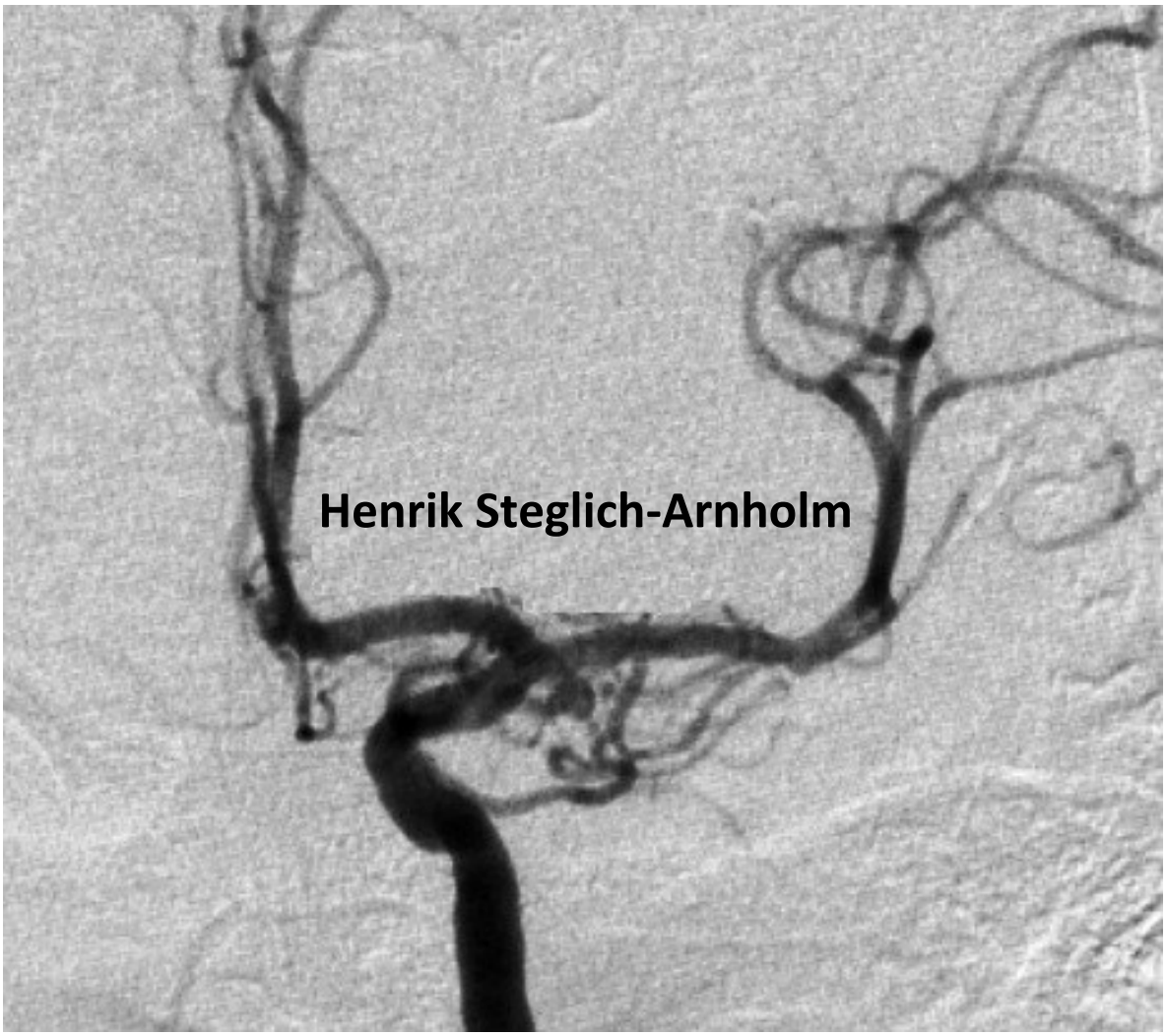
UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES

PhD Thesis

Propensity-Score Matched Clinical Radiographic Assessment and Systematic Review of Endovascular Therapy in the Management of Acute Anterior Circulation Ischemic Stroke – PREPARE



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This thesis has been submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen, November 30th 2016

Title: Propensity-Score Matched Clinical Radiographic Assessment and Systematic Review of Endovascular Therapy in the Management of Acute Anterior Circulation Ischemic Stroke – PREPARE

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Preface

The work in this PhD-thesis was carried out at the Department of Neurology, Rigshospitalet Blegdamsvej, Denmark and includes the following papers:

Paper 1: **Steglich-Arnholm H**, Holtmannspötter M, Kondziella D, Wagner A, Stavngaard T, Cronqvist ME, Hansen K, Højgaard J, Taudorf S, Krieger DW. *Thrombectomy assisted by carotid stenting in acute ischemic stroke management: benefits and harms.* Journal of Neurology. 2015. 262(12):2668–2675.

Paper 2: **Steglich-Arnholm H**, Holtmannspötter M, Kondziella D, Wagner A, Stavngaard T, Cronqvist ME, Hansen K, Højgaard J, Taudorf S, Krieger DW. *Rationale for extracranial carotid stenting in the acute ischemic stroke setting in patients with intracranial recanalization*. Currently in review.

Paper 3: **Steglich-Arnholm H**, Holtmannspötter M, Gluud C, Krieger DW. *Carotid artery stenting versus no stenting assisting thrombectomy for acute ischaemic stroke. A systematic review.* Draft manuscript.

Paper 4: **Steglich-Arnholm H**, Kondziella D, Wagner A, Cronqvist ME, Hansen K, Truelsen TC, Krarup LH, Højgaard J, Taudorf S, Iversen HK, Krieger DW, Holtmannspötter M. *Mechanical thrombectomy with the Embolus Retriever With Interlinked Cages in acute ischaemic stroke: ERIC, the new boy in the class.* Currently in review.

Other papers related to this work:

Steglich-Arnholm H, Krieger DW. *Carotid stent-assisted thrombectomy in acute ischemic stroke*. Future Cardiology. 2015. 11(5):615-632.

Steglich-Arnholm H, Holtmannspötter M, Gluud C, Krieger DW. *Carotid artery stenting versus no stenting assisting thrombectomy for acute ischaemic stroke. Protocol for a systematic review of randomised clinical trials with meta-analyses and Trial Sequential Analyses.* Systematic Reviews. DOI: 10.1186/s13643-016-0388-0.

Mørkenborg ML**, Steglich-Arnholm H**, Holtmannspötter M, Krieger DW. *Are current time delays in Endovascular treatment of stroke acceptable?* Journal of Neurological Disorders & Stroke. 2015. 3(2):1099.

Acknowledgements

First of all, I would like to thank Derk W. Krieger who was my principal supervisor for the first half of my PhD-programme. I really enjoyed our many very interesting discussions and he was always a great inspiration and mentor for me.

Secondly, I would like to thank my other two supervisors through my PhD-programme, Markus Holtmannspötter and Christian Gluud. Markus for teaching me the finer details of endovascular therapy and assessment of imaging that made me consider radiology as a specialty and Christian for teaching me never to confine with subpar evidence – no matter how abundant it may be!

Last but certainly not least, I would like to greatly thank my current principal supervisor Helle K. Iversen. She was my principal supervisor for the second half of my programme and played a major role in landing this thesis safely.

A grateful thanks goes to Johannes K. Jacobsen, Neurocentret and to the Department of Neurology for the opportunity to write this thesis, for financing, and for the help I have received through the past three years. Furthermore, I am grateful for the financial support from Lundbeckfonden for travel grants, from MicroVention for publication grants and from Boehringer Ingelheim.

A big thanks and an even bigger hug goes to everyone at NRU for embracing me in their cosy nest and research environment even though I still do not understand what half of you are working with.

Thank you to all my co-authors for careful critical revisions of my manuscripts.

A special thanks goes to Henrik Horwitz for revising my thesis and for your well thought comments.

And finally the biggest thanks go to my wife who has always been a huge support and somehow always able to cheer me up through the rough times.

Summary

Acute ischaemic stroke is a worldwide leading cause of death and disability. Through the last two years endovascular intracranial clot removal has proven effective for large vessel occlusion acute ischaemic stroke and is now the preferred treatment. However, several concerns still exist in acute stroke management. Two of these, carotid stenting in acute ischaemic stroke and performance of a novel thrombectomy device design, will be presented in this thesis.

Concerning the first problem, patients with concomitant extracranial carotid high-grade stenosis or occlusions and intracranial embolism present a special therapeutic conundrum since the carotid lesion constitutes an obstacle for intracranial access and may limit intracranial flow. Management of the carotid lesion during acute endovascular therapy is currently discussed because of the risk for procedural complications. This thesis assesses the outcomes and safety of carotid stenting in patients with concomitant extracranial carotid lesions and intracranial embolism. Both in patients that show intracranial recanalisation at the time of neurointervention and patients that required treatment with intracranial thrombectomy. Furthermore, the evidence for carotid stenting in this situation was evaluated through systematic review of the literature.

Concerning the second problem, thrombectomy device design has previously shown to be important for the efficacy of the device for clot removal. The classic stent-retriever design that was predominantly used in the recent randomised thrombectomy trials was originally invented for stabilisation of wide-necked aneurisms during coiling. Developments to this design have been suggested to improve performance for clot removal and this thesis investigates the performance of the Embolus Retriever with Interlinked Cages (ERIC) device by comparing with the performance of classic stent-retrievers.

Results presented in this thesis suggest that carotid stenting in acute ischaemic stroke performs reasonable compared to benchmarks from the recent randomised thrombectomy trials. Although clinical outcomes were good there may be an increased risk of symptomatic haemorrhagic complications. Currently, no randomised controlled trials on carotid stenting in acute stroke management exist. However, several observational studies suggest reasonable safety of this intervention for clinical trials to be performed. Furthermore, the results suggest that the novel design of the ERIC device performs at least equally compared to classic stent-retrievers and may even improve in certain procedural benchmarks.

Resume

Akut apopleksi er verden rundt en af de hyppigste årsager til handikap og død. Igennem de sidste to år har intrakraniel endovaskulær fjernelse af blodpropper vist sig effektiv i behandlingen af akut iskæmisk apopleksi og er nu den anbefalede behandling for denne sygdom. Der findes dog stadig flere ubesvarede spørgsmål for håndtering af akut apopleksi. To af disse problemstillinger, stenting af karotis-arterien i akut apopleksi og effektiviteten af et nyt device design til trombektomi, vil blive præsenteret i denne afhandling.

Vedrørende første problemstilling præsenterer patienter med kombinerede ekstrakranielle højgrads stenoser eller okklusioner og en intrakraniel embolus en særlig terapeutisk udfordring idet karotis læsionen udgør en forhindring for adgang til det intrakranielle kredsløb og kan hæmme forsyningen af blod intrakranielt. Behandling af karotis læsionen i det akutte forløb er omdiskuteret på grund af risikoen for procedure relaterede komplikationer. Denne afhandling undersøger resultaterne efter akut karotis stenting og sikkerheden af denne intervention. Både for patienter der viser intrakraniel rekanalisering på interventions tidspunktet og for patienter som kræver behandling med intrakraniel trombektomi. Herudover undersøges evidensen for karotis stenting for denne gruppe patienter i en systematisk litteraturgennemgang.

Vedrørende anden problemstilling har designet af trombektomi devicet tidligere vist sig at være vigtigt for effektiviteten af devicet til at fjerne blodpropper. Det klassiske design af stent-retrievere, som var det hyppigst brugte device design i de seneste randomiserede forsøg, blev oprindeligt udviklet til at stabilisere bred-basede aneurismer i forbindelse med coiling. Forbedringer til dette design er foreslået at kunne optimere dets ydeevne til fjernelse af blodpropper og denne afhandling undersøger ydeevnen af Embolus Retriever with Interlinked Cages (ERIC) devicet ved at sammenligne med ydeevnen af klassiske stent-retrievere.

Resultaterne, der præsenteres i denne afhandling tyder på, at karotis stenting i akut iskæmisk apopleksi yder rimeligt sammenlignet med standarden fra de seneste randomiserede trombektomi forsøg. Selv om de kliniske resultater i afhandlingen var gode kan der være en øget risiko for symptomatiske blødninger. Lige nu findes der ingen randomiserede forsøg på karotis stenting, men flere observationelle studier tyder på rimelige sikre procedurer som dermed baner vejen for fremtidige randomiserede forsøg. Yderligere tyder resultaterne på, at det nyskabende design af ERIC-devicet yder mindst lige så effektivt sammenlignet med klassiske stent-retrievere og endda kan være bedre på visse proceduremål.

Introduction

Acute ischaemic stroke is the second largest cause of death and the third largest cause of disability in Denmark and globally and the largest cause of acquired disability in adults[1,2]. It is estimated that 1.9 million neurons die every minute after stroke onset[3] and that the chance of successful treatment decreases with 3-8% for every 30 minutes delay to intracranial recanalisation[4,5]. Therefore, correct and timely treatment is paramount to restore cerebral perfusion and prevent permanent disability in acute ischaemic stroke patients.

Acute ischaemic stroke covers a very broad spectrum of 'disease'. Anatomically it varies from small vessel disease to large vascular occlusions and clinically it covers vague transient symptoms to devastating hemispheric deficits and even death. Although, some degree of cohesion between anatomy and clinical symptoms exist small occlusions may cause severe deficits and large occlusions may cause small deficits. Characterisation is therefore based on anatomical, pathophysiological, and clinical categories (Table 1).

TOAST Classification[6]	**Anatomical Classification**	**Clinical classification**
Large-artery atherosclerosis (embolus/thrombosis)	Anterior circulation stroke	Transitory ischaemic events (<24 hours)
Cardioembolism	Posterior circulation stroke	Minor stroke
Small-artery occlusion (lacunae)		Major stroke
Stroke of other causes		

Table 1 – Stroke classification

In general, large vessel occlusions cause more clinically severe strokes than small vessel occlusions and have a poor response to medical therapy thereby requiring more invasive treatment[7]. The anterior and posterior circulation supply very different parts of the brain and ischaemic stroke in these two territories are difficult to compare due to fundamental differences in clinical presentation, time-windows for treatment, and methods for therapy. Therefore, this thesis includes only large vessel occlusion acute ischaemic stroke in the anterior circulation.

Therapy for acute large vessel occlusion ischaemic stroke has evolved dramatically during the past four decades from relatively ineffective antithrombotic therapy over the more effective intravenous thrombolysis and now to effective intra-arterial mechanical clot removal. Since 2015, six randomised controlled trials[8–13] have shown overwhelming effect of mechanical thrombectomy (with or without medical therapy) of large vessel occlusions for acute ischaemic stroke compared to medical therapy alone.

However, several issues with regard to endovascular stroke therapy such as carotid stenting, choice of thrombectomy device, anaesthetic management, proximal or distal aspiration during intervention, etc. are still to be investigated[14]. This thesis will focus on two very important aspects of endovascular therapy for acute ischaemic stroke; carotid stenting in acute ischaemic stroke and the effect of thrombectomy device design on clot removal and clinical outcome.

Extracranial carotid lesions may impair blood flow to the intracranial arteries, may cause intracranial embolism, and may even constitute an obstacle for intracranial therapy - be it endovascular or medical therapy[15]. Carotid lesions in acute stroke can be managed with acute stenting with or without angioplasty, angioplasty alone, patent artery occlusion or medical therapy alone. Acute carotid stenting could improve cerebral perfusion, form access for intracranial intervention, and prevent recurrent embolism but is currently debated due to the risk of complications[16].

The design of the mechanical thrombectomy device has shown to play a major role in its efficacy for clot removal[17]. Currently, the most successful device is the so-called classic stent-retriever. This device has a tubular design and was the predominantly used device for mechanical thrombectomy devices in recent randomised controlled trials. However, recent developments to this design have been suggested to better procedural benchmarks and potentially result in improved clinical outcomes[18]. Thus the objectives of this thesis are:

Objectives

1. To evaluate the safety and efficacy of acute carotid stenting assisting mechanical thrombectomy in patients with concomitant extracranial carotid lesions and intracranial embolism.
2. To evaluate the safety and efficacy of acute stenting in patients initially presenting with concomitant extracranial carotid lesions and intracranial embolism that show signs of intracranial recanalisation at the time of neurointervention.
3. To evaluate the evidence for acute carotid stenting compared to no stenting assisting intracranial mechanical thrombectomy in patients with extracranial carotid lesions and intracranial embolism.
4. To evaluate the efficacy and safety of a novel thrombectomy device (Embolus Retriever with Interlinked Cages, ERIC) by comparing procedural and clinical benchmarks and adverse events to other thrombectomy devices.

Background

Anterior circulation vascular anatomy

The anterior cerebral circulation originates from the common carotid arteries that arise from the aortic arch on the left side and the brachiocephalic artery on the right side. The common carotid arteries continue upwards (rostral) and at the middle of the neck they bifurcate into the external carotid arteries (ECA) and the internal carotid arteries (ICA). The ECAs branch extracranially and supply the face and external cranium. The role of the ECAs in acute ischaemic stroke is to supply collateral blood flow to the intracranial vasculature retrograde through the ophthalmic arteries in case of a proximal ICA occlusion[19]. The ICAs do not branch extracranially but continue through the carotid canal.

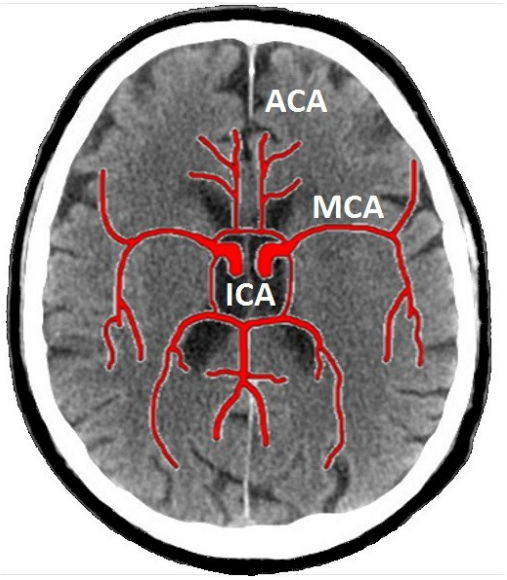

Figure 1 – Circle of Willis. ACA – Anterior cerebral artery. MCA – Middle cerebral artery. ICA – Internal carotid artery

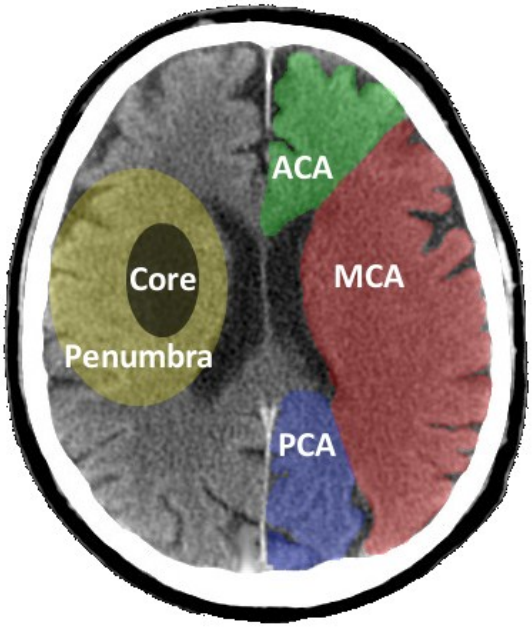

Figure 2 – Vascular distribution. ACA – Anterior cerebral artery. MCA – Middle cerebral artery. PCA – Posterior cerebral artery.

At the skull base, they branch into the anterior cerebral arteries (ACA) and middle cerebral arteries (MCA) (Figure 1). The ACAs continue frontal and upwards to supply the medial part of the frontal two thirds of the hemisphere (Figure 2, green) The MCAs continue lateral and up- and downwards to supply the lateral parts of the frontal two thirds of the hemisphere (Figure 2, red). The posterior third of the hemisphere is supplied from the posterior circulation (Figure 2, blue). This distribution of vascular blood supply results in low-flow / border zone areas in between vascular areas that are especially fragile for low flow situations such as in ipsilateral carotid stenosis or occlusions.

The vasculature of the anterior circulation is further categorised from the ICA and up into: extracranial ICA, petrous ICA (carotid canal) and distal ICA (bifurcation, ICA-T), ACA-A1-3 after each bifurcation of ACA and MCA-M1-5 after each bifurcation of MCA (Figure 1). This nomenclature is important for describing the exact anatomic location of blood clots or arterial lesions.

Extracranial carotid lesions

The extracranial carotid lesion is either caused by atherosclerosis or arterial dissection. Several differences apply to the pathophysiology of these two types of lesions. The atherosclerotic lesion is characterised by severe calcifications that have developed over years. Therefore it is also predominantly seen in elderly patients. The atherosclerotic lesion is often located at the ICA origin immediately after the CCA bifurcation and is a short/abrupt occlusion or high-grade stenosis that is rigid and may be difficult to cross with endovascular catheters. On the contrary carotid arterial dissections have often developed from a recent intimal tear that may occur spontaneously, related to trauma, or on the basis of arterial disease such as connective tissue disorders, vasculitis or fibromuscular dysplasia. Usually some sort of mechanical manipulation of the artery (such as blunt neck trauma or chiropractic manipulation) has occurred few weeks prior to the dissection[20] thereby creating a wall haematoma and a false lumen[21,22]. Carotid artery dissections often comprise a longer section of the artery that may be easier to penetrate compared to atherosclerotic lesions. Arterial dissection more often occur in younger patients and usually originate from the skull base[22]. Extracranial carotid lesions can be silent but may cause acute ischaemic stroke through various different pathophysiology. The lesion can be haemodynamically compromising in case of an insufficient circle of Willis (border zone infarct) or it can cause thromboembolism from an ulcerated atherosclerotic plaque or the intimal tear (embolic infarct)[23,24].This thesis will only focus on the thromboembolic mechanism.

Collateral blood supply

When one of the major arteries is blocked, the tissue downstream is in risk of ischaemic damage if sufficient supply of oxygen is no longer provided. One feature that can prevent or postpone damaging ischaemia is blood supply via collateral pathways around the occlusion. The anterior and the posterior circulation are connected in the circle of Willis by one anterior communicating artery between the two ACA arteries and two posterior communicating arteries between ICA and the posterior cerebral arteries (Figure 1). This circle of vessels ensures that collateral blood supply is able to reduce or prevent ischaemic damage when one supplying artery is occluded. In addition to provide alternate routes for blood flow, the circle of Willis may also be used as an alternate endovascular access to an intracranial clot if the supplying artery is occluded[25,26]. Individual variations in vascular anatomy may impair the normal functioning of the circle of

Willis, thereby increasing the vulnerability of the cerebral blood flow in case of a blocked supplying artery. In arterial vessel occlusions distal to the circle of Willis (MCA-M1-2 or ACA-A1-2) retrograde flow through leptomeningeal collateral blood vessels can to some extend prevent or prolong the time to ischaemic damage of the brain tissue at risk[27].

The ischaemic penumbra

When a large clot occludes an artery the perfusion of the tissue supplied by that artery drops and the tissue gets ischaemic and starts degenerating. When the brain tissue is subjected to less oxygen than is required for normal function the neurons starts swelling, which means further worsening of the perfusion and diffusion in the tissue. The tissue furthest away from the occlusion and surrounding collateral vessels suffer the most and is fasted pushed into irreversible cell damage and apoptosis. This area of irreversible damaged neuronal tissue is called the ischaemic core. Surrounding the ischaemic core is an area of reversibly damaged neuronal tissue called the ischaemic penumbra (Figure 2). As time goes on until revascularisation, the neurons in the ischaemic penumbra gives in to apoptosis and the ischaemic core with irreversible tissue damage increases. The time that brain tissue can withstand ischaemia depends on the perfusion of the tissue. The normal perfusion of brain tissue is 50-60 ml/100g (Figure 3). With cerebral blood flow (CBF) between 20 ml/100g and 50 ml/100g most neurons function normally. As CBF decreases below 20 ml/100g neurons stop functioning but can survive for hours (the ischaemic penumbra) and below CBF <10ml/100g the neurons die within minutes (the ischaemic core)[28]. Since tissue perfusion diminishes with the distance from the nearest vascularised vessel, collateral blood supply play a paramount role in preventing development of large irreversible ischaemic core.

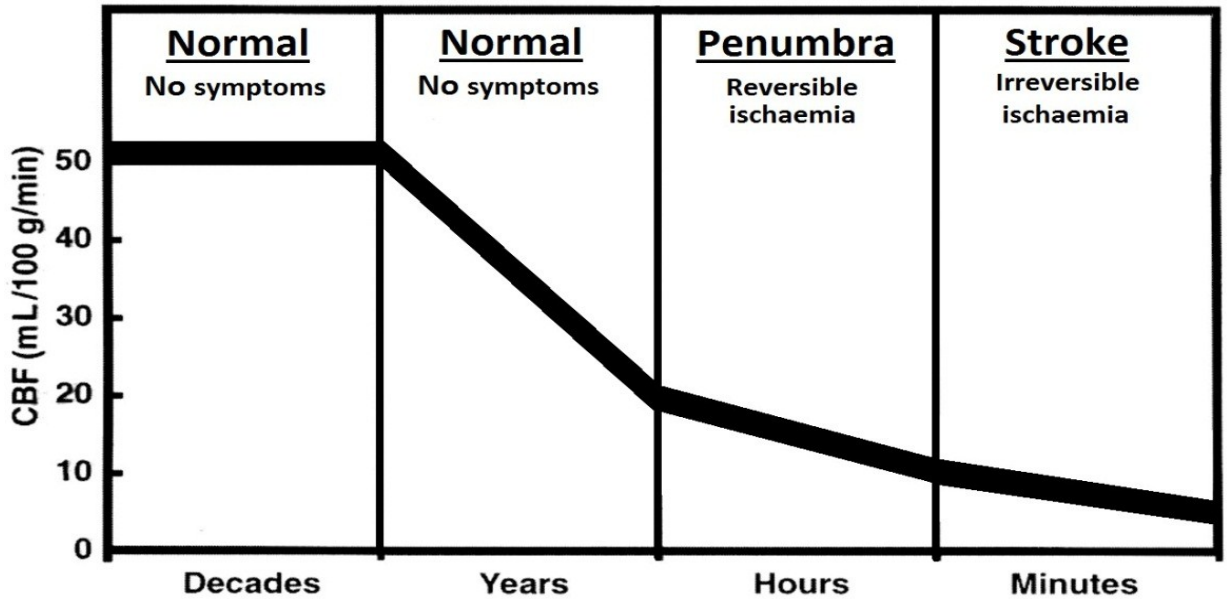

Figure 3 – Brain tissue perfusion and time to ischaemia. CBF – Cerebral blood flow.

Acute stroke diagnostics

When neurons stop functioning it shows as neurological deficits of the affected person such as paresis or numbness of an arm or leg, or the entire side of the body, or impaired ability to understand speech or verbal expression. A clinical scale has been designed to describe the deficits and the magnitude of these and thereby assess the severity of the stroke. This scale is called the National Institute of Health Stroke Scale (NIHSS) and ranges from 0 (no deficits) to 42 (complete coma)[29] and a score above 10 is usually considered a moderate to severe stroke indicating a large vessel occlusion.

The clinical symptoms are, however, not sufficient to diagnose a large vessel occlusion. The symptoms may be caused by a haemorrhage instead of an occlusion and a small lesion can cause severe symptoms if it is located in white matter/corticospinal nerve pathways[30]. Therefore acute neuroimaging is required in order to being able to make the correct diagnosis and plan the best therapy. The neuroimaging must be able to assess both the brain tissue as well as the vasculature. Brain tissue must be assessed for identifying already manifested infarct core that is beyond salvage and differential diagnostics (such as haemorrhage, tumour, abscesses, etc.). Vascular diagnostics must be able to identify any occlusions or stenosis that may be causing the acute stroke symptoms. In addition to these core assessments some may choose to assess the ischaemic penumbra with perfusion imaging or the blood flow with sonography. Perfusion imaging may be especially useful to assess sizes of both ischaemic penumbra and core and thereby the amount of potentially salvageable tissue in patients with delayed referral or unknown onset of symptoms. Currently these assessments are available through either computer tomography (CT) angiography (CTA), Magnetic Resonance Imaging (MRI) alone or in combination. Both modalities have advantages and disadvantages and the choice is made by availability, speed, contraindications and individual preferences. Sonography is less used in acute stroke diagnostics because it is very dependent on operator experience and is not able to assess viable brain tissue, however, because of its dynamic nature it can provide additional information to the other imaging modalities[31]. Sonography may be useful to assess whether a tight narrowing of a vessel is completely occluded or still show limited flow and to detect reversed flow in collateral vessels distal to the occlusion.

Acute stroke therapy – evolution of recanalisation

It has long been known that reversibility of acute ischaemic stroke symptoms is highly dependent on the time to recanalisation, and that treatment within hours after onset is paramount for the treatments to be effective[32,33]. For long, it remained a challenge to perform complete diagnostics within this short duration. Not until the 1990s where CT was routinely available in many stroke centres to exclude intracranial haemorrhages the NINDS trial was able to prove significant improved outcomes and reduced mortality with

intravenous thrombolysis within 3 hours of stroke onset[34]. A Cochrane review from 2014 of 27 trials involving 10,187 participants concluded that intravenous recombinant tissue plasminogen activator (iv-rtPA) given within six hours reduced the risk of death and disability (mRS≥3) at three to six months after stroke, and further showed that patients who had treatment initiated within the first three hours from symptom onset had the best prognosis[35]. Concurrent to the development of intravenous thrombolysis research was performed on intra-arterial thrombolysis with a special ambition for treating large clots. Although it had been possible to visualise intra-arterial occlusions using angiography since the 1930s it was not until the 1980s that intra-arterial thrombolysis was attempted[36], and not until 1998, with publication of the PROACT study, that catheter based thrombolysis was first demonstrated efficacious for recanalisation[37]. Since then development of mechanical approaches for clot removal have been investigated in order to improve rates of recanalisation without increasing rates of complications. Various designs have been attempted with various degrees of success. Introduction of the latest design of thrombectomy devices (the stent-retriever, Figure 4, A) has shown superior rates of recanalisation compared to older devices and therefore represents the standard design of thrombectomy devices today[38,39].

Randomised clinical trials comparing endovascular therapy as an adjuvant to medical therapy alone were first published in 2013 where three trials failed to show improved clinical outcome[40–42]. These trials had several methodological flaws and only had limited utilisation of stent-retrievers. In 2015 five randomised clinical trials showed superior recanalisation and clinical outcome with mechanical thrombectomy for acute ischaemic stroke[8–12], and an additional randomised controlled trial from 2016 confirmed these results[13]. Therefore, mechanical thrombectomy is now considered to be the gold standard therapy for acute ischaemic stroke caused by a large vessel occlusion. Iv-rtPA is still the recommended first-line therapy within 4.5 hours of symptom onset, but trials are being designed to test whether iv-rtPA is still necessary in patients with large vessel occlusions if EVT is available.

Endovascular procedural considerations

Arterial access is usually obtained by puncture of a femoral artery. However, axillary, radial and carotid access is also possible if femoral access cannot be gained. After puncture of the femoral artery an introducer sheath is usually introduced as a ‘gateway’ for further catheters. Through this access a long-bore sheath with a micro-guidewire is introduced into the cervical arteries. Because the patient prior to intervention has undergone diagnostic imaging the interventionalist has pre-procedural knowledge of the anatomy of each individual patient and can use this information to choose the appropriate catheters needed to gain access to the intracranial circulation. The interventionalist may choose to go directly to the culprit vasculature seen on the pre-procedural images or choose to perform diagnostic injections in the

collateral vasculature. The rationales for performing collateral injections are to visualise any potential thrombus dislodged during introduction of the endovascular catheters, to properly assess the collateralisation of the infarcted tissue, and to assess possibility for alternative routes to the culprit lesion via the circle of Willis. The rationale for going directly to the culprit lesion is to save crucial time and brain cells. If contralateral injections are not performed prior to thrombectomy diagnostic angiography is usually performed after intervention.

When access to the culprit intracranial lesion has been achieved the clot needs to be treated. The clot is passed with a micro-guidewire followed by a micro-catheter. Injections are made through the micro-catheter to ensure that the entirety of the clot has been passed. A mechanical clot-removal device is released distally to and through the clot ensuring that as much of the clot as possible is covered by the device. After a short period, which allows for interaction between the clot and the device, the clot-retrieval device with the clot attached is retracted into the catheter and removed. During the retraction of the clot-retriever, aspiration is usually performed. Either proximally from the carotid artery or distally from a distal access catheter placed just proximally to the clot. This process is repeated until satisfactory recanalisation is achieved. The quality of recanalsation is usually assessed according to the Thrombolysis in Cerebral Infarction scale (TICI)[43]. TICI is a five points scale from 0 (zero perfusion) to 3 (full perfusion) that evaluates recanalisation according to the initial occlusion (Table 2). Usually a result of TICI 2b or above is considered acceptable.

Grade 0	No anterograde flow beyond the point of occlusion.
Grade 1	The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run.
Grade 2a	Only partial filling (<2/3) of the entire vascular territory is visualised.
Grade 2b	Complete filling of all of the expected vascular territory is visualised, but the filling is slower than normal.
Grade 3	Anterograde flow into the bed distal to the obstruction occurs as promptly as into the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.

Table 2 - Thrombolysis in Cerebral Infarction (TICI) perfusion cathegories[43].

The stent-retriever

The stent-retriever that revolutionised endovascular stroke treatment was originally designed to be a fully retrievable re-sheathable stent to insert for providing stabilisation of the neck of wide necked aneurisms during coil treatment[44]. It was discovered that the stent was capable of interacting with clot material and capturing it in the stents meshed network. Furthermore, the tubular design of the stent meant that temporary reperfusion may already occur at deployment of the stent in the vessel. However, some

disadvantages of the classic stent-retriever design have been proposed. The tubular design means that the clot rests on the surface of the device and may be unprotected during retraction. The clot may then shear off during retraction and risk distal embolism/clot migration. Furthermore, the device rely on good interaction with the clot to capture it in the stent-retrievers meshed network which may be an issue with white, platelet rich clots[45]. Finally the stent-retriever has a large area in contact with the endothelium of the vessel wall when deployed risking causing intimal tears or induced vasospasm during retraction.

Various devices have been developed from the stent-retriever design. One of these suggestions is the Embolus Retriever with Interlinked Cages (ERIC, MicroVention). The ERIC® device consists as the name suggest of interlinked cages (Figure 4, B) and was designed specifically for clot removal. The design means that the device is able to fit into smaller delivery systems and reach more distal clots and that the clot is captured inside or in between the cages and may therefore be better protected during retraction of the device[18]. Furthermore, this feature is suggested to rely less on interaction with the clot making the thrombectomy a little faster and perhaps better in white, platelet rich clots. Finally the ERIC® device is suggested to be less in contact with the endothelium of the vessel wall during retraction. The disadvantage of this design is that no temporary perfusion immediately after deployment is expected.

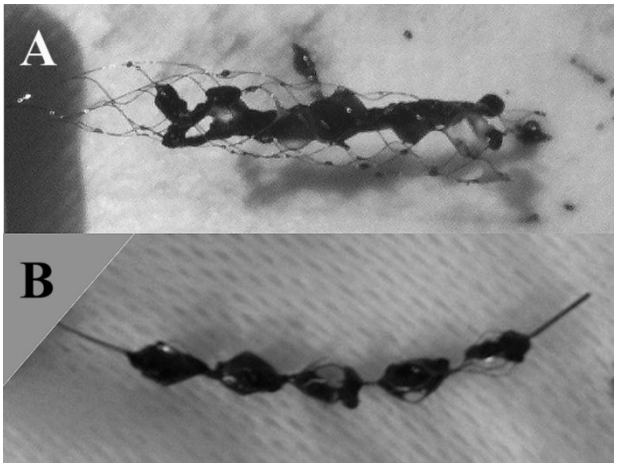

Figure 4 – Stent-retrievers.
A) Classic stent-retriever. B) ERIC stent-retriever

Methods

Setup for acute stroke management at the study institution (Paper 1,2,4)

The 5.5 million residents in Denmark are distributed between three comprehensive stroke centres each offering EVT to a geographically large area. In the eastern Denmark (2.5 million residents) acute ischaemic stroke therapy is organised in a 'hub-and-spokes' setting (Figure 5). Patients suspected to suffer from acute ischaemic stroke are referred to one of three primary stroke centres (the spokes). Here they are assessed clinically according to the NIHSS and with neuroimaging (CT or MRI) to confirm the acute ischaemic stroke suspicion. Some primary stroke centres routinely assess the size of the ischaemic penumbra with perfusion imaging while other asses for tissue early infarct signs in less/more than 1/3 of the MCA territory. Eligible

patients are treated with iv-rtPA and patients with large vessel occlusions are referred to the comprehensive stroke centre at Rigshospitalet in Copenhagen (the hub).

Figure 5 – Hub-and-spoke referral. PSC – Primary stroke centre. CSC – Comprehensive stroke centre. HT – Helicopter terminal

At Rigshospitalet seven stroke neurologists and five interventional neuroradiologists cover a 24/7 interventional stroke-team service with 30 minutes call-response. The stroke team is pre-noticed from the primary stroke-centres and the strategy and device choice for the procedure is prepared during patient transportation from information gathered from the patient history and neuroimaging acquired at the primary stroke-centre. This allows for direct referral to the angio-suite at Rigshospitalet to avoid unnecessary delays. At Rigshospitalet the patient is reassessed for stroke severity according to the NIHSS. In case of major changes in clinical appearance or delayed referral repeat neuroimaging may be considered before groin puncture to assess recanalisation in case of improvements or haemorrhagic complications/manifested large infarct in case of clinical deterioration or delay.

Furthermore, the comprehensive stroke centre in Copenhagen offers EVT to selected patients from near-by Swedish stroke centres and the isle of Bornholm and in rare occasions from the other two comprehensive stroke centres in Denmark or patients presenting with in-hospital stroke at Rigshospitalet.

Study population (Paper 1,2,4)

The catchment area of the comprehensive stroke-centre at Rigshospitalet comprises 2.5 million residents and on average treats 180 patients with EVT each year whereof approximately 135 patients have anterior circulation ischaemic stroke. Prospectively managed online patient charts were retrospectively reviewed and a database was built containing clinical and procedural information. Neuroimaging was reassessed on a PACS work-station and procedural details were recorded from the procedural descriptions.

Paper 1 study population:

The aim of this study was to evaluate the safety and efficacy of acute stenting assisting mechanical thrombectomy in patients with concomitant extracranial carotid lesions and intracranial embolism. For this study, all patients treated with EVT at Rigshospitalet were reviewed. Patients were treated from September

2011 through December 2014. Forty-seven patients presenting with extracranial carotid occlusions or high-grade stenosis and concomitant intracranial occlusions treated with extracranial stenting assisting intracranial thrombectomy were included.

Paper 2 study population:

The aim of this study was to evaluate the safety and efficacy of acute stenting in patients initially presenting with concomitant extracranial carotid lesions and intracranial embolism that show intracranial recanalisation at the time of neurointervention. For this study, all patients treated with EVT at Rigshospitalet were reviewed. Patients were treated from September 2011 through December 2015. Nineteen patients initially presenting with extracranial carotid occlusion or high-grade stenosis and concomitant intracranial occlusions but intracranial recanalisation at the time of EVT were included.

Paper 4 study population:

The aim of this study was to evaluate the efficacy and safety of the novel stent-retriever, ERIC, by comparing procedural and clinical outcomes and adverse events with classic stent-retrievers used at Rigshospitalet. The ERIC device has been available at Rigshospitalet since July 2013. For this study, only patients treated from January 2012 through December 2015 were reviewed. This period was chosen because a high and consistent number of patients have been treated through this period allowing for better comparison between patients treated with the ERIC® device since July 2013 and patients treated with classic stent-retrievers since 2012.

Standard procedural details

Right femoral access was usually achieved by co- or tri-axial access through a long-bore sheath (e.g. Destination 6F (Terumo, Leuven, Belgium), Neuron Max 6F (Penumbra Inc., Alameda, CA, USA), or Arrow 8-9F (Teleflex Medical Europe, Athlone, Ireland)) that was placed in the ipsilateral carotid artery. To guide the sheath or the long-bore catheter from the aortic arch into the carotid arteries a long standard guidecatheter with JB1 or SIM2 configuration (Cook Medical, Bloomington, IN, USA) was used. From the proximal ICA or distal CCA a distal access catheter (e.g. SOFIA (MicroVention, Tustin, CA, USA), Navien (Medtronic, Minneapolis, MN, USA), Fargo or Fargomax (BALT Extrusion, Montmorency, France), or 5MAX ACE or ACE 64 (Penumbra Inc)) was advanced usually in a tri-axial fashion via a microcatheter to avoid unnecessary vascular stress into the intracranial vasculature. If necessary, an additional proximal balloonguide catheter (e.g. Cello (Medtronic)) was placed through a large bore sheath (8 or 9Fr), before the distal access catheter was advanced through it. In case of an extracranial carotid lesion, the lesion was passed with a micro-guide wire and pre-dilated if necessary before one or several self-expandable carotid

stents were placed (e.g., Wallstent (Boston Scientific, Natick, MA, USA); LEO+ (BALT Extrusion); CASPER (MicroVention)). Stents were balloon-dilated when needed to ensure adequate width, wall-apposition, and flow. Carotid stenting was performed before or after thrombectomy at the interventionalist's discretion. In patients that did not receive pre-procedural antiplatelet therapy an intravenous loading dose of 500mg aspirin and/or a weight-adjusted half or full loading dose of GPIIb/IIIa inhibitor (eptifibatid (0.09-0.18 mg/kg) or abciximab (0.125-0.25 mg/kg)) was administered prior to stent deployment at the interventionalists discretion.

A micro-catheter (e.g. Prowler Select Plus (Codman Neuro, Raynham, NA, USA) or Headway 17-21 (MicroVention)) following a guide-wire (e.g. Traxcess 0.014" (MicroVention) or Transcend Platinum 0.014" (Stryker Neurovascular, Fremont, CA, USA)) was navigated through the clot after clot-location had been confirmed as initially seen on pre-procedural neuroimaging. Thrombectomy was performed using stent-retrievers and repeated as needed (e.g., Solitaire FR (Covidien/ev3, Irvine, CA, USA); ERIC (MicroVention); pREset (Phenox, Bochum, Germany). Thrombectomy was performed in combination with distal or proximal aspiration, or a combination of both, and choice of thrombectomy devices was left to the discretion of the neuro-interventionalist. Femoral haemostasis was ensured with vascular closure systems or manual compression.

The procedures were performed in general anaesthesia or conscious sedation. Conscious sedation was preferred when the patient was compliant and general anaesthesia was used in agitated patients and those who could not follow instructions during the procedure. A dedicated team of neuro-anaesthesiologists was available for all neuro-interventions.

Post-procedural management

Following acute EVT patients require tight monitoring. Those patients who had their procedures in general anaesthesia were mainly waked and extubated on the table before transferring to the neuro-intensive care unit. However, in especially clinically or procedurally severe cases or patients with prior endotracheal aspiration it may have been chosen to wake the patient at a later time-point. All patients were monitored for signs of clinical worsening with increase in stroke severity, decrease of consciousness, or uncontrollable high blood-pressure indicating haemorrhagic transformation of the infarct, renewed intracranial occlusion or malignant oedema of the infarcted tissue. In patients with carotid stenting the mean blood pressure was tightly controlled (70-100 mmHg) to prevent development of the cerebral hyperperfusion syndrome[46].

All patients were followed with a 24 hour CT scan to detect intracranial haemorrhagic complications or large infarcts in high risk of malignant development. Symptomatic intracranial haemorrhages were defined

as any intracranial haemorrhage causing a ≥4 increase in NIHSS[47]. After haemorrhagic complications had been excluded on follow-up imaging the patients were loaded with aspirin and continued for five days if it had not been administered during the procedure followed by life-long clopidogrel therapy. Patients that had a stent implanted received dual-antiplatelet therapy adjusted according to point-of-care platelet function testing (Multiplate analyzer, Roche, Switzerland) targeting more than 50% of ASPI- and ADP-receptor inhibition for at least 3 months. Patients with insufficient ADP-receptor inhibition were switched from clopidogrel to prasugrel antiplatelet therapy.

Discharge and follow-up

Patients were discharged to further specialised care and rehabilitation. At three months patients were invited to a clinical follow-up where their functional outcome was assessed according to the modified Rankin Scale (mRS, Table 3). A favourable outcome was defined as mRS 0-2. Patients with stents implanted had a follow-up CTA before their clinical exam to check for stent patency. Some patients were followed with duplex sonography for longer periods.

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

Table 3 - The modified Rankin Scale (mRS)[48]

Statistics

SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used to perform analyses with statistical significance set at $P < 0.05$.

Continuous variables were presented as means with range and standard deviation (SD) or medians with interquartile range (IQR) and compared with Students T-tests presenting difference in means and 95% confidence intervals (CI). Categorical variables were presented as numbers with percentages and compared by Fisher's exact test or χ^2 where appropriate with odds ratios (OR) and 95% CI.

To compare the two groups in Paper 4, a propensity score matching model was used. The propensity score is the conditional probability of assignment to a particular treatment given a vector of observed covariates. Patients were matched for the following observed covariates; stroke severity, interventionalist performing

the procedure, clot location, level of sedation during the procedure, and time-delay from neuroimaging to groin puncture in a 1:1 ratio[49]. Matched pairs were found using the 'Nearest available Mahalanobis metric matching within callipers defined by the propensity score' method[50].

Several sensitivity analyses were planned. Due to a skew in patient inclusion, subgroups of patients treated within the same time-period (July 2013 – December 2015) were compared. Furthermore, multivariate logistic regression analyses were used to find covariates associated with outcome and confirm the results from the propensity score matched analyses.

Literature review (Paper 3)

The systematic literature review was performed to assess the evidence for extracranial carotid stenting assisting intracranial thrombectomy in patients with concomitant extracranial carotid occlusions or high-grade stenosis and intracranial embolism. Thus, the intervention group consisted of patients with acute ischaemic stroke treated within 6 hours by intracranial thrombectomy and extracranial carotid stenting and the control group consisted of patients with extracranial carotid lesions and intracranial embolism treated with thrombectomy but with carotid lesions treated with angioplasty, patent artery occlusion, or no intervention.

The systematic review included randomised controlled trials for assessing benefits and harms of the intervention and quasi-randomised trials and observational studies for harms of the intervention.

The primary outcomes investigated were; all-cause mortality, dependent clinical outcome (mRS$\geq$3) and serious adverse events defined as any untoward event that was life-threatening, resulted in death or persistent or significant disability, or any other event that may have jeopardised the participant or required intervention to prevent it.

Secondary outcomes were; quality of life and non-serious adverse events.

Exploratory outcomes were; haemorrhagic complications, periprocedural adverse events, and recurrent ipsilateral ischaemic stroke during follow-up.

Electronic searches

The searches included the following electronic databases:

Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and Science Citation Index Expanded. An example of the search string can be found in Table 4.

1. exp Stents/
2. ((carotid and stent*) or CAS).mp.
3. exp Thrombectomy/
4. (thrombectom* or thrombolys*).mp
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. exp Brain Ischemia/
9. exp Carotid Stenosis/
10. (stroke or isch*emi* or (carotid and (occlusion or near-occlusion or stenos* or obstruct*)) or apople*).mp.
11. 8 or 9 or 10
12. 7 and 11

Table 4 - Example of search string (MEDLINE).

To identify further published, unpublished or planned or on-going trials regional databases, local food and drug administrations, homepages of companies producing stents, and reference lists of relevant trials were screened, and authors, colleagues, researchers active in the field, and manufactures of relevant interventional equipment were contacted.

No language restrictions were applied to the searches.

Two review authors (HSA & DWK) independently screened titles and abstracts identified by the searches, and two review authors (HSA & MH) independently extracted data from eligible studies onto pre-planned extraction forms. Disagreements were resolved by discussion among all authors.

Confidence intervals of proportions were calculated using the Clopper-Pearson exact confidence intervals.

Please see the full published protocol for further details[51].

Summary of main results

Paper 1

The aim of this paper was to evaluate the efficacy and safety of extracranial carotid stenting assisting intracranial thrombectomy for patients with extracranial carotid lesions and intracranial embolism.

The main findings of this paper were favourable clinical outcome in 32 (68%) patients despite a median pre-procedural NIHSS of 16. A total of 22 (47%) patients experienced early improvement all of which also experienced favourable three-month outcome. Favourable clinical outcome was associated with younger

age (9.7 years 95%CI (1.2-16.2, P=0.024)), lower NIHSS (3 points 95% CI (1-6), P=0.0037) and shorter procedural duration (37.2 minutes 95% CI (10.0-64.4, P=0.0085)). Extracranial carotid stenting performed before thrombectomy did not increase the time-delay from groin puncture to intracranial recanalisation compared with stenting performed after thrombectomy (18.2 min 95% CI (-9.9-46.3 min, P=0.20)).

The study also identified symptomatic intracranial haemorrhages in two patients (4%), and per-procedural acute stent-thrombosis in eight patients (17%), seven of which were successfully managed with local administration of GPIIb/IIIa inhibitor. In the last patient recanalisation was not attempted due to excellent collateral blood supply. Four (9%) patients died in-hospital. Thirty-nine (91%) patients had patent stents at follow-up while four (9%) stents had re-occluded, all of which had also experienced acute stent thrombosis during intervention.

Paper 2

The aim of this paper was to evaluate the efficacy and safety of carotid stenting in patients with initial extracranial carotid lesions and intracranial embolism but intracranial recanalisation at the time of intervention.

The main findings of this paper were favourable clinical outcome in 13 (68%) patients despite a median pre-procedural NIHSS of 11. Three (16%) patients died; one (5%) from in-stent thrombosis and two (11%) from symptomatic haemorrhages. In total, three (16%) patients had symptomatic intracranial haemorrhage. Thirteen (87%) patients had patent stents at follow-up and two (13%) patients had no radiological follow-up but were clinical stable. During long-term clinical follow-up (median 20 months, range 6-48 months) one patient died of cancer, one patient had a minor transitory ischaemic attack 29 months after stenting and the remaining 13 patients had no recurrent ischaemic events.

Paper 3

The aim of this paper was to evaluate the evidence for extracranial carotid stenting assisting intracranial thrombectomy in patients with concomitant extracranial carotid lesions and intracranial embolism.

The electronic searches identified 1464 references after duplicates were removed. Hand searching identified further 11 references. Thus, 1475 records were screened, and 1302 records were excluded after screening titles and abstracts. This left 173 records for full-text screening whereof 162 were excluded after full-text review. The authors of 16 studies were contacted in order to obtain missing data and two replied allowing their studies to be included. No randomised controlled trials were identified and 11 cohort studies were included for analysis. These studies reported 391 stented patients with follow-up and only two studies reported unexposed groups of 61 non-stented patients with follow-up. All studies were assessed

with serious risk of bias for all outcomes. The overall results are seen in Table 5. In the group of stented patients we were able to perform a subgroup analysis of patients treated with and without intravenous antiplatelet therapy. This analysis suggested fewer symptomatic intracranial haemorrhages in the group of patients not treated with intravenous antiplatelet therapy (4% [CI 0.8-11.2] vs. 9% [CI 5.4-12.7]).

	All-cause mortality	**mRS≥3**	**Serious adverse events**	**Non-serious adverse events**	**Symptomatic ICH**	**Periprocedural embolus into new territory**
Stented patients	66/391 – 17% [13.3-21.0]	207/391 – 53% [47.9-58.0]	35/222 – 16% [11.2-21.2]	7/222 – 3% [1.3-6.4]	30/355 – 8% [5.7-11.8]	13/206 – 6% [3.4-10.6]
Non-stented patients	9/61 – 15% [7.0-26.2]	35/61 – 57% [44.1-70.0]	4/63 – 6% [1.8-15.5]	2/63 – 3% [0.4-11.0]	4/30 – 13% [3.8-30.7]	2/63 – 3% [0.4-11.0]
Harms reported in stented patients	Symptomatic ICH 30/355 – 8%	Embolism during intervention 15/222 – 7%	In-stent thrombosis 11/223 – 5%	Dissection/ perforation of vessel 12/223 – 5%	Haemodynamic compromise during intervention 5/222 – 2%	All-cause mortality caused by ICH 22/66 – 33%

Table 5 - Overall results, Paper 3.
Numbers are presented as percentage with confidence intervals in brackets. ICH – Intracranial haemorrhage.

Paper 4

The aim of this study was to evaluate the efficacy and safety of a novel stent-retriever by comparing procedural and clinical outcomes and adverse events to classic stent-retrievers.

Two propensity score matched groups of 59 patients in each group were identified. Table 6 illustrates the baseline variables before and after adjustment for age, stroke severity, clot location, time to groin-puncture and neurointerventionalist performing the intervention.

The main findings when comparing the ERIC® group to the classic stent-retriever group were; equal rates of favourable recanalisation (86% vs 81% [OR 95% CI: 0.54-3.96, P=0.61]), favourable 3-months clinical outcome (46% vs. 40%, [OR 95% CI: 0.59-2.61, P=0.71]), and procedural adverse events (28% vs. 30% [OR 95% CI: 0.41-2.06, P=1.00]). The ERIC® group showed significantly shorter procedural durations (67.4 vs. 98.0 minutes [95% CI: 8-53 minutes, P=0.0085]) and less frequent use of secondary/rescue devices (18% vs. 39% [OR 95% CI: 0.14-0.80, P=0.021]). Furthermore, the rate of symptomatic intracranial haemorrhages (5% vs. 16% [OR 95% CI: 0.076-1.16, P=0.12]), procedural distal embolism (2% vs. 9%, [OR 95% CI: 0.02-1.64, P=0.21]), and number of thrombectomy passes (2.5 vs. 3.1 passes [95% CI: -0.1-1.3 passes, P=0.11]) were non-significantly lower in the ERIC® group. Both the multivariate and time-sensitivity analyses confirmed the main analyses.

	Before Propensity Score Matching			After Propensity Score Matching		
	ERIC N=59	**Non-ERIC N=257**	**P=**	**ERIC N=57**	**Non-ERIC N=57**	**P=**
Age (years)	70.0	68.4	0.41	69.7	70.1	0.87
Sex (male)	29 (49%)	145 (56%)	0.31	29 (51%)	31 (54%)	0.85
CCI 0 **CCI 1-3** **CCI ≥4**	27 (46%) 26 (44%) 6 (10%)	131 (51%) 111 (43%) 15 (6%)	0.44	27 (47%) 25 (44%) 5 (9%)	28 (49%) 27 (47%) 2 (4%)	0.50
Iv-rtPA	39 (66%)	184 (72%)	0.43	38 (67%)	41 (72%)	0.69
Clot location	ICA-T: 22 (37%) M1: 19 (32%) M2: 13 (22%) Other: 5 (8%)	ICA-T: 61 (24%) M1: 158 (61%) M2: 34 (13%) Other: 4 (2%)	<0.0001	ICA-T: 22 (39%) M1: 17 (30%) M2: 13 (23%) Other: 5 (8%)	ICA-T: 22 (39%) M1: 21 (37%) M2: 12 (21%) Other: 2 (3%)	0.63
NIHSS	17.4	16.8	0.36	17.4	17.5	0.91
Onset to image (minutes)	92.3	99.0	0.51	92.6	98.7	0.65
Image to groin (minutes)	167.0	145.3	0.037	167.0	150.5	0.20
General anaesthesia	34 (58%)	171 (67%)	0.23	33 (58%)	32 (56%)	1.00
Neurointerventionalist	1: 38 (64%) 2: 15 (25%) 3: 4 (7%) 4: 0 (0%) 5: 2 (3%)	1: 53 (21%) 2: 45 (18%) 3: 59 (23%) 4: 42 (16%) 5: 58 (23%)	<0.0001	1: 36 (63%) 2: 15 (26%) 3: 4 (7%) 4: 0 (0%) 5: 3 (4%)	1: 28 (49%) 2: 20 (35%) 3: 6 (11%) 4: 0 (0%) 5: 3 (5%)	0.51

Table 6 - Baseline variables before and after propensity score matching, Paper 4.
CCI: Charlson Comorbidity Index.

Discussion

Through the past three years endovascular stroke therapy has raised like the phoenix from the ashes of the neutral randomised controlled stroke trials published in 2013. It is now the gold standard therapy of acute ischaemic stroke caused by a large vessel occlusion and is recommended with level of evidence 1.A in Europe as well as in the USA[52,53]. As discussed in this thesis, this was only the first step paving the road for investigation of the several concerns that still exist in endovascular management of acute ischaemic stroke, two of which are: the role of acute carotid stenting and the importance of stent-retriever device design.

Carotid stenting assisting thrombectomy in acute stroke treatment (Paper 1,2,3)

Patients with acute ischaemic stroke caused by extracranial carotid occlusions or high-grade stenosis and concomitant intracranial embolism have previously shown worse outcomes and poorer response to

medical therapy compared to patients with only a single lesion[15]. Although the recent randomised controlled trials showed improved outcomes of endovascular therapy for these patients compared to medical therapy alone[54] these trials did not investigate the effect of carotid stenting. No guidelines exist on which patients to stent, if the carotid lesions should be stented before or after thrombectomy, how distal embolism should best be avoided, or how the platelet inhibition required to prevent acute stent thrombosis should be planned. This thesis demonstrates that carotid stenting in these patients appear to be reasonable safe and effective compared to other reports and to the recent randomised trials (Table 7) but that evidence from randomised controlled trials are currently absent.

	Study size	**Mean Age**	**Mean NIHSS**	**IV-rtPA**	**TICI 2b-3**	**mRS 0-2**	**Mortality**	**sICH**	**Acute stent thrombosis/ distal stent embolism**
Mechanical intracranial recanalisation plus carotid stenting									
Steglich-Arnholm (Paper 1)	47	64	16	85%	87%	68%	9%	4%	17%
Kwak et al (2013)[55]	35	65	12	23%	74%	63%	11%	3%	0%
Stampfl et al (2014)[56]	24	67	18	92%	63%	29%	17%	17%	0%
Behme et al (2015)[57]	170	64	15	72%	77%	36%	19%	9%	NR
Weighted averages$	**276**	**64**	**15**	**70%**	**77%**	**44%**	**16%**	**8%**	**8%**
Intracranial recanalisation without thrombectomy plus carotid stenting									
Steglich-Arnholm (Paper 2)	19	62	11	74%	89%	68%	16%	16%	16%
Malik et al (2011)[58]	18/77 (23%)#	63*	15*	NR	75%*	42%*	25%*	10%*	4%*
Son et al (2014)[59]	3/11 (27%)#	71*	7	100%	100%	100%	0%	NR	0%
Yoon et al (2015)[60]	7/42 (17%)#	71*	14*	64%*	76%*	55%*	6%*	9%*	4%*
Weighted averages$	**47**	**64**	**13**	**74%**	**82%**	**58%**	**17%**	**12%**	**9%**
Recent randomised thrombectomy trials[8–13] **(intervention arm)**									
Weighted averages$	**838**	**67**	**17**	**87%**	**69%**	**48%**	**14%**	**4%**	**NR**

Table 7 – Comparison with similar studies.

Abbreviations: NIHSS: National Institute of Health Stroke Scale, IV-rtPA: Intravenous recombinant tissue plasminogen activator, TICI: Thrombolysis In Cerebral Infarction Score, mRS: Modified Rankin Scale Score, sICH: Symptomatic intracranial hemorrhages defined by author, NR: Not reported
#Patients with intracranial recanalisation / entire study cohort, ¤Patients without extracranial stenting / entire study cohort, *Reports from entire study cohort, $Averages weighted according to study size.

The rationale for acute carotid stenting

An extracranial carotid lesion may be the cause of stroke for several reasons; haemodynamic impairment, small embolisms with impaired washout, or intracranial embolisms to large intracranial vessels. Only the last reason is covered in this thesis. EVT in this setting is challenging because of the extracranial carotid lesion. While most agree that lesser extracranial carotid lesions should not be managed, controversy exists whether to treat more severe extracranial carotid lesions acutely. The rationale for acutely stenting an extracranial carotid lesion is to secure the extracranial thrombogenic lesion thus easing access to the intracranial vasculature and preventing recurrent embolism, and to aid in intracranial reperfusion through recanalisation and reperfusion. Recurrent embolism has been suggested to occur in as many as 20% of patients within 72 hours of a symptomatic carotid event and the risk of severe re-stenosis or re-occlusion may be as high as 66%[61].The long-term durability of acutely placed stents was in Paper 2 suggested to be at least comparable to electively placed stents[62]. Furthermore, Paper 2 suggests that carotid stenting may aid in intracranial recanalisation and in some cases make thrombectomy unneeded. One theory behind this phenomenon is that the increased flow through the re-canalised carotid lesion may provide better access of iv-rtPA to the clot and washout of clot-material through increased regional cerebral blood flow[63] . This effect is not confined to the large occlusions but may be especially important to ensure washout of lesser emboli[64]. It is important to remember that even though results from this thesis suggest that intracranial recanalisation occur in 23% of patients initially presenting with concomitant extracranial carotid lesions and intracranial embolism this number may be too high. Several factors may explain the intracranial recanalisation observed. Firstly, the impeded flow through the ipsilateral intracranial vasculature may falsely be interpreted as clot-material or lesser clots may have appeared larger. Secondly, intracranial recanalisation may have occurred before the endovascular intervention had started because of iv-rtPA administered or from spontaneous recanalisation. This would in most cases lead to an improvement in clinical appearance of the patient. However, cellular stun, oedema from infarcted tissue, or 'bad clinical status' of the patient may cloud/hide this improvement[65]. Thirdly, carotid angioplasty with or without stenting, heparinised saline, antithrombotic drugs administered concomitant to stenting, or other procedural co-interventions may facilitate the intracranial recanalisation observed.

The other choice of therapy for these patients would be to avoid carotid stenting whenever possible and postpone stenting to the post-acute phase. Advantages of this approach would be to avoid the necessity of antiplatelet therapy administered during the acute phase of the ischaemic stroke. Antiplatelet therapy would instead be initiated over days and sufficient platelet inhibition could be ensured before progressing to stenting. It may even be decided to choose carotid endarterectomy instead of stenting for atherosclerotic lesions or medical therapy for atherosclerotic lesions or arterial dissections. The disadvantages of this approach are that in order to cross the catheters through the carotid occlusion or high-grade stenosis some degree of angioplasty would usually be needed. This is especially true for rigid atherosclerotic lesions. Another option could be to bypass the carotid lesion by accessing the intracranial occlusion via the collateral supplying arteries and the circle of Willis[25]. This indirect approach is however highly dependent on favourable anatomy of the circle of Willis.

Anterograde vs. retrograde stenting

Some argue that the carotid lesion should be treated before addressing the intracranial occlusion 'anterograde stenting' while others argue to postpone management of the carotid lesion until intracranial recanalisation has been achieved 'retrograde stenting'. The rationale for anterograde stenting is to provide anatomical orientation by increasing the flow through the carotid lesion assisting the thrombectomy, avoiding blind probing of the distal ICA, assisting intracranial thrombolysis by re-establishing the intracranial flow[66,67] [paper 2], and easing passage of larger guides, catheters and other tools by preventing vessel recoil. Furthermore, the distal occlusion may serve as distal protection from stent embolisms, especially in patients with intracranial ICA-T occlusions. The drawback of the anterograde stenting approach is potentially increased time to intracranial recanalisation which has been suggested by some studies[68,69] while not in others[70] or in Paper 1. This potential time-delay to intracranial recanalisation did not result in worse clinical outcomes[68,69]. The main argument for retrograde stenting is to address the intracranial occlusions as soon as possible[4,5]. Additionally, in retrograde stenting the carotid lesion would potentially be traversed only once because after removing the intracranial occlusion the carotid lesion could be stented when retracting your catheters. In the anterograde approach the carotid lesion needs to be catheterised at least twice – once for stenting and once, through the freshly stented carotid artery, for thrombectomy. However, if an embolus dislodges when the carotid lesion is managed in the retrograde approach it may dislodge in the recently recanalised intracranial vasculature or to new territories. Currently most centres seem to favour the anterograde approach[55,58,69,71–75]. This observation may, however, be biased if only patients that required stenting in order to traverse the carotid lesion were stented and patients where the catheters could traverse the carotid lesion without intervention were not stented.

Antiplatelet management during intervention – the dual-edged sword

Freshly deployed stents are thrombogenic until fully endothelialised[76]. In elective stenting you would ensure that a patient has sufficient inhibition of platelets before inserting a stent. In acute stenting patients are only treated with platelet inhibitors prior to the intervention, if this is part of the patients' usual medication. Therefore one has to ensure that the patient's platelets are acutely inhibited in order to prevent acute in-stent thrombosis. The assessment of harms in Paper 3 suggests that symptomatic haemorrhages and thrombotic complications were the most frequently reported harms of carotid stenting in acute stroke (Table 5).

Studies have shown that platelet inhibitors increase the risk of haemorrhagic complications when administered early after iv-rtPA[77]. Results from Paper 3 suggest that patients with acute stenting have a higher rate of symptomatic intracranial haemorrhages compared to benchmarks from the recent randomised controlled thrombectomy trials (8% [CI 5.7-11.8] vs. 4%[54], Table 7). This can be explained by two factors; the antiplatelet therapy administered during the intervention or the cerebral hyperperfusion syndrome[46] caused by opening of a chronic carotid lesion. The subgroup analysis in Paper 3 suggests that the main reason may be intravenous antiplatelet therapy since the subgroup of patients only receiving oral or no antiplatelet therapy during the intervention experienced half the rate of symptomatic haemorrhages compared to the subgroup of patients receiving intravenous antiplatelet therapy. It is, however, important to notice that the subgroup of patients not treated with intravenous antiplatelet therapy was small and the confidence intervals of the two proportions were wide and overlapping. Interestingly, the patients without intravenous antiplatelet therapy seemed to experience fewer adverse events not related to haemorrhages. This discrepancy is most likely caused by reporting bias – either because of the small study-size in the non-intravenous antiplatelet therapy subgroup or because studies with intravenous antiplatelet therapy were more focussed on reporting thrombotic complications. The over-all rate of thrombotic complications (stent-thrombosis and thrombotic embolisms during intervention) was slightly higher than the rate of symptomatic haemorrhages in Paper 3 (Table 5) suggesting that antiplatelet therapy is needed. Furthermore, our results from Paper 1 suggest that the thrombotic complications may be more severe than the haemorrhagic complications because 70% of patients with haemorrhagic complications still experienced a favourable clinical outcome where this was only true for 38% of patients with thrombotic complications.

The risk of symptomatic intracranial haemorrhages can be managed in two theoretical ways. Either iv-rtPA should be avoided if the patient is likely to require acute stenting or the administration of platelet inhibitors should be postponed to the post-acute phase in patients with low risk of acute stent-thrombosis. The first

option has already been investigated for acute large vessel occlusion treatment in an observational study finding that primary thrombectomy and avoidance of iv-rtPA could be the therapy of choice in the setting of direct referral to a comprehensive stroke centre[78]. A randomised controlled trial to confirm these findings is currently being planned[78]. However, in patients treated within a hub-and-spoke setting avoiding iv-rtPA at the primary stroke centre may not be ethically acceptable if the distance to the comprehensive stroke centre is too far because postponing treatment would mean decreasing the chance of a favourable clinical outcome. For these patients it would instead be possible to treat the patient with bridging platelet inhibitors (eg. GPIIb/IIIa inhibitors) instead of iv-rtPA. It is, however, important to remember that GPIIb/IIIa inhibitors previously have shown only to increase morbidity without improving clinical outcome when administered in acute ischaemic stroke[79]. The second option of postponing antiplatelet management to the post-acute phase is supported by the fact that all patients with stent-thrombosis at three months follow-up in Paper 1 also had some degree of stent-thrombosis during the intervention and none of the patients without stent-thrombosis during the acute intervention showed delayed stent-thrombosis. One might consider postponing platelet inhibitors in patients that received iv-rtPA prior to the intervention and that show amble flow through the stent, no residual stenosis, and no signs of acute stent-thrombosis. Delayed platelet inhibition could then be initiated within 24-48 hours after the procedure as it is currently recommended in the American and European guidelines[80,81]. The core caveat of this approach is whether the delay in platelet inhibition would lead to increased rates of acute stent-thrombosis and recurrent ischaemic strokes.

Ultimately it would require data from large samples and preferable randomised controlled trials before recommendations to how this dual-edged sword should best be handled without losing any fingers.

The importance of stent-retriever design for intracranial recanalisation (Paper 4)

The primary goal of endovascular therapy in acute ischaemic stroke is to achieve intracranial recanalisation. History has shown us that the design of the thrombectomy device plays a major role for its efficacy for clot removal and introduction of the stent-retriever design has been suggested to play a major role in the positive results from recent randomised controlled trials[82]. The results from Paper 4 suggest that further developments of the stent-retriever design may improve some procedural benchmarks. Recent studies have suggested safety and feasibility of using the ERIC® device for acute stroke therapy[83,84]. Our study was the first to compare the procedural benchmarks of the ERIC® device to other stent-retrievers.

The main findings were equal high rates of favourable recanalisation compared both to other stent-retrievers used at our centre and to previously published studies both reporting 83% favourable recanalisation[83,84]. Furthermore, the ERIC® device demonstrated decreased procedural durations compared

to classic stent-retrievers in our study. Although, time is an important prognostic factor for favourable clinical outcome we did not see this effect. This may be explained by a slightly longer time to groin puncture in the ERIC® group in spite of adjustment and the fact that the lowest boundary of the confidence interval was only 8 minutes. The average 30 minutes faster procedures, however, corresponds well with the non-significant 6% higher favourable clinical outcome in the ERIC® group in light of the 3-8% improved outcomes pr. 30 minutes shorter time to reperfusion suggested in previous studies[4,5]. Therefore, an effect on clinical outcome may have been missed by small numbers in this study.

Furthermore, we saw a lower rate of several thrombectomy devices used for achieving favourable recanalisation in the ERIC® group. Since the rates of favourable recanalisation were comparable in the two groups it may not be explained by reluctance with the operator to use another device than the ERIC® device. It might, however, be exposed to reporting bias of the operator. An improved performance of the ERIC® device for clot removal may further be supported by the lower numbers of procedural embolism into new territory and fewer thrombectomy passes needed to achieve intracranial recanalisation although these findings did not reach statistical significance. The faster procedural durations and the less need for an additional clot retriever device support the competence of the ERIC® device for swift and effective recanalisation.

The rates of adverse events were equal in the two groups suggesting reasonable safety of the ERIC device®. The number in the two groups were however too small to assess the different types of adverse events. We saw slightly fewer rates of symptomatic intracranial haemorrhages in the ERIC® group although the difference was not statistical significant. Interestingly we noticed a few more procedure-related haemorrhages in the ERIC® group. However, when looking into the details of these haemorrhages in the ERIC® group, one haemorrhage was caused by a classic stent-retriever used in rescue mode and one was caused by a vessel perforation from a microwire. The haemorrhages occurring after thrombectomy with the ERIC® device all occurred after thrombectomy in distal arteries (M2-M3). This suggest that even though the slimmer profile of the ERIC® device allows for thrombectomy into small MCA branches care should be taken when treating clots beyond the MCA-M1-M2 arteries. This is also supported by a review of individual patient data of the randomised controlled trials from 2015 from the HERMES collaboration that suggests only a non-significant benefit of endovascular treatment in MCA-M2 occlusions[54]. The observation that the ERIC® group experienced more procedure related haemorrhages although showing fewer parenchymal haemorrhages is explained by the haemorrhages associated with the ERIC® device were mostly minor asymptomatic subarachnoid haemorrhages.

An important factor for the performance of an interventional device is the operator using the device. The experience, skill and tenacity of the operator may not only affect the performance of the device in a given case but may also be important for the choice of the correct device in each case. Therefore, we adjusted for which neurointerventionalist performed the procedure and although it markedly reduced bias, it did not reduce it completely. Therefore, a randomised controlled trial is the only way to evaluate whether the ERIC® device performs at least equally compared to classic stent-retrievers.

Another important factor is the difference in time periods for treatment between the ERIC® group (mid 2013-2015) and the classic stent-retriever group (2012-2015). Patients treated in the early time period may have performed worse due to a learning curve among the operators or improvements in patient referral or management over time. However, the setup in our referral area has not changed markedly since 2012 and the referral has been high and consistent since 2012. Albeit, to check for any minor changes occurring within our referral area and the improved experience in our neurointerventionalist team, we performed a time sensitivity analysis only looking at patients treated within the same time-period (mid 2013–2015). This analysis confirmed the results of our primary analysis although with smaller groups that affected statistical significance for procedural duration.

This study suggested some improved procedural benchmarks using the ERIC® device for clot removal compared to classic stent-retrievers in acute ischaemic stroke treatment. However, no recommendations for clinical practice can be made from this study alone because of its observational design. Although we strived for reducing bias in our study Table 6 shows that some bias still existed after adjustment. In order to properly assess the benefits of the ERIC® retriever one would have to perform a randomised controlled trial.

Limitations

Several limitations adhere to the studies presented in this thesis. First the studies reported in Paper 1, 2 & 4 are all observational cohort studies. Paper 1 & 2 did not report an unexposed group and benefits of the intervention in view are very difficult to assess. Paper 4 compared with an unexposed group and although efforts were made to control for potential confounders some bias still existed after adjustment. Furthermore, the study design did not allow controlling for unmeasured confounders.

The outcomes reported in Paper 1, 2 & 4 were self-reported and not blinded to treatment. Therefore some overestimation of outcomes may have occurred. This should, however, only have limited effect on results

in the studies since the studies were designed after outcomes were assessed and potential bias is expected to occur equally in all study groups.

It is unknown how many patients who were never referred for endovascular treatment in the three cohort studies, however, all consecutive patients have been included and large numbers are not expected to have been missed because of the high capacity and 24/7 stroke service provided at Rigshospitalet.

In Paper 4, only the clot location and not clot size/burden or clot composition was available which may play an important role for efficacy of a stent-retriever[45]. Selection of devices for clot removal was based on the choice of the neurointerventionalist for each patient and even though no specific criteria for selection were used by our staff, our results may have been affected by selection bias.

The systematic review in Paper 3 is mostly challenged by the limited number of studies identified and the design of these studies. All studies were identified with serious risk of bias. Furthermore, significant heterogeneity between the studies and risk of reporting bias from patient cohorts with favourable results impedes the interpretation of the results.

Conclusion

The results in this thesis allow the following conclusions to be formed:

1. Carotid stenting assisting intracranial thrombectomy in acute ischaemic stroke show good outcomes and seems reasonably safe with the observed rates of favourable clinical outcome and adverse events. Nevertheless, the complications and adverse events observed call for clinical trials to ensure that benefits outweigh risks of this intervention.
2. Carotid stenting also show good outcomes and seems reasonably safe when intracranial recanalisation did not require mechanical clot-removal. However, only limited investigations to this important subject exist and further studies are urgently needed.
3. No evidence from randomised clinical trials on the benefits of carotid stenting assisting intracranial thrombectomy in acute ischaemic stroke has been identified and is urgently needed. Limitations in the current studies leave the evidence for this intervention at 'very low'. The identified studies suggest a reasonable safety-profile compared to recent randomised controlled stroke-trials paving the road for randomised controlled trials on this important topic.
4. The design of the ERIC® device seems to perform at least equally effective and safe for clot retrieval in acute ischaemic stroke compared to classic stent-retrievers. It even showed improvements in

certain important procedural benchmarks that were not reflected in improved clinical outcomes, possibly due to low statistical power. These promising findings need confirmation in clinical trials before any recommendations for clinical practice can be made.

Future perspectives

Though endovascular methods have been available for almost a century only the last decade has provided us with the prerequisites needed for performing effective endovascular stroke therapy. Now that the fundamentals are in order it seems time to focus on other important details of endovascular therapy for acute ischaemic stroke. Already, several trials on general anaesthesia vs. conscious sedation are being performed[85,86]. Such trials will provide understanding of the peri-interventional stroke management and should answer the important dilemma if you should strive for general anaesthesia which takes time and may affect patients' blood pressure during intervention or if you should strive for conscious sedation which is faster and affects patients' blood pressure less but may cause complications in less compliant patients. Since evidence from observational studies, as presented in this thesis, suggests reasonable safety and efficacy of carotid stenting in acute ischaemic stroke clinical controlled trials confirming the results in this thesis are expected within few years.

However, the next major revolutions in endovascular stroke therapy will, in my opinion, come from fundamental changes in prehospital stroke diagnostics and management. The complexity of endovascular acute ischaemic stroke therapy demands for specialised centres[87]. Since these centres usually cannot comprehend every patient suspected for acute ischaemic stroke, the endovascular stroke setup is ordinarily organised in a hub-and-spoke setting. This setting has its limitations since correct referral of the patient can be a time-delaying challenge. Acute stroke management has always been challenged by very advanced and demanding diagnostics of large vessel occlusion. The patient needs to be transported to the nearest hospital for neuroimaging potentially causing delay to diagnosis and treatment. As a comparison, patients with suspected myocardial infarction can have an electro cardiogram (ECG) performed in every ambulance and the result can be sent to a cardiologist at a coronary intervention capable centre. Thus, the diagnosis can be made early within the responding ambulance and the patient can be sent to the nearest coronary intervention centre or just the nearest hospital, whatever is needed. A similar attempt has been made in acute stroke management with introduction of the stroke ambulance (stroke-mobile) which is an ambulance carrying a portable CT-scanner. The CT scanner is, however, still large and heavy and it is not feasible to have in every ambulance. This method has shown significantly shorter time to diagnosis and treatment but no statistically significant increase in clinical outcomes[88]. Invention of the ECG-equivalent for

acute large vessel occlusion stroke diagnostics will dramatically reduce the time to treatment and potentially improve outcomes. Currently, several clinical assessment scales have been proposed to identify patients with high risk of having a large vessel occlusion in the pre-hospital setting[89–91]. A clinical scoring system will never be able to distinguish between ischaemic and haemorrhagic stroke but could be a cheap, easy and safe method for choosing which patients needs transferring to a primary stroke centre and which patients need transferring to a comprehensive stroke centre. Although promising, none of these scales have yet been validated in the pre-hospital setting. However, one randomised controlled trial using the RACE scale to assess patients with acute ischaemic stroke is currently recruiting patients (RACECAT)[92]. Other fundamentally different approaches have been attempted to increase the chance of a favourable outcome where it was sought to decelerate the expansion of the ischaemic core and thus compensate for the delay to treatment with ischaemic per-conditioning[93] or administration of neuroprotective agents[94] but with limited success.

Three years ago when I started this PhD-project the future of endovascular stroke therapy seemed dark after the recent publication of the three neutral trials. However, now the future seems bright after the pioneering REVASCAT[11] performed a SWIFT[12] CLEAN[8] ESCAPE[10] without a THRACE[13] from previous failures allowing us to EXTEND[9] our hopes for the future and PREPARE for future clinical trials.

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Paper 1-4

Paper 1

J Neurol (2015) 262:2668–2675
DOI 10.1007/s00415-015-7895-0

ORIGINAL COMMUNICATION

Thrombectomy assisted by carotid stenting in acute ischemic stroke management: benefits and harms

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Received: 10 August 2015 / Revised: 28 August 2015 / Accepted: 29 August 2015 / Published online: 7 September 2015

Abstract Extracranial carotid artery occlusion or high-grade stenosis with concomitant intracranial embolism causes severe ischemic stroke and shows poor response rates to intravenous thrombolysis (IVT). Endovascular therapy (EVT) utilizing thrombectomy assisted by carotid stenting was long considered risky because of procedural complexities and necessity of potent platelet inhibition—in particular following IVT. This study assesses the benefits and harms of thrombectomy assisted by carotid stenting and identifies factors associated with clinical outcome and procedural complications. Retrospective single-center analysis of 47 consecutive stroke patients with carotid occlusion or high-grade stenosis and concomitant intracranial embolus treated between September 2011 and December 2014. Benefits included early improvement of stroke severity (NIHSS $\geq$ 10) or complete remission within 72 h and favorable long-term outcome (mRS $\leq$ 2). Harms included complications during and following EVT. Mean age was 64.3 years (standard deviation $\pm$12.5), 40 (85 %) patients received IVT initially. Median NIHSS was 16 (inter-quartile range 14–19). Mean time from stroke onset to recanalization was 311 min (standard deviation $\pm$78.0). Early clinical improvement was detected in 22 (46 %) patients. Favorable outcome at 3 months occurred in 32 (68 %) patients. Expedited patient management was associated with favorable clinical outcome. Two (4 %) patients experienced symptomatic hemorrhage. Eight (17 %) patients experienced stent thrombosis. Four (9 %) patients died. Thrombectomy assisted by carotid stenting seems beneficial and reasonably safe with a promising rate of favorable outcome. Nevertheless, adverse events and complications call for additional clinical investigations prior to recommendation as clinical standard. Expeditious patient management is central to achieve good clinical outcome.

Keywords Stroke · Carotid stenting · Thrombectomy · Early improvement

Introduction

Acute occlusion or high-grade stenosis of the extracranial carotid artery with concurrent intracranial embolism was encountered in up to 20 % of patients in recent randomized acute ischemic stroke trials [1–3]. In these patients, the carotid lesion has released a distal embolus to the middle cerebral artery or carotid terminus typically associated with severe clinical deficits. Treatment of these patients with intravenous tissue plasminogen activator (iv-tPA) has suggested rates of clinical improvement of only 25 % [4, 5]. To increase the chance of a favorable clinical outcome, timely and effective reperfusion is mandatory to reverse the ischemic penumbra and achieve early clinical improvement [6]. Although early clinical improvement does not guarantee favorable long-term outcome, it may be used as a clinical marker for successful penumbral salvage [7, 8]. Endovascular therapy (EVT) has recently suggested

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superior recanalization rates and improved clinical outcome compared to medical therapy alone [1–3, 9, 10]. EVT facilitates access to the intracranial embolus directly through the carotid lesion or indirectly via collateral vessels [11]. The indirect access is technically challenging and highly dependent on favorable anatomy of the Circle of Willis. The direct access is more straightforward, but bears the risk of penetrating the wire through an occlusion unable to predict passage within the true lumen as well as dislodgement of thrombotic material distal to the carotid lesion. Carotid stent-assisted angioplasty has been suggested to address the concerns with the direct access in conjunction with intracranial clot retrieval or local thrombolysis. Besides the complexity of the procedure, the principle caveat of acute carotid stenting is the immediate need for antiplatelet therapy to avoid stent thrombosis. In spite of these concerns, thrombectomy assisted by carotid stenting has been attempted in this delicate situation and recent patient series suggest acceptable safety and feasibility [12–18].

The aim of this investigation was to assess the benefits and harms of thrombectomy assisted by carotid stenting in a large single-center cohort and to identify clinical and procedural factors associated with favorable outcome or serious adverse events. Benefits included early clinical improvement and functional 3-month outcome; harms included peri- and post-procedural complications.

Methods

Patient referrals

The catchment area of the study institution (Rigshospitalet, Copenhagen University Hospital) comprises 2.5 million residents, with 1860 of 15,900 stroke patients treated with iv-tPA. Three primary stroke-centers treat patients with iv-tPA and refer eligible patients for EVT to the comprehensive stroke-center at Rigshospitalet in a 'drip-and-ship' setting. Patients with serious neurological deficits presenting with National Institute of Health Stroke Scale (NIHSS) $\geq$10, large anterior vessel occlusion on CT-angiography (CTA), absence of early signs of extensive infarction (>1/3 of the middle cerebral artery territory) on CT, with no major improvement immediately after administration of, or contraindications to, iv-tPA get routinely transferred. At the comprehensive stroke-center, patients are clinically reassessed for recovery in transit or to confirm necessity of EVT. A team of six stroke neurologists and five neuro-interventionalists cover a 24/7 stroke-team service with 30 min response time.

All patient cases referred for EVT from September 2011 to December 2014 were screened for concomitant extracranial carotid occlusion or high-grade stenosis and intracranial embolism intended for thrombectomy assisted by stenting of the internal or common carotid artery and retrospectively reviewed by two authors (HSA and DWK). Clinical and laboratory data were extracted from paper and electronic charts. Procedural details were extracted from the procedure description and review of the neuroimaging on a PACS work-station (HSA, DWK and MH). All procedures were in accordance with the Declaration of Helsinki.

Endovascular procedure

EVT was performed in either conscious sedation or general anesthesia. A dedicated team of neuro-anesthesiologists was available for all neuro-interventions. Conscious sedation was preferred when the patient was compliant. General anesthesia was used in agitated patients and those who could not follow instructions during the procedure.

Assessment of the target vessel was obtained by diagnostic digital subtraction angiography (DSA) and compared with the prior CTA with respect to clot location and characteristics of the occlusions. The extracranial carotid lesion was classified as arterial dissection or atherosclerotic lesion, respectively, by the signature on DSA.

Trans-femoral artery access was primarily attempted. Access of the target vessel was achieved by triaxial access using a long sheath (6–9 Fr, 80–90 cm), large-bore coaxial catheter (6–8 Fr) and a diagnostic catheter (5 Fr), preshaped suitable for selecting the target vessel from the aortic arch. The extracranial carotid lesion was passed with a micro-guide wire and pre-dilated if necessary before one or several self-expandable carotid stents were placed [e.g., Wallstent (Boston Scientific, Natick, MA, USA); LEO+ (BALT Extrusion, Montmorency, France); CASPER (MicroVention, Tustin, CA, USA)]. Stents were balloon-dilated when needed to ensure adequate width, wall-apposition, and flow. Thrombectomy was performed using stent-retrievers and repeated as needed [e.g., Solitaire FR (Covidien/ev3, Irvine, CA, USA); ERIC (MicroVention, Tustin, CA, USA); pREset (Phenox, Bochum, Germany)]. Carotid stenting was performed before or after thrombectomy at the interventionalist's discretion. Femoral hemostasis was ensured with vascular closure systems or manual compression.

The total number of thrombectomy passes and quality of reperfusion were recorded. Successful recanalization was defined according to the thrombolysis in cerebral infarction (TICI) [19] scale as TICI 2b-3.

Post-procedural care

Following EVT, patients were transferred to a neuro-intensive care unit. In patients with successful stent

placement, blood pressure was targeted at a mean arterial pressure of 70–100 mmHg. Patients were transferred to rehabilitation within 72 h. Patients without clinical improvement and those experiencing complications were transferred to further specialized care. Prior to discharge and at 3 months carotid stent patency was assessed using CTA and/or duplex sonography.

Platelet inhibition

During EVT, patients received a loading dose of 500 mg aspirin intravenously and/or a weight-adjusted half or full loading dose of GPIIb/IIIa [eptifibatid (0.09–0.18 mg/kg) or abciximab (0.125–0.25 mg/kg)] at the interventionalist's discretion prior to stent deployment. After follow-up neuroimaging had excluded hemorrhage, patients received dual antiplatelet therapy with aspirin and clopidogrel adjusted according to point-of-care platelet function testing (Multiplate analyzer, Roche, Switzerland) targeting ≥50 % ASPI- and ADP-receptor inhibition for at least 3 months. Patients with insufficient ADP-receptor inhibition were switched to prasugrel antiplatelet therapy.

Outcomes

Stroke severity was assessed at admission and at discharge. Early clinical improvement was defined as an NIHSS improvement of NIHSS ≥10 or complete remission (NIHSS 0) within 72 h [20].

Patients were followed for 3 months and had their disability assessed according to the modified Ranking scale (mRS) with a standardized interview [21].

Procedure-related adverse events

Pre-specified adverse events, including prolonged hospitalization, hemorrhagic complications, death, and acute thrombotic complications were identified by reviewing the electronic charts, DSA-images, and procedure reports. Late thrombotic complications were identified on follow-up CTA or duplex sonography. Hemorrhagic complications were identified by reviewing follow-up CT performed 24 h after the procedure or earlier, if appropriate. Symptomatic hemorrhage was defined as hemorrhage in the depending territory with clinical worsening of NIHSS ≥4 [22].

Statistical analyses

Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $P < 0.05$.

Student's t test or Wilcoxon test were used for comparing numeric variables with difference in means and 95 % confidence interval (CI). Binary variables were compared by Fisher's exact test.

Results

Study population

From 361 patients referred for EVT, 62 patients with concomitant extracranial carotid lesions and intracranial embolism were identified. Forty-seven patients were treated with thrombectomy assisted by carotid stenting while 15 patients were treated with carotid stenting only since the intracranial clot had dissipated during transfer as a result of iv-rtPA, washout after spontaneous or procedural carotid revascularization, or from misinterpretation of initial neuroimaging due to the impeded carotid flow. These 15 patients did not require thrombectomy assisted by carotid stenting and were excluded from this investigation.

Thus, 47 patients matching the inclusion criteria were included in this study, 34 (72 %) were male. Mean age was 64.3 years [standard deviation (SD) ±12.5]. Median NIHSS was 16 [inter-quartile range (IQR) 14–20] at the primary stroke-center and 16 (IQR 14–19) prior to EVT. Forty (85 %) patients received iv-tPA at the primary

Table 1 Patient characteristics

Age (years)	64.3 ± 12.5
Male	34 (72 %)
Smoking	25 (60 %)
Arterial hypertension	21 (45 %)
Diabetes mellitus	1 (2 %)
Atrial fibrillation	2 (4 %)
Previous stroke	3 (6 %)
Hypercholesterolemia	7 (15 %)
Prior antiplatelet treatment	12 (26 %)
Atherosclerosis	32 (68 %)
Dissections	15 (32 %)
Carotid occlusion	32 (68 %)
Carotid high-grade stenosis	15 (32 %)
Non-dominant carotid lesion	29 (62 %)
M1-embolus	32 (68 %)
M2-embolus	1 (2 %)
Carotid-T embolus	14 (30 %)
Aspirin non-responders	0
Clopidogrel non-responders	20 (43 %)
Patients bridged with iv-tPA	40 (85 %)
NIHSS before iv-tPA	16 (14–20)
NIHSS before DSA	16 (14–19)

DSA digital subtraction angiography, *NIHSS* National Institute of Health Stroke Scale

Table 2 Patient management

Mean time from stroke onset to recanalization (min)	311.0 ± 78.0
Mean time from DSA start to finish (min)	84.8 ± 46.0
Mean time from iv-tPA to DSA start (min)	115.0 ± 26.9
Mean time from iv-tPA to antiplatelet therapy (min)	198.8 ± 99.4
GPIIb/IIIa inhibitor during procedure	31 (67 %)
Iv-aspirin during procedure	34 (74 %)
Patient distribution of carotid stents	
Wallstent	39 (83 %)
LEO+	7 (15 %)
CASPER	2 (4 %)
LVIS	1 (2 %)
Telescopic stenting technique	6 (13 %)
Patient distribution of stent retriever devices	
Solitaire FR	33 (70 %)
pREset	5 (11 %)
ERIC	5 (11 %)
Other thrombectomy devices	4 (8 %)
Thrombectomy passes	1 pass: 22 (47 %)
	2–3 passes: 18 (38 %)
	4 or more passes: 7 (15 %)
Recanalization TICI 2b-3	42 (87 %)
Conscious sedation (CS)	19 (40 %)
General anesthesia (GA)	27 (58 %)
CS converted to GA	1 (2 %)
Peri-procedural mean arterial pressure (mmHg)	90.1 ± 11.6

DSA digital subtraction angiography, *TICI* Thrombolysis in Cerebral Infarction Score

stroke-center. Thirty-two (68 %) patients presented with carotid occlusion and 15 (32 %) with carotid high-grade stenosis. Mean time from stroke onset to recanalization was 311 min (SD ± 78.0), mean time from iv-tPA to stent placement was 198.8 min (SD ± 99.4) and mean procedural duration was 84.8 min (SD ± 46.0). See Tables 1 and 2 for patient characteristics and management.

Clinical outcome

Twenty-two (46 %) patients experienced early clinical improvement. These patients had significant shorter time from stroke onset to recanalization [60.4 min CI (13.1–107.7), $P = 0.014$], and shorter procedural duration [26.5 min CI (0.6–52.5), $P = 0.046$] (Table 3).

Thirty-two (68 %) patients had favorable 3-month outcome. They had lower stroke severity [NIHSS 3 CI (1–6), $P = 0.0037$], younger age [9.7 years CI (1.2–16.2), $P = 0.024$], and shorter procedural duration [37.2 min CI (10.0–64.4), $P = 0.0085$] (Table 3).

All patients experiencing early clinical improvement also had favorable 3-month outcomes compared to only 40 % of those without early clinical improvement (Fig. 1).

Forty-two (87 %) patients had favorable recanalization.

In 18 (38 %) patients, all with atherosclerotic lesions, the extracranial carotid lesion was stented prior to thrombectomy. Preparatory carotid stenting was not associated with increased time to intracranial recanalization compared to initial thrombectomy [18.2 min CI (−9.9 to 46.3), $P = 0.20$]. There was no association between sedation management during the endovascular procedure and early improvement, 3-month outcome or any adverse events.

Adverse events

Twenty (43 %) patients showed hemorrhagic transformation or parenchymal hemorrhage on post-procedural CT (Table 4). Eighteen (39 %) patients had asymptomatic petechial hemorrhagic transformations and only two (4 %) patients had symptomatic parenchymal hemorrhages. Despite showing hemorrhagic transformation on follow-up CT, 10 patients showed early clinical improvement and 14 patients had a favorable 3-month outcome. There was no significant association between hemorrhagic transformation and type or dose of antiplatelet regimen, previous iv-tPA administration, or peri-procedural arterial blood pressure.

Table 3 Clinical outcome and associated factors

	mRS 0–2 $N = 32$ (68 %)	mRS 3–6 $N = 15$ (32 %)	EI $N = 22$ (47 %)	No EI $N = 25$ (53 %)
Age (years)	62 (±11.9)	70 (±12.0)	61 (±2.8)	67 (±2.3)
NIHSS	15 (±4)	18 (±3)	16 (±3)	16 (±5)
Onset to recanalization (min)	290 (±78.6)	312 (±89.9)	265 (±66.6)	325 (±85.2)
Procedural duration (min)	73 (±21.9)	109 (±39.0)	71 (±21.9)	97 (±57.9)

mRS modified Rankin Scale, *NIHSS* National Institute of Health Stroke Scale, *EI* early improvement

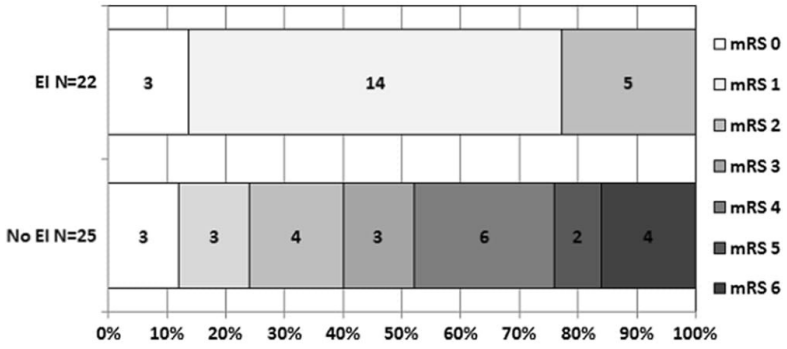

Fig. 1 Clinical outcome at 3 months. *Bar graph* of distribution of 3-month outcome in patients experiencing early improvement (EI) and no EI

Eight (17 %) patients had acute stent thrombosis during EVT (Table 4). Only one of those patients experienced early clinical improvement and three experienced favorable 3-month outcomes. In seven of those patients stent recanalization was achieved with local administration of GPIIb/IIIa inhibitor; in one patient recanalization was not attempted because of excellent collateral flow and complete intracranial recanalization. His stent was instead occluded with coils. Age, cause of carotid occlusion, number of thrombectomy passes, peri-procedural medication, or effectiveness of antiplatelet management according to ADP/ASPI inhibition were not associated with peri-procedural or late stent thrombosis. In one (2 %) patient, advancement of the stent through the carotid lesion failed initially, but was completed in a secondary procedure the following day.

Thirty-nine (91 %) patients had patent carotid stents at 3-month follow-up while four (9 %) patients had occluded stents. All patients with occluded stents at follow-up had also experienced partial or complete stent thrombosis during EVT.

One (2 %) patient experienced clot-dislodgement during thrombectomy. Distal embolization from the carotid stent was observed in three (7 %) patients. All had thrombectomy performed prior to carotid stenting and all emboli were successfully retrieved. In two patients air emboli were observed in post-procedural CT. Both had unfavorable outcome (Table 4).

Four (9 %) patients died in hospital 1–28 days after EVT (Table 4).

Discussion

Endovascular therapy for acute extracranial carotid occlusion or high-grade stenosis with intracranial embolism is considered risky and challenging. Procedural complexities, prolonged interventions and platelet inhibition are seen as hazardous in the acute ischemic stroke setting. On the contrary, these patients are prone to long-term dependency if vascular recanalization is not attempted. This study presents the largest single-center experience to date on thrombectomy assisted by carotid stenting in a setup resembling the ones used in recent randomized thrombectomy trials. The results of this study suggest that thrombectomy assisted by carotid stenting is beneficial and safe for a common dilemma in acute stroke management. Since the 3-month outcome in this study mirrors or even exceeds those in prior clinical trials, this study suggests that incorporation of thrombectomy assisted by carotid stenting in upcoming clinical investigations is necessary. Randomized clinical trials are warranted for assessing whether benefits outweigh the observed mostly asymptomatic 43 % hemorrhagic transformation and 17 % stent thrombosis in this study.

Early clinical improvement implies salvaged penumbral brain-tissue while the favorable 3-month outcome

Table 4 Adverse events with relation to EI and death

	EI	No EI	Death
Intracerebral hemorrhagic complications			
Asymptomatic hemorrhages	10	8	0
Symptomatic hemorrhages	0	2	2
Procedure-related complications			
Acute stent thrombosis	1	7	1*
Stent embolism	0	3	0
Thrombectomy embolism	0	1	0
Air embolism	0	2	1
Late stent thrombosis	0	4	†
Aspiration pneumonia/sepsis	0	1	1

EI early improvement

* The patient died of an acute reperfusion injury

† No information on reocclusion of the stent because of mortality

incorporates the long-term benefit of tissue salvaged. Early clinical improvement is reported to occur in about a quarter of these patients when treated with iv-tPA alone [4, 5]. Although using a particularly strict definition, the rate was 46 % in this study. Early clinical improvement obviously does not guarantee favorable long-term outcome, but it was a strong predictor of favorable 3-month outcome in this study and other reports [7, 8]. The rate of independent 3-month outcome in this series is comparable to previous series, reporting between 29 and 63 % favorable outcome [12–18], and resembles results from randomized thrombectomy trials with careful patient selection [9, 10].

Time from stroke onset to recanalization was associated with early clinical improvement, but not with favorable 3-month outcome. This discrepancy is, however, only seemingly inconsistent as early clinical improvement, implying penumbral salvage, is facilitated by expeditious intracranial clot removal. A substantial 40 % of patients without immediate clinical improvement still achieved independent 3-month outcomes. This may argue for extended time windows in patients presenting with extracranial carotid lesions and intracranial embolism in the absence of large early CT infarct signs. Alternatively, due to the skewed 3-month outcomes distribution, a time association may have been missed. Nonetheless, novel staged CT-angiography methodology [3] or CT-perfusion techniques [10] may provide a biological instead of chronological time window for future trials.

In this study, patients experiencing early clinical improvement and/or favorable 3-month outcome had shorter procedural durations. Even though no single patient or procedural adverse parameter could be identified to explain this time-dependency, difficult access into the intracranial vasculature is considered to herald procedural failure and compromise good clinical outcome. For instance, in 18 patients with atherosclerotic lesions, the coaxial guide-catheter could only be advanced after preparatory carotid stenting, which has been found to delay intracranial flow restoration in prior clinical investigations [12, 13]. However, in this series no single factor, but rather the sum of many interventional setbacks, seems to make the difference. Moreover, the risks of preparatory stenting have been discussed among interventionalists [23]. Some argue that recently deployed stents should not be crossed for fear of acute stent thrombosis while others argue that preparatory stenting is advantageous in the setting of distal clot-retrieval because it assists anatomic orientation, thus easing intracranial thrombectomy. This study supports the latter view because distal embolization was only detected when thrombectomy was performed prior to stenting and preparatory stenting did not significantly delay intracranial recanalization.

The rate of symptomatic hemorrhage observed in this study is aligned with previous reports [12–18] and recently published randomized clinical stroke trials [1–3, 9, 10]. The relatively high rate of asymptomatic hemorrhages observed in this study may advocate for restraining the use of intra-procedural intravenous antiplatelet therapy. However, the 17 % observed rate of intra-procedural stent thrombosis reaffirms the necessity of potent antiplatelet therapy administrated already during the procedure. Furthermore, it is important to consider that 14 of 20 (70 %) patients with hemorrhages still experienced a favorable 3-month outcome while this was true for only 3 of 8 (38 %) patients with intra-procedural stent thrombosis. Considering the disappointing rates of recanalization and clinical improvement with iv-tPA alone, and possible complications associated with concomitant thrombolytic and antiplatelet agent use, it may be argued to strive for primary EVT and away from 'bridging-thrombolysis' in these patients. Granting this observational study offers no final recommendations, interventional stroke care remains challenging and presents much opportunity for future clinical trials to advance the field by building evidence to tailor the treatment to individual patient needs. In light of recent positive randomized thrombectomy trials, clinical trials testing the efficacy of carotid stenting and the required co-interventions such as urgent antiplatelet therapy, blood pressure management, and potential delay to intracranial recanalization in the acute stroke setting, need to be conducted. Lessons from this and other experiences suggest that a randomized clinical trial with an estimated total sample size of only 135 patients [24] could show a doubling of favorable clinical outcome of thrombectomy assisted by carotid stenting versus medical management alone.

Limitations

This is a single-center retrospective cohort study and may not reflect clinical practice and outcomes observed at other centers. Although an accepted referral algorithm existed prior to this study, patients were referred on a case-by-case basis introducing possible selection bias. However, all consecutive patients were included and substantial numbers are not believed to have been missed due to the high capacity and 24/7 service provided. The number of patients that were not referred despite failure to improve or of those who improved following iv-tPA despite large vessel occlusions is unknown. However, the proportion of thrombectomy procedures assisted by carotid stenting compared to the total number of thrombectomy procedures is in accordance with other epidemiological data [25]. In addition, a learning curve over the study period may have interfered with some of the results. The investigators were blinded to outcome when analyzing images.

Conclusion

Intracranial thrombectomy assisted by stenting of extracranial carotid lesions is beneficial and seems reasonably safe with favorable clinical outcome. Nevertheless, adverse events and complications observed in this report require clinical trials to ensure that benefits outweigh harms for this intervention. Although no specific clinical or procedural details were associated with clinical outcome, rapid insight into stroke mechanism and expeditious management is essential for improving outcomes with this treatment modality.

Compliance with ethical standards

Conflicts of interest None.

Ethical standards The conduct of this study was approved by the Danish Data Protection Agency (j.nr. 30-1148) and the Danish Health and Medicines Authority (j.nr 3-3013-1017/1/).

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Paper 2

Rationale for extracranial carotid stenting in the acute ischemic stroke setting in patients with intracranial recanalization

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Disclosure of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest: None

Abbreviations:

EVT – Endovascular therapy

Abstract:

Background: In some patients selected for endovascular intervention of an extracranial carotid occlusion or high-grade stenosis with concomitant intracranial embolism, intracranial recanalization is found after crossing the carotid lesion with the diagnostic catheter. The rationale for acute stenting to repair the carotid lesion remains controversial in these patients.

Objective: This retrospective study reports harms and benefits of carotid stenting in acute ischemic stroke patients with intracranial recanalization and discusses the rationale for such intervention.

Methods: Single-center experience of 19 acute ischemic stroke patients from September 2011 to December 2015 initially presenting with extracranial carotid lesions and concomitant intracranial embolism but show resolved intracranial clots at the time of neurointervention. Clinical and radiological data were extracted from online patient-charts. Patients were followed for 3 months by clinical and radiographic evaluation.

Results: Eleven (58%) patients were male. Median age was 62 years (range 43-79). Median stroke severity before neurointervention was NIHSS 11 (range 3-23). Fourteen (74%) patients received drip-and-ship intravenous thrombolysis without substantial improvement. Median stroke-onset-to-carotid-revascularization time was 335 minutes (range 220-482). Thirteen (68%) patients had modified Ranking Scale 0-2 at follow-up. Two (11%) patients suffered intracerebral hemorrhages and died. One patient (5%) died following in-stent thrombosis and clinical deterioration.

Conclusion: Clinical and radiological outcomes of extracranial carotid stenting in acute ischemic stroke patients with intracranial recanalization conform to those of intracranial thrombectomy trials. However, serious complications observed calls for clinical trials to further assess the risk-benefit of this approach.

Key words: stroke carotid stenting intracranial recanalization

Introduction:

Some patients selected for endovascular therapy (EVT) for acute ischemic stroke caused by an extracranial carotid occlusion or high-grade stenosis with concomitant intracranial embolism have achieved intracranial recanalization at the time of intervention[1–3]. Extracranial carotid lesions are often associated with intracranial embolism and were encountered in up to 30% of participants in recent randomized EVT-trials[4–8]. As highly specialized expertise and resources are needed for EVT, it is in most places organized in a 'hub-and-spoke' concept[9] where primary stroke-centers (the spokes) assess and treat eligible patients with intravenous recombinant tissue plasminogen activator (iv-rtPA), and refer non-responding patients or patients with particular

severe strokes to a comprehensive stroke-center (the hub) for EVT. In the interest of time, and with pre-procedural neuroimaging already acquired at the primary stroke-center, diagnostic angiography is usually not considered before targeting the culprit intracranial occlusion. Instead, the extracranial carotid lesion is crossed with the endovascular wires and microcatheters and may sometimes require stenting before advancement of any further devices is possible in order to reach the intracranial occlusion.

Consequently, in as many as one in four patients presenting with a carotid lesion and concomitant intracranial embolism, distal intracranial recanalization is found after navigating the carotid lesion with the diagnostic microcatheter[1–3]. Recanalization may have occurred spontaneously, as a result of iv-rtPA, washout after spontaneous or procedural carotid revascularization, or from misinterpretation of initial neuroimaging due to the impeded carotid flow. If carotid stenting was not a prerequisite for gaining access to the intracranial vasculature in the first place, the interventionalist may choose to stent the extracranial carotid lesion to cover the exposed carotid lesion before retracting the catheters.

The rationale for acute carotid revascularization includes facilitation of washout of clot-material from downstream intracranial vessels, assuring adequate cerebral blood-flow and perfusion for tissue recovery, and reducing the risk of recurrent embolism from the culprit carotid lesion[10,11]. However, necessity for dual antiplatelet therapy to prevent in-stent thrombosis and/or potential embolization and the sudden increase in blood-flow after mending the carotid lesion may increase the risk for symptomatic intracerebral hemorrhage[12,13].

In this study, we report on harms and benefits of carotid stenting in a series of acute ischemic stroke patients with extracranial carotid lesions and concomitant intracranial embolism that had already recanalized at the time of neurointervention and discuss the rationale for that approach.

Methods:

The endovascular setup at our comprehensive stroke-center in Copenhagen has previously been described[14]. Within our referral-area three primary stroke-centers treat acute ischemic stroke patients with iv-rtPA if indicated and refer EVT-eligible patients to our comprehensive stroke-center in a ‘drip-and-ship’ setting. Patients are assessed for stroke severity according to the

National Institute of Health Stroke Scale (NIHSS) at both the primary and comprehensive stroke-center to confirm continuous necessity for intervention. Neuroimaging (usually computer tomography (CT) angiography) is mainly performed at the primary stroke-centers to exclude major manifested infarcts and detect large vessel occlusions and is only repeated at our comprehensive stroke-center in case of major clinical changes or delayed referral. In case of clinical improvement, diagnostic angiography is considered before accessing the culprit vessel to confirm an ongoing intracranial obstruction.

During EVT, access to the target vessel is achieved through a co- or tri-axial femoral access using a long sheath (6-8Fr, 80-90cm), a large-bore coaxial catheter (6-8Fr) and a diagnostic catheter (5Fr), pre-shaped suitable to select the target-vessel from the aortic arch. The carotid lesion is passed with a micro guide-wire and pre-dilated if necessary before one or several self-expandable carotid stents are placed (e.g. Wallstent (Boston Scientific, Natick, MA); LEO+ (BALT Extrusion, Montmorency, France), **online supplements table 1**). Stents are balloon post-dilated when needed to ensure adequate width, wall-apposition, and flow.

Prior to stent-placement, patients are loaded with 500 mg aspirin intravenously and/or a weight-adjusted half or full loading-dose of GPIIb/IIIa inhibitor (eptifibatid (0.09-0.18 mg/kg) or abciximab (0.125-0.25 mg/kg)).

After EVT, patients are monitored at a neuro-intensive care-unit with clinical status and mean arterial blood-pressure (MAP 70-100 mmHg) for at least 24 hours.

Twenty-four hour follow-up CT is performed to assess infarct-size and potential hemorrhagic transformation before dual antiplatelet-therapy is continued for three months (aspirin plus clopidogrel or prasugrel, adjusted according to platelet-function testing) followed by lifelong mono therapy. Symptomatic hemorrhages are defined as intracerebral hemorrhage causing more than 3 points increase in NIHSS[15].

Patients have 3-months follow-up with assessment of the modified Ranking Scale (mRS) and stent patency on duplex sonography or CT-angiography.

All patient cases treated with EVT for acute ischemic stroke from September 2011 to December 2015 were retrospectively reviewed. Patients with extracranial carotid lesions were selected for

this investigation and patients with resolved intracranial clots at the time of neurointervention were included. Clinical and procedural details were extracted from electronic charts, procedure descriptions and review of the neuroimaging studies.

Results:

From 413 patients with anterior circulation acute ischemic stroke referred to us for EVT, 84 patients (20%) with extracranial carotid lesions and intracranial embolism were identified. Sixty-three patients of which 47 have previously been reported[14], had persistent intracranial occlusions that required thrombectomy and were therefore excluded from this study. Nineteen patients (23%), included in this study, had extracranial carotid lesions but showed intracranial recanalization after traversal trough the carotid lesion (**Online illustrative case-history)**.

Median age was 62 years (range 43-79) (Table 1). Eleven patients (58%) were male. Median NIHSS at the primary stroke-centers was 13 (range 4-23) and NIHSS 11 (range 3-23) prior to EVT (Figure 1). Fourteen patients (74%) were treated with 'drip-and-ship' iv-rtPA. Eleven procedures (58%) were performed in general anesthesia and eight (42%) in conscious sedation. Twelve patients (63%) had carotid occlusions and seven patients (37%) had high-grade stenosis. Ten patients (53%) had arterial dissection and nine patients (47%) had atherosclerotic lesions. Median onset-to-carotid-revascularization time was 335 minutes (range 220-482). Stenting was successful in 18 patients (95%). One patient experienced continues stent-thrombosis and embolism despite antithrombotic medication and the interventionalist chose to coil the stent because of excellent collateral supply. He recovered without deficits (mRS=0 at follow-up). Five patients received aspirin, five patients received GPIIb/IIIa inhibitor, and nine patients received a combination of both prior to stent-placement. Thirteen patients (68%) had mRS of 0-2 at 3-months follow-up. Four patients (21%) had asymptomatic hemorrhagic transformations and three patients (16%) had symptomatic parenchymal hemorrhages. Three patients died, two (11%) from symptomatic intracranial hemorrhage (day 1 and 4) and one (5%) from in-stent thrombosis (day 1). Two patients (11%) had periprocedural in-stent thrombosis successfully managed with intra-arterial treatment. Of the 15 surviving patients with patent stents at discharge, thirteen (87%) had patent stents at 3-months follow-up and two (13%) had no radiological follow-up but was clinically stable. Long-term clinical follow-up (median 20 months, range 6-48) revealed that the one patient (7%) without

radiological follow-up died of cancer 7 months after stenting, one patient (7%) had minor transitory ischemic attack 29 months after stenting with no sequelae and the remaining 13 patients (86%) had no recurrent ischemic events.

Discussion:

Extracranial carotid occlusions or high-grade stenosis pose a significant therapeutic conundrum for endovascular management of acute ischemic stroke and possibly jeopardize sufficient cerebral perfusion even when intracranial recanalization has been achieved. After access to the intracranial vasculature was achieved, up to one in four patients initially presenting with concurrent extracranial carotid occlusion/high-grade stenosis and intracranial embolism were found to have recanalized intracranially in this and previous reports[1–3]. For these patients, acute carotid stenting may clinch and maintain cerebral perfusion, provide sufficient blood-flow to obtain further distal revascularization[10], and prevent recurrent embolism[11]. However, acute stenting also impose risks such as the so called 'breakthrough' of cerebral autoregulation caused by cerebral hyperperfusion after recanalization of a chronic carotid occlusion/near occlusion[12], and the risks associated with dual antiplatelet therapy required to prevent in-stent thrombosis in particular when iv-rtPA has been administered[13].

To our knowledge, this therapeutic conundrum has only been contemplated as anomalies in patient cohorts otherwise treated with extracranial stenting and endovascular intracranial revascularization[1–3] while actual patient data is still missing. This study presents the first experience on 19 patients suffering acute ischemic strokes from artery to artery intracranial embolism with extracranial carotid lesions and intracranial recanalization at the time of neurointervention treated with acute carotid artery stenting.

The results of this study are comparable to previous reports suggesting favorable clinical outcome in more than 40% of patients[1–3] and mortality rates of less than 25%[1–3] (Table 2). However, we observed a slightly higher rate of symptomatic intracranial hemorrhages in this study (16%) compared to other studies (9-10%)[1,3]. Because the natural history of patients presenting with intracranial recanalization without endovascular intervention and an extracranial carotid lesion is largely unknown, we have assessed ours and similar studies'[1–3] results by comparing to reports on 1) patients with intracranial recanalization achieved with mechanical thrombectomy and no

stenting[16–18], and 2) patients with acute ischemic stroke and carotid occlusions only treated with IV-rtPA[19] (Table 2).

Comparing to reports on patients with mechanical thrombectomy and ipsilateral carotid lesions without stenting[16–18] we find a similar safety profile, but interestingly, it appears that the 3-months outcomes were better with carotid stenting. Interpretation is, however, hampered by only small studies describing these patients, and not all studies reported whether the carotid lesions were addressed in the post-acute phase. Comparing to medical therapy alone[19] it appears that patients treated with carotid stenting achieve both improved rates of favorable clinical outcome and lower rates of mortality.

Benchmarks for EVT in acute ischemic stroke management have recently been established in five randomized controlled trials[4–8] encouraging recommendation of EVT with the highest evidence in the guidelines[20]. Although a direct comparison is impossible, this and previous published reports[1–3] on carotid stenting in patients with intracranial recanalization suggest results in line with the benchmarks from recent published thrombectomy trials (Table 2).

In our opinion, the predominant caveat of carotid stenting in acute ischemic stroke remains to be symptomatic intracranial hemorrhage. Carotid stenting seems to increase the risk of symptomatic intracranial hemorrhages compared both to medical therapy alone[19] and to the recent randomized thrombectomy trials[4–8]. This is most likely the result of potent antiplatelet administration accompanying acute stenting. However, the rate of in-stent thrombosis occurring during or immediately after the procedure of up to 16% observed in this and other studies[1,3] despite dual antiplatelet therapy displays the necessity for antithrombotic agents. Further improvements or alternatives to antiplatelet therapy are required in order to tailor the antithrombotic regimen to each patient and prevent both in-stent thrombosis and hemorrhagic complications in this setting.

The caveats of acute stenting may be avoided in patients where carotid stenting is not a prerequisite for gaining access to the intracranial vasculature by postponing management of the extracranial carotid lesion to a later time point which has been suggested to decrease the risk of the hyperperfusion phenomenon in elective stenting[21]. However, in patients with recently symptomatic carotid lesions recurrent embolism is estimated to occur in up to 20% of patients

within 72 hours[22], the risk of severe re-stenosis or re-occlusion may be as high as 66%[16], and insufficient cerebral perfusion may risk loss of salvageable cerebral tissue in the ischemic penumbra. Except for two patients that could not be radiologically studied, none of the surviving patients in our study had stent-occlusions or recurrent ischemic events at 3 months follow-up. Furthermore, no patient suffered fatal or disabling stroke during clinical follow-up suggesting that the long-term durability of acute stenting is satisfactory and comparable to the ICSS-study[23] further advocating the benefits of this intervention.

Our study suggests that this therapeutic conundrum is not a rare occurrence in endovascular acute ischemic stroke treatment and with an expected increase in patients referred for endovascular stroke therapy after the recent positive trials it will be faced more often in the future. Although results from this and previous reports suggest reasonable safety and feasibility of acute carotid stenting in patients with extracranial carotid lesions and intracranial recanalization, no final recommendations can be made from small non-randomized patient series. Therefore, more studies on this conundrum are urgently needed, preferably together with studies reporting the natural history of these patients. In the end clinical trials comparing efficacy and safety of acute carotid stenting versus delayed carotid management are required to answer the important question – to stent or not to stent?

Limitations: This is a single-center retrospective study with a limited sample-size and may not reflect clinical practice and outcomes observed at other centers. Although an accepted referral algorithm existed prior to this study, patients were referred on a case-by-case basis introducing possible selection bias. However, all consecutive patients were included and substantial numbers are not believed to have been missed due to the high capacity and 24/7 service provided. Results from this study should be interpreted with caution until validated in clinical studies.

Conclusion: Clinical and radiological outcomes after extracranial carotid stenting in acute ischemic stroke patients with intracranial recanalization seem satisfactory. However, periprocedural complications and post-procedural symptomatic intracranial hemorrhages observed call for clinical trials to assess the risk-benefit of this approach before recommendations for clinical practice can be made.

Ethical standards:

All procedures were in accordance with the Declaration of Helsinki. This study was approved by the Danish Health Authority (3-3013-1017/1) and the Danish Data Protection Agency (30-1148). Ethical committee approval was waived because of the retrospective nature of the study. The authors report no conflicts of interest for this study.

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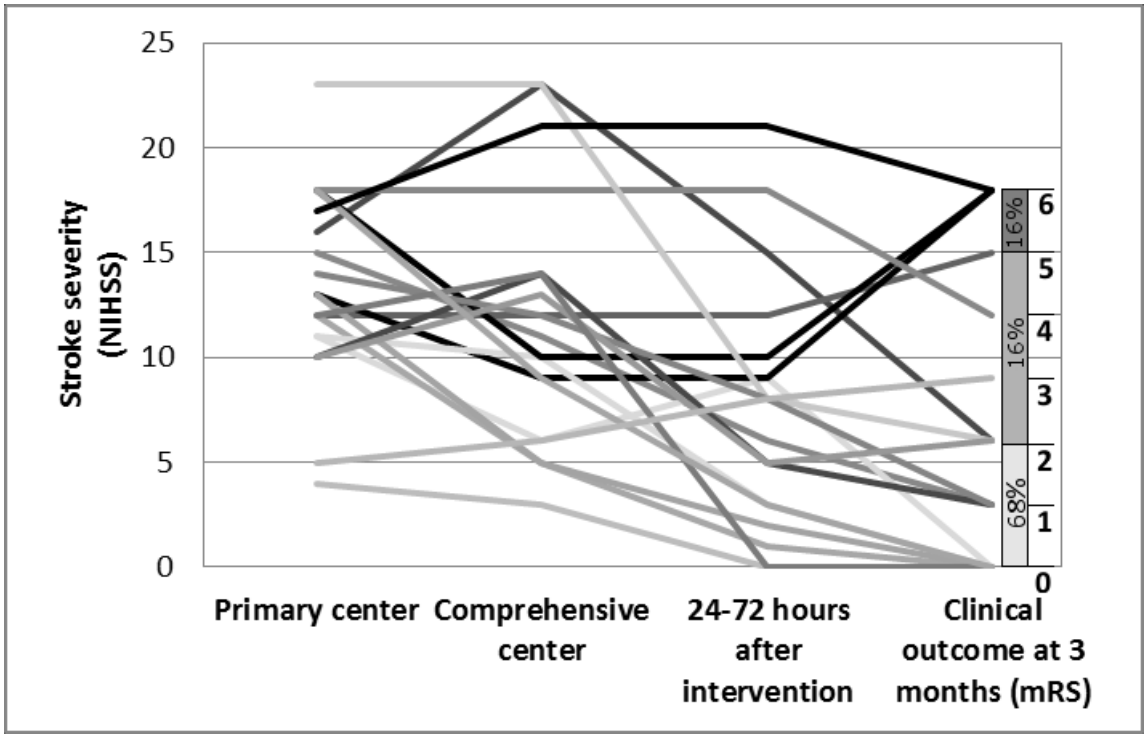


Figure 1 legend: Clinical course from first presentation to 72 hours with 3-months follow-up.

Table 1	
Age	62 years (43-79)
Male	11 (58%)
NIHSS primary stroke-center	13 (4-23)
NIHSS comprehensive stroke-center	11 (3-23)
Intravenous thrombolysis	14 (74%)
General anesthesia	11 (58%)
Onset-to-carotid-revascularization time	335 minutes (220-482)

Table 1 legend: Patient characteristics. Continuous variables are presented as median with range.

Abbreviations: NIHSS: National Institute of Health Stroke Scale.

Table 2									
	Study size	**Mean Age**	**Mean NIHSS**	**IV-rtPA**	**TICI 2b-3**	**mRS 0-2**	**Mortality**	**sICH**	**Acute stent thrombosis/ distal stent embolism**
Intracranial recanalization without EVT plus carotid stenting									
Authors' experience (2016)	19	62	11	74%	89%	68%	16%	16%	16%
Malik et al (2011)	18/77 (23%)#	63*	15*	NR	75%*	42%*	25%*	10%*	4%*
Son et al (2014)	3/11 (27%)#	71*	7	100%	100%	100%	0%	NR	0%
Yoon et al (2015)	7/42 (17%)#	71*	14*	64%*	76%*	55%*	6%*	9%*	4%*
Weighted averages$	**47**	**64**	**13**	**74%**	**82%**	**58%**	**17%**	**12%**	**9%**
Intracranial recanalization with EVT minus carotid stenting									
Lescher et al (2014)	30	68	15	73%	67%	37%	10%	13%	NR
Woodward et al (2015)	5/7¤ (71%)	64*	12*	29%*	100%	86%*	14%*	0%*	NR
Soize et al (2014)	9/11¤ (82%)	69*	19*	55%*	82%*	18%*	45%*	10%*	NR
Weighted averages$	**44**	**68**	**15**	**64%**	**74%**	**39%**	**18%**	**11%**	**NR**
Medical therapy alone									
ICARO (2012)	253	65	15	100%	NR	29%	26%	5%	NR
Recent randomized thrombectomy trials (intervention arm)									
MR-CLEAN (2015)	233	66	17	87%	59%	33%	19%	8%	NR
ESCAPE (2015)	165	71	16	73%	72%	53%	10%	4%	NR
SWIFT-PRIME (2015)	98	65	17	100%	88%	60%	9%	0%	NR
REVASCAT (2015)	103	66	17	68%	66%	44%	18%	5%	NR
EXTEND-IA (2015)	35	69	17	100%	86%	71%	9%	0	NR
Weighted averages$	**634**	**67**	**17**	**83%**	**69%**	**46%**	**14%**	**5%**	**NR**

Table 2 legend: Overview of studies for comparison.

Abbreviations: NIHSS: National Institute of Health Stroke Scale, IV-rtPA: Intravenous recombinant tissue plasminogen activator, TICI: Thrombolysis In Cerebral Infarction Score, mRS: Modified Rankin Scale Score, sICH: Symptomatic intracranial hemorrhages defined by author, NR: Not reported

#Patients with intracranial recanalization / entire study cohort

¤Patients without extracranial stenting / entire study cohort

*Reports from entire study cohort

$Averages weighted according to study size.

Online only table 1 – Detailed device list	
Devices	**Used in number of patients**
Access sheaths:	
6F Destination 90cm (*Terumo Interventional Systems, Tokyo, Japan*)	8 (42%)
6F-8F Arrow 80 cm (*Arrow International, Reading, PA, USA*)	6 (32%)
6F Neuron Max 80-90cm (*Penumbra Inc., Alameda, CA, USA*)	3 (16%)
Other:	2 (11%)
Diagnostic catheters:	
5F JB1 125cm (*Cook Medical, Bloomington, IN, USA*)	12 (63%)
5F SIM2 125cm (*Cook Medical, Bloomington, IN, USA*)	4 (21%)
6F Envoy MPD & SIM2 100cm (*Codman Neuro, Raynham, NA, USA*)	3 (16%)
DAC 0.038”-0.057” (*Concentric Medical Inc., Mountain View, CA, USA*)	2 (11%)
Other:	3 (16%)
Microcatheters:	
Prowler Select Plus (*Codman Neuro, Raynham, NA, USA*)	8 (42%)
Vasco (*BALT Extrusion, Montmorency, France*)	3 (16%)
Reflex/Navian (*Reverse Medical/Covidien, Irvine, CA, USA*)	8 (42%)
Guidewires:	
Traxcess .014” (*MicroVention, Tustin, CA, USA*)	9 (47%)
Transcend .014” (*Stryker Neurovascular, Fremont, CA, USA*)	4 (21%)
ChoICE PT .014” (*Boston Scientific, Natick, MA*)	4 (21%)
Synchro .014” (*Stryker Neurovascular, Fremont, CA, USA*)	1 (5%)
Carotid stents:	
Wallstent 5-7mm (*Boston Scientific, Natick, MA*)	14 (74%)
LEO+ 3.5-4.5mm(*BALT Extrusion, Montmorency, France*)	4 (21%)
Pharos Vitesse 4.5mm (*Micrus Endovascular, San José, CA, USA*)	2 (11%)
CASPER Carotid Artery Stent 7mm (*MicroVention, Tustin, CA, USA*)	2 (11%)
Neuroform EZ 3.5mm (*Stryker Neurovascular, Fremont, CA, USA*)	1 (5%)
Telescopic stenting technique	7 (37%)
Pre-dilatation (Maverick 2.0mm-3.5mm (*Boston Scientific, Natick, MA*))	7 (37%)
Post-dilatation (Maverick 3.5mm-5.5mm)	14 (74%)

Illustrative case history:

We present an acute stroke patient presenting with sudden onset of left-sided hemiparesis and hemianopia (NIHSS 15).

CTA at the primary stroke center 1 hour and 42 minutes after onset revealed a right extracranial ICA-dissection and concomitant M1-occlusion (Online figure 1 A+B).

The patient was treated with intravenous thrombolysis 2 hours and 20 minutes after symptom onset and was transferred to our comprehensive stroke-center.

The patient arrived at the comprehensive stroke-center 3 hours and 30 minutes after symptom onset and showed largely unchanged neuro deficit.

DSA in general anesthesia revealed an ICA-occlusion (Online figure 1, C), but after traversal of the ICA-occlusion intracranial recanalization was found. However, very slow flow was observed to the right hemisphere with no significant washout of contrast and hemodynamic compromise was suspected (Online figure 1, D).

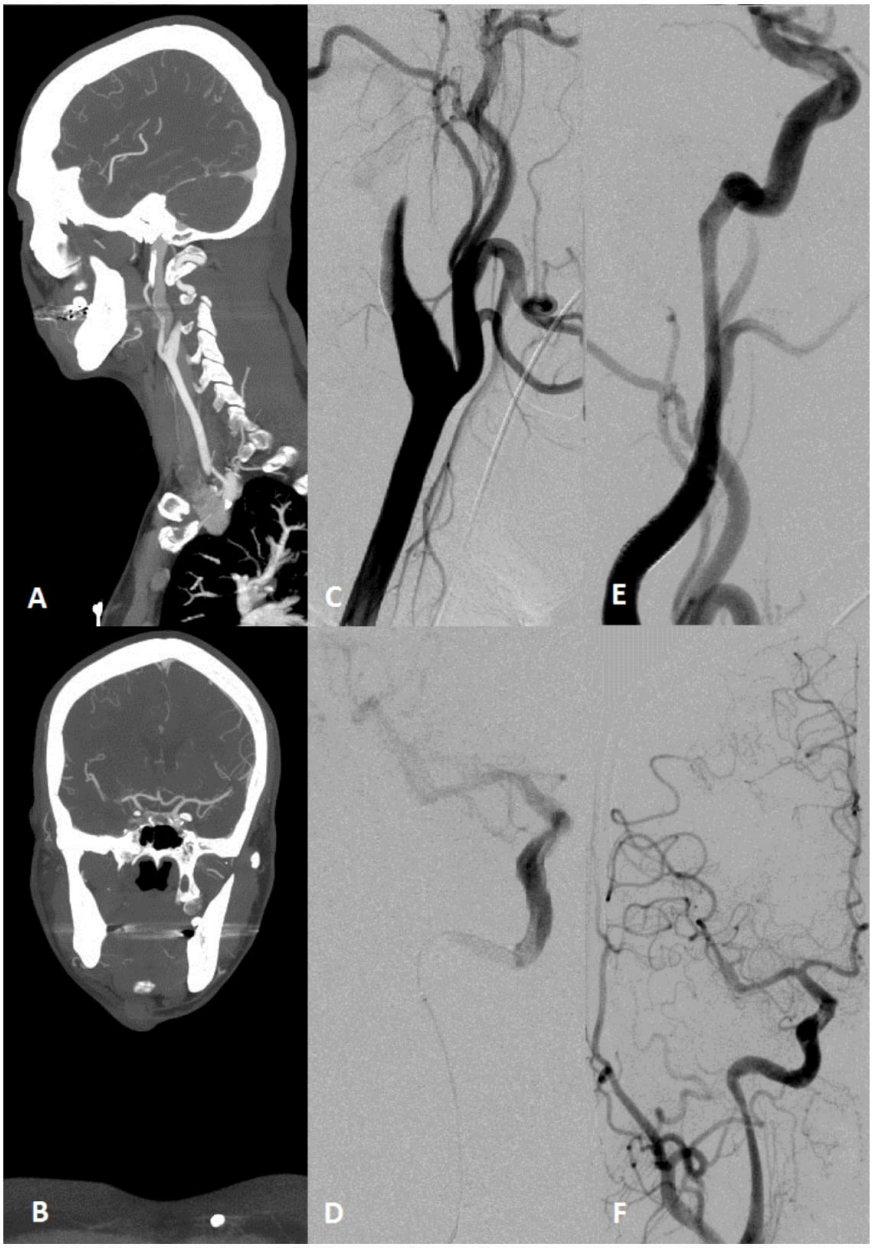
Therefore, the interventionalist chose to stent the carotid occlusion to ensure adequate cerebral perfusion and prevent further embolism from the extracranial carotid lesion. Carotid recanalization was achieved at 6 hours and 4 minutes after onset (Online figure 1, E+F).

Follow-up CT revealed a minor infarct and no intracranial hemorrhage (Online figure 2), and the patient had improved to NIHSS 6.

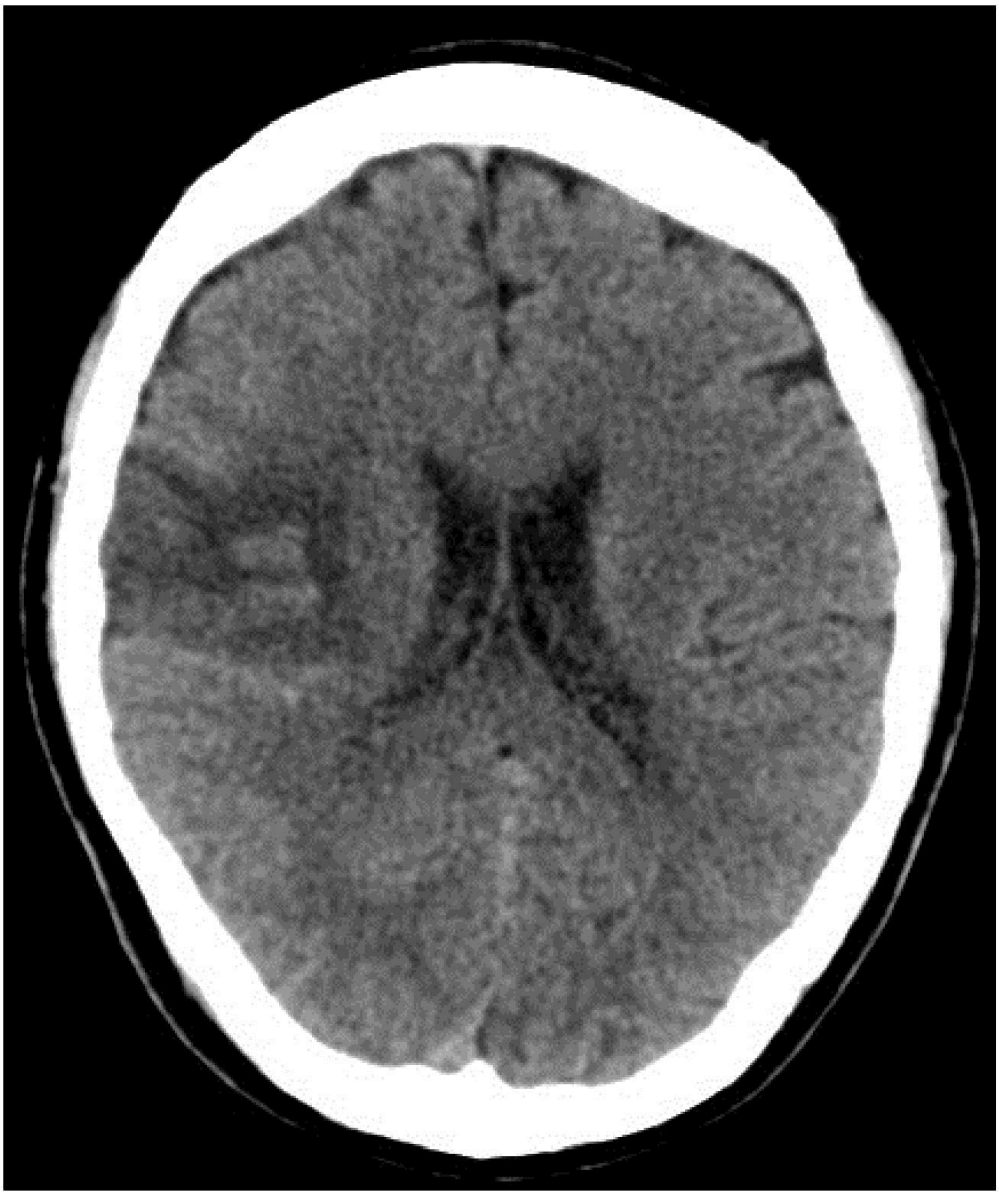
The patient continued to improve and at 3-months follow-up the stent was open and the patient presented a clinical outcome of mRS 2 with a persistent left-sided hemianopia and facial palsy.

Abbreviations:

NIHSS: NIH Stroke Scale; CTA: Computer tomography angiogram; ICA: Internal carotid artery; M1: Middle cerebral artery segment 1; DSA: Digital subtraction angiography; CT: computer tomography; mRS: Modified Rankin Scale.



Online figure 1: **A+B**, Concomitant ICA-M1 occlusions on CTA. **C**, ICA occlusion (dissection) on DSA. **D**, Injection distal to ICA-occlusion: M1 recanalized with hemodynamic compromise. **E**, ICA successfully stented. **F**, Intracranial recanalization.



Online figure 2: Follow-up CT 24 hours after intervention.

Paper 3

Carotid artery stenting versus no stenting assisting thrombectomy for acute ischaemic stroke. A systematic review.

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Abstract:

Background: In patients with intracranial large-vessel arterial occlusion, ipsilateral extracranial carotid artery occlusions or near-occlusions pose a significant obstacle in endovascular management of acute ischaemic stroke. Stenting of the carotid lesion may be beneficial in this situation to provide a stable access for introducing catheters through the carotid lesion into the intracranial vasculature and the target occlusion. Furthermore, carotid stenting may ensure ample blood-flow for wash-out of clot material and reperfusion of the ischaemic penumbral tissue. However, antiplatelet therapy administered to prevent stent-thrombosis and sudden increase in blood-flow after reopening

of the carotid lesion may increase the risk for intracranial haemorrhagic complications. This review aims to assess the benefits and harms of carotid stenting vs. no stenting assisting thrombectomy for acute ischaemic stroke.

Methods: We conducted a systematic review according to our published protocol. International and regional electronic databases were searched to identify eligible randomised clinical trials and grey literature was sought. We planned to include randomised controlled trials for assessing benefits and harms and quasi-randomised studies and observational studies for assessing harms of the intervention. The quality of the evidence identified was evaluated with the Grading of Recommendations Assessment, Development, and Evaluation.

Results: No randomised controlled trials were identified. We identified 11 observational studies with only two reporting unexposed groups. All studies were assessed having serious risk of bias leaving the quality of evidence at 'very low' for all outcomes. In total 391 patients with follow-up data were stented and 61 patients were not. Rates of all-cause mortality were 17% [13.3-21.0], modified Rankin Scale $\geq$ 3 were 53% [47.9-58.0], and symptomatic haemorrhages were 8% [5.7-11.8] among the stented patients.

Conclusion: No evidence from randomised controlled trials for carotid stenting assisting intracranial thrombectomy for acute ischaemic stroke was identified and the current quality of evidence for this intervention is 'very low'. This review suggest reasonable safety compared to recent benchmarks for endovascular acute ischaemic stroke therapy thus paving the road for future randomised controlled trials investigating this therapeutic conundrum.

Trial registration: Prospero CRD42016033346

Keywords: Stroke, thrombectomy, acute, carotid, carotid occlusion, stenting

Background

Description of the condition

Acute ischaemic stroke is the leading cause of acquired long-term disability and the fourth most common cause of death [1]. The severity of acute ischaemic stroke varies from minor focal neurological deficits over life-threatening hemispheric syndromes to death. Due to the high oxygen requirement of brain tissue, expeditious management is crucial for reversal of ischaemia and successful salvage of the tissue at risk [2]. Large intracranial emboli cause severe ischaemic stroke with poor outcome and poor response to medical therapy alone due to the large clot burden [3,4]. A particular harmful configuration of large vessel occlusions is the carotid artery occlusion or near-occlusion in combination with intracranial embolism. This configuration is suggested to be the cause of acute ischaemic stroke in up to 20% to 30% of patients with large vessel occlusions [5–9]. The carotid occlusion or near-occlusion is caused by an arterial dissection or atherosclerotic plaque. It releases an often large clot into the intracranial vasculature causing severe stroke symptoms. Usually, carotid occlusions or near-occlusions can be compensated haemodynamically via the circle of Willis [10], but not in the case of an embolus lodged in the middle cerebral artery [11].

Administration of intravenous recombinant tissue plasminogen activator (iv-rtPA) is currently the recommended first-line treatment for acute ischaemic stroke if it can be administered within 4.5 hours of symptom onset [12,13]. However, in patients suffering moderate to severe stroke from acute large vessel occlusions iv-rtPA is often ineffective [4,14]. Cohort studies suggest that iv-rtPA administration alone only leads to clinical improvement in 20% to 30% of patients with concomitant extracranial carotid and intracranial occlusions [14–17]. Carotid endarterectomy is not the preferred option, since surgery would only address the extracranial carotid lesion without access to the intracranial occlusion. Furthermore, open surgery is relatively contraindicated with recent iv-rtPA administration, as open surgery has a high complication rate in the very urgent phase of acute stroke [18], and is not advocated to repair carotid dissections [19].

Endovascular therapy with mechanical thrombectomy or intra-arterial thrombolysis of large intracranial occlusions have long been considered a possible adjuvant to medical therapy although initial randomised controlled trials failed to reveal clear benefits [20–22]. However, since 2015 six randomised controlled trials have shown superior outcomes of endovascular therapy compared with

medical therapy alone [7–9,23–26]. This lead to thrombectomy of large intracranial occlusions being recommended in the American Heart Association guidelines for acute ischaemic stroke therapy with the highest evidence (Class I, Level of Evidence A) [27]. The primary target of endovascular therapy in patients with carotid lesions and concomitant intracranial embolism is removal of the intracranial clot material. Endovascular therapy has the advantage of being able to access the intracranial thrombus either directly through the ipsilateral carotid lesion or indirectly via collateral vessels [28]. The indirect access via contralateral vessels is technically challenging and depends on favourable anatomy of the circle of Willis. The direct access is more straightforward but bares the risks with penetrating the wire through a carotid occlusion or near-occlusion unable to predict passage within the true lumen resulting in dissection of the vessel wall as well as dislodgement of thrombotic material distal to the carotid lesion.

Description of the intervention

The concerns of the direct access approach in endovascular management of acute ischaemic stroke can to some extend be compensated by carotid stent-assisted angioplasty [29]. A carotid stent can easily be provided through the catheters used for mechanical thrombectomy [11,30–37]. However, introduction into the carotid lesion poses an obstacle if the carotid artery is occluded or severely stenotic. In this case, the carotid lesion may need to be balloon pre-dilated with a balloon-catheter to ensure adequate lumen for traversal of the stent through the carotid lesion [11,30–37]. Carotid stents are mostly self-expanding which means they expand to a pre-specified diameter when subjected to the heat inside a vessel. However, some carotid lesions are so dense that the carotid stent needs balloon post-dilatation to ensure adequate lumen inside and flow through the stent. Other carotid lesions, in particularly dissections, are soft and do not necessarily require stenting prior to treating the intracranial occlusion. Such soft occlusions can be overcome by probing with the wire and assuring intraluminal passage by contrast injections through the microcatheter distal to the occlusion. Management of the soft carotid lesions may then be performed when retracting the catheters.

To prevent in-stent thrombosis, antithrombotic therapy is needed. To our knowledge, no evidence based antithrombotic regimen exists for carotid stenting in endovascular management of acute ischaemic stroke [38], and patients are treated on a patient-by-patient basis at the discretion of the neurointerventionalist using various protocols adapted from percutaneous coronary intervention. Most centres seem to favour administration of mono- or dual antiplatelet therapy immediately after

stent placement and continue with dual antiplatelet therapy after intracerebral haemorrhage has been excluded after the procedure [11,30,34,36,37].

How the intervention might work

Carotid stenting may be beneficial in acute ischaemic stroke treatment because deployment of a stent with or without angioplasty establishes immediate patency of the carotid lesion preventing vessel recoil and secures continuous catheter access to the intracranial vessels. It stabilises and protects the endothelium preventing iatrogenic dissection of the vessel wall. Furthermore, acute stenting ensures ample blood flow to the intracranial vasculature, especially in case of contralateral carotid lesions or unfavourable anatomy of the circle of Willis, and may assist intracranial recanalisation [38]. Other advantages of acute carotid stenting include acute prevention of recurrent thrombus formation and embolism from the carotid lesion, which is suggested to occur in up to 16% of patients within 24 hours [39], and avoidance of a subacute procedure to prevent recurrent ischaemic events [18,40]. Acute carotid stenting may, as mentioned above, be performed before or after addressing the intracranial occlusion. Stenting the carotid lesion prior to addressing the intracranial occlusion may provide anatomical orientation by increased flow through the carotid lesion, prevent blind probing of the distal carotid artery, and ease the passing of larger guides, catheters and other tools. Stenting after addressing the intracranial occlusion may result in shorter delay to intracranial recanalisation [33,34].

Carotid stenting in the acute ischaemic stroke setting is, however, not without concerns. Immediate dual antiplatelet therapy already administered during the procedure is required to prevent acute stent thrombosis [41]. Potent aggressive antiplatelet therapy may increase the risk of haemorrhagic stroke as well as procedural bleeding complications [42,43] – especially following recent iv-rtPA administration [44]. Furthermore, increased cerebral blood flow, seen in patients with recanalisation of chronic carotid occlusions or near-occlusions, may induce the cerebral hyper-perfusion syndrome and risk intracerebral haemorrhage [45]. Finally, if met with difficulties, preparatory carotid stenting may delay intracranial revascularisation [33,34].

Why it is important to do this review

To our knowledge, only observational studies have assessed this important topic [38]. All of these patient series seem to report reasonable benefit and safety [11,30–37]. A systematic review will

provide a thorough assessment of the evidence for this intervention and illustrate the areas that require further research. Because of the before mentioned risks of carotid stenting in acute ischaemic stroke, this review is important to assess if carotid stenting in endovascular therapy is beneficial and safe.

Objectives

To assess the benefits and harms of acute extracranial carotid artery stenting versus no stenting in patients with acute ischaemic stroke caused by an extracranial carotid occlusion or near-occlusion in association with thrombectomy for concomitant intracranial embolism.

Methods

Criteria for considering studies for this review

Types of studies

This review will include randomised clinical trials for assessments of benefits and harms and quasi-randomised studies and observational studies for assessments of harms of the intervention.

Types of participants

Participants were adults (≥18 years) with acute ischaemic stroke caused by a carotid artery occlusion or near-occlusion with concomitant ipsilateral embolism to a major intracranial vessel identified on CT-angiography, MR-angiography, or duplex sonography and confirmed on digital subtraction angiography. Participants need to be treated within 6 hours of symptom onset.

Types of interventions

The experimental group were patients who were randomised to undergo extracranial carotid stenting within the same procedure as the intracranial thrombectomy. Carotid stenting may be performed before or after intracranial thrombectomy using any endovascular stent device.

The comparison group were patients who were randomised to avoid carotid stent deployment. The comparison group may undergo carotid angioplasty without stenting, patent artery occlusion of the

carotid artery after successful thrombectomy, or no carotid intervention within the same procedure as intracranial thrombectomy.

Co-interventions were allowed if they were used equally in both the intervention and comparison groups. However, co-interventions (such as pre- or post-dilatation of the carotid artery to facilitate stent deployment) that are generally regarded as a prerequisite for the intervention were accepted as an integrated part of the experimental intervention. Antiplatelet therapy is administered within the endovascular procedure following stent-deployment in most patients of the intervention group while this is not the case for the comparison group and patients with successful carotid stenting have tightly controlled and treated mean arterial blood pressure typically not exceeding 100 mmHg after the procedure. These co-interventions were allowed as an integrated part of the experimental intervention although they are not used equal in both groups of a trial.

Types of outcome measures

Outcomes were assessed after three months (primary outcome time point) and at maximal follow-up.

Primary outcomes

- All-cause mortality.

- Dependent clinical appearance measured as a score on the modified Rankin Scale of 3 or more.

- Serious adverse events defined as: any untoward medical occurrence that is life threatening, results in death or persistent or significant disability, or any other event that may have jeopardised the participant or require intervention to prevent it [46].

Secondary outcomes

- Quality of life.

- Non-serious adverse events.

Exploratory outcomes

- Haemorrhagic complications (symptomatic/asymptomatic).

- Periprocedural embolic events into new territory.

- Recurrent ipsilateral ischaemic stroke during follow-up.

Search methods for identification of studies

Electronic searches

The searches included the following electronic databases:
- Cochrane Central Register of Controlled Trials
(http://www.thecochranelibrary.com/view/0/index.html)

- PubMed (http://www.ncbi.nlm.nih.gov/pubmed)

- Embase (http://www.embase.com)

- Stroke Trials Directory (www.strokecenter.org/trials)

- Clinicaltrials.gov (www.clinicaltrials.gov)

- Current controlled trials (www.controlled-trials.com)

- World Health Organisation's International Clinical Trials Registry Platform
(http://apps.who.int/trialsearch/Default.aspx)

Regional databases

- African Index Medicus (http://indexmedicus.afro.who.int/)

- Australasian Medical Index (http://www.nla.gov.au/ami/ and
http://www.informit.com.au/health.html)

- Chinese Biomedical Literature Database (CBM) (in Chinese) (http://www.imicams.ac.cn/)

- Index Medicus for the Eastern Mediterranean Region (http://www.emro.who.int/his/vhsl/)

- IndMED (http://indmed.nic.in/)

- KoreaMed (http://www.koreamed.org/SearchBasic.php)

- LILACS (http://lilacs.bvsalud.org/en/)

- Index Medicus for the South-East Asia Region (http://imsear.hellis.org/)

- Western Pacific Region Index Medicus (http://www.wprim.org/)

An example of the electronic database search presented in PubMed format:

1. exp Stents/
2. ((carotid and stent*) or CAS).mp.
3. exp Thrombectomy/
4. (thrombectom* or thrombolys*).mp
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. exp Brain Ischemia/
9. exp Carotid Stenosis/
10. (stroke or isch*emi* or (carotid and (occlusion or near-occlusion or stenos* or obstruct*)) or apople*).mp.
11. 8 or 9 or 10
12. 7 and 11

Searching other resources

To identify further published, unpublished, or on-going and planned trials the following measures were taken:

- Search Google Scholar.

- American Food and Drug Administration (FDA).

- European Medicines Agency (EMA).

- Health Canada (http://www.hc-sc.gc.ca/index-eng.php)

- Australian Therapeutic Goods Administration (TGA https://www.tga.gov.au/).

- China Food and Drug Administration (CFDA http://eng.sfda.gov.cn/).

- Brazilian Health Surveillance Agency (ANVISA http://portal.anvisa.gov.br/wps/portal/anvisa-ingles).

- Mexican Federal Commission for the Protection against Sanitary Risk (COFEPRIS http://www.cofepris.gob.mx/Paginas/Idiomas/Ingles.aspx)

- Argentinian National Administration of Drugs, Foodstuffs and Medical Technology (ANMAT http://www.anmat.gov.ar/principal_en.asp)

- Columbian National Food and Drug Surveillance Institue (INVIMA https://www.invima.gov.co/)

- Thailand Food and Drug Administration (TFDA http://www.fda.moph.go.th/eng/index.stm)

- Taiwan Food and Drug Administration (TFDA http://www.fda.gov.tw/EN/)

- Singapore Health Sciences Authority (HAS http://www.hsa.gov.sg/content/hsa/en.html)

- Japanese Pharmaceuticals and Medical Devices Agency (PMDA http://www.pmda.go.jp/english/index.html).

- South Korea Ministry of Food and Drug Safety (MFDS http://www.mfds.go.kr/eng/index.do)

- Indian Central Drugs Standard Control Organisation (http://cdsco.nic.in/forms/contentpage1.aspx?lid=1423)

- Home pages of companies producing devices for the interventions.

- Screening reference lists of relevant trials.

- Contact manufacturers of relevant interventional equipment.

- Contact authors, colleagues, and researchers active in the field.

- Identify and hand-search the proceedings of relevant conferences.

- Use the Science Citation Index Cited Reference search for forward tracking of relevant references.

No language or date restrictions were applied to the searches.

Data collection and analysis

Selection of studies

Two review authors (Henrik Steglich-Arnholm and Derk W. Krieger) independently screened titles and abstracts identified by the searches. Henrik Steglich-Arnholm, Derk W. Krieger, and Marcus Holtmannspötter assessed the full paper copies for inclusion into the review. Disagreements were resolved by discussion between the review authors.

Data extraction and management

Two review authors (Henrik Steglich-Arnholm and Markus Holtmannspötter) independently extracted data from each eligible trial onto a standard designed data extraction form. Review authors were not blinded to journal or institution. There were no disagreements.
Confidence intervals of proportions were calculated using the Clopper-Pearson exact confidence interval (CI).

Please see our published protocol for further details and planned analyses [47].

Dealing with missing data

Authors of the original studies were contacted in attempt to obtain further details.

Results

The search was performed by a trials search coordinator at the Copenhagen Trial Unit on April 12th 2016. Please see Figure 1 for the process of how studies were identified for inclusion into this review and Appendix 1 for studies excluded from this review. No randomised controlled trials were identified. We identified 11 cohort studies for inclusion where only two reported an unexposed group[11,34,37,48–54]. Unpublished data was obtained from two studies [53,54] after contacting the authors. All studies were assessed with having serious risk of bias for all outcomes.

The 11 included studies reported 392 patients with concomitant extracranial carotid lesions and intracranial embolism treated with extracranial carotid stenting and intracranial thrombectomy and only 63 patients treated without carotid stenting (Table 1). One study reported loss to follow-up in 1 stented patient and 2 non-stented patients, thus outcomes were known for 391 stented patients and 61 non-stented patients at 3 months (Table 2). To assess harms of the intervention we recorded all harms reported in the included studies and in further two single case reports (Table 3).

For the stented patients, we were able to identify five studies reporting orally administered or no antiplatelet therapy during intervention and five studies reporting intravenously administered antiplatelet therapy during intervention allowing us to perform a subgroup analysis comparing these studies (Table 4).

Discussion

Acute ischaemic stroke caused by concomitant extracranial carotid lesions and intracranial embolism is a devastating disease and pose a significant challenge for therapy. This review was unable to identify any evidence from randomised controlled trials for acute carotid stenting in this setting. Only 11 observational studies were identified and a mere two of them reported comparison groups with non-stented patients. All studies were assessed with having serious risk of bias.

Endovascular therapy with stent-retrievers has with the publication of six randomised controlled trials since 2015 shown high evidence for superiority for large vessel occlusion acute ischaemic stroke treatment compared to medical therapy alone [7–9,23,24,26]. Not all trials included patients with concomitant extracranial carotid lesions and intracranial embolism. Furthermore, carotid stenting was only performed in less than half of these patients in the trials in which they were included [7–9]. Meta-analysis of individual patient data from the first five randomised controlled trials have suggested improved outcomes with endovascular- compared to medical therapy in the 122 patients with concomitant extracranial carotid lesions and intracranial embolism [25]. This meta-analysis did, however, not investigate which effect carotid stenting had on the result. These trials currently represent the benchmarks for acute endovascular stroke therapy. Since we were only able to identify very few studies reporting an unexposed group, we will assess the harms and benefits of carotid stenting assisting intracranial thrombectomy by comparing results in this review with the benchmarks from the recent randomised controlled stroke trials.

The rates of serious adverse events (16%) and non-serious adverse events (3%) in this review is substantial lower than the rates reported in the recent randomised controlled trials (21.1%-54.5%) [7–9,24,26]. Although observational studies are often considered better for reporting rare adverse events, the regulatory requirements of clinical trials may result in more thorough recordings of adverse events compared to observational studies [55]. This is supported by the studies in this review almost exclusively reporting adverse events related to the nervous system. The most frequent adverse events reported were symptomatic intracranial haemorrhages followed by thromboembolism (Table 3).

The rate of symptomatic intracranial haemorrhages seemed higher in the studies in this review (8% [CI 5.7-11.8]) compared to trials reported in the meta-analysis [25] last year (4%) and the trial [26] from this year (2%). Symptomatic intracranial haemorrhage is a very severe complication which is illustrated in Table 3 suggesting that one third of all mortality was caused by intracranial haemorrhages. The higher haemorrhage rates in the group of stented patients may be explained by the antiplatelet therapy administered acutely within the procedure or by the cerebral hyperperfusion syndrome [45] caused by opening of a chronic carotid occlusion. In the subgroup analysis of patients treated with or without intravenous antiplatelet therapy in this review, the studies only administering oral or no antiplatelet therapy in the acute phase reported half the rate of symptomatic haemorrhages (4% [CI 0.8-11.2] compared to 9% [CI 5.4-12.7]). These 4% is comparable to the benchmarks from the randomised controlled trials [25,26] speaking in favour of intravenous antiplatelet therapy administered during the procedure being the main reason for the increased rate of haemorrhages observed. However, it is important to notice that only few patients without intravenous antiplatelet therapy were described and that the confidence intervals on the proportions in this subgroup analysis were wide and overlapping and a true difference may not exist.

Although potentially increasing the risk of intracranial haemorrhages, some sort of antiplatelet therapy assisting acute stenting seems necessary because stent-thrombosis and stent embolism was not a rare occurrence among stented patients (Table 3). Normally, the patient would be treated with antiplatelet therapy in amble time prior to stent-insertion to prevent thrombotic complications. But in the setting of acute ischaemic stroke platelet inhibition need to be addressed acutely. Interestingly, the subgroup analysis suggested fewer serious and non-serious adverse events in the group of studies not using intravenous antiplatelet therapy. Since antiplatelet therapy is expected to reduce the risk of stent-thrombosis and stent-embolism one would expect fewer embolisms and

stent-thrombosis and thus fewer adverse events. Because the intravenous antiplatelet therapy was reported in the studies' methods sections as routinely used in patients with carotid stenting and not as a consequence of thrombotic complications we do not believe that the increased rates of procedural adverse events in the intravenous antiplatelet groups reflects confounding by indication. Instead, this difference may be explained by reporting bias. Either affected by the small study-size in the non-intravenous antiplatelet therapy subgroup or because studies with intravenous antiplatelet therapy were more focussed on reporting thrombotic complications. In the end these proportions also have wide and overlapping confidence intervals and a larger sample, preferably from a randomised trial, could unravel this discrepancy.

The observed rates of all-cause mortality and dependent clinical outcome in this review were very similar between stented (17% [CI 13.3-21.0] and 53% [CI 47.9-58.0] respectively) and non-stented patients (15% [CI 7.0-26.2] and 57% [CI 44.1-70.0] respectively) suggesting equal benefice of the intervention (Table 2). However the group of non-stented patients was small and the included studies in this review were all assessed with serious risk of bias. Therefore the quality of evidence for these outcomes is very low and no recommendations can be made [56]. The potential benefice of carotid stenting is further supported by comparing to the rates of mortality and dependent clinical outcome reported in the meta-analysis of individual patient data (15% and 54% respectively [25]) suggesting that the risks of carotid stenting in acute ischaemic stroke may be equal to these benchmarks.

In the end, results from this review indicate reasonable safety for performing clinical trials on carotid stenting in acute ischaemic stroke. Such trials would have to at least answer the questions raised in this review: Should carotid stenting in this setting be strived for or avoided when possible? Is antiplatelet therapy best administered intravenously or enterally during the procedure? Are carotid stenting prior to or after intracranial recanalisation equal or do the order of intervention impact on outcomes?

Conclusion

Currently, only evidence from observational studies of the benefits and harms of extracranial carotid stenting assisting intracranial thrombectomy for acute ischaemic stroke exists. These studies do nevertheless suggest reasonable safety of the intervention compared to recently established benchmarks for endovascular acute ischaemic stroke therapy. The road is therefore paved towards

future randomised controlled trials assessing the benefits of carotid stenting in acute ischaemic stroke therapy.

Conflicts of interest

Markus Holtmannspötter is consulting and proctoring for MicroVention and Medtronic & Covidien.

Henrik Steglich-Arnholm, Derk W. Krieger, and Christian Gluud declare no conflicts of interest.

Funding

A research grant for covering article processing charges was supported by MicroVention. The grant provider did not participate in the production of this review and did not have access to the manuscript prior to its publication. No additional funding was required for this study.

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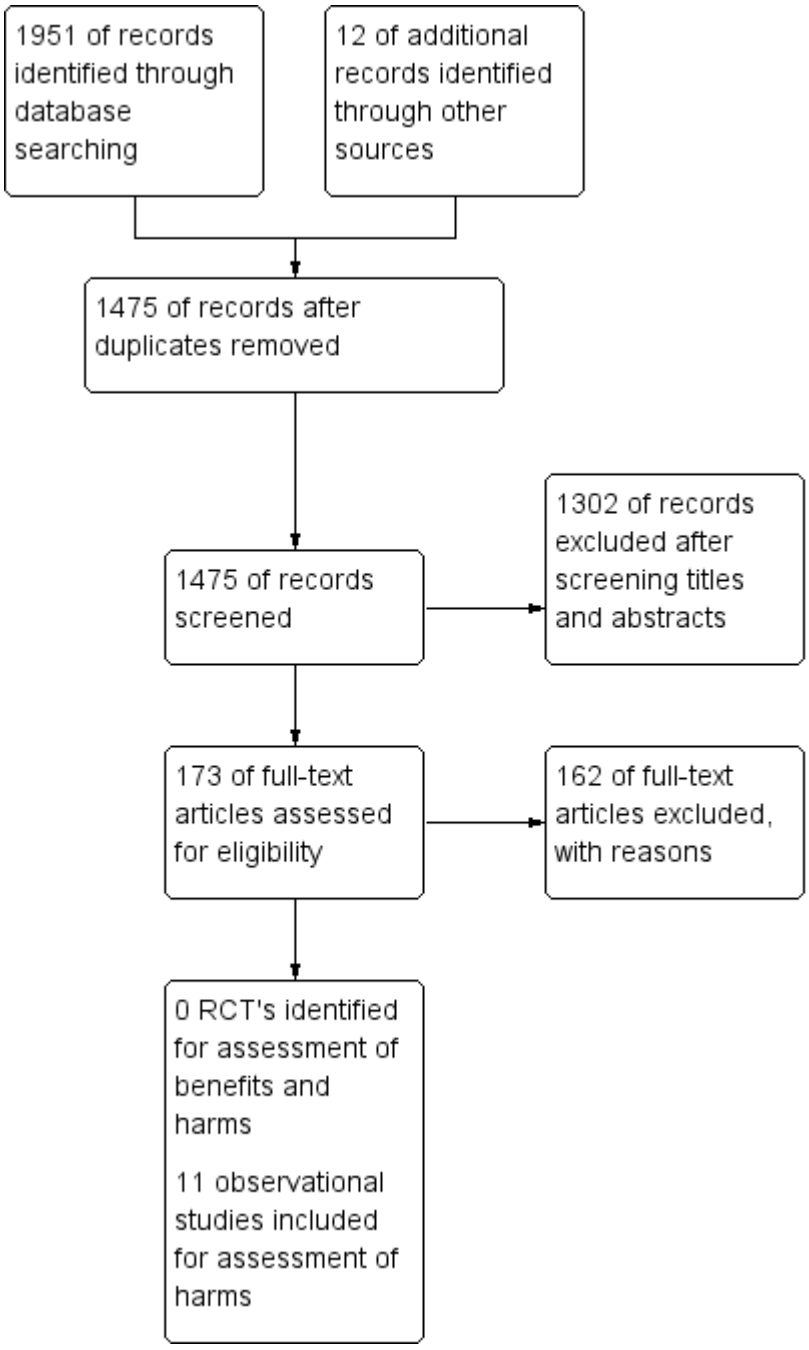
Figure 1 – Flow diagram



	Stented patients										Non-stented patients							
Study	**N**	**Age**	**Male Sex**	**NIHSS**	**IV-rtPA**	**Intracranial clot location**	**GA**	**IV PI**	**Anterograde stenting**	**Onset to recanalization**	**N**	**Age**	**Sex**	**NIHSS**	**IV-rtPA**	**Intracranial clot location**	**GA**	**Onset to recanalization**
Behme	170	64 (25-88)	70%	15 (12-19)	72%	MCA-M1: 58% MCA-M2: 10% ICA-T: 30% Other: 2%	NR	Yes	89%	296 (236-367)								
Choi	11	70 (54-82)	82%	15 (6-23)	NR	MCA: 73% ICA-T: 27%	0%	No	100%	263 (120-460)								
Cohen	24	66 (51-77)	83%	18 (14-28)	42%	MCA: 71% ICA-T: 25% Other: 4%	100%	No	NR	228 (120-330)								
Fahed	37	62 (SD ±10)	81%	16 (IQR 10-19)	73%	MCA: 6% ICA-T: 24%	62%	Yes	92%	357.1 (SD ±101.6)	33	64 (SD ±12)	58%	16 (IQR 12-20)	76%	MCA: 88% ICA-T: 12%	45%	359 (SD ±101)
Heck	23	70 (45-86)	NR	17 (9-25)	30%	MCA-M1: 52% MCA-M2: 9% ICA-T: 39%	NR	Yes: 57% No: 43%	NR	NR								
Lescher	9	66 (48-78)	59%*	15 (14-20)	74%*	MCA: 59%* ICA-T: 41%*	NR	No	NR	264 (163-361)	30	65 (38-92)	59%*	15 (6-20)	74%*	MCA: 59%* ICA-T: 41%*	NR	295 (136-504)
Lucena	20	67 (47-86)	70%	16 (7-28)	60%	MCA-M1: 50% MCA-M2: 5% ICA-T: 40% Other: 5%	NR	No	NR	336 (157-586)								
Son	11	71 (41-81)	73%	13 (5-23)	64%	MCA-M1: 36% MCA-M2: 36% ICA-T: 27%	0%	No	100%	NR								
Spiotta	16	68 (SD ±12)	50%	13 (SD ±4)	50%	MCA-M1: 75% MCA-M2: 19% ICA-T: 6%	NR	Yes	100%	NR								
Stampfl	24	67 (49-83)	88%	18 (IQR 15-22)	92%	MCA: 46% ICA-T: 54%	100%	Yes	88%	230 (123-634)								
Steglich-Arnholm	47	64 (SD ±13)	72%	16 (IQR 14-19)	85%	MCA-M1: 68% MCA-M2: 2% ICA-T: 30%	28 (60%)	Yes	38%	311.0 (SD ±78.0)								

Table 1 – Study overview

*Proportion of entire study-cohort

Continuous variables are presented as median with range or interquartile range (IQR) or mean with standard deviations (SD).

MCA – Middel cerebral artery

ICA – Internal carotid artery

NIHSS – National Institute of Health Stroke Scale

NR – Not reported

IV PI – Intravenous antiplatelet inhibitor during procedure

	Stented patients								Non-stented patients							
Study	**N**	**All-cause mortality**	**mRS≥3**	**Serious adverse events**	**Non-serious adverse events**	**Symptomatic intracranial haemorrhages**	**Embolus into new territory**	**Recurrent stroke during follow-up**	**N**	**All-cause mortality**	**mRS≥3**	**Serious adverse events**	**Non-serious adverse events**	**Symptomatic intracranial haemorrhages**	**Embolus into new territory**	**Recurrent stroke during follow-up**
Behme	170	32/170 – 19	108/170 – 64%	NR	NR	15/170 – 9%	NR	NR								
Choi	11	3/11 – 27%	6/11 – 55%	1/11 – 9%	0/11 – 0%	2/11 – 18%	0/11 – 0%	0/11 – 0%								
Cohen	24	2/24 – 8%	5/24 – 21%	0/24 – 0%	0/24 – 0%	0/24 – 0%	0/24 – 0%	0/24 – 0%								
Fahed	37	3/36* – 8%	18/36* – 50%	8/37 – 22%	6/37 – 16%	NR	6/37 – 16%	NR	33	6/31** – 19%	16/31* – 52%	4/33 – 12%	2/33 – 6%	NR	2/33 – 6%	NR
Heck	23	9/23 – 39%	11/23 – 48%	1/23 – 4%	0/23 – 0%	5/23 – 22%	0/23 – 0%	0/23 – 0%								
Lescher	9	1/9 – 11%	6/9 – 67%	0/9 – 0%	0/9 – 0%	0/9 – 0%	0/9 – 0%	NR	30	3/30 – 10%	19/30 – 63%	0/30 – 0%	0/30 – 0%	4/30 – 13%	0/30 – 0%	NR
Lucena	20	4/20 – 20%	13/20 – 65%	0/20 – 0%	0/20 – 0%	1/20 – 5%	0/20 – 0%	NR								
Son	11	1/11 – 9%	1/11 – 9%	5/11 – 45%	0/11 – 0%	0/11 – 0%	0/11 – 0%	0/11 – 0%								
Spiotta	16	3/16 – 19%	7/16 – 44%	2/16 – 13%	0/16 – 0%	1/16 – 6%	NR	NR								
Stampfl	24	4/24 – 17%	17/24 – 71%	4/24 – 17%	0/24 – 0%	4/24 – 17%	3/24 – 13%	NR								
Steglich-Arnholm	47	4/47 – 9%	15/47 – 32%	14/47 – 30%	1/47 – 2%	2/47 – 4%	4/47 – 6%	NR								
Total [CI]	**392**	**66/391 – 17% [13.3-21.0]**	**207/391 – 53% [47.9-58.0]**	**35/222 – 16% [11.2-21.2]**	**7/222 – 3% [1.3-6.4]**	**30/355 – 8% [5.7-11.8]**	**13/206 – 6% [3.4-10.6]**	**0/69 – 0% [0-5.2]**	**63**	**9/61 – 15% [7.0-26.2]**	**35/61 – 57% [44.1-70.0]**	**4/63 – 6% [1.8-15.5]**	**2/63 – 3% [0.4-11.0]**	**4/30 – 13% [3.8-30.7]**	**2/63 – 3% [0.4-11.0]**	**NR**

Table 2 – Study outcomes

*One patient lost to follow-up

** Two patients lost to follow-up

Continuous variables are presented as median with range or interquartile range (IQR) or mean with standard deviations (SD).

mRS – Modified Rankin Scale

NR – Not reported

[CI] – Confidence interval (95%)

Table 3 - All harms reported

Symptomatic intracranial haemorrhages	30/355 – 8%
In-stent thrombosis	11/223 – 5%
Dissection/perforation of vessel	12/223 – 5%
Haemodynamic compromise during intervention	5/222 - 2%
Embolism to same territory/stent-embolism	15/222 – 7%
Thrombectomy embolism	4
Air embolism	2
Stent-embolism	3
Distal embolism, unspecified	6
All-cause mortality	66/391 - 17%
Caused by sICH	22/66 – 33%

sICH – Symptomatic intracranial haemorrhages.

Table 4 – Subgroup analysis

Outcome	Intravenous antiplatelet therapy		No intravenous antiplatelet therapy	
sICH				
	Behme	15/170	Choi	2/11
	Fahed	NR	Cohen	0/24
	Spiotta	1/16	Lescher	0/9
	Stampfl	4/24	Lucena	1/20
	Steglich-Arnholm	2/47	Son	0/11
Total		22/257 – 9% [5.4-12.7]		3/75 – 4% [0.8-11.2]
All-cause mortality				
	Behme	32/170	Choi	3/11
	Fahed	3/36	Cohen	2/24
	Spiotta	3/16	Lescher	1/9
	Stampfl	4/24	Lucena	4/20
	Steglich-Arnholm	4/47	Son	1/11
Total		46/293 – 16% [11.7-20.4]		11/75 – 15% [7.6-24.7]
mRS≥3				
	Behme	108/170	Choi	6/11
	Fahed	18/36	Cohen	5/24
	Spiotta	7/16	Lescher	6/9

	Stampfl	17/24	Lucena	13/20
	Steglich-Arnholm	15/47	Son	1/11
		165/293 – 56% [50.4-62.1]		31/75 – 41% [30.1-53.3]
Serious adverse events				
	Behme	NR	Choi	1/11
	Fahed	8/37	Cohen	0/24
	Spiotta	2/16	Lescher	0/9
	Stampfl	4/24	Lucena	0/20
	Steglich-Arnholm	14/47	Son	5/11
		28/124 – 23% [15.6-31.0]		6/75 – 8% [3.0-16.6]
Non-serious adverse events				
	Behme	NR	Choi	0/11
	Fahed	6/37	Cohen	0/24
	Spiotta	0/16	Lescher	0/9
	Stampfl	0/24	Lucena	0/20
	Steglich-Arnholm	1/47	Son	0/11
		7/124 – 6% [2.3-11.3]		0/75 – 0% [0.0-4.8]
Periprocedural embolus into new territory				
	Behme	NR	Choi	0/11
	Fahed	6/37	Cohen	0/24
	Spiotta	NR	Lescher	0/9
	Stampfl	3/24	Lucena	0/20
	Steglich-Arnholm	4/47	Son	0/11
		13/108 – 12% [6.6-19.7]		0/75 – 0% [0.0-4.8]

sICH – Symptomatic intracranial haemorrhages

mRS – Modified Rankin Scale

Included studies (9 studies)	
(Behme, Mpotsaris, Zeyen, Psychogios, et al. 2015)	Multi-centre case-report of 170 cases
(José E Cohen et al. 2014)	Single-centre case-report of 24 cases
(Stampfl et al. 2014)	Single-centre case-report of 24 cases
(Heck and Brown 2014)	Single-centre case-report of 23 cases
(Spiotta, Lena, et al. 2015)	Single-centre case-report of 16 cases
(Lucena et al. 2016)	Single-centre case-report of 20 cases
(Steglich-Arnholm et al. 2015)	Single-centre case-report of 47 cases
(Choi et al. 2014)	Single-centre case-report of 11 cases
(Lescher et al. 2015)	Cohort study of 39 patients (9 stented)
Included after additional unpublished data from authors (2 studies)	
(Fahed et al. 2016)	Cohort study of 70 patients (37 stented)
(Son et al. 2015)	11/22 with tandem occlusions.
Small case-reports (N<10) only included for assessment of harms (9 references)	
(Dababneh et al. 2014)	N=7, unknown thrombectomy device. Also did not report harms.
(Gao et al. 2015)	N=2, stent-retriever
(Mishra et al. 2015)	N=7, stent-retriever
(Scheperjans et al. 2012)	N=2, Trevo/No intracranial treatment
(Soize et al. 2014)	N=2, stent-retriever
(Spiotta, Vargas, et al. 2015)	N=4, 1 stent-retriever, 1 stented, 1 aspiration
(Tasal, Asil, and Goktekin 2013)	N=1, Solitaire
(Tasal et al. 2013)	N=7, Solitaire
(Wetter et al. 2013)	N=1, Solitaire
Excluded for method for intracranial recanalisation (36 references)	
(Kwak et al. 2013)	Method for intracranial recanalisation.
(Abou-Chebl, Vora, and JS 2009)	Method for intracranial recanalisation.
(Malik et al. 2011)	Method for intracranial recanalisation.
(Nedeltchev et al. 2005)	Method for intracranial recanalisation.
(Ratanaprasatporn et al. 2013)	Method for intracranial recanalisation.
(Seet, Wijdicks, and Rabinstein 2012)	Method for intracranial recanalisation.
(Hauck et al. 2011)	Method for intracranial recanalisation.
(Matsubara et al. 2013)	Method for intracranial recanalisation.
(Dalyai et al. 2013)	Method for intracranial recanalisation.
(Bae et al. 2008)	Method for intracranial recanalisation.
(Dorado et al. 2013)	Method for intracranial recanalisation.
(Abboud 2005)	Method for intracranial recanalisation.
(Baik et al. 2011)	Method for intracranial recanalisation.
(Baumgartner et al. 2007)	Method for intracranial recanalisation.
(Bellon et al. 2001)	Method for intracranial recanalisation.
(Dababneh et al. 2012)	Method for intracranial recanalisation.
(Dabitz et al. 2007)	Method for intracranial recanalisation.

(Day and Adams 2012)	Method for intracranial recanalisation.
(Fateri et al. 2005)	Method for intracranial recanalisation.
(Garcia et al. 2012)	Method for intracranial recanalisation.
(Findlay, Ashforth, and Dean 2002)	Method for intracranial recanalisation.
(Hui et al. 2011)	Method for intracranial recanalisation.
(Hwang et al. 2013)	Method for intracranial recanalisation.
(Jakubowska et al. 2008)	Method for intracranial recanalisation.
(Wang et al. 2007)	Method for intracranial recanalisation.
(Jha et al. 2009)	Method for intracranial recanalisation.
(Kwon et al. 2011)	Method for intracranial recanalisation.
(Lavallee et al. 2007)	Method for intracranial recanalisation.
(Srinivasan et al. 2006)	Method for intracranial recanalisation.
(Lekoubou et al. 2010)	Method for intracranial recanalisation.
(Yano et al. 2007)	Method for intracranial recanalisation.
(Loh et al. 2011)	Method for intracranial recanalisation.
(MIYAMOTO et al. 2008)	Method for intracranial recanalisation.
(Mourand et al. 2010)	Method for intracranial recanalisation.
(Ohta et al. 2011)	Method for intracranial recanalisation.
(Padalino and Deshaies 2012)	Method for intracranial recanalisation.
(Jose E. Cohen et al. 2008)	Method for intracranial recanalisation.
Excluded for not only reporting tandem occlusions (5 references)	
(Yoon et al. 2015)	42/47 had tandem occlusions
(Duijsens et al. 2015)	10/16 had tandem occlusions
(Papanagiotou et al. 2011)	18/22 had tandem occlusions
(Soize et al. 2014)	11/42 had tandem occlusions.
(Fischer et al. 2013)	76/201 had tandem occlusions
Dublicated reports of other studies (9 references)	
(Jovin et al. 2005)	Used as a centre in (Malik et al. 2011).
(Maurer, Joachimski, and Berlis 2014)	Used as a centre in (Behme, Mpotsaris, Zeyen, MN, et al. 2015)
(José E. Cohen et al. 2011)	Highly likely to be part of another case series in same institution (José E Cohen et al. 2014)
(José E. Cohen et al. 2014)	Highly likely to be part of another case series in same institution (José E Cohen et al. 2014)
(Jose E. Cohen et al. 2010)	Highly likely to be part of another case series in same institution (José E Cohen et al. 2014)
(José E Cohen et al. 2013)	Highly likely to be part of another case series in same institution (José E Cohen et al. 2014)
(Lockau et al. 2015)	Used as a centre in (Behme, Mpotsaris, Zeyen, MN, et al. 2015)
(Mpotsaris et al. 2013)	Used as a centre in (Behme, Mpotsaris, Zeyen, MN, et al. 2015)
(Brekenfeld et al. 2005)	Patients are reported elsewhere (Nedeltchev et al. 2005)

Excluded for missing data (4 references)

(Grigoryan et al. 2016)	Only 52/100 patients treated within 6 hours. 67/100 were stented. All patients reported as one group.
(Machi et al. 2012)	5/10 patients stented. All patients are reported as one group.
(Puri et al. 2015)	25/28 are anterior tandem occlusion. 3 are posterior.
(Tütüncü et al. 2014)	11/14 patients with tandem occlusion had thrombectomy. 4/11 were stented. Reported as one group.

Mixed reasons (8 references)

(Bazan et al. 2015)	No acute stenting.
(R Gupta et al. 2006)	Irrelevant observational study
(Rishi Gupta et al. 2011)	Irrelevant observational study
(Ma et al. 2014)	Irrelevant observational study
(Theiss et al. 2004)	No acute stenting
(Parthasarathy et al. 2015)	Include patients within 12 hours.
(Hinman et al. 2013)	No acute stenting
(Toyoda et al. 2007)	No acute stenting

Not reporting tandem occlusions (15 references)

(Ciftci et al. 2004)	No tandem occlusions
(Egashira et al. 2013)	No tandem occlusions
(Eichel et al. 2012)	No tandem occlusions
(Hong et al. 2014)	No tandem occlusions
(Loret et al. 2013)	No tandem occlusions
(Kim et al. 2012)	No tandem occlusions
(Lee, Koh, and Choi 2010)	No tandem occlusions
(Li et al. 2012)	No tandem occlusions
(Mamopoulos et al. 2012)	No tandem occlusions
(Nikas et al. 2007)	No tandem occlusions
(Singh et al. 2015)	No tandem occlusions
(Song et al. 2008)	No tandem occlusions
(van den Berg 2008)	No tandem occlusions
(Villwock et al. 2014)	No tandem occlusions
(Zaidat et al. 2004)	No tandem occlusions

Papers with no patient data (21 references)

(Boutchakova and Papanagiotou 2016)	Review paper, no patient data
(Bruno and Meyers 2014)	Commentary paper, no patient data
(Cundy 2002)	Review paper, no patient data
(Darling et al. 2016)	Review paper, no patient data

(Ding 2014)	Letter to the editor, no patient data
(Fargen and Hoh 2013)	Commentary paper, no patient data
(Frerichs, Baker, and Norbash 2002)	Review paper, no patient data
(Gandhi, Christiano, and Prestigiacomo 2009)	Review paper, no patient data
(Gralla et al. 2012)	Review paper, no patient data
(Higashida et al. 1996)	Review paper, no patient data
(Mokin et al. 2012)	Review paper, no patient data
(Randall et al. 2005)	Editorial, no patient data
(Reith 2009)	Editorial, no patient data
(Rosenberg, Chen, and Prabhakaran 2010)	Review paper, no patient data
(Savitz and Mattle 2013)	Opinion paper, no patient data
(Schroth and R 2015)	Editorial, no patient data
(Steglich-Arnholm and Krieger 2015)	Review paper, no patient data
(Tallarita et al. 2010)	Review paper, no patient data
(Taylor and Qureshi 2007)	Commentary paper, no patient data
(Toni et al. 2015)	Guidelines paper, no patient data
(Xavier, Tiwari, and Kansara 2012)	Review paper, no patient data
Conference abstracts (54 references)	

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Paper 4

MECHANICAL THROMBECTOMY WITH THE EMBOLUS RETRIEVER WITH INTERLINKED CAGES IN ACUTE ISCHAEMIC STROKE: ERIC, THE NEW BOY IN THE CLASS.

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Presentation:

Results from this study were presented at the European Stroke Organization Conference 2016.

Word count: 4293

Abstract:

Background: The Embolus Retriever with Interlinked Cages (ERIC®) device is a novel stent-retriever for mechanical thrombectomy. It consists of interlinked cages, and could improve procedural benchmarks and clinical outcome compared to classic stent-retrievers. This study compares rates of recanalization, favorable clinical outcome, procedural adverse events and benchmarks between the ERIC®-device and classic stent-retrievers.

Methods: Propensity score matched analysis of patients treated between 2012 and 2015. From 545 patients treated with thrombectomy, 316 patients were included. Mean age was 69 years (±13), mean baseline NIHSS was 17 (±5), 174 (55%) were male, and ERIC® was used as the primary thrombectomy device in 59 (19%) patients. Patients were matched 1:1 for NIHSS, clot location, delay to groin puncture, neurointerventionalist and anesthetic management and 57 pairs were identified.

Results: Patients treated with the ERIC®-device compared to classic stent-retrievers showed equal rates of recanalization (86% vs 81%, P=0.61), equal favorable 3-months clinical outcome (mRS 0-2: 46% vs 40%, P=0.71), and procedural adverse events (28% vs 30%, P=1.00). However, in patients treated with the ERIC®-device thrombectomy procedures were less time-consuming (67 minutes vs. 98 minutes, P=0.0085) and a rescue device was needed less often (18% vs. 39%, P=0.021) compared to classic stent-retrievers.

Conclusion: Mechanical thrombectomy using the ERIC®-device is effective and safe. Rates of favorable procedural and clinical outcomes are at least as good as with classic stent-retrievers. Of note, the ERIC®-device might be time-saving and decrease the need for rescue devices. This promising result calls for replication in larger prospective clinical trials.

Abbreviations:

EVT – Endovascular therapy

ERIC® – Embolus Retriever with Interlinked Cages

CCI – Charlson Comorbidity Index

HI – Hemorrhagic infarction

SD – Standard deviation

CI – Confidence interval

Introduction:

The design of thrombectomy devices plays an important role for the efficacy of mechanical thrombectomy for acute ischemic stroke[1]. This is illustrated by the introduction of the stent-retriever design that was a driving factor for the positive results of the randomized controlled trials published in 2015[2–6]. These studies showed improved recanalization rates and, importantly, improved clinical outcome with endovascular therapy (EVT) compared to medical therapy alone for large embolic acute ischemic stroke[1]. In contrast to these trials, the negative EVT-trials published in 2013[7–9] mainly used older thrombectomy devices such as coil-retrievers or mechanical clot disintegrators combined with aspiration systems.

Classic stent-retrievers have a tubular design and were originally designed to support the endovascular coil-treatment of wide necked intracranial aneurisms by neck remodelling[10]. During mechanical thrombectomy for acute ischemic stroke, stent-retrievers function by squeezing the clot against the vessel wall and over minutes interacting with the clot thereby entangling the clot in the stent's meshed network and sometimes establish temporary reperfusion of the affected territory. However, the tubular design also means that the clot rests on the surface of the stent-retriever (Figure 1, A) and may risk fragmentation or shearing off during thrombectomy causing distal embolization, so-called clot migration. In addition, a large proportion of the stent-retriever's surface area is in contact with and possibly interacts with the endothelium of the vessel wall when deployed which may lead to intimal injuries and/or induced vasospasm during retraction[11].

Second-generation stent-retrievers consisting of an interlinked cage design devised specifically for clot removal have recently been introduced. One of these second generation stent-retrievers is the Embolus Retriever with Interlinked Cages (ERIC®, MicroVention, Tustin, CA, USA). Proposed advantages of the interlinked cage design compared to classic stent-retrievers are: less fragmentation and shaving of the clot due to retention within or in-between the cages (Figure 1, B), less contact and interaction of the stent-retriever with the vessel wall, relying less on interaction with the clot, and the possibility to use a thinner delivery system (0.017" low profile microcatheter) allowing for improved access in challenging patient anatomy[12].

Introduction of this new stent-retriever design may improve procedural benchmarks, clinical outcome, and ensure high rates of procedural success. In this retrospective study from a high-

volume tertiary level stroke-center, we aimed to examine the safety and efficacy of the ERIC® device by comparing outcomes and procedural benchmarks with classic stent-retrievers.

Methods:

This case-control study was approved by the Danish Health Authority (3-3013-1017/1) and the Danish Data Protection Agency (30-1148). All patients were treated within the Declaration of Helsinki.

The endovascular setup at our comprehensive stroke-center in Copenhagen has previously been described[13]. Seven stroke neurologists and five neuro-interventionalists cover a 24/7 stroke-team service with 30 min response time. Patients were predominantly referred from primary stroke-centers where initial clinical assessment and diagnostic imaging were performed and IV-rtPA administered. Stroke severity was assessed according to the NIHSS. We retrospectively reviewed all patients referred to us for anterior circulation acute ischemic stroke from January 2012 to December 2015. Only patients treated with a mechanical thrombectomy using a stent-retriever were included in this study. The ERIC® device has been available at our center since July 2013. We included all patients treated with classic stent-retrievers from 2012 to 2015 for the comparison group. This time-period was chosen because patient flow has been high and consistent during these four years and our clinical setup has not changed since 2012.

Clinical and interventional details were extracted from prospectively recorded patient charts. Patient comorbidity was assessed according to the Charlson Comorbidity Index (CCI)[14]. Neuro-images were reviewed by two authors (HSA & MH). Clot location was defined on the DSA and categorized into ICA bifurcation (ICA-T), MCA before major bifurcation (MCA-M1) or after major bifurcation (MCA-M2), or “other” clot location in case of distally located clots or intracranial carotid siphon occlusion without involvement of the bifurcation.

Neurointerventions:

Right femoral access was predominantly used. A large-bore long sheath or coaxial catheter was placed in the ipsilateral carotid artery (e.g. Destination 6F (Terumo, Leuven, Belgium), Neuron Max 6F (Penumbra Inc., Alameda, CA, USA), or Arrow 8-9F (Teleflex Medical Europe, Athlone, Ireland)). A long standard guidecatheter with JB1 or SIM2 configuration (Cook Medical, Bloomington, IN,

USA) was used to guide the sheath or the large-bore coaxial catheter from the aortic arch into the carotid arteries. From a stable position in the proximal ICA or distal common carotid artery a distal access catheter (e.g. SOFIA (MicroVention), Navien (Medtronic, Minneapolis, MN, USA), Fargo or Fargomax (BALT Extrusion, Montmorency, France), or 5MAX ACE or ACE 64 (Penumbra Inc)) was advanced into the intracranial vasculature; usually in a triaxial fashion via a microcatheter to avoid unnecessary vessel stress. If necessary, an additional proximal balloonguide catheter (e.g. Cello (Medtronic)) was placed through a large bore sheath (8 or 9Fr), before the distal access catheter was advanced through it.

After clot location had been confirmed as initially seen on pre-procedural CTA, a micro-catheter (e.g. Prowler Select Plus (Codman Neuro, Raynham, NA, USA) or Headway 17-21 (MicroVention)) following a guide-wire (e.g. Traxcess 0.014" (MicroVention) or Transcend Platinum 0.014" (Stryker Neurovascular, Fremont, CA, USA)) was navigated through the clot. The guide-wire was then substituted for a stent-retriever which was deployed within the clot. In cases using the ERIC® device, the largest possible number of cages was placed distal to the clot while still covering the entire clot with the device. Patients that were not treated with the ERIC® device had been treated with classic stent-retrievers from various companies (e.g. Solitaire FR (Medtronic) or pREset (Phenox, Bochum, Germany) (Online Supplements, Table S1). Thrombectomy was performed in combination with distal or proximal aspiration, or a combination of both, and choice of thrombectomy devices was left to the discretion of the neuro-interventionalist. Furthermore, conscious sedation or general anesthesia, extra-cranial carotid stenting, and per-procedural antithrombotic therapy was managed on a case-by-case basis.

Post-procedural management:

Patients were observed at a neuro-intensive care unit at least until 24 hour post-procedural follow-up NCCT had excluded major intracranial hemorrhages or risk of malignant infarction. ICH were classified according to the ECASS-II criteria into hemorrhagic infarcts (HI) and parenchymal hemorrhages (PH)[15]. In case of uncertainty between residual contrast or HI on 24 hour NCCT and no following NCCT within few days, the image was attributed to HI. Afterwards patients were discharged for neurorehabilitation and follow-up was arranged at three months post-stroke with clinical assessment according to the mRS.

Outcome measures:

The main outcome was favorable recanalization defined as a TICI score of 2b-3[16]. Secondary outcomes included: favorable clinical outcome defined as mRS 0-2 at 3 months, procedural adverse events defined as any untoward event occurring during neurointerventions, symptomatic ICH defined as any intracranial hemorrhage causing a clinical deterioration of $\geq$ 4 points on the NIHSS[15], and procedural benchmarks (procedural duration, number of thrombectomy passes, and need for more than one thrombectomy device).

Statistical analysis:

Variables are presented as means ± standard deviation (SD) and range for continuous variables and number with percentage for categorical variables. Means are compared with Students T-test and 95% confidence interval (CI) of the difference in means is presented. Categorical variables are compared with χ^2 or Fishers Exact test where appropriate and 95% CI of the OR is presented.

We performed a propensity score matched analysis comparing patients treated with the ERIC® device to patients treated with classic stent-retrievers at our center in a 1:1 ratio[17], using the 'Nearest available Mahalanobis metric matching within calipers defined by the propensity score' method[18]. The following covariates were used to calculate the propensity score: stroke severity, the neuro-interventionalist in charge of the procedure, clot location, time from neuroimaging to groin puncture, and level of sedation during the procedure. Baseline variables were compared before and after matching to check for reduction of bias.

Due to the unevenly distributed time-periods for the ERIC® (July 2013 – December 2015) and the classic stent-retriever group (January 2012 – December 2015), we planned a time-sensitivity analysis using only patients treated within the same time-period. Furthermore, our results were compared to multivariate regression analyses with backwards elimination of covariates with nonsignificant associations to outcomes.

All analyses were performed using SAS Statistical Software Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results:

We identified 545 patients with acute ischemic stroke referred for mechanical thrombectomy in the study period. Of these, 413 patients had anterior circulation stroke and 69 patients not treated with a stent-retriever and 28 patients with missing follow-up (referred from a nearby Swedish stroke-center) were excluded (Figure 2).

Thus 316 patients were included. The mean age was 68.7 years (SD ±13, range 27-94); 174 (55%) were male; 158 (50%) had no previous comorbidity; 84 (27%) had atrial fibrillation; and the mean NIHSS was 16.9 (SD ±5, range 0-28) prior to EVT. IV-rtPA was administered in 223 (71%) patients; the mean onset to image time was 97.8 minutes (SD ±64, range 10-517); the mean image to groin time was 149.3 minutes (SD ±62, range 27-459); 205 (65%) of procedures were performed in general anesthesia; 64 (20%) patients had ipsilateral carotid stenting; 83 (26%) patients had ICA-T occlusions; 177 (56%) had MCA-M1 occlusions; 47 (15%) had MCA-M2 occlusions; and 9 (3%) had occlusion in other intracranial arteries (Table 1).

We identified 59 patients treated with the ERIC® device as primary thrombectomy device and 257 patients treated with classic stent-retrievers. Propensity scoring identified 57 matched pairs and we compared baseline characteristics before and after matching (Table 2).

The ERIC® group showed equal rates of favorable recanalization (86% vs 81% [OR 95% CI: 0.54-3.96, P=0.61]), favorable 3-months clinical outcome (46% vs. 40%, [OR 95% CI: 0.59-2.61, P=0.71]), and procedural adverse events (28% vs. 30% [OR 95% CI: 0.41-2.06, P=1.00]) compared to the classic stent-retriever group and non-significantly fewer parenchymal ICH (7% vs. 14% [OR 95% CI: 0.13-1.63, P=0.36), symptomatic ICH (5% vs. 16% [OR 95% CI: 0.076-1.16, P=0.12]), and distal embolism (2% vs. 9%, [OR 95% CI: 0.02-1.64, P=0.21]) (Table 3). Procedural adverse events are presented in detail in the Online Supplements (Table S2).

The ERIC® group showed significantly shorter procedural durations (67.4 vs. 98.0 minutes [95% CI: 8-53 minutes, P=0.0085]) and less frequent use of secondary/rescue devices (18% vs. 39% [OR 95% CI: 0.14-0.80, P=0.021]). The number of thrombectomy passes was not statistically different (2.5 vs. 3.1 passes [95% CI: -0.1-1.3 passes, P=0.11]) compared to the classic stent-retriever group (Table 3).

Sensitivity analyses

In the time-sensitivity analysis on 199 patients treated from July 2013 to December 2015, we only identified 37 matched pairs. This analysis still showed equal rates of favorable recanalization (OR 95% CI: 0.43-5.22, P=0.75), clinical outcome (OR 95% CI: 0.62-3.93, P=0.64), procedural adverse events (OR 95% CI: 0.22-1.63, P=0.80), symptomatic ICH (OR 95% CI: 0.08-2.74, P=1.0), and distal embolism (OR 95% CI: 0.02-2.16, P=0.36) (Table 3). The procedural duration remained numerically shorter in the ERIC® group, albeit this difference was no longer statistically significant (74.1 vs 90.8 minutes [95% CI: -8-41], P=0.18). The number of thrombectomy passes remained statistically insignificant (2.5 vs. 3.4 passes [95% CI: -0.16-1.95], P=0.096), and the significantly less frequent use of secondary/rescue device remained (OR 95% CI: 0.11-0.87, P=0.043) (Table 3). The multivariate regression analyses confirmed that thrombectomy using the ERIC® retriever was not associated with either favorable recanalization or favorable clinical outcome but predicted shorter procedural duration and less need for a secondary device (Online supplements, Table S3).

Discussion

This study examined the efficacy and safety of the ERIC® device by comparing with classic stent-retrievers and identified equal rates of favorable recanalization and clinical outcome, equal procedural adverse events and improvements in some procedural benchmarks. Possible drawbacks with the design of the classic stent-retrievers are dependency of time-consuming interaction with the clot which also may be problematic in white, platelet rich clots[19], and vulnerability of the clot during retraction as it is retained on the outside of the stent-retriever. New generations of thrombectomy devices were designed to overcome these disadvantages. The interlinked cages design of the ERIC® and similar devices capture the clot within and in-between the cages and rely less on interaction with the clot, possibly allowing for faster and gentler clot removal. Additionally, the ERIC® device has a slimmer profile and can be used through low profile microcatheters. Although still unproven, stent-retrievers designed specifically for clot removal such as the ERIC® device may improve procedural benchmarks during thrombectomy and could have a positive effect on clinical outcome. Although previous studies[20,21] have suggested reasonable efficacy and safety with the ERIC® device for mechanical thrombectomy, our study is the first to compare procedural benchmarks and clinical outcome with classic stent-retrievers.

The main finding of our study was equal rates of favorable recanalization between the ERIC® group and the classic stent-retriever group. Furthermore, our rate was comparable to the two published case series both reporting 83% favorable recanalization using the ERIC® device for thrombectomy[20,21]. The rates of favorable recanalisation using classic stent-retrievers are already high and it is unlikely that any new device will provide more than the 80%-90% TICI 2b-3 seen in recent randomized controlled trials[2–6]. These high rates of favorable recanalization were, however, not reflected in equally high rates of favorable clinical outcome suggesting that there may still be potential for procedure-related improvements. Therefore, it may be more relevant to explore improvements in other procedural benchmarks than the rate of favorable recanalization. We identified statistically significant shorter procedural duration and a less frequent use of secondary endovascular devices with the ERIC as compared to classic stent-retriever devices. These factors both suggest slightly improved performance of the ERIC® device compared to classic stent-retrievers. These benchmark improvements were not directly reflected in improved 3-months clinical outcome where we identified equal rates of favorable clinical outcome but, interestingly, the shorter procedural duration of 30 minutes and the 6% absolute difference in rates of favorable clinical outcome in favor of the ERIC® group in our study correspond very well with previous data, suggesting that every 30 minutes delay to reperfusion decreases the rate of favorable 3-months clinical outcome with 3-8%[22,23]. Although we identified an average of 30 minutes shorter procedural duration in the ERIC® group, it is important to remember that the difference may be as little as 8 minutes as illustrated by the lower limit of the confidence interval. Furthermore, we saw a difference in delay to groin puncture between the two groups. Even though we attempted to adjust for this difference, Table 2 shows that a bias towards longer delay to groin puncture in the ERIC® group may still exist after adjustment although this was no longer statistically significant. If better balanced, the difference in 3-months outcome between the two groups may have been even greater. Our rate of favorable clinical outcome (46%) was comparable with the two case series (33-48%[20,21])

Concerning the safety of mechanical thrombectomy with the ERIC® device we found equal rates of adverse events compared to classic stent-retrievers. We observed only one patient with distal embolus after thrombectomy in the ERIC® group and five patients in the classic stent-retriever group. Although it is tempting to speculate that this might signify an improved protection of the

clot inside the device during retraction of the ERIC® retriever, these numbers are too small and the results needs be confirmed by large prospective studies.

In the ERIC® group we identified six patients with procedure related intracranial hemorrhagic complications compared to two patients in the classic stent-retriever group. Four of the six hemorrhages were related to thrombectomy with the ERIC® retriever, one hemorrhage was caused by a microwire perforation, and one hemorrhage was related to thrombectomy with a classic stent-retriever. All four hemorrhages that appeared after thrombectomy with the ERIC® device were performed in distal branches (distal MCA-M2-M3) where the risk of thrombectomy may be increased[24]. This suggests that even though the design of the ERIC® device allows for low profile microcatheters that may have easier access to distal branches the risk-benefit must be carefully evaluated when performing thrombectomy beyond the MCA-M1/M2 branches. Even though we identified a few more procedure related hemorrhages in the ERIC® group, most were clinically silent minor subarachnoid hemorrhages, and only two of the six hemorrhages in the ERIC® group were symptomatic. One ICH appeared after MCA-M1 thrombectomy with a classic stent-retriever used as a rescue device (expired day 5). The other ICH appeared after MCA-M3 thrombectomy with an ERIC® 3x20 device which led to coiling of the vessel. The patient deteriorated from NIHSS 18 to NIHSS 27 (3-months mRS=4). The rate of symptomatic hemorrhage observed in this study was comparable with the two case series (0-8%[20,21]). Although, we identified slightly fewer symptomatic hemorrhages in the ERIC® group, the rates represent very few cases and the results need to be interpreted with caution. In the time sensitivity analysis we saw even rates of symptomatic hemorrhages between the two groups further supporting that the risks of thrombectomy with the ERIC® device is equal to classic stent-retrievers.

Limitations:

This study represents experience from a single stroke-center with a limited sample size and results may vary from other centers. However, we identified very similar results compared to other studies[20,21]. Procedural details were recorded before clinical outcome was known and this study was not designed when clinical outcomes were assessed. Only the clot location was available and not clot size/burden or clot composition which may play an important role for efficacy of a stent-retriever[19]. Selection of devices for clot removal was based on discretion of the

neurointerventionalist and even though no specific criteria were used by our staff, our results may have been affected by selection bias. We observed a considerable reduction of bias after propensity score matching (Table 2), but important factors such as: individual interventionalists' skill, speed, and aggressiveness and time-delay to groin-puncture, which may both affect procedural success and clinical outcome, could have been better balanced. In order to obtain truly comparable groups a randomized controlled trial would be needed. Although we do not believe that our setup has undergone significant changes in the last four years a potential learning curve may have affected our results favoring results for the ERIC® stent. However, the time-sensitivity analysis for patients treated within the same time-periods (July 2013 – December 2015) confirmed the results of our primary analysis but with a smaller sample size. Our results are further strengthened by the multivariate analysis of variables associated with outcomes also confirming the results of our primary analysis (Online supplements, Table S3).

Conclusions:

Mechanical thrombectomy using the ERIC® device is effective and safe and is associated with at least equal rates of favorable procedural and clinical outcomes as compared to classic stent-retrievers. The interlinked cages design of the ERIC® device showed improvements in procedural benchmarks, which did not translate into improved clinical outcome, possibly due to low statistical power. These promising results warrant further evaluation by larger prospective clinical trials.

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Tables:

Table 1	**N=316**
Age (years)	68.7 (SD±13) range 27-94
Sex (male)	174 (55%)
Diabetes	38 (12%)
Hyperlipidemia	100 (32%)
Hypertension	183 (58%)
Known atrial fibrillation	84 (27%)
Prior stroke	39 (12%)
CCI 0 CCI 1-3 CCI 4-10	158 (50%) 137 (43%) 21 (7%)
IV-rtPA	223 (71%)
Clot location	ICA-T: 83 (26%) M1: 177 (56%) M2: 47 (15%) Other: 9 (3%)
NIHSS	16.9 (SD±5) range 0-28
Extracranial carotid stenting	64 (20%)
Onset to image (minutes)	97.8 (SD±64) range 10-517
Image to groin (minutes)	149.3 (SD±62) range 27-459
Onset to TICI (minutes)	325.0 (SD±106) range 102-900
General anesthesia	205 (65%)

Table 1: Baseline characteristics

Table 2	Before Propensity Score Matching			After Propensity Score Matching		
	ERIC N=59	**Non-ERIC N=257**	**P=**	**ERIC N=57**	**Non-ERIC N=57**	**P=**
Age (years)	70.0	68.4	0.41	69.7	70.1	0.87
Sex (male)	29 (49%)	145 (56%)	0.31	29 (51%)	31 (54%)	0.85
CCI 0 **CCI 1-3** **CCI ≥4**	27 (46%) 26 (44%) 6 (10%)	131 (51%) 111 (43%) 15 (6%)	0.44	27 (47%) 25 (44%) 5 (9%)	28 (49%) 27 (47%) 2 (4%)	0.50
Known atrial fibrillation	15 (25%)	69 (27%)	0.87	14 (25%)	17 (30%)	0.67
IV-rtPa	39 (66%)	184 (72%)	0.43	38 (67%)	41 (72%)	0.69
Clot location	ICA-T: 22 (37%) M1: 19 (32%) M2: 13 (22%) Other: 5 (8%)	ICA-T: 61 (24%) M1: 158 (61%) M2: 34 (13%) Other: 4 (2%)	<0.0001	ICA-T: 22 (39%) M1: 17 (30%) M2: 13 (23%) Other: 5 (8%)	ICA-T: 22 (39%) M1: 21 (37%) M2: 12 (21%) Other: 2 (3%)	0.63
NIHSS	17.4	16.8	0.36	17.4	17.5	0.91
Extracranial carotid stenting	13 (22%)	51 (20%)	0.72	13 (23%)	10 (18%)	0.64
Onset to image (minutes)	92.3	99.0	0.51	92.6	98.7	0.65
Image to groin (minutes)	167.0	145.3	0.037	167.0	150.5	0.20
General anesthesia	34 (58%)	171 (67%)	0.23	33 (58%)	32 (56%)	1.00
Neurointervent ionalist	1: 38 (64%) 2: 15 (25%) 3: 4 (7%) 4: 0 (0%) 5: 2 (3%)	1: 53 (21%) 2: 45 (18%) 3: 59 (23%) 4: 42 (16%) 5: 58 (23%)	<0.0001	1: 36 (63%) 2: 15 (26%) 3: 4 (7%) 4: 0 (0%) 5: 3 (4%)	1: 28 (49%) 2: 20 (35%) 3: 6 (11%) 4: 0 (0%) 5: 3 (5%)	0.51

Table 2: Comparison of clinical and treatment characteristics before and after propensity score matching.

Table 3	Primary analysis			Time sensitivity analysis		
	ERIC N=57	**Non-ERIC N=57**	**P=**	**ERIC N=37**	**Non-ERIC N=37**	**P=**
TICI 2b-3	49 (86%)	46 (81%)	0.61	32 (86%)	30 (81%)	0.75
OR 95% CI		0.54-3.96			0.43-5.22	
mRS 0-2	26 (46%)	23 (40%)	0.71	17 (46%)	14 (38%)	0.64
OR 95% CI		0.59-2.61			0.62-3.93	
Mortality	11 (19%)	12 (21%)	1.00	7 (19%)	7 (19%)	1.00
OR 95% CI		0.36-2.24			0.39-3.45	
Procedural duration (minutes)	67.4	98.0	0.0085	74.1	90.8	0.18
95% CI of difference in means		8.0-53.2			-7.8-41.1	
Number of passes (passes)	2.5	3.1	0.11	2.5	3.4	0.096
95% CI of difference in means		-0.1-1.3			-0.2-2.0	
Several devices needed	10 (18%)	22 (39%)	0.021	7 (19%)	16 (43%)	0.043
OR 95% CI		0.14-0.80			0.11-0.87	
Parenchymal hemorrhages	4 (7%)	8 (14%)	0.36	4 (11%)	2 (6%)	0.67
OR 95% CI		0.13-1.63			0.24-9.55	
Symptomatic hemorrhages	3 (5%)	9 (16%)	0.12	3 (8%)	4 (11%)	1.00
OR 95% CI		0.076-1.16			0.08-2.74	
Distal embolism	1 (2%)	5 (9%)	0.21	1 (3%)	4 (11%)	0.36
OR 95% CI		0.02-1.64			0.02-2.16	
Procedural adverse events	16 (28%)	17 (30%)	1.00	11 (30%)	13 (35%)	0.80
OR 95% CI		0.41-2.06			0.22-1.63	

Table 3: Comparison of procedural- and clinical outcome after propensity score matching for primary- and time-sensitivity analysis.

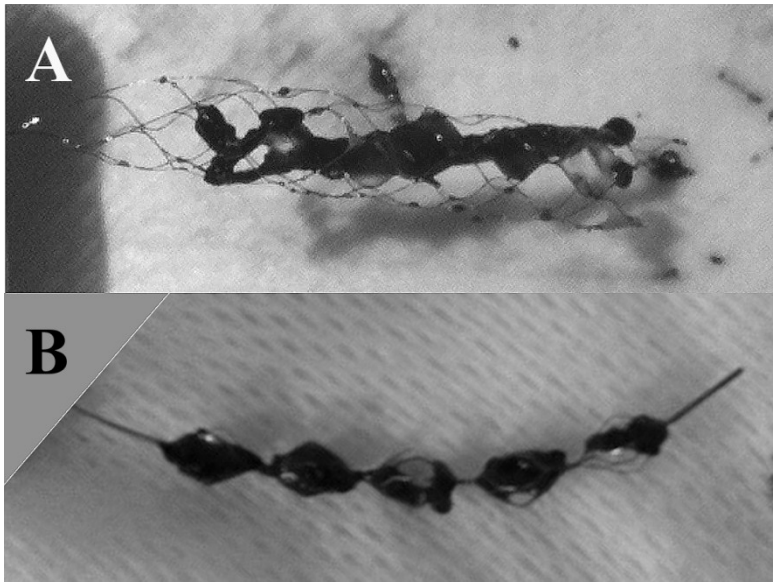

Figure 1:

Figure illustrating the differences in clot retainment between the outside of classic stent-retrievers (A) and inside the cages of the ERIC® device (B).

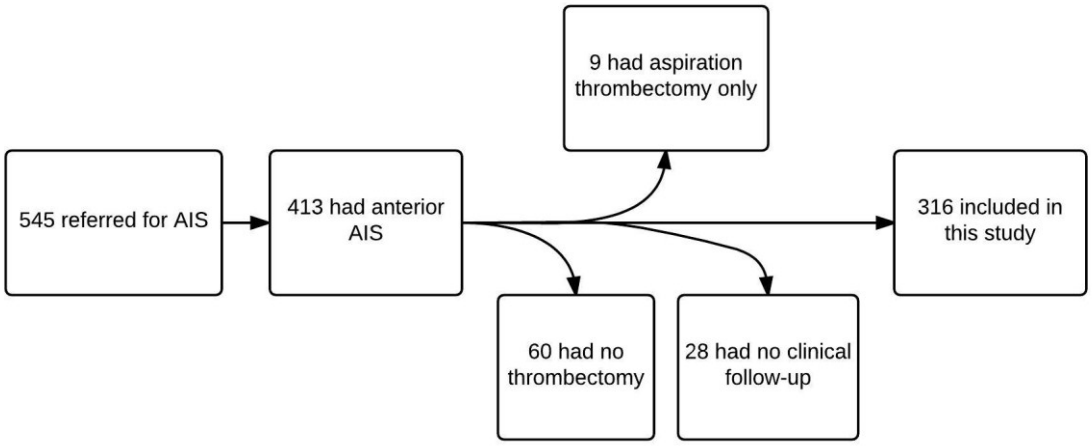

Figure 2:

Flowchart of patient inclusion.

Online supplements:

Table S1 – Stent-retrievers used

Device	Used in number of patients
Solitaire FR (Medtronic, Minneapolis, MN, USA)	255
ERIC (MicroVention, Tustin, CA, USA)	79
pREset (Phenox, Bochum, Germany)	30
Capture (MindFrame, Irvine, CA, USA)	24
EmboTrap (Neuravi, Galvane, Ireland)	18
Other	13

Table S2 - Procedural adverse events

ERIC N=57	Non-ERIC N=57
Failed thrombectomy x2	Failed thrombectomy x3
Puncture of femoral vein x1	Stent-retriever detachment x2
Carotid/central embolus/stent thrombosis x4	Carotid stent-thrombosis/embolus x4
Stent-retriever embolus x1	Stent-retriever embolus x5
Procedural hemorrhage x6	Procedural hemorrhage x2
ICA-dissection x1	ICA-dissection x1
Femoral embolus x1	

Table S3 - Multivariate analyses

Covariates	P=
Covariates significantly associated with favorable recanalization	
ERIC® device	**P=0.94**
NIHSS	P=0.035
Interventionalist	P=0.030
Covariates significantly associated with favorable clinical outcome	
ERIC® device	**P=0.92**
Onset to TICI	P<0.0001
Age	P=0.0001
NIHSS	P<0.0001
CCI >1	P=0.014
Covariates significantly associated with procedural duration	
ERIC® device	**P=0.0084**
Interventionalist	P<0.0001
NIHSS	P=0.0002
Extracranial stenting	P=0.0001
Covariates significantly associated with number of thrombectomy passes	
ERIC® device	**P=0.38**
Clot location	P=0.0063
Covariates significantly associated with need for several devices	

ERIC® device	**P=0.012**
Interventionalist	P=0.0034
Clot location	P=0.0080
NIHSS	P=0.018
Covariates significantly associated with symptomatic hemorrhages	
ERIC® device	**P=0.36**
Onset to TICI	P=0.019
Covariates significantly associated with procedural adverse events	
ERIC® device	**P=0.96**
Interventionalist	P=0.032
NIHSS	P=0.036