patients and shorter door-to-groin times in case of acute stroke.[30] Compared to other papers evaluating the effective patient dose of MDCT applications the high-dose biphasic FDCT-A has a substantially higher effective dose compared to MDCT-A (8.9 vs. 3.3 mSv). However if we compare the low-dose biphasic FDCT-A with MDCT-A the difference diminishes (2.8 vs. 3.3 mSv).[42] If we compare the 7s whole-brain protocol to whole-brain MDCT application the effective dose is less than 1 mSv higher (2.4 vs. 1.7 mSv).[43] In comparison the difference between the FDCT perfusion and the MDCT perfusion is only 20 %.[42, 46]

Except for the high-dose biphasic FDCT-A protocol, FDCT-applications used in neuroradiology have effective doses, which do not deviate more than one mSv from previously reported values for MDCT applications. Using a lower dose per frame can reduce the effective dose of the FDCT-A protocol substantially. The effective dose to the eye lens in a commonly used stroke paradigm exceeds the recommended annual dose by two-folds, prompting for strategies to decrease the effective lens dose especially in younger patients.

Tables

FDCT Protocol	20s DR Head	7s DR Head	mpFDCTA HD	mpFDCT low-dose	Bolus-tracking	FDCT Perf
Number of rotations	1	1	2	2	-	10
Tube potential (kV)	109	109	70	70	73	77
dose/frame (μGy/f)	1.82	1.82	1.20	0.36	3.00	0.36
Rotation angle (degree)	200	200	200	200	-	200
Angulation step (degree/frame)	0.4 °	0.4°	0.8°	0.8°	-	0.8
Number of images	500	500	2 x 250	2 x 250	2 per second	10 x 250
Scan time / rotation (s)	20	7	10	10	-	5
Coverage	Whole-Brain	Whole-Brain	Head and Neck	Head and Neck	Head and Neck	Whole-Brain
Lens-Dose (mGy)	24.4	22.7	60.4	13.8	0.25 / s*	45.6
Effective dose (mSv)	2.6	2.4	8.9	2.8	0.047 /s*	5.9

* dose rate

Table 1: Summary of the FDCT protocols and their effective dose measurements

Figures

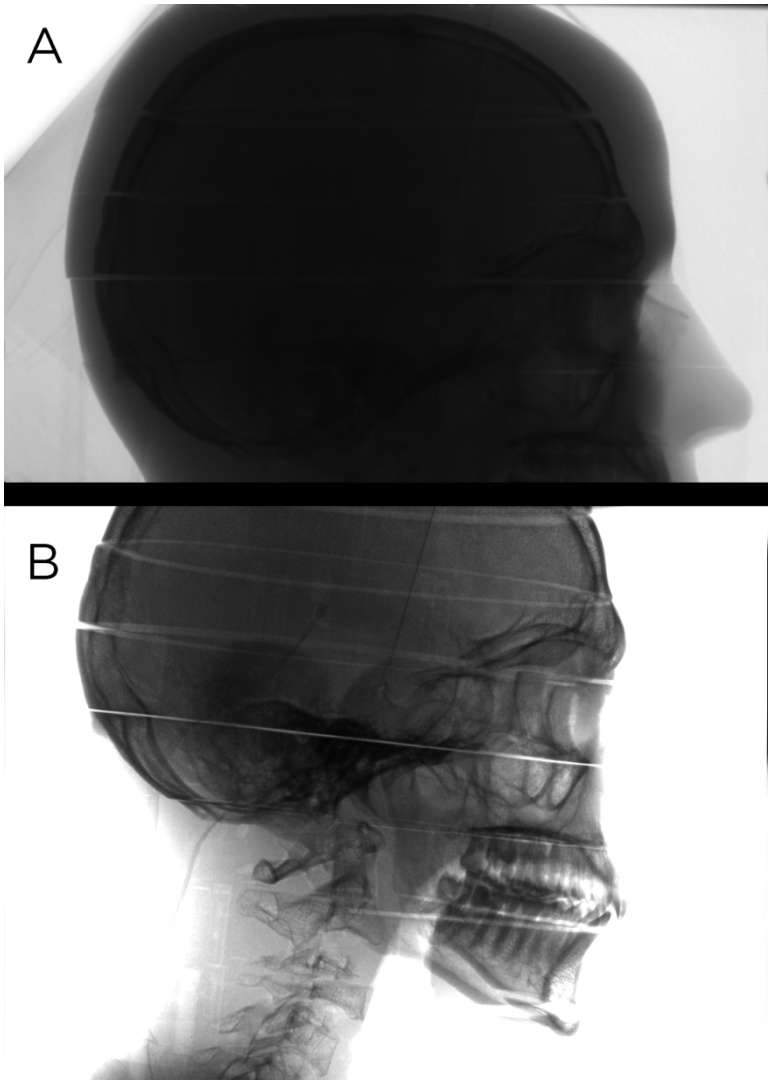

Figure 1: The position of the investigated area and the coverage length in FDCT and DSA. Positioning (A) was used for the 20s DR Head, 7s DR Head and FDCT perfusion protocol, (B) was used for the mpFDCT HD, mpFDCT Low-Dose and Bolus-tracking protocol.

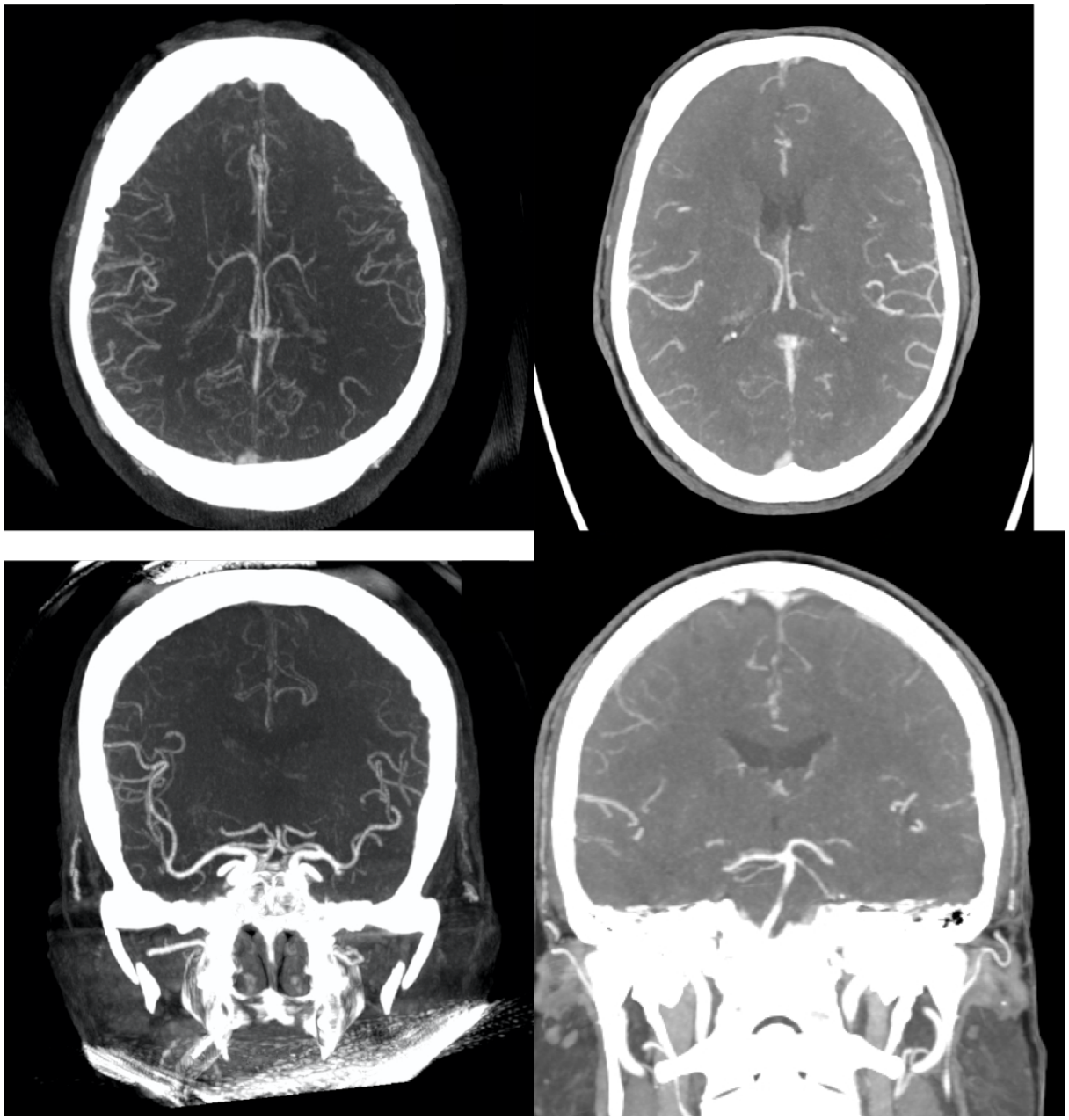

Figure 2: Illustration of maximum intense projections (MIPs) reconstructed transversal from an FDCT-A (A), transversal from an MDCT-A (B), coronal from an FDCT-A (C) and coronal from an MDCT-A (D)

6.2 Effective dose measurements of the latest generation angiographic system in acute stroke patients – a comparison to the newest multidetector CT generation

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Abstract

Background and Purpose

Acute ischemic stroke (AIS) patients are increasingly triaged with One Stop Management approaches, resulting in baseline imaging with a flat-detector CT (FDCT). This study aims to estimate the effective dose to patient of a novel cervical and intracranial FDCT-angiography (FDCT-A) and an FDCT-perfusion (FDCT-P) protocol and compare it to the effective dose of analogous multidetector CT (MDCT) protocols.

Materials and Methods

We estimated the effective dose to patient according to the ICRP 103 using an anthropomorphic phantom with metal oxide semiconductor field effect transistor (MOSFET) dosimeters. Placement was done according to the organ map provided by the phantom manufacturer. We used 100 measurement points within the phantom and eighteen MOSFET dosimeters were placed on the surface of the phantom. All protocols followed the manufacture`s specifications and patient positioning and collimation was performed as in routine clinical practice. Measurements were obtained on a latest-generation angiography and MDCT system with identical placement of the MOSFET dosimeters.

Results

The estimated effective doses of the investigated perfusion protocols were 4.52 mSv (FDCT-perfusion without collimation), 2.88 mSv (FDCT-perfusion with collimation) and 2.17 mSv (MDCT-perfusion). A novel protocol called portrait FDCT-angiography that has a comparable z-axis coverage area to MDCT-angiography had an estimated effective dose of 0.91 mSv, while the dose from MDCT was 1.35 mSv.

Conclusion

The estimated effective dose to the patient for FDCT-perfusion and -angiography on a modern bi-plane angiography system do not deviate substantially from analogous MDCT protocols.

Key Words: Cone-beam computed tomography; flat detector computer tomography; Stroke; Radiation dosage; Perfusion; Angiography

List of abbreviations

AIS	Acute ischemic stroke
FDCT	Flat-detector CT
FDCT-A	FDCT angiography
FDCT-P	FDCT perfusion
MDCT	Multi-detector CT
MOSFET	Metal oxide semiconductor field effect transistor
OSM	One Stop Management
RO	Region of Interest

Introduction

Implementing a One Stop Management (OSM) workflow can substantially shorten door to groin and door to reperfusion times.[29, 54] It can, furthermore, lead to improved patient outcomes according to a recently published randomized-controlled trial.[55] The OSM workflow combines diagnostic imaging and interventional therapy of acute ischemic stroke (AIS) patients in one room -- the angiography suite. FDCT is used for the initial diagnostic imaging, rather than the traditional approach in which the patient must first be transported to the multidetector CT (MDCT) room for diagnostic imaging and then subsequently to the angiography suite for treatment.[29] One possible disadvantage of FDCT compared to MDCT is the limited coverage of FDCT angiography (FDCT-A) as it is impossible to simultaneously visualize the intracranial vessels, the extracranial vessels and the aortic arch. This limitation was recently partially resolved by the introduction of a new portrait FDCT-A prototype in which the detector is rotated by 90° for an increased field of view. Furthermore, a recent publication showed a strong correlation between FDCT-perfusion (FDCT-P) and MDCT-P for the automated measurements of ischemic core and ischemic penumbra volumes in AIS patients, suggesting that FDCT-P can be used as effectively and reliably as MDCT-P.[56] Despite the growing use of these protocols, the effective dose to the patient and, more specifically, the dose to the lens of the eye were not systematically compared to analogous MDCT protocols.

In the present study, we utilize a phantom to measure the effective dose to patient and the eye lens dose of FDCT-P, portrait FDCT-A and compare the results obtained to those obtained from analogous MDCT protocols.

Materials and Methods

Phantom

We used an adult male ATOM phantom 701-C (Computerized Imaging Reference Systems, Inc., Norfolk, VA, USA) to measure the effective dose (Figure 1), which represents a body of a male human with a height of 173 cm and a body weight of 73 kg. The phantom consists of averaged materials for soft, bone, lung, and brain tissues. The phantom is equipped with 39 slices of 2.5 cm thickness; all of them having cavities for detector placement in a 1.5 cm x 1.5 cm grid with a 0.5 cm diameter.

Dosimeters

For assessing the organ dose, we used metal oxide semiconductor field effect transistor (MOSFET) TN 1002RD-H dosimeters equipped to the mobileMOSFET system, model TN-RD-70-W (Best Medical Canada Ltd., Ottawa, ON, Canada). The mobileMOSFET system consists of a remote monitoring dose verification software, a Bluetooth^{tm} wireless transceiver, and a reader module that acts as a channel between MOSFET dosimeters and software. Up to five MOSFET dosimeters can be connected to one reader. In this study, eight readers and forty MOSFET dosimeters were used for simultaneous

measurements. Prior to the measurements, all MOSFET dosimeters were calibrated. For calibration purposes each of the MOSFET dosimeters was irradiated with a specified dose. The dose was then measured with an ionization chamber (PM500-CII 52.8210, Capintec Inc., Ramsey, NJ, USA) connected to the Unidos dosimeter (PTW, Freiburg, Germany) as described before.[57]

C-arm angiography and CT systems

We performed the measurements on an ARTIS icono biplane angiography system with a neuro tabletop and mattress (Siemens Healthcare GmbH, Forchheim, Germany) and on a SOMATOM Force CT scanner (Siemens Healthcare GmbH, Forchheim, Germany) with syngo CT VB20 software. For measurements on the ARTIS icono system, the A-plane C-arm was placed in the anteroposterior position and the field of view for 3D imaging was set in the head region of the phantom. The perfusion measurements on the ARTIS icono system were performed with and without collimation of the X-ray field (Figure 2). The cranio-caudal collimation and positioning of the phantom were applied according to the procedure specific settings used in the clinical workflow at the University Hospital Basel. The scan z-coverage in the collimated setup was 15 cm. The 15 cm were derived from averaging the scan z-coverage of all scans performed at the University Hospital Basel. The protocol is described in detail elsewhere.[58] For perfusion measurements on the SOMATOM Force CT scanner we used the standard acquisition protocol from the manufacturer. The scan z-coverage for perfusion measurements on the SOMATOM Force system is 11.4 cm.

In addition, we investigated the 3D imaging protocols for visualization of the carotid and intracranial arteries. The acquisition protocols for both systems were used as in clinical practice. For measurements on the ARTIS icono system, the detector was used in portrait mode without collimation (Figure 3). The imaging protocol with the detector in portrait mode (i.e., rotated by 90°) is the latest 3D imaging prototype on the ARTIS icono. For 3D imaging of the carotid arteries on the SOMATOM Force CT scanner the CARE Dose4D and CARE kV technologies were applied. To ensure comparable results, we used the same z-coverage area for the FDCT- and MDCT- angiography, i.e excluding the aortic arch. We summarized the technical parameters of the 3D acquisition protocols for both systems in tables 1 and 2.

Estimation of effective dose

To estimate the organ dose, we placed the MOSFET dosimeters in 118 measurement points in the ATOM phantom and on the phantom surface. The locations of the measurement points within the phantom were defined according to the organ map provided by the phantom manufacturer. These locations represent the anatomical position of different organs (brain, eye lenses, salivary glands, thyroid, oesophagus, bone surface, lung, liver, stomach, pancreas, adrenal gland, small intestine, spleen, kidney, red bone marrow, bladder, gonads etc.). To fit the MOSFET dosimeters within the phantom holes, each dosimeter was placed into the tissue-equivalent holder. The skin dose was measured by 18

dosimeters positioned on the surface of the phantom at slices 4, 10, 17, 28 and 38. We used the same distribution and positioning of the dosimeters in all measurements.

With the identical setup of dosimeters, we repeated all 3D-imaging protocols three times to ensure adequate radiation of the dosimeters outside of the direct radiation field. The organ dose was calculated as the mean value of the measured data from all dosimeters placed into the respective organ sites. For organs such as skin, red bone marrow, oesophagus and lungs that, depending on the applied 3D-imaging protocol and the scanned area, were exposed to both direct and scatted radiation, the fraction of directly irradiated organ volume in the head and neck region was considered for calculation of organ dose. The fraction of the directly irradiated skin area was estimated according to the so-called "rule of nines" used in trauma and emergency medicine to assess the total body surface area involved in burn patients.[59] We estimated it to be 8% for the whole head region and 10% for the head and neck region. The red bone marrow in the whole head region was considered to be roughly 10% and in the head and neck region roughly 15% of total body red marrow.[60] This data was used to calculate the effective dose according to the guidelines of the International Commission on Radiological Protection (ICRP) 103.[61] The radiation-weighting factor for X-ray was assumed to be 1 in concordance with the ICRP 103.[61]

The accuracy of our measurements was estimated to be ±20%. This estimation considers all possible sources of errors, such as uncertainty for the reference dosimeter, uncertainty for estimation of calibration factors and the uncertainty for calculation of dose for each organ location.

Results

We summarize the estimated effective dose to patient values for the investigated FDCT protocols in table 1 and the investigated MDCT protocols in table 2.

The estimated effective dose to patient of the FDCT-P protocol is 4.52 mSv without collimation and 2.88 mSv with collimation. The collimated dose of FDCT-P is 33% higher than the measured dose on MDCT (2.17 mSv). Eye lens doses of the perfusion protocols are two-fold higher on MDCT (122 mGy) compared to uncollimated FDCT (67 mGy) and collimated FDCT (56 mGy).

The estimated effective dose to patient of the portrait FDCT-A (0.91 mSv) is 48% lower than the effective dose of the corresponding MDCT-A protocol (1.35 mSv). The eye lens dose is also lower at 8 mGy compared to 11.8 mGy.

In all measurements, at least 95% of the radiation was recorded in the brain, red bone marrow, salivary glands, lung, esophagus and thyroid. The remaining organs received less than 5% of the radiation, rendering them relatively clinically unimportant. A detailed overview of the dose distribution can be found in the tables 3 and 4.

Discussion

Our study has the following main findings: 1) collimation has a powerful impact on the estimated effective dose to patient, as it can reduce the dose by almost 50%, 2) the estimated effective dose to patient of the collimated FDCT perfusion and of the portrait FDCT angiography does not deviate substantially from analogous MDCT protocols, and, 3) eye lens dose appears to be similar on FDCT and MDCT.

Two prior publications estimating the effective dose to patient of FDCT-P on predecessor systems (Artis Q and Artis Axiom, Siemens Healthineers Erlangen, Germany), reported higher doses with 5.9 and 5.1 mSv respectively.[58, 62] However, these measurements must be compared to our uncollimated dose results (4.52 mSv), as no use of collimation was reported in either publication. In this case, a 12 % difference to the measurements of Struffert et al. is well within the margin of error, however, the 30% difference to our prior publication[58] is outside this margin. This difference could partly be explained by a different phantom and fewer measurement points. Furthermore, the directly and indirectly irradiated tissues were not analysed separately in our previous publication, which could have led to an overestimation of the organ doses, especially red bone marrow.[60] From a clinical standpoint, the collimated dose of FDCT-P is of more importance, as the z-coverage can easily be reduced to parallel the parameters of MDCT-P. Even more relevant is our result that the effective dose estimated for the collimated FDCT-P is only slightly higher than with MDCT-P (33%) despite the considerably larger z-axis coverage area of 15 cm compared to the MDCT-P coverage of 11.4 cm (Figure 2 for reference). Nevertheless, MDCT-P for the triage of late-window stroke patients has been validated in two randomized-controlled trials[63, 64] while the technical equivalence of FDCT perfusion has yet to be established. A recent pilot trial of 13 patients showed promising results with high correlation for both ischemic core volume measurements on FDCT and MDCT perfusion and, also, for follow-up infarct volumes.[56] We presuppose that our current results will contribute to the effort to reproduce such clinically meaningful results in larger patient collectives.

While it is widely accepted that FDCT offers higher spatial resolution for high-contrast structures (e.g., vessels and bones), an essential shortcoming of FDCT-angiography is the limited z-coverage area.[42] This problem is largely solved by the development of a portrait FDCT-angiography protocol which has a z-coverage area large enough to simultaneously visualize the Circle of Willis and the intra- and extracranial carotid arteries down to their origins (Figure 4). This information is vital for planning interventions, as the aortic arch configuration can influence the optimal vascular access site (e.g., radial versus femoral) and which catheters should be used for navigation to the intracranial vessels.[65, 66] Another difference between FDCT- and MDCT-angiography is that the timing of the acquisition after the injection of the contrast-media bolus is operator dependent. In contrast to MDCT-A, in which an automated Hounsfield Unit threshold trigger is typically used for the start of the scan (by placing an ROI in the ascending aorta), the scan start has to be executed manually on FDCT-A.[30] To address this difference, we developed a ‘bolus watching’ protocol in which digital subtraction angiography is used

to monitor the visible influx of contrast media into the common carotid arteries (following a 10 sec delay after intravenous contrast injection) in order to manually initiate the 3D-angiography.[30] According to previous measurements, this adds only minor radiation dose.[58]

The overall dose for perfusion and angiography on FDCT is, at 3.79 mSv, only slightly higher (8%) as compared to MDCT. This difference is well below the accuracy threshold for effective dose to patient measurements and, therefore, could be neglected. Both protocols (Perfusion and Angiography) are often used, even in the early time-window of thrombolysis, as it is more commonly recognized that perfusion plays an important role in the detection of medium and distal vessel occlusions[67, 68], i.e., as potential targets for mechanical thrombectomy.[69] Recent measurements have shown an effective dose of 2 mSv for non-contrast FDCT parenchymal imaging, which is comparable to MDCT.[43, 70] As the cumulative dose of commonly used protocols in One Stop Management of acute ischemic stroke does not differ substantially from routine MDCT, we anticipate that our findings will mitigate dose considerations in the triage decisions of AIS patients.

The lower dose to the lens of the eye from FDCT-P compared to MDCT-P is explained by the reduced range of rotation of the flat detector, which is between 200 and 220 degrees for most protocols with the radiation source being, importantly, below the patient.[53] However, it should be noted that the eye lens doses for the perfusion protocols have to be interpreted with caution as we were not able to incline the head of the phantom. Flexing the head towards the chin, as is performed for MDCT-P at our institution, might reduce the direct irradiation of the lens and, therefore, might reduce the dose substantially.[71] With regard to the standard MDCT-A protocol, the effect of inclining the head should not have a relevant proportional impact due to the large z-coverage area. However, there is an alternative protocol (HeadAngio_Xcare) using an organ-based tube current modulation. which can reduce the eye lens dose. In this protocol the direct X-ray exposure to the eye lens is reduced by lowering the X-ray tube current for a certain range of projection angles when the eye lenses are facing towards the X-ray tube. This protocol was not evaluated in this paper. Overall, the certainty for the magnitude of the reduction of lens dose is low, as we were not able to incorporate all influencing factors.

One major strength of our study is that we used an anthropomorphic phantom with an identical measurement set-up for both systems. This allows a reproducible comparison between different X-ray imaging modalities, acquisition protocols and studies. This approach is superior to other measurement approaches, such as simulations or CT dose index (CTDI) based approaches, because modern C-arm devices typically use a 210° rotation compared to MDCT, which has a 360° rotation. In the case of FDCT, this leads to a nonuniform dose distribution with the peak dose occurring in the central plane, on the side of the phantom closest to the radiation source.[52] Furthermore, the larger z-coverage of FDCT compared to MDCT renders traditional, weighted CTDI approaches impractical.[53] Another strength of our study is that we measured analogous protocols on both systems, enabling us to directly compare the effective dose to patient from modern stroke imaging protocols.

However, our study has some limitations as well. The ATOM phantom is constructed to represent a broad cohort of different patients. Therefore, the actual dose to a patient might differ from the dose measured with the ATOM phantom. As the ICRP 103 does not define the distribution and number of measurement points within the phantom, the investigator typically chooses these parameters.[61] This fact can lead to differences in the estimated effective dose depending on the number and position of measurement points within an anthropomorphic phantom. In addition, Roser et al. showed that the organ-equivalent dose values calculated from discrete measurements might underestimate the simulated organ dose that was calculated based on continuous dose distribution by up to 50 %.[72] In the clinical routine, variance to our phantom study could occur not only with the collimation of the X-ray field but also the region of interest, through normal practitioner and patient differences. However, as these parameters can be largely standardized in stroke protocols and, since the coverage areas of the FDCT were at least as large as on the MDCT, our collimated results should be generalizable to clinical routine.

Conclusion

The estimated effective dose to patient for FDCT-perfusion and -angiography protocols on a modern bi-plane angiography system do not deviate substantially from analogous MDCT protocols.

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Competing interests

Research agreement with Siemens Healthineers (money paid to the institution).

Tables

3D-imaging Protocol Parameters	**60sDCT Head Perfusion (10 rotations)**		**4sDCT Head Portrait (1 rotation)**
Reconstructed volume size (diameter, cm x height, cm)	24 x 18.5 (uncollimated)	24 x 15*	18.5 x 24 (uncollimated)
Tube voltage, kV (nominal)	70	70	90
Dose/frame, nGy/f (nominal)	360	360	1200
Rotation range	200°	200°	200°
Angulation step, °/f	0.8	0.8	0.8
Eye lens dose, mGy (mean)	65 and 69 (67)	54 and 58 (56)	7.7 and 8.3 (8)
Estimated effective dose, mSv	4.52	2.88	0.91

Table 1: Technical parameters of investigated 3D-imaging protocols (brain perfusion, portrait angiography with head and neck angiography), measured eye lens dose (for left, right eye and mean) and effective dose for anthropomorphic ATOM male phantom on ARTIS Icono. * - collimation was defined based on usual clinical workflow at the University Hospital Basel.

3D-imaging Protocol Parameters	NeuroVPCT_Prolonged, DynMulti4D	NeuroVPCT_Prolonged, Head Angio
Scan coverage, cm	11.4	24
Tube voltage, kV	70	90
Scan duration, s	60	NA
Number of cycles @ 1.5 s cycle time	30	NA
CTDIvol, mGy	144.2	19,9
DLP, mGy*cm	2169.5	550
Eye lens dose, mGy (mean)	119 and 125 (122)	11.8 and 11.7 (11.8)
Estimated effective dose, mSv	2.17	1.35

Table 2: Technical parameters of investigated protocols (brain perfusion and head and neck angiography), measured eye lens dose (for left, right eye and mean) and effective dose for anthropomorphic ATOM male phantom on SOMATOM Force

Organ	60sDCT Head Perfusion (10 rotations, uncollimated)	60sDCT Head Perfusion (10 rotations, collimated)	4sDCT Head Portrait (1 rotation)
Brain	100.8	84.7	11.8
Salivary glands	56.2	7.4	11.4
Thyroid	3.5	1.8	6.1
Lung	1.3	0.8	0.2
Red bone marrow	17.4	12.1	2.4
Oesophagus	1.1	0.7	0.8

Table 3: Organ dose in milligray for selected organs and tissues of investigated 3D-imaging protocols on the ARTIS Icono.

Organ	**NeuroVPCT_Prolonged, DynMulti4D**	**NeuroVPCT_Prolonged, Head Angio**
Brain	71.6	7.8
Salivary glands	6.4	8
Thyroid	1.3	17.2
Lung	0.4	1.3
Red bone marrow	9.2	1.3
Oesophagus	0.4	2.0

Table 4: Organ dose in milligray for selected organs and tissues of investigated 3D-imaging protocols on the SOMATOM Force.

Figures

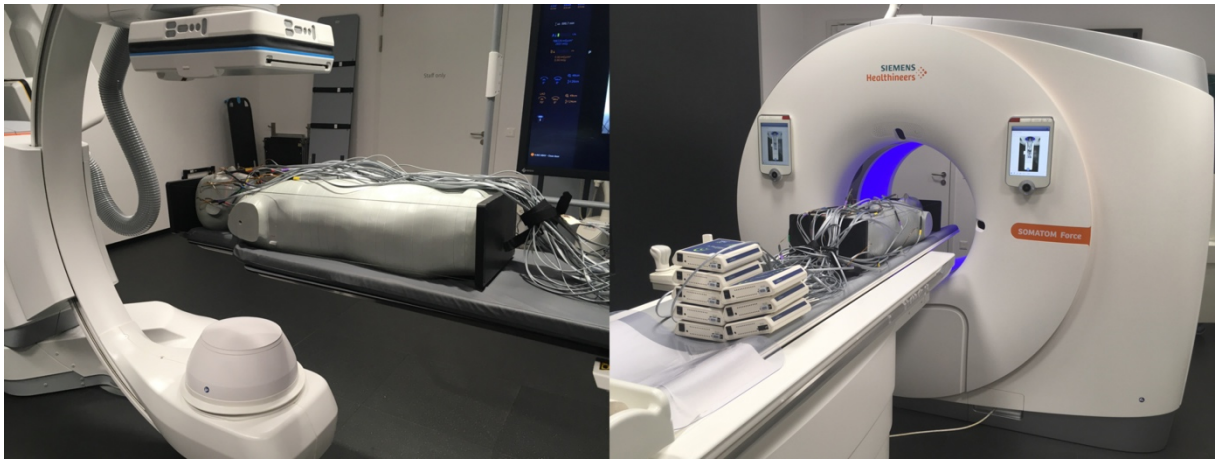

Figure 1: The anthropomorphic ATOM phantom used for effective dose measurement: phantom in experimental setup for 3D acquisition equipped with MOSFET dosimeters on ARTIS icono biplane angiography system (left) and on SOMATOM Force CT scanner (right).

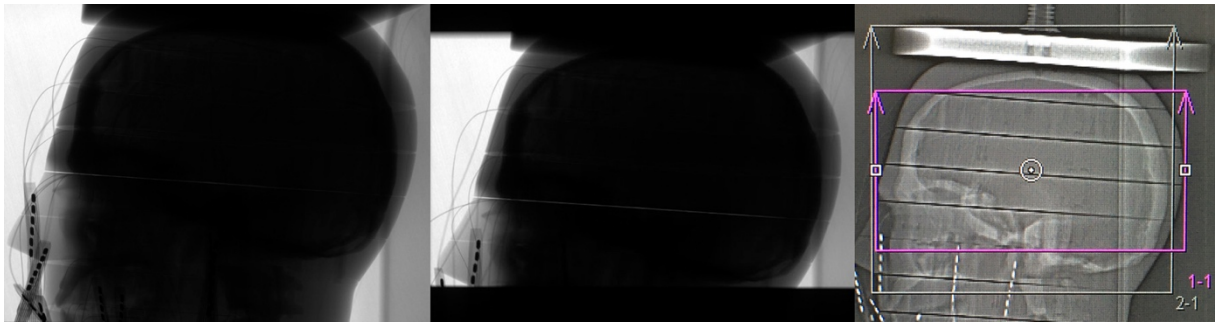

Figure 2: Lateral view of the investigated head area of the phantom for uncollimated measurement (left) and collimated measurement (middle) of the 60s DCT Head perfusion protocol on the ARTIS icono and for perfusion measurement on SOMATOM Force (right)

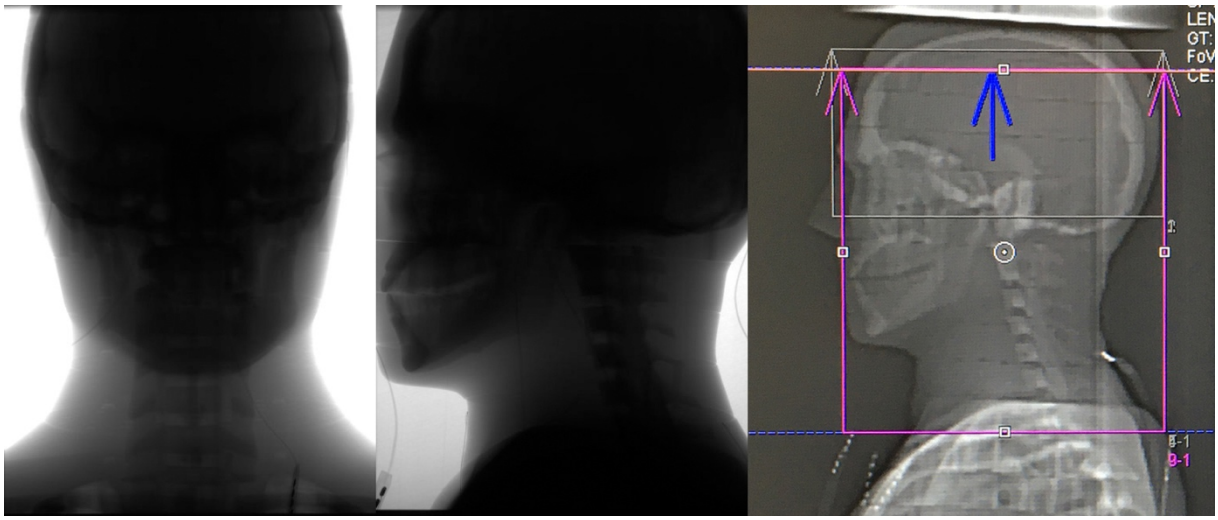

Figure 3: The position of the investigated head area of the phantom for carotids measurement on the ARTIS icono in frontal view (left) and in lateral view (middle) and on SOMATOM Force in lateral view (right).

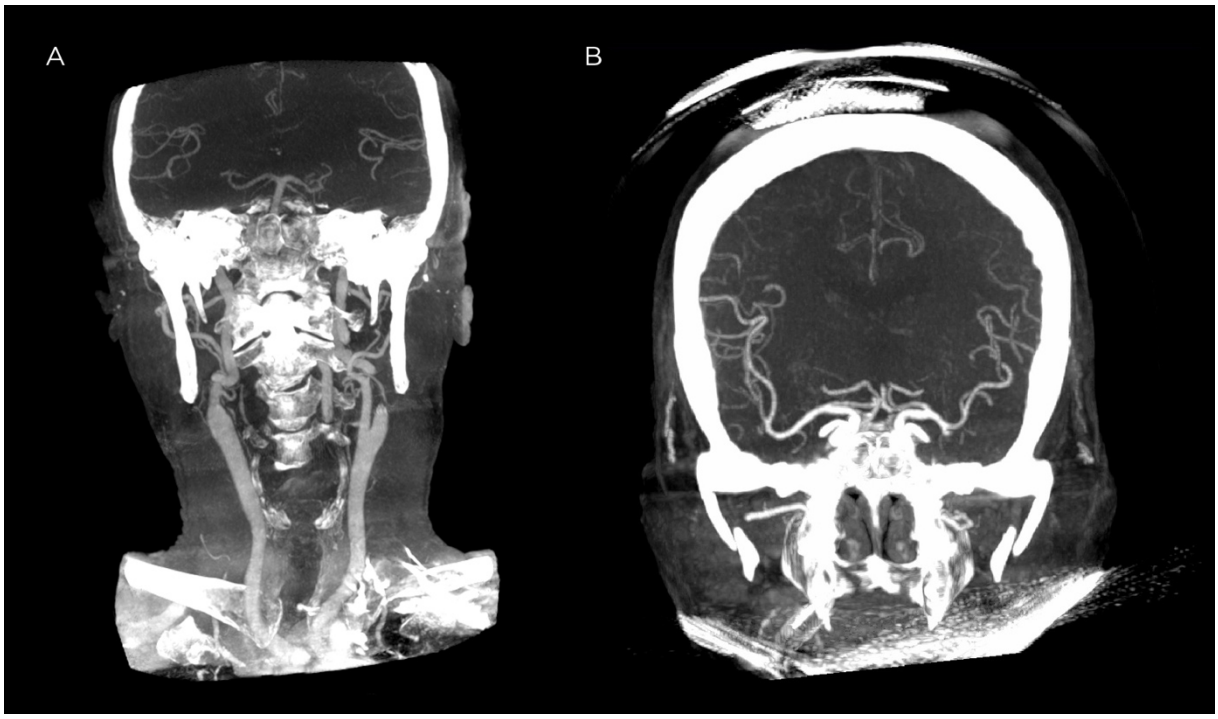

Figure 4: Comparison of coverage area of portrait FDCT-A (A) and landscape FDCT-A (B) (based on reconstructed coronal maximum intense projections (MIPs)

7. Second Topic: Distribution of diagnosis, clinical and imaging characteristics in suspected acute ischemic stroke patients

In this topic we present the distribution of different diagnosis (acute ischemic stroke with or without a vessel occlusion, hemorrhagic stroke, or stroke mimic) in a cohort of consecutive, suspected acute ischemic stroke patients, which presented over one year to a tertiary German university hospital.

This data is of importance for the planning of trials and resources especially if confronted with expanding indications for endovascular treatment.

7.1 Distribution of diagnoses, clinical and imaging characteristics in 1,322 consecutive suspected stroke patients

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ABSTRACT

Background

Endovascular thrombectomy (EVT) has become standard of care for large vessel occlusion strokes but several barriers for implementing an optimal organization of stroke management remain. Major issues include the lack of reliable data on the percentage of stroke patients potentially eligible for EVT especially in times of expanding indications for EVT. Our aim was therefore to study the frequencies of possibly EVT eligible patients such as patients with medium vessel occlusions, patients with low Alberta Stroke Program Early Computed Tomography Scores (ASPECTS), patients presenting in an extended time-window after onset of symptoms and patients with mild symptoms at presentation (National Institutes of Health Stroke Scale, NIHSS ≤ 5). We also give detailed imaging and clinical information about the patients presenting with intracranial hemorrhage and other ischemic stroke mimics stratified by symptoms at presentation.

Methods

Cohort-study of all consecutive patients with suspected acute stroke presenting to a tertiary care center in Germany between 1st September 2016 and 31st August 2017. Baseline and follow-up clinical and imaging characteristics were collected from patients' medical charts.

Results

Of 1322 patients with a suspected acute stroke, 592 (44.8%) had ischemic strokes, 221 (16.7%) hemorrhagic strokes, 190 (10.9%) transient ischemic attacks (TIAs) and 319 (24.1%) were classified as stroke mimics. Stroke severity was mild (NIHSS ≤ 5) in 866 (65.5%), 15.7% of the patients with an occlusion of the anterior circulation had an ASPECTS ≤ 5, 17.4% of the patients with an ischemic stroke had distal vessel occlusions and 49% of the patients presented later than 6 hours after onset of symptoms.

Conclusion

Our results help to plan resources in thrombectomy-capable centers in times of expanding indications for EVT where resources will have to be adjusted to patients with low-NIHSS, low-ASPECTS, distal occlusions and patients presenting in the extended time-window, which may altogether account for additional 20% of all ischemic stroke patients.

Introduction

Endovascular thrombectomy (EVT) has become standard of care for large vessel occlusion strokes and acute management of ischemic stroke has dramatically changed since the demonstration of the efficacy of EVT.[20] However, several barriers for implementing an optimal organization of stroke management remain. A major issue among them is the lack of reliable data on the percentage of stroke patients eligible for EVT and their characteristics. Even though the number of patients with large vessel occlusions and occlusions of the M2-segment of the middle cerebral artery has been estimated,[21, 73-76] detailed information about further characteristics such as frequency of stroke mimics and intracranial hemorrhages is lacking. Moreover, the available information is mostly confined to large vessel occlusion strokes but in times of expanding indications for EVT,[21] the frequency of more medium vessel occlusions, the distribution of Alberta Stroke Program Early Computed Tomography Score (ASPECTS), the time-window of presentation and the National Institutes of Health Stroke Scale (NIHSS) of those patients are also of crucial importance for planning thrombectomy resources. We therefore conducted a cohort study of consecutive patients admitted with suspected stroke to a tertiary care hospital and describe all these strategically important variables. We also give detailed imaging and clinical information about the patients presenting with intracranial hemorrhage and other ischemic stroke mimics and stratify the results by NIHSS at presentation.

Methods

The authors declare that the underlying data will be made available upon reasonable request by the corresponding author.

Study population

This study includes a prospectively collected cohort of all consecutive patients with suspected acute stroke presenting to a tertiary care center in Germany between September 1st 2016 and August 31st 2017. Acute stroke was suspected, if (1) patients were transported to the hospital from an ambulance under the "stroke code (high probability of stroke according to the emergency doctor or paramedic)", (2) presented independently to the hospital and were triaged as suspected acute stroke after the first contact or (3) were transferred from another hospital either with a confirmed stroke or suspected stroke. Patients were identified by screening reports of all head CTs performed in the study period and were validated by checking neurological clinical reports. All acute patients with suspected acute stroke undergo emergent CT at our center. Demographic information and risk factors were collected from the hospital information system. The National Institute of Health Stroke Scale (NIHSS) is routinely collected by certified stroke neurologist on admission and discharge. The final diagnosis and modified Rankin Scale Score at discharge (mRS) were obtained from the final clinical report. Imaging findings were obtained through

reviewing all scans - occlusion location was rated on baseline CT angiography (CTA) and validated on the Digital Subtraction Angiography (DSA) images if available. The Alberta Stroke Program Early CT Score (ASPECTS) was only evaluated in ischemic stroke patients with an occlusion of the anterior circulation. Additionally, the ABCD2 score estimating the risk of stroke after transient ischemic attack and minor stroke was calculated.[77] Medium Vessel Occlusions were defined as an occlusion visible on the CTA other than the M1, ICA or BA. Small vessel occlusions were defined as an acute ischemic stroke (as determined by the non-contrast CT or perfusion CT) with no visible occlusion on the CTA. The local ethics committee waived the need for a formal application or a separate consent concerning the inclusion in our observational database.

Hospital Setting

The hospital has 1,563 beds and has 55,159 inpatient and 222,303 outpatient cases per year. The Department of Neurology has 4,791 inpatient cases per year (as per 2017). It serves as the primary tertiary hospital for eight German districts and has a catchment area of roughly 1,100,000 persons and 6,500 square kilometers. The largest city within its catchment area has 118,911 inhabitants and the region has a below average population density. It is part of a stroke network with an integrated imaging service and serves as a referral center for 17 primary hospitals.

Statistical analyses

Statistical analysis was performed using GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA, https://www.graphpad.com/, 2021). Parametric variables are stated as mean ± standard deviation (SD). Non-parametric or ordinary variables are presented as median and interquartile range (IQR). No interference statistics were performed. All data are presented for the whole collective, patients with a mild stroke (NIHSS ≤ 5), a moderate stroke (NIHSS 6 – 12) and for patients with a severe stroke (NIHSS > 12)

Results

In the one-year study period, 1322 patients presented with a suspected acute stroke, of whom 592 (44.8%) had ischemic strokes, 110 (8.3%) intraparenchymal hemorrhages (ICHs), 90 (6.8%) subarachnoid hemorrhages (SAHs), 21 (1.6%) subdural hematomas (SDHs), 190 (14.4%) transient ischemic attacks (TIAs) and 319 (24.1%) were classified as stroke mimics. Mean age at admission was 70.8 years (standard deviation (SD) ±14.9 years), 385 (29.1%) were more than 80 years old, and 605 (45.8%) were female. Stroke severity was mild (NIHSS ≤ 5) in 866 (65.5%), moderate (NIHSS 6 – 12) in 282 (21.3%) and severe (NIHSS ≥ 13) in 174 (13.2%) patients. Arterial imaging was performed in 837 patients (63.3%) and of those 296 (22.4%) patients received additional CT perfusion (CTP). Overall, 135 (10.2%) patients underwent EVT and 167 (12.6%) of the patients were treated with intravenous

tissue plasminogen activator (i.v.-tPA). In total 675 patients (51.1%) presented within 6 hours of symptom onset, 172 patients (13%) between 6 – 12 hours of onset, 278 patients (21%) between 12 – 24 hours of onset and 197 patients (14.9%) even later than 24 hours after onset of symptoms. Detailed information on baseline and imaging characteristics is presented in table 1.

Suspected stroke patients with mild symptoms (NIHSS ≤ 5)

Most patients presented with mild symptoms (866 patients; 65.5%); and among those ischemic stroke (300 patients; 34.6%), stroke mimics (289; 33.4%), and TIA (169; 19.5%) were the most common diagnoses. Additionally, 65 patients had SAHs (7.5%), 33 (3.8%) ICHs and 10 (1.2%) SDHs. Median NIHSS was 2 (IQR 2 – 4) and mean age was 69.1 years (SD ± 15.3). 44.3% underwent native CT only, while arterial imaging was performed in the remaining 55.7%. Eighty-three patients (9.6%) underwent additional CTP.

Out of the 300 ischemic strokes, 168 (56%) were deemed acute and a causative occlusion was found in 72 (24%) patients. Out of the 72 occlusions, 19 (26.4%) were large-vessel occlusions (defined as ICA, M1 and BA) and the remaining 53 (73.6%) were medium vessel occlusions; for a detailed overview of the occlusion locations please refer to table 1.

EVT was performed in 15 patients (5%) and i.v.-tPA was administered in 48 (16%) of the ischemic strokes. ASPECTS was very low (0 – 3) in 1 patient (2.1%), low (4 - 5) in 2 patients (4.2%), medium (6 – 8) in 10 patients (20.8%) and high (9 – 10) in 35 patients (72.9%) with an occlusion in the anterior circulation.

Although only mildly affected, excellent functional outcome (defined as mRS ≤ 1) was only achieved in 47.1% of the patients and 70.2% were functionally independent (mRS ≤ 2) at discharge.

Suspected stroke patients with moderate symptoms (NIHSS 6 - 12)

In this group (n=282 patients; 21.3%) 163 (57.8%) patients were diagnosed as ischemic stroke, 49 (17.4%) as ICH, 18 (6.4%) as SAH, 9 (3.2%) as SDH, 20 (7.7%) as TIA and 23 (8.2%) patients had stroke mimics. Median NIHSS was 9 (IQR 8 – 11) and mean age was 73.5 years (SD ± 13.8). Within this group, 27% underwent native CT only, while arterial imaging was performed in the remaining 73%. One hundred and ten patients (39%) underwent additional CTP.

Out of the 163 ischemic strokes, 124 (76.1%) were deemed acute and a causative occlusion was found in 79 (48.5%) patients. Out of the 79 occlusions, 28 (35.4%) were large-vessel occlusions and the remaining 51 (64.6%) were medium vessel occlusions. EVT was performed in 41 patients (25.2%) and i.v.-tPA was administered in 62 (38%) of the ischemic stroke patients. ASPECTS was very low in 1 (1.5%) patient, low in 4 patients (6.1%), medium in 15 patients (22.7%) and high in 46 (69.7%) of the patients with an occlusion in the anterior circulation. Excellent outcome was achieved in 25.8%, while

39.9% were functionally independent at discharge. In-hospital mortality was 9.2%. ICHs were far more common in this group with a frequency of 17.4%.

Suspected stroke patients with severe symptoms (NIHSS ≥13)

In this group ischemic stroke was most the most common diagnosis (129 patients, 74.1%), followed by ICH (28 patients, 16.1%), SAH and stroke mimics (each 7 patients, 4%), SDH (2 patients, 1.1%), and TIA (1 patient, 0.6%). Median NIHSS was 17 (IQR 14 – 21) and mean age was 74.8 years (SD ± 12.7). Within this group 14.4% underwent native CT only, while arterial imaging was performed in the remaining 85.6%. One hundred and three patients (59.2%) underwent additional CTP. Out of the 129 ischemic strokes, 101 (78.3%) were deemed acute and a causative occlusion was found in 119 (92.2%) patients. Out of the 119 occlusions, 93 (78.2%) were large-vessel occlusions and the remaining 26 (21.8%) were medium vessel occlusions. EVT was performed in 79 (61.2%) and i.v.-tPA was administered in 57 patients (44.2%) with ischemic stroke. ASPECTS was very low in 6 (5.5%), low in 21 (19.1%), medium in 36 (32.7%) and high in 47 (42.7%) patients with an occlusion of the anterior circulation. Excellent outcome was achieved in 9.3%, while 16.3% of the patients were functionally independent at discharge. In-hospital mortality was 21.8%.

Discussion

Our study has several major findings: 1) it shows that a substantial proportion of patients with suspected stroke present with medium vessel occlusions, which are potentially eligible for EVT; 2) it provides evidence that most suspected stroke patients present with mild symptoms to the emergency department (65.5% had an NIHSS ≤ 5); 3) it shows that a substantial proportion of stroke patients with an occlusion of the anterior circulation presents with an ASPECTS of ≤ 5 (15.7 %) and 4) a large proportion of patients presents in an extended time-window of 6-24h after onset of symptoms (34.0 %) or even later than 24 hours (14.9 %).

These results demonstrate that it is important to plan resources in thrombectomy-capable centers not only for patients with LVO and selection criteria in randomized trials but also for patients with low NIHSS, low-ASPECTS patients, patients with distal occlusions and patients presenting in extended time-windows. Recent guidelines of the American Heart Association/American Stroke Association (AHA/ASA) and the European Stroke Organization (ESO)/European Society of Minimally Invasive Neurological Therapy (ESMINT)[32, 78] already partially account for these upcoming changes, and a recent review on expanding indication for EVT gives a foresight on the direction in which EVT will move with the help of advanced imaging and better endovascular devices.[21] In this context, our study shows that an additional percentage of up to 20 % of all patients with ischemic strokes might be candidates for EVT. This estimate is in line with an analysis for late-window patients by Jadhav et al. based on DAWN

and DEFUSE-3 inclusion criteria.[79] As we were not able to evaluate the impact of pre-stroke disability, this group might even be larger, as these patients get recognized as candidates for EVT as well.[80] Therefore, resource planning in the future should address these developments since substantially higher numbers of EVT patients will lead to higher workloads for neurointerventionalists and other subspecialties such as anesthesiologists. Since the training of such specialists takes years, hospitals should act now and invest in better training capabilities.[81] Moreover, our study gives detailed information about the distribution of stroke mimics such as different types of intracranial hemorrhages. It shows the overall frequency of all types of intracranial hemorrhages combined was 14.9 % in our cohort which is in line with larger epidemiological studies.[82, 83] It further suggests that the occurrence of ICH increases whereas SAH gets less common with increasing NIHSS.

Compared to previous studies, the frequency of LVOs was comparable with ~25% having LVOs in total and of those ~15% having M1-, 9 % distal ICA-, and 1.5 % basilar artery -occlusions.[76] This demonstrates the external validity of our results. The frequency of medium vessel occlusions was with 17.4% lower compared to other studies who reported frequencies between 24 and 43%.[84, 85] One possible explanation may be that only 22.4% of the patients in our study underwent perfusion imaging and medium vessel occlusions might get frequently missed on CT angiography alone.[86]

Another finding is the high morbidity and mortality in patients with mild to moderate symptoms (NIHSS $\leq$ 5) at presentation with only 70% of the stroke patients being functionally independent (mRS $\leq$ 2) at discharge. This further underlines the potential importance of performing EVT in patients with low NIHSS. At last, our study is the first study describing the distribution of ASPECTS values in a consecutive cohort of patients with suspected stroke. This adds further information to the general understanding of the distribution of ischemic stroke patients at initial presentation and adds information on how many patients can be expected to be included when low-ASPECTS trials will present positive results for performing EVT.[87, 88]

Limitations

Our study has limitations partly attributed to it's single-center, retrospective design. Moreover, more patients may have been classified as ischemic stroke and less as TIA if the admission imaging modality would have been MRI instead of CT. The definition of the upper NIHSS bound of the moderate stroke group was made based on our best judgment as there is no clear consensus on this definition and it can be argued that other values in a range from 10 to 15 would have been a better fit. However, we present a comparably large consecutive cohort with detailed clinical and imaging information that partially was not available before and that is urgently needed to adjust resources in thrombectomy-capable centers.

Conclusion

Our results predict an increase of EVT eligible patients of up to another 20% of all ischemic stroke patients. In this context, this study helps to plan resources in thrombectomy-capable centers in times of expanding indications for EVT where resources will have to be adjusted to patients with low-NIHSS, low-ASPECTS, distal occlusions and patients presenting in the extended time-window.

Tables

Variable	All patients (n = 1322)	NIHSS ≤ 5 (n=866, 65.5%)	NIHSS 6 – 12 (n=282, 21.3%)	NIHSS ≥ 13 (n=174, 13.2%)
Female, n (%)	605 (45.8%)	378 (43.6%)	136 (48.2%)	91 (52%)
Age, Mean (SD)	70.8 (± 14.9)	69.1 (±15.3)	73.5 (±13.8)	74.8 (±12.7)
Over 80 years old	385 (29.1%)	222 (25.6%)	99 (35.1%)	64 (36.8%)
NIHSS, Median (IQR)	4 (2 – 8)	2 (2 – 4)	9 (8 – 11)	17 (14 – 21)
Transfer Patients	240 (18.2%)	110 (12.7%)	62 (22.0%)	68 (39.1%)
First diagnostic step				
Native CT	485 (36.7%)	384 (44.3%)	76 (27.0%)	25 (14.4%)
CT + CTA	519 (39.3%)	387 (44.7%)	89 (31.6%)	43 (24.7%)
CT + CTA + CTP	296 (22.4%)	83 (9.6%)	110 (39.0%)	103 (59.2%)
Polytrauma CT	22 (1.6%)	12 (1.4%)	7 (2.4%)	3 (1.7%)
Diagnosis				
Ischemic Stroke**, n (%)**	592 (44.5%)	300 (34.6%)	163 (57.8%)	129 (74.1%)
Acute Stroke	424 (71.6%)	193 (64.3%)	119 (73%)	112 (86.8%)
Media Ischemia	393 (66.4%)	168 (56.0%)	124 (76.1%)	101 (78.3%)
SVO	321 (54.2%)	228 (76%)	84 (51.5%)	9 (7%)
ICA	53 (9%)	12 (4%)	10 (6.1%)	31 (24%)
M1	88 (14.9%)	5 (1.7%)	27 (16.6%)	56 (43.4%)
M2	57 (9.6%)	19 (6.3%)	23 (14.1%)	15 (11.6%)
M3	17 (2.9%)	9 (3%)	4 (2.4%)	4 (3.1%)
VA	18 (3%)	11 (3.7%)	5 (3.1%)	2 (1.6%)
BA	9 (1.5%)	2 (0.7%)	1 (0.6%)	6 (4.7%)
P1	13 (2.2%)	8 (2.6%)	4 (2.5%)	1 (0.8%)
P2	6 (1%)	3 (1%)	3 (1.8%)	0 (0%)
A1	1 (0.2%)	0 (0%)	0 (0%	1 (0.8%)
A2	9 (1.5%)	3 (1.0%)	2 (1.2%)	4 (3.1%)
ICH**, n (%)**	110 (8.3%)	33 (3.8%)	49 (17.4%)	28 (16.1%)
Loco typico	52 (47.3%)	23 (69.7%%)	21 (42.8%)	8 (28.6%)
Atypical	58 (52.7%)	10 (30.3%)	28 (57.2%)	20 (71.4%)
SAH**, n (%)**	90 (6.8%)	65 (7.5%)	18 (6.4%)	7 (4%)
Conservative Treatment	50 (55.5%)	44 (67.7%)	4 (22.2%)	2 (28.6%)
Clipping	16 (17.8%)	9 (13.8%)	5 (27.8%)	2 (28.6%)
Coiling	24 (26.7%)	12 (18.5%)	9 (50%)	3 (42.8%)
TIA**, n (%)**	190 (14.4%)	169 (19.5%)	20 (7.1%)	1 (0.6%)
ABCD2 0 - 3	70 (36.8%)	67 (39.8%)	3 (15%)	0 (0%)
ABCD2 4 – 5	90 (47.4%)	78 (46.5%)	12 (60%)	0 (0%)
ABCD2 6 - 7	30 (15.8%)	23 (13.7%)	5 (25%)	1 (100%)
Mimic**, n (%)**	319 (24.1%)	289 (33.4%)	23 (8.2%)	7 (4%)

***SDH*, n (%)**	21 (1.6%)	10 (1.2%)	9 (3.2%)	2 (1.1%)
Thrombectomy, n (%)	135 (10.2%)	15 (1.7%)	41 (14.5%)	79 (45.4%)
i.v. tPA	167 (12.6%)	48 (5.5%)	62 (22%)	57 (32.8%)
ASPECTS				
0 - 3, n (%)	8 (3.6%)	1 (2.1%)	1 (1.5%)	6 (5.5%)
4 – 5, n (%)	27 (12.1 %)	2 (4.2%)	4 (6.1%)	21 (19.1%)
6 - 8, n (%)	61 (27.2%)	10 (20.8%)	15 (22.7%)	36 (32.7%)
9 – 10, n (%)	128 (57.1%)	35 (72.9%)	46 (69.7%)	47 (42.7%)
Previous Stroke, n (%)	255 (19.3%)	141 (16.3%)	73 (25.9%)	41 (23.6%)
Previous TIA, n (%)	85 (6.4%)	61 (7.0%)	14 (5%)	10 (5.7%)
Coronary Heart Disease, n (%)	253 (19.3%)	153 (17.7%)	65 (23%)	35 (20.1%)
Peripheral artery disease, n (%)	71 (5.4%)	50 (5.8%)	13 (4.6%)	8 (4.6%)
Heart Failure, n (%)	105 (7.9%)	56 (6.5%)	31 (11%)	18 (10.3%)
Smoking, n (%)	220 (16.6%)	151 (17.4%)	49 (17.4%)	20 (11.5%)
Alcohol, n (%)	83 (6.2%)	46 (5.3%)	17 (6%)	20 (11.5%)
Hypertension, n (%)	897 (67.9%)	562 (64.9%)	207 (73.4%)	128 (73.6%)
Hyperlipidemia, n (%)	507 (38.4%)	325 (37.5%)	118 (41.8%)	64 (36.8%)
Diabetes Mellitus, n (%)	310 (23.4%)	183 (21.1%)	78 (27.7%)	49 (28.2%)
Atrial Fibrillation, n (%)	250 (18.9%)	111 (12.8%)	67 (23.8%)	72 (41.4%)
Persistent Foramen Ovale, n (%)	359 (27.2%)	234 (27%)	84 (29.8%)	41 (23.6%)
Oral anticoagulation, n (%)	241 (18.2%)	138 (16.1%)	62 (22%)	41 (23.6%)
Onset (Last Seen Well) to Door (h)				
< 4.5, n (%)	609 (46.1%)	337 (39%)	161 (57.1%)	111 (63.8%)
4.5 – 6, n (%)	66 (5.0%)	40 (4.6%)	16 (5.7%)	10 (5.7%)
6 - 12, n (%)	172 (13%)	113 (13%)	37 (13.1%)	22 (12.7%)
12 - 24, n (%)	278 (21%)	213 (24.6%)	42 (14.9%)	23 (13.2%)
> 24, n (%)	197 (14.9%)	163 (18.8%)	26 (9.2%)	8 (4.6%)

ASPECTS Alberta Stroke Program Early CT Score, BA Basilar Artery, CTA CT Angiography, CTP CT Perfusion, ICA Internal Carotid Artery, ICH Intraparenchymal Hemorrhage, IQR Interquartile Range, i.v. tPA intravenous tissue plasminogen activator, NIHSS, National Institute of Health Stroke Scale, mRS modified Rankin Scale, SAH, Subarachnoid Hemorrhage SD Standard deviation, SDH, Subdural Hemorrhage, SVO Small Vessel Occlusion, TIA Transient ischemic attack, VA Vertebral Artery

Tables 1: Baseline characteristics

Variable	All patients (n = 1322)	NIHSS ≤ 5 (n=866)	NIHSS 6 – 12 (n=282)	NIHSS ≥ 13 (n=174)
Length of Stay (days), Median (IQR)	4 (1 – 9)	4 (1 – 7)	6 (1 – 12)	8 (3 – 15)
Discharge location				
Previous environment, n (%)	566 (42.8%)	498 (57.5%)	52 (18.4%)	16 (9.2%)
Nursing Home, n (%)	210 (15.9%)	112 (12.9%)	62 (22.0%)	36 (21,1%)
Rehabilitation, n (%)	436 (33%)	225 (26%)	130 (46.1%)	81 (46.3%)
In hospital Dead, n (%)	112 (8.5%)	31 (3.6%)	39 (13.8%)	42 (24.1%)
NIHSS at discharge, Median (IQR)	1 (0 – 5)	0 (0 – 2)	5 (2 – 10)	12 (5 – 22)
mRS at discharge, Median (IQR)	2 (1 – 4)	1 (0 – 3)	2 (3 – 5)	5 (4 – 5)
mRS 0 , n (%; cumulative within group %)	286 (21.6%; 21.6%)	256 (29.6%; 29.6%)	22 (7.8%; 7.8%)	8 (4.6%; 4.6%)
mRS 1 n (%; cumulative within group %)	271 (20.5%; 42.1%)	216 (24.9%; 54.5%)	46 (16.3%; 24.1%)	9 (5.1%; 9.7%)
mRS 2 n (%; cumulative within group %)	196 (14.8%; 56.9%)	144 (16.6%; 71,1%)	43 (15.2%; 39.3%)	9 (5.1%; 14.9%)
mRS 3 n (%; cumulative within group %)	166 (12.6%; 69.6%)	105 (12.1%; 83.2%)	44 (15.6%; 54.9%)	17 (9.7%; 24.6%)
mRS 4 n (%,: cumulative within group %)	159 (12%; 81.6%)	71 (8.2%; 91.4%)	54 (19.1%; 74%)	34 (19.4%; 44%)
mRS 5 n (%; cumulative within group %)	104 (7.9%; 89.5%)	16 (1.8%; 93.2%)	33 (11.7%; 85.7%)	55 (32%; 76%)
mRS 6 n (%; cumulative within group %)	112 (8.4%; 97.9%)	31 (3.6%; 96.8%)	39 (13.9%; 95.6%)	42 (24%; 100%)
mRS unknown (%; cumulative within group %)	28 (2.1%; 100%	27 (3.2%; 100%)	1 (0.4%; 100%)	0 (0%; 100%)
Hemicraniectomy, n (%)	41 (3.1%)	16 (1.8%)	16 (5.7%)	9 (5.1%)

IQR Interquartile Range, NIHSS, National Institute of Health Stroke Scale, mRS modified Rankin Scale

Table 2: Overview of outcome variables stratified by severity

8. Third Topic: A systematic overview of the available evidence regarding One Stop management and direct to angiography approaches for the triage of AIS patients

In this topic we will summarize the available evidence regarding One Stop management and direct to angiography approaches. We will give an overview over achieved time metrics in different studies and their implications on functional outcome and safety parameters such as symptomatic intracranial hemorrhage and all-cause mortality.

This work was the foundation for a grant application to the Swiss National Science funds for a randomized controlled trial.

8.1 Direct to angiography suite approaches for the triage of suspected acute stroke patients - a systematic review and meta-analysis

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Abstract

Background

Increasing evidence suggests improved time metrics leading to better clinical outcomes when stroke patients with suspected large vessel occlusion (LVO) are transferred directly to the angiography suite (DTAS) compared to cross-sectional imaging followed by transfer to the angiography suite. We performed a systematic review and meta-analysis on the efficacy and safety of DTAS approaches.

Methods

This study was registered in PROSPERO (CRD42020213621). We searched Embase, Medline, Scopus and clinicaltrials.gov for studies comparing outcomes of DTAS and conventional triage. Eligible studies were assessed for risk of bias. We performed a random-effects meta-analysis on the differences of median door to groin and door to reperfusion times between intervention and control group. Secondary outcomes included good outcome at 90 days (modified Rankin Scale≤2,) rate of symptomatic intracranial hemorrhage (sICH) and mortality within 90 days.

Results

Eight studies (1 randomized, 1 cluster-randomized trial and 6 observational studies) with 1,938 patients were included. Door to groin and door to reperfusion times in the intervention group were on median 29.0 minutes (min) (95%-confidence interval (CI) 14.3–43.6; p<0.001) and 32.1 min (95%-CI 15.1–49.1; p<0.001) shorter compared to controls. Prespecified subgroup analyses for transfer (n=1,753) and mothership patients (n = 185) showed similar reductions of the door-to-groin and door-to-reperfusion times in response to the intervention. The odds of good outcome did not differ significantly between both groups but were numerically higher in the intervention group (Odds ratio: 1.38, 95%-CI: 0.97-1.95; p=0.07). There was no significant difference for mortality and sICH between the groups.

Conclusion

DTAS approaches for the triage of suspected LVO patients led to a significant reduction in door to groin and door to reperfusion times but an effect on functional outcome was not detected. The subgroup analysis showed similar results for transfer and mothership patients.

Introduction

Mechanical thrombectomy (MT) after intravenous thrombolytic treatment with recombinant tissue plasminogen activator (iv-rtPA), which has been shown to be superior to iv-rtPA alone[20], is now standard of care for acute ischemic stroke due to large-vessel occlusion (LVO). Clinical outcome is highly dependent on fast restoration of blood flow, and as such, the benefit of MT rapidly decreases with treatment delays.[89] Hence, current guidelines emphasize workflow speed as a key component of acute stroke care[13, 32]. The Stroke Treatment Academic Industry Roundtable identified the shortening of time to reperfusion to the minimum possible as an important variable in stroke treatment and as a priority target in stroke research.[90] While the time from symptom onset to admission can only be influenced at a policy level, door to groin and door to reperfusion times are highly dependent on intra-hospital procedures and structures.[91] Standard procedure in most hospitals is to triage suspected stroke patients by Multidetector Computed Tomography (MDCT) or Magnet Resonance Imaging (MRI). If a target occlusion for MT is identified, the patient is then transported to the angiography suite for emergent MT. One possible approach to reduce door to groin and door to reperfusion times are so called “one-stop management” or “direct to angiography suite” (DTAS) approaches, with diagnostic imaging and MT both performed in the angiography suite and bypassing an extra diagnostic imaging stop.[35] However, the effect of DTAS approaches on reducing time to treatment and clinical outcomes is a matter of debate, and results of recent randomized trials have shown conflicting results.[92, 93] We therefore performed a systematic review and meta-analysis in order to examine the efficacy and safety of DTAS approaches for rapid initiation of MT.

Methods

This systematic review and meta-analysis was registered at PROSPERO (CRD42020213621). All analyses are reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.[94] All data and supporting materials are available within the article and an online-only Data Supplement.

Search Strategy

We developed the search strategies in collaboration with an information specialist (C.A.-H.). It was peer-reviewed by a second information specialist. We searched the bibliographic databases Embase (via embase.com excluding conference abstracts), Medline (via Ovid), Scopus, and clinicaltrials.gov (Primary search August 31, 2020; last update August 18, 2021). Search strings around the concepts stroke, MT, and DTAS were composed of database-specific subject headings (where applicable) and text word synonyms. The complete search strategies are deposited in the online-only Data Supplement.

To complement the results of direct database searching we screened the bibliographic references of all included articles and the citing articles of those indexed in Scopus or the Web of Science.

Eligibility

Studies were included if they compared DTAS triage approaches to conventional triage approaches of suspected acute ischemic stroke patients and reported effect on door to groin and door to reperfusion times. Studies had to report either the median and interquartile range (IQR) or the mean and standard deviation (SD) of door to groin and door to reperfusion times for a DTAS workflow and for a control group. All types of studies (including observational and case-matched studies) were included. Only studies from peer-reviewed journals were included to safeguard the quality of data. Reviews, conference abstracts, editorials and guidelines were excluded. We included all articles that had an English title and abstract. For manuscripts written in other languages, we contacted the corresponding author, asking for the results in English. We restricted our search to studies published in 2010 or later, since DTAS approaches were not feasible in earlier years (the first patient triaged via a DTAS approach was reported in 2017[95]) nor was MT established as routine care before 2010.

Screening, Data Extraction and Outcomes

The search results were exported to Endnote X9 and de-duplicated using the Bramer method.[96] Two reviewers (A.B. and I.T.) screened references based on titles and abstracts. Selected references were retrieved in full-text. Two authors (A.B. and I.T) independently assessed the eligibility of all retrieved studies. In case of disagreement a third author (MN. P.) made the final judgement. Data were extracted by two authors (A.B. and I.T). In case of publications from the same study with overlapping time-periods, the publication with the larger number of patients was chosen. The filled-in data extraction forms can be found in the supplement. In case of missing data, the corresponding authors were contacted at least twice by e-mail and missing data was obtained for all studies.

The primary outcome variables of interest were the median differences (including IQR) of door to groin and door to reperfusion times between the intervention and control group. The secondary outcome variables of interest were the rates of 72-hour symptomatic intracranial hemorrhage (sICH)[97], 90-day good functional outcome (i.e, modified Rankin Scale (mRS) ≤ 2) and 90-day mortality for both groups. Predictors of interest were pre-hospital screening methods, type of pre-interventional imaging and study characteristics such as study design, the year of the study and sample size.

Risk of Bias Assessment

Risk of bias assessment was done independently by two authors (A.B. and I.T.). Risk of bias of non-randomized studies was assessed with the ROBINS-I tool, which was developed by the Cochrane Collaboration and categorizes risk of systematic bias as low, moderate, serious and critical.[98] If a study was rated critical i.e., did not provide useful data in at least one domain, it was excluded from the meta-

analysis.[98] For randomized studies the ROB 2 tool was used. The risk categories were low risk, some concerns, and high risk.[99]

Statistical analyses

All analyses were performed in R version 4.0.3 (2020-10-10). To perform a meta-analysis on the primary outcomes of interest, we used the quantile estimation method proposed by McGrath et al.[100] as implemented in the R package 'metamedian'. After estimating the variance of the difference in medians in each study, studies were meta-analyzed using random effects model per the inverse variance method. For the binary secondary outcome measures of good functional outcome (mRS ≤ 2), 72-hour sICH, and 90-day mortality, we calculated odds ratio estimates using random effects models with the R package 'metafor' and the DerSimonian-Laird estimator for the amount of heterogeneity.[101]

A prespecified subgroup analysis on the primary outcome measures was performed for mothership patients (patients presenting directly to the comprehensive stroke center) and transfer patients (patients presenting first to a primary stroke center from which they were transferred for MT to a comprehensive stroke center).

Results

Our literature search identified 4,414 potentially relevant unique articles out of which 33 were retained for full-text review (Figure 1; a detailed overview of excluded studies can be found in the supplemental material under part 5). Five studies had to be excluded because of potentially overlapping patients.[33, 35, 102-104] All of these studies were from the same author groups and contained overlapping time periods. Out of these studies, we chose those with the longest time periods to include the largest number of patients possible. As Sarraj et al.[105] included for the endpoint door to groin the data from the transfer patients from Requena et al. (2020)[106], we chose to only include Sarraj et al. in this analysis. However, the mothership patients (n=79) from Requena et al. (2020) [106] were used in all other analyses and the transfer patients for the analysis of door to reperfusion times.

A total of eight studies met our inclusion criteria and were included in the meta-analysis on effects of DTAS approaches (Table 1). Additional data were obtained for five of these eight studies to perform meta-analysis on subgroups.[92, 93, 106-108] Additionally, two ongoing randomized controlled studies (NCT03969511 and NCT04701684) were identified on clinicaltrials.gov, but results were not available at the time of analysis.

Eight studies with 1938 patients (704 intervention group, 1234 control group) reported the effect of DTAS approaches on door to groin and seven studies with 1068 patients (517 intervention group, 551 control group) on door to reperfusion times.

We were able to perform subgroup analysis for transfer patients in seven studies (n = 1753; 626 intervention and 1127 control) on door to groin times and in seven studies (n = 883, 439 intervention and 444 control) on door to reperfusion times. Subgroup analysis for mothership patients was done in all four studies, which included mothership patients (n=185 mothership patients; 78 intervention group and 107 control group).

Studies differed in design with one randomized study, one cluster-randomized study, two studies that reported results from case-matched patients (with different criteria although all used baseline National Institute of Health Stroke Scale (NIHSS) and age) and three studies that reported on consecutive patients. Seven of eight studies were monocentric. Detailed assessment of risk of bias is available in the online-only supplement. The most common source of bias was selection bias or possible confounding due to the retrospective nature of most studies. Risk of Bias was rated serious in 3 of 8 (37.5%) studies.

Primary analysis: time from door to groin and door to reperfusion

Time from door to groin and door to reperfusion was significantly shorter in the DTAS group in 7 of 8 (87.5%) studies. Random-effects meta-analysis of 8 studies showed a significant difference of median door to groin times of 29.0 min (95% confidence interval (CI) 14.3 – 43.6; p <0.001) and of median door to reperfusion times of 32.1 min (95% CI 15.1 – 49.1; p <0.001) in favor of DTAS (Figure 2; Table 2). High I^2 values indicated considerable heterogeneity among studies for both primary endpoints (door to groin and door to reperfusion). As prespecified (PROSPERO entry CRD42020213621) we performed subgroup analysis for both primary endpoints for transfer and mothership patients. In transfer patients both door to groin and door to reperfusion times were significantly shorter. The median difference of door to groin times was 22.5 min (95% CI 7.9 – 37.1) and of door to reperfusion times was 34.3 min (95% CI 18.0 – 50.7) in favor of the DTAS group. (Figure 3 A and B) Also, in mothership patients both door to groin and door to reperfusion times were significantly shorter in DTAS patients with a median difference of 30.7 min (95% CI 8.1 – 53.3) and 26.6 min (95% CI 4.8 – 48.4). (Figure 3 C and D).

Secondary analysis: Clinical outcomes and safety endpoints

Random effects meta-analysis on secondary endpoints did not detect any significant differences (Table 3). Numerically the odds of a good functional outcome were higher in the intervention group than in the control group (OR: 1.38, 95% CI: 0.97-1.95; eFigure 1 in the supplemental material). However, the difference did not reach statistical significance, and overall, the evidence for an effect of the intervention on the probability of a good outcome is only moderate. The incidence of 72-hour sICH (OR 0.84; 95% CI 0.58 – 1.24) and 90-day mortality (OR 0.74; 95% CI 0.48 – 1.15) appeared not to differ between groups (eFigure 2 and 3).

Discussion

This systematic review and meta-analysis included eight studies with a total of 704 patients in the DTAS and 1234 patients in the control group. Our findings show that DTAS approaches for the triage of acute stroke patients with a suspected LVO lead to a significant reduction in both door to groin and door to reperfusion times. (median reduction of 29.0 min (95% CI 14.3 - 43.6) and 32.1 min (95%-CI 15.5 – 49.1)) Although we are uncertain about the impact on functional outcome at 90 days, the pooled estimates favored the intervention. We did not find any difference in mortality within 90 days and the occurrence of sICH. These findings should be interpreted with caution due to the small number of studies and the different design approaches, which have resulted in substantial heterogeneity in both the intervention and control group.

All eight studies in this meta-analysis included transfer patients, in whom DTAS was associated with shorter door to groin and door to reperfusion times. A possible explanation might be that staff and other resources could be prepared prior to patient`s arrival. Furthermore, in these patients the LVO was confirmed at the referring hospital in most cases, leading to a clear indication for performing MT. These processes can be further optimized if the primary stroke centers and comprehensive stroke centers are integrated in a network and use tools such as teleconsulting and teleradiology.[109] Our results support a recent expert statement, recommending repeated imaging in transfer patients only in cases of clinical deterioration or improvement,[110] as this can significantly reduce door to treatment times in these patients.

In mothership patients (extracted from four studies) we observed similar effects. The lower certainty of the effect might be attributable to low statistical power due to a substantially lower number of patients (145 mothership vs 1753 transfer patients). Since there are often long distances between the emergency department, CT/MRI suite and angiography suite[111], one would expect greater time savings with a DTAS approach in mothership patients. However, there might be other structural factors limiting the effect of DTAS in mothership patients. Due to the absence of a reliable pre-hospital screening tool in stroke patients, the first focused neurological exam in mothership patients is often done in the emergency room, possibly leading to a later activation of the angiography team. This is especially problematic during off-hours when interventionalists are on call and have to reach the hospital from home. One possible approach to overcome this limitation is the utilization of pre-hospital scales for in the field detection of LVOs, such as the Rapid Arterial Occlusion Evaluation (RACE) scale[112], the Los Angeles Motor Score (LAMS)[113], the Prehospital Acute Stroke Severity (PASS) scale[114] and the Field Assessment Stroke Triage for Emergency Department (FAST-ED) scale as described by Ribo et al.[102, 103, 106]. All these scales have limited accuracy for the identification of LVOs, with sensitivity ranging from 38-62% and specificity ranging from 80-93% [115, 116]. A further validation of the RACE scale with a threshold of ≥ 5 in a sample of 1822 patients, showed that 35% of the patients presented with an LVO and 20% were eligible for EVT.[117] As recent literature suggests that an LVO can be detected with very high sensitivity with a FDCT angiography, the detection within the angiosuite should not pose a problem.[34] Furthermore,

advances with FDCT perfusion enable the physician to also detect smaller, distal occlusions such as M2 or M3 occlusions.[118] However, even under optimal circumstances the workload of the angiography team will increase if DTAS is adopted in mothership patients.[110] Another strategy to prevent angiosuite overload might be to use a specialized vascular neurologist team on admission for the selection of patients with high probability of LVO. A recent study even found the largest effect of DTAS on functional outcome in patients presenting in the very early (1 – 3h) time-window[106], which might be explained by a faster stroke lesion growth in patients with hyperacute stroke.[119] As mothership patients routinely present earlier than transfer patients, future trials on DTAS in mothership patients should be a primary focus. This is underscored by a recent analysis showing that every 10 minutes of earlier treatment initiation in patients undergoing MT increases the net monetary benefit of the intervention by $10,915.[23]

Our study could not show an effect on functional outcome (albeit a trend in favor of DTAS was apparent). Interestingly the results of the two included randomized studies were conflicted with Pfaff et al. finding no effect on functional outcome, while Requena et al. found significantly better odds for functional independence in patients triaged with a DTAS approach.[92, 93] This might be attributable to specific factors associated with a certain center, e.g. a specially trained ambulance services or stroke network and highlights the need for well-designed multicenter trials to examine the benefit of DTAS with more certainty. The fact that the rate of sICH was not higher in the DTAS arm is promising, since reliable hemorrhage exclusion on flat detector CT (FDCT) is still a topic of discussion. Our results are in-line with a prior analysis indicating that hemorrhage detection can be done with adequate safety on FDCT.[36] As recent studies showed the value of bridging therapy in LVO patients this should be further addressed in adequately powered studies.[120, 121]

This study has several limitations. The number of studies is small, and we observed considerable heterogeneity of the study results. Heterogeneity could be attributed to the following reasons: a) While in three studies[92, 108, 122] non-contrast FDCT and FDCT angiography were performed prior to groin puncture, the remaining studies performed only minimal (non-contrast FDCT) or no imaging prior to groin puncture, b) the distances between emergency room, MDCT suite and angiography suite varied in all studies[111], c) the usage of pre-hospital scales was heterogenous among studies and might have influenced door to groin and door to reperfusion times as they allow to skip the emergency department completely, and d) studies differed in designs. However, as these variations were consistent within the studies, we do not think they influenced the direction of the effect. In addition, most data were collected retrospectively in a single center design without blinding of personnel and participants, possibly leading to performance bias. Furthermore, due to missing data we were not able to adjust our meta-analysis for parameters, which also influence clinical outcome such as metrics of salvageable tissue, i.v. thrombolysis rates, the success of MT (e.g., final modified thrombolysis in cerebral infarction scores). As these parameters significantly influence clinical outcome, our inability to adjust for them might

potentially account for the lack of statistical differences in the present meta-analysis. However, since all but one study[92] showed a similar effect direction, these results can provide valuable insight on the possible effects of DTAS approaches. Lastly, given that the number of included studies was small, and it is a rapid evolving topic, regular updates are warranted.

Conclusion

Direct to angiography suite approaches for the triage of suspected LVO patients lead to a significant improvement of in-hospital workflow time metrics. However, in our meta-analysis, they did not translate into improved clinical outcomes. This highlights the need for well-designed randomized, multicenter trials to evaluate the effect of DTAS approaches in different hospital settings.

Tables

Author	Country	Study design	Study period	Intervention group (n)	Control Group (n)	Mothership / Transfer	Included in Meta-Analysis
Aoki et al.[107]	Japan	Retrospective, Consecutive Patients, Single Center	2012 – 2018	40	27	Only Transfer	Yes
Bouslama et al.[122]	USA	Retrospective, Case-Control, Single Center	2016 – 2017	49	49	Only Transfer	Yes
Jadhav et al.[123]	USA	Retrospective, Consecutive Patients, Single Center	2013 – 2016	111	150	Only Transfer	Yes
Pfaff et al.[92]	Germany	Prospective, Cluster-randomized, non-blinded, Per-Protocol analysis	2017 – 2019	26	34	Mothership (30%) / Transfer (70%)	Yes
Psychogios et al.[108]	Germany	Retrospective, Case-Control, Single Center	2016 - 2018	43	43	Mothership (56%) / Transfer (44%)	Yes
Requena et al.[106]	Spain	Retrospective, Case-Control, Single Center	2016 – 2019	174	175	Mothership (23%) / Transfer (77%)	Yes
Requena et al.[93]	Spain	Randomized, Blinded endpoint evaluation, Single Center	2018 – 2020	74	64	Mothership (29%)/ Transfer (71%)	Yes
Sarraj et al.[105]	USA, Spain	Retrospective, Cohort study, multicenter	2014 – 2020	327	813	Only Transfer	Yes

Table 1: Overview over studies included in Systematic Review/Meta-Analysis

	No. of Studies	No. of Patients (Intervention/Control Group)	Weighted median difference, min (95% CI)
Door to groin time			
All patients	8	1938 (704 / 1234)	29.0 (14.3 – 43.6)
Transfer only	7	1753 (626 / 1127)	22.5 (7.9 – 37.1)
Mothership patients only	4	185 (107 / 78)	30.7 (8.1 – 52.3)
Door to reperfusion time			
All patients	7	1068 (517 / 551)	32.1 (15.1 – 49.1)
Transfer only	7	883 (439 / 444)	34.3 (18.0 – 50.7)
Mothership patients only	4	185 (78 / 107)	26.6 (4.8 – 48.4)

Table 2: Random-Effects Meta-Analysis of Differences in Median door to groin and door to reperfusion times

	No. of Studies	No. of Patients (Intervention/Control Group)	Odds Ratio (95% CI)
Good functional outcome (mRS ≤ 2 at 90 days	8	1938 (704 / 1234)	1.38 (0.97 – 1.95)
Symptomatic intracranial hemorrhage	8	1938 (704 / 1234)	0.84 (0.58 – 1.24)
Mortality at 90 days	8	1938 (704 / 1234)	0.74 (0.48 – 1.15)

Table 3: Random-Effects Meta-Analysis of Secondary Outcomes

Figures

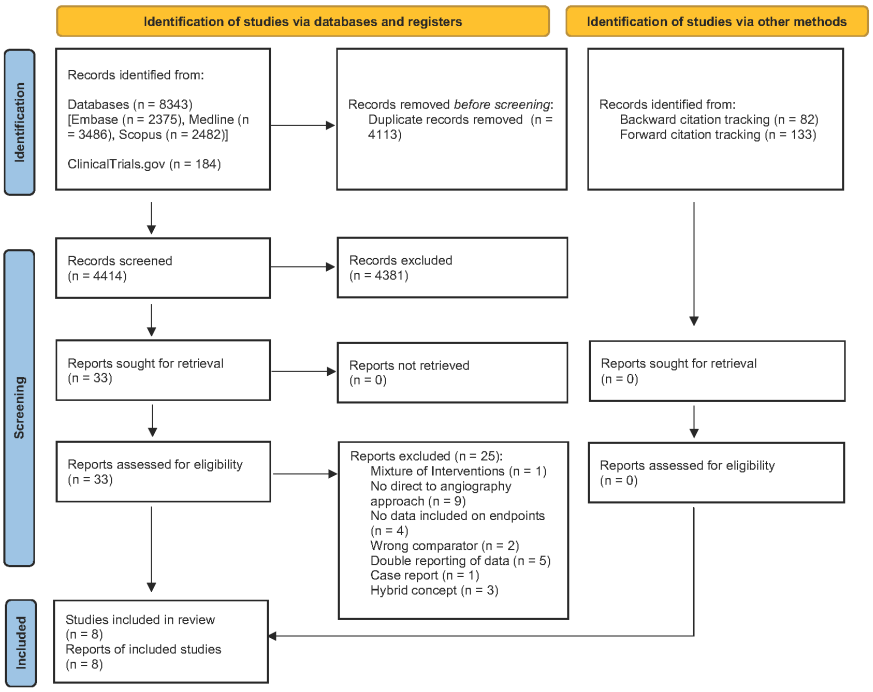


Figure 1: Flowchart of included and excluded articles, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines

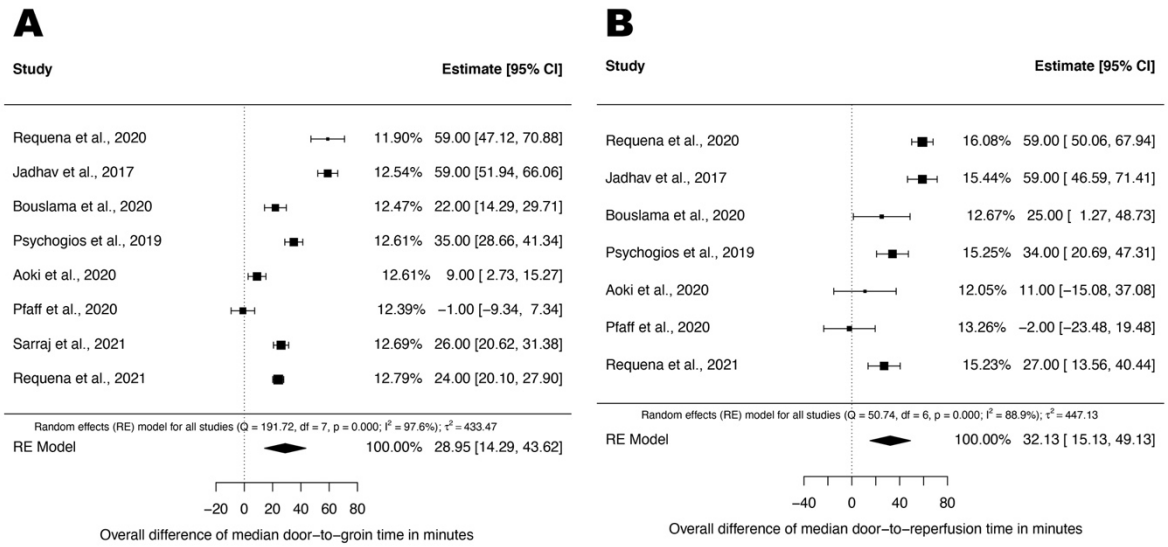


Figure 2: Forest plots of the median differences on door to groin times (A) and door to perfusion times (B) between DTAS and traditional triaged patients.

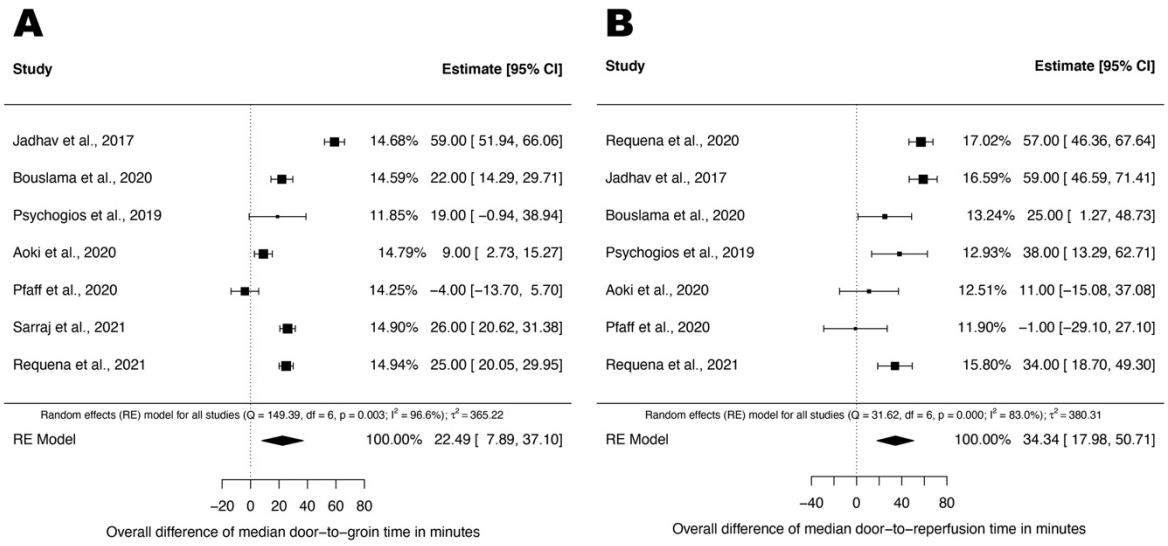


Figure 3: Forest plots for the subgroup analysis of transfer patients of the median differences of door to groin times (A) and door to perfusion times (B) between DTAS and traditional triaged patients

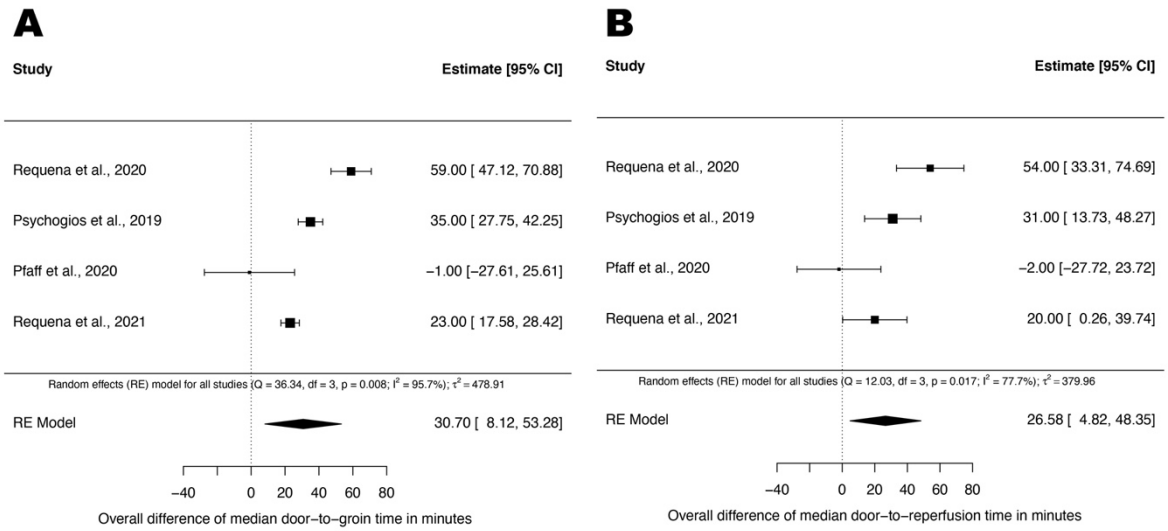


Figure 4: Forest plot for the subgroup analysis of mothership patients of the median differences of door to groin times (A) and door to perfusion times (B) between DTAS and traditional triaged patients.

Supplementary material for the paper:

Direct to angiography suite approaches for the triage of suspected acute stroke patients – a systematic review and meta-analysis

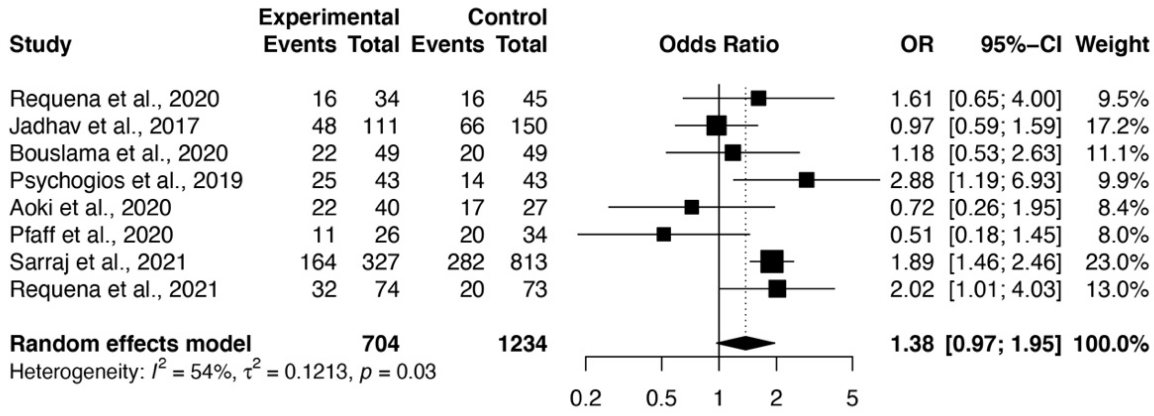
Brehm Alex MD, Tsogkas Ioannis MD, Ospel Johanna M. MD, Appenzeller-Herzog Christian PhD, Junya Aoki MD, Kazumi Kimura MD, Pfaff Johannes A.R. MD, MBHA, Möhlenbruch Markus A. MD, Requena Manuel MD, Ribo Marc J. PhD MD, Sarraj Amrou MD, Sporns Peter MD MBA, Psychogios Marios-Nikos MD

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	supplement
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	supplement
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

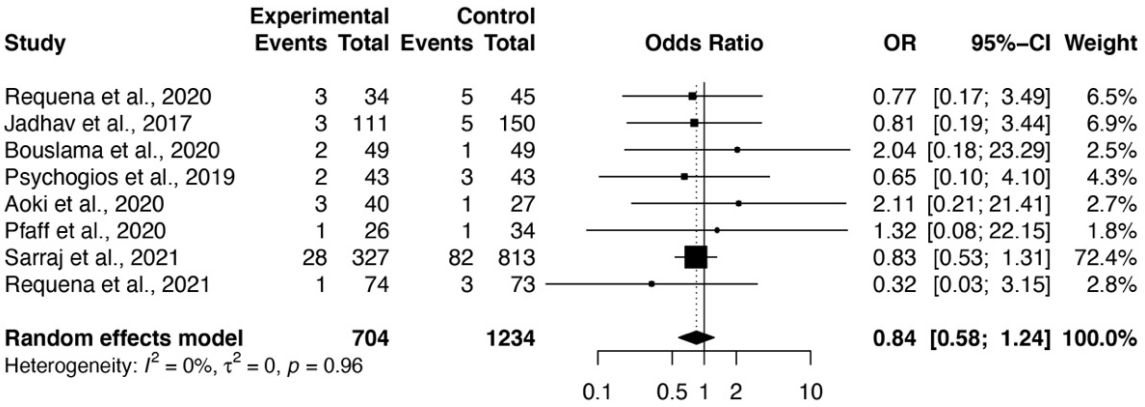
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, figure1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6, table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplement
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2 and figure 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 2 and 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplement
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7 – 10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

Part 1 – Additional Forest Plots

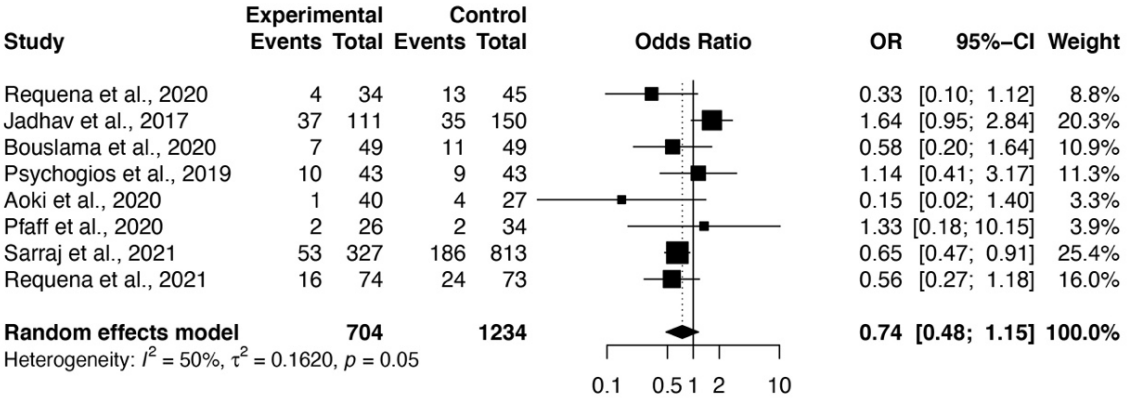
eFigure 1: Forest plot of meta-analysis on good clinical outcome (modified Rankin Scale ≤ 2)



eFigure 2: Forest plot of meta-analysis on symptomatic intracranial hemorrhage



eFigure3: Forest plot of meta-analysis on mortality within 90 days



Part 2: Risk of Bias Assessment

2.1 Overall Risk of Bias of all Studies

Study	Risk of Bias Assessment	Assessment Tool
Aoki et al. 2020	Serios	Robins I
Bouslama et al. 2020	Moderate	Robins I
Jadhav et al. 2017	Serios	Robins I
Pfaff et al. 2020	Some Concerns	Rob 2 CRT
Psychogios et al. 2019	Serious	Robins I
Requena et al. 2020	Moderate	Robins I
Requena et al. 2021	Low	Rob 2
Sarray et al. 2021	Moderate	Robins I

2.2 Detailed overview of risk domains for the randomized studies

Domain of Bias	Pfaff et al. 2020	Requena et al. 2020
Domain 1a: Risk of bias arising from the randomization process	Some concerns	Low
Domain 1b: Risk of bias arising from the timing of identification or recruitment of participants in a cluster-randomized trial	Low	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Low	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Low	Low
Domain 3: Risk of bias due to missing outcome data	Low	Low
Domain 4: Risk of bias in measurement of the outcome	Low	Low
Domain 5: Risk of bias in selection of the reported result	Some concerns	Low

2.3 Detailed overview of risk domains for the observational studies

Domain of Bias	Aoki et al. 2020	Bouslama et al. 2020	Jadhav et al. 2017	Psychogios et al. 2019	Requena et al. 2020	Sarray et al. 2021
Confounding	Serious	Moderate	Serious	Serious	Moderate	Moderate
Selection of participants into the study	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Classification of intervention	Low	Low	Low	Low	Low	Low
Deviations from intended interventions	Low	Low	Low	Low	Low	Low
Missing Data	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Measurement of Outcomes	Low	Low	Low	Low	Low	Low
Selection of reported results	Low	Low	Low	Low	Low	Low

Part 3: Search Strategy for the different databases

Embase.com

('cerebrovascular accident'/de OR 'cardioembolic stroke'/de OR 'occlusive cerebrovascular disease'/de OR 'middle cerebral artery occlusion'/de OR 'brain embolism'/de OR 'brain ischemia'/de OR 'brain infarction'/de OR 'brain embolism'/de OR ('brain'/de AND ('thromboembolism'/de OR

'embolism'/de OR 'thrombosis'/de)) OR (stroke* OR ictus OR ((cerebrovascular OR 'cerebro vascular' OR 'cerebrum vascular' OR cerebral OR cerebri OR brain OR intracranial OR intra-cranial OR intracerebral OR intra-cerebral OR carotid OR neural OR hemispher* OR 'circle of willis') NEAR/3

(accident* OR lesion* OR insult* OR attack* OR insufficienc* OR arrest* OR failure* OR injur* OR vasculopath* OR occlu* OR obstruct* OR thrombosis OR phlebothrombosis OR thromboembolism OR thrombus OR thrombi OR blockage OR clot OR interruption OR obliterat* OR embol* OR ischemi* OR ischaemi* OR infarct* OR 'blood flow disturbance' OR 'blood flow disorder' OR 'circulation disorder' OR 'circulatory disorder')) OR apoplexia OR apoplexy OR apoplectic OR 'ischaemic seizure*' OR 'ischemic seizure*' OR 'ischaemic encephalopath*' OR 'ischemic encephalopath*' OR CVA OR AIS OR ((Heubner* OR MCA OR ACA OR PCA) NEAR/3 (infarct* OR syndrome*))):ab,ti)

AND

('thrombectomy'/exp OR 'endovascular surgery'/exp OR 'embolectomy'/exp OR 'thrombectomy device'/exp OR 'endovascular therapy'/de OR (thrombectom* OR embolectom* OR 'mechanical thrombolysis' OR 'mechanical clot disruption' OR ((endovascular OR intravascular OR intraarterial OR endo-vascular OR intra-vascular OR intra-arterial OR neuroendovascular) NEXT/3 (procedure* OR surgery OR treatment* OR management OR therapy OR recanalization* OR recanalization* OR revascularization* OR revascularization* OR 're-canalization*' OR 're-canalization*' OR 're-vascularization*' OR 're-vascularisation*' OR technolog* OR 'clot retrieval' OR 'clot removal')) OR

'stent retriever*' OR stentriever* OR merci OR solitaire OR trevo OR mindframe OR soehendra OR AngioJet OR APERIO OR ASPIRE OR BONnet OR FlowTriever OR pREset OR 'Revive device' OR Rotarex OR 3MAX OR 4MAX OR 5MAX OR 'ACE 64' OR 'ACE 68' OR Amplatz OR Angiojet OR ASPIREX OR CAT8 OR 'Diver CE' OR EPAR OR 'Fast Funnel' OR Hydrolyser OR Indigo OR ThromCat OR X-Sizer OR Xpeedior):ab,ti)

AND

('time to treatment'/de OR 'workflow'/de OR 'time factor'/de OR 'flat detector computed tomography'/de OR (((time* OR timing OR delay*) NEAR/3 (treatment* OR therap* OR intervention* OR recanalization OR recanalisation OR re-canalization OR re-canalisation OR reperfusion OR re- perfusion OR groin OR angiosuite OR angio-suite OR angiography OR neuroangiosuite OR neuroangio-suite OR neuroangiography OR door-to-needle OR puncture)) OR 'procedural time*' OR workflow OR 'work flow' OR 'time factor*' OR triage* OR (flat NEAR/3 (CT OR 'computed tomography')) OR (direct* NEAR/3 (angiosuite OR angio-suite OR angiography OR neuroangiosuite OR neuroangio-suite OR neuroangiography)) OR ((bypass* OR circumvent* OR avoid* OR omit* OR skip*) NEAR/3 (multidetector OR multi-detector OR emergency OR 'CT suite' OR 'Computed Tomography suite' OR 'CT room' OR 'Computed Tomography room')) OR 'one stop'):ab,ti)

NOT

(('animal'/de OR 'animal experiment'/exp OR 'nonhuman'/de) NOT ('human'/exp OR 'human experiment'/de))

NOT

[conference abstract]/lim

Medline (Ovid)

(exp stroke/ OR exp "intracranial embolism and thrombosis"/ OR brain ischemia/ OR (brain/ AND

("embolism and thrombosis"/ OR thromboembolism/ OR embolism/ OR thrombosis/)) OR (stroke* OR ictus OR ((cerebrovascular OR cerebro vascular OR cerebrum vascular OR cerebral OR cerebri OR brain OR intracranial OR intra-cranial OR intracerebral OR intra-cerebral OR carotid OR neural OR hemispher* OR circle of willis) ADJ3 (accident* OR lesion* OR insult* OR attack* OR insufficienc* OR arrest* OR failure* OR injur* OR vasculopath* OR occlu* OR obstruct* OR thrombosis OR phlebothrombosis OR thromboembolism OR thrombus OR thrombi OR blockage OR clot OR interruption OR obliterat* OR embol* OR ischemi* OR ischaemi* OR infarct* OR blood flow disturbance OR blood flow disorder OR circulation disorder OR circulatory disorder)) OR apoplexia OR apoplexy OR apoplectic OR ischaemic seizure* OR ischemic seizure* OR ischaemic encephalopath* OR ischemic encephalopath* OR CVA OR AIS OR ((Heubner* OR MCA OR ACA OR PCA) ADJ3 (infarct* OR syndrome*))).ab,ti.)

AND

(exp thrombectomy/ OR endovascular procedures/ OR exp embolectomy/ OR (thrombectom* OR embolectom* OR mechanical thrombolysis OR mechanical clot disruption OR ((endovascular OR intravascular OR intraarterial OR endo-vascular OR intra-vascular OR intra-arterial OR neuroendovascular) ADJ3 (procedure* OR surgery OR treatment* OR management OR therapy OR recanalization* OR recanalization* OR revascularization* OR revascularization* OR re-canalization* OR re-canalization* OR re-vascularization* OR re-vascularisation* OR technolog* OR clot retrieval OR clot removal)) OR stent retriever* OR stentriever* OR merci OR solitaire OR trevo OR mindframe OR soehendra OR AngioJet OR APERIO OR ASPIRE OR BONnet OR FlowTriever OR pREset OR Revive device OR Rotarex OR 3MAX OR 4MAX OR 5MAX OR ACE 64 OR ACE 68 OR Amplatz OR Angiojet OR ASPIREX OR CAT8 OR Diver CE OR EPAR OR Fast Funnel OR Hydrolyser OR Indigo OR ThromCat OR X-Sizer OR Xpeedior).ab,ti.)

AND

(time-to-treatment/ OR workflow/ OR time factors/ OR triage/ OR (((time* OR timing OR delay*) ADJ3 (treatment* OR therap* OR intervention* OR recanalization OR recanalisation OR re- canalization OR re-canalisation OR reperfusion OR re-perfusion OR groin OR angiosuite OR angio-suite OR angiography OR neuroangiosuite OR neuroangio-suite OR neuroangiography OR door-to-needle OR puncture)) OR procedural time* OR workflow OR work flow OR time factor* OR triage* OR (flat ADJ3 (CT OR computed tomography)) OR (direct* ADJ3 (angiosuite OR angio-suite OR angiography OR neuroangiosuite OR neuroangio-suite OR neuroangiography)) OR ((bypass* OR circumvent* OR avoid* OR omit* OR skip*) ADJ3 (multidetector OR multi-detector OR emergency OR CT suite OR Computed Tomography suite OR CT room OR Computed Tomography room)) OR one stop).ab,ti.)

NOT (exp animals/ NOT humans/)

Scopus

TITLE-ABS((stroke* OR ictus OR ((cerebrovascular OR "cerebro vascular" OR "cerebrum vascular" OR cerebral OR cerebri OR brain OR intracranial OR intra-cranial OR intracerebral OR intra-cerebral OR carotid OR neural OR hemispher* OR "circle of willis") W/5 (accident* OR lesion* OR insult* OR attack* OR insufficienc* OR arrest* OR failure* OR injur* OR vasculopath* OR occlu* OR obstruct* OR thrombosis OR phlebothrombosis OR

thromboembolism OR thrombus OR thrombi OR blockage OR clot OR interruption OR obliterat* OR embol* OR ischemi* OR ischaemi* OR infarct* OR "blood flow disturbance" OR "blood flow disorder" OR "circulation disorder" OR "circulatory disorder")) OR apoplexia OR apoplexy OR apoplectic OR "ischaemic seizure" OR "ischemic seizure" OR "ischaemic encephalopathy" OR "ischemic encephalopathy" OR CVA OR AIS OR ((Heubner* OR MCA OR ACA OR PCA) W/5 (infarct* OR syndrome*))))

AND

TITLE-ABS((thrombectom* OR embolectom* OR "mechanical thrombolysis" OR "mechanical clot disruption" OR ((endovascular OR intravascular OR intraarterial OR endo-vascular OR intra-vascular OR intra-arterial OR neuroendovascular) W/5 (procedure* OR surgery OR treatment* OR management OR therapy OR recanalization* OR recanalization* OR revascularization* OR revascularization* OR "re-canalization" OR "re-canalization" OR "re-vascularization" OR "re-vascularisation" OR technolog* OR "clot retrieval" OR "clot removal")) OR "stent retriever" OR stentriever* OR merci OR solitaire OR trevo OR mindframe OR soehendra OR AngioJet OR APERIO OR ASPIRE OR BONnet OR FlowTriever OR pREset OR "Revive device" OR Rotarex OR 3MAX OR 4MAX OR 5MAX OR "ACE 64" OR "ACE 68" OR Amplatz OR Angiojet OR ASPIREX OR CAT8 OR "Diver CE" OR EPAR OR "Fast Funnel" OR Hydrolyser OR Indigo OR ThromCat OR X-Sizer OR Xpeedior))

AND

TITLE-ABS((((time* OR timing OR delay*) W/5 (treatment* OR therap* OR intervention* OR recanalization OR recanalisation OR re-canalization OR re-canalisation OR reperfusion OR re-perfusion OR groin OR angiosuite OR angio-suite OR angiography OR neuroangiosuite OR neuroangio-suite OR neuroangiography OR door-to-needle OR puncture)) OR "procedural time" OR workflow OR "work flow" OR "time factor" OR triage* OR (flat W/5 (CT OR "computed tomography")) OR (direct* W/5 (angiosuite OR angio-suite OR angiography OR neuroangiosuite OR neuroangio-suite OR neuroangiography)) OR ((bypass* OR circumvent* OR avoid* OR omit* OR skip*) W/5 (multidetector OR multi-detector OR emergency OR "CT suite" OR "Computed Tomography suite" OR "CT room" OR"Computed Tomography room")) OR "one stop"))

Clinical Trials.gov

(stroke* OR ictus OR "cerebrovascular accident" OR apoplexia OR CVA OR AIS)

AND

(thrombectom* OR embolectom* OR "mechanical thrombolysis" OR "endovascular treatment" OR "stent retriever")

Part 4: Data extraction forms

Abbreviations:

1st first quartile, 3rd third quartile, c, control, dTG, door to groin, dTR, door to reperfusion, GO good outcome, i, intervention, M Mothership, Me, median, Mor, mortality, sICH symptomatic intracranial hemorrhage, T Transfer

This data extraction form was used for the primary analysis except for door to reperfusion times

study	n_c	n_i	dTG_c_Me	dTG_c_1st	dTG_c_3rd	dTg_i_Me	dTG_i_1st	dTG_i_3rd	GO_c	GO_i	sICH_c	sICH_i	Mor_c	Mor_i
Psychogios_2019	43	43	60	48	68	25	19	30	14	25	3	2	9	10
Aoki_2020	27	40	31	27	40	22	16	31	17	22	1	3	4	1
Bouslama_2020	49	49	55	44.5	66	33	26.5	47	20	22	1	2	11	7
Jadhav_2017	150	111	81	46	91	22	12	25	66	48	5	3	35	37
Requena_2020	45	34	78	57	100	19	16	23	16	16	5	3	13	4
Pfaff_2020	34	26	40	31	48	41	30	48	20	11	1	1	2	2
Requena_2021	73	74	42	35	51	18	15	24	20	32	3	1	24	16
Sarraj_2021	813	327	60	37	95	34	20	62	282	164	82	28	186	53

study	T_n_c	T_n_i	T_dTG_c_Me	T_dTG_c_1st	T_dTG_c_3rd	T_dTG_i_Me	T_dTG_i_1st	T_dTG_i_3rd
Psychogios_2019	13	25	40	30	69	21	19	26
Aoki_2020	27	40	31	27	40	22	16	31
Bouslama_2020	49	49	55	44.5	66	33	26.5	47
Jadhav_2017	150	111	81	46	91	22	12	25
Requena_2020	NA	NA	NA	NA	NA	NA	NA	NA
Pfaff_2020	23	19	33	30	43	37	25	45
Requena_2021	52	55	42	34	51	17	15	25
Sarraj_2021	813	327	60	37	95	34	20	62

study	M_n_c	M_n_i	M_dTG_c_Me	M_dTG_c_1st	M_dTG_c_3rd	M_dTG_i_Me	M_dTG_i_1st	M_dTG_i_3rd
Psychogios_2019	30	18	61	54	67	26	25	38
Aoki_2020	NA	NA	NA	NA	NA	NA	NA	NA
Bouslama_2020	NA	NA	NA	NA	NA	NA	NA	NA
Jadhav_2017	NA	NA	NA	NA	NA	NA	NA	NA
Requena_2020	45	34	78	57	100	19	16	23
Pfaff_2020	11	7	46	40	85	47	44	54
Requena_2021	21	19	43	39	51	20	17	23

Sarraj_2021	NA	NA	NA	NA	NA	NA	NA	NA

Data extraction form for the primary analysis and secondary analysis of door to reperfusion times

study	n_c	n_i	dTR_c_Me	dTR_c_1st	dTR_c_3rd	dTR_i_Me	dTR_i_1st	dTR_i_3rd
Psychogios_2019	43	43	102	85	117	68	53	89
Aoki_2020	27	40	67	56	122	56	43	80
Bouslama_2020	49	49	110	80	153	85	57.5	115.5
Jadhav_2017	150	111	125	81	146	66	39	84
Requena_2020	175	174	114	90	142	55	40	80
Pfaff_2020	34	26	78	58	92	80	66	118
Requena_2021	73	74	84	63	117	57	43	77
Sarraj_2021	813	327	NA	NA	NA	NA	NA	NA

study	T_n_c	T_n_i	T_dTR_c_Me	T_dTRR_c_1st	T_dTR_c_3rd	T_dTR_i_Me	T_dTR_i_1st	T_dTR_i_3rd
Psychogios_2019	13	25	102	68	109	64	51	88
Aoki_2020	27	40	67	56	122	56	43	80
Bouslama_2020	49	49	110	80	153	85	57.5	115.5
Jadhav_2017	150	111	125	81	146	66	39	84

Requena_2020	130	140	110	79	137	53	39	73
Pfaff_2020	23	19	73	57	91	74	64	122
Requena_2021	52	55	90	69	121	56	43	76
Sarraj_2021	813	327	NA	NA	NA	NA	NA	NA

study	M_n_c	M_n_i	M_dTR_c_Me	M_dTR_c_1st	M_dTR_c_3rd	M_dTR_i_Me	M_dTR_i_1st	M_dTR_i_3rd
Psychogios_2019	30	18	103	85	121	72	58	87
Aoki_2020	NA	NA	NA	NA	NA	NA	NA	NA
Bouslama_2020	NA	NA	NA	NA	NA	NA	NA	NA
Jadhav_2017	NA	NA	NA	NA	NA	NA	NA	NA
Requena_2020	45	34	127	104	154	73	47	97
Pfaff_2020	11	7	87	73	95	89	74	107
Requena_2021	21	19	80	55	90	60	51	85
Sarraj_2021	NA	NA	NA	NA	NA	NA	NA	NA

Part 5: Detailed list of excluded studies

No	Reference	Reason for exclusion
1	Janssen PM, Venema E, Dippel DWJ. Effect of workflow improvements in endovascular stroke treatment: A systematic review and meta-analysis. Stroke 2019;50:665-674.	Mixture of interventions (Anesthesia, direct to angiography, organization of angioroom etc.)
2	Kansagra AP, Wallace AN, Curfman DR, et al. Streamlined triage and transfer protocols improve door-to-puncture time for endovascular thrombectomy in acute ischemic stroke. Clinical Neurology and Neurosurgery 2018;166:71-75.	Wrong comparator (Comparison over time (quarters) with change in pre-transfer imaging; for example, pre-transfer CT-A rate increased significantly)
3	Menéndez ES, Espot PG, Macho LC, Rodríguez-Samaniego MT, Santana Román KE, Fueyo MRD. Implementation of a protocol for direct stroke patient transfer and mobilization of a stroke team to reduce times to reperfusion. Emergencias 2019;31:385-390.	Double reporting of data (at least partly included in Requena et al. 2020)
4	Qureshi AI, Egila H, Adil MM, et al. "No turn back approach" to reduce treatment time for endovascular treatment of acute ischemic stroke. Journal of Stroke and Cerebrovascular Diseases 2014;23:e317-e323.	No direct to angiography suite approach evaluated
5	Aghaebrahim A, Streib C, Rangaraju S, et al. Streamlining door to recanalization processes in endovascular stroke therapy. Journal of NeuroInterventional Surgery 2017;9:340-345.	No direct to angiography suite approach evaluated
6	Sablot D, Farouil G, Laverdure A, Arquizan C, Bonafe A. Shortening time to reperfusion after transfer from a primary to a comprehensive stroke center. Neurology: Clinical Practice 2019;9:417-423.	No direct to angiography suite approach evaluated
7	Bohmann FO, Kurka N, du Mesnil de Rochemont R, et al. Simulation-Based Training of the Rapid Evaluation and Management of Acute Stroke (STREAM)—A Prospective Single-Arm Multicenter Trial. Frontiers in Neurology 2019;10.	No direct to angiography suite approach evaluated
8	Hung SC, Lin CJ, Guo WY, et al. Toward the era of a one-stop imaging service using an angiography suite for neurovascular disorders. BioMed Research International 2013;2013.	Review; no data included
9	Clarençon F, Rosso C, Degos V, et al. Triage in the Angiography Suite for Mechanical Thrombectomy in Acute Ischemic Stroke: Not Such a Good Idea. AJNR American journal of neuroradiology 2018;39:E59-E60.	Comment, no data given
10	Mashni SK, O'Neal CR, Abner E, Lee J, Fraser JF. Time Intervals for Direct Versus Transfer Cases of Thrombectomy for Stroke in a Primarily Rural System of Care. Journal of Stroke and Cerebrovascular Diseases 2020;29.	No direct to angiography suite approach evaluated
11	Psychogios MN, Behme D, Schregel K, et al. One-stop management of acute stroke patients minimizing door-to-reperfusion times. Stroke 2017;48:3152-3155.	Double reporting (included in Psychogios et al. 2020)
12	Mendez B, Requena M, Aires A, et al. Direct transfer to Angio-suite to reduce workflow times and increase	Double reporting (included in Requena et al. 2020)

	favorable clinical outcome a case-control study. Stroke 2018;49:2723-2727.	
13	Ribo M, Boned S, Rubiera M, et al. Direct transfer to angiosuite to reduce door-to-puncture time in thrombectomy for acute stroke. Journal of NeuroInterventional Surgery 2018;10:221-224.	Double reporting (included in Requena et al. 2020)
14	Brehm A, Tsogkas I, Maier IL, et al. One-stop management with perfusion for transfer patients with stroke due to a large-vessel occlusion: Feasibility and effects on in-hospital times. American Journal of Neuroradiology	Double reporting (included in Psychogios et al. 2020)
15	Psychogios MN, Bähr M, Liman J, Knauth M. One Stop Management in Acute Stroke: First Mothership Patient Transported Directly to the Angiography Suite. Clinical Neuroradiology 2017;27:389-391.	Case report
16	Tong E, Komlosi P, Wintermark M. One-stop-shop stroke imaging with functional CT. European Journal of Radiology 2015;84:2425-2431.	No data included on endpoint
17	Ragoschke-Schumm A, Yilmaz U, Kostopoulos P, et al. Stroke Room': Diagnosis and Treatment at a Single Location for Rapid Intraarterial Stroke Treatment. Cerebrovascular Diseases 2015;40:251-257.	Hybrid concept: MDCT and angiography suite in the same room
18	Pfaff J, Herweh C, Pham M, et al. Mechanical thrombectomy using a combined CT/C-arm X-ray system. Journal of NeuroInterventional Surgery 2016;8:621-625.	Hybrid concept: MDCT and angiography suite in the same room
19	Pfaff J, Schönenberger S, Herweh C, et al. Influence of a combined CT/C-arm system on periprocedural workflow and procedure times in mechanical thrombectomy. European Radiology 2017;27:3966-3972.	Hybrid concept: MDCT and angiography suite in the same room
20	Jeon SB, Ryoo SM, Lee DH, et al. Multidisciplinary Approach to Decrease In-Hospital Delay for Stroke Thrombolysis. J Stroke 2017;19:196-204.	No direct to angiography suite approach evaluated
21	McTaggart RA, Yaghi S, Cutting SM, et al. Association of a primary stroke center protocol for suspected stroke by large-vessel occlusion with efficiency of care and patient outcomes. JAMA Neurology 2017;74:793-800.	No direct to angiography suite approach evaluated
22	Mehta BP, Leslie-Mazwi TM, Chandra RV, et al. Reducing door-to-puncture times for intra-arterial stroke therapy: A pilot quality improvement project. Journal of the American Heart Association 2014;3.	No direct to angiography suite approach evaluated
23	Schregel K, Behme D, Tsogkas I, et al. Effects of Workflow Optimization in Endovascularly Treated Stroke Patients - A Pre-Post Effectiveness Study. PLoS ONE 2016;11.	No direct to angiography suite approach evaluated
24	Li W, Burgin WS, Beba Abadal K, Mokin M, Ren Z. Direct angiographic intervention for acute ischemic stroke with large vessel occlusion. Neurol Res 2021:1-6.	Review; no data included
25	van Meenen LCC, Arrarte Terreros N, Groot AE, et al. Value of repeated imaging in patients with a stroke who are transferred for endovascular treatment. J Neurointerv Surg 2021.	Wrong comparator (Patients in the conventional triage arm presented with changing symptoms, i.e. improved or worsened stroke)

9. Discussion and future directions

This PhD thesis addressed several challenges and research gaps in the field of stroke treatment with a special focus on the optimization of the management and triage of suspected acute stroke patients. The first topic focused on effective dose to patient measurements of often used protocols in stroke care both on angiography and multidetector CT systems. The second topic examined the diagnosis, clinical characteristics, and presentation of over 1,000 consecutive, suspected acute ischemic stroke patients in a tertiary university hospital in Germany and in the final topic the available evidence regarding One Stop management and direct to angiography approaches was summarized and analyzed.

Overall, this PhD thesis could be seen as the foundation for the conductance of already planned and starting larger trials (see chapter 9.4 Outlook and further perspectives).

9.1 Effective dose to patient measurements of the latest angiography systems in acute stroke patients

The first main topic of this thesis (section 6.1 and 6.2) was the experimental measurement of the effective dose of commonly used imaging protocols on the newest generation angiography systems (ARTIS Q and icono, Siemens Healthineers GmbH, Erlangen Germany) and multidetector CT (SOMATOM Force, Siemens Healthineers GmbH, Erlangen, Germany). The key finding was that the effective dose to patients of FDCT protocols commonly used for imaging of suspected AIS patients does not deviate substantially from analogous protocols on multidetector CT. Further important results were that (a) the eye lens dose on angiography systems might be lower compared to MDCT due to the different rotational angel of the FDCT (220 degrees on the FDCT with the source of the radiation mainly under the patient versus 360 degrees on MDCT) and (b) that colimitation can reduce the effective dose substantially (by approximately 50%).

These findings are highly relevant to clinical practice as they show that dose considerations should not be an issue if confronted with triage decisions in suspected AIS patients and that patients are not at risk of excess radiation due to a One Stop management approach.

9.2 Distribution of diagnosis, clinical and imaging characteristics in suspected acute ischemic stroke patients

Planning of resources is of high importance in both clinical trials and clinical practice especially if faced with widening indications. In the second topic (section 7.1), we therefore conducted a cohort-based analysis of suspected AIS patients presenting to a tertiary hospital over the course of one year. The key finding was that a substantial proportion of the patients presented either with a (1) medium vessel occlusion, (2) an Alberta Stroke Program Early CT score (ASPECTS) of less or equal to 5 (15.7% of the patients with an occlusion in the anterior circulation) or later than 6 hours after symptom onset

(48.9%). In these patient collectives the indication for EVT is still a matter of debate and no clear consensus exists.[78, 124]

Currently multiple randomized-controlled trials (RCTs) are addressing the question if the indication of EVT should be widened to include these patient collectives. For example, for patients with a large core infarct (ASPECTS ≤ 5) the TENSION trial[88] and the SELECT-2 trial[125] are evaluating if EVT has a benefit in this patient cohort. For patients with MeVOs our workgroup is conducting the DISTAL trial (clinicaltrials.gov identifier NCT05029414) but also the DISCOUNT trial (clinicaltrials.gov identifier NCT05029414) is recruiting patients. Both trials have similar in-/exclusion criteria and the same primary endpoint. The MR CLEAN-Late trial[126] evaluates if EVT has a beneficial effect in patients presenting after 6 hours who do not fulfill the very strict mismatch criteria of the DAWN[79] and DEFUSE-3[64] trials.

Overall, it can be expected that the indication for EVT will be widened in the future and in this context our data is of high practical value for planning resources accordingly.[127] The data can also be used to estimate the feasibility of a new research project as it gives a good overview over the expected patient collectives in a tertiary university hospital.

9.3 Direct to angiography suite approaches for the triage of suspected acute stroke patients - a systematic review and meta-analysis

Systematic reviews and meta-analysis are used to summarize the available evidence but also to identify evidence gaps and patient groups which were underrepresented in the so far conducted trials.[128] The main results of our systematic review and meta-analysis were that One Stop management and direct to angiography approaches can significantly reduce door to groin (i.e., time from hospital admission to the start of the endovascular treatment of the AIS) and door to reperfusion (i.e., time from hospital admission to the end of the endovascular treatment) times but are not associated with a clear effect on outcome. We further did not find any signal of harm since the rates of symptomatic intracranial hemorrhage and all-cause mortality were comparable between groups. Another important finding was, that while we were able to include 1,938 patients, only 185 (9.5%) of these patients were mothership patients (i.e., patients presenting directly to the treating hospital without prior diagnostics). Over 90% were transfer patients, in which the diagnosis was already confirmed in an external hospital. This result was surprising since mothership patients routinely present earlier to the treating hospital and time-savings might have greater effects in these patients.[119]

Due to this evidence gap and the fact that there is growing consensus that transfer patients with an externally diagnosed AIS should not undergo repetitive imaging in the treating hospital if their clinical presentation is stable[129], we decided in the planning for a trial proposal (see section 9.4.2) to focus on this so far underrepresented patient group. The observed effect-size in the meta-analysis for the mothership patients was the basis for sample size calculations and for the feasibility assessment.

9.4 Outlook and further perspectives

This PhD thesis can be seen as the foundation for further trials with the goal to optimize the Management and Triage of suspected AIS patients. During my work on this thesis, I started two main projects in parallel, which we will further pursue in the future. The first project the SPINNERS trial is designed to evaluate the diagnostic accuracy of FDCT imaging for the detection of intracranial hemorrhages and the second project the GET-FAST trial will be a randomized controlled trial evaluating the effect of a One Stop management approach on the clinical outcome of suspected AIS patients.

9.4.1 SPINNERS trial

One potential hurdle for the implementation of One Stop management approaches for the triage of suspected acute ischemic stroke patients is that diagnostic equivalence of FDCT imaging compared to MDCT imaging to differentiate between ischemic and hemorrhagic stroke was not established.[130, 131] A missed intracranial hemorrhage, i.e. an hemorrhagic stroke (which make up between 15 and 20% of all severely affected stroke patients according to our analysis of the Swiss Stroke Registry) could have potentially dramatical (and lethal) consequences due to different treatment strategies.[97] Although, we were able to show on the last generation of FDCT systems that the detection of an intracranial hemorrhage is possible with very high sensitivity and specificity, this was not sufficient to establish diagnostic equivalence.[36] This failure can be attributed mainly to the retrospective nature of the study, which is prone to bias but also to the patient population which was examined. In this study we mainly examined patients which have undergone an intervention. Therefore, it could be argued that the images of the FDCT and MDCT are not comparable as they were pre- and post-interventional. Furthermore, the patient group in this study was not identical with the patient group which would undergo imaging in real-life clinical cohorts (i.e., patients before an intervention with an unknown cause for the stroke).

To address this issue, we will launch a prospective trial evaluating the diagnostic accuracy of FDCT for the detection of an intracranial hemorrhage. This trial is called:

“ProSPective evaluation of the dIagnostic accuracy of siNe spiN non-contrast flat-dEtectoR CT (FDCT) for the detection of intracranial hemorrhage in Stroke patients - an open labelled, multicenter, non-inferiority comparison of flat detector CT (FDCT) to multi detector CT (MDCT) with blinded assessment of outcome events (SPINNERS Trial)”

We obtained funding from Siemens Healthineers GmbH (Erlangen, Germany) for the complete trial and will apply for ethical approval in Basel in March 2022. It is the goal to enroll 252 patients over the course of 24 months at up to 12 centers in Switzerland, Austria, and the USA. This trial has the potential to demonstrate the diagnostic equivalence of FDCT imaging for the detection of intracranial hemorrhages in suspected AIS patients.

9.4.2 GET-FAST trial

Although there is consensus that reducing time to treatment in AIS patients to the minimum should be a prime target in stroke therapy, there is no high-level evidence for the different in-hospital triage approaches.[26] The classical approach for the triage of suspected AIS patients is to transport the patient first to the CT room and after diagnosis of a treatable vessel occlusion to the angiography room for treatment. This triage approach leads even in highly specialized centers to door to groin times of at least 60 minutes.[27, 132] Due to patient transport and logistical circumstances no further time reductions can be realized with this approach. One possible approach to reduce time delays within the hospital is to transport patients directly from the emergency room to the angiography room for diagnosis of a vessel occlusion and subsequent treatment (One-Stop management). In this case imaging is made with FDCT in case of MDCT. We were already able to show in a large patient collective that this approach can lead to door to groin times of approx. 30 minutes [29]

One randomized controlled trial has evaluated a slightly different approach (a so called direct to angiography approach) and was able to show a possible effect on the clinical outcome.[93] However, the trial had important short comings, reducing the generalizability of the results to other settings: (1) They performed a modified intention to treat analysis, including only patients with a treatable large vessel occlusion (LVO). As it is impossible to know prior to brain imaging (and randomization) if a suspected AIS patient has his symptoms due to an LVO, hemorrhage or a small vessel occlusion (SVO; not treatable by EVT), it is in our opinion of pivotal importance to show, that this effect is not offset by possible harm to patients with hemorrhagic or SVO strokes (approx. 15% of the targeted population). (2) The trial was monocentric, (3) used a very specific pre-hospital alert system and (4) included a high number of transfer patients with externally diagnosed LVO. Also, a second cluster randomized trial, which was halted premature, was not able to show any effect on outcome.[92] Therefore, current guidelines and recommendations were not changed.[78, 133] As our systematic review and meta-analysis has shown a substantial reduction in door to groin times comparable to our publications on this topic but no clear effect on outcome, we think that proper designed randomized controlled trials should be a prime target of current and future research in the field of AIS treatments.[54]

We therefore applied with partners from Germany and Austria over the Weave funding instrument for the support of the Swiss National Science Funds to start the *One-Stop manaGemEnT For A Swift initiation of endovascular Therapy (GET-FAST)* trial. GET-FAST is a pragmatic, multicenter, randomized (ratio 1:1), open label, superior trial with blinded endpoint assessment (PROBE design). It aims to evaluate the effect of One-Stop management on the degree of disability and dependence in daily activities 90 days after a suspected AIS compared to standard triage pathways. This trial differs in important points from so far conducted trials and planned trials by other groups:

(1) A suspected, severe AIS can be caused in general by three distinct pathologies (a) a large or medium vessel occlusion, (b) a small vessel occlusion or (c) an intracranial hemorrhage. As we perform a diagnostic non-invasive FDCT angiography only patients with a treatable occlusion (medium or large) must undergo groin puncture and DSA. Patients with a small vessel occlusion or an intracranial hemorrhage (approx. 15% of the population in clinical routine) do not have to undergo groin puncture as a DSA is not beneficial for them but puts them at an excess risk for iatrogenic hemorrhage or stroke.[134, 135]

(2) We will perform a true intention to treat analysis including all patients randomized. This approach was chosen as One-Stop management must be beneficial for the whole patient population undergoing this triage approach and not only for a subset (patients with a treatable vessel occlusion). This is important since there is ongoing debate if One-Stop management might harm patients with a small vessel occlusion or an intracranial hemorrhage due to a lower quality of the non-contrast FDCT compared to multidetector CT.[136, 137]

(3) As there is growing consensus that transfer patients with an externally diagnosed LVO should not undergo repetitive imaging in the treating hospital if their clinical presentation is stable, the proposed GET-FAST trial will only include mothership patients.[129] Furthermore, mothership patients present routinely earlier to the hospital and in these patients swift reperfusion is of special interest since they more often include fast progressors (i.e., patients in which infarction is rapid due to missing collaterals).[138]

Overall, we think this topic is of great importance for the future care of suspected AIS patients and that our proposed One Stop management approach has not only the potential to reduce door to groin times but also lead to better patient outcomes. We firmly believe that this will the future way of stroke triage and hope to be able to contribute to this paradigm change in the future.

10. Contributions by the PhD Candidate

The projects from the first topic of the thesis (Dose measurements of FDCT protocols used in acute ischemic stroke) were designed by me in cooperation with my primary supervisor. I performed and/or supervised all measurements for the projects, did the analysis of the data and drafted the manuscripts. The manuscripts were revised by the co-authors and my primary supervisor.

The project from the second topic (Distribution of diagnoses, clinical and imaging characteristics in 1,322 consecutive suspected stroke patients) was designed by me in cooperation with my primary supervisor and Peter Sporns. I performed the data analysis alone and wrote the manuscript together with Peter Sporns.

The project from the third topic (Direct to angiography suite approaches for the triage of suspected acute stroke patients – a systematic review and meta-analysis) was planned and conducted by me. The literature search was done in cooperation with the University Library Basel and the data analysis with the Department of Clinical Research (University Hospital Basel). I drafted the manuscript and the revision. The manuscript was revised by the co-authors and my primary supervisor.

Besides my work in the aforementioned projects, during my PhD I wrote together with my primary supervisor an application to the Swiss National Funds for a large multicentric trial (EnDovascular therapy plus best medical treatment (BMT) versus BMT alone for MedIum VeSsel Occlusion sTroke - a prAgmatic, international, multicentre, randomized triaL (DISTAL)), which was ultimately approved by the Swiss National Funds in June 2021 (33IC30_198783). I am listed as a project partner. After securing funding for the trial, I wrote the protocol, and we were able to start the trial in December 2021 (clinicaltrials.gov identifier NCT05029414). I was able to obtain further funding from the Bangerter and Rhyner Stiftung for this trial. The trial will recruit in at least 6 countries in approx. 40-50 centers. I was and am involved in the regulatory process in all countries. We estimate the trial to be completed in 3 years.

Together with my primary supervisor I led the project to start a clinical trial for the *Prospective evaluation of the sensitivity and specify of non-contrast flat detected computer tomography (FDCT) for the detection of intracranial bleedings.* This project is of special interest regarding the theme of this PhD thesis as it is still a matter of debate if non-contrast FDCT can reliably detect intracranial hemorrhages in suspected acute ischemic stroke patients. The status of the project is that we secured a grant for the full financing of the project from Siemens Healthineers GmbH (Erlangen, Germany). I also wrote the clinical investigation plan, and we will apply for ethical approval in Basel in March 2022. We estimate to include the first patient in Basel at the latest in May 2022. The study will be conducted multicentric with up to 12 sites in Switzerland, Austria, and the USA. I will be the scientific lead in this trial.

The data gathered for the third topic was further used for an application to the SNF over the Weave instrument for the funding of a randomized-controlled trial. The goal of the trial is to evaluate a One Stop management approach for the triage of suspected acute ischemic stroke patients with the main endpoint independence and disability in daily activities 90 days after the stroke. Based on previous work from my primary supervisor I wrote the full application and coordinated the submission.

I am involved as a sub investigator in the ESCAPE-NEXT study, the SELECT-2 study and several registries (SURF, ASSIST, STAR, EVA-TRISP, TRISP).

Thanks to my wide involvement in the research activities of our Clinical Imaging and Stroke Analysis Group at the University Hospital of Basel, during my PhD I had the opportunity to contribute as first author or coauthor in several publications from our group and provided independent reviews for several papers in peer-reviewed Journals (BMC Neurology, Clinical Neuroradiology, PLOS One, Investigative Radiology, American Journal of Neuroradiology, Journal of Clinical Medicine, Journal of Neurointerventional Surgery, Brain Sciences, Frontiers in Neurology).

11. Conclusion

In conclusion the main findings of this PhD thesis, which addressed a wide array of challenging topics in the Optimization of the Management and Triage of stroke patients in the acute phase, are the following:

(1) Effective dose to patients of FDCT protocols used routinely for the diagnosis of an acute ischemic stroke due to a large-vessel occlusion are comparable to analogous MDCT protocols. Therefore, dose considerations should not play a role if confronted with triage decisions in suspected acute ischemic stroke patients. Colimitation should be used if possible as it can reduce the effective dose substantially.

(2) Depending on the severity the frequency of patients with an ischemic stroke is high with 73% (NIHSS 6 – 12) and 86.8%. (NIHSS ≥ 13) in real-life cohorts. This has important implications for the planning of EVT-resources but also for the planning of randomized controlled trials.

(3) One Stop management and direct to angiography approaches lead to significant reductions in door to groin and door to reperfusion times but the effect on outcome is unclear. Mothership patients were underrepresented in so far conducted trials, pointing to the need of dedicated randomized controlled trials for this patient collective.

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13. Curriculum Vitae

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Academic Career

08/2019 – 08/2022	PhD Program "Clinical Research" at the University Basel Title of Thesis: Optimization of the Management and Triage of stroke patients in the acute phase Primary Supervisor: Prof Marios-Nikos Psychogios Secondary Supervisor: Prof Stefan Engelter
21. December 2016	Dr. med. univ. (University of Vienna) Title of Thesis: Delineating the neural pathways of emotional control using event related potentials, Grade: 1.0 Supervisor: ao. Univ. Prof. Mag. Dr. Ulrike Willinger
2010 – 2016	Faculty of Medicine Medical University Vienna, Austria
2005 – 2009	Bachelor of Science Faculty of Engineering FH Wedel, Germany

Current Position

From 05/2021	Senior Scientific Expert, Department of Neuroradiology, University Hospital Basel
07/2019 – 05/2021	Research Coordinator of the Department of Neuroradiology, University Hospital Basel (Postdoc)
From 07/2019	Group Coordinator, workgroup "CSI Basel: Clinical Stroke and Imaging analysis lab", University Hospital Basel, Basel, Switzerland 55 peer-reviewed publications; 1446 citations; h-index 19
01/2018 – 06/2019	Research fellow in the Department of Neuroradiology, University Hospital Goettingen (50% clinical research, 50% clinical work)
02/2017 – 12/2017	Resident in the Department of Neurology, University Hospital Goettingen (100% clinical work)