2020-10-06

Expanding the evidence of endovascular treatment for acute ischemic stroke: patient–centered outcomes, population–level impact, and patients presenting with mild stroke symptoms

Zerna, Anna Charlotte

UNIVERSITY OF CALGARY

Expanding the evidence of endovascular treatment for acute ischemic stroke: patient–centered outcomes, population–level impact, and patients presenting with mild stroke symptoms

by

Anna Charlotte Zerna

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

GRADUATE PROGRAM IN COMMUNITY HEALTH SCIENCES

CALGARY, ALBERTA

OCTOBER, 2020

Abstract

Endovascular treatment (EVT) for anterior circulation acute ischemic stroke due to large-vessel occlusion is the new standard of care resulting in reduced disability compared to medical treatment. Practice guidelines recommend the use of EVT but can only speak to the evidence provided by clinical trials and might not be appropriate when complex medical decisions need to consider the heterogeneity of patients in routine clinical care.

Brought about by the limitations of the clinical trials, the work described in this doctoral thesis aimed to assess the long–term sustainability of efficacy of EVT, the utilization of post–stroke outcomes that are patient–centered and more meaningful to affected individuals, and the effectiveness of EVT in patient populations that have not been part of clinical trial cohorts. These are commonly older patients with comorbidities and patients presenting with mild stroke symptoms.

The miFUNCTION scale was shown to display greater granularity in the mild to moderately–severe disability range post–stroke compared to the modified Rankin Scale and thus provide more insight into the patient's ability and capacity to engage in meaningful life roles after EVT. In a population–based analysis, adult patients undergoing EVT spent on average more than one week longer at home within the first 90 days compared with patients receiving medical treatment. Home-time was used as a novel, health-economic, and patient-centered outcome. For patients presenting with mild symptoms, EVT resulted in similar 90–day outcomes compared to medical management despite an increased risk of neurological deterioration at 24 hours. Due to uncertainty regarding the risk–benefit–ratio, a well–designed clinical trial will need to establish how best to treat these patients.

Overall, the work described here provides greater understanding of how the benefits and risks of EVT might vary across the population and differ from the rather homogenous patient cohort that has been assessed in the clinical trials. The results of this research will be meaningful to patients who experience acute ischemic strokes caused by large vessel occlusion and also aid with economic and regulatory decisions to more broadly offer and organize EVT across Alberta and beyond.

Preface

Chapter 2. Portions of the introductory text are adapted with permission from Zerna C, Thomalla G, Campbell BCV, Rha JH, Hill MD. Current practice and future directions in the diagnosis and acute treatment of ischemic stroke. *Lancet* 2018; 392: 1247–1256.

Chapter 3. This chapter has been published as: Zerna C., Goyal M. Long–term outcome of endovascular therapy for ischemic stroke. *Nature Reviews Neurology* 2017; 13: 387–388.

Chapter 5. This chapter has been published as: Zerna C, Burley T, Green TL, Dukelow SP, Demchuk AM, Hill MD. Comprehensive assessment of disability post–stroke using the newly developed miFUNCTION scale. *International Journal of Stroke* 2020; 15: 167–174.

Chapter 6. This chapter has been published as: Zerna C, Rogers E, Rabi DM, Demchuk AM, Kamal N, Mann B, Jeerakathil T, Buck B, Shuaib A, Rempel J, Menon BK, Goyal M, Hill MD. Comparative Effectiveness of Endovascular Treatment for Acute Ischemic Stroke: A Population–Based Analysis. *Journal of the American Heart Association* 2020 Apr 7;9:e014541.

Chapter 7. This chapter has been published online ahead of print: Volny O*, Zerna C*, Tomek A, Bar M, Rocek M, Padr R, Cihlar F, Nevsimalova M, Jurak L, Havlicek R, Kovar M, Sevcik P, Rohan V, Fiksa J, Cernik D, Jura D, Vaclavik D, Cimflova P, Puig J, Dowlatshahi D, Khaw AV, Fainardi E, Najm M, Demchuk AM, Menon BK, Mikulik R, Hill MD. Thrombectomy vs.

Medical Management in Low NIHSS Acute Anterior Circulation Stroke. Neurology. *Neurology*. First published September 28, 2020, DOI: https://doi.org/10.1212/WNL.0000000000010955

Chapter 8. Portions of the discussion text are adapted with permission from the Handbook of Neuroemergency Trials, 2nd Edition. Zerna C, Holodinsky JK, Goyal M, Hill MD. "Implications for New Trials in Acute Ischemic Stroke in the New Era of Endovascular Therapy" pp. 305–313, Academic Press/Copyright Elsevier (2017).

Acknowledgements

This research would not have been possible without the financial support of the Hotchkiss Brain Institute at the University of Calgary and Alberta Innovates Health Solutions.

I would like to thank my supervisor, Dr. Michael Hill, for his guidance and support through each stage of the process in developing this body of research. You have provided me with many great opportunities over the past four years that have shaped who I have become academically.

Many thanks go to the members of my supervisory committee, Drs. Doreen Rabi and Andrew Demchuk, whose feedback has helped me to consider my research questions and findings in a broader context.

I would like to acknowledge Mr. Tyler Burley's work on the miFUNCTION scale, which he has developed for his master's project. I'm thankful to have collaborated with him.

I am grateful to all colleagues and fellow students whom I have had the pleasure to work with during this and other related projects. Thank you for the stimulating conversation and encouragement.

And finally to my family and especially my husband, thank you for your patience and continuous support during this time and always.

Table of Contents

List of Tables

List of Figures and Illustrations

List of Symbols, Abbreviations and Nomenclature

Abbreviation	Definition
ACA	Anterior Cerebral Artery
ADL	Activities of Daily Living
AIC	Akaike's Information Criterion
AIS	Acute Ischemic Stroke
ARISE II	Analysis of Revascularization in Ischemic Stroke With EmboTrap
ARR	Absolute Risk Reduction
ASPECTS	Alberta Stroke Program Early CT Score
ASTER	Contact Aspiration vs Stent Retriever for Successful Revascularization
ATLANTIS–B	Alteplase Thrombolysis for Acute Non–interventional Therapy in Ischemic Stroke
B_PROUD	Berlin Pre–hospital Or Usual Delivery of Stroke Care
BEST–MSU	Benefits of Stroke Treatment Delivered Using a Mobile Stroke Unit
BI	Barthel Index
BRISK	Brisk Recanalization Ischemic Stroke Kit
CI	Confidence Interval
COMPASS	Direct Aspiration First Pass Technique
CT	Computed Tomography
CTA	Computed Tomography Angiography
CTP	Computed Tomography Perfusion
DAWN	Diffusion Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention
DEFUSE–3	Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3
DWI	Diffusion–Weighted Imaging

Abbreviation	Definition
ECASS	European Cooperative Acute Stroke Study
ECC	Endovascular–Capable Centre
EMS	Emergency Medical Services
ENACT	Evaluating Neuroprotection in Aneurysm Coiling Therapy
ENDOLOW	Endovascular Therapy for Low NIHSS Ischemic Strokes
EQ5D–5L	5 Level European Quality Of Life 5 Dimension Scale
ESCAPE	Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke
ESCAPE–NA1	Safety and Efficacy of NA–1 in Subjects Undergoing Endovascular Thrombectomy for Stroke
EVT	Endovascular Treatment
EXTEND–IA	Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra–Arterial
FLAIR	Fluid–Attenuated Inversion Recovery
GAIN	Glycine Antagonist [gavestinel] In Neuroprotection
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HERMES	Highly Effective Reperfusion Using Multiple Endovascular Devices
ICA	Internal Carotid Artery
ICF	International Classification of Functioning, Disability, and Health
ICH	Intracerebral Hemorrhage
IMS	Interventional Management of Stroke
INR	International Normalized Ratio
INTERRSeCT	Identifying New Approaches to Optimise Thrombus Characterization for Predicting Early Recanalization and Reperfusion With IV Alteplase and Other Treatments Using Serial CT Angiography study
IQR	Interquartile Range
IRB	Institutional Review Board

Abbreviation	Definition
IST–3	International Stroke Trial 3
IV	Intravenous
IVtPA	Intravenous Tissue Plasminogen Activator
LVO	Large Vessel Occlusion
MCA	Middle Cerebral Artery
MOSTE	Minor Stroke Therapy Evaluation
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
MR RESCUE	Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NNT	Number Needed To Treat
non–ECC	Non–Endovascular–Capable Centre
NOR–TEST	Norwegian Tenecteplase Stroke Trial
OR	Odds Ratio
POSITIVE	Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy
PROACT–2	Intra–arterial Prourokinase for Acute Ischemic Stroke
PROVE–IT	Precise and Rapid Assessment of Collaterals Using Multi–phase CTA in the Triage of Patients With Acute Ischemic Stroke for IA Therapy
QuICR	Quality Improvement and Clinical Research
REVASCAT	Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset

Abbreviation	Definition
sICH	Symptomatic Intracranial Hemorrhage
SIS	Stroke Impact Scale
SITS–MOST	Safe Implementation of Treatment in Stroke—Monitoring Study
SITS–TBY	Safe Implementation of Treatment in Stroke—Thrombectomy
SR	Student researcher
SS–QOL	Stroke Specific Quality of Life Scale
SWIFT–PRIME	Solitaire™ with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke
SYNTHESIS	Local Versus Systemic Thrombolysis for Acute Ischemic Stroke
TASTE	Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation
TEMPO–2	TNK–tPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion 2
THRACE	Trial and Cost Effectiveness Evaluation of Intra–arterial Thrombectomy in Acute Ischemic Stroke
TNK	Tenecteplase
tPA	Tissue Plasminogen Activator
TWIST	Tenecteplase in Wake–up Ischemic Stroke Trial
WHO	World Health Organization

CHAPTER 1 Statement of Author Contributions

Below is a statement of the contribution of each author for the multi–authored manuscripts included in this thesis.

- **Zerna C**, Thomalla G, Campbell BCV, Rha JH, Hill MD. Current practice and future directions in the diagnosis and acute treatment of ischemic stroke. *Lancet* 2018; 392: 1247–1256.

CZ wrote the first draft of the manuscript and produced the figures. All authors contributed critical edits and revisions to the final draft of the manuscript. Portions of this manuscript are adapted with permission and included in CHAPTER 2.

- **Zerna C**, Goyal M. Long–term outcome of endovascular therapy for ischemic stroke. *Nature Reviews Neurology* 2017; 13: 387–388.

CZ wrote the first draft of the manuscript and produced the figures. CZ and MG contributed critical edits and revisions to the final draft of the manuscript. This manuscript in its entirety is included in CHAPTER 3.

- **Zerna C,** Burley T, Green TL, Dukelow SP, Demchuk AM, Hill MD. Comprehensive assessment of disability post–stroke using the newly developed miFUNCTION scale. *International Journal of Stroke*. 2020; 15: 167–174.

CZ and MDH designed the study. CZ performed the analysis, created the figures and tables, and wrote the first draft of the manuscript. All authors revised the manuscript for important intellectual content. CZ assumes the responsibility for the integrity of the manuscript. This manuscript in its entirety is included in CHAPTER 5.

- **Zerna C,** Rogers E, Rabi DM, Demchuk AM, Kamal N, Mann B, Jeerakathil T, Buck B, Shuaib A, Rempel J, Menon BK, Goyal M, Hill MD. Comparative Effectiveness of Endovascular Treatment for Acute Ischemic Stroke: A Population–Based Analysis. *Journal of the American Heart Association*. 2020 Apr 7;9:e014541.

CZ and MDH designed the study. ER performed the linkage of the registry data with the administrative database. CZ performed the analysis, created the figures and tables, and wrote the first draft of the manuscript. All authors revised the manuscript for important intellectual content. CZ assumes the responsibility for the integrity of the manuscript. This manuscript in its entirety is included in CHAPTER 6.

- Volny O***, Zerna C*,** Tomek A, Bar M, Rocek M, Padr R, Cihlar F, Nevsimalova M, Jurak L, Havlicek R, Kovar M, Sevcik P, Rohan V, Fiksa J, Cernik D, Jura D, Vaclavik D, Cimflova P, Puig J, Dowlatshahi D, Khaw AV, Fainardi E, Najm M, Demchuk AM, Menon BK, Mikulik R, Hill MD. Thrombectomy vs. Medical Management in Low NIHSS Acute Anterior Circulation Stroke. *Neurology*. Published online ahead of print September 28, 2020, DOI: https://doi.org/10.1212/WNL.0000000000010955.

*joint first authors. CZ, OV, and MDH designed the study. CZ performed the analysis, created the figures and tables. CZ and OV wrote the first draft of the manuscript. All authors revised the manuscript for important intellectual content. CZ assumes the responsibility for the integrity of the manuscript. This manuscript in its entirety is included in CHAPTER 7.

- Handbook of Neuroemergency Trials, 2nd Edition. **Zerna C**, Holodinsky JK, Goyal M, Hill MD. "Implications for New Trials in Acute Ischemic Stroke in the New Era of Endovascular Therapy" pp. 305–313, Academic Press/Copyright Elsevier (2017).

CZ wrote the first draft of the manuscript and produced the figures. All authors contributed critical edits and revisions to the final draft of the manuscript. Portions of this manuscript are adapted with permission and included in CHAPTER 8.

CHAPTER 2 Introduction

This chapter is adapted from a narrative review that was originally published in Lancet: Zerna C, Thomalla G, Campbell BCV, Rha JH, Hill MD. Current practice and future directions in the diagnosis and acute treatment of ischemic stroke. Lancet 2018; 392: 1247–1256. This chapter serves as an introduction to the thesis.

2.1 Current Practice and Future Directions in the Diagnosis and Acute Treatment of Ischemic Stroke

2.2 Introduction

Arterial stroke syndromes are characterized by a sudden loss of neurological function due to brain or retinal ischemia (around 85 %) or intracerebral haemorrhage (around 15 %) (Figure 1, Figure 2). Venous stroke syndromes are much less common than arterial strokes (less than one percent of all strokes), present subacutely and are caused by cerebral venous sinus or cortical vein thrombosis. Stroke syndrome presentations can be transient or permanent and range from mild to fatal. The historical epidemiological definition differentiating transient ischemic attacks and ischemic stroke on the basis of the duration of their symptoms (less or more than 24 hours) is now outdated because duration does not accurately predict the pathology. Magnetic resonance imaging (MRI) studies have shown that symptom duration greater than one hour is strongly associated with irreversible ischemia on diffusion–weighted (DWI) MRI and thus clinically defined transient ischemic attacks might not be transient on a tissue level.[1] A transient ischemic attack is not a pathological entity itself but rather the mildest form on the spectrum of ischemic stroke syndrome presentations. Whereas intracerebral haemorrhage (ICH) does not have a well

proven acute treatment, ischemic stroke is immediately treatable with reperfusion therapy and this chapter will focus on the management of acute ischemic stroke syndromes.

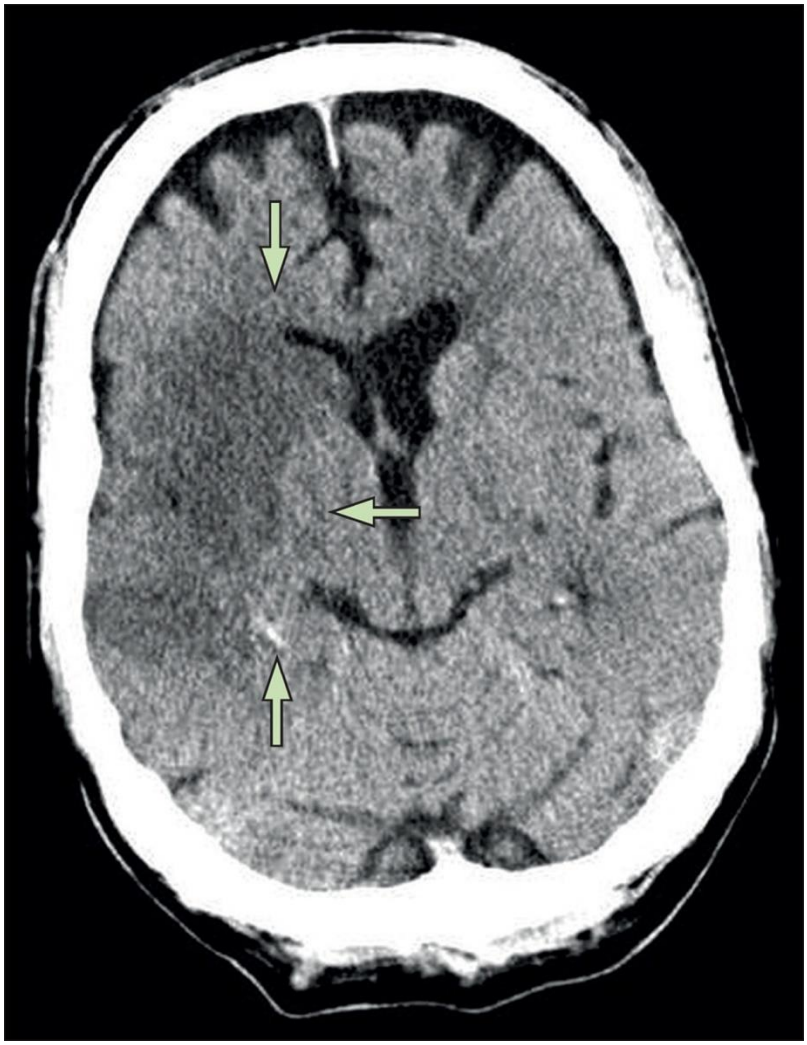


Figure 1: Non–Contrast CT of a Patient Presenting with a Right–Hemispheric Stroke Syndrome

The scan reveals hypoattenuating brain tissue and focal swelling in the right middle cerebral artery territory consistent with an acute ischemic stroke.

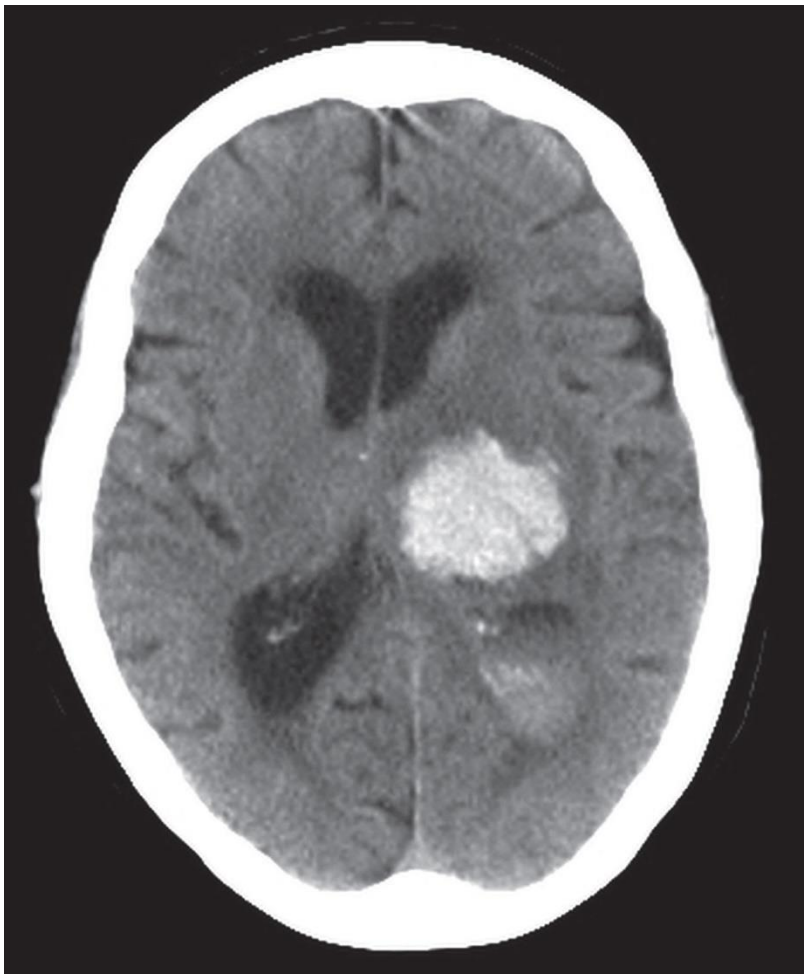


Figure 2: Non–Contrast CT of a Patient Presenting with a Hypertensive Intracerebral Hemorrhage Originating from the Left Thalamus Extending into the Left Lateral Ventricle

Ischemic stroke is caused by a focal occlusion or stenosis of an artery or multiple arteries in the brain (intracranial occlusion) or leading to the brain (extracranial cervical artery occlusion). These focal occlusions occur because of a variety of mechanisms, including cardioembolism, artery–to–artery thromboembolism, occlusive arterial disease, and small vessel disease, whose differentiation is important for tailored secondary stroke prevention. However,

detailed mechanistic information is most often neither readily available in the acute setting, nor necessarily relevant to the choice of acute treatment.

2.3 Types of Acute Stroke that Should be Treated

All disabling strokes should be considered for immediate treatment (Table 1). The severity of the neurological deficit in the context of a person's activities and their quality of life before stroke defines what is meant by disabling. The National Institutes of Health Stroke Scale (NIHSS) score, originally designed as a research tool to quantify the baseline clinical neurological deficit in acute stroke trials, is widely used as a clinical assessment in hospitals for neurological deficits related to stroke. However, it is a guide that does not weight deficits or disability equally and is therefore a tool to aid, but not a substitute for, the clinical judgment of stroke severity. The score can range from 0 to 42 points as a summation of criterion–based integer scores in eleven different domains of neurological function. As a clinical guide to the scale, a score of 0–5 points suggests a mild stroke, 6–15 a moderate stroke, and greater than 15 a severe stroke. Although there is no formal lower threshold, a score of more than five points typically warrants consideration for acute treatment with thrombolysis in almost all cases; with lesser scores, treatment should be considered in the context of a person's premorbid quality of life and activities as well as the disability resulting from acute symptoms. However, practice varies globally, with some clinicians regarding treatment of minor stroke with thrombolysis as a standard of care and others considering thrombolysis of minor stroke to be an important unresolved research question. Patients with minor stroke are at risk of subsequent deterioration and disability.[2] Establishing the balance between risk and benefit is the impetus for ongoing randomized clinical trials of thrombolysis in minor stroke.[3]

Table 1: Indications for Thrombolysis

Indications	• Disabling (in the context of a person's activities and their pre–stroke quality of life) acute ischemic stroke inpatients aged 18 years or older • Favourable CT brain imaging (ASPECTS score of five or higher, no extensive regions of clear hypoattenuation)
Absolute Contraindications	• CT brain imaging reveals acute intracranial haemorrhage • Active or recent bleeding at a non–compressible site (e.g. recent gastrointestinal bleed, recent intracranial or major surgery, recent major trauma)
Relative Contraindications*	• Presentation more than four and a half hours from time last seen well • Coagulopathy (platelet count less than 100 Gpt/L, international normalized ratio (INR) greater than 1·7, activated partial thromboplastin time greater than 40 seconds, or prothrombin time greater than 15 seconds) • Blood pressure more than 185/110 mmHg • Current treatment with an anticoagulant (thrombin or factor Xa inhibitor, heparin, low–molecular weight heparin), unless laboratory coagulations tests results are normal (INR less than or equal to 1.7) or provide proof of normal coagulation status • Prior intracranial haemorrhage within three months • Prior ischemic stroke within three months • Systemic malignancy • Intracranial malignant neoplasm • Intracranial arterial dissection • Blood glucose less than 2 mM or greater than 22 mmol/L • Suspected or diagnosed aortic dissection • Large (greater than 10 mm) unruptured and unsecured intracranial aneurysm • Previous high burden of cerebral microbleeds (more than ten) • Pregnancy

Thrombolysis indications, relative and absolute contraindications adapted from the Canadian Stroke Best Practice Recommendations: Hyperacute Care Guidelines (Update 2015),[4, 5] 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke: A Guideline for Healthcare Professionals From The

American Heart Association/American Stroke Association, and European Stroke Organization Guidelines for management of ischemic stroke and transient ischemic attack 2008.[7] ASPECTS = Alberta Stroke Program Early Computed Tomography Scale. *Relative contraindications mean that a clinical judgment must be made on the risk versus predicted benefit for treatment. For example, risk is low for patients with low or high baseline serum glucose or prior ischemic stroke, or for those with existing intracranial unruptured aneurysms, but many trials excluded these patients from enrolment. Risk is probably somewhat higher, but not quantifiable, and the benefit less well known in patients with systemic malignancy or prior intracerebral haemorrhage or some degree of coagulopathy.

Acute treatment for ischemic strokes aims to restore brain tissue perfusion. Restoration is achieved medically using a thrombolytic drug or by intervention with endovascular treatment (EVT), or both. Only a few of the total population of patients with ischemic stroke are eligible for acute therapy because the stroke is either non–disabling or contraindications to thrombolysis (Table 1) exist. Approximately 25 % of all ischemic strokes are eligible for medical thrombolysis and 10 - 12 % eligible for EVT. Since EVT is only applicable to a large vessel occlusion (LVO), arterial imaging is necessary to define the location of the occlusion.

2.4 Imaging as the Biomarker for Ischemic Stroke

Unlike the analogous situation in acute coronary syndromes with high–specificity serum troponin T levels, there is no serum biomarker for acute ischemic stroke. Known protein markers such as S100β and neuron–specific enolase levels measured at 24–72 hours correlate with infarct volume.[7] However, no single or combination of the available blood biomarkers provides differentiation of ischemic stroke and ICH with sufficient diagnostic accuracy to guide acute stroke treatment.[8] Even though glial fibrillary acidic protein levels were found to be 20 times higher in ICH than in ischemic stroke, high levels can also occur in other neurodegenerative, neoplasmal, and infectious diseases of the central nervous system.[9] A clear differentiation between ischemic stroke and ICH is only achieved by neuroimaging.

Because of its fast acquisition and widespread availability, non–contrast computed tomography (CT) is most widely used for acute stroke syndromes. Non–contrast CT allows differentiation between ischemic stroke and ICH and, in the case of an ischemic stroke, allows quantification of the extent of early ischemic changes by applying the Alberta Stroke Program Early CT Score (ASPECTS), a 10–point score that subtracts a point for each region of parenchymal hypoattenuation within the anterior circulation.[10] Scan quality, training, and experience affect the inter–rater reliability of ASPECTS but splitting the scale into categories as a dichotomy or trichotomy improves reproducibility.[11] Lower scores are predictive of a poor functional outcome and similarly, lower scores are associated with an increased risk of intraparenchymal haemorrhage associated with thrombolysis.[12, 13] A normal non–contrast CT does not rule out an acute ischemic stroke; non–contrast CT has a low negative predictive value for small ischemic volumes and therefore is commonly normal in minor or clinically resolved ischemic stroke. Non–contrast CT can exclude alternate causes for neurological symptoms such as subdural haematoma, brain tumour, or other space–occupying lesions.

Computed tomography angiography (CTA) uses iodinated radio–contrast media to image intracranial and extracranial blood vessels. CTA is used to identify proximal vessel occlusions as possible target lesions for EVT and should be a concurrent imaging study for patients with stroke. Neurointerventionalists can plan an endovascular procedure with CTA information about aortic arch tortuosity, Willisian and pial collateral status, as well as the site, characteristics, and length of the intracranial thrombus. The collateral status is estimated by comparing backfilling pial arteries in the affected hemisphere (distal to the occlusion) to the unaffected hemisphere. Poor collateral status is associated with larger volumes of irreversibly injured brain (ischemic

core) at baseline and worse functional outcome after reperfusion therapies, independent of patient age, vessel occlusion, and time since symptom onset.[14, 15] Assessment of collateral status has improved with the development of multiphase CTA, which generates time–resolved images of pial arteries by triggering the first scan in the late arterial phase on the basis of bolus monitoring and acquiring two subsequent scans without additional contrast in the mid–venous and late–venous phase. Multiphase CTA imaging is only minimally vulnerable to poor contrast–bolus timing and patient motion and the asymmetry in collateral filling can be used to help identify distal intracranial occlusions, even for inexperienced scan readers.[16]

Similarly, computed tomography perfusion (CTP) assesses collateral blood flow by repeatedly imaging the brain during transit of a rapidly administered bolus of intravenous (IV) contrast injection. CTP produces maps of the total amount and delay in arrival of blood flowing through the brain vasculature and improves diagnostic confidence in differentiating ischemic stroke from mimics (e.g. a stroke will show a region of hypoperfusion and up to 50 % of acute seizures will show a region of hyperperfusion). Whereas CTA images the larger vessels only, CT perfusion includes capillary and venular flow. Quantitative perfusion thresholds are used to estimate tissue that is already irreversibly damaged (core), tissue that is likely to infarct but salvageable with reperfusion (ischemic penumbra), and tissue that is not threatened but might have reduced blood flow (benign oligemia). CTP thresholds that estimate ischemic core and penumbra have been validated by comparison with follow–up infarction, defined by DWI, often done within an hour of CTP, or with follow–up infarction in patients who have reperfused within 24 hours after stroke onset.

The predictive thresholds for these tissue states vary with imaging–to–reperfusion time.[17, 18] Data from a multicenter cohort study showed that a CTP-derived T_{max} threshold of around >16 seconds on average, has the highest sensitivity and specificity to predict irreversible damage even when reperfused within 90 minutes from CTP imaging). A lower T_{max} threshold of ≈>12.5 seconds is associated with irreversible damage even if reperfusion is achieved between 90 to 180 minutes from CTP.[17] Conversely, this means that even brain regions with severe perfusion impairment might be salvageable with timely reperfusion and thus the predictive value of CTP core estimates is imperfect. In practice with existing treatment paradigms, a severe reduction (e.g. relative cerebral blood flow < 30 % of normal brain) has shown utility as a marker of irreversible injury in several trials, including late–window treatment trials.[19 - 24] Automated software now allows timely post–processing of CTP functional maps that are robust to common artifacts, allowing rapid clinician interpretation.[24] However, care is required to avoid delaying treatment decisions because of the time taken to acquire, transfer, post–process, and interpret CTP data.

MRI provides some diagnostic advantages compared with non–contrast CT, but in most centres takes longer to access and acquire. DWI maps show early ischemic changes within minutes from stroke onset and a correlating apparent diffusion coefficient map visualises the extent of cytotoxic oedema caused by brain ischemia. There is no equivalent CT technique or parameter, although regional hypoattenuation on CT is highly predictive of restricted diffusion on MRI.[26] MRI is especially useful in detecting minor strokes and differentiating ischemic stroke from mimics in the setting of ischemic lesions of small volume (Figure 3), multiple embolic lesions, and in posterior circulation strokes where the skull base creates bony artefacts on non–

contrast CT. Time–of–flight MR angiography enables a flow–dependent visualisation of the brain arteries without the need for a contrast agent. Susceptibility–weighted imaging allows for the detection of ICH with high sensitivity, and the detection of cerebral microbleeds not captured by non–contrast CT, which might indicate underlying pathophysiologies, such as cerebral amyloid angiopathy, and might be associated with an increased risk of intracranial haemorrhage after IV thrombolysis.[27] Specific MRI patterns of infarction might suggest a stroke mechanism, and, within limits, can date stroke age.[28] A mismatch between DWI and fluid–attenuated inversion recovery (FLAIR) sequence has been proposed as the criterion for the selection of patients who will benefit from thrombolytic therapy even though their time of stroke onset is unknown. In the WAKE–UP trial, IV thrombolysis with alteplase guided by DWI–FLAIR mismatch was effective and resulted in a significantly better functional outcome than placebo in patients with stroke of unknown symptom onset.[29] This imaging approach is used in other ongoing clinical trials to further test the efficacy and safety of IV thrombolysis in acute stroke syndromes with unknown time of symptom onset (NCT02002325). Contrary to usual static vascular imaging techniques, contrast–enhanced dynamic MR angiography now allows time–resolved assessment of arterial occlusions, cerebral hemodynamics, and collateral circulation in the acute setting.[30] MR perfusion imaging can use a gadolinium contrast agent and produces similar maps to CTP. Arterial spin labelling perfusion imaging does not require contrast injection but the delay in endogenous tracer arrival limits measurements of cerebral blood flow within the territory affected by stroke.[31]

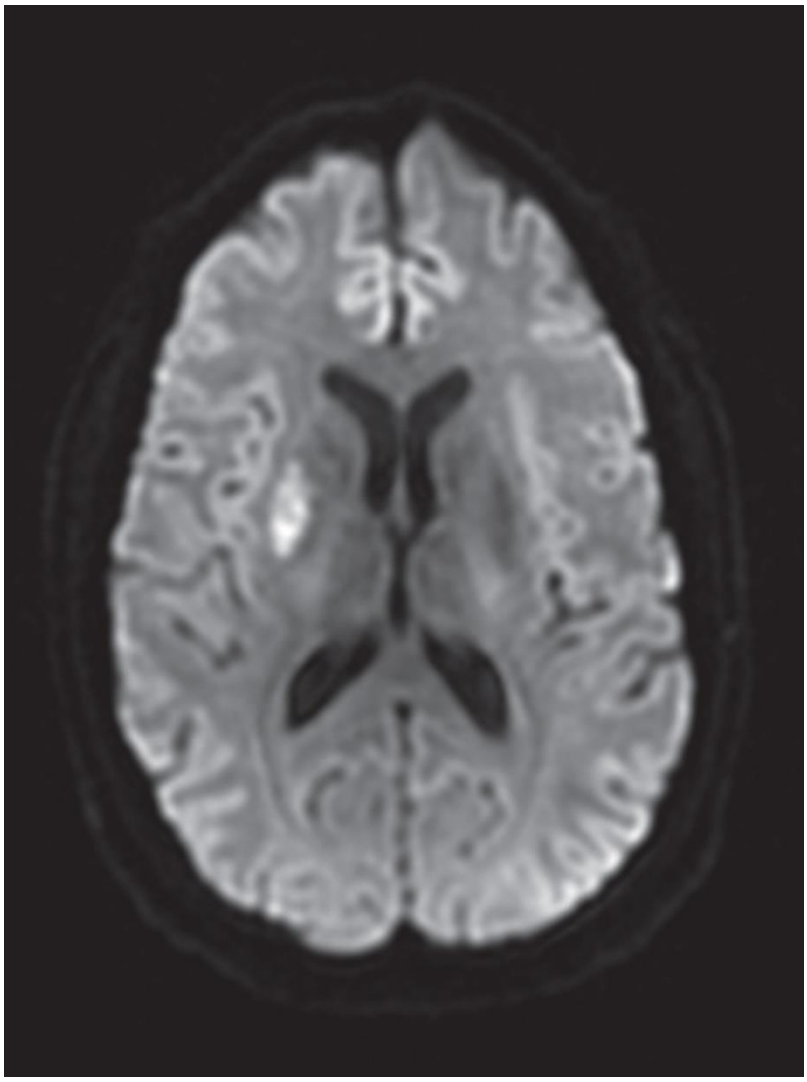


Figure 3: MRI Showing an Acute Ischemic Stroke in the Right Lentiform Nucleus

Imaging is the most important biomarker in acute ischemic stroke; it can define the cause, show the extent of potentially salvageable brain tissue, and aid the selection of acute therapies. With additional imaging, time spent on imaging acquisition and processing delays treatment initiation. The threshold for when sufficient information is available to make a correct therapeutic decision should be short. Acute ischemic stroke is a medical emergency and the

average infarct progression of an untreated middle cerebral artery (MCA) stroke leads to a loss of 1.9 million neurons per minute, which means that each one minute delay of treatment is correlated with a loss of 1.8 days' healthy life.[32] The chance of poor outcome with treatment increases while time passes with each additional test obtained.[33]

2.5 Acute Treatment of Ischemic Stroke

2.5.1 Thrombolytic Therapy

Open angiographic evidence of occlusions of the carotid artery and the more distal vascular tree was first documented in the late 1930s. However, early studies using fibrinolytic agents did not progress to larger randomized trials because non–invasive imaging of the brain and neurovasculature was not available until half a century later.[34] IV urokinase and streptokinase did not improve clinical outcomes and, in some studies, were associated with increased risk of ICH and have since been abandoned.[35, 36] Subsequently, alteplase—a single–chain recombinant tissue plasminogen activator (tPA)—has been successfully shown to be an efficacious treatment for stroke and subsequently marketed worldwide for acute ischemic stroke treatment. The NINDS tPA stroke trial showed an increase in good outcomes at three months using 0.9 mg/kg IV alteplase compared with placebo in two parallel trials, leading to the licensing of alteplase in a three hour time window from stroke symptom onset.[37] The European Cooperative Acute Stroke Study (ECASS) II and Alteplase Thrombolysis for Acute Non–interventional Therapy in Ischemic Stroke (ATLANTIS–B) trials were neutral for their chosen primary outcomes but were combined in a pooled individual patient meta–analysis including over 2000 patients treated within 360 minutes from stroke symptom onset.[38, 39] This post–hoc

analysis showed a distinct benefit of alteplase that was greater the earlier it was given, approaching a neutral effect at 270 minutes (4.5 hours) from symptom onset.[40] The ECASS III trial verified the sustained benefit of alteplase in the three to four and a half hour window but established that any delay in alteplase administration increased the risk of treatment–associated symptomatic ICH (sICH).[41] Thus, time from stroke onset to treatment initiation, although an unreliable surrogate marker for the extent of brain ischemia, has been shown to be a strong effect modifier for alteplase treatment when pooling multiple large studies, showing no average benefit of alteplase administration after 270 minutes from stroke symptom onset.[42] IST–3, the largest thrombolysis trial, took almost a decade to complete. Although treating many patients at the periphery of present guidelines the trial showed improved functional outcome due to thrombolysis within six hours that was even preserved in the elderly (> 50 % of patients were aged > 80 years).[43] An updated systematic review and meta–analysis including over 10,000 patients showed that thrombolysis given within six hours produced functional benefits and that those treated within the first three hours derived substantially more benefit than those treated later (Table 2).[44]

Table 2: Efficacy and Safety of Acute Ischemic Stroke Treatment

	Effect on 90–day outcome (mRS 0–1)	Effect on safety (sICH within 36 hours)	ARR	NNT
Thrombolysis				
0–3 hours	1.75 (1.35–2.27)	6.67 (4.11–10.84)	0.098	10
3–4.5 hours	1.26 (1.05–1.51)	–	0.053	19
>4.5 hours	1.15 (0.95–1.40)	–	0.02	50
Endovascular treatment				
0–12 hours	2.49 (1.84–3.35)	0.99 (0.60–1.63)	0.14	7

Data are OR (95 % CI), unless otherwise indicated. Data are from the meta–analysis by the Stroke Thrombolysis Trialists' Collaborative Group and the HERMES collaboration.[45, 46] No meta–analysis has been done to assess the effect of endovascular treatment beyond 12 h. mRS = modified Rankin Scale. sICH = symptomatic (a deterioration in National Institutes of Health Stroke Scale Score of ≥ 4) intracranial haemorrhage type 2 within 24 hours (SITS–MOST definition[47]); OR = odds ratio. ARR = absolute risk reduction. NNT = number needed to treat to benefit one additional patient.

The large number of patients in the International Stroke Trial 3 (IST–3) trial allowed for multiple secondary analyses that were informative. Despite increased risk of sICH, thrombolysis has a net clinical benefit in patients with leukoaraiosis on baseline imaging and should not be withheld on the basis of this finding alone.[48] Prespecified subgroups in IST–3 did not show differing functional outcomes but thrombolysis was associated with increased odds of sICH among patients who had previously taken antiplatelet agents.[49] The subsequent ENCHANTED trial comparing low–dose versus standard–dose alteplase treatment in patients on prior antiplatelet therapy was neutral. However, there were fewer sICHs in the low–dose alteplase group, particularly among patients without prior antiplatelet treatment.[50] Many studies have

speculated that patients on prior antiplatelet treatment are at greater risk for sICH, partly related to the greater occurrence of vascular risk factors that warrant antiplatelet treatment. Data on the thrombolysis–associated risk of sICH in patients with dual antiplatelet treatment are limited by the small number of outcomes.[51, 52] Further randomized clinical trials are necessary to identify a subgroup of patients who would potentially benefit from low–dose alteplase treatment. Another multicentre, randomized controlled trial comparing patients who were given IV aspirin versus placebo within 90 minutes after IV thrombolysis treatment was stopped early because of an excess incidence of sICH and no evidence of benefit at three months in the aspirin group.[53]

Alteplase has insufficient efficacy for early recanalization in proximal vessel occlusions. Other thrombolytic agents, such as desmoteplase, showed a good safety profile within a nine hour window but failed to show efficacy in another study.[54 - 57] Small studies comparing tenecteplase (TNK) with alteplase have shown TNK to have superior fibrinolytic activity with increased rates of reperfusion.[58, 59] However, the Norwegian Tenecteplase Stroke Trial (NOR–TEST) trial showed that TNK was not superior to alteplase in 1100 patients with acute ischemic stroke, despite the drugs having a similar safety profile.[60] NOR–TEST has been criticized for enrolling a high number of patients with stroke mimics and treating a population of low clinical stroke severity.[61] Nevertheless, ease of use, higher reperfusion rates, and safety could result in TNK replacing alteplase. The Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra–Arterial (EXTEND–IA) TNK trial showed that TNK before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome than alteplase among patients with ischemic stroke treated within four and half hours of symptom onset.[62] Six other ongoing phase 3 trials (TNK–tPA Versus Standard of Care for Minor Ischemic Stroke With

Proven Occlusion 2 (TEMPO–2): NCT02398656; Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation (TASTE): ACTRN12613000243718; Tenecteplase in Wake–up Ischemic Stroke Trial (TWIST): NCT03181360; The Norwegian Tenecteplase Stroke Trial 2 (NOR-TEST2): NCT0385400; Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke (AcT): NCT03889249; and Tenecteplase in Stroke Patients Between 4.5 and 24 Hours (TIMELESS) NCT03785678) will provide further data.

2.5.2 Endovascular Therapy

After the exciting but preliminary results of the Intra–arterial Prourokinase for Acute Ischemic Stroke (PROACT–2) trial in 1999 showing improved outcome for patients with proximal MCA occlusions treated with intra–arterial pro–urokinase, subsequent trials (Local Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS)–Expansion, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), and Interventional Management of Stroke (IMS) III) investigating the benefits of EVT for acute ischemic stroke produced neutral results. A combination of factors, including trial design features, insufficiently clear imaging selection criteria, slow treatment process times, and the use of various older devices might have contributed to these neutral results.[63]

In 2015 and 2016, six positive trials (Multicentre Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE), EXTEND–IA, Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT), Solitaire™ with the

Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT–PRIME), and Trial and Cost Effectiveness Evaluation of Intra–arterial Thrombectomy in Acute Ischemic Stroke (THRACE)) of EVT for LVO of the anterior circulation established this therapy as a new standard of care. Each of these trials enrolled 70–500 previously healthy patients aged 18 years or older presenting with varying stroke severity up to 12 hours from symptom onset, as well as optional additional IV thrombolysis treatment and extracranial occlusions.[21, 22, 64 - 67] Many of the trials emphasized speed in achieving recanalization and thus targeted a major shortcoming of previously neutral trials. Careful imaging–based selection of the most appropriate patients, recognition of the importance of fast workflow, and the high reperfusion rates led to the overwhelming efficacy of EVT compared to standard care alone (Figure 4).

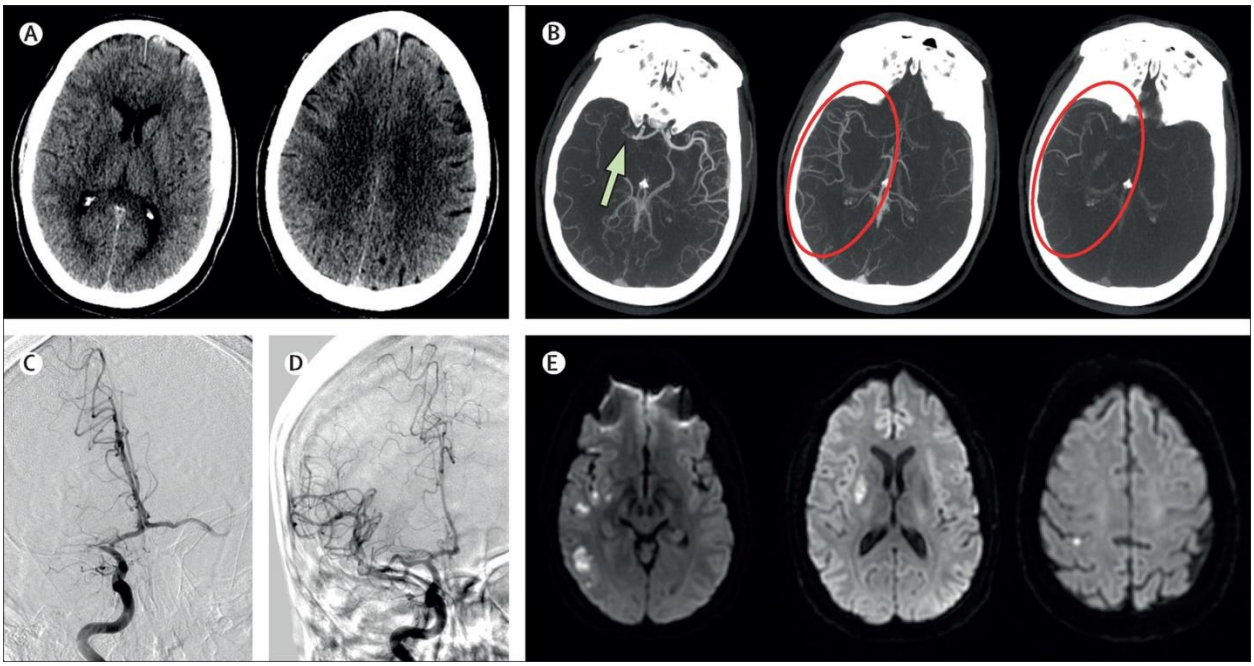


Figure 4: Imaging Modalities used to Diagnose and Treat Acute Ischemic Stroke

A 56–year–old man who was last seen normal at 2300 hours. He awoke at 0500 hours with left–sided weakness of the arm, leg, and face, as well as moderate dysarthria, and visual neglect (NIHSS score of 11). (A) Non–contrast CT of the head; (B) multiphase CT angiography in peak arterial, mid–venous, and late–venous phase (from left to right) showing the middle cerebral artery occlusion at the M1 segment (green arrow) and delayed arrival of the contrast agent with subsequent delayed washout in the right middle cerebral artery (red circles); (C) first intracranial angiographic run confirming a right middle cerebral artery occlusion; (D) final intracranial angiographic run post stent retrieval showing (near) complete reperfusion; (E) next day follow–up MRI showing a small volume ischemic lesion in the right middle cerebral artery territory. Patient clinically improved to an NIHSS score of 4.

The pooled, individual–patient meta–analysis showed improved functional outcome at 90 days for patients who had received EVT compared with those who had not.[45] Most patients in these trials were treated within six hours from symptom onset, but even late presenters (5.5–12 hours from symptom onset) in the ESCAPE trial had a treatment effect favouring EVT across all clinical outcomes.[68] The Diffusion Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN) trial showed that EVT was beneficial in highly selected

patients 6–24 hours after symptom onset when compared with medical treatment alone. Selection with CTP or DWI-MRI to identify potentially salvageable brain tissue was required.[69] The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE–3 trial), similarly requiring advanced CTP or perfusion MRI for patient selection, was halted early and showed that patients receiving EVT 6–16 hours after time last seen normal resulted in better functional outcomes than medical treatment.[23] These two trials emphasize the relevance of the *tissue window* (with imaging as the biomarker identifying salvageable brain tissue) as the physiological signature that defines a patient with treatable stroke. The Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy (POSITIVE) trial (NCT01852201), assessing a similar imaging paradigm, has been terminated in late 2019 but the publication of the results is still pending. Despite these late–window studies, fast delivery of treatment remains crucial; the SWIFT–PRIME trial reported that reperfusion within 150 minutes from symptom onset in the intervention arm led to a 91 % estimated probability of functional independence, which decreased by 10 % over the next hour and by 20 % with every subsequent hour of delay.[70]

Stent retrieval is a common first choice of neurointerventionalists and these devices have been used almost exclusively in clinical trials within the past five years. In the Contact Aspiration vs Stent Retriever for Successful Revascularization (ASTER) trial first–line contact aspiration during EVT compared with stent retrieval did not result in an increased successful revascularisation rate.[71] Previously acquired pilot data by another group using contact aspiration have shown lower procedure times and device costs compared with stent retrieval. The recently published Direct Aspiration First Pass Technique (COMPASS) trial found that direct aspiration

first pass technique during EVT was non–inferior to stent–retriever first line technique when comparing functional outcome at 90 days.[72] Newer devices, like the EmboTrap device, have been investigated in single–arm studies (ARISE II) and shown to demonstrate high rates of substantial reperfusion and functional independence at 90 days.[73]

2.5.3 Stroke Systems of Care

Since fast treatment is so important to good outcomes, organisation of stroke care is essential for timely treatment initiation. EVT can only be performed at selected capable stroke centres (usually tertiary hospitals), whereas thrombolytic treatment is available more widely at smaller hospitals. Patients identified in the field with a disabling stroke can therefore be either directly transported to an endovascular capable centre, even if that means bypassing a closer primary stroke centre (*mothership* model), or be transported to the nearest primary stroke centre for thrombolytic treatment first and then, if appropriate, be transferred to the endovascular capable centre (*drip and ship* model). Transport times and distribution of primary centres and endovascular capable centres will determine the optimal approach. Telemedicine can be used to assist decision making for either of the models, as neurologists stationed at an endovascular capable centre can be consulted by health–care providers in primary stroke centres or even pre–hospital care providers in ambulances.

Mobile stroke units are ambulances equipped with a CT scanner, a point of care laboratory, and specialized staff and allow for early diagnosis aided by neuroimaging and thus identify eligibility and even initiate thrombolytic treatment on route to the hospital.[74, 75] There are ongoing efforts to develop pre–hospital stroke scales to differentiate large artery occlusions from other types of strokes to allow the most appropriate triage.[76] Additionally, multiple ongoing trials

are assessing current transportation dilemmas, such as being taken directly to an endovascular capable centre versus directly to a primary stroke centre for patients with suspected LVO (NCT02795962), and initiation of thrombolytic treatment on a mobile stroke unit versus in the hospital (Benefits of Stroke Treatment Delivered Using a Mobile Stroke Unit (BEST–MSU): NCT02190500; Berlin Pre–hospital Or Usual Delivery of Stroke Care 2.0 (B_PROUD 2.0): NCT03931616). How patients are best advanced through the health system to have timely and appropriate access to acute stroke treatment will be an evolving standard depending on geography, infrastructure, population density, politics, and technology.

An integral part of geographical access to acute stroke care is how to optimize the workflow in each of the contributing sectors to treat patients with ischemic stroke as quickly as possible. Systematic quality improvements can lead to much faster door–to–needle times compared with those being currently achieved, without an increase in complications. Helsinki University Hospital (Helsinki, Finland) established a high standard by lowering their median door–to–needle times to 20 minutes in 2011; the hospital's model was then successfully replicated at the Royal Melbourne Hospital (Melbourne, Australia) and improvements in the United States have been reported by the Target Stroke initiative.[77 - 79] The key to shorter door–to–needle time is a well-organized stroke service, the so–called chain of recovery. Emergency call centres, paramedics, and the emergency department of the receiving hospital must work seamlessly together. Clinical assessment, imaging, and decision making for thrombolysis and EVT need to occur in parallel rather than sequentially and hospital pre–notification with transport of the patient direct to the CT scanner on the ambulance stretcher are the key to achieving a revised door–to–needle time target of 30 minutes or lower.[80]

All patients with acute stroke, whether it is ischemic or haemorrhagic, benefit from stroke unit care.[81] This benefit holds true after successful reperfusion therapy. Acute stroke unit care is designed to prevent complications such as pulmonary embolism and aspiration pneumonia. Diagnostic work–up at a stroke unit makes early secondary prevention possible based on the cause of the stroke. Treatment of risk factors and evaluation of the need for rehabilitation can be initiated early at the stroke unit. Evidence–based stroke unit care will increase the likelihood of good functional outcome of stroke patients.[82]

2.5.4 Adjuvant and Novel Therapies for Ischemic Stroke

Future technology to improve stroke diagnosis in the field, advances in neuroimaging, improvements in medical reperfusion therapy, advances in catheters to optimize complete reperfusion rates, and adjuvant medication to reduce permanent brain injury are all under active investigation. Importantly, improvements in catheters for stroke treatment might be influenced by regional differences in disease burden. In Asia, intracranial stenosis due to underlying intracranial atherosclerosis is a more prevalent cause of stroke than in the rest of the world.[83] Such residual intracranial stenosis might require angioplasty and stenting or the use of antiplatelet infusion medication.[84] Potential improvements in medical therapy in general include sonothrombolysis and continued investigation of TNK as a primary thrombolytic drug.[85]

Attempts to translate beneficial findings of high–flow oxygen and hypothermia from preclinical models to human models have been previously disappointing. Yet, adjuvant therapy for stroke is evolving. While over 1000 putative neuroprotective compounds have not been translated from the laboratory to humans, most were tested in an ischemia–reperfusion model (temporary MCA occlusion).[86] Human stroke due to LVO does not commonly show early

reperfusion with medical treatment, but advances in EVT have resulted in a true human ischemia–early reperfusion model. Molecules such as the peptide NA–1 (also known as Tat–NR2B9c or nerinetide) have been investigated in this setting.[87] The Safety and Efficacy of NA–1 in Subjects Undergoing Endovascular Thrombectomy for Stroke (ESCAPE–NA1) trial showed that the proportion of patients achieving good functional outcome at 90 days after EVT was not improved by nerinetide compared to placebo but there was effect modification resulting in the inhibition of treatment effect in patients receiving alteplase and there was indeed benefit in the subgroup that did not receive alteplase.[88] Since magnesium sulphate has been shown to be safe in the pre–hospital setting, a trial investigating the potential for the molecule to preserve ischemic penumbra until the patient can undergo EVT with definite recanalization might be considered.[89] The medical management of hyperglycaemia, hypertension, and hyperthermia or pyrexia in acute ischemic stroke remains to be further defined. Although it is well proven that hyperglycaemia, elevated or very low blood pressure and elevated body temperature are all associated with poor outcomes, it is not known whether intervention will actually result in better outcomes.[90 - 92]

Finally, innovation might occur in stroke treatment processes. Imaging with dynamic angiography equipment can allow a direct–to–angiography workflow, further reducing door–to–treatment time. As the technology for this approach to imaging improves and becomes installed in hospitals, the approach to treatment of selected patients to increasingly take place is expected. This evolution will be accelerated if non–invasive technology plus clinical evaluation allows the reliable identification of LVO in the pre–hospital setting.

2.6 Conclusion and Future Directions

The framework for acute ischemic stroke therapeutics is fast treatment with a door–to–needle time target of 30 minutes or less and rapid escalation to EVT for patients with LVO. Advanced neuroimaging, including arterial imaging, is the cornerstone for effective guidance of acute stroke treatment. Regional systems of stroke care are affected by geography, infrastructure, including financial resources, population density, politics, and technology and must be optimized to allow timely access to thrombolytic therapy and EVT. Because primary and comprehensive stroke centres must improve their workflow to achieve these target metrics, there is a substantial incentive to develop alternative thrombolytic agents that are easy to use, such as TNK. With the establishment of EVT and a true human–ischemia–reperfusion model, adjuvant therapies can be investigated. Acute stroke therapy is one of the most important advances in the therapeutics of neurological diseases and the future for new treatments looks promising.

2.7 Rationale and Objectives of this Thesis

While EVT has revolutionized acute ischemic stroke care, the randomized controlled trials showing the efficacy of the treatment have different limitations:

- The clinical endpoint of mRS score was assessed 90 days post stroke even though previous studies in humans suggest that there is a three to six months window of heightened neuroplasticity and even a gradient of enhanced sensitivity to rehabilitation treatment beyond 12 months post stroke which could result in delayed functional recovery.[93]
- The mRS score as the chosen clinical end–point captures only two of the functional dimensions of interest that are affected after a stroke (body functions

and structure as well as activity) but has difficulties depicting the social dimension of participation. The scale also lacks sensitivity at the lower end of the disability spectrum and the inter–observer variability is high.

- The studied patient cohort was rather homogenous and narrow–defined to increase the likelihood of showing efficacy of the treatment under investigation.

The objective of this research was thus to assess the sustainability of the efficacy of EVT beyond 90 days post stroke, to utilize post–stroke outcomes that are patient–centered and more meaningful to the affected individuals, and to investigate the efficacy of EVT in patient populations that have not been part of the randomized controlled clinical trial cohort but are commonly affected by LVO acute ischemic strokes and might benefit from the treatment as well. The results of this research will be meaningful to individual patients who experience acute ischemic strokes caused by LVO and also aid with economic and regulatory decisions to more broadly offer and organize EVT across the province of Alberta and beyond.

2.8 Thesis Structure

This thesis is structured as a manuscript based dissertation. To fulfil the objectives described above a program of research was developed and six manuscripts produced and published. CHAPTER 2 is an adaption of a narrative review published in *Lancet* about the current practice and future directions in the diagnosis and acute treatment of ischemic stroke and serves as an introduction to this thesis. CHAPTER 3 is a commentary published in *Nature Reviews Neurology* and speaks to the long–term benefits of EVT. CHAPTER 4, not in manuscript format, provides a detailed description of the methodology across the entire program of research in addition to the methods section of each originally published article. CHAPTER 5

is an original research article published in *International Journal of Stroke* which describes the development of the miFUNCTION scale, its psychometric properties, and its use as an endpoint within a randomized controlled trial of EVT compared to medical management for acute ischemic stroke. CHAPTER 6 is an original research article published in *Journal of the American Heart Association* which describes the relative effectiveness of EVT in a population–based analysis of the entire province of Alberta while utilizing home–time as a novel and patient–centered outcome. CHAPTER 7 is an original research article published online ahead of print in *Neurology* which describes the treatment effect of EVT compared to medical management in patients presenting with low stroke severity by performing a propensity–score matched analysis. CHAPTER 8, not in manuscript format, provides further discussion of the work presented in Chapters 5 through 7, future directions, and conclusions. In part, it utilizes a book chapter published in the *Handbook of Neuroemergency Trials.* Each chapter contains individually numbered reference lists. A complete bibliography of all cited works in alphabetical order appears at the end of the thesis.

2.9 References

1. Albers GW, Caplan LR, Easton JD, Fayad PB, Mohr JP, Saver JL, et al. Transient ischemic attack--proposal for a new definition. *The New England journal of medicine*. 2002;347:1713-1716

2. Coutts SB, Modi J, Patel SK, Aram H, Demchuk AM, Goyal M, et al. What causes disability after transient ischemic attack and minor stroke?: Results from the ct and mri in the triage of tia and minor cerebrovascular events to identify high risk patients (catch) study. *Stroke; a journal of cerebral circulation*. 2012;43:3018-3022

3. Bivard A, Huang X, Levi CR, Spratt N, Campbell BCV, Cheripelli BK, et al. Tenecteplase in ischemic stroke offers improved recanalization: Analysis of 2 trials. *Neurology*. 2017;89:62-67

4. Casaubon LK, Boulanger JM, Blacquiere D, Boucher S, Brown K, Goddard T, et al. Canadian stroke best practice recommendations: Hyperacute stroke care guidelines, update 2015. *International journal of stroke : official journal of the International Stroke Society*. 2015;10:924-940

5. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke; a journal of cerebral circulation*. 2018;49:e46-e110

6. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovascular diseases (Basel, Switzerland)*. 2008;25:457-507

7. Ahmad O, Wardlaw J, Whiteley WN. Correlation of levels of neuronal and glial markers with radiological measures of infarct volume in ischaemic stroke: A systematic review. *Cerebrovascular diseases (Basel, Switzerland)*. 2012;33:47-54

8. Hasan N, McColgan P, Bentley P, Edwards RJ, Sharma P. Towards the identification of blood biomarkers for acute stroke in humans: A comprehensive systematic review. *British journal of clinical pharmacology*. 2012;74:230-240

9. Seder DB. Serum Glial Fibrillary Acidic Protein in Acute Stroke. *Neurocritical Care*. 2020;33:35-36.

10. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. Aspects study group. Alberta stroke programme early ct score. *Lancet (London, England)*. 2000;355:1670-1674

11. Gupta AC, Schaefer PW, Chaudhry ZA, Leslie-Mazwi TM, Chandra RV, Gonzalez RG, et al. Interobserver reliability of baseline noncontrast ct alberta stroke program early ct score for intra-arterial stroke treatment selection. *AJNR. American journal of neuroradiology*. 2012;33:1046-1049

12. Dzialowski I, Hill MD, Coutts SB, Demchuk AM, Kent DM, Wunderlich O, et al. Extent of early ischemic changes on computed tomography (ct) before thrombolysis: Prognostic value of the alberta stroke program early ct score in ecass ii. *Stroke; a journal of cerebral circulation*. 2006;37:973-978

13. Hill MD, Demchuk AM, Goyal M, Jovin TG, Foster LD, Tomsick TA, et al. Alberta stroke program early computed tomography score to select patients for endovascular treatment: Interventional management of stroke (ims)-iii trial. *Stroke; a journal of cerebral circulation*. 2014;45:444-449

14. Khatri P, Abruzzo T, Yeatts SD, Nichols C, Broderick JP, Tomsick TA. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. *Neurology*. 2009;73:1066-1072

15. Sheth SA, Sanossian N, Hao Q, Starkman S, Ali LK, Kim D, et al. Collateral flow as causative of good outcomes in endovascular stroke therapy. *Journal of neurointerventional surgery*. 2016;8:2-7

16. Yu AY, Zerna C, Assis Z, Holodinsky JK, Randhawa PA, Najm M, et al. Multiphase ct angiography increases detection of anterior circulation intracranial occlusion. *Neurology*. 2016;87:609-616

17. d'Esterre CD, Boesen ME, Ahn SH, Pordeli P, Najm M, Minhas P, et al. Time-dependent computed tomographic perfusion thresholds for patients with acute ischemic stroke. *Stroke; a journal of cerebral circulation*. 2015;46:3390-3397

18. Bivard A, Kleinig T, Miteff F, Butcher K, Lin L, Levi C, et al. Ischemic core thresholds change with time to reperfusion: A case control study. *Annals of neurology*. 2017;82:995-1003

19. Campbell BC, Christensen S, Levi CR, Desmond PM, Donnan GA, Davis SM, et al. Cerebral blood flow is the optimal ct perfusion parameter for assessing infarct core. *Stroke; a journal of cerebral circulation*. 2011;42:3435-3440

20. Cereda CW, Christensen S, Campbell BC, Mishra NK, Mlynash M, Levi C, et al. A benchmarking tool to evaluate computer tomography perfusion infarct core predictions against a dwi standard. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2016;36:1780-1789

21. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *The New England journal of medicine*. 2015;372:1009-1018

22. Saver JL, Goyal M, Diener HC. Stent-retriever thrombectomy for stroke. *The New England journal of medicine*. 2015;373:1077

23. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *The New England journal of medicine*. 2018

24. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *The New England journal of medicine*. 2018;378:11-21

25. Campbell BC, Yassi N, Ma H, Sharma G, Salinas S, Churilov L, et al. Imaging selection in ischemic stroke: Feasibility of automated ct-perfusion analysis. *International journal of stroke : official journal of the International Stroke Society*. 2015;10:51-54

26. Barber PA, Hill MD, Eliasziw M, Demchuk AM, Pexman JH, Hudon ME, et al. Imaging of the brain in acute ischaemic stroke: Comparison of computed tomography and magnetic resonance diffusion-weighted imaging. *Journal of neurology, neurosurgery, and psychiatry*. 2005;76:1528-1533

27. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, et al. Cerebral microbleeds: A guide to detection and interpretation. *The Lancet. Neurology*. 2009;8:165-174

28. Thomalla G, Boutitie F, Fiebach JB, Simonsen CZ, Nighoghossian N, Pedraza S, et al. Stroke with unknown time of symptom onset: Baseline clinical and magnetic resonance imaging data of the first thousand patients in wake-up (efficacy and safety of mri-based thrombolysis in wake-up stroke: A randomized, doubleblind, placebo-controlled trial). *Stroke; a journal of cerebral circulation*. 2017;48:770-773

29. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, et al. Mri-guided thrombolysis for stroke with unknown time of onset. *The New England journal of medicine*. 2018

30. Hernandez-Perez M, Puig J, Blasco G, Perez de la Ossa N, Dorado L, Davalos A, et al. Dynamic magnetic resonance angiography provides collateral circulation and hemodynamic information in acute ischemic stroke. *Stroke; a journal of cerebral circulation*. 2016;47:531-534

31. Kane I, Carpenter T, Chappell F, Rivers C, Armitage P, Sandercock P, et al. Comparison of 10 different magnetic resonance perfusion imaging processing methods in acute ischemic stroke: Effect on lesion size, proportion of patients with diffusion/perfusion mismatch, clinical scores, and radiologic outcomes. *Stroke; a journal of cerebral circulation*. 2007;38:3158-3164

32. Meretoja A, Keshtkaran M, Saver JL, Tatlisumak T, Parsons MW, Kaste M, et al. Stroke thrombolysis: Save a minute, save a day. *Stroke; a journal of cerebral circulation*. 2014;45:1053-1058

33. Goyal M, Fargen KM, Menon BK. Acute stroke, bayes' theorem and the art and science of emergency decision-making. *Journal of neurointerventional surgery*. 2014;6:256-259

34. Sussman BJ, Fitch TS. Thrombolysis with fibrinolysin in cerebral arterial occlusion. *Journal of the american medical association*. 1958;167:1705-1709

35. Fletcher AP, Alkjaersig N, Lewis M, Tulevski V, Davies A, Brooks JE, et al. A pilot study of urokinase therapy in cerebral infarction. *Stroke; a journal of cerebral circulation*. 1976;7:135-142

36. Meyer JS, Gilroy J, Barnhart MI, Johnson JF. Therapeutic thrombolysis in cerebral thromboembolism. Double-blind evaluation of intravenous plasmin therapy in carotid and middle cerebral arterial occlusion. *Neurology*. 1963;13:927-937

37. Tissue plasminogen activator for acute ischemic stroke. The national institute of neurological disorders and stroke rt-pa stroke study group. *The New England journal of medicine*. 1995;333:1581-1587

38. Brott TG, Haley EC, Jr., Levy DE, Barsan W, Broderick J, Sheppard GL, et al. Urgent therapy for stroke. Part i. Pilot study of tissue plasminogen activator administered within 90 minutes. *Stroke; a journal of cerebral circulation*. 1992;23:632-640

39. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The atlantis study: A randomized controlled trial. Alteplase thrombolysis for acute noninterventional therapy in ischemic stroke. *Journal of the american medical association*. 1999;282:2019-2026

40. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, et al. Association of outcome with early stroke treatment: Pooled analysis of atlantis, ecass, and ninds rt-pa stroke trials. *Lancet (London, England)*. 2004;363:768-774

41. Bluhmki E, Chamorro A, Davalos A, Machnig T, Sauce C, Wahlgren N, et al. Stroke treatment with alteplase given 3.0-4.5 h after onset of acute ischaemic stroke (ecass iii): Additional outcomes and subgroup analysis of a randomised controlled trial. *The Lancet. Neurology*. 2009;8:1095-1102

42. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al. Time to treatment with intravenous alteplase and outcome in stroke: An updated pooled analysis of ecass, atlantis, ninds, and epithet trials. *Lancet (London, England)*. 2010;375:1695-1703

43. Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [ist-3]): A randomised controlled trial. *Lancet (London, England)*. 2012;379:2352-2363

44. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *The Cochrane database of systematic reviews*. 2014:Cd000213

45. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet (London, England)*. 2016;387:1723-1731

46. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. *Lancet (London, England)*. 2014;384:1929-1935

47. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the safe implementation of thrombolysis in stroke-monitoring study (sits-most): An observational study. *Lancet (London, England)*. 2007;369:275-282

48. Charidimou A, Pasi M, Fiorelli M, Shams S, von Kummer R, Pantoni L, et al. Leukoaraiosis, cerebral hemorrhage, and outcome after intravenous thrombolysis for acute ischemic stroke: A meta-analysis (v1). *Stroke; a journal of cerebral circulation*. 2016;47:2364-2372

49. Lindley RI, Wardlaw JM, Whiteley WN, Cohen G, Blackwell L, Murray GD, et al. Alteplase for acute ischemic stroke: Outcomes by clinically important subgroups in the third international stroke trial. *Stroke; a journal of cerebral circulation*. 2015;46:746-756

50. Robinson TG, Wang X, Arima H, Bath PM, Billot L, Broderick JP, et al. Low- versus standard-dose alteplase in patients on prior antiplatelet therapy: The enchanted trial (enhanced control of hypertension and thrombolysis stroke study). *Stroke; a journal of cerebral circulation*. 2017;48:1877-1883

51. Diedler J, Ahmed N, Sykora M, Uyttenboogaart M, Overgaard K, Luijckx GJ, et al. Safety of intravenous thrombolysis for acute ischemic stroke in patients receiving antiplatelet therapy at stroke onset. *Stroke; a journal of cerebral circulation*. 2010;41:288-294

52. Xian Y, Federspiel JJ, Grau-Sepulveda M, Hernandez AF, Schwamm LH, Bhatt DL, et al. Risks and benefits associated with prestroke antiplatelet therapy among patients with acute ischemic stroke treated with intravenous tissue plasminogen activator. *Journal of the american medical association, neurology*. 2016;73:50-59

53. Zinkstok SM, Roos YB. Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke: A randomised controlled trial. *Lancet (London, England)*. 2012;380:731-737

54. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, et al. The desmoteplase in acute ischemic stroke trial (dias): A phase ii mri-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke; a journal of cerebral circulation*. 2005;36:66-73

55. Furlan AJ, Eyding D, Albers GW, Al-Rawi Y, Lees KR, Rowley HA, et al. Dose escalation of desmoteplase for acute ischemic stroke (dedas): Evidence of safety and efficacy 3 to 9 hours after stroke onset. *Stroke; a journal of cerebral circulation*. 2006;37:1227-1231

56. Hacke W, Furlan AJ, Al-Rawi Y, Davalos A, Fiebach JB, Gruber F, et al. Intravenous desmoteplase in patients with acute ischaemic stroke selected by mri perfusion-diffusion weighted imaging or perfusion ct (dias-2): A prospective, randomised, double-blind, placebo-controlled study. *The Lancet. Neurology*. 2009;8:141-150

57. Albers GW, von Kummer R, Truelsen T, Jensen JK, Ravn GM, Gronning BA, et al. Safety and efficacy of desmoteplase given 3-9 h after ischaemic stroke in patients with occlusion or high-grade stenosis in major cerebral arteries (dias-3): A double-blind, randomised, placebo-controlled phase 3 trial. *The Lancet. Neurology*. 2015;14:575-584

58. Parsons M, Spratt N, Bivard A, Campbell B, Chung K, Miteff F, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *The New England journal of medicine*. 2012;366:1099-1107

59. Coutts SB, Dubuc V, Mandzia J, Kenney C, Demchuk AM, Smith EE, et al. Tenecteplase-tissue-type plasminogen activator evaluation for minor ischemic stroke with proven occlusion. *Stroke; a journal of cerebral circulation*. 2015;46:769-774

60. Logallo N, Novotny V, Assmus J, Kvistad CE, Alteheld L, Ronning OM, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (nor-test): A phase 3, randomised, open-label, blinded endpoint trial. *The Lancet. Neurology*. 2017;16:781-788

61. Etherton MR, Barreto AD, Schwamm LH, Wu O. Neuroimaging paradigms to identify patients for reperfusion therapy in stroke of unknown onset. *Frontiers in neurology*. 2018;9:327

62. Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *The New England journal of medicine*. 2018;378:1573-1582

63. Zerna C, Hegedus J, Hill MD. Evolving treatments for acute ischemic stroke. *Circulation research*. 2016;118:1425-1442

64. Berkhemer OA, van Zwam WH, Dippel DW. Stent-retriever thrombectomy for stroke. *The New England journal of medicine*. 2015;373:1076

65. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *The New England journal of medicine*. 2015;372:1019-1030

66. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *The New England journal of medicine*. 2015;372:2296-2306

67. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (thrace): A randomised controlled trial. *The Lancet. Neurology*. 2016;15:1138-1147

68. Evans JW, Graham BR, Pordeli P, Al-Ajlan FS, Willinsky R, Montanera WJ, et al. Time for a time window extension: Insights from late presenters in the escape trial. *AJNR. American journal of neuroradiology*. 2017

69. Jovin TG, Saver JL, Ribo M, Pereira V, Furlan A, Bonafe A, et al. Diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention with trevo (dawn) trial methods. *International journal of stroke : official journal of the International Stroke Society*. 2017:1747493017710341

70. Goyal M, Jadhav AP, Bonafe A, Diener H, Mendes Pereira V, Levy E, et al. Analysis of workflow and time to treatment and the effects on outcome in endovascular treatment of acute ischemic stroke: Results from the swift prime randomized controlled trial. *Radiology*. 2016;279:888-897

71. Lapergue B, Blanc R, Gory B, Labreuche J, Duhamel A, Marnat G, et al. Effect of endovascular contact aspiration vs stent retriever on revascularization in patients with acute ischemic stroke and large vessel occlusion: The aster randomized clinical trial. *Journal of the american medical association*. 2017;318:443-452

72. Turk AS, 3rd, Siddiqui A, Fifi JT, De Leacy RA, Fiorella DJ, Gu E, et al. Aspiration thrombectomy versus stent retriever thrombectomy as first-line approach for large vessel occlusion (compass): A multicentre, randomised, open label, blinded outcome, non-inferiority trial. *Lancet (London, England)*. 2019;393:998-1008

73. Zaidat OO, Bozorgchami H, Ribo M, Saver JL, Mattle HP, Chapot R, et al. Primary results of the multicenter arise ii study (analysis of revascularization in ischemic stroke with embotrap). *Stroke; a journal of cerebral circulation*. 2018;49:1107-1115

74. Ebinger M, Winter B, Wendt M, Weber JE, Waldschmidt C, Rozanski M, et al. Effect of the use of ambulance-based thrombolysis on time to thrombolysis in acute ischemic stroke: A randomized clinical trial. *Journal of the american medical association*. 2014;311:1622-1631

75. Walter S, Kostopoulos P, Haass A, Keller I, Lesmeister M, Schlechtriemen T, et al. Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: A randomised controlled trial. *The Lancet. Neurology*. 2012;11:397-404

76. Hastrup S, Damgaard D, Johnsen SP, Andersen G. Prehospital acute stroke severity scale to predict large artery occlusion: Design and comparison with other scales. *Stroke; a journal of cerebral circulation*. 2016;47:1772-1776

77. Meretoja A, Strbian D, Mustanoja S, Tatlisumak T, Lindsberg PJ, Kaste M. Reducing in-hospital delay to 20 minutes in stroke thrombolysis. *Neurology*. 2012;79:306-313

78. Meretoja A, Weir L, Ugalde M, Yassi N, Yan B, Hand P, et al. Helsinki model cut stroke thrombolysis delays to 25 minutes in melbourne in only 4 months. *Neurology*. 2013;81:1071-1076

79. Fonarow GC, Zhao X, Smith EE, Saver JL, Reeves MJ, Bhatt DL, et al. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. *Journal of the american medical association*. 2014;311:1632-1640

80. Kamal N, Holodinsky JK, Stephenson C, Kashayp D, Demchuk AM, Hill MD, et al. Improving door-to-needle times for acute ischemic stroke: Effect of rapid patient registration, moving directly to computed tomography, and giving alteplase at the computed tomography scanner. *Circulation. Cardiovascular quality and outcomes*. 2017;10

81. Organised inpatient (stroke unit) care for stroke. *The Cochrane database of systematic reviews*. 2013:Cd000197

82. Candelise L, Gattinoni M, Bersano A, Micieli G, Sterzi R, Morabito A. Stroke-unit care for acute stroke patients: An observational follow-up study. *Lancet (London, England)*. 2007;369:299-305

83. Bang OY. Intracranial atherosclerosis: Current understanding and perspectives. *Journal of stroke*. 2014;16:27-35

84. Toyoda K, Koga M, Hayakawa M, Yamagami H. Acute reperfusion therapy and stroke care in asia after successful endovascular trials. *Stroke; a journal of cerebral circulation*. 2015;46:1474-1481

85. Barlinn K, Tsivgoulis G, Barreto AD, Alleman J, Molina CA, Mikulik R, et al. Outcomes following sonothrombolysis in severe acute ischemic stroke: Subgroup analysis of the clotbust trial. *International journal of stroke: official journal of the International Stroke Society*. 2014;9:1006-1010

86. O'Collins VE, Macleod MR, Donnan GA, Horky LL, van der Worp BH, Howells DW. 1,026 experimental treatments in acute stroke. *Annals of neurology*. 2006;59:467-477

87. Cook DJ, Teves L, Tymianski M. Treatment of stroke with a psd-95 inhibitor in the gyrencephalic primate brain. *Nature*. 2012;483:213-217

88. Hill MD, Goyal M, Menon BK, Nogueira RG, McTaggart RA, Demchuk AM, et al. Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (escape-na1): A multicentre, double-blind, randomised controlled trial. *Lancet (London, England)*. 2020;395:878-887

89. Saver JL, Starkman S, Eckstein M, Stratton SJ, Pratt FD, Hamilton S, et al. Prehospital use of magnesium sulfate as neuroprotection in acute stroke. *The New England journal of medicine*. 2015;372:528-536

90. Berge E, Cohen G, Lindley RI, Sandercock P, Wardlaw JM, Sandset EC, et al. Effects of blood pressure and blood pressure-lowering treatment during the first 24 hours among patients in the third international stroke trial of thrombolytic treatment for acute ischemic stroke. *Stroke; a journal of cerebral circulation*. 2015;46:3362-3369

91. Poppe AY, Majumdar SR, Jeerakathil T, Ghali W, Buchan AM, Hill MD. Admission hyperglycemia predicts a worse outcome in stroke patients treated with intravenous thrombolysis. *Diabetes care*. 2009;32:617-622

92. Geurts M, Scheijmans FE, van Seeters T, Biessels GJ, Kappelle LJ, Velthuis BK, et al. Temporal profile of body temperature in acute ischemic stroke: Relation to infarct size and outcome. *BMC neurology*. 2016;16:233

93. Ballester BR, Maier M, Duff A, Cameirao M, Bermudez S, Duarte E, et al. A critical time window for recovery extends beyond one-year post-stroke. *Journal of neurophysiology*. 2019;122:350-357

CHAPTER 3 Long–Term Outcome of Endovascular Therapy for Ischemic Stroke

This chapter is comprised of an editorial originally published in Nature Reviews Neurology: Zerna C., Goyal M. Long–term outcome of endovascular therapy for ischemic stroke. Nature Reviews Neurology 2017; 13, 387–388. This chapter comments on the sustainability of efficacy of endovascular treatment for acute ischemic stroke due to proximal anterior circulation large vessel occlusion.

3.1 Summary

In patients with acute ischemic stroke resulting from anterior circulation occlusion, endovascular therapy provides greater long–term benefits than does intravenous tissue Plasminogen activator (IVtPA). However, further improvement of systems of care and research regarding adjunct therapies is still needed.

3.2 Commentary

Advances in stroke imaging, availability of new thrombectomy devices, and emphasis by neurovascular care teams on speed of workflow have paved the way for success of six randomized controlled trials of EVT for acute ischemic stroke (Figure 5). In October 2014, the MR CLEAN investigators were the first to report superiority of EVT for acute ischemic stroke caused by anterior circulation occlusion.[1] This result led to early termination of enrolment for four other trials of endovascular therapy: ESCAPE, EXTEND–IA, SWIFT–PRIME, and REVASCAT. A meta–analysis of these trials, all of which used modified Rankin Scale (mRS) score at 90 days as their primary outcome, showed that patients who received EVT had significantly reduced disability compared with those who received standard medical treatment

(OR 2.49, 95 % CI 1.76–3.53; $P < 0.0001$).[2] Now, the MR CLEAN and REVASCAT investigators have published long–term follow–up results at two years and one year, respectively.[3, 4]

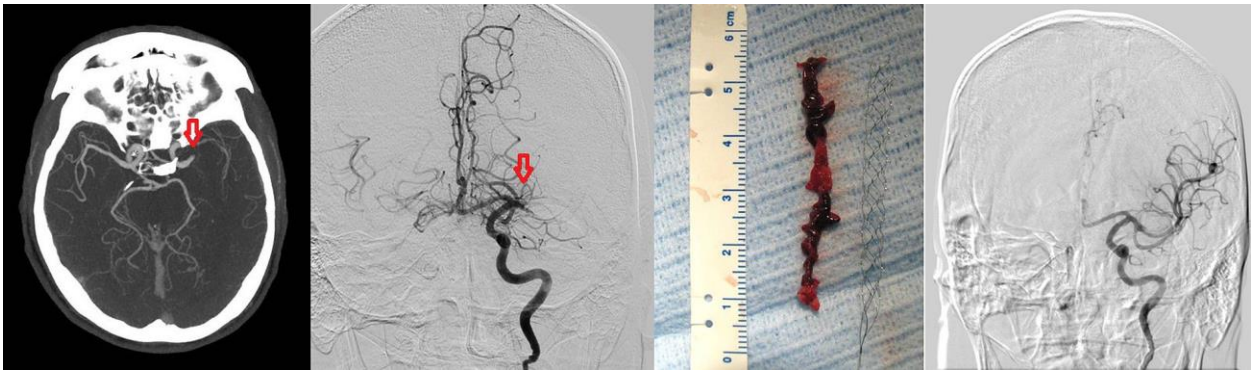


Figure 5: Endovascular Treatment in Acute Ischemic Stroke

From left to right: a | CT angiography showing left middle cerebral artery occlusion. b | First conventional angiography run confirming left middle cerebral artery occlusion. c | Retrieved thrombus with the stent retriever device that was used. d | Final conventional angiography run showing restored flow to the left middle cerebral artery territory.

In total, 391 of 500 patients enrolled in MR CLEAN (78.2 %) had two–year follow–up data and were included in the analysis, which resulted in an adjusted OR of 1.68 (95 % CI 1.15–2.45) for distribution of mRS scores, in favor of EVT over conventional treatment.[3] The REVASCAT investigators also found a persistent benefit of endovascular therapy: analysis of mRS scores at one year, which were available for 205 of 206 patients (99.5 %), resulted in an adjusted OR of 1.80 (95 % CI 1.02–2.99).[4] These results are not surprising in view of the fact that acute ischemic stroke is an episodic event and not a chronic illness. If one adequately treats the initial stroke event and subsequently controls the underlying risk factors that originally led to the occurrence of the stroke, then the initial effect size of interventional treatment compared with conservative treatment will be preserved.

This concept of preserved effect was previously demonstrated in the initial trial of tPA versus standard medical therapy for acute ischemic stroke that was published in 1995.[5] In this trial, the primary outcome (mRS score) measured at three months favored treatment with tPA; similarly, the long–term six–month and 12–month data continued to show outcomes in favor of the tPA arm.[6] The study group did not collect data on subsequent treatment of patients beyond three months, but no meaningful differences were apparent between the groups with regard to carotid endarterectomy, use of anticoagulant or antiplatelet agents, antihypertensive treatment, or hospitalization for any cause within the first three months. Consequently, the observation of early beneficial effects that persisted for one year strongly suggests that the improved outcome was due to treatment with tPA.[6]

Information regarding vital status at two years post–stroke was available for 459 of 500 patients enrolled in the MR CLEAN trial. The cumulative two–year mortality was 26.0 % in the EVT group and 31.0 % in the control group (adjusted HR 0.9, 95 % CI 0.6–1.2, $P = 0.46$).[3] The increase in mortality in both groups compared with the 90–day follow–up data observed in the MR CLEAN trial is part of the natural history of the disease, as many patients with severe disability (mRS = 5) have limited life expectancy, probably owing to multiple factors, including pneumonia, other infections, and deep vein thrombosis with pulmonary embolism.

The long–term follow–up results of the MR CLEAN and REVASCAT trials show a similar degree of superiority of endovascular therapy over control therapy to the 90–day results. The REVASCAT investigators found that 89 % of the treatment effect at one year was already observed at 90 days, and 80 % of the treatment effect at one year was already observed at five days.[4] If the effect of an acute therapy (either tPA or endovascular therapy) on the initial post–

stroke deficit is maintained, it is only logical to conclude that early outcome predicts the results of long–term outcome measures. This association is also a reflection of the success of strategies aimed at secondary prevention of acute stroke. Similarly to REVASCAT, the ESCAPE investigators found that early post–baseline markers of stroke severity (NIH Stroke Scale trajectory) in the first 48 hours post–stroke could accurately predict outcomes among individuals treated with endovascular therapy.[7]

These trials have had a major effect on stroke treatment, but further improvement is required. Implementation science has come a long way since the evidence–based movement took root to promote higher–quality, patient–focused care, but patients still receive substandard, variable care that is all too frequently inappropriate and unsafe.[8] A number of patients with LVOs are probably missing out on treatment because of a lack of timely access to the appropriate hospital, rapid brain death, and/or technical challenges to achieving rapid reperfusion. Although endovascular therapy increases initial treatment costs, this approach is projected to improve quality–adjusted life expectancy and reduce health–care costs over a lifetime horizon compared with tPA.[9] Reorganization of regional transport systems should be prioritized in order to expand access to endovascular therapy and organize systems of care to shorten door–to–reperfusion times, as well as to centralize treatment to high–volume comprehensive stroke centers with coverage 24 hours a day, seven days a week.[10] Improved technology and training of frontline staff are needed to better triage patients who are likely to be suitable candidates for EVT.

The success of endovascular therapy has created an effective human–ischemia–reperfusion model. Testing of new treatments in the pre–hospital arena or at primary stroke

centers will facilitate knowledge translation from animal work into patients, and could result in promising adjunct therapies that prevent infarct growth.

3.3 References

1. Berkhemer OA, van Zwam WH, Dippel DW. Stent-retriever thrombectomy for stroke. *The New England journal of medicine*. 2015;373:1076

2. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet (London, England)*. 2016;387:1723-1731

3. van den Berg LA, Dijkgraaf MG, Berkhemer OA, Fransen PS, Beumer D, Lingsma HF, et al. Two-year outcome after endovascular treatment for acute ischemic stroke. *The New England journal of medicine*. 2017;376:1341-1349

4. Davalos A, Cobo E, Molina CA, Chamorro A, de Miquel MA, Roman LS, et al. Safety and efficacy of thrombectomy in acute ischaemic stroke (revascat): 1-year follow-up of a randomised open-label trial. *The Lancet. Neurology*. 2017;16:369-376

5. Tissue plasminogen activator for acute ischemic stroke. The national institute of neurological disorders and stroke rt-pa stroke study group. *The New England journal of medicine*. 1995;333:1581-1587

6. Kwiatkowski TG, Libman RB, Frankel M, Tilley BC, Morgenstern LB, Lu M, et al. Effects of tissue plasminogen activator for acute ischemic stroke at one year. National institute of neurological disorders and stroke recombinant tissue plasminogen activator stroke study group. *The New England journal of medicine*. 1999;340:1781-1787

7. Sajobi TT, Menon BK, Wang M, Lawal O, Shuaib A, Williams D, et al. Early trajectory of stroke severity predicts long-term functional outcomes in ischemic stroke subjects: Results from the escape trial (endovascular treatment for small core and anterior circulation proximal occlusion with emphasis on minimizing ct to recanalization times). *Stroke; a journal of cerebral circulation*. 2017;48:105-110

8. Rapport F, Clay-Williams R, Churruca K, Shih P, Hogden A, Braithwaite J. The struggle of translating science into action: Foundational concepts of implementation science. *Journal of evaluation in clinical practice*. 2017

9. Shireman TI, Wang K, Saver JL, Goyal M, Bonafe A, Diener HC, et al. Cost-effectiveness of solitaire stent retriever thrombectomy for acute ischemic stroke: Results from the swift-prime trial (solitaire with the intention for thrombectomy as primary endovascular treatment for acute ischemic stroke). *Stroke; a journal of cerebral circulation*. 2017;48:379-387

10. Holodinsky JK, Williamson TS, Kamal N, Mayank D, Hill MD, Goyal M. Drip and ship versus direct to comprehensive stroke center: Conditional probability modeling. *Stroke; a journal of cerebral circulation*. 2017;48:233-238

CHAPTER 4 Methods

This chapter contains all methodologies used in this thesis. Due to manuscript space limits, the methods sections in the manuscript–based chapters 5 through 7 are brief. The following pages will serve as an expansion on those methodologies. Section 4.1 will explain the necessity for evidence of the benefits of endovascular treatment beyond the randomized controlled trials. Section 4.2 pertains directly to methods used in CHAPTER 5, section 4.3 pertains directly to the methods used in CHAPTER 6, and section 4.4 pertains directly to the methods used in CHAPTER 7.

4.1 External Validity

The validity of a study is usually separated into two components: internal validity of the inferences as they pertain to members of the source population (from which was sampled), and external validity of the inferences as they pertain to people outside of that population (also called the target population).[1] The internal validity of a study will be strengthened if the researcher is either able to perform random probability sampling from the defined source population or minimize selection bias during the sampling process if one is unable to perform random probability sampling. Once internal validity has been established, external validity or generalizability is the "big picture" interpretation of a study's results and judges how they can be applied beyond the source population (or how representative they are of the target population).[2]

4.1.1 Randomized Controlled Trials

Randomized controlled trials are conducted to prove efficacy, meaning that the outcome is a preferably pure effect of the exposure under strictly controlled conditions.[3] These strictly controlled conditions usually include:

- comparison to placebo or standard medical treatment control group
- stringent inclusion and exclusion criteria
- standardized exposure (applied by the research team)
- objective outcome measurement (usually blinded meaning without knowledge whether the exposure occurred or not)
- monitored compliance and attrition

In case those conditions are met, they result in high internal validity.

The results from randomized controlled trials are then often broadly generalized to the target population and assumed to have external validity, even though the study sample was derived by using stringent inclusion and exclusion criteria, rather than being a random population probability sample.[2] For example, the randomized controlled trials published in 2015/2016 evaluating EVT have only included a few patients with presenting NIHSS below 5 points, presentation beyond 12 hours from symptom onset, very elderly patients, more distal occlusions of the anterior circulation, or patients with pre–existing disability. However, in clinical practice, EVT is offered to these patients even though the benefit–risk ratio might not be clear.

Randomized controlled trials sometimes also lack generalizability as they have short study periods or insufficient cohort sizes to identify rare but serious adverse events related to the

treatment, might rely on surrogate markers to save time and costs, and select high-risk patients to have an adequate number of end points.[4]

Generalizability does not necessarily mean that a research study replication in a different population would lead to the exact same results. If a study were to be replicated in a different population (hospital/region/country), results might differ not because the exposure–outcome association changes but because of varying exposure, outcome and extraneous variable frequency in the now studied populations. These other populations are likely different in many ways but are not fundamentally different in ways that would affect the conclusion about the exposure–outcome association.[2] But due to financial restraints, limited resources and loss of equipoise for randomized clinical trials, research studies are usually not replicated in different settings to prove that this is actually true. Of course there are some cases in which generalizability is actually violated when the underlying pathophysiology is argued to be substantially different between source and target population (i.e. strokes in cancer patients might develop differently due to the hormonal and immunogen changes the body undergoes when a tumor is present).

Current evidence-based grading systems are favoring randomized controlled trials which may lead to inadequate consideration of alternative sources of evidence which are explained in the following.[5]

4.1.2 Pragmatic and Registry–based Randomized Trials

Effectiveness compared to efficacy research acknowledges that the outcome might be a combination effect of the exposure plus effects from placebo, undeclared concomitant exposures, and social desirability or context factors.[3] Effectiveness does not ask if an exposure can have an

effect on the outcome under controlled circumstances but rather whether the exposure does have an effect on the outcome in a real–world setting.

Common features of effectiveness research are[3]:

- rarely compare to a placebo control group
- wider (more inclusive) inclusion and exclusion criteria
- exposure is not standardized and mirrors clinical practice
- possibly subjective outcome measurements
- compliance and attrition are not monitored

One type of study to address this question of effectiveness within a real–world setting is a so–called pragmatic trial. The main advantage of a pragmatic trial is that it potentially enhances generalizability since inclusion and exclusion criteria might be broader and the exposure and follow–up assessments may more closely mirror the real world and routine clinical practice. Common criticism includes the high rates of loss to follow–up, non–adherence to the exposure, and unblinded exposures.[6] These issues are challenging but also part of the real–world clinical care where patients sometimes do not attend follow–up visits, stop taking their medication, and are aware of their treatments as are their healthcare providers. These issues need to be addressed in order for them to not cause a biased estimate which can for example be done by avoiding additional and artificial follow–up visits, intention–to–treat analysis, and objective outcome measurements. Another common criticism is that pragmatic trials often need a larger sample size to detect small effects in heterogeneous populations because there is a lot of "noise" to the signal.[6] This criticism suggests that pragmatic trials might not be a good use of research funds or their conduct might not be feasible. To address this, utilization of existing resources is a key

feature. Within healthcare, there is a huge collection of so–called secondary data (data that have not been generated for research purposes) for administrative or policy–related purposes. These secondary data have been stored in registries to inform about health trends, healthcare provider billings, and other topics. The number and comprehensiveness of registries has increased in recent years due to the use of electronic health records for data retrieval as well as soft– and hardware that are able to capture and store these large amounts of data. Registry–based randomized trials use existing registries as a platform for patient identification and follow–up assessments and are thus a special form of pragmatic trials. Their main advantage is the lower cost since an infrastructure is already in place. However, disadvantages might be the low data quality (depending on the initial purpose of the registry) and ethical issues (informed consent, withdrawal, and monitoring) in addition to the ones explained for all pragmatic trials above.

Pragmatic trials in general and registry–based randomized trials more specifically are methodologies to address effectiveness research questions but their potential disadvantages need to be acknowledged and addressed during the design stage of such a trial.

4.1.3 Observational Studies

Randomization is a desirable feature of research studies since it controls for measured and unmeasured confounding during the design stage of the study and the effect of the outcome can be more easily attributed to the exposure but it is only possible in such scenarios where equipoise exists. In an observational study, the exposure is not randomly assigned but its occurrence is instead observed.

Observational studies are helpful for the following scenarios:

- An exposure is known to be harmful or beneficial but the magnitude of effect outside of a randomized controlled trial might be of interest for policy decisions and public health interventions.
- Equipoise exists and resources to run an explanatory or pragmatic trial are not available but a research question needs to be answered.
- An exposure cannot be randomized (such as certain lifestyle choices, being female, having a low socioeconomic status…)
- Complimentary evidence of effectiveness in addition to randomized controlled trials needs to be obtained before recommendations and guidelines are changed.
- Generating of new research hypotheses.

Criticisms of observational studies have been the potential of bias from unknown or unmeasured confounding variables and the belief that such studies overestimate treatment effects.[5] However, a prior study that used meta-analyses to identify randomized controlled trials and observational studies that examined the same clinical topics found that well-designed observational studies did not systematically overestimate the magnitude of association and had less variability in point estimates than the randomized controlled trials.[7] Of course the four main types of observational studies (cohort studies, case-control-studies, cross-sectional studies, and ecologic studies) each have their strengths and weaknesses but not considering observational studies when randomized controlled trial data are unavailable just leaves health care providers with large information gaps. The goal of research must thus be actionable data that have been

derived in a transparent and objective way (with acknowledgement of methodological limitations) and are sufficient for clinical and public health decision making.[4]

This dissertation contains several observational studies to expand the evidence of EVT for acute ischemic stroke focusing on patient–centered outcomes, the population–level impact of EVT, and the effectiveness of EVT in patients presenting with mild stroke symptoms. The methods of those observational studies are explained in more detail in the following with Section 4.2 pertaining directly to methods used in CHAPTER 5, section 4.3 pertaining directly to the methods used in CHAPTER 6, and section 4.4 pertaining directly to the methods used in CHAPTER 7.

4.2 Analyzing Ordinal Data

4.2.1 Ordinal Data as Stroke Outcomes

The stroke literature and stroke research encompass all different types of data, both categorical and continuous. Categorical data have meaningful categories and are either nominal (the categories can be named but have no implied order) or ordinal (the categories can be ranked but have no mathematical properties). Continuous data can be divided into infinitely smaller categories and can consist of ones that have both interval (the order and difference between levels is meaningful but there is no absolute zero) and ratio properties (the order and difference between levels is meaningful and there is an absolute zero) and ones that just have interval but no ratio properties. Table 3 shows examples for the types of data that have been utilized in this thesis, the scale they have been analyzed on and the properties of such scale.

Table 3: Types of Data

Type of Data	Scale	Meaningful properties of scale	Examples in this thesis
Categorical Data			
Nominal Data	Nominal scale		
Ordinal Data	Ordinal scale	Order	mRS, miFUNCTION
• Count Data	Ratio scale	Order, distance, absolute zero value	90-day home-time
Continuous Data			
	Interval scale	Order, distance	
	Ratio scale	Order, distance, absolute zero value	

An example of ordinal data is the mRS which is the most commonly used outcome variable in stroke research to quantify post–stroke disability. The mRS consists of seven levels covering the entire range of functional outcomes post–stroke from no symptoms to death.[8] The assigned numbers 0 to 6 make it possible to order the functional outcome scores hierarchically but these levels have no mathematical properties, meaning that the disability of a mRS score of 4 is not twice the disability of the score of 2 and the difference in disability between a mRS score of 0 and 1 (no symptoms at all vs. mild symptoms) is not the same as the difference in disability between 5 and 6 (completely dependent vs. dead). But the levels are easy to grasp and a single–point improvement on the scale is clinically meaningful as it usually means that the patient regained independence in at least one area of their lives. The miFUNCTION scale, introduced and assessed in CHAPTER 5, is another example of ordinal data. It consists of 16 levels covering the entire range of functional outcomes post-stroke in more detail.

4.2.2 Dichotomizing Ordinal Data

Non–parametric test statistics (e.g. logistic regression analysis) do not make any assumption about the underlying distribution of the outcome variable which is why they are used for categorical data (including ordinal data) which are not normally distributed.

Ordinal outcome variables with multiple levels might seem to be more difficult to analyze. That is why dichotomization of ordinal outcome variables has been used to simplify the statistical analysis and make results more intuitive (disease has occurred or not occurred; clinical improvement has occurred or not occurred). This is done by either utilizing cut points that have been used in prior research studies or the median of the study sample. However, there are several problems when dichotomizing ordinal outcome variables which are described and illustrated below: [9 - 11]

- Information is lost because different outcome levels are merged together. For example, if an exposure variable had a mild effect across all levels of the outcome variable mRS (shifting 1 to 0, 2 to 1, 3 to 2, and so on), it would be difficult to detect since dichotomization makes many of these effects go unnoticed as they now occur within the newly merged categories (Figure 6). The outcomes of the exposed and unexposed groups now seem more similar to one another than they actually are which would support the null hypothesis that no difference exists. Thus, the statistical power (and sample size) to detect a true association between the exposure variable and the outcome variable would need to be increased under these conditions.

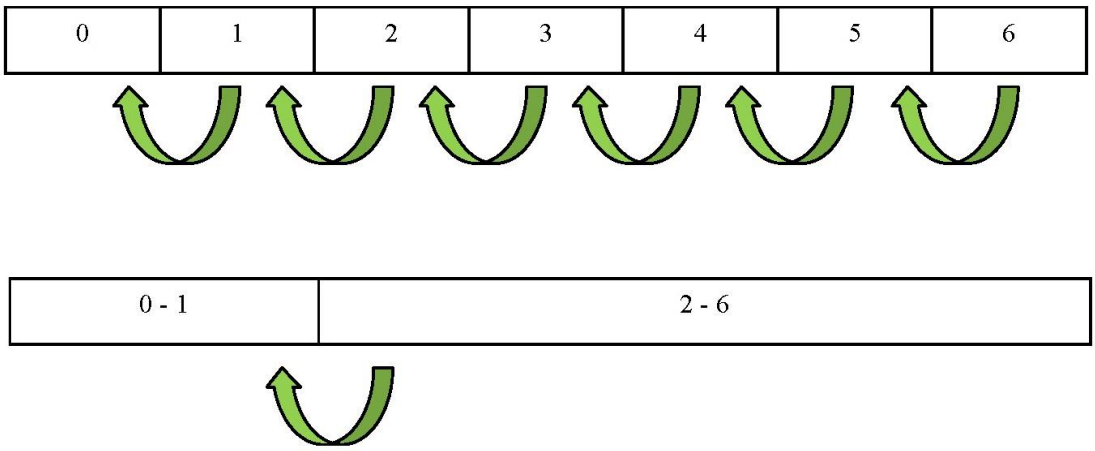


Figure 6: Loss of Information when Dichotomizing an Ordinal Variable

Diagram illustrating the actual effect of the exposure on the ordinal outcome variable (above) and the remaining effect that would be detectable once the ordinal outcome variable is dichotomized (below).

- Data points that are close to one another but now on opposite sides of the cut point are classified as being very different even though they are rather similar. This might influence the interpretation of the exposure–outcome association of interest.
- The merging of categories could lead to a higher variability of extraneous variables within the newly merged categories and thus residual confounding even though its adjustment in the analysis stage has been tried. Residual confounding can distort the exposure–outcome association of interest.
- A dose–response relationship between the exposure variable and the outcome variable cannot be displayed. That could influence the judgement of causality of the association and hinder a better understanding of the underlying mechanism that would inform future research hypotheses and studies.

- Dichotomization focuses on only one health state transition (the one across the cut point) but ignores positive and negative effects that occur at other health state transitions (Figure 7, Figure 8). Not capturing beneficial or harmful associations between the exposure or outcome variable could lead to either not pursuing promising prevention strategies and treatments or making harmful recommendations regarding prevention strategies and treatments, respectively. If harmful associations are not captured in early study phases, subsequent studies that are destined to fail would be conducted wasting healthcare resources.

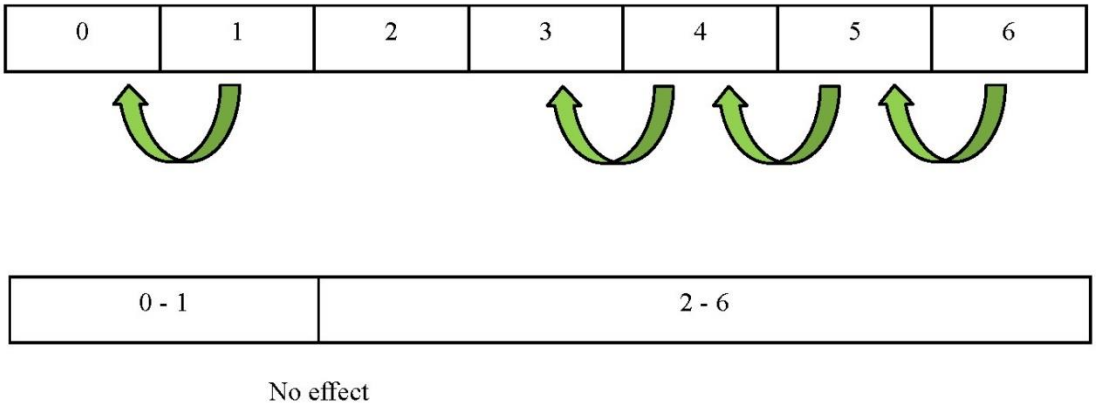


Figure 7: Missing the Effect when Dichotomizing an Ordinal Variable

A clustering of effects of the exposure variable on the ordinal outcome variable occurs at both ends of the scale (above) but neither of them is captured by a dichotomization of the ordinal outcome variable in the middle of the scale (below).

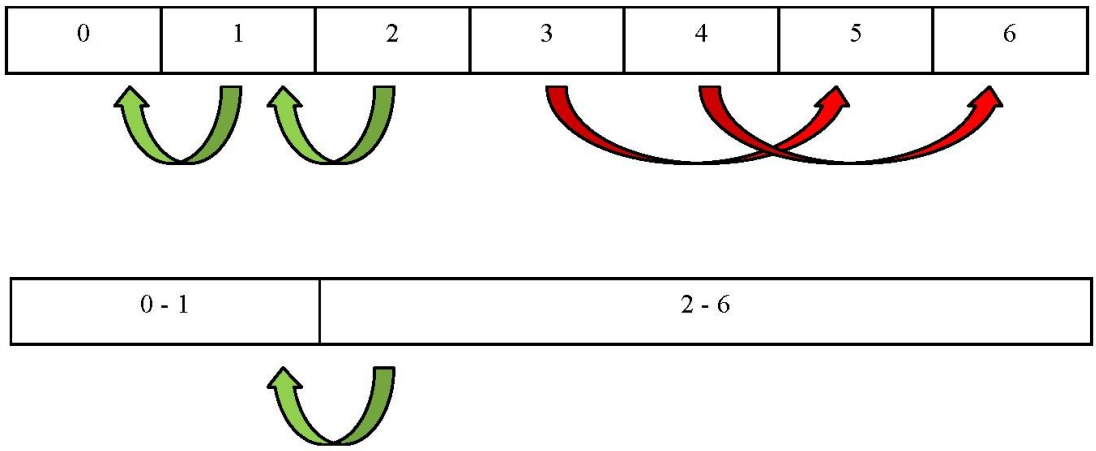


Figure 8: Missing Important Health Transitions when Dichotomizing an Ordinal Variable

A beneficial effect of the exposure variable on the ordinal outcome variable occurs at the lower end of the scale and a harmful one at the upper end of the scale (above) but the dichotomization of the ordinal outcome variable only captures a benefit in the middle of the scale and ignores the harm (below).

- By anticipation of the outcome variable distribution (for example the exposure is life–saving but not disability–sparing), the cut point might be chosen for efficacy reasons so that a statistically significant association is likely to be found. However, the results of those efficacy efforts might not have any clinical importance because patients might value the change from severe to moderate or minor disability more than surviving heavily disabled just for the sake of surviving.
- Since cut points are chosen arbitrarily, the differences in methods and results will hamper a later meta–analysis of data when trying to combine different studies that have utilized such dichotomization methods.

4.2.3 Advanced Ordinal Data Analysis Methods

The above issues demonstrate why reducing an ordinal outcome variable to a binary outcome variable can lead to erroneous results and complicate the interpretation of the exposure–outcome association. Other methods are able to retain the inherent ranking of data and can produce measures of effect that summarize an association across all levels of the ordinal outcome variable.[12] These methods can analyze ordinal outcome variables as their numerical ranked levels if the intervals between the consecutive levels are considered to be equivalent.[13] According to a survey, stroke physicians and patients in Western countries value health state transitions across all the mRS scores, with the frequent exception of transitions from severe disability (mRS 5) to death (mRS 6), which is why these two levels could be collapsed into a single worst outcome category and then all intervals between consecutive levels could be considered equivalent.[14]

The most commonly used ordinal regression method is the proportional odds model which can be thought of as a logistic regression for each cut-point across the mRS and then a calculation of a summary OR under the assumption that the individual ORs are the same (proportional odds assumption).[15] This delivers a clinically interpretable parameter but the proportional odds assumption needs to be met and the summary OR risks being misinterpreted as a simple OR instead of an average across multiple thresholds.

Another option to analyze ordinal data like the mRS scale is a permutation test. By doing so, patients with a specific mRS score in the treatment group (e.g. mRS score 0) are matched with all other respective mRS scores in the comparator group (e.g. mRS scores 1 through 6) so that the number of pairs of patients is simply the product of the number of patients in each combination.[15] The number of pairs where the mRS score for the treatment is higher, lower, or

tied with the comparator is then expressed as percentages, respectively. This allows a meaningful statement to both patients and healthcare providers that out of 100 patients given a treatment instead of the comparator, x number of patients will be better with the treatment, whereas x number of patients will be better with the comparator, and x number of patients appear the same with either treatment. The approach is flexible for the analysis of confounding and effect modification, uses the entire spectrum of the mRS, and avoids the proportional odds assumption which means that intervals between consecutive levels of the ordinal variable do not need to be equivalent.[15]

Even though methods exist to preserve the inherent ranking of ordinal data, all possible individual dichotomizations were used to assess the performance of miFUNCTION across every possible cut–point of the disability spectrum. This allowed a more detailed comparison with the currently most commonly used scale in stroke research (mRS) while avoiding the above–mentioned disadvantages of dichotomizing at a single cut-point only.

4.3 Displaying and Analyzing Count Data

If observations can only take non–negative integer values (numbers that can be written without fractional components) such data are called count data. Analyzing count data can be challenging and suboptimal strategies include rescaling count data to a set of categories and using cross–tabulation or even collapsing the count data to a dichotomy so that they can be analyzed using logistic regression analysis.[16] As already explained above, these approaches can lead to a loss of information depending on the chosen cut–point, a loss of statistical power, and the count data likely violate assumptions that need to be met for certain statistical methods. More

appropriate methods to graphically display and analyze count data exist and are discussed in more detail below.

4.3.1 Displaying Count Data

Violin plots are a more advanced method of graphical data distribution assessment compared to the conventional box plot as they draw a kernel density plot around a box plot as shown (Figure 9). Thus, violin plots are especially useful when assessing multimodal data. The white dot represents the median, the thicker gray bar the interquartile range (IQR), and the thinner gray line represents the rest of the distribution (aside from outliers which are beyond the distance of 1.5 times the IQR from the 25^{th} or 75^{th} percentile). The violin shape is the kernel density plot which illustrates the probability of a subject to take on a given value. The wider the shape of the violin plot, the higher the probability.

The patient–centered outcome that is used in CHAPTER 6 is 90–day home–time. Home-time refers to the number of days that the patient was back at his/her respective premorbid living situation without an increase in level of care within 90 days of the index stroke event. The premorbid living situation was determined from administrative health data and was assigned as any form of continuing care facility if that is where the patient had resided in the two-week period before the index stroke admission or was otherwise inferred to be the private home. By definition, patients who died in hospital after the index stroke admission have a home-time of 0 days. Since 90–day home–time had a bimodal distribution in the cohort studied in CHAPTER 6 due to excess zero counts and many counts around 80–90 days home–time, the use of violin plots was the most appropriate way to present the data.

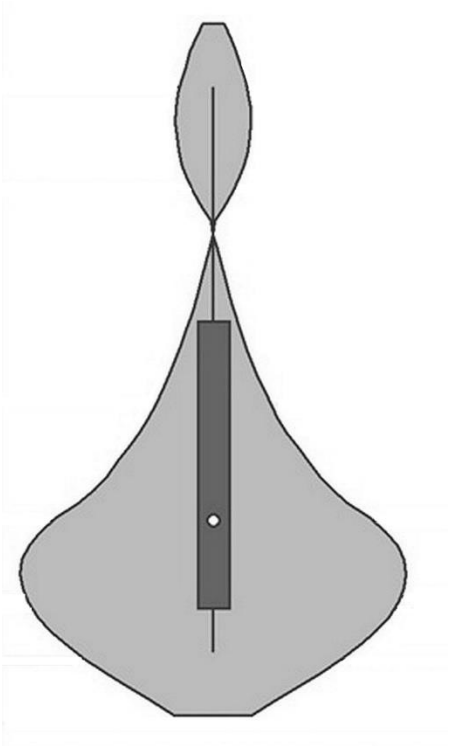


Figure 9: Violin Plot

The violin plot displays the data as a hybrid of a box–whisker–plot and a kernel density function.

4.3.2 Analyzing Count Data

One method for analyzing count data is Poisson regression analysis. Poisson regression analysis assumes the logarithm of the dependent variable can be modeled by a linear combination of independent variables. The dependent variable is a count that follows a Poisson distribution meaning that its mean and variance are equal.

However, if the count data show more dispersion (variability) than the Poisson distribution and regression model can account for, a negative binomial regression model can be considered. A negative binomial regression model can analyze count data that follow a negative

binomial distribution. This model loosens the more restrictive assumption made by the Poisson model that the variance needs to be equal to the mean.[16]

In many cases as well as in using the patient–centered outcome of 90–days home–time the distribution of the data requires an even more sophisticated analysis method. The amount of days that can be spent at home during the first 90 days is 0 at the minimum and 90 at the maximum (if patients were theoretically to be discharged on the same day of the procedure). Since many patients did not return to their home or prior residence within 90 days of the index stroke as they stayed in hospital, a rehabilitation facility or were transferred to a long–term care facility, the data utilized for the comparative effectiveness research in CHAPTER 6 had frequent zero-value observations.[17] One option to accommodate would be to use a zero–inflated negative binomial regression model which is based on a zero–inflated probability distribution and thus allows for frequent zero–valued observations. However, zero-inflated models estimate two equations simultaneously, one for the positive count model and one for the frequent zero-value observations with both depending on the same variables. But in the case of 90–days home–time, a model is needed that allows the determination of the outcome variable's value when it assumes a count to depend on different variables from those determining the initial probability of occurrence versus non-occurrence (frequent zero-value observations) of the outcome.

For such circumstances, John C. Cragg developed the Cragg hurdle regression model.[18] With a hurdle model there are two processes, one generating the frequent zero-value observations and one generating the positive count values but these two models are not constrained to be the same (i.e. they can depend on different variables). As a first process of the Cragg hurdle regression model, a Bernoulli probability directs the binary outcome of 0 (failure,

hurdle is not crossed, patient does not return to home within 90 days after stroke) or 1 (success defined as any positive (non–zero) count, hurdle is crossed, patient does return home within 90 days after stroke). As a second process of the model, once the hurdle is crossed, a truncated-at-zero count model dictates the conditional distribution of the positive count values (actual days spent back at home).[17]

4.3.3 Evaluating Count Data Analysis Methods

Multiple aspects of the distribution of data are of interest including the amount of (over–) dispersion, skewness or shape, and whether there are frequent zero-value observations when assessing the goodness of fit of any regression model.[19] One way to do so is assessing so–called rootograms. A rootogram plots rectangular bars for the observed frequencies and a curve for the expected frequencies on a square–root scale to graphically compare the two. Rootograms can be plotted in a standing, hanging or suspended style. The standing rootogram simply plots the rectangular bars for the observed frequencies and a curve for the expected frequencies. The hanging rootogram aligns all deviations between observed and expected frequencies along the horizontal axis by having the rectangular bars representing the observed frequencies drawn downward from the expected frequencies curve. It is thus easier to visually assess the deviations between the two. The suspended rootogram emphasizes mainly the deviations (rather than the observed frequencies) and draws rectangular bars for the differences between expected and observed frequencies.

To determine the most appropriate regression model to analyze the 90–day home–time, hanging rootograms were plotted for visual assessments (Figure 10, Figure 11).

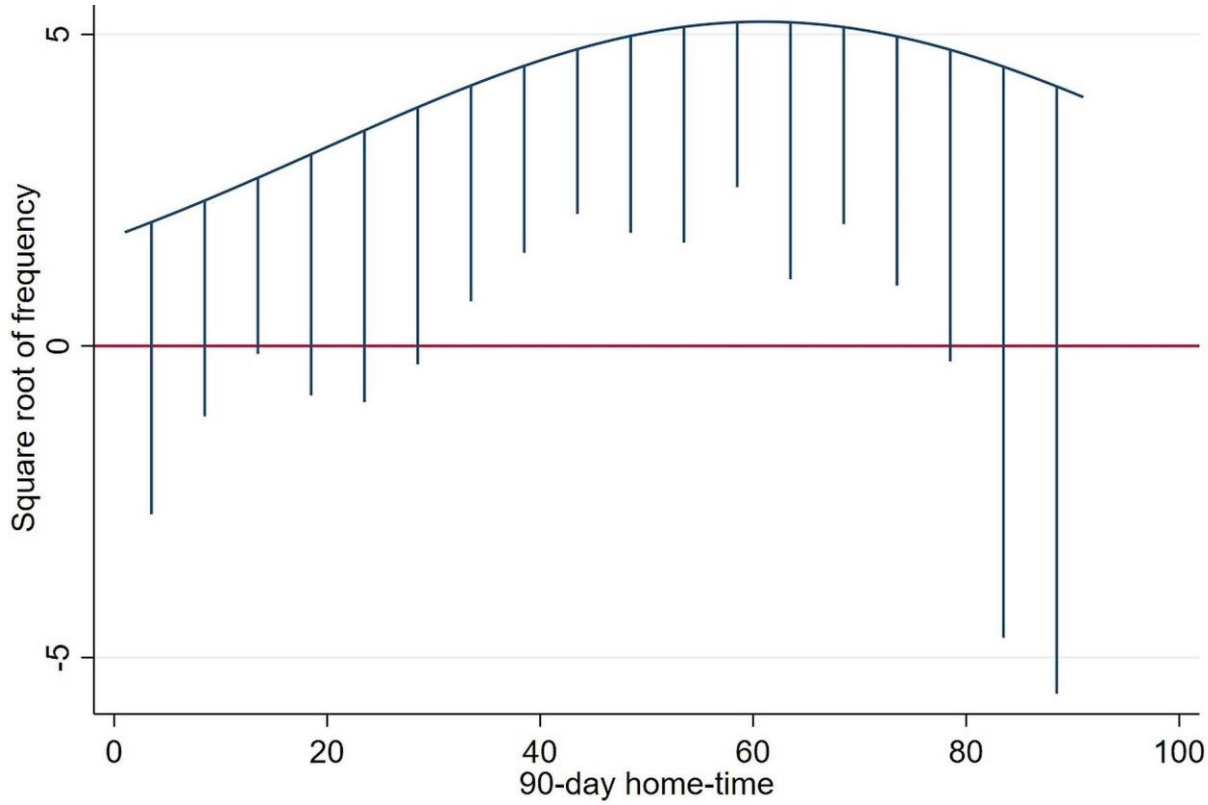


Figure 10: Hanging Rootogram for Cragg Hurdle Regression Model

The rootogram for the Cragg hurdle regression model shows that the data exhibit fewer middle value counts as well as many large value counts.

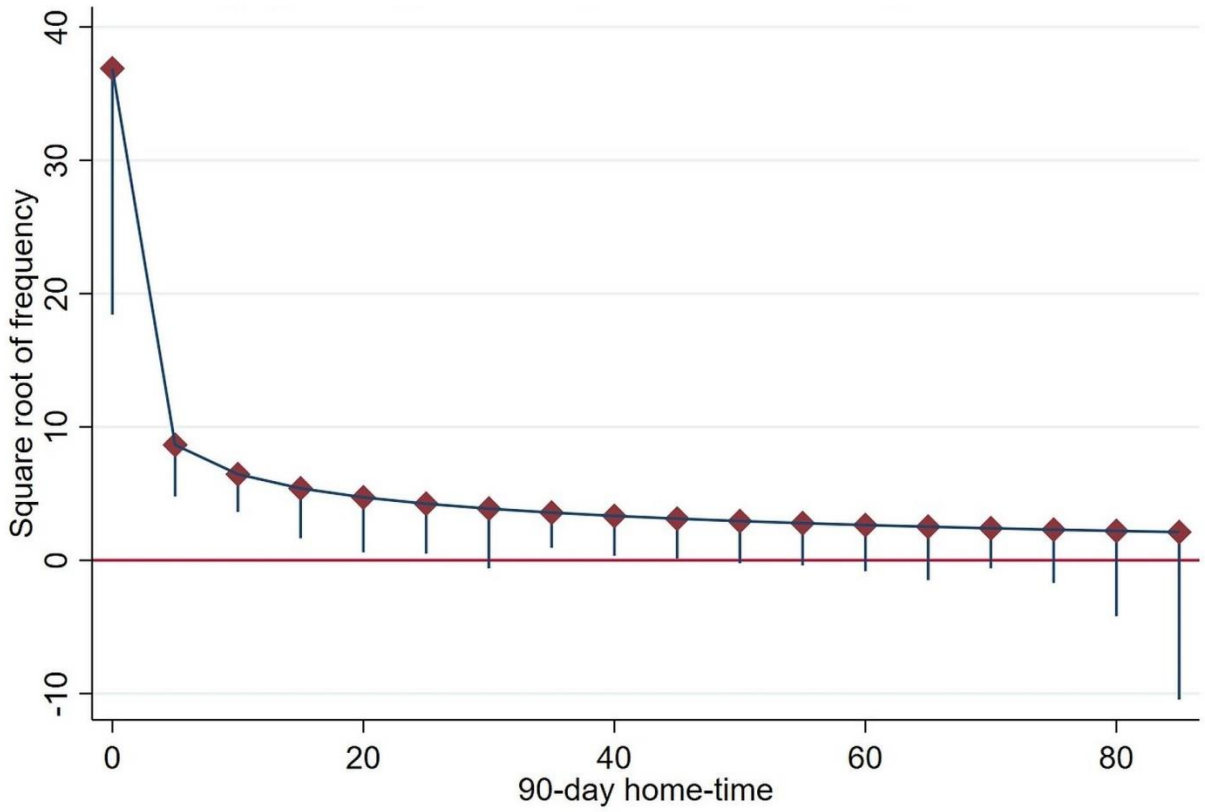


Figure 11: Hanging Rootogram for Zero–Inflated Negative Binomial Regression

The rootogram for the zero–inflated negative binomial regression model shows that the data have way too few small value counts and too many large value counts (with the much larger range on the y–axis compared to the hanging rootogram for the Cragg hurdle regression model).

The Akaike information criterion (AIC) is another assessment for the quality of a statistical model applied to a certain set of data. A statistical model as a representation of the data–generating process will almost never be exact and thus encounter some loss of information. The AIC represents the relative amount of information that was lost by using a statistical model and thus indirectly speaks to the quality of that statistical model for the given data.[20] The lower

the AIC, the lower the loss of information and thus the more appropriate the statistical model selection.

The AIC for the Cragg hurdle regression model was 4699.299. The AIC for the zero–inflated negative binomial regression model was 5413.309. Taking both the graphical assessment via the hanging rootogram as well as the AIC into consideration, it was decided that the Cragg hurdle regression model was the more appropriate fit for the data utilized for the comparative effectiveness research in CHAPTER 6.

4.4 Addressing Confounding in Observational Studies

4.4.1 Controlling Confounding in the Design Stage

Confounding in the design stage of a study can be controlled by restriction (patients who have been exposed to a potential confounding variable are excluded from the study), randomization (due to the law of large numbers, the distribution of confounding variables will be approximately equal between groups due to random assignment of exposure) or matching (selecting an exposed and unexposed patient who share the characteristic of (non–)exposure to a confounding variable).[21]

4.4.2 Controlling Confounding in the Analysis Stage

Confounding in the analysis stage of a study can be controlled by stratification (dividing the study population by the value of a third variable and calculating an effect measure of the exposure–outcome association within each stratum), regression modelling (effect estimate of the model is adjusted for the effect of potential confounders that are included in the model),

instrumental variable analysis (isolating average direct effects of the exposure on the outcome independent of unobserved sources of variability)or matching.

4.4.3 Matching

Retrospective cohort studies often choose non-contemporaneous controls as their non–exposure group. For example, the project detailed in CHAPTER 7 of this thesis retrospectively identified acute stroke patients with CTA proven anterior circulation occlusion and admission NIHSS ≤ 6. For this purpose, EVT data from the Safe Implementation of Treatments in Stroke—Thrombectomy registry (SITS–TBY) were retrieved and compared to the medical management data derived from the INTERRSeCT and PROVE–IT study. These individuals in the SITS-TBY registry have suffered an acute ischemic stroke due to a LVO and have been given with EVT as per the health provider's discretion. They were chosen to receive EVT because they had a perceived lower risk than other patients and were expected to benefit. This phenomenon is called "confounding by indication" and means that the individuals who receive the treatment likely differ in terms of their (prognostic) extraneous variables from those that did not receive treatment in the control group consistent of data from the INTERRSeCT and PROVE–IT study.[22] With stroke specifically this could mean that the individuals who received the EVT were more likely younger and overall healthier (i.e. had less comorbidities). The non–randomized indication for the treatment therefore confounds or distorts the exposure–outcome association of interest and affects the magnitude of the estimated effect of the treatment. However, since the results of this thesis are aimed to aid policy–makers with decisions regarding resource allocation, it is paramount that the estimated effects are as close as possible to the true effect.

In such circumstances, when randomization is not available, matching can be used to generate a non–exposed group that is similar in its distribution of extraneous variables to the exposed group.[22] The differences between the treatment and control group can no longer be the results of the potential confounding variables. However, matching can only account for imbalances of known and accurately measured potential confounding variables. Unknown and imprecisely measured potential confounding variables can still lead to residual confounding.

Another potential drawback of matching is, that it makes the exposed and non–exposed individuals and controls similar in terms of the matching factors but if these factors are strongly associated with the exposure, it can also make exposed and non–exposed individuals similar in terms of exposure and thus bias the estimated effect towards null.[23]

4.4.3.1 Propensity Score Matching

Matching can be done on one or several potential confounding variables. However, a more sophisticated method is to use a single score derived out of multiple potential confounding variables that estimates the probability of receiving the treatment. This score is called propensity score.

Two individuals, one of whom received treatment and the other did not, can be compared during the analysis if their propensity scores are similar (i.e. having a similar probability of receiving treatment). There are different matching algorithms that can utilize the propensity scores and they should technically all yield similar results if the sample size is large enough. However, with smaller sample sizes the performance of the matching algorithm depends on the data structure of the groups. There are four different groups of matching algorithms as further explained below:

- Nearest Neighbor Matching: A treated subject is matched to that untreated subject whichever has the closest propensity score. This matching algorithm can be performed with replacement (i.e. an untreated subject can be used several times) or without replacement (i.e. an untreated subject can only be matched once and is no longer available for further matching). If nearest neighbor matching is done without replacement, the quality of the matching depends on the order in which the subjects are being matched and it should thus be ensured that a random order is being followed.[24] This matching algorithm does not differentiate if the nearest neighbor is close or far away so the quality of the matching depends on the propensity score distribution in the treatment and control group.
- Caliper and Radius Matching: For each treated subject, an untreated subject is only chosen as a matching partner if it lies within a caliper (propensity score range) of the treated subject and thus poor matches are avoided if the nearest neighbor is far away. However, this means that some treated subjects will not find a match within the given caliper and be dropped from the matching process and the sample size decreases. Another variation of this matching algorithm is called radius matching and uses all untreated subjects within a certain radius from a treated subject as matches. A drawback might be to define/determine the most appropriate caliper or radius values ahead of time.[24]
- Stratification and Interval Matching: With this algorithm, the propensity score range of both the treated and untreated subject that have common support is divided into strata and the matching process continues within each stratum. A

criticism is that the number of strata will affect the quality of matching. One possibility to correct this is to first check if propensity scores between treated and untreated subjects are balanced within each strata and secondly, check the balance of the potential confounding variables to see if the propensity score was correctly specified.[24]

- Kernel and Local Linear Matching: These two algorithms use the weighted averages of a number or even all of the untreated subjects to create a match for each treated subject. Depending on the distance between the propensity score of the untreated subject and the treated subject, different kernel weights are utilized.[24] An advantage is that the variance is lower because more information is utilized to determine the matching partner. However, since a number or even all untreated subjects are used, this could include poor matches (meaning they have dissimilar propensity scores).

4.4.4 Propensity Score Matching with Counterfactual Outcomes

To avoid dropping observations and reducing the sample size, advanced matching algorithms can work with potential or so–called counterfactual outcomes. Estimation of how much a treatment has changed the frequency of the outcome is done by estimating the frequency of the outcome in a case where the patient not been treated and compare the two.[1] However, because the patient was treated, the absence of treatment is counterfactual and cannot be observed. Therefore the outcome frequency in the non–treated group is observed as a substitute. The same is done for the untreated subjects where the treated group is observed as a substitute for the counterfactual. Propensity score matching estimators in an advanced matching algorithm

impute the missing counterfactual outcome for each subject by using an average of the outcomes of similar subjects that receive the other treatment level. Similarity between subjects is based on propensity score using the nearest–neighbor method with replacement. The treatment effect is then computed by taking the average of the difference between the observed and counterfactual outcomes for each subject. Thus each observation is utilized during the advanced matching algorithm and the sample size is not reduced. This advanced matching algorithm was used in CHAPTER 7.

4.4.5 Propensity Score Matching Diagnostics

It is very important to check the overlap and area of common support of propensity scores between the treated and untreated groups. This can be done visually using overlap plots or numerically by comparing their minima and maxima or the density distribution of propensity scores in each group. Both of these matching diagnostics have been utilized in CHAPTER 7. Observations with no common support usually get dropped from the dataset. For the remaining observations for which common support has been established, a matching algorithm must be chosen. Once the matching algorithm has been executed, the balance of confounding variables between the treatment and the control group should be checked. Such balance diagnostics should include comparing the means and prevalences of single covariates between treated and untreated subjects as well as graphical comparisons of the distribution of continuous variables between treated and untreated subjects. Since the propensity score should function as a balancing score, these steps serve as a test as to whether the propensity-score model has been adequately specified.[25] It can be challenging to choose which confounding factors should be included in the model to calculate the propensity score. Including too few variables could lead to residual

confounding as not all known factors that influenced the treatment decision have been considered and thus a difference between treatment and control might actually be due to the still existing differences in baseline characteristics. Including too many variables may lead to higher variability of the estimated propensity scores and thus difficulties with the common support or overlap between the propensity scores in the treatment and control group. Balancing diagnostics will help determine if the propensity score model needs further adjustment.

4.4.6 Other Methods of Using Propensity Scores

Aside from matching, three other methods of using propensity scores have been described: covariate adjustment using propensity scores (using the propensity score as a covariate in a multivariate logistic regression model), stratification using propensity scores (for example stratifying on the quintiles of the propensity score could be expected to eliminate approximately 90 per cent of the bias due to an imbalance of measured confounders), and inverse probability of treatment weighting using propensity scores (calculating the probability of exposure which is then used as a weight in the subsequent analysis).[25, 26]

4.5 References

1. Rothman KJG, S.; Poole, C.; Lash, T.L. Validity in epidemiologic studies. *Modern epidemiology*. Lippincott Williams & Wilkins; 2008:128-147.

2. Kukull WA, Ganguli M. Generalizability: The trees, the forest, and the low-hanging fruit. *Neurology*. 2012;78:1886-1891

3. Ernst E, Pittler MH. Efficacy or effectiveness? *Journal of internal medicine*. 2006;260:488-490

4. Frieden TR. Evidence for health decision making - beyond randomized, controlled trials. *The New England journal of medicine*. 2017;377:465-475

5. Irving M, Eramudugolla R, Cherbuin N, Anstey KJ. A critical review of grading systems: Implications for public health policy. *Evaluation & the health professions*. 2017;40:244-262

6. Thabane L, Kaczorowski J, Dolovich L, Chambers LW, Mbuagbaw L. Reducing the confusion and controversies around pragmatic trials: Using the cardiovascular health awareness program (chap) trial as an illustrative example. *Trials*. 2015;16:387

7. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *The New England journal of medicine*. 2000;342:1887-1892

8. Broderick JP, Adeoye O, Elm J. Evolution of the modified rankin scale and its use in future stroke trials. *Stroke; a journal of cerebral circulation*. 2017;48:2007-2012

9. Altman DG, Royston P. The cost of dichotomising continuous variables. *BMJ (Clinical research ed.)*. 2006;332:1080

10. Dawson NV, Weiss R. Dichotomizing continuous variables in statistical analysis: A practice to avoid. *Medical decision making: an international journal of the Society for Medical Decision Making*. 2012;32:225-226

11. Bath PM, Lees KR, Schellinger PD, Altman H, Bland M, Hogg C, et al. Statistical analysis of the primary outcome in acute stroke trials. *Stroke; a journal of cerebral circulation*. 2012;43:1171-1178

12. Scott SC, Goldberg MS, Mayo NE. Statistical assessment of ordinal outcomes in comparative studies. *Journal of clinical epidemiology*. 1997;50:45-55

13. Armstrong BG, Sloan M. Ordinal regression models for epidemiologic data. *American journal of epidemiology*. 1989;129:191-204

14. Savitz SI, Benatar M, Saver JL, Fisher M. Outcome analysis in clinical trial design for acute stroke: Physicians' attitudes and choices. *Cerebrovascular diseases (Basel, Switzerland).* 2008;26:156-162

15. Howard G, Waller JL, Voeks JH, Howard VJ, Jauch EC, Lees KR, et al. A simple, assumption-free, and clinically interpretable approach for analysis of modified rankin outcomes. *Stroke; a journal of cerebral circulation*. 2012;43:664-669

16. Gardner W, Mulvey EP, Shaw EC. Regression analyses of counts and rates: Poisson, overdispersed poisson, and negative binomial models. *Psychological bulletin*. 1995;118:392-404

17. Zerna C, Rogers E, Rabi DM, Demchuk AM, Kamal N, Mann B, et al. Comparative effectiveness of endovascular treatment for acute ischemic stroke: A population-based analysis. *Journal of the American Heart Association*. 2020;9:e014541

18. Cragg JG. Some statistical models for limited dependent variables with application to the demand for durable goods. *Econometrica*. 1971;39:829-844

19. Kleiber C, Zeileis A. Visualizing count data regressions using rootograms. *The American Statistician*. 2016;70:296-303

20. Akaike H. A new look at the statistical model identification. *IEEE Transactions on Automatic Control*. 1974;19:716-723

21. Patten SB. Confounding and effect modification in analytical studies. *Epidemiology for canadian students: Principles, methods and critical appraisal*. Brush Education Inc.; 2015:164-179.

22. D'Agostino RB, Kwan H. Measuring effectiveness. What to expect without a randomized control group. Medical care. 1995;33:As95-105

23. Rothman KJ, Greenland S, Lash TI. Design strategies to improve study accuracy. *Modern epidemiology*. Lippincott Williams &Wilkins; 2008:168-182.

24. Caliendo M, Kopeinig S. Some practical guidance for the implementation of propensity score matching. *Journal of Economic Surveys*. 2008;22:31-72

25. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Statistics in Medicine*. 2009;28:3083-3107.

26. Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. *Statistics in Medicine*. 2006;25:2084-2106.

CHAPTER 5 Comprehensive Assessment of Disability Post–Stroke Using the Newly Developed miFUNCTION Scale

This chapter comprises of an original research article originally published in the International Journal of Stroke: Zerna C, Burley T, Green TL, Dukelow SP, Demchuk AM, Hill MD. Comprehensive assessment of disability post–stroke using the newly developed miFUNCTION scale. International Journal of Stroke. 2020; 15: 167–174. It describes the development, assessment of psychometric properties and utilization of the miFUNCTION scale in a randomized controlled trial investigating endovascular treatment in an attempt to overcome the shortcoming of the modified Rankin Scale. Due to manuscript brevity, an expansion of the methods outlined here can be found in CHAPTER 4.

5.1 Introduction

Stroke is a leading cause of death globally and a principal cause of long–term disability in industrialized nations.[1] Advances in thrombolytic therapy, specialized stroke unit care and most recently EVT for acute ischemic stroke have significantly improved survival rates and increased the number of survivors returning to community.[2 - 4] However, residual disability following stroke presents a significant economic burden with increasing evidence suggesting rehabilitation needs up to a year following stroke, including addressing deficits in cognition, perception and emotion.[5 - 8] Established assessment tools are not sensitive enough to accurately identify all differences in disability in the stroke population.[9] In 2000, the World Health Organization (WHO) developed a patient–centered International Classification of Functioning, Disability and Health (ICF). Depending on the size and location of infarct, a stroke may affect

three separate but related functional dimensions: the body dimension (body functions and structure), the individual dimension (activity), and the social dimension (participation).[1] A prior review by the European Stroke Organization Outcomes Working Group has identified 47 outcome measures in stroke trials with mRS, Barthel index (BI), and Stroke Impact Scale (SIS) being the most common ones.[10] The mRS arguably lacks sensitivity at the minor disability end of the scale and thus has difficulty to depict the patient's engagement in meaningful life roles.[10 - 12] Further, inter–observer variability is high enough to be an important source of misclassification error.[13, 14] Although the BI is considered to have strong validity, a key weakness is the floor/ceiling effect when trying to measure change at the extreme ends of the scale.[15] Even though the quality of life assessment is aided by incorporating memory, thinking, and social roles, the SIS is time consuming to administer and thus rarely used in the acute stroke setting.[16] The diversity of available outcome measures is testament to the current available options being imperfect. By recognizing the evolving needs of stroke survivors and an inability to capture disability as it is now understood, there exists an opportunity to reconcile this discrepancy with the development of a new post–stroke disability measurement tool. This new tool has to mirror the successes of the mRS with respect to ease and efficiency of use, while providing a more comprehensive assessment of disability following stroke. The purpose of this research was to conduct a pilot study for initial psychometric analyses of reliability and validity of a newly developed post–stroke disability assessment tool (miFUNCTION) that aligns with ICF, by assessing stroke survivors who presented to an outpatient stroke prevention clinic. This research also aimed to further evaluate the validity of the miFUNCTION scale by applying it to a clinical trial of EVT and compare its performance to other commonly used disability measures.

5.2 Methods

5.2.1 Rating Scale Development (2012)

An inter–disciplinary development team of stroke specialists (stroke neurologist, stroke physiatrist, occupational therapists, physical therapist, registered nurse and nurse scientist, all with at least 10 years of work experience and all working in both the acute and rehabilitation setting across the spectrum of acute care facility to community care) was assembled to develop a tool to assess disability following stroke. This was done in co–production between academic and non–academic partners. In 2012, this tool named miFUNCTION was iteratively modified by consensus.

The development team met regularly for 10 months, having round table discussions to define disability, aspects that were important in each of their patient's assessments, and ensure differentiation from similar constructs (e.g., immobility). The construct of disability was framed using the WHO ICF with an intended target population of stroke survivors in an outpatient clinic follow–up after discharge from hospital. A scoping review of the literature on functional outcome scales for stroke was conducted, with a focus on the most commonly used scales (e.g., mRS, BI, SIS, Stroke Specific Quality of Life Scale (SS–QOL)) and special consideration that the scales should reflect impairment, activity limitation, and participation restriction. Case examples of mRS assessment of patients were used to determine areas where difficulties arise.

Researchers then selected a response format and assembled an initial item pool by consensus decision items were then reviewed for face validity by stroke neurologists and allied health practitioners external to the original development team, discussed, and either discarded or sent back to the development team for revision. Considerations for format selection include:

- Type of format (e.g., structured versus unstructured)
- Number of response options
- Relevant content
- Number of response items
- Clarity of language

In the present study, these steps were dynamic and iterative, undergoing nine versions before settling on the finally implemented format.

An algorithm was designed and utilized as the data collection tool for the planned pilot study (Supplemental Figure I). By prompting evaluators to follow a question tree, it was predicted that inter–rater reliability would be maximized, while insuring the appropriate questions were included in the assessment. The format of the question tree was used in the pilot study.

5.2.2 Design and Data Collection of Pilot Study (early 2013)

A pilot study was conducted to do an initial assessment of the psychometric properties of miFUNCTION. Ethics approval was obtained from the Conjoint Health Research Ethics Board. A convenience sample of study participants was recruited from an accessible population of stroke survivors in the metropolitan area of Calgary, Alberta, in early 2013. The clinic is located at the Foothills Medical Centre, which provides services to over two million people from Calgary, southern Alberta, southeastern British Columbia, and southern Saskatchewan. Annually, the clinic serves approximately 2500 patients, including stroke survivors as well as new referrals from the community (i.e., primary care physicians) and city emergency departments.

Participants were eligible for inclusion to the study if they had been diagnosed with stroke (any severity) within 60 days; this timeframe was established to allow any potential stroke–related disability to manifest. Finally, the participants needed to be able to understand English or have a family member or other proxy available to respond on their behalf. All patients presenting to the Stroke Prevention Clinic who met inclusion/exclusion criteria were eligible for the study. A graduate student researcher (SR) in consultation with clinic staff recruited potential participants. Clinic staff approached potential participants during the nursing assessment component of their clinic visit and asked if they would be interested in participating in the study. If agreeable, the SR obtained fully informed and signed consent. A convenience sample of 30 participants was achieved over the course of five months in early 2013.

The SR was trained and certified for the mRS. There were five clinic nurses who participated in data collection for the study. Each was previously certified for the mRS as well as being experienced neuroscience nurses. miFUNCTION was demonstrated for them by the SR and each nurse demonstrated understanding of its administration through return demonstration and observation by the SR. Further descriptive data were collected by the SR and included the participants' hospital identification number, age, and sex.

First, the clinic nurse administered miFUNCTION as part of the nursing assessment component of the clinic visit, followed by the administration of the mRS. Once the clinic nurse was done with her assessment, the SR administered the same assessment being blinded to the previous results. After the SR had completed the assessments, an informal debrief was conducted between the two assessors to illicit any salient observations from the administration of the

instruments. The physician/patient interaction portion of the visit variably occurred before or after the SR assessment, but these specific data were not gathered.

5.2.3 Design and Data Collection of ESCAPE Trial (2013 until early 2015)

Eligibility criteria for the ESCAPE trial have been previously described.[15] Adults with disabling ischemic stroke were enrolled within 12 hours from symptom onset if they had an occluded proximal artery in the anterior circulation, a small infarct core and at least moderate collateral circulation. The ethics board at each site approved the trial. Participants were randomized to receive rapid EVT plus medical treatment or medical treatment alone. Participants in both groups could receive IV alteplase according to local guidelines. Demographics, medical history, and stroke severity were assessed at baseline. The primary outcome (mRS) as well as secondary (miFUNCTION, NIHSS, and BI) and safety outcomes was assessed at 90 days by trained personnel unaware of the treatment–group assignments. For ease of implementation as an electronic case report form, the format of the miFUNCTION scale was changed into a scoring sheet and is shown in Figure 12 as used in the ESCAPE trial.

miFUNCTION

Disability Level	Score	Description
No disability	☐ 0	**Perfectly normal:** no symptoms
	☐ 1	**Symptoms only:** back to all prior activities
Minimal disability	☐ 2	**A *slight* reduction/modification of a valued activity(s) but otherwise normal:** valued activities include job/career, volunteering, sports, hobbies, driving, socialization **AND** walks without aids
Mild disability	☐ 3	**A *substantial* reduction or loss of a valued activity(s) but walking independently:** valued activities include job/career, volunteering, sports, hobbies, driving, socialization **AND** walks without aids
	☐ 4	**Able to perform all complex home management but wheelchair/walker dependent:** has difficulty with valued activities but is able to do Complex Home Management caring for others, child rearing, shopping, finances, scheduling/ household management **EVEN THOUGH ambulates** with a walker or wheelchair
	☐ 5	**Complex Home Management impaired, not wheelchair/walker dependent:** caring for others, child rearing, shopping finances, or scheduling/household management slightly impaired **BUT** walks with or without a can/AFO
Moderate disability	☐ 6	**Complex Home Management impaired and wheelchair/walker dependant:** caring for others, child rearing, shopping, finances, or scheduling/household management substantially impaired **AND** ambulates with a walker or wheelchair
	☐ 7	**Basic Home management *slightly* impaired but ambulating normally:** housekeeping, food preparation, laundry or self medication slightly impaired **BUT** is able to walk indoors with or without aids
	☐ 8	**Basic Home Management impaired but ambulating indoors:** housekeeping, food preparation, laundry, or self medication impaired **BUT** able to walk indoors with or without aids
	☐ 9	**Basic Home Management impaired and cannot walk:** housekeeping, food preparation, laundry, or self-medication impaired **AND** cannot walk
Moderately severe disability	☐ 10	**Can do all but one basic activity and transfers independently:** one of dressing, toileting, grooming or feeding affected by **BUT** transfers independently
	☐ 11	**Can do basic activities but requires assistance with transfers:** one or two dressing, toileting, grooming or feeding affected **AND** needs assistance with transfers
	☐ 12	**Needs help for everything *except* feeding:** but may be left alone for short periods of time **AND** able to call for help
Severe disability	☐ 13	**Needs help for everything but out of bed at times:** cannot be left alone **BUT** does spend time out of bed
	☐ 14	**Bedridden:** Restricted to bed with constant care
Death	☐ 15	**Death**

Figure 12: miFUNCTION Score Sheet as Used in the ESCAPE Trial Case Report Forms

5.2.4 Data Analysis of Pilot Study

Standard descriptive statistics were used to measure central tendency and variability of patient characteristics. Inter–rater reliability was assessed using the Kappa statistic. Values of 0–0.20 have been previously defined as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1 as almost perfect agreement.[17]

Convergent validity was established using pairwise correlation against the mRS. Correlation coefficients in the order of 0.10 were considered small/weak, those of 0.30 medium/moderate, and those of 0.50 large/strong in terms of magnitude of effect size.[18]

5.2.5 Data Analysis of ESCAPE trial

Standard descriptive statistics were used to measure central tendency and variability of patient characteristics. Convergent validity was established using pairwise correlation against the mRS, NIHSS, BI score, and 5 Level European Quality Of Life 5 Dimension Scale (EQ5D–5 L) score. Criterion validity was assessed using logistic regression analysis. Effect estimates for miFUNCTION at 90 days were calculated, with adjustment for age, sex, baseline NIHSS score, location of occlusion (internal carotid artery (ICA) vs. MCA segment 1 vs. MCA segment 2), and treatment with IV alteplase (yes vs. no). Interaction terms were not included. Backwards elimination to reach a parsimonious model was used. Analyses were performed using SPSS (Version 19, IBM Analytics, Armonk, NY) and STATA (Stata 14; Stata Corp., College Station, TX).

5.3 Results

5.3.1 Pilot Study

Consecutive patients presenting to the Stroke Prevention Clinic were approached for participation in the pilot study. Thirty participants were successfully enrolled during eleven data collection events, with only one refusal for participation. The median participant age was 69 years (IQR 28), consisting of 40 % female participants. Since assessment at the Stroke Prevention Clinic required at least sitting mobility, patient's mRS scores ranged from 0 to 4 and miFUNCTION scores ranged from 0 to 10 excluding bedridden patients. A detailed summary of participant assessments is provided in the Supplemental Table I.

Inter–rater reliability between the nurse and the SR was moderate for the miFUNCTION ($\kappa = 0.585$) and substantial for mRS ($\kappa = 0.734$). A scatterplot for visualization of the levels of agreement can be found in Supplemental Figure II. miFUNCTION and mRS were strongly correlated (Pearson's $\rho = 0.821$).

5.3.2 ESCAPE Trial

The median age was 70.9 years (IQR 21.2), consisting of 52.4 % females. The median NIHSS score was 17 (IQR 7). Slightly more than half of the patients (52.4 %) underwent EVT whereas the others had been randomized to medical treatment only. Overall, no or mild disability (mRS 0–2) was achieved in 130 (41.3 %) patients at 90 days post–stroke.

The distribution of miFUNCTION scores within each mRS level is presented in Table 4. The correlation of miFUNCTION with the mRS was almost perfect (Pearson's $\rho = 0.9439$) (Figure 13). The correlation with NIHSS score and BI score was strong (Pearson's $\rho = 0.7853$

and Pearson's $\rho = -0.8831$, respectively) and moderate with EQ5D–5L score (Pearson's $\rho = -0.5962$).

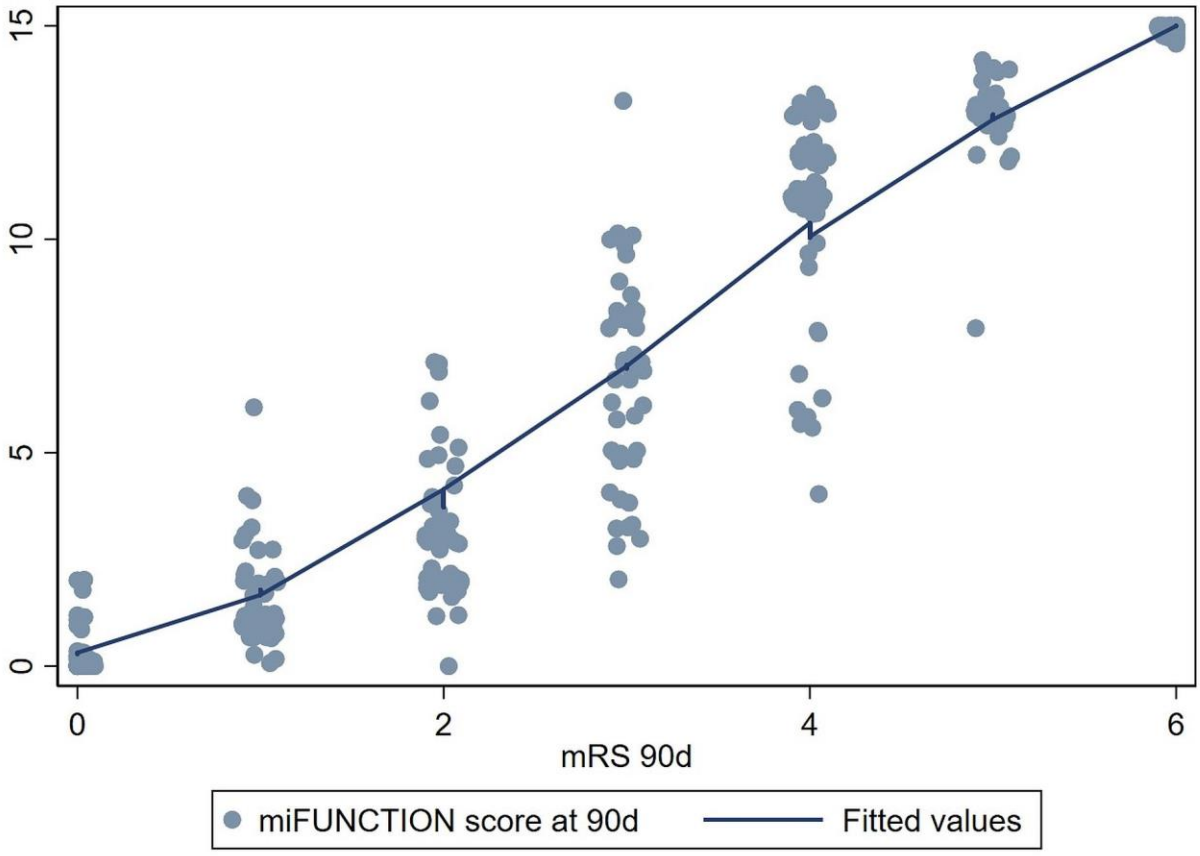


Figure 13: Scatterplot of Modified Rankin Scale and miFUNCTION Scores at 90 days within the ESCAPE Trial

The line of best fit was generated using locally weighted scatterplot smoothing.

Table 4: miFUNCTION Score Distribution by Level of Modified Rankin Scale Score at 90 days within the ESCAPE Trial

	Modified Rankin Scale score							
miFUNCTION score	**0** (n = 35)	**1** (n = 49)	**2** (n = 46)	**3** (n = 49)	**4** (n = 58)	**5** (n = 29)	**6** (n = 45)	**N/A** (n = 4)
0	77 %	6 %	2 %	–	–	–	–	–
1	14 %	53 %	4 %	–	–	–	–	–
2	9 %	23 %	37 %	2 %	–	–	–	–
3	–	10 %	26 %	10 %	–	–	–	–
4	–	4 %	11 %	6 %	2 %	–	–	–
5	–	–	11 %	12 %	–	–	–	–
6	–	2 %	2 %	8 %	10 %	–	–	–
7	–	–	7 %	17 %	2 %	–	–	–
8	–	–	–	23 %	3 %	3 %	–	–
9	–	–	–	4 %	2 %	–	–	–
10	–	–	–	10 %	3 %	–	–	–
11	–	–	–	–	29 %	–	–	–
12	–	–	–	–	23 %	14 %	–	–
13	–	–	–	2 %	26 %	62 %	–	–
14	–	–	–	–	–	21 %	–	–
15	–	–	–	–	–	–	100 %	–
N/A	–	2 %	–	6 %	–	–	–	100 %

N/A means not applicable.

The effect size of the multivariable models using mRS and miFUNCTION as an outcome scale was similar across all possible dichotomization cut–offs. Detailed results are displayed in Table 5.

Table 5: Results of Multivariable Logistic Regression Models using both mRS and miFUNCTION at 90 days within the ESCAPE Trial as an Outcome Variable

	mRS			miFUNCTION	
Favorable outcome defined as	**Adjusted OR**	**95 % CI**	**Favorable outcome defined as**	**Adjusted OR**	**95 % CI**
0–1	2.88	1.64–5.07	0–2	3.42	1.95–5.99
0–2	3.45	2.05–5.78	0–5	3.32	1.99–5.55
0–3	3.52	2.09–5.95	0–9	3.66	2.13–6.26
0–4	2.72	1.48–5.01	0–12	2.98	1.63–5.44
0–5	2.38	1.15–4.92	0–14	2.34	1.13–4.84

5.4 Discussion

Our study shows that miFUNCTION performs well on psychometric measurement assessment in both a routine outpatient setting and as part of an acute international clinical stroke trial. The tool shows greater granularity in the mild to moderately–severe disability range after a stroke and thus provides more insight into both the patient's ability and capacity to engage in meaningful life roles. With further work, this tool will be a valuable addition to future research studies as well as the clinical setting to assess disability post–stroke.

Several attempts have been made to address the reliability of the mRS, with varying degrees of success in addressing the issue of inter–observer variability.[9, 14] By developing miFUNCTION, the goal was to reduce inter–observer variability. Using a decision–tree asking closed questions, inter–observer reliability should be favorable when using miFUNCTION. However, the inter–rater reliability in the pilot study was lower than that of the mRS score

assessment, and there had been ten incidences of divergence between observers. The data demonstrate that only one occasion of divergence can be fully attributed to observer variation. The remaining nine variations were respondent–driven, possibly caused by the respondent's interpretation of the question or wording. For example, can the word “capable” be distinguished from “able” or “willing”? Reducing ambiguity of questions may be achieved by consistently phrasing questions as “Do you go to social gatherings …” rather than “Are you capable of going to social gatherings,” as the former will allow for an assessment of participation restriction rather than lack of will to participate. The format of the tool was changed when it was used in the clinical trial and instead of a decision tree, assessors were provided with a list of miFUNCTION scores and their disability description according to the branches of the decision tree. They were then asked to choose one score which reduced the ambiguity of respondent interpretation discussed above.

The face and content validity of miFUNCTION have been ensured with development by an interdisciplinary team and review by a panel of content experts. The tool's criterion validity was shown by near perfect correlation with the mRS score and its convergent and discriminant validity by correlation with the NIHSS score, BI score, and EQ5D–5L score. miFUNCTION also demonstrated strong correlation with the mRS in two different settings thus demonstrating concurrent validity. Of note, the Pearson correlation coefficient can be affected by extreme values which may exaggerate the strength of the relationship. In Table 4, the distribution of miFUNCTION scores within the mRS categories 2 to 4 is broad. Assessment of miFUNCTION certainly needs attention to detail because of the small differences in the descriptors of adjacent categories. Even though the descriptions were supposed to reduce respondent ambiguity as

described above, they might need greater clarity in phrasing to simplify assessment. The fitted values in Figure 15, however, still show a strong association between the miFUNCTION and mRS assessment.

A possible limitation is that patients were only indirectly involved in the tool's development as their feedback was communicated by experienced members of the interdisciplinary study team who worked with them closely in regard to multiple activities. Though unlikely, valuable insight into how easily questions were understood from a patient perspective or what domains of recovery are most important to patients were potentially missed. This study has not tested miFUNCTION longitudinally so the tool's sensitivity to changes in disability over time cannot be commented on.

5.5 Conclusion

miFUNCTION demonstrated strong correlation with the mRS in different settings thus showing the scales ability to assess post–stroke disability. Validity was high but inter–rater reliability remains an issue. Reducing inter–rater variability might be achieved by extending the algorithm of miFUNCTION to include fixed phrased questions/concise descriptions. This will have to be explored in further research.

5.6 References

1. Bouffioulx E, Arnould C, Thonnard JL. Satisfaction with activity and participation and its relationships with body functions, activities, or environmental factors in stroke patients. *Archives of physical medicine and rehabilitation*. 2011;92:1404-1410

2. Tissue plasminogen activator for acute ischemic stroke. The national institute of neurological disorders and stroke rt-pa stroke study group. *The New England journal of medicine*. 1995;333:1581-1587

3. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet (London, England)*. 2016;387:1723-1731

4. Smith EE, Hassan KA, Fang J, Selchen D, Kapral MK, Saposnik G. Do all ischemic stroke subtypes benefit from organized inpatient stroke care? *Neurology*. 2010;75:456-462

5. Wood JP, Connelly DM, Maly MR. 'Getting back to real living': A qualitative study of the process of community reintegration after stroke. *Clinical rehabilitation*. 2010;24:1045-1056

6. Ellis-Hill C, Robison J, Wiles R, McPherson K, Hyndman D, Ashburn A. Going home to get on with life: Patients and carers experiences of being discharged from hospital following a stroke. *Disability and rehabilitation*. 2009;31:61-72

7. Kwon S, Hartzema AG, Duncan PW, Min-Lai S. Disability measures in stroke: Relationship among the barthel index, the functional independence measure, and the modified rankin scale. *Stroke; a journal of cerebral circulation*. 2004;35:918-923

8. Edwards DF, Hahn MG, Baum CM, Perlmutter MS, Sheedy C, Dromerick AW. Screening patients with stroke for rehabilitation needs: Validation of the post-stroke rehabilitation guidelines. *Neurorehabilitation and neural repair*. 2006;20:42-48

9. Quinn TJ, McArthur K, Dawson J, Walters MR, Lees KR. Reliability of structured modified rankin scale assessment. *Stroke; a journal of cerebral circulation*. 2010;41:e602; author reply e603

10. Rankin J. Cerebral vascular accidents in patients over the age of 60. I. General considerations. *Scottish medical journal*. 1957;2:127-136

11. Rankin J. Cerebral vascular accidents in patients over the age of 60. Ii. Prognosis. *Scottish medical journal*. 1957;2:200-215

12. Rankin J. Cerebral vascular accidents in patients over the age of 60. Iii. Diagnosis and treatment. *Scottish medical journal*. 1957;2:254-268

13. Quinn TJ, Dawson J, Walters MR, Lees KR. Reliability of the modified rankin scale: A systematic review. *Stroke; a journal of cerebral circulation*. 2009;40:3393-3395

14. Saver JL, Filip B, Hamilton S, Yanes A, Craig S, Cho M, et al. Improving the reliability of stroke disability grading in clinical trials and clinical practice: The rankin focused assessment (rfa). *Stroke; a journal of cerebral circulation*. 2010;41:992-995

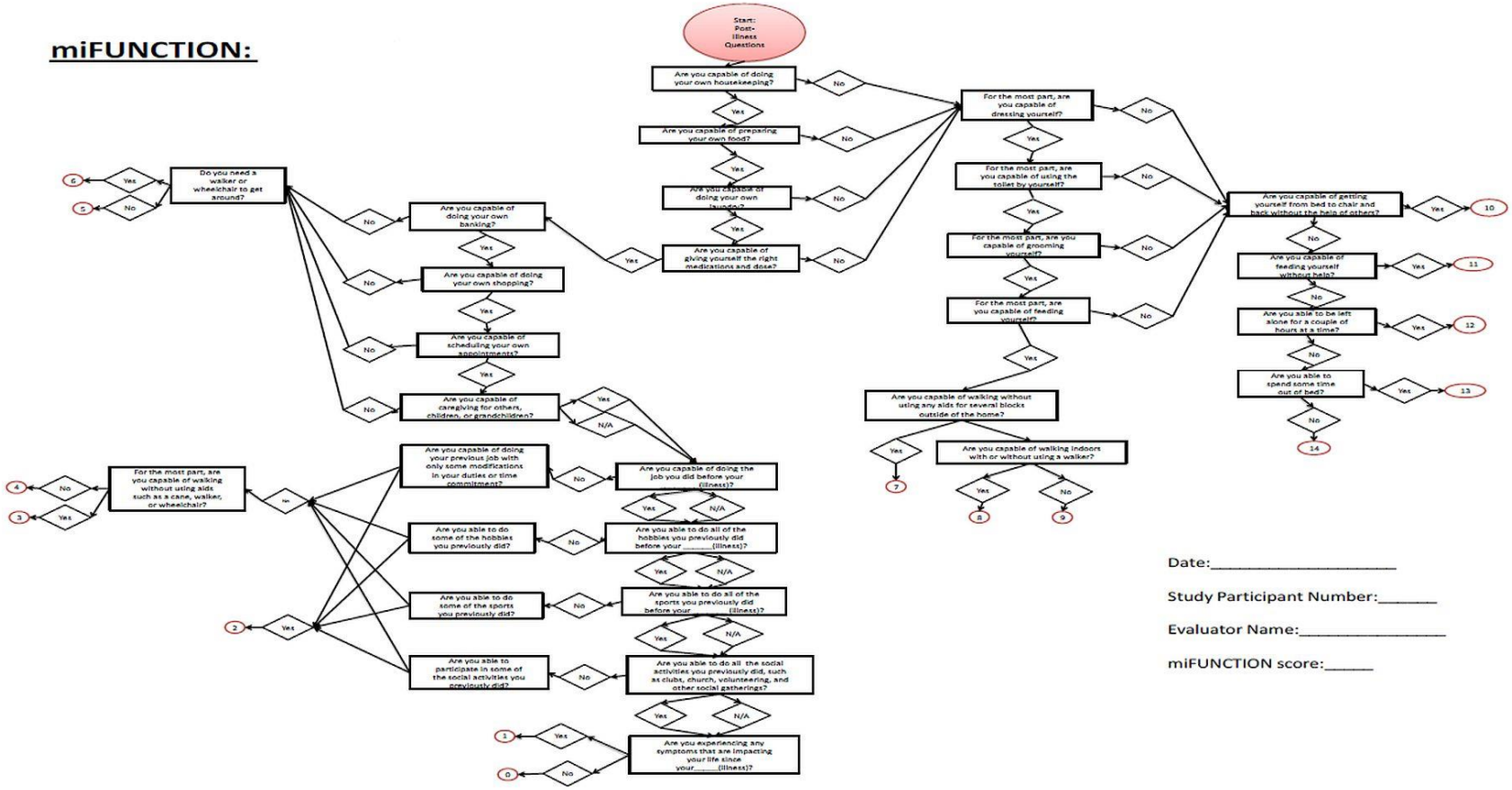
15. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *The New England journal of medicine*. 2015;372:1019-1030

16. Quinn TJ, Dawson J, Walters MR, Lees KR. Exploring the reliability of the modified rankin scale. *Stroke; a journal of cerebral circulation*. 2009;40:762-766

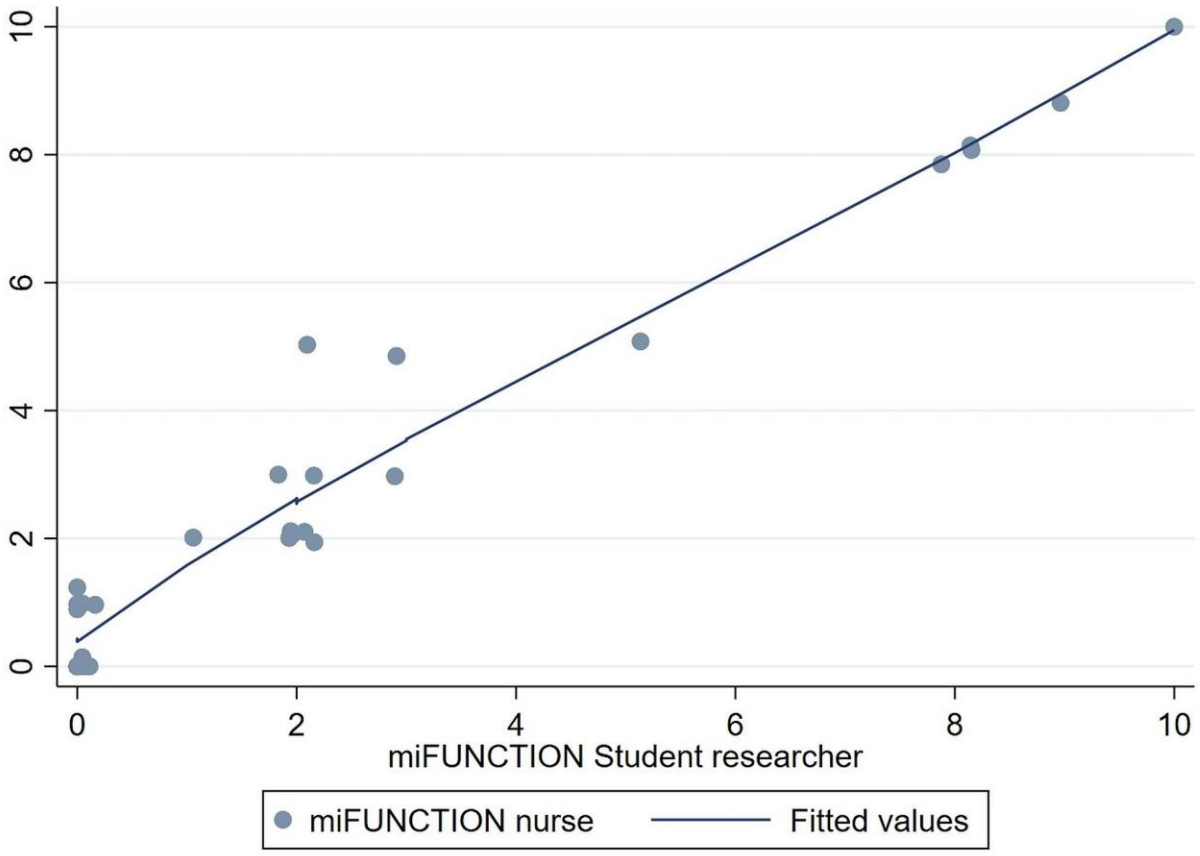
17. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33:159-174

18. Hemphill JF. Interpreting the magnitudes of correlation coefficients. *The American psychologist*. 2003;58:78-79

5.7 Supplemental Material



Supplemental Figure I: Decision tree used for miFUNCTION assessment in the pilot study



Supplemental Figure II: Scatterplot showing Agreement of miFUNCTION Scores in the Pilot Study

Supplemental Table I: Results of miFUNCTION Assessments of each Participant in the Pilot Study

Participant	Age	Evaluator miFUNCTION	Student Researcher miFUNCTION	Evaluator mRS	Student Researcher mRS
1	60	3	2	0	0
2	62	0	0	0	0
3	78	5	2	2	2
4	71	0	0	0	0
5	81	8	8	3	3
6	73	0	0	0	0
7	72	1	0	1	1
8	57	0	0	0	0
9	64	1	0	1	1
10	78	8	8	3	3
11	83	5	5	2	2
12	76	1	0	1	0
13	44	2	2	3	3
14	30	2	1	2	1
15	94	0	0	0	0
16	85	9	9	4	4
17	50	2	2	2	2
18	34	2	2	1	1
19	57	0	0	0	0
20	76	1	0	0	0
21	84	8	8	2	2
22	76	1	0	1	0
23	50	2	2	1	1
24	43	0	0	0	0
25	31	2	2	1	2
26	76	3	2	3	2
27	90	10	10	4	4
28	52	0	0	0	0
29	47	5	3	2	2
30	67	3	3	3	1

CHAPTER 6 Comparative Effectiveness of Endovascular Treatment for Acute Ischemic Stroke—A Population–Based Analysis

This chapter is comprised of an original research article originally published in the Journal of the American Heart Association: Zerna C, Rogers E, Rabi DM, Demchuk AM, Kamal N, Mann B, Jeerakathil T, Buck B, Shuaib A, Rempel J, Menon BK, Goyal M, Hill MD. Comparative Effectiveness of Endovascular Treatment for Acute Ischemic Stroke: A Population–Based Analysis. Journal of the American Heart Association. 2020 Apr 7;9:e014541. It shows real–world evidence of the effectiveness of endovascular treatment since the patient cohort in randomized controlled trials are rather homogenous and narrow defined and do not reflect routine clinical practice. Due to manuscript brevity, an expansion of the methods outlined here can be found in CHAPTER 4.

6.1 Introduction

EVT of acute ischemic stroke in the anterior circulation caused by large-vessel occlusion has been established as the new standard of care. In randomized trials, eligibility varied slightly by age, baseline stroke severity, treatment time from stroke onset, concurrent alteplase treatment, and extracranial carotid artery occlusion or stenosis, but the results of each of the trials clearly favor EVT. A meta-analysis of all trials showed that EVT led to reduced disability compared with control patients who received standard medical treatment alone (OR 2.49, 95 % CI 1.76–3.53).[1]

Multiple practice guidelines recommending the use of EVT were published shortly after conclusion of these positive trials. Clinical practice guidelines, in an attempt to promote optimal

care for all patients, do not consider the heterogeneity of the patient population or the complexity of medical decisions and are tightly aligned with the evidence provided by clinical trials.[2] As a result, healthcare providers are often left to consider therapeutic interventions in patients who may not have met the eligibility criteria for trial participation (namely, older adults with significant comorbidity). In such instances, population-based comparative effectiveness research can be useful after efficacy is well established in clinical trials and in this case help ensure that the largest appropriate group of patients gains access to this life-saving and disability-sparing treatment.[3]

Our objective was to conduct a population-based study of EVT in the province of Alberta, Canada, and provide greater understanding of how the benefits and risks of EVT might vary across the population. This knowledge will inform the clinical decision-making process on EVT. The primary outcome was home-time, which is a novel and patient-centered outcome that reflects health circumstances that are easy to understand and meaningful to patients and their caregivers. It was hypothesized that there would be at least a 15 % difference in effect size between all patients across the province who presented with an acute ischemic stroke caused by a large-vessel occlusion in the anterior circulation and who were treated with EVT compared with the medical treatment arm of the ESCAPE trial.

6.2 Methods

Data supporting the findings of this study are not publicly available at this time.

6.2.1 Provincial EVT Data

Data are from the QuICR Registry. The registry was designed for quality improvement purposes and captures and tracks all treated acute stroke patients in the province of Alberta, Canada. Alberta has an estimated population of four million, and its area is ≈660,000 km^2. There are two comprehensive stroke centres (in Calgary and Edmonton) and 15 primary stroke centres. The registry data are collected in routine clinical care and considered part of the medical record. The current study was approved by the local ethics committee, and informed consent by individual participants was waived. Date were extracted over three years from April 2015 to March 2018 to cover a time period between publication of the positive endovascular trials up until the publication of the two clinical trials evaluating imaging selection and EVT in late presenting patients (DAWN and DEFUSE-3), which might have changed practice patterns.

We included all patients aged ≥ 18 years that underwent EVT for an acute ischemic stroke caused by a proximal large-vessel occlusion of the anterior circulation (ICA, MCA M1 and M2 segments, or ACA). Patients with posterior circulation stroke and patients not residing in the province of Alberta were excluded because the primary outcome could not be obtained for them. Data of interest were age, sex, stroke severity according to NIHSS score, date and time of stroke onset or time last seen well, IV alteplase treatment (yes/no), and interval time metrics for treatment. Onset-to-treatment time was defined as time from onset to first hyperacute treatment (either IV alteplase or EVT).

6.2.2 Linkage With Administrative Health Data and Outcomes

We captured outcomes in clinical routine using administrative data. Administrative health data are not generated for research purposes but instead are collected for payment, monitoring,

planning, priority setting, and evaluation of health systems.[4] These data can come from different interactions with the healthcare system (through hospitalizations, ambulatory care, and emergency department visits) and are usually captured over a prolonged period.

The primary outcome of the study was home-time. Home-time refers to the number of days that the patient was back at his/her respective premorbid living situation without an increase in level of care within 90 days of the index stroke event. The premorbid living situation was determined from administrative health data and was assigned as any form of continuing care facility if that is where the patient had resided in the two-week period before the index stroke admission or was otherwise inferred to be the private home. By definition, patients who died in hospital after the index stroke admission have a home-time of 0 days. Initially developed from data of the Glycine antagonist [gavestinel] in neuroprotection (GAIN) International trial, home-time was found to be a useful and robust outcome marker for stroke in 2008.[5] Recent work has shown that home-time is obtainable in a complete population through administrative health data collection, which makes it less vulnerable to attrition bias compared with prospective studies.[6] Home-time after stroke was found to be a valid proxy marker for functional recovery, according to an analysis of Medicare beneficiaries in the United States as well as a large linked data analysis of the Scottish Stroke Care Audit with routine healthcare data.[7, 8] Discharge to home from hospital within the Canadian health system depends solely on the patient's functional status; it is not governed by administrative rules for length of stay. If the patient is in need of rehabilitation or indefinitely not able to care for himself/herself, discharge will occur to an alternate care facility (e.g. rehabilitation facility or long-term care facility) instead of home. Stay in such facilities is well coded through administrative data.

Secondary outcomes included dichotomized home-time at 90 days (> 80 equivalent mRS 0–1 and > 50 equivalent to mRS 0–2, according to prior correlation[6]) and mortality at 90 days, which was determined from linkage with the provincial vital statistics registry.

6.2.3 ESCAPE Trial: Historical Control Data (Medical Treatment)

The historical control group within this study was the medical treatment arm from the ESCAPE trial.[9] The trial involved sites across the world, but most patients (64.7 %) were from Canada, making it an ideal control group. Patients with disabling stroke were enrolled within 12 hours of onset, and only included if imaging revealed all of the following: small infarct core, defined as ASPECTS score ≥ 6; an occlusion of the anterior circulation involving a proximal artery; and moderate to good collateral circulation. Home-time and mortality at 90 days were collected as part of the trial. Onset-to-treatment time was defined as time from onset to first hyperacute treatment (in this case IV alteplase). The ESCAPE trial EVT group was analyzed as a reference to provide context for the study results.

6.2.4 Minimal Detectable Difference

Using the available sample size over three years with a power of 80 %, it was estimated that the study will be able in patients who received EVT to detect a 15.5 % decrease in the risk of not returning home (home-time 0) within 90 days compared with patients who received medical treatment alone.

6.2.5 Missing Data

Within the provincial EVT group, 43 (7.5 %) patients had missing NIHSS scores, and 6 (1.0 %) patients had missing onset-to-treatment times. The NIHSS scores were imputed with the

group mean and the onset-to-treatment times with the group median from the remaining available data. Within the ESCAPE trial data, only one patient had a missing onset-to-treatment time and three patients had missing 90-day outcomes in the medical treatment group. The onset-to-treatment time was imputed with the group median from the remaining available data and mortality at 90 days with the worst possible outcome (death) but conducted a sensitivity analysis with the best possible outcome (alive). Thirty-two patients who did not receive IV alteplase did not have an onset-to-treatment time recorded. Those times were imputed with the formula of randomization time plus 30 minutes, similar to the approach used in the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke (HERMES) trials collaboration analyses.[10] In the ESCAPE trial EVT group, one patient had a missing onset-to-treatment time and three patients had missing 90-day home-times, which were again imputed with the median from the remaining available data.

6.2.6 Statistical Analysis

Standard descriptive statistics were used to measure central tendency and variability of baseline characteristics. Visualization of home-time was shown using violin plots.

Home-time as the primary outcome was truncated at 0 and had excess 0 counts. The minimum amount of days that can be spent at home during the first 90 days is 0, and the maximum is 90 days (if patients were theoretically to be discharged on the same day of the procedure). Because many patients did not return to their home/prior residence within 90 days of the index stroke, the data had excess 0 counts. The use of a negative binomial regression model was explored by graphic assessment (hanging rootogram) as well as other analysis (Akaike's information criterion) for model fit. A Cragg hurdle regression model was used because it

provided the best fit for the data.[11] As a first part of the Cragg hurdle regression model, a Bernoulli probability directs the binary outcome of 0 (failure, hurdle is not crossed, or patient does not return to home within 90 days after stroke) or 1 (success defined as any positive count, hurdle is crossed, or patient does return home within 90 days after stroke). For the second part of the model, once the hurdle is crossed, a truncated-at-0 count model is used. IV alteplase treatment, EVT, age, and baseline NIHSS score were selected as a priori hurdle variables on the basis of their clinical significance for post–stroke outcomes and discharge disposition. In addition, the clinically important baseline variables age, sex, onset-to-treatment time, NIHSS score, and IV alteplase status were included as covariates in the truncated-at-0 count model. Imaging variables were not included because these were not routinely available. Margins plots were used to visualize the effects of the individual variables on the conditional mean estimates of 90-day home-time.

For the secondary outcomes, which were both binary, logistic regression analysis was used to model dichotomized home-time (> 80 equivalent to mRS 0–1 and > 50 equivalent to mRS 0–2, according to prior correlation[6]) and mortality at 90 days. The same clinically relevant baseline variables as stated above were included in those models.

$P < 0.05$ (two–sided) was considered to indicate statistical significance. All statistical analyses were performed using STATA (Stata 16; Stata Corp, College Station, TX).

6.2.7 Results

Within the three-year period (April 2015 to March 2018), 611 patients were treated with EVT in the province of Alberta. Twenty-six patients who had a permanent residence outside of province, meaning their outcome could not be determined through administrative health data

linkage, had to be excluded as well as nine additional patients who were treated for an isolated occlusion in the posterior circulation. The remaining 576 patients constituted the EVT group of the analysis. The medical treatment group of the ESCAPE trial had a sample size of 150 patients.

The median age of all patients was 70 years (IQR 59–81 years), and 47.8 % were women. The median NIHSS score at baseline was 17 (IQR 13–20). IV alteplase was given to 56.6 % (326/576) patients in the EVT group and 78.7 % (118/150) patients in the control group. Further baseline characteristics are shown in Table 6. The median 90-day home-time was 16 (IQR 0–81) days in the EVT group compared with 0 (IQR 0–65) days in the medical treatment group. The difference in distribution of home-time between both groups is illustrated in Figure 14.

Table 6: Baseline Characteristics

Variable	ESCAPE Control Group	ESCAPE EVT Group	QuICR EVT Group
Age [years], median (25 %–75 %)	70.1 (60.2–81.4)	71.3 (60.3–81.4)	70.2 (58.2–80.7)
Female [%]	52.7	47.9	46.5
Race [%]			
Asian	6	6.1	8.9
Black	4	4.8	0.2
Caucasian	87.3	87.3	46.7
First Nations	N/A	N/A	1.2
Hispanic	N/A	N/A	1.2
undetermined	2.7	1.8	41.8
NIHSS, median (25 %–75 %)	17 (12–20)	16 (13–20)	17 (12–21)
IV alteplase given [%]	78.7	72.7	56.6
Onset–to–treatment time [minutes], median (25 %–75 %)	145.5 (92–229)	126 (90–210)	140 (90–250)
Onset–to–treatment time [%]			
< 4.5 hours	84.67	81.21	76.91
4.5–6 hours	5.33	4.85	6.94
> 6 hours	10	13.94	16.15
Death at day 90 [%]	19.1	11.5	19.6
Time to death [days], median (25 %–75 %)	7 (2–17)	5 (2–35)	7 (3–14)
Discharge disposition [%]			
Home	15.3	23.6	27.5
Home with support	12	12.1	5.5
Rehabilitation	49.3	47.9	25.7
Long–term care	10.7	7.9	3.9
Death	12.7	7.3	16.9
Transfer to other hospital	N/A	N/A	20.5

Variable	ESCAPE Control Group	ESCAPE EVT Group	QuICR EVT Group
Home time [%]			
≥ 80 days (equivalent mRS 0–1)	28	29.1	35.6
≥ 50 days (equivalent mRS 0–2)	31.3	64.8	38

ESCAPE indicates Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EVT, endovascular treatment; mRS, modified Rankin Scale; N/A, not applicable; NIHSS, National Institutes of Health Stroke Scale; and QuICR, Quality Improvement and Clinical Research.

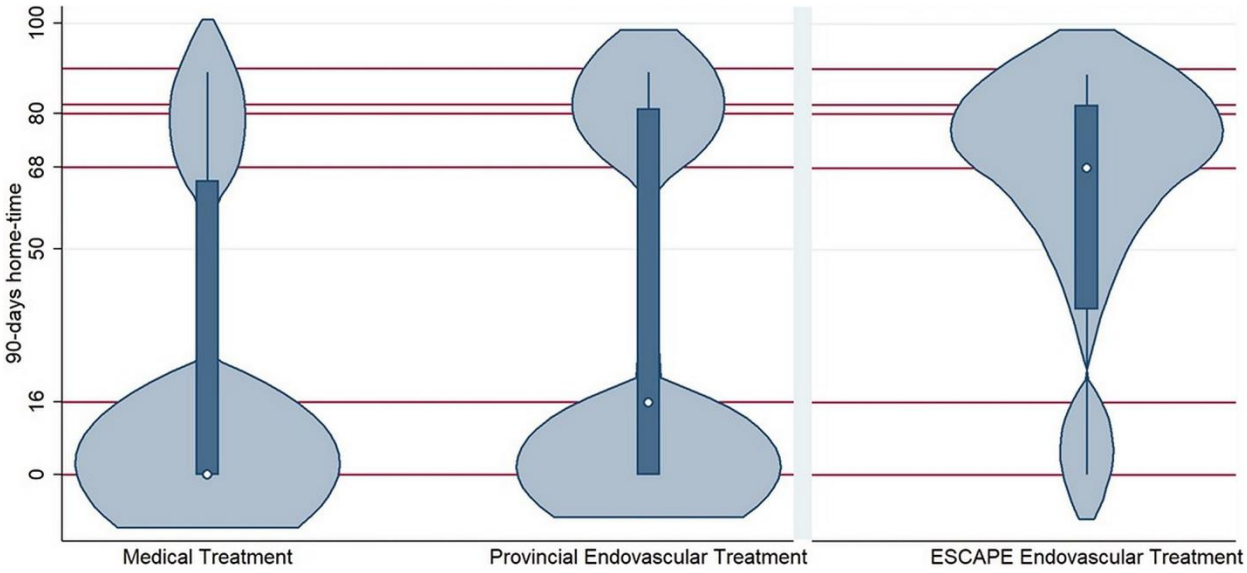


Figure 14: Violin plots of 90–Day Home–Time Return to Baseline by Treatment

Violin plots illustrate the probability density distributions of home-time for medical treatment and endovascular treatment. Medians are marked by the white dot, and the interquartile range is marked by a vertical blue bar. Non–outlier values are marked by the thinner vertical blue line. Median home-time (quartiles 1–3): medical treatment 0 (0–65) days and endovascular treatment 16 (0–81) days. ESCAPE indicates Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times.

EVT was associated with an increased 90–day home-time by an average eight and a half days compared with medical treatment alone in adjusted analysis ($P = 0.009$). A similar association was found with IV alteplase ($P = 0.010$), with an average 7.1 days increase in home-time. The non–modifiable predictors age and higher NIHSS score were associated with decreased 90-day home-time (both $P < 0.001$). Every five-year increase in age was associated with 2.3 days less time at home within the first 90 days after stroke. Every 5–point increase in the baseline NIHSS score signifying increased stroke severity was associated with 7.8 days less time at home within the first 90 days after stroke. The modifiable predictor onset-to-treatment time was also associated with a mean decrease of 90-day home-time after stroke ($P = 0.001$). A 50–minute delay in onset-to-treatment time was associated with a mean decrease of 90–day home-time by one day (meaning a 30–minute delay led to ≈0.5 days less home-time). Patient sex was not associated with 90-day home-time. Detailed results of the model and comparative results of the ESCAPE trial EVT group are displayed in Figure 15, Figure 16, and Table 7. There was no evidence of collinearity among the independent variables (the variance inflation factors for all variables were < 5).

Table 7: Results from Cragg Hurdle Regression Analysis of Home–Time at 90 Days

	QuICR EVT Group	**ESCAPE EVT Group**
	Conditional mean estimate [days] (mean, 95 % CI)	**Conditional mean estimate [days] (mean, 95 % CI)**
Endovascular treatment given	8.5 (2.1–14.9)	25.7 (20.1–31.2)
Intravenous alteplase given	7.1 (1.7–12.5)	3.4 (-5.7–12.6)
Sex (being female)	-1.1 (-4.2–1.9)	5.9 (1.8–10.0)
Age (per year older)	-0.5 (-0.6–0.3)	-0.5 (-0.7–0.3)
NIHSS score (per point higher)	-1.6 (-2.0–1.2)	-1.5 (-2.1–0.9)
Onset–to–treatment time (per minute longer)	-0.02 (-0.03–0.01)	0.003 (-0.02–0.02)

Data are given as conditional mean estimate (95 % CI) days. EVT indicates endovascular treatment; ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; NIHSS, National Institutes of Health Stroke Scale; and QuICR, Quality Improvement and Clinical Research.

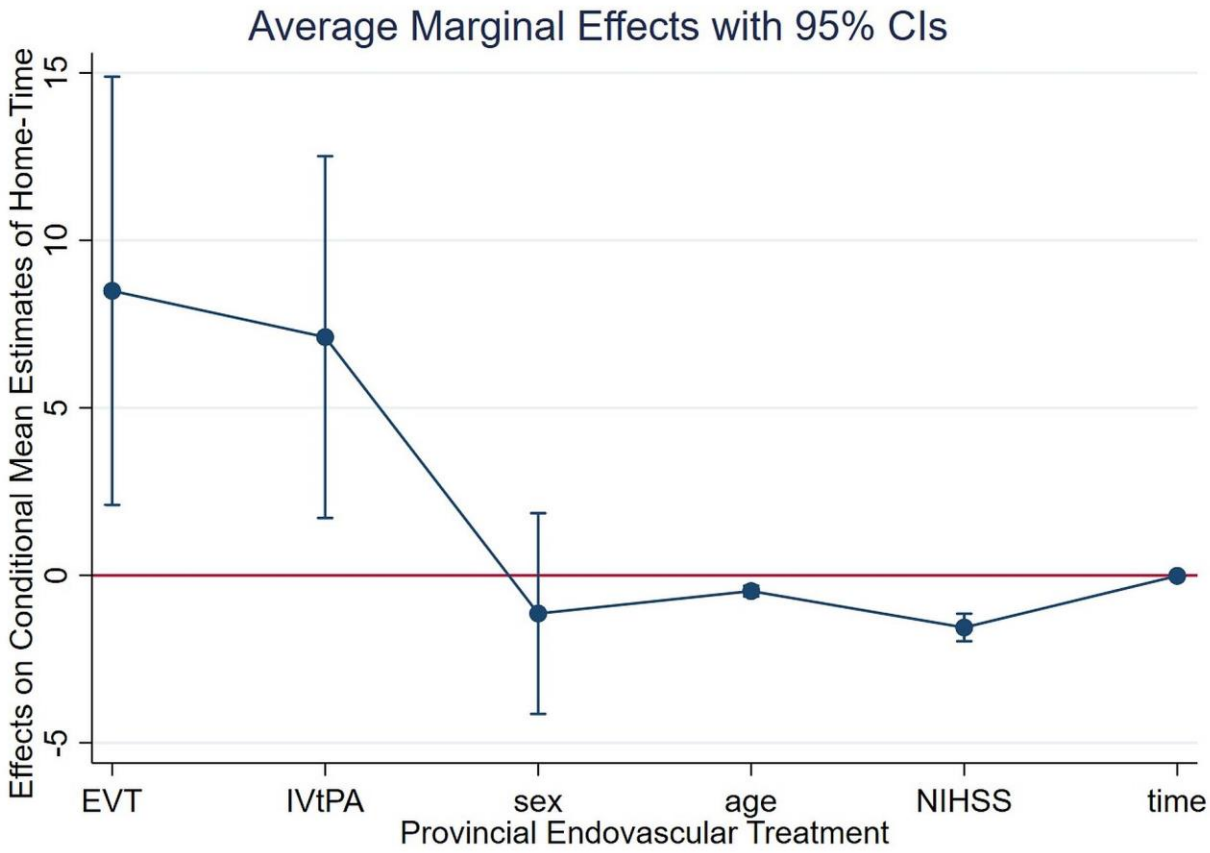


Figure 15: Margins Plot showing the Effect of Baseline Variables on the Conditional Mean Estimates of 90-Day Home-Time in the Provincial Endovascular Treatment (EVT) group

IVtPA indicates intravenous tissue Plasminogen Activator (alteplase); NIHSS, National Institute of Health Stroke Scale; and time, onset-to-treatment-time.

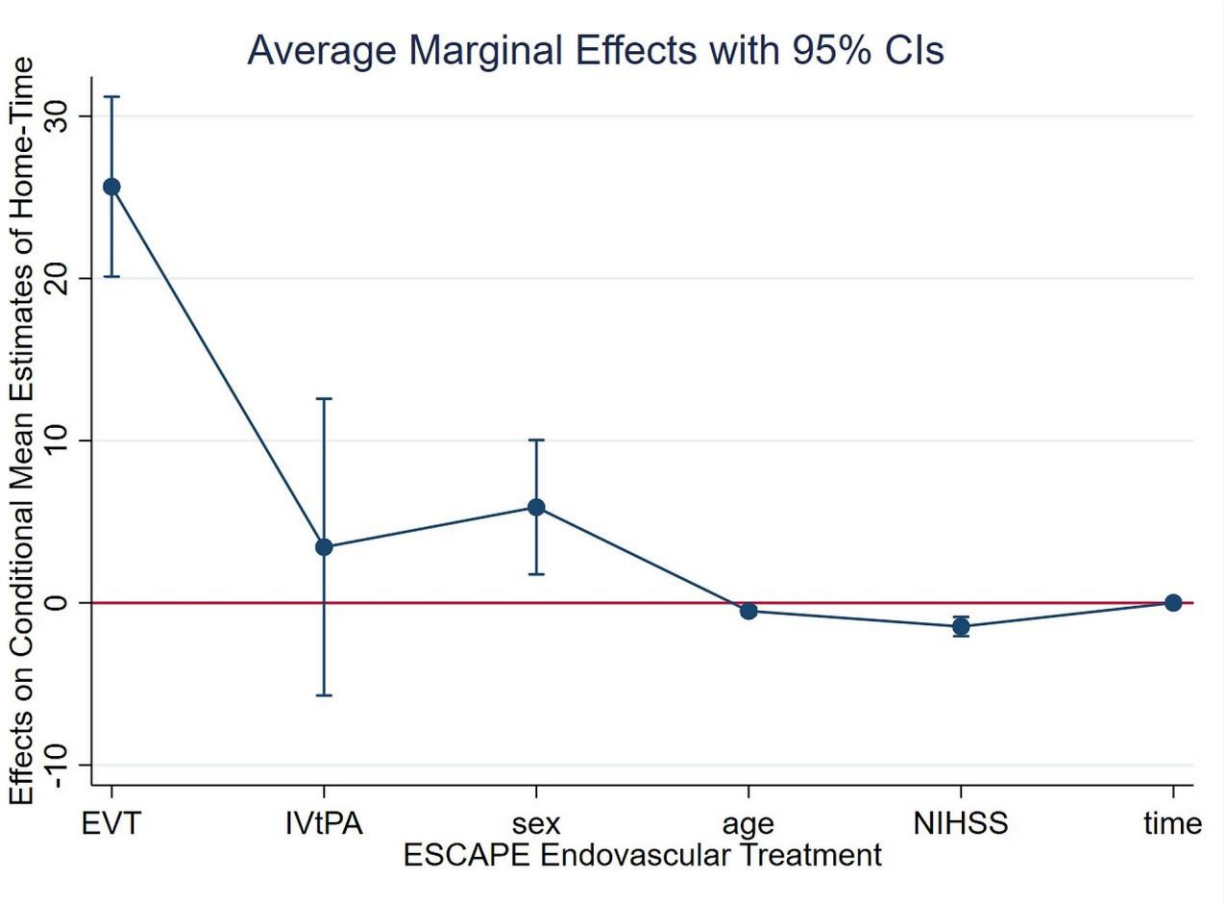


Figure 16: Margins Plot showing the Effect of Baseline Variables on the Conditional Mean Estimates of 90-Day Home-Time in the ESCAPE Trial Endovascular Treatment group

EVT indicates endovascular treatment, IVtPA intravenous tissue Plasminogen Activator (alteplase); NIHSS, National Institute of Health Stroke Scale; and time, onset-to-treatment-time.

Provincial EVT was associated with home-time > 80 days (equivalent to mRS 0–1) with an OR of 1.62 (95 % CI, 1.06–2.47) and home-time > 50 days (equivalent to mRS 0–2) with an OR of 1.78 (95 % CI, 1.16–2.75) in a logistic regression analysis adjusted for age, sex, NIHSS, IV alteplase treatment, and onset-to-treatment time. In comparison, EVT within the ESCAPE trial was also associated with home-time > 80 days with an OR of 4.55 (95 % CI, 2.74–7.56) and home-time > 50 days (equivalent to mRS 0–2) with an OR of 1.70 (95 % CI, 0.99–2.93).

There was no association between EVT and mortality at 90 days (OR, 0.76; 95 % CI, 0.47–1.24) in adjusted analysis. However, older age and higher NIHSS were independent predictors of mortality at 90 days (both $P < 0.001$). These results remained true in sensitivity analysis (Supplemental Table II). This association was further explored by stratification according to treatment modality and found differences in mortality rates as well as onset-to-treatment times across subgroups. Details are provided in Table 8.

Table 8: Stratum–Specific Results according to Treatment Modality

	Neither EVT nor intravenous alteplase **n = 32**	**Only intravenous alteplase** **n = 118**	**Only EVT** **n = 283**	**EVT and intravenous alteplase** **n = 293**
Mortality at 90 days [%]	15.63	22.03	24.03	15.36
Age [years], median	70.6	70.1	71.3	69.5
NIHSS, median	16.5	17	17	17
Onset–to–treatment time [minutes], median	317	125	198	105
Female sex [%]	56.3	51.7	48.4	44.7
Home time [%]				
≥ 80 days (equivalent mRS 0–1)	25	28.8	29.3	40.8
≥ 50 days (equivalent mRS 0–2)	31.3	31.4	32.2	43.7

EVT indicates endovascular treatment; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

6.3 Discussion

Our study shows that adult patients undergoing EVT for acute ischemic stroke caused by a proximal vessel occlusion spent on average more than one week longer at home within the first 90 days compared with patients receiving medical treatment alone. Home-time is a novel, health-economic, and patient-centered outcome that reflects health circumstances that are both easy to understand and meaningful to the patients, their caregivers or family, and the health system.

Other efforts of comparative effectiveness research on EVT for acute ischemic stroke have been made or are currently underway. Endovascular therapy has been shown to significantly reduce healthcare use up to one year after stroke.[12] The ongoing prospective TREVO Retriever Registry represents real-world data with stent retriever and to date demonstrated similar reperfusion rates and outcomes in the community compared with the rigorous centrally adjudicated randomized controlled trials.[13] Concurrently, the MR CLEAN Registry (Multicentre Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) concluded that EVT in routine clinical practice was at least as effective and safe as in the setting of a randomized controlled trial when using mRS as the outcome.[14] The real-world evidence of the current study confirms the external validity of the clinical trials, but with attenuated effect size when compared with the ESCAPE trial treatment group.[9] However, these data in combination with other comparative effectiveness research are relevant to effectively translate the results of the randomized controlled trials to the greatest number of stroke patients possible and strengthen the evidence for EVT compared with medical treatment alone in patients with acute ischemic stroke caused by large-vessel occlusion.

The effect size of IV alteplase in this study was similarly large and resulted in 7.1 days more home-time within 90 days. Of note, the provincial EVT group included several distal anterior circulation occlusions (M2 and Anterior Cerebral Artery [ACA]), which with their smaller thrombus burden would be more susceptible to a thrombolytic effect. IV alteplase in both the EVT groups as well as the medical treatment group was given per physician's discretion. Patients who presented early and with less comorbidities would have been given IV alteplase.

These patients have a higher likelihood of good outcome compared with their non–IV alteplase-eligible counterparts, which translates to longer home-time within 90 days.

Age and baseline stroke severity emerged once again as non–modifiable predictors of worse outcome or, in terms of this study, less home-time within 90 days.[15] The same association was true with prolonged onset-to-treatment time, which is in keeping with multiple studies, including an analysis of data from the Get With The Guidelines-Stroke Program, showing that earlier IV alteplase treatment was associated with reduced sICH rates and higher rates of discharge home after acute ischemic stroke.[16] Further analysis from the HERMES collaborators showed that the paradigm "time is brain" also holds true with EVT.[10] As such, the process metric of onset-to-treatment time (and its counterpart door-to-needle time) can and should be used as the focus for stroke system performance improvement, which will result in improved patient outcomes, including more home-time.[17, 18]

The MR CLEAN, SWIFT-PRIME, EXTEND-IA, and REVASCAT trials found no difference in mortality between their EVT groups and medical treatment groups.[19 - 22] In contrast, the ESCAPE trial documented reduced mortality in the EVT group at 90 days (10.4 % versus 19.0 %, rate ratio 0.5, 95 % CI 0.3–1.0), which is likely because of the fast treatment times observed in this trial.[9] In this current study, EVT was not associated with mortality. Stratification by IV alteplase status showed that the subgroup who had received only EVT but no IV alteplase had the highest mortality rate and a median onset-to-treatment time that was > 60 minutes longer than the subgroup who received IV alteplase only and > 90 minutes longer than the subgroup who received both EVT and IV alteplase. An average patient with acute ischemic stroke caused by large-vessel occlusion loses 1.9 million neurons each minute in which the stroke is untreated,

and delayed presentation is a strong predictor of poor outcome and mortality.[23] With the delay in onset-to-treatment time comes the observed higher mortality in the EVT only group, which might be an important reason why this study was not able to replicate the survival benefit of EVT.

Overall, EVT in routine care has a slightly reduced effect size.

A key strength of this study is that it represents the complete case capture of an entire population in the province of Alberta and therefore reflects real-world practice at a population level. Thus, data should be generalizable to other provinces and territories across Canada and elsewhere if EVT is provided in similarly high-volume experienced centres and the patient population has similar racial diversity. Home-time as a patient-centered outcome marker has the advantage of having complete ascertainment because it can be established through linkage with an administrative health database.

Even though Canadians have universal access to publicly funded health care and thus hospitalization and in-patient rehabilitation, numeric home-time may not account for the amount of social and financial support that each patient has that might influence his/her ability to actually return home. Thus, the average home-time herein incorporates the average socioeconomic status of the province of Alberta. Comorbidity data to complete further adjusted outcome estimates are not available, and only limited data on the occurrence of sICHs or procedural complications exist. In this respect, home-time provides a meaningful global outcome assessment, but it does obscure some details on the adverse effect of major treatment complications.

6.4 Clinical Perspective

What Is New?

- Estimation of the effect of EVT for acute ischemic stroke in a complete population.
- Using home-time as a novel and patient-centered outcome meaningful to the patients, their caregivers/family, and the health system.

What Are the Clinical Implications?

- Adult patients undergoing EVT for acute ischemic stroke on average spent more than one week longer at home within the first 90 days compared with patients receiving medical treatment alone.
- Real-world evidence confirmed the external validity of the clinical trials, but with attenuated effect size when compared with the more selected ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) trial treatment group.
- Home-time as a meaningful patient-centered outcome has the advantage of having complete ascertainment because it can be established through linkage with an administrative health database.

6.5 Conclusions

EVT for acute ischemic stroke caused by large-vessel occlusion is effective according to this province-wide population-based study and results in an increase of 90-day home-time by an average of eight and a half days.

6.6 References

1. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet (London, England)*. 2016;387:1723-1731

2. Woolf SH. Do clinical practice guidelines define good medical care? The need for good science and the disclosure of uncertainty when defining 'best practices'. *Chest*. 1998;113:166s-171s

3. Kukull WA, Ganguli M. Generalizability: The trees, the forest, and the low-hanging fruit. *Neurology*. 2012;78:1886-1891

4. Yu AY, Holodinsky JK, Zerna C, Svenson LW, Jette N, Quan H, et al. Use and utility of administrative health data for stroke research and surveillance. *Stroke; a journal of cerebral circulation*. 2016;47:1946-1952

5. Quinn TJ, Dawson J, Lees JS, Chang TP, Walters MR, Lees KR. Time spent at home poststroke: "Home-time" a meaningful and robust outcome measure for stroke trials. *Stroke; a journal of cerebral circulation*. 2008;39:231-233

6. Yu AYX, Rogers E, Wang M, Sajobi TT, Coutts SB, Menon BK, et al. Population-based study of home-time by stroke type and correlation with modified rankin score. *Neurology*. 2017;89:1970-1976

7. Fonarow GC, Liang L, Thomas L, Xian Y, Saver JL, Smith EE, et al. Assessment of home-time after acute ischemic stroke in medicare beneficiaries. *Stroke; a journal of cerebral circulation*. 2016;47:836-842

8. McDermid I, Barber M, Dennis M, Langhorne P, Macleod MJ, McAlpine CH, et al. Home-time is a feasible and valid stroke outcome measure in national datasets. *Stroke; a journal of cerebral circulation*. 2019;50:1282-1285

9. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *The New England journal of medicine*. 2015;372:1019-1030

10. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: A meta-analysis. *Journal of the American Association*. 2016;316:1279-1288

11. Cragg JG. Some statistical models for limited dependent variables with application to the demand for durable goods. *Econometrica*. 1971;39:829-844

12. Kamal N, Rogers E, Stang J, Mann B, Butcher KS, Rempel J, et al. One-year healthcare utilization for patients that received endovascular treatment compared with control. *Stroke; a journal of cerebral circulation*. 2019;50:1883-1886

13. Binning MJ, Bartolini B, Baxter B, Budzik R, English J, Gupta R, et al. Trevo 2000: Results of a large real-world registry for stent retriever for acute ischemic stroke. *Journal of the American Heart Association*. 2018;7:e010867

14. Jansen IGH, Mulder M, Goldhoorn RB. Endovascular treatment for acute ischaemic stroke in routine clinical practice: Prospective, observational cohort study (mr clean registry). *BMJ (Clinical research ed.)*. 2018;360:k949

15. Rost NS, Bottle A, Lee JM, Randall M, Middleton S, Shaw L, et al. Stroke severity is a crucial predictor of outcome: An international prospective validation study. *Journal of the American Heart Association*. 2016;5

16. Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV, Pan W, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *Journal of the American Association*. 2013;309:2480-2488

17. Kamal N, Holodinsky JK, Stephenson C, Kashayp D, Demchuk AM, Hill MD, et al. Improving door-to-needle times for acute ischemic stroke: Effect of rapid patient registration, moving directly to computed tomography, and giving alteplase at the computed tomography scanner. *Circulation. Cardiovascular quality and outcomes*. 2017;10

18. Kamal N, Shand E, Swanson R, Hill MD, Jeerakathil T, Imoukhuede O, et al. Reducing door-to-needle times for ischaemic stroke to a median of 30 minutes at a community hospital. *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques*. 2019;46:51-56

19. Berkhemer OA, van Zwam WH, Dippel DW. Stent-retriever thrombectomy for stroke. *The New England journal of medicine*. 2015;373:1076

20. Saver JL, Goyal M, Diener HC. Stent-retriever thrombectomy for stroke. *The New England journal of medicine*. 2015;373:1077

21. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *The New England journal of medicine*. 2015;372:1009-1018

22. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *The New England journal of medicine*. 2015;372:2296-2306

23. Saver JL. Time is brain--quantified. *Stroke; a journal of cerebral circulation*. 2006;37:263-266

6.7 Supplemental Material

Supplemental Table II: Results from Logistic Regression Analysis of Mortality at 90 days

	Odds Ratio	**95 % CI lower limit**	**95 % CI lower limit**
Endovascular treatment given	0.76	0.47	1.24
Age	1.04	1.03	1.06
NIHSS	1.07	1.04	1.11
Endovascular treatment given	0.88	0.54	1.44
Age	1.05	1.03	1.06
NIHSS	1.07	1.03	1.11

Three missing values imputed with worst outcome (upper results) and best outcome (lower results). CI indicates confidence interval and NIHSS National Institutes of Health Stroke Scale.

CHAPTER 7 Thrombectomy vs. Medical Management in Low NIHSS Acute Anterior Circulation Stroke

This chapter is comprised of an original research article published online ahead of print in Neurology: Volny O, Zerna C*, Tomek A, Bar M, Rocek M, Padr R, Cihlar F, Nevsimalova M, Jurak L, Havlicek R, Kovar M, Sevcik P, Rohan V, Fiksa J, Cernik D, Jura D, Vaclavik D, Cimflova P, Puig J, Dowlatshahi D, Khaw AV, Fainardi E, Najm M, Demchuk AM, Menon BK, Mikulik R, Hill MD. Thrombectomy vs. Medical Management in Low NIHSS Acute Anterior Circulation Stroke. Neurology, First published September 28, 2020, DOI: https://doi.org/10.1212/WNL.0000000000010955. It aims to establish if endovascular treatment should be utilized for strokes presenting with milder symptoms using data from observational studies. Due to manuscript brevity, an expansion of the methods outlined here can be found in CHAPTER 4.*

CHAPTER 8 Discussion and Conclusions

8.1 Introduction

EVT for anterior circulation acute ischemic stroke due to large–vessel occlusion has been established as the new standard of care resulting in reduced disability compared to medical treatment based on multiple randomized clinical trials and a meta–analysis published in 2015 and 2016. Since then the use of EVT has been recommended by practice guidelines but they can only speak to the evidence provided by the randomized clinical trials and might not be appropriate when complex medical decisions need to consider the heterogeneity of patients in routine clinical care. Generalizing the results from randomized controlled trials to a broader patient population is often criticized and issues with this process have led to difficulties with knowledge translation to clinical practice. This dissertation aimed to assess the long–term sustainability of efficacy of EVT, to utilize post–stroke outcomes that are patient–centered and more meaningful to the affected individuals, and to investigate the effectiveness of EVT in patient populations that have not been part of the clinical trial cohort, most commonly older patients with comorbidities and patients presenting with mild stroke symptoms.

8.2 Key Findings

8.2.1 Comprehensive Assessment of Disability after Endovascular Treatment

The miFUNCTION scale was able to show greater granularity in the mild to moderately severe disability range overcoming the lack in sensitivity of the mRS at the minor disability end of the scale.[1] With that, the scale provides more insight in the patient's ability and capacity to engage in meaningful life roles which is the social dimension that has been emphasized by the

WHO when developing the patient–centered ICF. The miFUNCTION scale performed well on psychometric measurement assessment and had high construct and criterion validity. The assessment showed equal performance in a routine outpatient setting (the Stroke Prevention Clinic at Foothills Medical Centre in Calgary) as well as part of an acute randomized controlled trial that was conducted internationally (the ESCAPE trial). With further improvement, the miFUNCTION scale could be a useful alternative or addition to currently used outcome scales.

8.2.2 Comparative Effectiveness of Endovascular Treatment

In a complete case capture of the entire population in the province of Alberta reflecting real-world practice at a population level, adult patients undergoing EVT for acute ischemic stroke caused by a proximal vessel occlusion spent on average more than one week longer at home within the first 90 days compared with patients receiving medical treatment alone.[2] Home-time is a novel, health-economic, and patient-centered outcome that reflects health circumstances that are both easy to understand and meaningful to the patients, their caregivers or family, and the health system. It comprises the additional advantage of having complete ascertainment because home–time can be established through linkage with an administrative health database.

The strength of this study was that the complete source population was sampled and thus selection bias has been minimized. The real-world evidence of this study confirms the external validity of the randomized clinical trials, even though an attenuated effect size compared with the ESCAPE trial treatment group, for example, was observed. Still, these data in combination with other comparative effectiveness research are relevant to effectively translate the results of the randomized controlled trials to the greatest number of stroke patients possible and strengthen the evidence for EVT compared to medical treatment alone in patients with acute ischemic stroke

caused by LVO. The results should be generalizable to other provinces and territories across Canada and elsewhere if EVT is provided in similarly high-volume experienced centers and the patient population has similar racial diversity.

The non–modifiable predictors younger age and lower baseline stroke severity were associated with reduced 90–day home–time. Prolonged onset-to-treatment time was also associated with reduced 90–day home–time and as such, the process metric of onset-to-treatment time (and its counterpart door-to-needle time) can and should be used as the focus for stroke system performance improvement, which will result in improved patient outcomes, including longer home-time.

8.2.3 Endovascular Treatment for Stroke presenting with Mild Symptoms

The study of EVT for acute ischemic stroke due to LVO in patients presenting with low NIHSS resulted in similar proportions of excellent functional outcome at 90 days and all–cause 90–day mortality when compared to medical management. These results were observed despite an association of EVT treatment with neurological deterioration at 24 hours.

Multiple studies have shown that when low NIHSS patients with LVOs are left hyperacutely untreated (as they are often considered too mild for thrombolysis and EVT), up to one third end up disabled or dead at the 90–day follow–up. On the other hand, it is known that there is a clear relationship between recanalization and favorable or excellent outcome in patients with acute ischemic stroke due to LVO. The concern is that hyperacute treatment might cause possible harm and the benefit–risk–ratio is still unclear.

A well–designed randomized controlled trial would be able to finally answer the uncertainty regarding EVT for low NIHSS strokes.

8.3 Limitations

Limitations arise from the methodology and the data availability within each research project. The paragraphs below will outline them for each study that was undertaken.

8.3.1 Comprehensive Assessment of Disability after Endovascular Treatment

When trying to address the shortcomings of the mRS—the inter–observer variability that could be a source of misclassification error—the miFUNCTION scale does not outperform the mRS in its current adaption. Providing a decision tree with closed questions was predicted to favorably affect the inter–observer variability. However, looking at instances of disagreement between observers, it turned out that the majority of them were respondent–driven, meaning they likely resulted from the respondent's interpretation of the closed question. When developing the miFUNCTION scale, patients were only indirectly involved in the rating scales development since their feedback was relied through the allied healthcare providers that worked with them. This might be a reason that the ease with which patients can understand and interpret the closed questions being asked during the assessment has been overestimated. A possible way to improve on this would be to rephrase the questions in a consistent way to reduce the ambiguity and get feedback from patients directly or test the ease of understanding in a small pilot study. Another limitation is that no comment can be made on the sensitivity of the miFUNCTION tool to detect longitudinal changes in disability over time since the assessment in both the outpatient and randomized controlled trial setting were only done at one point in time. Additionally, previous studies in humans suggest that there is a three to six months window of heightened neuroplasticity and even a gradient of enhanced sensitivity to rehabilitation treatment beyond 12 month post stroke which could result in delayed functional recovery.[3] This means that any

outcome scale applied at three months post–stroke might miss some functional recovery that happens beyond this point. Furthermore, the miFUNCTION scale was predominantly used within a North American context and might not reflect the way disability is understood or experienced in other cultures.

8.3.2 Comparative Effectiveness of Endovascular Treatment

Although Canadians have universal access to publicly funded healthcare and thus their hospitalization and in-patient rehabilitation is covered, there might be costs they have to incur to actually return home (e.g. transportation to outpatient rehabilitation/doctor's offices/grocery stores, medical support devices, cleaning support for the home…) after a stroke. Home–time is a novel and patient-centered outcome, but it may not account for the amount of social and financial support that patients have available to return home and is thus a reflection of the average socioeconomic status of the province of Alberta. Comorbidity data were not available in the province–wide QuICR registry and so the outcome estimates could not be further adjusted. However, prior studies have shown that age, baseline stroke severity, and speed of treatment, variables that were available and thus included in the analysis, are the most important covariates that determine outcome after stroke. Data were also limited on the occurrence of intracranial hemorrhages and procedural complications which means that home–time is more of a global outcome assessment that includes any effect of the possible adverse effects of major treatment complications. The complete case capture of a whole province should allow for generalization to other provinces in Canada and globally, only limited by the population characteristics of Alberta and that EVT was performed in experienced high–volume centers which might not reflect the health system scenario elsewhere.

8.3.3 Endovascular Treatment for Stroke presenting with Mild Symptoms

The research project evaluating EVT in low NIHSS presenting acute ischemic stroke due to LVO is limited by its retrospective nature and even though confounding was controlled for by using advanced statistical methods, there is still a risk of residual confounding. For example, even though occlusion location was incorporated into the propensity score model, a measure of early ischemic change was not incorporated since these data were simply not available. Data on the occurrence of sICH were also not consistently available and could thus not be incorporated into the analysis. It is known and addressed in CHAPTER 5 that the mRS lacks sensitivity at the minor disability end of the scale. However, the three observational data sources utilized in this research project used the mRS since it is one of the most commonly used outcome markers in stroke. This might have reduced the power to detect a significant difference in the primary outcome measure. The sample size of the matched analysis is larger than those of prior studies but might still have negatively affected the statistical power to detect a true difference in the primary outcome between the patients who received EVT and the patients that received medical management.

8.4 Directions of Future Research

Mortality and morbidity remain high from acute ischemic stroke, the commonest neurological emergency. Although major advances have recently been made through clinical trials and alternate pieces of evidence, like the ones produced through this body of research, there is still much work to be done. As is common, more and new questions have arisen that will influence how future trials and studies will be designed. Owing to the safety and efficacy of the combined approach of IV alteplase and EVT, this treatment is the current standard of care in

daily practice as well as clinical trials. The key principles are intertwined and explained in the following paragraphs.

8.4.1 Treatment of Minor Stroke Patients with Large Vessel Occlusion

The treatment of patients with minor strokes varies globally, with some clinicians regarding treatment of minor stroke with thrombolysis or even EVT as a standard of care and others considering it to be an important unresolved research question. Patients with lower NIHSS scores can experience serious disability in the context of one's premorbid quality of life and activities. If left untreated, they are at risk of subsequent deterioration and disability, especially in the presence of a LVO where one in four patients suffers early neurologic deterioration resulting in poorer outcome.[4 - 7]

The Calgary–led and currently enrolling TEMPO–2 trial (NCT02398656) is investigating the use of low dose TNK (0.25 mg/kg) versus standard of care (antiplatelet treatment choice at the discretion of the investigator) in patients that present with a NIHSS score of < 6 and an ASPECTS > 7 within 12 hours from symptom onset. A total of 1274 patients will be enrolled and the primary endpoint is a responder analysis where return to the baseline level of neurological functioning is defined as follows: if pre–morbid mRS is 0–1 then mRS 0–1 at 90 days is a good outcome. If pre–morbid mRS is 2 then mRS 0–2 is considered a good outcome. As discussed previously, the mRS lacks sensitivity at the lower disability end because the number of categories makes it difficult to detect small improvements even though they might have occurred. TEMPO-2 and other minor stroke studies could benefit from using the miFUNCTON scale that was evaluated in CHAPTER 5 as an outcome measure as the tool shows greater granularity in the mild to moderately–severe disability range after a stroke and thus

provides more insight into both the patient's ability and capacity to engage in meaningful life roles. Reducing the inter–rater variability might be achieved by extending the algorithm of miFUNCTION to include fixed phrased questions/concise descriptions.

The propensity-score matched analysis of EVT compared to best medical management for large vessel anterior circulation occlusion in patients presenting with minor stroke in CHAPTER 7 resulted in similar proportions of excellent functional outcome at 90 days and comparable all–cause 90–day mortality. The potential benefit of EVT in this setting is known through the clear relationship between recanalization and favorable/excellent outcome but the hyperacute treatment has possible harm that has not been well assessed in observational studies yet. The currently recruiting Endovascular Therapy for Low NIHSS Ischemic Strokes (ENDOLOW) trial (NCT04167527) tests the hypothesis that patients presenting within eight hours of onset with acute ischemic stroke due proximal LVO and low baseline stroke severity scores (NIHSS 0–5) will have better 90–day clinical outcomes (mRS distribution) with immediate EVT compared to initial medical management. The estimated sample size of this North–American based trial will be 200 patients and study completion is anticipated to occur in early 2021. Additionally, the French Minor Stroke Therapy Evaluation (MOSTE) trial (NCT03796468) will evaluate EVT in LVO acute ischemic stroke with minor symptoms (NIHSS < 6) in patients last seen well within 24 Hours. This trial has just started recruitment in June 2020 and is planning to enroll 824 patients. The methodology papers have not been published yet but if these two trials are well-designed and executed, they will hopefully be able finally answer the question about the risk–benefit–ratio of EVT for low NIHSS strokes.

8.4.2 Treatment of Late Presenting Patients with Large Vessel Occlusion

Advanced imaging and the *tissue window* are the key physiological markers in acute ischemic stroke and should guide patient selection for clinical trials, now also considering unwitnessed strokes or strokes–on–awakening. Individual patient level data drawing from the five randomized controlled trials revealed that while mechanical thrombectomy, performed in the vast majority of cases with stent retrievers and within six hours of time last seen well, is associated with a strong overall treatment effect, the benefit of this approach declines with increasing time from stroke onset to substantial reperfusion. Indeed, the HERMES collaborators reported that at 7.3 hours from time–last–seen–well to achievement of reperfusion, statistically significant evidence of average benefit from endovascular therapy can no longer be demonstrated.[8] The DAWN trial showed that thrombectomy (with the TREVO device) plus medical management lead to superior clinical outcomes at 90 days compared to medical management alone in acute ischemic stroke due to proximal anterior circulation occlusion when treatment is initiated within 6–24 hours of last seen normal. Selection with CTP or DWI-MRI to identify potentially salvageable brain tissue and a small ischemic core was required.[9] There was a statistically significant 73 % relative risk reduction of dependency in activities of daily living (ADL) favoring the intervention arm. The co–primary endpoint of favorable outcome (mRS 0–2) at day 90 was reached by 48.6 % in the intervention arm but only 13.1 % in the control arm, which was again statistically significant.[10] Similarly, the DEFUSE–3 study, examining a 6–16 hour onset–to–treatment time window using CTP imaging for patient selection has been halted early for efficacy and showed that EVT was associated with a favorable shift in the distribution of functional outcomes on the mRS at 90 days (OR 2.77; $P < 0.001$).[11] Patients had to present

with a favorable ischemic core–to–penumbra ratio to be eligible. Although the DAWN and DEFUSE–3 trial showed that mechanical thrombectomy in the late window is safe, the imaging criteria the trials employed are likely to be conservative in selecting patients.[12] The resulting selective patient cohorts are thus not reflective of the majority of patients presenting with an acute ischemic stroke due to proximal vessel occlusion beyond six hours from time–last–seen–well. Therefore, a Calgary–led multicenter retrospective cohort study of patients treated beyond six hours from time last seen normal using EVT in clinical routine between February 2015 and December 2017 is currently underway. A total of eleven centers in Canada, the United States, Germany, and Australia are participating. The primary outcome is the mRS score at 90 days and safety outcomes are the proportion of sICH after treatment and procedural complications from the EVT. Results are expected in 2021 and will provide information about expanding EVT to patients presenting in a later time window.

8.4.3 Adjuvant Therapies for Patients with Large Vessel Occlusion

Therapies directed at different molecular components of the ischemic cascade in an attempt to prevent ischemic tissue from progressing to irreversible infarction are summarized under the term neuroprotective strategy of acute ischemic stroke treatment. So far, a fundamental problem of translating promising pre-clinical findings of over 1000 agents into usable therapies has been the fact that for the longest time human community–onset stroke due to large artery occlusion has been essentially a permanent occlusion model. In the preclinical models, neuroprotective strategies have been only minimally effective, if at all, in permanent occlusion models. With endovascular therapy as the new standard of care, a human analog of the preclinical transient ischemia–reperfusion model has been created.[13] These advances in IV and

intra–arterial therapy for acute ischemic stroke will have a profound effect on how neuroprotection should be considered.[14] Agents that were previously abandoned might find renewed applicability and new molecules such as the peptide drug, NA–1 (also known as Tat–NR2B9c), which reduced the volume of strokes after MCA occlusion in both rodents and non–human primates as well as the volume and number of strokes after the intra–arterial injection of small emboli in non–human primates, could be tested.[15, 16] The Evaluating Neuroprotection in Aneurysm Coiling Therapy (ENACT) trial, a multicentre randomized study including 185 human subjects to receive either single IV infusion of NA–1 or saline control at the termination of the endovascular procedure, showed that neuroprotection in human acute ischemic stroke is achievable.[17] The subsequent and recently completed Calgary–led ESCAPE–NA1 trial showed that the proportion of patients achieving good functional outcome at 90 days after EVT was not improved by nerinetide compared to placebo but there was effect modification resulting in the inhibition of treatment effect in patients receiving alteplase.[18] Since there was benefit in the subgroup of patients that did not receive alteplase, a future Calgary-led trial will focus on testing the hypothesis that nerinetide is safe and effective in reducing global disability in these patients and possibly provide a viable adjuvant therapy for alteplase–ineligible patient on route to the ECC.

8.5 Clinical Practice Guidelines

The goal of research must be actionable data that have been derived in a transparent and objective way (with acknowledgement of methodological limitations) to inform clinical decision making. Such decisions should be supported by clinical practice guidelines, which have been developed by panels of experts with access to the available evidence, an understanding of the

clinical problem, and research methods.[19] Since the 1970s various systems for grading of evidence have been used but provided different results and many implicit decisions went into the process. Most often the study design was the decisive factor in these approaches. However, randomized controlled trials are not always feasible and, in some instances, observational studies may provide better evidence. This is for example the case when looking into rare adverse effects of an exposure, if an exposure cannot be randomized, and when complimentary evidence in more heterogeneous patient populations is needed In more recent years, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach has tackled the shortcomings of these various systems and assists clinical practice guideline developers in summarizing evidence for a recommendation in a standardized and transparent matter.[20] In an initial step, even though randomized controlled trials start off with a higher grade of evidence than observational studies or other types of evidence, this grade is decreased if limitations (e.g. in study quality, consistency, directness, precision, bias) exist or increased if strengths (e.g. strength of association, dose response gradient, well-controlled confounding) can be detected. After additionally considering the balance of benefits and harms as well as benefits and costs, a strength of recommendation – that is, the extent to which one can be confident that adherence will do more good than harm – will be given.[20] The GRADE approach takes study design and quality into account such that well-designed observational studies have a chance to contribute as much to clinical decision and policy making as once were only randomized controlled trials able to do.

8.6 Conclusion

This thesis provides a greater understanding of how the benefits and risks of EVT might vary across the population and differ from the rather homogenous patient cohort that has been assessed in the randomized controlled trials. The results of this research will be meaningful to individual patients who experience acute ischemic strokes caused by LVO and also aid with economic and regulatory decisions to more broadly offer and organize EVT across the province of Alberta and beyond.

8.7 References

1. Zerna C, Burley T, Green TL, Dukelow SP, Demchuk AM, Hill MD. Comprehensive assessment of disability post-stroke using the newly developed mifunction scale. *International journal of stroke: official journal of the International Stroke Society*. 2020;15:167-174

2. Zerna C, Rogers E, Rabi DM, Demchuk AM, Kamal N, Mann B, et al. Comparative effectiveness of endovascular treatment for acute ischemic stroke: A population-based analysis. *Journal of the American Heart Association*. 2020;9:e014541

3. Ballester BR, Maier M, Duff A, Cameirao M, Bermudez S, Duarte E, et al. A critical time window for recovery extends beyond one-year post-stroke. *Journal of neurophysiology*. 2019;122:350-357

4. Kim JT, Park MS, Chang J, Lee JS, Choi KH, Cho KH. Proximal arterial occlusion in acute ischemic stroke with low nihss scores should not be considered as mild stroke. *PloS one*. 2013;8:e70996

5. Rajajee V, Kidwell C, Starkman S, Ovbiagele B, Alger JR, Villablanca P, et al. Early mri and outcomes of untreated patients with mild or improving ischemic stroke. *Neurology*. 2006;67:980-984

6. Coutts SB, Modi J, Patel SK, Demchuk AM, Goyal M, Hill MD. Ct/ct angiography and mri findings predict recurrent stroke after transient ischemic attack and minor stroke: Results of the prospective catch study. *Stroke; a journal of cerebral circulation*. 2012;43:1013-1017

7. Coutts SB, Modi J, Patel SK, Aram H, Demchuk AM, Goyal M, et al. What causes disability after transient ischemic attack and minor stroke?: Results from the ct and mri in the triage of tia and minor cerebrovascular events to identify high risk patients (catch) study. *Stroke; a journal of cerebral circulation*. 2012;43:3018-3022

8. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet (London, England)*. 2016;387:1723-1731

9. Jovin TG, Saver JL, Ribo M, Pereira V, Furlan A, Bonafe A, et al. Diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention with trevo (dawn) trial methods. *International journal of stroke : official journal of the International Stroke Society*. 2017:1747493017710341

10. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *The New England journal of medicine*. 2018;378:11-21

11. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *The New England journal of medicine*. 2018;378:708-718

12. Evans JW, Graham BR, Pordeli P, Al-Ajlan FS, Willinsky R, Montanera WJ, et al. Time for a time window extension: Insights from late presenters in the escape trial. *AJNR. American journal of neuroradiology*. 2017

13. Klourfeld E, Zerna C, Al-Ajlan FS, Kamal N, Randhawa P, Yu AY, et al. The future of endovascular treatment: Insights from the escape investigators. *International journal of stroke : official journal of the International Stroke Society*. 2016;11:156-163

14. Henninger N, Fisher M. Extending the time window for endovascular and pharmacological reperfusion. *Translational stroke research.* 2016;7:284-293

15. Bratane BT, Cui H, Cook DJ, Bouley J, Tymianski M, Fisher M. Neuroprotection by freezing ischemic penumbra evolution without cerebral blood flow augmentation with a postsynaptic density-95 protein inhibitor. *Stroke; a journal of cerebral circulation*. 2011;42:3265-3270

16. Cook DJ, Teves L, Tymianski M. Treatment of stroke with a psd-95 inhibitor in the gyrencephalic primate brain. *Nature*. 2012;483:213-217

17. Hill MD, Martin RH, Mikulis D, Wong JH, Silver FL, Terbrugge KG, et al. Safety and efficacy of na-1 in patients with iatrogenic stroke after endovascular aneurysm repair (enact): A phase 2, randomised, double-blind, placebo-controlled trial. The Lancet. *Neurology*. 2012;11:942-950

18. Hill MD, Goyal M, Menon BK, Nogueira RG, McTaggart RA, Demchuk AM, et al. Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (escape-na1): A multicentre, double-blind, randomised controlled trial. *Lancet (London, England)*. 2020;395:878-887

19. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. for the GRADE Working Group. Grading quality of evidence and strength of recommendations. *British Medical Journal*. 2004,;328:1490.

20. Kredo T, Bernhardsson S, Machingaidze S, Young T, Louw Q, Ochodo E, et al.. Guide to clinical practice guidelines: the current state of play. *International Journal for Quality in Health Care*. 2016;28:122-128.

Alphabetical Bibliography

Ahmad O, Wardlaw J, Whiteley WN. Correlation of levels of neuronal and glial markers with radiological measures of infarct volume in ischaemic stroke: A systematic review. *Cerebrovascular diseases (Basel, Switzerland)*. 2012;33:47-54

Akaike H. A new look at the statistical model identification. *IEEE Transactions on Automatic Control*. 1974;19:716-723

Albers GW, Caplan LR, Easton JD, Fayad PB, Mohr JP, Saver JL, et al. Transient ischemic attack--proposal for a new definition. *The New England journal of medicine*. 2002;347:1713-1716

Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *The New England journal of medicine*. 2018;378:708-718

Albers GW, von Kummer R, Truelsen T, Jensen JK, Ravn GM, Gronning BA, et al. Safety and efficacy of desmoteplase given 3-9 h after ischaemic stroke in patients with occlusion or high-grade stenosis in major cerebral arteries (dias-3): A double-blind, randomised, placebo-controlled phase 3 trial. *The Lancet. Neurology*. 2015;14:575-584

Altman DG, Royston P. The cost of dichotomising continuous variables. *BMJ (Clinical research ed.)*. 2006;332:1080

Armstrong BG, Sloan M. Ordinal regression models for epidemiologic data. *American journal of epidemiology*. 1989;129:191-204

Asdaghi N, Yavagal DR, Wang K, Mueller-Kronast N, Bhatt N, Gardener HE, et al. Patterns and outcomes of endovascular therapy in mild stroke. *Stroke; a journal of cerebral circulation*. 2019;50:2101-2107

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. for the GRADE Working Group. Grading quality of evidence and strength of recommendations. *British Medical Journal*. 2004,;328:1490.

Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Statistics in Medicine*. 2009;28:3083-3107.

Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. *Statistics in Medicine*. 2006;25:2084-2106.

Ballester BR, Maier M, Duff A, Cameirao M, Bermudez S, Duarte E, et al. A critical time window for recovery extends beyond one-year post-stroke. *Journal of neurophysiology*. 2019;122:350-357

Bang OY. Intracranial atherosclerosis: Current understanding and perspectives. *Journal of stroke*. 2014;16:27-35

Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. Aspects study group. Alberta stroke programme early ct score. *Lancet (London, England)*. 2000;355:1670-1674

Barber PA, Hill MD, Eliasziw M, Demchuk AM, Pexman JH, Hudon ME, et al. Imaging of the brain in acute ischaemic stroke: Comparison of computed tomography and magnetic resonance diffusion-weighted imaging. *Journal of neurology, neurosurgery, and psychiatry*. 2005;76:1528-1533

Barber PA, Zhang J, Demchuk AM, Hill MD, Buchan AM. Why are stroke patients excluded from tpa therapy? An analysis of patient eligibility. *Neurology*. 2001;56:1015-1020

Barlinn K, Tsivgoulis G, Barreto AD, Alleman J, Molina CA, Mikulik R, et al. Outcomes following sonothrombolysis in severe acute ischemic stroke: Subgroup analysis of the clotbust trial. *International journal of stroke : official journal of the International Stroke Society*. 2014;9:1006-1010

Bath PM, Lees KR, Schellinger PD, Altman H, Bland M, Hogg C, et al. Statistical analysis of the primary outcome in acute stroke trials. *Stroke; a journal of cerebral circulation*. 2012;43:1171-1178

Berge E, Cohen G, Lindley RI, Sandercock P, Wardlaw JM, Sandset EC, et al. Effects of blood pressure and blood pressure-lowering treatment during the first 24 hours among patients in the third international stroke trial of thrombolytic treatment for acute ischemic stroke. *Stroke; a journal of cerebral circulation*. 2015;46:3362-3369

Berkhemer OA, van Zwam WH, Dippel DW. Stent-retriever thrombectomy for stroke. *The New England journal of medicine*. 2015;373:1076

Binning MJ, Bartolini B, Baxter B, Budzik R, English J, Gupta R, et al. Trevo 2000: Results of a large real-world registry for stent retriever for acute ischemic stroke. *Journal of the American Heart Association*. 2018;7:e010867

Bivard A, Huang X, Levi CR, Spratt N, Campbell BCV, Cheripelli BK, et al. Tenecteplase in ischemic stroke offers improved recanalization: Analysis of 2 trials. *Neurology*. 2017;89:62-67

Bivard A, Kleinig T, Miteff F, Butcher K, Lin L, Levi C, et al. Ischemic core thresholds change with time to reperfusion: A case control study. *Annals of neurology*. 2017;82:995-1003

Bluhmki E, Chamorro A, Davalos A, Machnig T, Sauce C, Wahlgren N, et al. Stroke treatment with alteplase given 3.0-4.5 h after onset of acute ischaemic stroke (ecass iii): Additional outcomes and subgroup analysis of a randomised controlled trial. *The Lancet. Neurology*. 2009;8:1095-1102

Bouffioulx E, Arnould C, Thonnard JL. Satisfaction with activity and participation and its relationships with body functions, activities, or environmental factors in stroke patients. *Archives of physical medicine and rehabilitation*. 2011;92:1404-1410

Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (thrace): A randomised controlled trial. *The Lancet. Neurology*. 2016;15:1138-1147

Bratane BT, Cui H, Cook DJ, Bouley J, Tymianski M, Fisher M. Neuroprotection by freezing ischemic penumbra evolution without cerebral blood flow augmentation with a postsynaptic density-95 protein inhibitor. *Stroke; a journal of cerebral circulation*. 2011;42:3265-3270

Broderick JP, Adeoye O, Elm J. Evolution of the modified rankin scale and its use in future stroke trials. *Stroke; a journal of cerebral circulation*. 2017;48:2007-2012

Brott TG, Haley EC, Jr., Levy DE, Barsan W, Broderick J, Sheppard GL, et al. Urgent therapy for stroke. Part i. Pilot study of tissue plasminogen activator administered within 90 minutes. *Stroke; a journal of cerebral circulation*. 1992;23:632-640

Caliendo M, Kopeinig S. Some practical guidance for the implementation of propensity score matching. *Journal of Economic Surveys*. 2008;22:31-72

Campbell BC, Christensen S, Levi CR, Desmond PM, Donnan GA, Davis SM, et al. Cerebral blood flow is the optimal ct perfusion parameter for assessing infarct core. *Stroke; a journal of cerebral circulation*. 2011;42:3435-3440

Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *The New England journal of medicine*. 2015;372:1009-1018

Campbell BC, Yassi N, Ma H, Sharma G, Salinas S, Churilov L, et al. Imaging selection in ischemic stroke: Feasibility of automated ct-perfusion analysis. *International journal of stroke : official journal of the International Stroke Society*. 2015;10:51-54

Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *The New England journal of medicine*. 2018;378:1573-1582

Campbell BCV, van Zwam WH, Goyal M, Menon BK, Dippel DWJ, Demchuk AM, et al. Effect of general anaesthesia on functional outcome in patients with anterior circulation ischaemic stroke having endovascular thrombectomy versus standard care: A meta-analysis of individual patient data. *The Lancet. Neurology*. 2018;17:47-53

Candelise L, Gattinoni M, Bersano A, Micieli G, Sterzi R, Morabito A. Stroke-unit care for acute stroke patients: An observational follow-up study. *Lancet (London, England)*. 2007;369:299-305

Casaubon LK, Boulanger JM, Blacquiere D, Boucher S, Brown K, Goddard T, et al. Canadian stroke best practice recommendations: Hyperacute stroke care guidelines, update 2015. *International journal of stroke : official journal of the International Stroke Society*. 2015;10:924-940

Cereda CW, Christensen S, Campbell BC, Mishra NK, Mlynash M, Levi C, et al. A benchmarking tool to evaluate computer tomography perfusion infarct core predictions against a dwi standard. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2016;36:1780-1789

Charidimou A, Pasi M, Fiorelli M, Shams S, von Kummer R, Pantoni L, et al. Leukoaraiosis, cerebral hemorrhage, and outcome after intravenous thrombolysis for acute ischemic stroke: A meta-analysis (v1). *Stroke; a journal of cerebral circulation*. 2016;47:2364-2372

Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The atlantis study: A randomized controlled trial. Alteplase thrombolysis for acute noninterventional therapy in ischemic stroke. *Journal of the american medical association*. 1999;282:2019-2026

Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *The New England journal of medicine*. 2000;342:1887-1892

Cook DJ, Teves L, Tymianski M. Treatment of stroke with a psd-95 inhibitor in the gyrencephalic primate brain. *Nature*. 2012;483:213-217

Coutts SB, Dubuc V, Mandzia J, Kenney C, Demchuk AM, Smith EE, et al. Tenecteplase-tissue-type plasminogen activator evaluation for minor ischemic stroke with proven occlusion. *Stroke; a journal of cerebral circulation*. 2015;46:769-774

Coutts SB, Modi J, Patel SK, Aram H, Demchuk AM, Goyal M, et al. What causes disability after transient ischemic attack and minor stroke?: Results from the ct and mri in the triage of tia and minor cerebrovascular events to identify high risk patients (catch) study. *Stroke; a journal of cerebral circulation*. 2012;43:3018-3022

Coutts SB, Modi J, Patel SK, Demchuk AM, Goyal M, Hill MD. Ct/ct angiography and mri findings predict recurrent stroke after transient ischemic attack and minor stroke: Results of the prospective catch study. *Stroke; a journal of cerebral circulation*. 2012;43:1013-1017

Cragg JG. Some statistical models for limited dependent variables with application to the demand for durable goods. *Econometrica*. 1971;39:829-844

D'Agostino RB, Kwan H. Measuring effectiveness. What to expect without a randomized control group. *Medical care*. 1995;33:As95-105

Dargazanli C, Arquizan C, Gory B, Consoli A, Labreuche J, Redjem H, et al. Mechanical thrombectomy for minor and mild stroke patients harboring large vessel occlusion in the anterior circulation: A multicenter cohort study. *Stroke; a journal of cerebral circulation*. 2017;48:3274-3281

Davalos A, Cobo E, Molina CA, Chamorro A, de Miquel MA, Roman LS, et al. Safety and efficacy of thrombectomy in acute ischaemic stroke (revascat): 1-year follow-up of a randomised open-label trial. *The Lancet. Neurology*. 2017;16:369-376

Davis MJ, Menon BK, Baghirzada LB, Campos-Herrera CR, Goyal M, Hill MD, et al. Anesthetic management and outcome in patients during endovascular therapy for acute stroke. *Anesthesiology*. 2012;116:396-405

Dawson NV, Weiss R. Dichotomizing continuous variables in statistical analysis: A practice to avoid. *Medical decision making : an international journal of the Society for Medical Decision Making*. 2012;32:225-226

d'Esterre CD, Boesen ME, Ahn SH, Pordeli P, Najm M, Minhas P, et al. Time-dependent computed tomographic perfusion thresholds for patients with acute ischemic stroke. *Stroke; a journal of cerebral circulation*. 2015;46:3390-3397

Diedler J, Ahmed N, Sykora M, Uyttenboogaart M, Overgaard K, Luijckx GJ, et al. Safety of intravenous thrombolysis for acute ischemic stroke in patients receiving antiplatelet therapy at stroke onset. *Stroke; a journal of cerebral circulation*. 2010;41:288-294

Dzialowski I, Hill MD, Coutts SB, Demchuk AM, Kent DM, Wunderlich O, et al. Extent of early ischemic changes on computed tomography (ct) before thrombolysis: Prognostic value of the alberta stroke program early ct score in ecass ii. *Stroke; a journal of cerebral circulation*. 2006;37:973-978

Ebinger M, Winter B, Wendt M, Weber JE, Waldschmidt C, Rozanski M, et al. Effect of the use of ambulance-based thrombolysis on time to thrombolysis in acute ischemic stroke: A randomized clinical trial. *Journal of the american medical association*. 2014;311:1622-1631

Edwards DF, Hahn MG, Baum CM, Perlmutter MS, Sheedy C, Dromerick AW. Screening patients with stroke for rehabilitation needs: Validation of the post-stroke rehabilitation guidelines. *Neurorehabilitation and neural repair*. 2006;20:42-48

Ellis-Hill C, Robison J, Wiles R, McPherson K, Hyndman D, Ashburn A. Going home to get on with life: Patients and carers experiences of being discharged from hospital following a stroke. *Disability and rehabilitation*. 2009;31:61-72

Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. *Lancet (London, England)*. 2014;384:1929-1935

Ernst E, Pittler MH. Efficacy or effectiveness? *Journal of internal medicine*. 2006;260:488-490

Etherton MR, Barreto AD, Schwamm LH, Wu O. Neuroimaging paradigms to identify patients for reperfusion therapy in stroke of unknown onset. *Frontiers in neurology*. 2018;9:327

Evans JW, Graham BR, Pordeli P, Al-Ajlan FS, Willinsky R, Montanera WJ, et al. Time for a time window extension: Insights from late presenters in the escape trial. *AJNR. American journal of neuroradiology*. 2017

Fletcher AP, Alkjaersig N, Lewis M, Tulevski V, Davies A, Brooks JE, et al. A pilot study of urokinase therapy in cerebral infarction. *Stroke; a journal of cerebral circulation*. 1976;7:135-142

Fonarow GC, Liang L, Thomas L, Xian Y, Saver JL, Smith EE, et al. Assessment of home-time after acute ischemic stroke in medicare beneficiaries. *Stroke; a journal of cerebral circulation*. 2016;47:836-842

Fonarow GC, Zhao X, Smith EE, Saver JL, Reeves MJ, Bhatt DL, et al. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. *Journal of the american medical association*. 2014;311:1632-1640

Frieden TR. Evidence for health decision making - beyond randomized, controlled trials. *The New England journal of medicine*. 2017;377:465-475

Furlan AJ, Eyding D, Albers GW, Al-Rawi Y, Lees KR, Rowley HA, et al. Dose escalation of desmoteplase for acute ischemic stroke (dedas): Evidence of safety and efficacy 3 to 9 hours after stroke onset. *Stroke; a journal of cerebral circulation*. 2006;37:1227-1231

Gardner W, Mulvey EP, Shaw EC. Regression analyses of counts and rates: Poisson, overdispersed poisson, and negative binomial models. *Psychological bulletin*. 1995;118:392-404

Geurts M, Scheijmans FE, van Seeters T, Biessels GJ, Kappelle LJ, Velthuis BK, et al. Temporal profile of body temperature in acute ischemic stroke: Relation to infarct size and outcome. *BMC neurology*. 2016;16:233

Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *The New England journal of medicine*. 2015;372:1019-1030

Goyal M, Fargen KM, Menon BK. Acute stroke, bayes' theorem and the art and science of emergency decision-making. *Journal of neurointerventional surgery*. 2014;6:256-259

Goyal M, Jadhav AP, Bonafe A, Diener H, Mendes Pereira V, Levy E, et al. Analysis of workflow and time to treatment and the effects on outcome in endovascular treatment of acute ischemic stroke: Results from the swift prime randomized controlled trial. *Radiology*. 2016;279:888-897

Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet (London, England)*. 2016;387:1723-1731

Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, et al. Cerebral microbleeds: A guide to detection and interpretation. *The Lancet. Neurology*. 2009;8:165-174

Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovascular diseases (Basel, Switzerland)*. 2008;25:457-507

Gupta AC, Schaefer PW, Chaudhry ZA, Leslie-Mazwi TM, Chandra RV, Gonzalez RG, et al. Interobserver reliability of baseline noncontrast ct alberta stroke program early ct score for intra-arterial stroke treatment selection. *AJNR. American journal of neuroradiology*. 2012;33:1046-1049

Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, et al. The desmoteplase in acute ischemic stroke trial (dias): A phase ii mri-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke; a journal of cerebral circulation*. 2005;36:66-73

Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, et al. Association of outcome with early stroke treatment: Pooled analysis of atlantis, ecass, and ninds rt-pa stroke trials. *Lancet (London, England)*. 2004;363:768-774

Hacke W, Furlan AJ, Al-Rawi Y, Davalos A, Fiebach JB, Gruber F, et al. Intravenous desmoteplase in patients with acute ischaemic stroke selected by mri perfusion-diffusion weighted imaging or perfusion ct (dias-2): A prospective, randomised, double-blind, placebo-controlled study. *The Lancet. Neurology*. 2009;8:141-150

Hasan N, McColgan P, Bentley P, Edwards RJ, Sharma P. Towards the identification of blood biomarkers for acute stroke in humans: A comprehensive systematic review. *British journal of clinical pharmacology*. 2012;74:230-240

Hastrup S, Damgaard D, Johnsen SP, Andersen G. Prehospital acute stroke severity scale to predict large artery occlusion: Design and comparison with other scales. *Stroke; a journal of cerebral circulation*. 2016;47:1772-1776

Haussen DC, Lima FO, Bouslama M, Grossberg JA, Silva GS, Lev MH, et al. Thrombectomy versus medical management for large vessel occlusion strokes with minimal symptoms: An analysis from stopstroke and gestor cohorts. *Journal of neurointerventional surgery*. 2018;10:325-329

Heldner MR, Zubler C, Mattle HP, Schroth G, Weck A, Mono ML, et al. National institutes of health stroke scale score and vessel occlusion in 2152 patients with acute ischemic stroke. *Stroke; a journal of cerebral circulation*. 2013;44:1153-1157

Hemphill JF. Interpreting the magnitudes of correlation coefficients. *The American psychologist*. 2003;58:78-79

Henninger N, Fisher M. Extending the time window for endovascular and pharmacological reperfusion. *Translational stroke research*. 2016;7:284-293

Hernandez-Perez M, Puig J, Blasco G, Perez de la Ossa N, Dorado L, Davalos A, et al. Dynamic magnetic resonance angiography provides collateral circulation and hemodynamic information in acute ischemic stroke. *Stroke; a journal of cerebral circulation*. 2016;47:531-534

Hill MD, Demchuk AM, Goyal M, Jovin TG, Foster LD, Tomsick TA, et al. Alberta stroke program early computed tomography score to select patients for endovascular treatment: Interventional management of stroke (ims)-iii trial. *Stroke; a journal of cerebral circulation*. 2014;45:444-449

Hill MD, Goyal M, Menon BK, Nogueira RG, McTaggart RA, Demchuk AM, et al. Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (escape-na1): A multicentre, double-blind, randomised controlled trial. *Lancet (London, England)*. 2020;395:878-887

Hill MD, Martin RH, Mikulis D, Wong JH, Silver FL, Terbrugge KG, et al. Safety and efficacy of na-1 in patients with iatrogenic stroke after endovascular aneurysm repair (enact): A phase 2, randomised, double-blind, placebo-controlled trial. *The Lancet. Neurology*. 2012;11:942-950

Holodinsky JK, Williamson TS, Kamal N, Mayank D, Hill MD, Goyal M. Drip and ship versus direct to comprehensive stroke center: Conditional probability modeling. *Stroke; a journal of cerebral circulation*. 2017;48:233-238

Howard G, Waller JL, Voeks JH, Howard VJ, Jauch EC, Lees KR, et al. A simple, assumption-free, and clinically interpretable approach for analysis of modified rankin outcomes. *Stroke; a journal of cerebral circulation*. 2012;43:664-669

Irving M, Eramudugolla R, Cherbuin N, Anstey KJ. A critical review of grading systems: Implications for public health policy. *Evaluation & the health professions*. 2017;40:244-262

Jansen IGH, Mulder M, Goldhoorn RB. Endovascular treatment for acute ischaemic stroke in routine clinical practice: Prospective, observational cohort study (mr clean registry). *BMJ (Clinical research ed.)*. 2018;360:k949

Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *The New England journal of medicine*. 2015;372:2296-2306

Jovin TG, Saver JL, Ribo M, Pereira V, Furlan A, Bonafe A, et al. Diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention with trevo (dawn) trial methods. *International journal of stroke : official journal of the International Stroke Society*. 2017:1747493017710341

Kamal N, Holodinsky JK, Stephenson C, Kashayp D, Demchuk AM, Hill MD, et al. Improving door-to-needle times for acute ischemic stroke: Effect of rapid patient registration, moving directly to computed tomography, and giving alteplase at the computed tomography scanner. *Circulation. Cardiovascular quality and outcomes*. 2017;10

Kamal N, Rogers E, Stang J, Mann B, Butcher KS, Rempel J, et al. One-year healthcare utilization for patients that received endovascular treatment compared with control. *Stroke; a journal of cerebral circulation*. 2019;50:1883-1886

Kamal N, Shand E, Swanson R, Hill MD, Jeerakathil T, Imoukhuede O, et al. Reducing door-to-needle times for ischaemic stroke to a median of 30 minutes at a community hospital. *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques*. 2019;46:51-56

Kane I, Carpenter T, Chappell F, Rivers C, Armitage P, Sandercock P, et al. Comparison of 10 different magnetic resonance perfusion imaging processing methods in acute ischemic stroke: Effect on lesion size, proportion of patients with diffusion/perfusion mismatch, clinical scores, and radiologic outcomes. *Stroke; a journal of cerebral circulation*. 2007;38:3158-3164

Khatri P, Abruzzo T, Yeatts SD, Nichols C, Broderick JP, Tomsick TA. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. *Neurology*. 2009;73:1066-1072

Kim JT, Park MS, Chang J, Lee JS, Choi KH, Cho KH. Proximal arterial occlusion in acute ischemic stroke with low nihss scores should not be considered as mild stroke. *PloS one*. 2013;8:e70996

Kleiber C, Zeileis A. Visualizing count data regressions using rootograms. *The American Statistician*. 2016;70:296-303

Klourfeld E, Zerna C, Al-Ajlan FS, Kamal N, Randhawa P, Yu AY, et al. The future of endovascular treatment: Insights from the escape investigators. *International journal of stroke : official journal of the International Stroke Society*. 2016;11:156-163

Kredo T, Bernhardsson S, Machingaidze S, Young T, Louw Q, Ochodo E, et al.. Guide to clinical practice guidelines: the current state of play. *International Journal for Quality in Health Care*. 2016;28:122-128.

Kukull WA, Ganguli M. Generalizability: The trees, the forest, and the low-hanging fruit. *Neurology*. 2012;78:1886-1891

Kwiatkowski TG, Libman RB, Frankel M, Tilley BC, Morgenstern LB, Lu M, et al. Effects of tissue plasminogen activator for acute ischemic stroke at one year. National institute of neurological disorders and stroke recombinant tissue plasminogen activator stroke study group. *The New England journal of medicine*. 1999;340:1781-1787

Kwon S, Hartzema AG, Duncan PW, Min-Lai S. Disability measures in stroke: Relationship among the barthel index, the functional independence measure, and the modified rankin scale. *Stroke; a journal of cerebral circulation*. 2004;35:918-923

Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33:159-174

Lapergue B, Blanc R, Gory B, Labreuche J, Duhamel A, Marnat G, et al. Effect of endovascular contact aspiration vs stent retriever on revascularization in patients with acute ischemic stroke and large vessel occlusion: The aster randomized clinical trial. *Journal of the american medical association*. 2017;318:443-452

Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al. Time to treatment with intravenous alteplase and outcome in stroke: An updated pooled analysis of ecass, atlantis, ninds, and epithet trials. *Lancet (London, England)*. 2010;375:1695-1703

Lindley RI, Wardlaw JM, Whiteley WN, Cohen G, Blackwell L, Murray GD, et al. Alteplase for acute ischemic stroke: Outcomes by clinically important subgroups in the third international stroke trial. *Stroke; a journal of cerebral circulation*. 2015;46:746-756

Logallo N, Novotny V, Assmus J, Kvistad CE, Alteheld L, Ronning OM, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (nor-test): A phase 3, randomised, open-label, blinded endpoint trial. *The Lancet. Neurology*. 2017;16:781-788

Maas MB, Furie KL, Lev MH, Ay H, Singhal AB, Greer DM, et al. National institutes of health stroke scale score is poorly predictive of proximal occlusion in acute cerebral ischemia. *Stroke; a journal of cerebral circulation*. 2009;40:2988-2993

McDermid I, Barber M, Dennis M, Langhorne P, Macleod MJ, McAlpine CH, et al. Home-time is a feasible and valid stroke outcome measure in national datasets. *Stroke; a journal of cerebral circulation*. 2019;50:1282-1285

Menon BK, Al-Ajlan FS, Najm M, Puig J, Castellanos M, Dowlatshahi D, et al. Association of clinical, imaging, and thrombus characteristics with recanalization of visible intracranial occlusion in patients with acute ischemic stroke. *Journal of the american medical association*. 2018;320:1017-1026

Meretoja A, Keshtkaran M, Saver JL, Tatlisumak T, Parsons MW, Kaste M, et al. Stroke thrombolysis: Save a minute, save a day. *Stroke; a journal of cerebral circulation*. 2014;45:1053-1058

Meretoja A, Strbian D, Mustanoja S, Tatlisumak T, Lindsberg PJ, Kaste M. Reducing in-hospital delay to 20 minutes in stroke thrombolysis. *Neurology*. 2012;79:306-313

Meretoja A, Weir L, Ugalde M, Yassi N, Yan B, Hand P, et al. Helsinki model cut stroke thrombolysis delays to 25 minutes in melbourne in only 4 months. *Neurology*. 2013;81:1071-1076

Meyer JS, Gilroy J, Barnhart MI, Johnson JF. Therapeutic thrombolysis in cerebral thromboembolism. Double-blind evaluation of intravenous plasmin therapy in carotid and middle cerebral arterial occlusion. *Neurology*. 1963;13:927-937

Mikulik R. Personal communication. 2020

Mishra SM, Dykeman J, Sajobi TT, Trivedi A, Almekhlafi M, Sohn SI, et al. Early reperfusion rates with iv tpa are determined by cta clot characteristics. *AJNR. American journal of neuroradiology*. 2014;35:2265-2272

Nagel S, Bouslama M, Krause LU, Kupper C, Messer M, Petersen M, et al. Mechanical thrombectomy in patients with milder strokes and large vessel occlusions. *Stroke; a journal of cerebral circulation*. 2018;49:2391-2397

Nedeltchev K, Schwegler B, Haefeli T, Brekenfeld C, Gralla J, Fischer U, et al. Outcome of stroke with mild or rapidly improving symptoms. *Stroke; a journal of cerebral circulation*. 2007;38:2531-2535

Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *The New England journal of medicine*. 2018;378:11-21

O'Collins VE, Macleod MR, Donnan GA, Horky LL, van der Worp BH, Howells DW. 1,026 experimental treatments in acute stroke. *Annals of neurology*. 2006;59:467-477

Organised inpatient (stroke unit) care for stroke. *The Cochrane database of systematic reviews*. 2013:Cd000197

Parsons M, Spratt N, Bivard A, Campbell B, Chung K, Miteff F, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *The New England journal of medicine*. 2012;366:1099-1107

Patten SB. Confounding and effect modification in analytical studies. *Epidemiology for canadian students: Principles, methods and critical appraisal*. Brush Education Inc.; 2015:164-179.

Pfaff J, Herweh C, Pham M, Schonenberger S, Nagel S, Ringleb PA, et al. Mechanical thrombectomy in patients with acute ischemic stroke and lower nihss scores: Recanalization rates, periprocedural complications, and clinical outcome. *AJNR. American journal of neuroradiology*. 2016;37:2066-2071

Poppe AY, Majumdar SR, Jeerakathil T, Ghali W, Buchan AM, Hill MD. Admission hyperglycemia predicts a worse outcome in stroke patients treated with intravenous thrombolysis. *Diabetes care*. 2009;32:617-622

Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke; a journal of cerebral circulation*. 2018;49:e46-e110

Quinn TJ, Dawson J, Lees JS, Chang TP, Walters MR, Lees KR. Time spent at home poststroke: "Home-time" a meaningful and robust outcome measure for stroke trials. *Stroke; a journal of cerebral circulation*. 2008;39:231-233

Quinn TJ, Dawson J, Walters MR, Lees KR. Exploring the reliability of the modified rankin scale. *Stroke; a journal of cerebral circulation*. 2009;40:762-766

Quinn TJ, Dawson J, Walters MR, Lees KR. Reliability of the modified rankin scale: A systematic review. *Stroke; a journal of cerebral circulation*. 2009;40:3393-3395

Quinn TJ, McArthur K, Dawson J, Walters MR, Lees KR. Reliability of structured modified rankin scale assessment. *Stroke; a journal of cerebral circulation*. 2010;41:e602; author reply e603

Rajajee V, Kidwell C, Starkman S, Ovbiagele B, Alger JR, Villablanca P, et al. Early mri and outcomes of untreated patients with mild or improving ischemic stroke. *Neurology*. 2006;67:980-984

Rankin J. Cerebral vascular accidents in patients over the age of 60. I. General considerations. *Scottish medical journal*. 1957;2:127-136

Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. *Scottish medical journal*. 1957;2:200-215

Rankin J. Cerebral vascular accidents in patients over the age of 60. III. Diagnosis and treatment. *Scottish medical journal*. 1957;2:254-268

Rapport F, Clay-Williams R, Churruca K, Shih P, Hogden A, Braithwaite J. The struggle of translating science into action: Foundational concepts of implementation science. *Journal of evaluation in clinical practice*. 2017

Robinson TG, Wang X, Arima H, Bath PM, Billot L, Broderick JP, et al. Low- versus standard-dose alteplase in patients on prior antiplatelet therapy: The enchanted trial (enhanced control of hypertension and thrombolysis stroke study). *Stroke; a journal of cerebral circulation*. 2017;48:1877-1883

Rost NS, Bottle A, Lee JM, Randall M, Middleton S, Shaw L, et al. Stroke severity is a crucial predictor of outcome: An international prospective validation study. *Journal of the American Heart Association*. 2016;5

Rothman KJ, Greenland S, Lash TI. Design strategies to improve study accuracy. *Modern epidemiology*. Lippincott Williams &Wilkins; 2008:168-182.

Rothman KJG, S.; Poole, C.; Lash, T.L. Validity in epidemiologic studies. *Modern epidemiology*. Lippincott Williams & Wilkins; 2008:128-147.

Sajobi TT, Menon BK, Wang M, Lawal O, Shuaib A, Williams D, et al. Early trajectory of stroke severity predicts long-term functional outcomes in ischemic stroke subjects: Results from the escape trial (endovascular treatment for small core and anterior circulation proximal occlusion with emphasis on minimizing ct to recanalization times). *Stroke; a journal of cerebral circulation*. 2017;48:105-110

Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [ist-3]): A randomised controlled trial. *Lancet (London, England)*. 2012;379:2352-2363

Santos EMM, d'Esterre CD, Treurniet KM, Niessen WJ, Najm M, Goyal M, et al. Added value of multiphase cta imaging for thrombus perviousness assessment. *Neuroradiology*. 2018;60:71-79

Sarraj A, Hassan A, Savitz SI, Grotta JC, Cai C, Parsha KN, et al. Endovascular thrombectomy for mild strokes: How low should we go? *Stroke; a journal of cerebral circulation*. 2018;49:2398-2405

Saver JL, Filip B, Hamilton S, Yanes A, Craig S, Cho M, et al. Improving the reliability of stroke disability grading in clinical trials and clinical practice: The rankin focused assessment (rfa). *Stroke; a journal of cerebral circulation*. 2010;41:992-995

Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV, Pan W, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *Journal of the american medical association*. 2013;309:2480-2488

Saver JL, Goyal M, Diener HC. Stent-retriever thrombectomy for stroke. *The New England journal of medicine*. 2015;373:1077

Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: A meta-analysis. *Journal of the american medical association*. 2016;316:1279-1288

Saver JL, Starkman S, Eckstein M, Stratton SJ, Pratt FD, Hamilton S, et al. Prehospital use of magnesium sulfate as neuroprotection in acute stroke. *The New England journal of medicine*. 2015;372:528-536

Saver JL. Time is brain--quantified. *Stroke; a journal of cerebral circulation*. 2006;37:263-266

Savitz SI, Benatar M, Saver JL, Fisher M. Outcome analysis in clinical trial design for acute stroke: Physicians' attitudes and choices. *Cerebrovascular diseases (Basel, Switzerland)*. 2008;26:156-162

Scott SC, Goldberg MS, Mayo NE. Statistical assessment of ordinal outcomes in comparative studies. *Journal of clinical epidemiology*. 1997;50:45-55

Seder DB. Serum Glial Fibrillary Acidic Protein in Acute Stroke. *Neurocritical Care*. 2020;33:35-36.

Shang X, Lin M, Zhang S, Li S, Guo Y, Wang W, et al. Clinical outcomes of endovascular treatment within 24 hours in patients with mild ischemic stroke and perfusion imaging selection. *AJNR. American journal of neuroradiology*. 2018;39:1083-1087

Sheth SA, Sanossian N, Hao Q, Starkman S, Ali LK, Kim D, et al. Collateral flow as causative of good outcomes in endovascular stroke therapy. *Journal of neurointerventional surgery*. 2016;8:2-7

Shireman TI, Wang K, Saver JL, Goyal M, Bonafe A, Diener HC, et al. Cost-effectiveness of solitaire stent retriever thrombectomy for acute ischemic stroke: Results from the swift-prime trial (solitaire with the intention for thrombectomy as primary endovascular treatment for acute ischemic stroke). *Stroke; a journal of cerebral circulation*. 2017;48:379-387

Smith EE, Abdullah AR, Petkovska I, Rosenthal E, Koroshetz WJ, Schwamm LH. Poor outcomes in patients who do not receive intravenous tissue plasminogen activator because of mild or improving ischemic stroke. *Stroke; a journal of cerebral circulation*. 2005;36:2497-2499

Smith EE, Fonarow GC, Reeves MJ, Cox M, Olson DM, Hernandez AF, et al. Outcomes in mild or rapidly improving stroke not treated with intravenous recombinant tissue-type plasminogen activator: Findings from get with the guidelines-stroke. *Stroke; a journal of cerebral circulation*. 2011;42:3110-3115

Smith EE, Hassan KA, Fang J, Selchen D, Kapral MK, Saposnik G. Do all ischemic stroke subtypes benefit from organized inpatient stroke care? *Neurology*. 2010;75:456-462

Sussman BJ, Fitch TS. Thrombolysis with fibrinolysin in cerebral arterial occlusion. *Journal of the american medical association*. 1958;167:1705-1709

Thabane L, Kaczorowski J, Dolovich L, Chambers LW, Mbuagbaw L. Reducing the confusion and controversies around pragmatic trials: Using the cardiovascular health awareness program (chap) trial as an illustrative example. *Trials*. 2015;16:387

Thomalla G, Boutitie F, Fiebach JB, Simonsen CZ, Nighoghossian N, Pedraza S, et al. Stroke with unknown time of symptom onset: Baseline clinical and magnetic resonance imaging data of the first thousand patients in wake-up (efficacy and safety of mri-based thrombolysis in wake-up stroke: A randomized, doubleblind, placebo-controlled trial). *Stroke; a journal of cerebral circulation*. 2017;48:770-773

Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, et al. Mri-guided thrombolysis for stroke with unknown time of onset. *The New England journal of medicine*. 2018

Tissue plasminogen activator for acute ischemic stroke. The national institute of neurological disorders and stroke rt-pa stroke study group. *The New England journal of medicine*. 1995;333:1581-1587

Toyoda K, Koga M, Hayakawa M, Yamagami H. Acute reperfusion therapy and stroke care in asia after successful endovascular trials. *Stroke; a journal of cerebral circulation*. 2015;46:1474-1481

Turk AS, 3rd, Siddiqui A, Fifi JT, De Leacy RA, Fiorella DJ, Gu E, et al. Aspiration thrombectomy versus stent retriever thrombectomy as first-line approach for large vessel occlusion (compass): A multicentre, randomised, open label, blinded outcome, non-inferiority trial. *Lancet (London, England)*. 2019;393:998-1008

van den Berg LA, Dijkgraaf MG, Berkhemer OA, Fransen PS, Beumer D, Lingsma HF, et al. Two-year outcome after endovascular treatment for acute ischemic stroke. *The New England journal of medicine*. 2017;376:1341-1349

Volny O, Bar M, Krajina A, Cimflova P, Kasickova L, Herzig R, et al. A comprehensive nationwide evaluation of stroke centres in the czech republic performing mechanical thrombectomy in acute stroke in 2016. *Ceska a Slovenska Neurologie a Neurochirurgie* 2017;113:445-450

Volny O, Krajina A, Belaskova S, Bar M, Cimflova P, Herzig R, et al. Mechanical thrombectomy performs similarly in real world practice: A 2016 nationwide study from the czech republic. *Journal of neurointerventional surgery*. 2018;10:741-745

Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the safe implementation of thrombolysis in stroke-monitoring study (sits-most): An observational study. *Lancet (London, England)*. 2007;369:275-282

Walter S, Kostopoulos P, Haass A, Keller I, Lesmeister M, Schlechtriemen T, et al. Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: A randomised controlled trial. *The Lancet. Neurology*. 2012;11:397-404

Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *The Cochrane database of systematic reviews*. 2014:Cd000213

Wolman DN, Marcellus DG, Lansberg MG, Albers G, Guenego A, Marks MP, et al. Endovascular versus medical therapy for large-vessel anterior occlusive stroke presenting with mild symptoms. *International journal of stroke : official journal of the International Stroke Society*. 2020;15:324-331

Wood JP, Connelly DM, Maly MR. 'Getting back to real living': A qualitative study of the process of community reintegration after stroke. *Clinical rehabilitation*. 2010;24:1045-1056

Woolf SH. Do clinical practice guidelines define good medical care? The need for good science and the disclosure of uncertainty when defining 'best practices'. *Chest*. 1998;113:166s-171s

Xian Y, Federspiel JJ, Grau-Sepulveda M, Hernandez AF, Schwamm LH, Bhatt DL, et al. Risks and benefits associated with prestroke antiplatelet therapy among patients with acute ischemic stroke treated with intravenous tissue plasminogen activator. *Journal of the american medical association, neurology*. 2016;73:50-59

Yu AY, Holodinsky JK, Zerna C, Svenson LW, Jette N, Quan H, et al. Use and utility of administrative health data for stroke research and surveillance. *Stroke; a journal of cerebral circulation*. 2016;47:1946-1952

Yu AY, Zerna C, Assis Z, Holodinsky JK, Randhawa PA, Najm M, et al. Multiphase ct angiography increases detection of anterior circulation intracranial occlusion. *Neurology*. 2016;87:609-616

Yu AYX, Rogers E, Wang M, Sajobi TT, Coutts SB, Menon BK, et al. Population-based study of home-time by stroke type and correlation with modified rankin score. *Neurology*. 2017;89:1970-1976

Zaidat OO, Bozorgchami H, Ribo M, Saver JL, Mattle HP, Chapot R, et al. Primary results of the multicenter arise ii study (analysis of revascularization in ischemic stroke with embotrap). *Stroke; a journal of cerebral circulation*. 2018;49:1107-1115

Zerna C, Burley T, Green TL, Dukelow SP, Demchuk AM, Hill MD. Comprehensive assessment of disability post-stroke using the newly developed mifunction scale. *International journal of stroke : official journal of the International Stroke Society*. 2020;15:167-174

Zerna C, Hegedus J, Hill MD. Evolving treatments for acute ischemic stroke. *Circulation research*. 2016;118:1425-1442

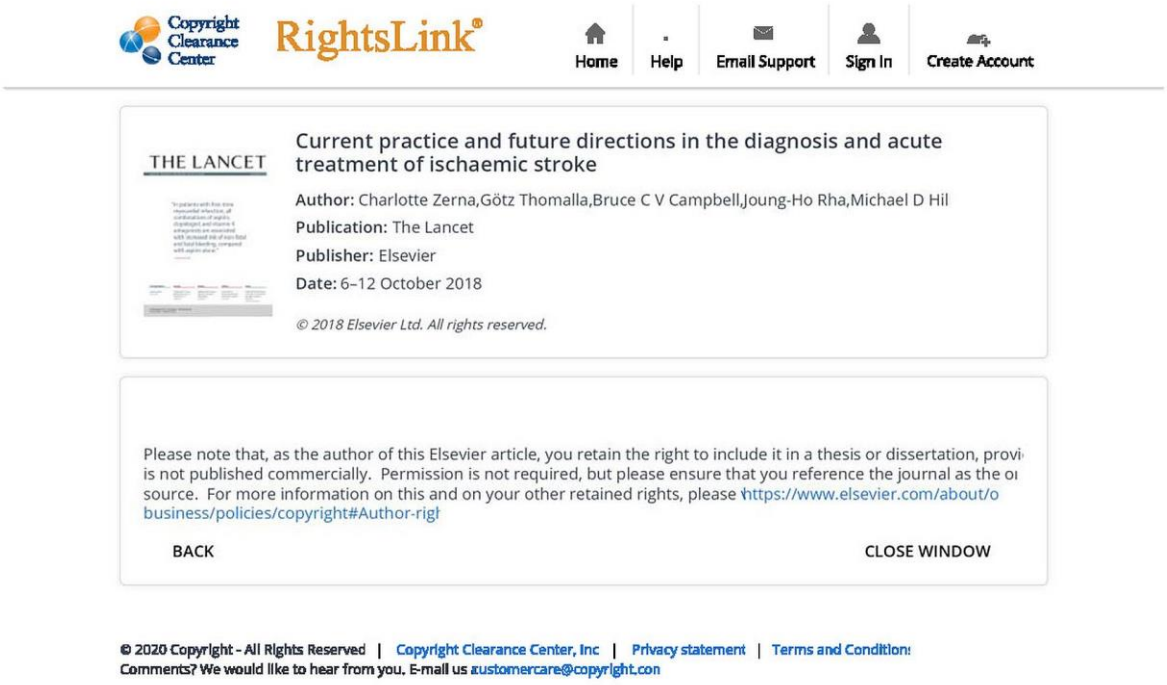
Zerna C, Rogers E, Rabi DM, Demchuk AM, Kamal N, Mann B, et al. Comparative effectiveness of endovascular treatment for acute ischemic stroke: A population-based analysis. *Journal of the American Heart Association*. 2020;9:e014541

Zinkstok SM, Roos YB. Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke: A randomised controlled trial. *Lancet (London, England)*. 2012;380:731-737

Appendix A—Copyright Permission Forms From Previously Published Chapters

Permission for CHAPTER 2:

The author of the Elsevier article retains the right to include it in a thesis or dissertation, providing that it is not published commercially.



Permission for CHAPTER 3:

Ownership of copyright remains with the author and he/she retains the non–exclusive right to reproduce the contribution in whole or in part in any printed volume (book or thesis) of which they are the author(s).

Copyright Clearance Center RightsLink®

Home | Help | Email Support | Sign in | Create Account

SPRINGER NATURE

Long-term outcome of endovascular therapy for ischaemic stroke

Author: Charlotte Zerna et al

Publication: Nature Reviews Neurology

Publisher: Springer Nature

Date: Jun 2, 2017

Copyright © 2017, Springer Nature

Author Request

If you are the author of this content (or his/her designated agent) please read the following. If you are not the author of this content, please click the Back button and select no to the question "Are you the Author of this Springer Nature content?".
Ownership of copyright in original research articles remains with the Author, and provided that, when reproducing the contribution or extracts from it or from the Supplementary Information, the Author acknowledges first and reference publication in the Journal, the Author retains the following non-exclusive rights:
To reproduce the contribution in whole or in part in any printed volume (book or thesis) of which they are the author(s).
The author and any academic institution, where they work, at the time may reproduce the contribution for the purpose of course teaching.
To reuse figures or tables created by the Author and contained in the Contribution in oral presentations and other works created by them.
To post a copy of the contribution as accepted for publication after peer review (in locked Word processing file, of a PDF version thereof) on the Author's own web site, or the Author's institutional repository, or the Author's funding body's archive, six months after publication of the printed or online edition of the Journal, provided that they also link to the contribution on the publisher's website.
Authors wishing to use the published version of their article for promotional use or on a web site must request in the normal way.

If you require further assistance please read Springer Nature's online author reuse guidelines.

For full paper portion: Authors of original research papers published by Springer Nature are encouraged to submit the author's version of the accepted, peer-reviewed manuscript to their relevant funding body's archive, for release six months after publication. In addition, authors are encouraged to archive their version of the manuscript in their institution's repositories (as well as their personal Web sites), also six months after original publication.

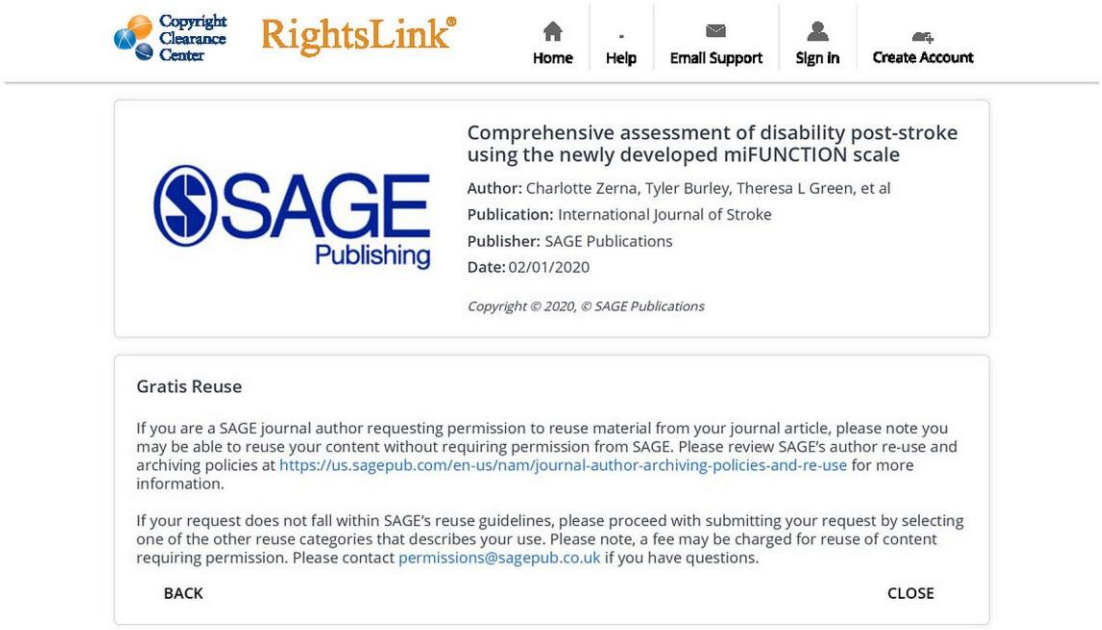
v1.0

BACK CLOSE WINDOW

© 2020 Copyright - All Rights Reserved | Copyright Clearance Center, Inc. | Privacy statement | Terms and Conditions
Comments? We would like to hear from you. E-mail us at customercare@copyright.com

Permission for CHAPTER 5:

The author may use the work in a dissertation or thesis, including where the dissertation or thesis will be posted in any electronic institutional Repository or database.



SAGE's Author Archiving and Re-Use Guidelines

These guidelines should be followed by authors of Contributions published in a SAGE subscription journal, including authors whose Contributions were published under a previous version of the author guidelines. For a list of exceptions to these guidelines, please see below.

Three versions of the Contribution are referenced in these guidelines:

- **Original Submission:** the version submitted by the author before peer review
- **Accepted Manuscript:** version updated to include the author's revisions after peer review, prior to any typesetting for the journal. This is often the version accepted by the editor
- **Final Published PDF:** copy-edited and typeset Publisher's PDF, the same version published on the journal's website

Green Open Access: SAGE's Archiving and Sharing Policy

You may share the **Original Submission** or **Accepted Manuscript** at any time and in any format. Your sharing of the **Original Submission** or **Accepted Manuscript** may include posting a downloadable copy on any website, saving a copy in any repository or network, sharing a copy through any social media channel, and distributing print or electronic copies.

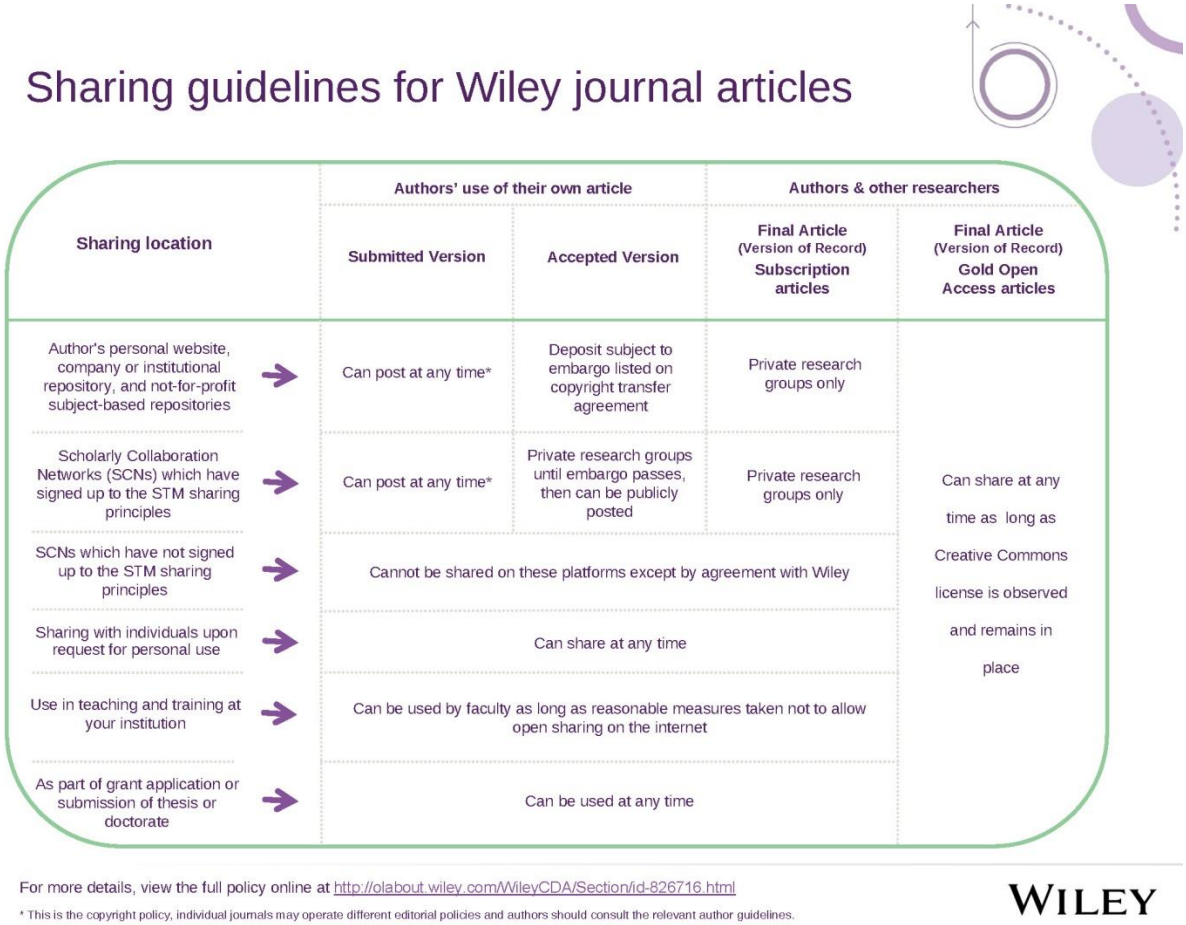
For information on use of Institutional Repository (IR) copies by authors and IR users, see Posting to an Institutional Repository - Green Open Access.

You may use the **Final Published PDF** (or **Original Submission** or **Accepted Manuscript**, if preferred) in the following ways:

- in relation to your own teaching, provided that any electronic distribution maintains restricted access
- to share on an individual basis with research colleagues, provided that such sharing is not for commercial purposes
- in your dissertation or thesis, including where the dissertation or thesis will be posted in any electronic Institutional Repository or database
- in a book authored or edited by you, at any time after the Contribution's publication in the journal.

Permission for CHAPTER 6:

Author can user their own article at any time as part of a grant application or submission of thesis or doctorate.



Sharing guidelines for Wiley journal articles

Sharing location	Authors' use of their own article		Authors & other researchers	
	Submitted Version	Accepted Version	Final Article (Version of Record) Subscription articles	Final Article (Version of Record) Gold Open Access articles
Author's personal website, company or institutional repository, and not-for-profit subject-based repositories →	Can post at any time*	Deposit subject to embargo listed on copyright transfer agreement	Private research groups only	Can share at any time as long as Creative Commons license is observed and remains in place
Scholarly Collaboration Networks (SCNs) which have signed up to the STM sharing principles →	Can post at any time*	Private research groups until embargo passes, then can be publicly posted	Private research groups only	
SCNs which have not signed up to the STM sharing principles →	Cannot be shared on these platforms except by agreement with Wiley			
Sharing with individuals upon request for personal use →	Can share at any time			
Use in teaching and training at your institution →	Can be used by faculty as long as reasonable measures taken not to allow open sharing on the internet			
As part of grant application or submission of thesis or doctorate →	Can be used at any time			

For more details, view the full policy online at http://olabout.wiley.com/WileyCDA/Section/id-826716.html

* This is the copyright policy, individual journals may operate different editorial policies and authors should consult the relevant author guidelines.

WILEY

Restricted permission for CHAPTER 7:

RE: Welcome to Production for Your Article (NEUROLOGY2020090498R1) in Neurology - [EMID:473bf4d75581ad44]

Andrea Rahkola <ARahkola@neurology.org>
Wed 2020-09-30 1:59 PM
To: Charlotte Zerna <charlotte.zerna@ucalgary.ca>
Cc: Heise, Jessica <Jessica.Heise@wolterskluwer.com>

4 attachments (3 MB)
090498-FINAL-MS.docx; AANIP_524_2_090498_Figure_1.tif; AANIP_524_2_090498_Figure_2_Color.tif; AANIP_524_2_090498_Figure_3_Color.tif;

[△EXTERNAL]

Dear Zerna,

Thank you for reaching out with your question and for your concern regarding embargo. Indeed, the embargo has lifted and you may include the final peer-reviewed manuscript of the article in your thesis. I have attached that manuscript Word document to this email (090498-FINAL-MS), along with the final 3 figures (AANIP_524_2_090498_Figure_1; AANIP_524_2_090498_Figure_2_Color; AANIP_524_2_090498_Figure_3_Color).

You are free to use the final peer-reviewed manuscript in your print thesis at this time, and in your electronic thesis 12 months after the article's publication date. Please note that the manuscript may only appear in your electronic thesis if it will be password protected.

Best wishes,

Andrea Rahkola
Production Editor
Neurology® Editorial Office
American Academy of Neurology
201 Chicago Avenue
Minneapolis, MN 55415
Ph: 612-928-6155 Fax: 612-454-2748
arahkola@neurology.org www.neurology.org

Permission for CHAPTER 8:

RE: Obtain permission request - Book (1013633)

Rights and Permissions (ELS) <Permissions@elsevier.com>
Thu 2020-05-14 10:40 AM
To: Charlotte Zerna <charlotte.zerna@ucalgary.ca>

Dear Dr. Charlotte Zerna

We hereby grant you permission to reprint the aforementioned material at no charge **in your thesis, in print and on the University web site** subject to the following conditions:

1. If any part of the material to be used (for example, figures) has appeared in our publication with credit or acknowledgement to another source, permission must also be sought from that source. If such permission is not obtained then that material may not be included in your publication/copies.

2. Suitable acknowledgment to the source must be made, either as a footnote or in a reference list at the end of your publication, as follows:

   "This article was published in Publication title, Vol number, Author(s), Title of article, Page Nos, Copyright Elsevier (or appropriate Society name) (Year)."

3. Your thesis may be submitted to your institution in either print or electronic form.

4. Reproduction of this material is confined to the purpose for which permission is hereby given.

5. This permission is granted for non-exclusive world **English** rights only. For other languages please reapply separately for each one required. Permission excludes use in an electronic form other than as specified above. Should you have a specific electronic project in mind please reapply for permission.

6. Should your thesis be published commercially, please reapply for permission.