

Automated CT Perfusion Imaging to Aid in the Selection of Patients With Acute Ischemic Stroke for Mechanical Thrombectomy: A Health Technology Assessment

Key Messages

What Is This Health Technology Assessment About?

An acute ischemic stroke is caused by a blockage of an artery in the brain by a blood clot. When the blood clot is in a large artery, removing the blood clot (called mechanical thrombectomy) within 24 hours of the stroke can improve outcomes and reduce a person's risk of long-term disability. The goal of mechanical thrombectomy is to return blood supply to affected areas of the brain.

Medical imaging, specifically computed tomography (CT) or magnetic resonance imaging (MRI), can be used to identify people who are eligible for mechanical thrombectomy. Although MRI is the most accurate option, it is not always widely available in a timely fashion. However, CT can be used to assess blood flow to the brain (brain perfusion). Brain images acquired from CT scans can be automatically processed by computer. With automated CT perfusion imaging, the results can be reviewed and communicated quickly.

This health technology assessment looked at how effective automated CT perfusion imaging is in selecting patients for mechanical thrombectomy. It also looked at the cost-effectiveness and budget impact of publicly funding automated CT perfusion imaging. Patient preferences and values are expected to closely align with the potential improved outcomes resulting from use of this imaging technology, so we did not engage directly with patients.

What Did This Health Technology Assessment Find?

Based on a previous Health Quality Ontario analysis, mechanical thrombectomy is clinically effective and cost-effective for patients within 6 hours after a stroke. Evidence from this health technology assessment shows that in some patients, treatment with mechanical thrombectomy is also effective up to 24 hours after a stroke when informed by automated CT perfusion imaging. Automated CT perfusion imaging has acceptable sensitivity and specificity for detecting brain areas that have been affected by stroke within 24 hours of symptoms onset. With automated CT perfusion imaging, a small percentage of patients may be incorrectly classified as eligible or ineligible for mechanical thrombectomy.

We estimated that mechanical thrombectomy informed by automated CT perfusion imaging to assess eligibility would likely be cost-effective for eligible patients up to 24 hours after a stroke. Publicly funding automated CT perfusion imaging in Ontario would lead to additional costs of \$1.3 million in the first year and \$0.9 million each year after that.

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ABSTRACT

Background

Stroke is a sudden interruption in the blood supply to a part of the brain, causing loss of neurological function. It is the third leading cause of death in Canada and affects mainly older people. In the acute setting, neuroimaging is integral to stroke evaluation and decision-making. The neuroimaging results guide patient selection for mechanical thrombectomy. Using automated image processing techniques facilitates efficient review of this information and communication between centres. We conducted a health technology assessment of automated CT perfusion imaging as a tool for selecting stroke patients with anterior circulation occlusion for mechanical thrombectomy. This assessment included an evaluation of clinical effectiveness, cost-effectiveness, and the budget impact of publicly funding automated CT perfusion imaging.

Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each study using QUADAS-2 or the Cochrane risk-of-bias tool, and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and approximated cost-effectiveness based on previous analyses. We also analyzed the budget impact of publicly funding automated CT perfusion imaging to evaluate people with acute ischemic stroke in Ontario.

Results

Automated CT perfusion imaging had a sensitivity of 84% for identifying the infarct core (dead tissue that does not recover despite restoring blood flow with mechanical thrombectomy), compared with diffusion-weighted MRI imaging at 24 hours. One study reported that 7% of patients were misclassified with respect to eligibility for mechanical thrombectomy (either erroneously classified as eligible or erroneously classified non-eligible). Two randomized controlled trials (DEFUSE 3 and DAWN) demonstrated the efficacy of mechanical thrombectomy up to 24 hours after stroke onset, with patient selection guided by automated CT perfusion imaging. These data showed that a significantly higher proportion of patients in the mechanical thrombectomy group achieved functional independence compared with the standard care group (DEFUSE 3: risk ratio: 2.67 [95% confidence interval 1.60–4.48]; DAWN: adjusted rate difference: 33% [95% credible interval 21%–44%]; GRADE: Moderate).

A previous health technology assessment in stroke patients presenting at 0 to 6 hours after stroke symptom onset and the results from recent randomized controlled trials for patients presenting at 6 to 24 hours informed the evaluation of cost-effectiveness. Mechanical thrombectomy informed by automated CT perfusion imaging to assess eligibility is likely to be cost-effective for patients presenting at 6 to 24 hours after stroke symptom onset. The annual budget impact of publicly funding automated CT perfusion imaging in Ontario over the next 5 years would be \$1.3 million in year 1 and \$0.9 million each year thereafter. Some of the costs of automated CT perfusion imaging could be offset by avoiding unnecessary patient transfers between hospitals.

Conclusions

Automated CT perfusion imaging has an acceptable sensitivity and specificity for detecting brain areas that have been affected by stroke. In patients selected for mechanical thrombectomy using automated CT perfusion imaging, there was significant improvement in functional independence. Mechanical thrombectomy informed by automated CT perfusion imaging is likely to be cost-effective. We estimate that publicly funding automated CT perfusion imaging in Ontario would result in additional costs of \$1.3 million in year 1 and \$0.9 million per year thereafter.

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OBJECTIVE

This health technology assessment evaluates the effectiveness of automated computed tomography (CT) perfusion imaging to aid in the selection of patients for mechanical thrombectomy after acute ischemic stroke caused by large-vessel occlusion in the anterior circulation. It also evaluates the cost-effectiveness and budget impact of publicly funding automated CT perfusion imaging.

BACKGROUND

Health Condition

Stroke is a sudden interruption in the blood supply to part of the brain, causing loss of neurological function. It is the third leading cause of death in Canada¹ and affects mainly older people. More than 80% of strokes are caused by a sudden blockage of the arteries (ischemic stroke).² Another type of stroke is caused by the rupture of a blood vessel that causes bleeding into the brain (hemorrhagic stroke). Symptoms of stroke can include sudden weakness or loss of sensation on one side of the body, difficulty speaking, difficulty seeing, headache, confusion, or loss of balance. Without treatment, these symptoms may persist and affect a person's quality of life.

According to CorHealth Ontario, of the approximately 13,000 Ontarians who survive an acute care hospitalization for a stroke or transient ischemic attack each year, about 1,100 are admitted to complex continuing care and 1,300 to long-term care within 180 days of discharge from acute care.³ Almost 60% of stroke survivors in complex continuing care and long-term care have limitations in their ability to communicate.³

Clinical Need and Target Population

Ischemic stroke is an emergency condition that is treatable with thrombolysis (breaking up the blood clot with medication) and/or mechanical thrombectomy (removing the clot using a minimally invasive procedure). A stroke can seriously harm a person if the blood supply to the affected area of the brain is not restored. Stroke can cause disability, negatively affect quality of life, and even cause death. Immediate treatment of patients with the symptoms of stroke is of utmost importance.

Approximately 30% of acute ischemic strokes are because of an occlusion (a blockage) in a large blood vessel in the brain.⁴ In these patients, mechanical thrombectomy performed within 6 hours after the onset of stroke can substantially reduce brain damage, improve patient outcomes, and reduce the risk of long-term disability.⁵ Imaging evidence of tissue viability beyond 6 hours can be used to select patients for mechanical thrombectomy, and advances in neuroimaging (such as the development of tools for automated post-processing) have played a significant role in selecting eligible patients for this procedure.

Current Treatment Options

Tissue Plasminogen Activator

Eligible patients can undergo intravenous thrombolysis (dissolving of blood clots) using an enzyme called a tissue plasminogen activator (tPA) within 4.5 hours of the onset of an ischemic stroke. However,

intravenous tPAs have multiple constraints: large blood clots may not respond to enzymatic breakdown; tPAs must be administered within a narrow time window; and tPAs come with a risk of cerebral and systemic hemorrhage (bleeds in the brain or elsewhere in the body).⁶ In patients who do not respond to intravenous thrombolysis, intra-arterial thrombolysis can be performed by delivering the tPA directly to the site of the occlusion.

Mechanical Thrombectomy

In patients with a large-vessel occlusion in the anterior circulation (intracranial internal carotid artery and middle cerebral artery), recanalization of the obstructed vessel (opening of the blockage) can also be achieved using mechanical devices to retrieve the blood clot.⁷ Mechanical thrombectomy allows for the rapid removal of clots in the large proximal arteries and establishes reperfusion (restores blood flow) in tissues that lack sufficient blood supply. Mechanical thrombectomy can be performed as a primary intervention, or as a secondary treatment in patients who do not recanalize after intravenous thrombolysis. Mechanical thrombectomy refers to retraction, aspiration, use of a retrievable stent (stent retriever), and ultrasound-augmented fibrinolysis.⁷

Randomized controlled trials in stroke patients with a large-vessel occlusion in the anterior circulation have shown the benefit of mechanical thrombectomy if it is performed within the first 6 hours after the onset of stroke symptoms. With new-generation thrombectomy devices, the odds of achieving functional independence (defined as scores of 0 to 2 on the modified Rankin Scale⁸) was doubled in patients who received mechanical thrombectomy plus medical therapy compared to those who received medical therapy alone.⁹ Health Quality Ontario published a meta-analysis of those trials in 2016.⁵

More recent randomized controlled trials have investigated whether the benefits of mechanical thrombectomy could be realized if the time window were extended beyond 6 hours. The DEFUSE 3 trial¹⁰ provided evidence for the effectiveness of mechanical thrombectomy within 16 hours after the onset of symptoms, and the DAWN trial¹¹ provided support for the use of mechanical thrombectomy within 24 hours in carefully selected patients.

About a quarter of patients with ischemic stroke have an unclear time of onset.¹² These patients may not be considered for tPA therapy, because they have likely missed the time window of 4.5 hours recommended by current guidelines. However, with advanced imaging modalities, patients who show evidence of salvageable brain tissue can be identified and selected for mechanical thrombectomy.

The goal of mechanical thrombectomy is to provide reperfusion in areas of the brain that are in danger of further infarction (tissue death). When ischemic stroke occurs, it forms a central area of dead tissue called the infarct core. The tissues in this area are irreversibly damaged and cannot be salvaged by any treatment. However, the area surrounding the infarct core contains tissues that are still receiving blood through collateral arteries, but the blood supply is not adequate for long periods, and ischemia may progress to infarction if local perfusion is not restored. This area is called the penumbra and is the target for treatment with mechanical thrombectomy.

The volume of the infarct core and penumbra have clinical implications for decision-making related to mechanical thrombectomy. It has been suggested that in patients with an infarct core volume greater than 70 mL, mechanical thrombectomy is futile.¹³ Recent trials have adopted a threshold of 70 mL, although the exact threshold is still under consideration. Using CT perfusion imaging, the mismatch ratio

(the ratio of the penumbra volume to the infarct core volume) can be calculated; it is used as a key indicator of patients who may benefit from mechanical thrombectomy.

Guidelines for the Management of Acute Ischemic Stroke

Based on the results of randomized controlled trials, current Canadian and United States guidelines for the management of stroke recommend mechanical thrombectomy within 24 hours for stroke patients who have occlusion of large arteries in the anterior circulation and who meet the eligibility criteria for this procedure.

The Canadian Best Practice Recommendations for Acute Stroke Management (sixth edition)¹⁴ advise that highly selected patients with large-vessel occlusion can be treated with mechanical thrombectomy within 24 hours of symptom onset (i.e., arterial access within 24 hours of onset) and patients with stroke discovered on awakening should receive endovascular therapy (evidence level A). The Canadian guideline further recommends that centres using CT perfusion imaging should use a system that provides reproducible objective measurements of the ischemic core and tissue at risk of further infarction to select patients for endovascular therapy. The guideline recommends that the location of the occlusion and the presence of good collateral filling be viewed through CT angiography (CTA). The use of a third-generation or higher helical scanner with programming for multiphase CTA and CT perfusion is also recommended.

The American Heart Association¹⁵ published an update to their 2015 guideline on the treatment of acute ischemic stroke that advocated for the management of select patients with mechanical thrombectomy beyond 6 hours. This guideline recommends mechanical thrombectomy for those who present at 6 to 16 hours of last known normal, who have large-vessel occlusion in the anterior circulation, and who meet the DEFUSE 3¹⁰ or DAWN¹¹ eligibility criteria (class I [strong recommendation]; level of evidence A [based on high-quality evidence from more than one randomized controlled trial]). For 16 to 24 hours after stroke symptom onset, the American Heart Association guideline recommends mechanical thrombectomy in select patients with acute ischemic stroke who have large-vessel occlusion in the anterior circulation and meet other DAWN¹¹ eligibility criteria within 16 to 24 hours of the last known normal (class IIa [moderate recommendation]; level of evidence BR [moderate quality of evidence based on one or more randomized controlled trials]).

Imaging Techniques in Stroke

Neuroimaging is integral to stroke evaluation and decision-making in the acute setting. After obtaining an adequate history and preliminary images using a CT scan or magnetic resonance imaging (MRI), clinicians determine the type of stroke. After hemorrhagic stroke has been ruled out, patients are screened to see whether an accessible large blood vessel in the anterior circulation is occluded. Eligible patients who show evidence of salvageable brain tissues can be considered for mechanical thrombectomy and may require transfer to another center to receive this treatment.

CT Protocol

The complete CT protocol—which includes non-contrast CT (NCCT), CTA, and CT perfusion—can be performed to provide a comprehensive evaluation of an acute stroke. An NCCT scan is usually the initial imaging modality used in patients who present with symptoms of stroke, primarily because of its accessibility and short acquisition time. The NCCT scan plays a key role in ruling out hemorrhagic stroke

and assessing early ischemic changes in the brain or other lesions that may mimic the symptoms of stroke, such as neoplasms (e.g., tumours) or arteriovenous malformations. After NCCT, if ischemic stroke is suspected, a CTA is performed to assess the location and extent of the blockage, the collateral circulation (circulation provided by nearby vessels), and the presence of plaques in the carotid arteries. With CTA, it is also possible to identify patients at risk of infarct growth according to the status of the collateral circulation.¹⁶ Multiphase CTA is a newer technique that allows for the assessment of collaterals and has been shown to be an independent predictor of clinical outcomes after thrombectomy. In Ontario, CT and multiphase CTA are the standard imaging modalities for all suspected strokes. Finally, CT perfusion imaging is performed to differentiate the penumbra from irrevocably damaged tissue. With CT perfusion, an injected contrast agent passes through the brain tissue to provide information about brain hemodynamics. Images from CT perfusion can help clinicians to determine the location, size, and volume of the affected areas. The CT perfusion process includes data acquisition, post-processing, and analysis of the images by neuroradiologists.

CT Perfusion Imaging Versus MRI

Diffusion-weighted imaging using MRI is the most accurate modality for assessing cerebral infarctions and the hemodynamic status of the injured area; it is considered the “gold standard” in a number of studies. According to the recent Canadian guideline on stroke management,¹⁴ MRI is superior to CT in terms of diagnostic sensitivity for small infarcts and may provide additional information that could guide diagnosis, prognosis, and decision-making. However, MRI is not always available in a timely fashion or in small or rural hospitals. In addition, patient contraindications such as the presence of metal medical devices or implants may limit its use. The disadvantage of CT perfusion imaging with 16- or 64-channel scanners is that these scanners do not cover the entire brain parenchyma. More advanced 256- and 320-channel CT scanners can image the whole brain, but they involve a higher dose of radiation to the brain.

Perfusion Maps

During CT perfusion imaging, as the injected contrast agent passes through the brain tissue in a selected area (region of interest), it creates two curves for the passage of arterial and venous blood in the tissues of the selected areas (time-attenuation curves). These curves provide information that is used to calculate perfusion parameters. The perfusion parameters are cerebral blood volume, cerebral blood flow, mean transit time, time to peak, and time to maximum tissue contrast density. By comparing the value of the perfusion parameters in the affected and normal tissue, automated CT perfusion imaging creates maps of the area with infarction and the area with salvageable tissue. Definitions of CT perfusion parameters and their interpretation are presented in Table 1.

Table 1: Definition and Interpretation of CT Perfusion Parameters in Ischemic Stroke

Term	Definition	Unit of Measurement	Interpretation	
			Penumbra	Infarct Core
Mean transit time	Average amount of time it takes blood to transit through the given volume of brain	Seconds	Elevated	Elevated
Cerebral blood flow	Volume of flowing blood moving through a given volume of brain in a specific amount of time	mL of blood per 100 g of brain tissue per minute	Mildly decreased	Markedly decreased
Cerebral blood volume	Volume of flowing blood for a given volume of brain	mL of blood per 100 g of brain tissue	Normal or mildly increased	Markedly decreased
Time to peak	Time to the peak of the concentration time curve	Seconds	Delayed	Delayed
Time to maximum tissue contrast density	Time from the baseline to the maximum density of the contrast bolus	Seconds	Delayed	Delayed

Sources: Lui et al., 2010¹⁷; Lin et al., 2013.¹⁸

To create colour-coded perfusion maps, thresholds for the above perfusion parameters must be specified. For example, at a threshold of greater than 6 seconds for mean transit time and greater than 2 mL/100 mL for cerebral blood volume in specific areas, green pixels on the map will indicate salvageable brain tissue; however, if the mean transit time is greater than 6 seconds and the cerebral blood volume is less than 2 mL/100 mL, the area would be considered infarct core and the map would show red pixels. Studies have used different thresholds, and the optimal thresholds for perfusion parameters is of ongoing interest.

Health Technology Under Review

Brain images acquired using CT perfusion imaging or MRI can undergo non-automated or automated post-processing. In non-automated CT perfusion imaging, radiologists manually input arterial inflow function and venous outflow function. Although, non-automated CT perfusion imaging may aid in the selection of patients for mechanical thrombectomy up to 24 hours after the onset of stroke, it is not commonly used in Ontario. Most physicians prefer automated CT perfusion imaging because of its convenience, speed, validated default cutoff parameters, and capacity to continuously improve its performance (CorHealth Ontario, email communication, August 2019; Timo Krings, MD, personal communication, February 2019; Wieslaw Oczkowski, MD, email communication, August 2019).

Several automated imaging platforms are available for installation on commercial CT and MRI scanners. These imaging platforms facilitate the post-processing of data and can create perfusion maps in a very short time. The maps can be used as a guide for selecting patients who are eligible for mechanical thrombectomy. The addition of automated imaging to the imaging armamentarium may assist with treatment decisions in the fast-paced environment of emergency departments.

The RAPID neuroimaging platform (IschemaView, Menlo Park, CA) was the most commonly used platform in published randomized controlled trials. The RAPID neuroimaging platform includes several modules (e.g., RAPID CT perfusion, RAPID MRI, RAPID CT angiography, RAPID ASPECTS, etc.) that can be purchased individually or together.¹⁹ Although we were interested primarily in the RAPID CT perfusion

module for this health technology assessment, hospitals generally purchase the entire RAPID neuroimaging platform. The automated CT perfusion post-processing technique has a default for selection of the brain region of interest that can be manually adjusted when correction is necessary. Throughout this report, we refer to the RAPID neuroimaging platform when we are considering the broader platform with multiple modules, and we refer to RAPID CT perfusion when we are specifically considering the RAPID automated CT perfusion imaging module.

It has been suggested that automated CT perfusion imaging can produce perfusion maps that are spatially consistent with those produced by non-automated imaging; the benefit of automated imaging is elimination of variable results among centres.²⁰ Automated imaging is installed on CT scanners and requires a separate dedicated computer. It automatically sends the results to the hospital's picture archiving and communication system, and can also send the perfusion map via email or to communication devices such as smart phones for immediate review by the stroke team in a very short time frame (about 5 to 7 minutes).²¹

One disadvantage of automated CT perfusion imaging is that it may interpret artificial lesions caused by patient movement (artifacts) as true lesions. The software automatically counts these artifacts in the computation of the infarct core volume. Although some imaging allows for the correction of artifacts, the ability to correct is limited to the small degrees of patient motion in the scanner. Still, these artifacts can be easily identified by neuroradiologists or other stroke specialists and removed from the computation. It has been suggested that the analysis and interpretation of CT perfusion imaging data should always be performed by experts with a specialty in reviewing CT perfusion images, because the potential for pitfalls in interpretation exist if expertise in CT perfusion imaging is lacking. With accurate data acquisition and valid interpretation, post-processed data acquired through automated or non-automated CT perfusion imaging can help identify and measure the infarct core and potentially salvageable ischemic tissue. Given that automated CT perfusion imaging has made post-processing easier and faster, interventional neuroradiologists in stroke centres have shown growing interest in adopting this technology for routine clinical practice.

Regulatory Information

Table 2 shows the automated CT perfusion imaging platforms that are licensed in Canada.

Table 2: Automated CT Perfusion Imaging Platforms Licensed in Canada

Name	Manufacturer (Location)	Licence Number
RAPID	IschemaView (Menlo Park, CA, United States)	101594
IntelliSpace Portal	Philips Healthcare (Best, the Netherlands)	90048
Syngo Volume Perfusion CT Neuro	Siemens Healthcare (Erlangen, Germany)	35736
Vitrea	Vital Images, Toshiba (Minnetonka, MN, United States)	61191
AW Volumeshare2–CT Perfusion 4	General Electric (Milwaukee, WI, United States)	73045

Ontario Context

In Ontario, automated CT perfusion imaging platforms are not publicly funded. Eleven hospitals in Ontario offer mechanical thrombectomy, and five use automated imaging to select patients for this procedure. In these hospitals, the cost of purchasing and maintenance of the automated imaging platforms is managed through hospital budgets. Some centres in Ontario use multiphase CTA to select patients for mechanical thrombectomy up to 12 hours post-stroke (Albert Jin, MD, personal communication, April 3, 2019). Other provinces currently using automated CT perfusion imaging are British Columbia, Alberta, and Quebec.

In Ontario hospitals that have a comprehensive stroke program, patients arriving with symptoms of stroke are treated according to the hospital's acute stroke protocol. Patients who arrive earlier (i.e., within 4.5 hours of stroke onset) may have indications for thrombolytic therapy. Some hospitals have a large-vessel imaging screening protocol as part of their emergency department triage to determine whether the large arteries of the brain are occluded.

In Ontario, many smaller emergency departments do not have 24-hour access to contrast-enhanced CT imaging. In these hospitals, identifying who would benefit from a transfer to a comprehensive stroke centre is a challenging issue, but in theory, developing the capacity to rapidly acquire CT and CT perfusion images to make treatment decisions could reduce the number of unnecessary transfers to stroke centres.

In addition, automated CT perfusion imaging may extend the time window for mechanical thrombectomy, thereby increasing the number of potential candidates for this procedure. The use of automated CT perfusion imaging may help in handling the workflow increase in emergency departments and allow hospitals to synchronize their operations to manage stroke patients in a faster, more standardized way. This is most applicable to tPA-only centres, which could use this technology to refine their protocols for screening patients and selecting them for tPA or transfer for mechanical thrombectomy.

Expert Consultation

We engaged with experts in the specialty areas of interventional neuroradiology, neurology, and diagnostic radiology to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD 42019141465), available at <https://www.crd.york.ac.uk/PROSPERO>.

CLINICAL EVIDENCE

Research Question

- What is the accuracy of automated computed tomography (CT) perfusion imaging in identifying infarct core in patients with acute ischemic stroke in the anterior circulation?
- What are the clinical outcomes of mechanical thrombectomy up to 24 hours after stroke onset among patients deemed eligible for this procedure based on automated CT perfusion imaging?

Methods

Clinical Literature Search

We performed a clinical literature search on April 5, 2019, to retrieve studies published from database inception until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Health Technology Assessment database, and the National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.²²

We created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites as well as clinical trial and systematic review registries. The grey literature search was updated on September 12, 2019. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception until April 5, 2019
- Randomized controlled trials, observational studies, systematic reviews, and meta-analyses

Exclusion Criteria

- Editorials, commentaries, case reports, conferences abstracts, letters
- Animal and in vitro studies
- Studies that compared different imaging platforms

Participants

Inclusion Criteria

- Adults (≥ 18 years) with acute ischemic stroke caused by large-vessel occlusion in the anterior circulation

Exclusion Criteria

- Pediatric stroke
- Hemorrhagic stroke

Intervention

Inclusion Criteria

- Automated CT perfusion imaging

Exclusion Criteria

- Automated imaging for post-processing diffusion-weighted imaging (DWI) and perfusion-weighted imaging data generated by magnetic resonance imaging (MRI) scanners (in cases of mixed CT and MRI, studies that reported that less than 50% of the patients received MRI were included)

Outcome Measures

- Diagnostic accuracy (sensitivity, specificity, positive predictive value, negative predictive value) using DWI or non-contrast CT as the reference standard
- Clinical utility:
 - Mortality
 - Functional independence
 - Intracranial hemorrhage

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence²⁰ and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion.

Data Extraction

We extracted relevant data on study characteristics and risk of bias items using a data form to collect information on the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration and years, participant allocation, allocation sequence concealment, blinding, reporting of missing data, reporting of outcomes, whether the study compared two or more groups)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, outcome definition and source of information, unit of measurement, upper and lower limits [for scales], time points at which the outcomes were assessed)

Statistical Analysis

Meta-analysis was not possible for the diagnostic accuracy outcomes; we undertook a descriptive summary of the results reported in each study. For clinical utility outcomes, we conducted a meta-analysis of the data from randomized controlled trials to obtain a pooled estimate for functional independence. We used Stata statistical software (version 11.2)²³ to perform a meta-analysis on the reported rates of functional independence and produce a forest plot. We used the risk ratio and its 95% confidence interval as the summary statistic to display the difference between groups. We used a random-effects model to pool the data and the chi-square test to determine statistical heterogeneity among studies.

Critical Appraisal of Evidence

We assessed risk of bias using the QUADAS-2 tool²⁴ for diagnostic accuracy studies and the Cochrane risk-of-bias tool²⁵ for randomized controlled trials (Appendix 2).

We evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.²⁶ The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Results

Clinical Literature Search

The search of the clinical literature yielded 2,254 citations published from database inception to April 5, 2019. We identified 12 additional studies from other sources. We identified 14 studies that met our inclusion criteria. See Appendix 3 for a list of studies excluded after full-text review. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

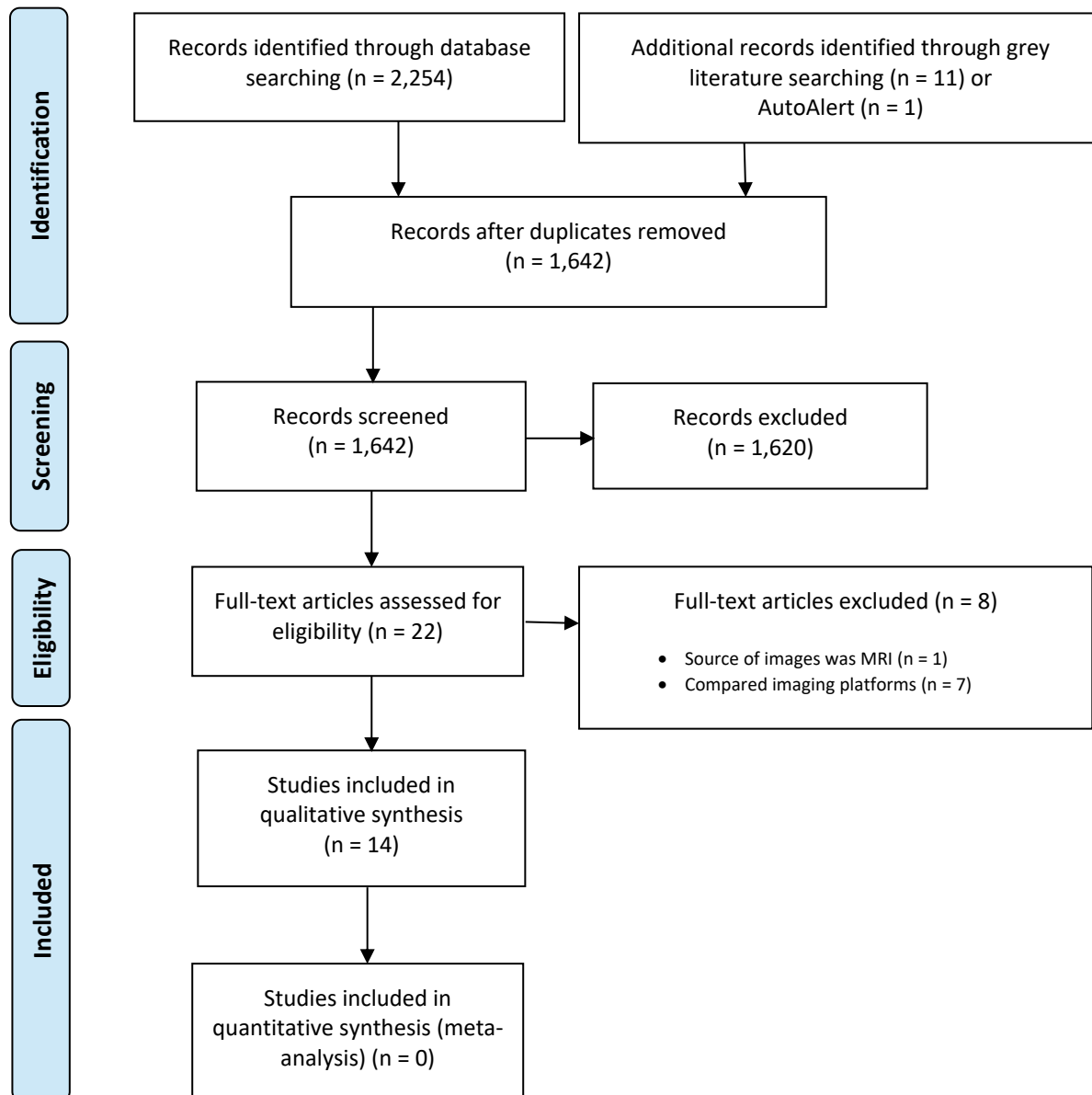


Figure 1: PRISMA Flow Diagram—Clinical Search Strategy

Source: Adapted from Moher et al.²⁷

Abbreviation: MRI, magnetic resonance imaging; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Diagnostic Accuracy

Characteristics of Included Studies

Four studies reported on the accuracy of automated CT perfusion imaging to identify the infarct core and estimate lesion volume.²⁸⁻³¹ Two studies reported on misclassification rates and/or technical failure.^{32,33} Two studies reported on the accuracy of automated CT perfusion imaging in predicting favourable and poor outcomes.^{34,35} Study characteristics are shown in Table 3.

We identified no studies that compared the accuracy of CT perfusion imaging data post-processed by automated imaging with CT angiography (CTA) or multiphase CTA.

Table 3: Characteristics of Included Diagnostic Accuracy Studies

Author, Year	Study Design and Period	Imaging	Patients, N	M/F	Age, Mean (SD)	NIHSS, Median (IQR) ^a	Time From Stroke Onset, h	Follow-up Assessment Method	Treatment	Select Thresholds
Siegler et al, 2019 ³³ United States	Retrospective registry Jun 2017–Dec 2017	RAPID	60	24/36	Median (IQR) (64–84)	16 (11–22)	Median: 6.2	MRI: 17 (28%)	tPA: 17 (28%)	Tmax > 6 s rCBF < 30%
Hoving et al, 2018 ³¹ Australia	IPD-MA HERMES trial: Jan 2010–May 2017 EXTEND-IA TNK: Mar 2015–Oct 2017	RAPID (version 4.5)	120	61/59	69.6 (12.9)	16 (14–21)	< 6 Median: 1.8	DWI ≤ 24 h	NA	rCBF < 30% normal
Haussen et al, 2016 ³⁰ United States	Retrospective Sep 2010–Mar 2015	RAPID (version 4.5.0)	114 ^b Group 1: 93 Group 2: 21	Group 1: 46/47 Group 2: 14/7	Group 1: 64.2 (15.6) Group 2: 60.2 (16.5)	Mean (SD) Group 1: 18.7 (5.6) Group 2: 15.8 (4.9)	To groin puncture: 7	DWI < 72 h MRI FLAIR > 72 h (before discharge)	MT	Core ≤ 50 mL Tmax > 10 s ≤ 100 mL Absolute mismatch ≥ 15 mL Mismatch ratio 1.8
Benson et al, 2015 ²⁸ United States	Retrospective Jan 2006–Jul 2011	Toshiba, VITREA workstation	86	NR	AIS: 63.6 (15.8) Control: 58.8 (13.7)	NR	< 12	DWI (mean 5.2 h)	No tPA between CTP and DWI	rCBV decrease ≥ 40% TTP elevation ≥ 7 s
Campbell et al, 2015 ³² Australia	Prospectively collected data in EXTEND-IA trial	NR	776	NR	NR	NR	> 9	NR	tPA	Core volume < 70 mL Tmax > 6 s CBF < 30% normal Mismatch ratio > 1.2
Dehkarghani et al, 2015 ³⁴ United States	Retrospective Feb 2011–Dec 2013	RAPID	47	NR	Median (range): 70 (33–94)	15 (16)	≤ 12 Mean: 3.5	DWI: 77% NCCT: 23% before discharge	IV tPA: 23 (52%) Arterial tPA or MT: 10 (23%)	rCBV < 30% normal rCBF < 30% normal Tmax tested: > 4, > 6, > 8, > 10 s
Gueskens et al, 2015 ²⁹ Netherlands	Prospectively collected data in MR-CLEAN trial	NR	35	NR	NR	Decrease ≥ 2	≥ 6	NCCT 5–7 days (n = 33) 24 h (n = 2)	NR	rMTT ≥ 145% CBV < 2.0 mL/100 g
Inoue et al, 2012 ³⁵ United States	Retrospective May 2009–May 2011	RAPID	42	18/24	74 (14)	13 (6–19)	≤ 3 Mean: 1.5	MRI 36 h after tPA therapy	tPA after imaging	CBF < 30% normal Tmax tested: > 6, > 8, > 10 s Core volume > 85 mL

Abbreviations: AIS, acute ischemic stroke; CTP, computed tomography perfusion; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; IPD-MA, individual patient data meta-analysis; IQR, interquartile range; IV, intravenous; M/F, male/female; MRI, magnetic resonance imaging; MT, mechanical thrombectomy; NCCT, non-contrast computed tomography; NIHSS, National Institute of Health Stroke Scale; NR, not reported; rCBF, relative cerebral blood flow; rCBV, relative cerebral blood volume; SD, standard deviation; Tmax, time to maximum tissue contrast density; tPA, tissue plasminogen activator; TTP, time to peak.

^aNIHSS scores range from 0 to 42; higher scores indicate more severe neurologic deficits.

^bGroup 1: patients without extracranial anterior circulation occlusion; Group 2: patients with extracranial anterior circulation occlusion.

Identifying the Infarct Core and Estimating Volume

Several studies reported on the accuracy of automated CT perfusion imaging in identifying the infarct core and measuring the affected area.

Hoving et al³¹ conducted a meta-analysis of individual patient data from eight randomized controlled trials that included stroke patients with large-vessel occlusion in the anterior circulation. This study compared the accuracy of automated CT perfusion imaging with follow-up DWI as the reference standard. Seven of the trials were included in a previous analytical study by the HERMES collaboration^{6,7,36-40} and one was the EXTEND-IA TNK trial.⁴¹ For the meta-analysis, the authors selected patients who had adequate CT perfusion and 24-hour DWI, had received mechanical thrombectomy, and had successful reperfusion of greater than 50% of the affected arterial territory. Sixty-one patients from the HERMES study and 59 patients from EXTEND-IA TNK met the inclusion criteria.

Meta-analysis of individual patient data showed that in 101 of the 120 patients, automated CT perfusion imaging identified the infarct core detected by DWI (sensitivity 84%). However, it underestimated the volume of the infarct core by a median volume of 25.4 mL (interquartile range [IQR] 10–63.7 mL). In 19 patients (16%), the infarct core lesions detected by DWI were not detected by automated CT perfusion imaging (false negative lesions). The median volume of missed lesions was 13.1 mL (IQR 7.9–21.3 mL). In 91 of 120 patients, automated imaging showed ischemic lesions in some areas that were not seen by DWI (false lesions), resulting in overestimation of the infarct core. Of those, 21 patients (18%) had a core volume overestimation of 5 to 10 mL, and 17 (14%) had a core volume overestimation of greater than 10 mL. In 63 patients (53%), the core overestimation was small (≤ 5 mL).

Three single-arm studies²⁸⁻³⁰ also reported on the number of lesions and/or their volume as assessed by automated CT perfusion imaging compared with DWI.

Benson et al²⁸ reviewed 1,085 CT studies performed over 5.5 years. Patients who underwent both CT perfusion and DWI within 12 hours of symptom onset were included ($n = 43$). The authors also selected another 43 age-matched patients with negative DWI as controls. Lesions of less than 1.5 mL (lacunar infarcts) were excluded from the analysis. Also, only lesions on the middle cerebral artery were included. The penumbra was tissue with normal cerebral blood volume and with relative time to peak elevation, mean transit time prolongation, or reduction in relative cerebral blood flow greater than 60%. For comparison, three neurologists with more than 5 years of experience and blinded to final results, patient histories, follow-up images, and other CT perfusion parameters scored the CT perfusion and DWI images according to the Alberta Stroke Program Early CT Score (ASPECTS). Each of the reviewers tabulated ASPECTS for “infarct core” and “core and penumbra.” Of 43 patients, 36 (84%) with positive DWI had lesions less than or equal to 70 mL, and the remaining seven had lesions greater than 70 mL. Automated CT perfusion imaging correctly categorized patients with larger lesions (> 70 mL) and smaller lesions (≤ 70 mL). Ranges for the accuracy of automated CT perfusion imaging in identifying the infarct core and infarct core plus penumbra are shown in Table 4.

Haussen et al³⁰ investigated the effect of extracranial steno-occlusive disease (occlusion of blood vessels outside of the skull) on volume estimation in stroke patients with large-vessel occlusion in the anterior circulation. We included this study because it reported on the volume of the estimated and final infarct core; included patients with acute ischemic stroke who had full reperfusion with mechanical thrombectomy; and used automated CT perfusion imaging to guide patient selection. The investigators measured the difference in the volume of the infarct core and the penumbra between groups of

patients with and without steno-occlusive disease, using delay-corrected perfusion processing. The presence of extracranial steno-occlusive disease was determined using angiographic images. The final infarct volume was determined by follow-up DWI (within 72 hours of stroke) or MRI fluid-attenuated inversion recovery (FLAIR) images afterward. When MRI was not performed because of contraindications, non-contrast CT (NCCT) was used to determine the final infarct core.

In this study, a target mismatch profile was found in 61 patients (65%) without extracranial steno-occlusive disease and in 13 (62%) of those with extracranial steno-occlusive disease ($P = .08$). The mean difference in volume between the estimated and final infarct core for the groups without and with steno-occlusive disease were 17.8 (standard deviation [SD] 41.3) and 24.2 (SD 41.2; $P = .05$). The authors concluded that with optimized CT perfusion imaging using delay correction and optimized thresholding, the presence of extracranial steno-occlusive disease did not significantly influence the results.

Geuskens et al²⁹ used data from the MR-CLEAN trial to investigate the accuracy of automated CT perfusion imaging in measuring the infarct core volume. Patients in this study had more than 10 cm head coverage with CT. Final infarct was determined at 5 to 7 days of follow-up by NCCT, except in two patients, for whom 24-hour NCCT was used. Automated CT perfusion imaging overestimated the volume of the infarct core by a median of 30.4 mL (IQR 20.9–77). The infarct core volume assessed by automated imaging was 49.7 mL, but follow-up NCCT showed the size of the infarct core to be 30.4 mL.

Table 4 shows results of the studies that reported on the diagnostic accuracy of automated CT perfusion imaging in identifying the infarct core and measuring the volume of the lesion.

Table 4: Diagnostic Accuracy of Automated CT Perfusion Imaging—Identifying Infarct Core and Estimating Volume

Study	Diagnostic Accuracy, %	Infarct Core Volume, mL	Volumetric Difference, mL
Hoving et al, 2018 ³¹	Sensitivity: 101/120 (84%) False negative rate: 19/120 (16%)	Median (IQR) DWI ≤ 24 hours CTP: 7.8 (1.8–19.9) DWI: 30.8 (14.9–67.6)	Median (IQR) 25.4 (10–63.7)
Haussen et al, 2016 ³⁰	NR	Mean (SD) DWI < 72 hours Without ECSD CTP: 19.7 (25.5) DWI: 37.5 (45.6) With ECSD CTP: 20.8 (19.3) DWI: 45 (47.1)	Mean (SD) Without ECSD 17.8 (41.3) With ECSD 24.2 (41.2)
Benson et al, 2015 ²⁸	Core only ^a Sensitivity: 72.1%–76.6% Specificity: 86%–95.3% PPV: 83.8%–93.9% NPV: 75.5%–80.4% Accuracy: 79.1%–86% Core + penumbra ^a Sensitivity: 74.4%–83.3% Specificity: 86.4%–93.2% PPV: 85%–91.4% NPV: 78.4%–85.4% Accuracy: 83.7%–88.4%	Mean (SD) DWI ≤ 12 hours DWI: 34.5 (48.1) CTP core only: 28.7 (39.4)	5.8 (95% CI, –13 to 24.7)
Gueskens et al, 2015 ²⁹	NR	Median (IQR) NCCT 5–7 days CTP: 49.7 (29.9–132) NCCT: NR	Mean (SD) Overestimated volume 30.4 (20.9–77)

Abbreviations: CT, computed tomography; CTP, CT perfusion; DWI, diffusion-weighted imaging; ECSD, extracranial steno-occlusive disease; IQR, interquartile range; NCCT, non-contrast CT; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; SD, standard deviation.

^aRanges for three reviewers.

Automated CT perfusion imaging also detected lesions that were artifacts (false positives) and were not identified by DWI. In the study by Siegler et al,³³ 26 of 60 lesions (43%) were false positives, and in 16 of those (62%), the artifactual findings were attributed to excess patient motion in the scanner. In the study by Campbell et al,³² 70 of 776 lesions (9%) were false positives (Table 5).

Table 5: Automated CT Perfusion Imaging—Rate of Artifactual Findings

Study	Artifactual Lesions (False Positives)
Siegler et al, 2019 ³³	26/60 (43%)
Hoving et al, 2018 ³¹	91/120 (76%) Volume of false lesions, median (IQR), mL: < 5 mL: 1.1 (0.3–3.1); n = 63 (53%) 5–10 mL: 6.9 (5.9–8.1); n = 21 (18%) > 10 mL: 18.3 (14.3–25.5); n = 17 (14%)
Campbell et al, 2015 ³²	70/776 (9%)
Geuskens et al, 2015 ²⁹	Volume of false lesions, median (IQR), mL: 30.4 (20.9–77) False discovery rate ^a : 62% (49%–80%)

^aFalse discovery rate was calculated by dividing the misclassified core volume by the total ischemic core volume.

Misclassification Rate

Two studies reported on the misclassification rate of automated CT perfusion imaging.^{32,33}

Campbell et al³² reported on mismatch misclassification and technical failure with automated CT perfusion imaging using data from the EXTEND trial⁴² (gathered over 6 months in five study centres involving 776 patients). For thresholds, the authors selected a mismatch ratio of greater than 1.2 and an absolute mismatch volume of greater than 10 mL. Two stroke neurologists evaluated the imaging maps and reported that the rate of technical failure (uninterpretable maps) was 26 of 776 (3.4%). Most of the technical failures were due to patient motion in the scanner (n = 23), but three were due to contrast bolus failure. The experts overruled mismatch classification detected by the imaging in 70 of 776 patients (9%). The errors in mismatch calculation by automated CT perfusion imaging were due to artifacts that resulted in an overestimation of the infarct core. The artifacts were caused by patient motion, causing delay in time to maximum tissue contrast density (Tmax) in specific areas of the brain. The artifacts were more in the base of the skull and the orbit; in this study, a research version of the RAPID software was used that did not automatically exclude structures below the base of the skull.

Siegler et al³³ examined data from a stroke registry. The study was conducted in three stroke centres, but most of the patients (n = 52) were evaluated at one hospital, which was the sole centre for endovascular intervention. The authors investigated whether the artifactual findings from automated CT perfusion imaging resulted in an overestimation of the affected area and misclassified patients for mechanical thrombectomy. Patients with large-vessel occlusion of the anterior circulation (n = 60) were included if the time since they were last known well was 24 hours or less.

Two independent readers with knowledge of clinical symptoms and the location of the occlusion manually assessed the lesions identified by automated imaging.³³ The readers calculated the true volume of the ischemic area by excluding areas outside of expected vascular distribution or brain tissue, such as the sinuses or skull. The automated imaging identified lesions in 57 patients (95%). In 26 patients (43%), the imaging found additional artifactual lesions, although the volume of the artifactual abnormalities in most patients was low. The median volume of the artifactual lesions was 12 mL (IQR 3–16 mL). Following evaluation by the readers and recalculation of the mismatch ratio, one patient was reclassified: the mismatch ratio was initially estimated at 2.04 (eligible for thrombectomy), but the

readers found that the presence of artifacts led to miscalculation, and reassessed the ratio at 1.4 (ineligible for mechanical thrombectomy).

In the same study,³³ three (5%) patients with arterial occlusion who would have been eligible for thrombectomy were not identified by automated CT perfusion imaging. One was not detected at a threshold of Tmax greater than 6 seconds but was detected at Tmax greater than 4 seconds and had a large penumbra of 159 mL. This patient's score on the baseline National Institute of Health Stroke Scale (NIHSS) was 20, indicating neurological deficit. The patient was selected and underwent mechanical thrombectomy. The second patient had an NIHSS score of 26, but the lesion was not detected using a threshold of Tmax greater than 6 seconds. The lesion was detected when Tmax greater than 4 seconds was used. In these two patients, clinical symptoms were useful and directed clinicians toward the correct decisions. In a third patient who had an occlusion in the middle cerebral artery, automated imaging did not detect the infarct core at any Tmax threshold.

The total number of patients who were incorrectly classified (either misclassified as eligible for mechanical thrombectomy when they weren't, or missed as eligible for the procedure) using the initially selected threshold for Tmax was 4 of 60 (7%).³³ The authors suggested that clinicians should review the CT perfusion images directly, with knowledge of the patient's clinical presentation, other images (such as CTA), and vascular distribution to avoid inappropriate management of stroke patients and unnecessary transfers to stroke centres based on automated post-processing of the images. This study supported the need for experienced clinicians to interpret automated perfusion imaging. Table 6 shows findings of the two studies.

Table 6: Diagnostic Accuracy of Automated CT Perfusion Imaging—Misclassification Rate

Study	Incorrectly Identified Patient as Eligible	Missed Eligible Patients
Siegler et al, 2019 ³³	1/60	3/60
Campbell et al, 2015 ³²	70/776 (9%; 95% CI, 7.1%–11.3%)	NR

Abbreviations: CI, confidence interval; CT, computed tomography; NR, not reported.

Predicting Favourable or Poor Clinical Outcomes

Two studies investigated the accuracy of automated CT perfusion imaging for identifying patients who would have favourable or poor clinical outcomes.^{34,35}

In the study by Dehkharghani et al,³⁴ the authors constructed a receiver operating characteristics (ROC) curve and determined sensitivity and specificity values to identify the optimal operating values for each perfusion parameter in predicting favourable clinical outcomes. The final infarct core was measured by DWI at the time of discharge from hospital in 77% of patients and by CT in the rest. The median infarct core volume was 34 mL (IQR 94 mL). A good clinical outcome (defined as a modified Rankin Scale [mRS] score of ≤ 2 at 3 months) was observed in 16 of 47 patients (34%). The strongest predictor of favourable clinical outcomes was final follow-up infarct volume (area under the ROC curve 96% [95% CI, 91%–100%]). Based on automated CT perfusion imaging, core cerebral blood volume had the highest accuracy among perfusion parameters for predicting good clinical outcomes (area under the ROC curve 86% [95% CI, 74%–96%]). The area under the ROC curve for core cerebral blood flow was 81% (95% CI, 68%–93%).

In the study by Inoue et al,³⁵ a poor clinical outcome was defined as an mRS score of 5–6 at 30 days. Initially, the authors used the parametric thresholds of infarct core greater than 85 mL and Tmax greater than 8 seconds to identify patients with poor clinical outcomes. Using these thresholds, four of the 42 patients met the criteria for poor outcomes after thrombolysis. However, based on ROC analysis, the investigators determined that the optimal threshold for poor clinical outcomes was an infarct core of greater than 53 mL, as determined by cerebral blood flow. Using this threshold, one additional patient met the criteria for a poor clinical outcome, for a total of 5 (12%). Four of the five patients died during acute hospitalization, and one had an mRS score of 5 at 30 days. Using the optimal threshold determined by ROC analysis, the sensitivity and specificity of cerebral blood flow for identifying patients who would have poor clinical outcomes were 67% and 100%, respectively. Table 7 shows the findings of the above studies.

Table 7: Diagnostic Accuracy of Automated CT Perfusion Imaging—Predicting Favourable or Poor Clinical Outcomes

Study	Sensitivity	Specificity	Accuracy (95% CI)
Dehkharghani et al, 2015 ³⁴	Final infarct core: 91% CTP parameters: rCBV: 85% rCBF: 73% Tmax > 6: 77%	Final infarct core: 88% CTP parameters: rCBV: 78% rCBF: 72% Tmax > 6: 72%	Final infarct core: 96% (91%–100%) CTP parameters: rCBV: 86% (74%–96%) rCBF: 81% (68%–93%) Tmax > 6: 77% (63%–92%)
Inoue et al, 2012 ³⁵	CBF > 53 mL: 67% CBF > 85 mL: 56%	CBF > 53 mL: 100% CBF > 85 mL: 100%	—

Abbreviations: CI, confidence interval; CTP, computed tomography perfusion; CBF, cerebral blood flow; rCBF, relative cerebral blood flow; rCBV, relative cerebral blood volume; Tmax, time to maximum tissue contrast density.

Clinical Utility

Characteristics of Included Studies

Six studies^{6,10,11,37,43,44} used automated CT perfusion imaging to select patients for mechanical thrombectomy. Four of these studies were randomized controlled trials,^{6,10,11,37} and two were observational studies.^{43,44} Four studies included patients who presented within 6 hours after the onset of symptoms,^{6,37,43,44} and two^{10,11} included patients who presented beyond 6 hours after the onset of symptoms. We identified no studies that directly compared outcomes between patients whose treatment was guided by automated CT perfusion imaging and patients whose treatment was guided by non-automated CT perfusion imaging.

In the included studies, the degree of success in revascularization was assessed using Thrombolysis in Cerebral Infarction (TICI) scores. This scoring system has a range of 0 to 3. Grade 0 indicates no perfusion; grade 2a indicates reperfusion of less than half of normal; grade 2b indicates reperfusion of more than half of normal; and grade 3 indicates complete reperfusion at the site of the previously occluded territory.³⁷ In a modified version (mTICI), an additional category (c) has been added to the scale for patients with near-complete perfusion.

Study characteristics are presented in Table 8.

Table 8: Characteristics of Included Studies That Provided Clinical Outcomes

Author, Year	Study Design and Period	Imaging Modality Software	Patients, N	M/F	Age, Mean (SD)	NIHSS, Median (IQR) ^a	Time From Stroke Onset, Median (IQR) h	tPA, n (%)	Select Thresholds	Success of Recanalization/ Reperfusion ^{b,c}
Vanicek et al, 2019 ⁴⁴	Retrospective single arm Jan 2016–Dec 2017	CT: 100% RAPID	62	32/30	70.1 (13.6)	16 (13–20)	To imaging: 1.5 To groin puncture: 2.75 (2.25–4.6)	43 (69.4)	CBF < 30% Tmax > 6 s	TICI 2b/3: 42/62 (68%)
Albers et al, 2018 ¹⁰	RCT May 2016–May 2017	CT: 73% MRI: 27% RAPID	182	MT: 46/46 SC: 44/46	Median (IQR) MT: 70 (59–79) SC: 71 (59–80)	MT: 16 (10–20) SC: 16 (12–21)	Symptom onset to randomization MT: 10.9 (8.8–12.4) SC: 10.7 (8.7–13.1) Imaging to groin puncture MT: 1 (0.7–1.5)	MT: 10 (11) SC: 8 (9)	Infarct < 70 mL Penumbra ≥ 15 mL Mismatch ratio ≥ 1.8 Tmax > 6 s	Complete recanalization at 24 h MT: 65/83 (78%) SC: 14/77 (18%) OR (95% CI): 4.31 (2.65–7.01) P < .001
Nogueira et al, 2018 ¹¹	RCT Sep 2014–Feb 2017	CT: 64% MRI: 36% RAPID	206	MT: 42/65 SC: 51/48	MT: 69.4 (14.1) SC: 70.7 (13.2)	MT: 17 (13–21) SC: 17 (14–21)	Symptom onset to randomization MT: 4.8 (3.6–6.2) SC: 5.6 (3.6–7.8) Last seen well to randomization MT: 12.2 (10.2–16.3) SC: 13.3 (9.4–15.8) Randomization to groin puncture 0.3 (0.2–0.5)	MT: 5 (5) SC: 13 (13)	Infarct < 50 mL Ischemic to infarct ratio ≥ 1.8	Recanalization at 24 h MT: 82/107 (77%) SC: 39/99 (39%) RR (95% CrI): 2 (2–4) P < .001
Campbell et al, 2015 ³⁷	RCT Aug 2012–Oct 2014	CT: 100% RAPID	70	MT: 17/18 SC: 17/18	MT: 68.6 (12.3) SC: 70.2 (11.8)	MT: 17 (13–20) SC: 13 (9–19)	To tPA MT: 2.1 (1.6–2.7) SC: 2.4 (1.8–3) To groin puncture MT: 3.5 (2.8–4.2)	All (within 4.5 h)	Infarct < 70 mL CBF < 30% Tmax > 6 s	Recanalization at 24 h MT: 33/35 (94%) SC: 15/35 (43%) OR (95% CI): 29 (5.4–155) P < .001

Author, Year	Study Design and Period	Imaging Modality Software	Patients, N	M/F	Age, Mean (SD)	NIHSS, Median (IQR) ^a	Time From Stroke Onset, Median (IQR) h	tPA, n (%)	Select Thresholds	Success of Recanalization/ Reperfusion ^{b,c}
Saver et al, 2015 ⁶ SWIFT-PRIME; 39 centres; United States and Europe	RCT Dec 2012– Nov 2014	CT: CTP was the primary baseline imaging RAPID	196 MT: 98 SC: 98	MT: 54/44 SC: 45/53	MT: 65 (12.5) SC: 66.3 (11.3)	MT: 17 (13–20) SC: 17 (13–19)	To randomization MT: 3.1 (2.4–4.2) SC: 3.2 (2.2–4.4) To groin puncture 3.7 (2.8–4.6)	All (within 4.5 h)	Infarct ≤ 50 mL Tmax > 10 s ≤ 100 mL Mismatch volume ≥ 15 mL Mismatch ratio ≥ 1.8	Recanalization ≥ 90% at 27 h MT: 53/64 (83%) SC: 21/52 (40%) RR (95% CI): 2.05 (1.45–2.91) P < .001
Turk et al, 2013 ⁴³	Retrospective single arm Period NR	CT: 100% GE Advantage Windows/ Siemens Leonardo	247	116/131	66 (NR)	18 (NR)	To groin puncture: 6 (range, 1.5–77)	116 (47)	NR	TICI 2b/3: 184/247 (75%)

Abbreviations: CBF, cerebral blood flow; CI, confidence interval; CrI, credible interval; CT, computed tomography; CTP, CT perfusion; IQR, interquartile range; M/F, male/female; MRI, magnetic resonance imaging; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; NR, not reported; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio; SC, standard care; SD, standard deviation; TICI, Thrombolysis in Cerebral Infarction; Tmax, time to maximum tissue contrast density; tPA, tissue-type plasminogen activator.

^aNIHSS scores range from 0 to 42; higher scores indicate more severe neurologic deficits.

^bRecanalization refers to reopening of an occluded vessel. Reperfusion refers to restoring blood flow in a formerly occluded vessel.

^cTICI scores range from 0 to 3. Grade 0 indicates no perfusion, grade 2a indicates reperfusion of less than half, grade 2b indicates reperfusion of more than half, and grade 3 indicates complete reperfusion at the site of the previously occluded territory.

Randomized Controlled Trials That Selected Patients for Mechanical Thrombectomy Within 6 Hours of Stroke Onset

The two trials that randomized patients who presented within 6 hours after symptom onset were the SWIFT-PRIME⁶ (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment; NCT01657461) and the EXTEND-IA³⁷ (Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial; NCT01492725). Both trials included stroke patients with occlusions in the proximal anterior circulation and hypothesized that mechanical thrombectomy with a stent retriever in addition to intravenous thrombolysis would increase reperfusion rates and improve functional outcomes compared to thrombolysis alone. In both trials, lesion volumes were determined by automated CT perfusion imaging, and patients with a large infarct core and no evidence of clinically important salvageable tissue were excluded (those patients had a higher risk of symptomatic cerebral hemorrhage and edema, so mechanical thrombectomy may have been futile). Both trials enrolled patients based on their target mismatch profile, and both stopped early because an interim analysis showed that the prespecified efficacy criteria had been met.

In the SWIFT-PRIME trial,⁶ tPA was initiated within 4.5 hours after symptom onset. Patients were randomly assigned to one of the two treatment groups using a 1:1 ratio. Lesion volume and target mismatch were determined by automated CT perfusion imaging. The eligibility criteria included an available target mismatch profile, a small infarct core, and a large region of penumbra. The target mismatch profile was defined as follows: infarct core 50 mL or less; the volume of tissue with a Tmax delay of more than 10 seconds not greater than 100 mL; mismatch volume 15 mL or more; and mismatch ratio at least 1.8. Target mismatch imaging was performed in 83 of 98 patients (85%) in the mechanical thrombectomy group and in 75 of 97 patients (77%) in the standard care group. In the mechanical thrombectomy group, 69 of 83 patients (83%) had target mismatch profile, compared with 64 of 75 patients (85%) in the control group. A malignant profile (core infarct greater than 50 mL and/or Tmax greater than 10 seconds) was detected in 13 of 83 (15.7%) in the mechanical thrombectomy group and 9 of 75 (12%) in the standard care group.

In the EXTEND-IA trial,³⁷ tPA therapy was initiated within 4.5 hours after symptom onset, and mechanical thrombectomy was initiated within 6 hours and completed within 8 hours after stroke. An infarct core was diagnosed if the relative cerebral blood flow (rCBF) was less than 30% of that of normal tissue, and the penumbra was distinguished from minimally hypoperfused areas if Tmax was greater than 6 seconds. At 24 hours of follow-up, 54 patients had undergone MRI and 13 had undergone repeat CT perfusion. Three patients had no 24-hour data available.

Randomized Trials That Selected Patients for Mechanical Thrombectomy Within 6 to 24 Hours of Stroke Onset

Two randomized controlled trials performed mechanical thrombectomy beyond 6 hours and patient selection in these trials was guided by automated CT perfusion imaging. The DEFUSE 3 trial¹⁰ (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke—NCT02586415) was conducted at 38 centres in the United States, and the DAWN trial¹¹ (DWI or CT perfusion Assessment with Clinical Mismatch in the Triage of Wake-up and Late Presenting Strokes Undergoing Neurointervention with Trevo—NCT02142283) was conducted in 26 centres. Both trials included patients who had large-vessel occlusion in the proximal anterior circulation and randomized patients into two arms: mechanical thrombectomy plus standard care and standard care only. In both trials, patients eligible for mechanical

thrombectomy were identified using RAPID automated image processing (Appendix 4). Both trials were terminated early because the prespecified efficacy boundary had been exceeded.

In the DEFUSE 3 trial,¹⁰ mechanical thrombectomy could be performed if patients were in the time window of 6 to 16 hours after they were last seen well. The type of stroke was “on awakening” in 50% of patients, “during wakefulness” in 13.7%, and “witnessed” in 36.3%. Both perfusion imaging and mechanical thrombectomy were performed at the trial site hospital. The protocol required that mechanical thrombectomy be initiated within 90 minutes after qualifying images. Overall, the median time from stroke onset to clot removal was 11.5 hours (IQR, 9.2–12.8 hours).

In that trial,¹⁰ patients were eligible if the infarct core volume was less than 70 mL and the penumbra absolute volume was at least 15 mL. The ratio of the penumbra to the infarct core had to be at least 1.8. The volume of the penumbra was estimated from the volume of tissue with a Tmax greater than 6 seconds. Post-operative clinical assessment was performed at 24 hours after randomization, and at 30 days and 90 days. The baseline imaging methods used in this study were CT perfusion in 133 (73%) and MRI in 49 (27%). Administration of tPA occurred in 11% of patients in the mechanical thrombectomy group and 9% in the standard care group. All patients who were assigned to mechanical thrombectomy underwent the procedure.

In DEFUSE 3,¹⁰ patients had a small infarct core (median volume 9.4 mL [IQR, 2.3–25.6 mL] in the mechanical thrombectomy group and 10.1 mL [IQR, 2.1–24.3 mL] in the standard care group) and a large penumbra (median volume 114.7 mL [IQR, 79.3–146.3 mL] in the mechanical thrombectomy group and 116.1 mL [IQR, 73.4–158.2 mL] in the standard care group), resulting in a high mismatch ratio (11.8 in the mechanical thrombectomy group and 10.2 in the standard care group).

In the DAWN trial,¹¹ the time window was 6 to 24 hours since patients were last known well. Patients were randomly assigned to receive mechanical thrombectomy or standard care alone, using a 1:1 ratio. The type of stroke was “on awakening” in 55.3% of patients, “unwitnessed” in 32.5%, and “witnessed” in 12.1%. A total of 206 patients were included, of which 128 were randomized within 6 hours after symptoms were first observed (74 in the mechanical thrombectomy group and 54 in the standard care group), and 78 patients were randomized beyond 6 hours after symptoms were first observed (33 in the mechanical thrombectomy group and 45 in the standard care group). Infarcts involving more than one-third of the middle cerebral artery were excluded. The imaging modalities for patient selection were CT perfusion and MRI in 64% and 36% of patients, respectively. Patients either did not meet the criteria for tPA therapy because of late presentation or had received tPA but had a persistent occlusion when they were eligible for enrolment. Thrombectomy was performed in 105 of 107 patients in the mechanical thrombectomy arm. The median time from when symptoms were first observed was 4.8 hours (IQR, 3.6–6.2) in the mechanical thrombectomy group and 5.6 hours (IQR, 3.6–7.8) in the standard care group.

In the DAWN trial,¹¹ patients had small infarct core (median volume 7.6 mL [IQR, 2–18 mL] in the mechanical thrombectomy group and 8.9 mL [IQR, 3–18.1 mL] in the standard care group). The size of the penumbra was not reported. In this study, mRS scores were weighted according to average values calculated from patient- and clinician-centred studies (utility-weighted mRS). Scores on the utility-weighted mRS range from 0 (death) to 10 (no symptom of disability). The mean utility-weighted mRS scores at 90 days were 5.5 (SD 3.8) in the mechanical thrombectomy group and 3.4 (SD 3.1) in the standard care group; the adjusted difference and 95% credible interval were 2 (1.1–3); the posterior probability of superiority was greater than 0.999.

Single-Arm Trials That Used Automated CT Perfusion Imaging to Select Patients for Mechanical Thrombectomy

We identified two single-arm retrospective studies^{43,44} that used automated CT perfusion imaging to select patients for mechanical thrombectomy. These studies included stroke patients with large-vessel occlusion in the anterior circulation.

One single-centre study⁴⁴ included patients within 6 hours after the onset of stroke and used automated CT perfusion imaging. The authors of this study compared their results with those of four randomized controlled trials that used the same automated CT perfusion imaging for patient selection.^{6,10,11,37} The median volumes of the infarct core and penumbra were 20 mL (IQR, 2–36 mL) and 145.5 (IQR, 107–184 mL), respectively. The proportion of patients who gained functional independence (mRS 0–2 at 90 days) was close to that of the SWIFT-PRIME study⁶ (37% and 35%, respectively) but lower than that reported for the EXTEND-IA trial³⁷ (72%).

The other study⁴³ was a retrospective review of patients treated at three comprehensive stroke centres in the United States. In this study, the average time from the last point the patient was seen well to groin puncture was 8.2 hours (median 6 hours). Patients with one-third or more of the middle cerebral artery occluded, or those in whom the penumbra was 50% or less of the ischemic area were not selected for mechanical thrombectomy. The primary method of treatment was mechanical aspiration.

Patients were divided into two groups for analysis: 8 hours or less from symptom onset, and more than 8 hours from symptom onset. The mean times to treatment for the two groups were 4.8 hours and 16.4 hours, respectively. In the group presenting at 8 hours or less, 55% of the patients received tPA, compared with 27% in the group presenting at more than 8 hours. The authors found that most of the clinical outcomes were similar between the two groups. Complete recanalization (reopening of an occluded vessel) did not differ between groups (complete recanalization rate of 71.7% for those presenting at 8 hours or less, versus 81.1% for those presenting at more than 8 hours; $P = .15$). Mortality was 24.9% for those presenting at 8 hours or less and 20.3% for those presenting at more than 8 hours ($P = .5$). Functional independence was 42.8% for those presenting at 8 hours or less and 41.9% for those presenting at more than 8 hours ($P = 1.0$). An interesting finding was the effect of recanalization on 90-day functional outcomes. Of those who achieved recanalization, 50.6% had an mRS of 0 to 2, compared with 19% of those who were not recanalized. As well, 35.3% of those who were recanalized had worse functional outcomes (mRS 4–6), compared with 73% of those who were not recanalized. Administering tPA did not significantly influence the number of patients who achieved good clinical outcomes (45% of those treated with tPA versus 41% of those who were not).

Mortality

Five of the studies reported on mortality at 90 days.^{6,10,11,37,43} None of the randomized controlled trials demonstrated a significant difference in mortality between mechanical thrombectomy and standard care and the pooled effect size was not significant (RR 0.73 [95% CI, 0.51–1.05]). The retrospective review by Turk et al⁴³ reported a mortality rate of 23.5%.

Table 9 shows mortality rates in the two arms of the randomized controlled trials.

Table 9: Mortality Rates in Randomized Controlled Trials That Selected Patients for Mechanical Thrombectomy Using Automated CT Perfusion Imaging

Study	Mechanical Thrombectomy, n (%)	Standard Care, n (%)	RR/OR (95% CI)
Within 6 Hours of Stroke Onset			
Campbell et al, 2015 ³⁷ EXTEND-IA	3 (9)	7 (20)	OR 0.45 (0.1–2.1); <i>P</i> = .31
Saver et al, 2015 ⁶ SWIFT-PRIME	9 (9)	12 (12)	RR 0.74 (0.33–1.68); <i>P</i> = .5
Within 6 to 24 Hours of Stroke Onset			
Albers et al, 2018 ¹⁰ DEFUSE	13 (14)	23 (26)	RR 0.55 (0.3–1.02); <i>P</i> = .05
Nogueira et al, 2018 ¹¹ DAWN	20 (19)	18 (18)	RR 1.0 (1.0–2.0); <i>P</i> = 1.00

Abbreviations: CI, confidence interval; CT, computed tomography; OR, odds ratio; RR, risk ratio.

Functional Independence

Six studies^{6,10,11,37,43,44} reported on the rate of functional independence (mRS score ≤ 2 at 90 days). Significantly more patients who received mechanical thrombectomy gained functional independence. The rates of functional independence for patients who underwent mechanical thrombectomy in the two single-arm trials were 37.1%⁴⁴ and 42.5%.⁴³

In the DEFUSE 3 trial,¹⁰ the risk ratio for functional independence comparing the two study arms was relatively higher when MRI was used to select patients (RR 3.17 [95% CI, 1.35–7.43]) than when CT was used (RR 2.5 [95% CI, 1.32–4.75]). However, no direct comparison was reported.

The rates of functional independence for the randomized controlled trials are shown in Table 10.

Table 10: Rates of Functional Independence in Randomized Controlled Trials That Selected Patients for Mechanical Thrombectomy Using Automated CT Perfusion Imaging^a

Study	Mechanical Thrombectomy, n (%)	Standard Care, n (%)	RR/OR (95% CI)
Within 6 Hours of Stroke Onset			
Campbell et al, 2015 ³⁷ EXTEND-IA	25 (71)	14 (40)	OR NR; <i>P</i> = .01
Saver et al, 2015 ⁶ SWIFT-PRIME	59 (60)	33 (35)	RR 1.7 (1.23–2.33); <i>P</i> < .001
Within 6 to 24 Hours of Stroke Onset			
Albers et al, 2018 ¹⁰ DEFUSE	41 (45)	15 (17)	RR 2.67 (1.60–4.48); <i>P</i> < .001
Nogueira et al, 2018 ¹¹ DAWN	52 (49)	13 (13)	Adjusted difference (95% CrI): 33% (21%–44%); Posterior probability of superiority: > 0.999

Abbreviations: CI, confidence interval; CrI, credible interval; CT, computed tomography; mRS, modified Rankin Scale; NR, not reported; OR, odds ratio; RR, risk ratio.
^aFunctional independence was defined as mRS 0–2 at 90 days. Scores on the mRS range from 0 (no symptom) to 6 (death).

We performed a meta-analysis to obtain a pooled estimate for the rate of functional independence reported by the randomized controlled trials. The resulting pooled estimate showed a significant improvement in the rate of functional independence with mechanical thrombectomy, compared with standard care (Figure 2).

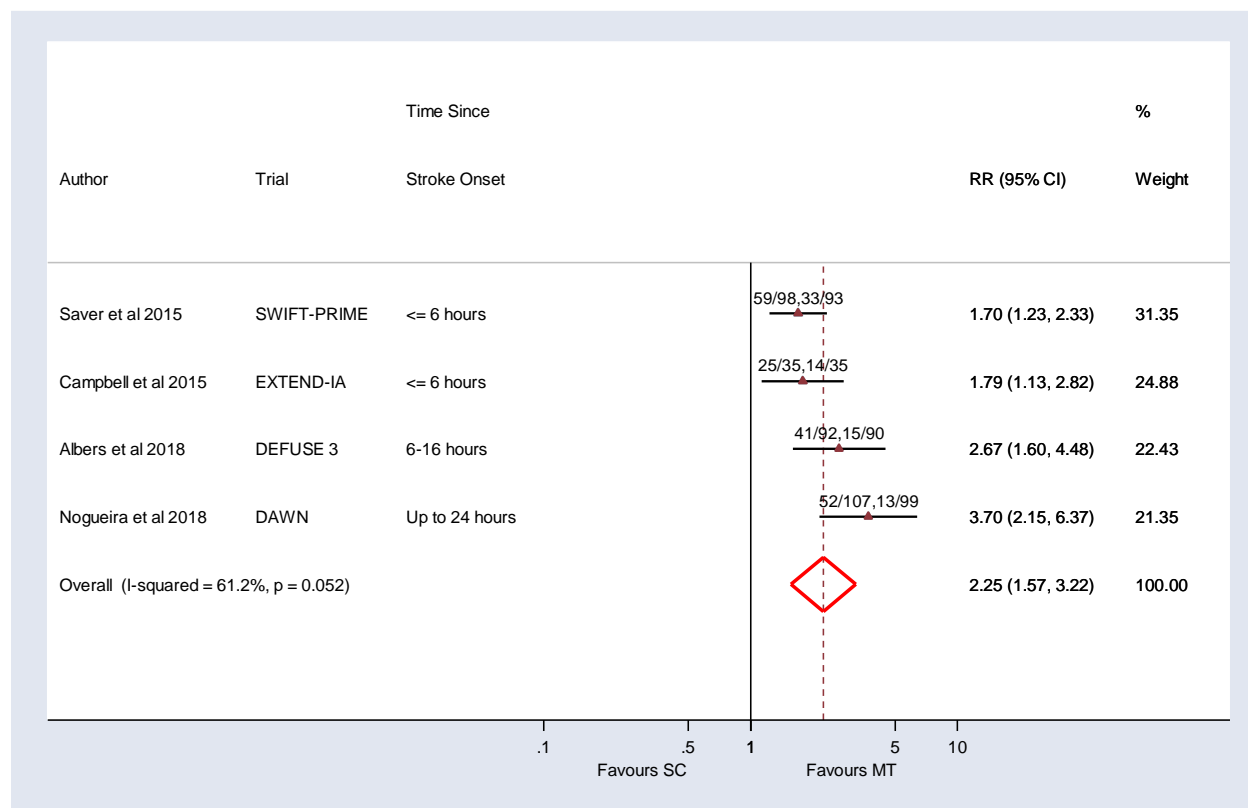


Figure 2: Risk Ratio for Functional Independence Comparing Mechanical Thrombectomy With Standard Care

Abbreviations: CI, confidence interval; MT, mechanical thrombectomy; RR, risk ratio; SC, standard care.

Intracranial Hemorrhage

The rate of symptomatic intracranial hemorrhage in patients who underwent mechanical thrombectomy in the retrospective review by Turk and colleagues⁴³ was 8%. The rates of intracranial hemorrhage for the mechanical thrombectomy and standard care arms of the four randomized controlled trials^{6,10,11,37} are shown in Table 11.

Table 11: Rate of Intracranial Hemorrhage in Randomized Controlled Trials That Selected Patients for Mechanical Thrombectomy Using Automated CT Perfusion Imaging

Study	Parenchymal Hematoma, n (%)	Symptomatic Intracranial Hemorrhage, n (%)	Subarachnoid Hemorrhage, n (%)
Within 6 Hours of Stroke Onset			
Campbell et al, 2015 ³⁷ EXTEND-IA	36 hours post-treatment MT: 4 (11) SC: 3 (9) P = .99	36 hours post-treatment MT: 0 (0) SC: 2 (6) P = .5	NR
Saver et al, 2015 ⁶ SWIFT-PRIME	27 hours post-randomization MT: 5 (5) SC: 7 (7) P = .57	27 hours post-randomization MT: 0 (0) SC: 3 (3) P = .12	MT: 4 (4) SC: 1 (1) P = .37
Beyond 6 Hours of Stroke Onset			
Albers et al, 2018 ¹⁰ DEFUSE	24 hours MT: 8 (9) SC: 3 (3) OR (95% CI): 2.61 (0.73–14.69) P = .21	36 hours post-randomization MT: 6 (7) SC: 4 (4) OR (95% CI): 1.47 (0.4–6.55) P = .75	NR
Nogueira et al, 2018 ¹¹ DAWN	24 hours post-stroke MT: 2 (1.9) SC: 1 (1)	24 hours post-stroke MT: 6 (6) SC: 3 (3) RR (95% CI): 2 (1–7) P = NR	24 hours post-stroke MT: 1 (0.9) SC: 0 (0)

Abbreviations: CI, confidence interval; CT, computed tomography; MT, mechanical thrombectomy; NR, not reported; OR, odds ratio; RR, risk ratio; SC, standard care; SD, standard deviation.

Risk of Bias in the Included Studies

Diagnostic Accuracy

We assessed risk of bias in the diagnostic accuracy studies using the QUADAS-2 tool.²⁴ The populations of these studies were stroke patients with large-vessel occlusion of the anterior circulation, similar to the population of interest for this review. The studies used automated CT perfusion imaging, and the reference standard for accuracy outcomes was follow-up DWI, which is a validated and acceptable reference standard. The risk of bias was also low for the timing and flow domains of the tool. The overall risk of bias for accuracy studies was low. The GRADE for diagnostic accuracy outcomes was moderate,²⁶ downgraded because the results of diagnostic studies are considered as a proxy for patient outcomes (Appendix 2).

Clinical Utility

We assessed risk of bias in the randomized controlled trials that compared mechanical thrombectomy with standard care using the Cochrane risk-of-bias tool.²⁵ We determined the risk of bias in these trials to be low. The GRADE for clinical outcomes was moderate, downgraded because measures of effectiveness reported by these randomized controlled trials were indirect evidence of the effectiveness of automated CT perfusion imaging (Appendix 2).

Discussion

Earlier studies suggested that mechanical thrombectomy was superior to intravenous thrombolysis in strokes caused by large-vessel occlusion of the anterior circulation, if performed within 6 hours after stroke onset.⁹ Soon after the results of those earlier trials were published, the effectiveness of mechanical thrombectomy within an extended time window (6–24 hours) became the focus of further randomized controlled trials – DEFUSE 3 and DAWN.^{10,11} The results of these trials have also shown significant improvement in functional outcomes in patients who underwent mechanical thrombectomy compared with those who did not.

In all trials, patient eligibility for mechanical thrombectomy (i.e. trial inclusion) was partly based on automated CT perfusion imaging. However, the extended time window (6-24hours) trials apply to patients with clearly defined extent of core infarct vs. penumbra based on automated CT perfusion imaging. The vast majority of patients enrolled in both trials had a small infarct core and were in the slow-growing core category.⁴⁵ The mismatch ratio in both trials was greater than 10, meaning that the size of the penumbra was at least 10 times larger than the infarct core. Also, in these trials, tPA therapy was not administered to most patients because of its limited time window for effectiveness, so the usual improvement following tPA therapy did not occur in many patients in the control arms. Although it is not possible to isolate the effect of each factor that contributed to the positive outcomes in the mechanical thrombectomy group, automated CT perfusion imaging certainly played a part in the selection of appropriate patients for mechanical thrombectomy.

Although the DEFUSE 3¹⁰ and DAWN¹¹ trials used MRI in some patients, most patients underwent CT imaging (73% in DEFUSE 3 and 64% in DAWN). Although MRI sensitivity for detecting lesions is superior to CT, MRI may not be available in many emergency departments. In contrast, CT scanners are more widely available and accessible and because stroke patients need to be rapidly assessed, CT perfusion imaging can be used to triage stroke patients in emergency departments. However, the fact that CT-based techniques for stroke involve radiation exposure to the head should also be considered.

Analysis of individual patient data from randomized controlled trials of mechanical thrombectomy showed that automated CT perfusion imaging had a sensitivity of 84% in identifying the infarct core but underestimated the infarct core volume.³¹ However, there are methodological challenges in estimating the true infarct core volume. It is possible that the infarct core grows during the time between initial and follow-up images if reperfusion is delayed or unsuccessful.

We did not identify any studies that compared automated CT perfusion imaging with non-automated CT perfusion imaging. Automated CT perfusion imaging facilitates image post-processing more quickly and easily. It also provides a good communication system for stroke teams in any geographic region. It could be a useful tool for standardizing the assessment of CT perfusion images across centres and reducing the variability of results.

The selected thresholds for CT perfusion parameters, which plays a role in the calculation of target mismatch ratios, can vary significantly across imaging platforms or among stroke centres. Based on these thresholds, imaging modalities identify and measure the infarct core and the penumbra and calculate the target mismatch ratio. In one of the studies we reviewed,³³ two patients were misclassified (not selected for mechanical thrombectomy) using a Tmax of greater than 6 seconds but were selected for mechanical thrombectomy using a Tmax of greater than 4 seconds. In this context, the validation and standardization of thresholds will result in more accurate selection of patients.

Our analysis showed that automated CT perfusion imaging may underestimate or overestimate the volume of the infarct core, and this may influence the target mismatch ratio. The imaging software might automatically include artifacts in the assessment of the ischemic area. Careful analysis and interpretation of the images and perfusion maps by a neuroradiologist, along with clinical information, are critical for triaging patients successfully using automated CT perfusion imaging.

The studies we reviewed reported using a variety of CT scanners, mostly 16- or 64-channel, which resulted in a limited brain coverage and decreased the accuracy of the CT perfusion findings. Although more advanced 256- and 320-channel CT scanners can be used to image the whole brain, they involve higher doses of radiation to the brain. As well, although DWI allows the entire brain to be scanned and is a more sensitive imaging modality than CT perfusion in assessing the brain lesions, MRI is not widely or readily available in acute stroke settings. In the absence of MRI, CT perfusion can help in triaging acute stroke patients for mechanical thrombectomy.

The effectiveness of CT perfusion for triaging stroke patients for thrombectomy is highly dependent on the way the source images are post-processed and evaluated. Multicentre randomized clinical trials had to standardize their image processing methods and reduce variability across different centres, and they relied on automated CT perfusion imaging to do this.^{10,11}

Physicians with a lack of experience in imaging interpretation may not accurately assess ischemic lesions. Overestimation of the infarct core volume could result in the unwarranted exclusion of patients who could benefit from reperfusion, decreasing their chance of improving neurological function. On the other hand, underestimation of the infarct core volume could result in a futile intervention. It is critically important that images be evaluated by clinicians with knowledge and expertise in the interpretation of perfusion maps and stroke evaluation.

Strengths and Limitations

To our knowledge, this health technology assessment is the first to systematically review the evidence for diagnostic accuracy and clinical outcomes related to the use of automated CT perfusion imaging to select acute stroke patients for mechanical thrombectomy up to 24 hours from symptom onset. We have highlighted the challenges inherent in studies intended to determine the accuracy of automated CT perfusion imaging in identifying and measuring the infarct core, as well as the issues related to artifacts caused by patient motion during scanning, which can affect the calculations.

The reference standard in the studies we reviewed was mostly follow-up DWI. It is known that the infarct may grow in the interval between baseline and follow-up imaging if reperfusion is not performed immediately, or if reperfusion is incomplete. In these situations, the follow-up comparator will be an imperfect reference standard. However, because the sensitivity of 84% we found was based on patients with greater than 50% reperfusion, and the specificity of 86% to 95% was from a study that performed both CT perfusion imaging and DWI less than 12 hours after symptom onset, the risk of inaccurate estimates for accuracy was minimal.

One limitation of this review was that the clinical outcomes reported by studies that used automated CT perfusion imaging to select patients for mechanical thrombectomy provided only indirect evidence of the effectiveness of automated CT perfusion imaging and could not be isolated from the effectiveness of mechanical thrombectomy. In addition, both CT and MRI scanners were used in the randomized

controlled trials, and it was not possible to estimate the effectiveness for patients who underwent only CT perfusion imaging at baseline.

Another limitation that related to a limitation inherent in CT perfusion studies was that most studies used 16- or 64-channel CT scanners, limiting brain coverage during scanning; lesions outside the coverage of the CT scan were not visualized.

Conclusions

Diagnostic Accuracy

- Automated CT perfusion imaging likely has a sensitivity of 84% and a specificity of 86% to 95% in identifying the infarct core (GRADE: Moderate)
- Automated CT perfusion imaging estimated a lower volume of infarct core than DWI MRI (median 25.4 mL) and a larger volume of infarct core than delayed non-contrast CT (median 30.4 mL; GRADE: Moderate)
- Automated CT perfusion imaging shows artifactual lesions outside the core area (false lesions). This was seen in 43% to 76% of patients in studies we reviewed. However, most false lesions can be detected by experts and removed from calculation (GRADE: Moderate)
- With automated CT perfusion imaging, misclassification for mechanical thrombectomy likely occurs in 7% of patients (GRADE: Moderate)

Clinical Utility

- Randomized controlled trials that used automated imaging to select patients for mechanical thrombectomy reported the following clinical outcomes:
 - A significant difference between mechanical thrombectomy and standard care for functional independence (mRS ≤ 2 at 90 days) in favour of mechanical thrombectomy (GRADE: Moderate)
 - No significant difference between mechanical thrombectomy and standard care for 90-day mortality or intracranial hemorrhage (GRADE: Moderate)

ECONOMIC EVIDENCE

Research Question

What is the cost-effectiveness of automated computed tomography (CT) perfusion imaging to aid in the selection of patients for mechanical thrombectomy up to 24 hours after stroke onset?

Methods

Economic Literature Search

We performed an economic literature search on April 23, 2019, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the assessment period. We performed targeted grey literature searching of health technology assessment agency sites, clinical trial and systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry. The grey literature search was updated on September 12, 2019. See Clinical Literature Search, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published from inception until April 23, 2019
- Cost–benefit analyses, cost-effectiveness analyses, cost-minimization analyses, or cost–utility analyses

Exclusion Criteria

- Unpublished studies, narrative reviews of the literature, study protocols, guidelines, conference abstracts, and editorials

Population

- Adults (> 18 years) with acute ischemic stroke up to 24 hours from stroke symptom onset

Intervention

- Automated CT perfusion imaging to aid in the selection of patients with acute ischemic stroke for mechanical thrombectomy

Outcome Measures

- Mean estimates of effects and costs
- Incremental costs
- Incremental effectiveness outcomes (e.g., quality-adjusted life-years [QALYs])
- Incremental cost-effectiveness ratios (ICERs)
- Incremental net benefit

Literature Screening

A single reviewer reviewed titles and abstracts and identified no studies likely to meet the eligibility criteria.

Results***Economic Literature Search***

The literature search yielded 46 citations published from inception to April 23, 2019, after removing duplicates. We identified no studies that met our inclusion criteria. Figure 3 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.²⁷

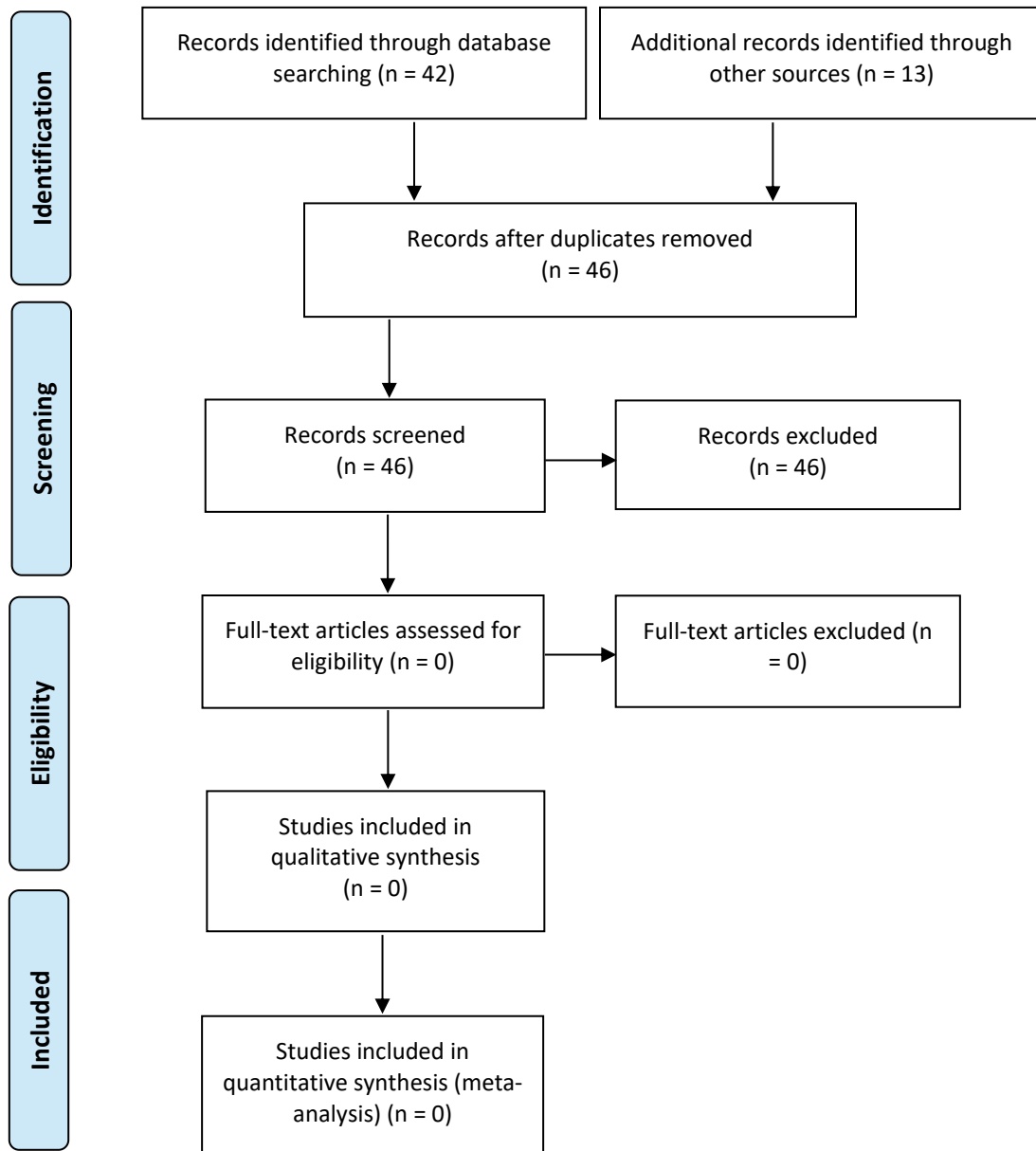


Figure 3: PRISMA Flow Diagram—Economic Search Strategy

Source: Adapted from Moher et al, 2009.²⁷

Conclusions

We identified no studies evaluating the cost-effectiveness of automated CT perfusion imaging to aid in the selection of patients with acute ischemic stroke for mechanical thrombectomy up to 24 hours from stroke symptom onset. Thus, the cost-effectiveness of using automated CT perfusion imaging to select patients for mechanical thrombectomy in Ontario and elsewhere is unknown.

PRIMARY ECONOMIC EVALUATION

Currently in Ontario, mechanical thrombectomy is publicly funded for patients who present 0 to 6 hours after stroke symptom onset. These patients are generally assessed for their eligibility to undergo mechanical thrombectomy using CT and CT angiography. However, automated CT perfusion imaging may also aid in the selection of patients for mechanical thrombectomy when they present in an extended time window (up to 24 hours after stroke symptom onset). Thus, we focused on patients presenting at 6 to 24 hours after stroke symptom onset. The cost-effectiveness of using automated CT perfusion imaging to select patients for mechanical thrombectomy compared to standard medical care—where stroke patients who present 6 to 24 hours after stroke symptom onset would not be eligible for mechanical thrombectomy—is inseparably linked to the cost-effectiveness of mechanical thrombectomy. For acute ischemic stroke patients presenting 6 to 24 hours after stroke symptom onset, standard medical care often includes aspirin and standard deep vein thrombosis prevention.¹⁰ Based on a previous Health Quality Ontario analysis,⁵ mechanical thrombectomy is cost-effective for other time windows (e.g., 0 to 6 hours after stroke symptom onset). In addition, as reported in the clinical review section of this health technology assessment,^{10,11} in properly selected patients, the effect of mechanical thrombectomy at 6 to 24 hours after symptom onset is also effective. Because of this, it is likely that mechanical thrombectomy in the 6- to 24-hour time window would be cost-effective if patients were properly selected for this treatment.

For these reasons, we did not conduct a primary economic evaluation; instead, we used the previous Health Quality Ontario economic evaluation of mechanical thrombectomy at 0 to 6 hours after stroke symptom onset to approximate the cost-effectiveness of mechanical thrombectomy and automated CT perfusion imaging at 6 to 24 hours.^{5,46} We have provided an approximation showing that mechanical thrombectomy informed by automated CT perfusion imaging at 6 to 24 hours after stroke symptom onset is likely to be cost-effective; see Appendix 5 for more details on the results of this analysis. We also assessed the economic impact of funding automated CT perfusion imaging by conducting a budget impact analysis.

BUDGET IMPACT ANALYSIS

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding automated CT perfusion imaging to aid in the selection of patients for mechanical thrombectomy up to 24 hours after stroke onset in selected hospitals in Ontario?

Background

This section describes issues related to the use of automated CT perfusion imaging in the current context and its potential implementation in the future.

- Canadian recommendations:* The 2018 Canadian Stroke Best Practice Recommendations¹⁴ extended the time window for mechanical thrombectomy for highly selected patients with additional advanced neurovascular imaging up to 24 hours after stroke symptom onset (the time window was previously up to 6 hours). The recommendations also noted that “sites using CTP [CT perfusion] imaging should utilize software that provides reproducible objective measurements of ischemic core and penumbra.”¹⁴ Most patients treated with mechanical thrombectomy at 0 to 6 hours after stroke symptoms onset can be selected using CT and CT angiography; automated CT perfusion imaging is especially useful for selecting patients at 6 to 24 hours after stroke symptom onset. Therefore, we focused on estimating the budget impact of publicly funding automated CT perfusion imaging to select patients for mechanical thrombectomy specifically in the 6- to 24-hour time window. Currently, RAPID CT perfusion¹⁹ is the platform clinically validated to select stroke patients for mechanical thrombectomy at 6 to 24 hours after stroke symptom onset
- Current practice for automated CT perfusion imaging:* The potential users of automated CT perfusion imaging in Ontario include 11 hospitals that provide mechanical thrombectomy (MT hospitals) and 31 referral hospitals that do not provide mechanical thrombectomy but do refer selected patients for mechanical thrombectomy (referral hospitals). At present, five of 11 MT hospitals, and six of 31 referral hospitals are using the RAPID neuroimaging platform to select patients for mechanical thrombectomy at 6 to 24 hours after stroke symptom onset (CorHealth Ontario, email communication, October 2019). RAPID CT perfusion (i.e., automated CT perfusion imaging) is one of several modules in the RAPID neuroimaging platform. At the time of writing this report, the costs of automated CT perfusion imaging were supported through funding from hospital foundations or other funding.
- Use of non-automated CT perfusion imaging:* Experts have suggested that only a small number academic hospitals have trained radiologists or technologists who can perform non-automated processing of CT perfusion images, and that this processing is institution-based and could not be used for routine clinical care (CorHealth Ontario, email communication, August 2019; Wieslaw Oczkowski, MD, email communication, August 2019; Grant Stotts, MD, email communication, October 2019). Therefore, we did not include non-automated CT perfusion mapping in the budget impact analysis.
- Demand versus current funded cases of mechanical thrombectomy:* The number of quality-based procedure (QBP)–funded cases of mechanical thrombectomy continues to increase (597 cases in 2017/18; 732 cases in 2018/19; and 860 cases in 2019/20). However, the overall need for mechanical thrombectomy is still higher than QBP-funded volumes. The current provincial need is an estimated 1,791 cases per year for mechanical thrombectomy in patients who present 0 to

6 hours after stroke symptom onset (CorHealth Ontario, email communication, August 2019). Hospitals that provide mechanical thrombectomy may not have the capacity to address the provincial need, and for this reason QBP-funded volumes have been increased incrementally each year. Expanding the time window for mechanical thrombectomy to include patients at 6 to 24 hours after stroke symptom onset would increase the total potential pool of eligible patients with ischemic stroke. However, given the constraints of health care resources, it is difficult to estimate how many additional stroke patients would receive mechanical thrombectomy at 6 to 24 hours

- *The cost of automated CT perfusion imaging versus stroke treatments:* Compared to health care costs for stroke patients, the cost of purchasing automated CT perfusion imaging is relatively low. The cost of an annual licence for RAPID CT perfusion is up to \$26,000 (list price) per hospital. Based on internal Ministry of Health data, the cost of one QBP-funded mechanical thrombectomy case is \$29,631 (Ministry of Health, email communication, August 2019), including the procedure and other standard stroke care during hospitalization. A 2012 study evaluating stroke costs in Canada reported that the average first-year cost for stroke was \$89,042 (adjusted to 2019 CAD)⁴⁷
- *Public payer perspective versus hospital perspective:* We aimed to explore the cost associated with automated CT perfusion imaging at the system level. Because the use of automated CT perfusion imaging will be associated with patient transfers from referral hospitals to MT hospitals for mechanical thrombectomy, health care costs may be reallocated between hospitals: a saving for one hospital may lead to spending for another hospital. Although understanding the gains or losses for individual hospitals was not the primary goal of our analysis, such cost estimates may be useful for hospitals in planning their budgets. Therefore, we considered costs from the perspective of the Ontario Ministry of Health in the reference case analysis, and from a hospital perspective in the scenario analyses

Methods

Analytic Framework

We estimated the budget impact of publicly funding automated CT perfusion imaging to aid in the selection of patients with an acute ischemic stroke for mechanical thrombectomy in select hospitals; our estimate was the cost difference between two scenarios: (1) current clinical practice without specific public funding for automated CT perfusion imaging (the current scenario); and (2) anticipated clinical practice with specific public funding for automated CT perfusion imaging (the new scenario). At present, RAPID CT perfusion¹⁹ is the most common automated CT perfusion imaging option used in clinical trials and in MT hospitals in Ontario to aid in the selection of patients for mechanical thrombectomy at 6 to 24 hours after stroke symptom onset.^{10,11} Thus, we focused on CT perfusion imaging using RAPID in this budget impact analysis.

We conducted a reference case analysis and several scenario analyses. Our reference case analysis represented the analysis with the most likely set of input parameters and model assumptions. Our scenario analyses explored how the results would be affected by varying input parameters and model assumptions.

In the reference case analysis, we included only the cost of purchasing automated CT perfusion imaging licences and the associated costs of implementation and radiologists' training time for the following reasons:

- For hospitals that have already purchased automated CT perfusion imaging, stroke patient management would be the same after public funding was implemented
- It was difficult to make accurate estimates of what the volume of mechanical thrombectomies would be at 6 to 24 hours (e.g., constraint health care resource) over the next 5 years

Key Assumptions

- The number of MT hospitals and referral hospitals will not change over the next 5 years
- The total number of patients with ischemic stroke will increase over the next 5 years
- The number of funded mechanical thrombectomy cases will continue to increase over the next 5 years
- Using automated CT perfusion imaging would be a part of the routine work of a radiologist or stroke neurologist, and the workload of using automated CT perfusion imaging would be minimal; thus, we excluded the professional fees for using the imaging
- Costs for training on automated CT perfusion imaging would be incurred in only the first year

Target Population

The target population is patients in Ontario with acute ischemic stroke presenting at a hospital at 6 to 24 hours after stroke symptom onset and potentially eligible for mechanical thrombectomy. We excluded patients with ischemic stroke who presented at a hospital 0 to 6 hours after stroke symptom onset; the main objective of using automated CT perfusion imaging is to evaluate patients at 6 to 24 hours after stroke symptom onset to identify who may be eligible for mechanical thrombectomy.¹⁴ We also excluded patients with transient ischemic attack.

Number of Hospitals Expected to Use Automated CT Perfusion Imaging

We classified hospitals according to the following three categories⁴⁸:

- Hospitals that provide mechanical thrombectomy, tissue plasminogen activator (tPA) treatment, and CT perfusion (MT hospitals)
- Hospitals that administer tPA treatment and perform CT perfusion (tPA hospitals)
- Hospitals that do not provide mechanical thrombectomy or tPA treatment and that may or may not have CT perfusion capacity (other hospitals)

The number of ischemic stroke patients in 2017/18 in each of these three categories is provided in Table 12.

Table 12: Number of Ischemic Stroke Cases by Hospital Category, 2017/18

Hospital Category ^a	Treatment Provided			Hospitals, n ^b	MT, n ^c	Ischemic Stroke Cases, n (%) ^d
	MT	tPA	CTP Imaging			
MT hospitals	Yes	Yes	Yes	10	604	4,817 (34.19)
tPA hospitals	No	Yes	Yes	35	—	5,480 (38.90)
Other hospitals	No	No	Mixed ^e	122 ^f	—	3,791 (26.91)
All	—	—	—	167	604	14,088 (100)

Abbreviations: CT, computed tomography; CTP, CT perfusion; MT, mechanical thrombectomy; QBP, quality-based procedure; tPA, tissue plasminogen activator.

^aMT hospitals provide mechanical thrombectomy, tPA treatment, and CT perfusion; tPA hospitals administer tPA and perform CT perfusion; other hospitals do not provide mechanical thrombectomy or tPA treatment, and may or may not have CT perfusion capacity.

^bOntario and Local Health Integration Network 2017/18 Stroke Report Cards and Progress Reports.⁴⁸ In 2019/20, 1 tPA hospital upgraded to an MT hospital, for a total of 11 MT hospitals and 34 tPA hospitals.

^cIntelliHealth Ontario (Canadian Classification of Health Interventions codes 1.JE.57-GQ-AA, 1.JW.57.GP-GX, and 1.JX. 57.GP-GX).⁴⁹ Actual mechanical thrombectomy cases basically matched QBP-funded cases (597 in 2017/18).

^dNumber of hospital admissions due to acute ischemic stroke in 2017 (Discharge Abstract Database).

^eSome hospitals in this category could perform CT perfusion imaging.

^fThe number of hospitals may vary from year to year, because it includes all hospitals that admitted a stroke patient.

In 2019/20, Ontario had 11 MT hospitals and 34 tPA hospitals (in 2019/20, 1 tPA hospital upgraded to an MT hospital), and 95.8% of the Ontario population lived within 4 hours of an MT hospital. We assumed that no additional MT hospitals would be approved over the next 5 years (CorHealth Ontario, email communication, September 2019).

We consulted with clinical experts about the potential users of automated CT perfusion imaging. It would be used by the 11 MT hospitals, but we also expected that it would be useful at most tPA hospitals—designated stroke or tele-stroke hospitals that serve as referral sites for mechanical thrombectomy (i.e., most tPA hospitals, Table 12; CorHealth Ontario, email communication, September 2019). In referral hospitals, automated CT perfusion imaging can help identify candidates who will be in the extended time window (6 to 24 hours after stroke symptom onset) by the time they arrive at an MT hospital, and doctors can refer only eligible patients to MT hospitals for mechanical thrombectomy. Using automated CT perfusion imaging in referral hospitals could help avoid the unnecessary transfer of patients who are not eligible for mechanical thrombectomy and appropriately transfer those who would benefit from the procedure. We estimated that about 42 hospitals could benefit from using automated CT perfusion imaging in next 5 years (11 MT hospitals + 31 referral hospitals [35 tPA hospitals – 1 tPA hospital upgraded to an MT hospital – 3 hospitals providing tPA to walk-in patients who are not redirected to MT hospitals]).

Although stroke patients may present at any hospital, automated CT perfusion imaging is not expected to be used in non-tPA (“other”) hospitals, because they may not be able to provide this advanced imaging in a timely manner (CorHealth Ontario, email communication, August 2019). Thus, we did not consider “other hospitals” in this budget impact analysis.

Stroke Hospitalizations and Mechanical Thrombectomies

We used the Discharge Abstract Database from IntelliHealth Ontario to estimate the number of people hospitalized for ischemic stroke each year from 2013 to 2017.⁴⁹ We used the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada codes I63.0 to I63.9 and H34.0 to H34.1 to identify patients with acute ischemic stroke. Historical data showed that the number

of people hospitalized for ischemic stroke increased over time, from 11,080 in 2013 to 14,088 in 2017 (Appendix 6, Table A4); this number from the IntelliHealth Ontario database was approximately the same as the estimates from other agencies (CorHealth Ontario, telephone communication, June 2019). We assumed a 5% annual increase in the number of people with ischemic stroke. We then projected the total number of people with ischemic stroke over the next 5 years (year 1 is 2019; Table 13).

We found no published literature evaluating the time from stroke symptom onset to hospital admission in Ontario. A recent Canadian study⁵⁰ found that 95% to 97% of the Ontario population lives within 3.5 to 6 hours of a stroke hospital via emergency medical services, and 97% to 99% live within self-driving distances. Most people can arrive at a hospital within 6 hours (Wieslaw Oczkowski, MD, email communication, August 2019; Grant Stotts, MD, email communication, August 2019). The Canadian Stroke Best Practice Recommendations also suggest that for patients presenting at 6 to 24 hours after stroke symptom onset, mechanical thrombectomy is used for highly selected patients based on dedicated neurovascular imaging.¹⁴ Therefore, we expected that the volume of patients receiving mechanical thrombectomy at 6 to 24 hours would not be large. We assumed that 90% of people undergoing mechanical thrombectomy would present at 0 to 6 hours after stroke symptom onset, and the remaining 10% would present at 6 to 24 hours.

The number of funded mechanical thrombectomy cases has been increasing, and we assumed that this trend would continue over the next several years for the following reasons:

- Mechanical thrombectomy demonstrates substantial health benefits
- The demand for mechanical thrombectomy is increasing
- The number of patients with ischemic stroke is increasing
- The mechanical thrombectomy time window has been extended from less than 6 hours to up to 24 hours

However, it has been difficult to make an accurate projection of the growth rate of mechanical thrombectomy cases. We considered two annual growth rates (15% and 5%) in this budget impact analysis. If the volume of mechanical thrombectomy increased by 15% per year, the number of mechanical thrombectomies occurring at 6 to 24 hours after stroke symptom onset would increase from 86 in year 1 to 150 in year 5. At a growth rate of 5% per year, the number of mechanical thrombectomies would increase from 86 in year 1 to 104 in year 5 (Table 13).

Table 13: Patients Hospitalized for Ischemic Stroke and Mechanical Thrombectomy

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients hospitalized for acute ischemic stroke in Ontario, n	15,532	16,309	17,124	17,980	18,879
Hospitals providing MT, n	11	11	11	11	11
Referral hospitals, n	31	31	31	31	31
MT, 15% increase per year, total n	860	989	1,137	1,308	1,504
0 to 6 hours, n	774	890	1,023	1,177	1,354
6 to 24 hours, n	86	99	114	131	150
MT, 5% increase per year, total n	860	903	948	995	1,045
0 to 6 hours, n	774	813	853	896	941
6 to 24 hours, n	86	90	95	99	104

Abbreviation: MT, mechanical thrombectomy.

Uptake and Current and New Intervention Mix

We assumed that the costs to the Ministry of Health in the current scenario were zero. We also assumed full access (uptake of 100%) to automated CT perfusion imaging over 5 years for all MT hospitals and referral hospitals (42 hospitals in total).

Resources and Costs

We estimated the costs that would be incurred by the Ontario Ministry of Health if automated CT perfusion imaging were to be publicly funded. We considered the following costs: the cost of the imaging software; first-year health care costs for stroke patients (including mechanical thrombectomy and other health care costs); and costs of between-hospital patient transfers (i.e., ambulance services). In the reference case analysis, we included only the cost of purchasing automated CT perfusion imaging licences and the associated costs of implementation and radiologists' training time. We included costs in other categories in the scenario analyses. Costs are expressed in 2019 CAD.⁵¹

Cost of Automated CT Perfusion Imaging

The manufacturer (iSchemaView RAPID¹⁹) provided the 2019 purchase price for RAPID CT perfusion (single module) and the RAPID neuroimaging platform (including several modules and the capacity to conduct other neurovascular diagnostic procedures). In general, hospitals purchase the entire RAPID neuroimaging platform, not RAPID CT perfusion alone. The prices for the RAPID neuroimaging platform are 20% to 38% more than RAPID CT perfusion alone. The prices for automated CT perfusion imaging are shown in Table 14. RAPID CT perfusion in MT hospitals often connects to more than two scanners, so we assumed that MT hospitals would purchase a licence for unlimited scanners (\$26,000/year). We assumed that referral hospitals would purchase a licence for two connected scanners (\$20,000/year).

Table 14: Cost of Automated CT Perfusion Imaging

Imaging	Annual Licence per Hospital ^a
RAPID CT Perfusion Alone	
2 connected scanners per hospital/facility	\$20,000
Unlimited connected scanners per hospital/facility	\$26,000
Implementation/optimization/training (one-time fee)	\$9,750 (2 or more scanners)
RAPID Neuroimaging Platform, Including RAPID CT Perfusion^{b,c}	
2 connected scanners per hospital/facility	\$27,500
Unlimited connected scanners per hospital/facility	\$32,500
Implementation/optimization/training (one-time fee)	\$12,350 (2 or more scanners)

Abbreviations: CT, computed tomography.

^aAll costs are in 2019 CAD.

^bThe RAPID neuroimaging platform includes the Alberta Stroke Program Early CT Score (ASPECTS), CT angiography, CT perfusion, and magnetic resonance imaging diffusion and perfusion.

^cThese costs were used in the scenario analyses.

According to IschemaView RAPID,¹⁹ it takes up to 30 minutes to be trained to use automated CT perfusion imaging, and up to 2 hours for all RAPID modules. Training also includes instructions on manual correction for image improvement. We assumed that each MT hospital would have 12 radiologists to receive training, and each referral hospital would have 8. We estimated that the cost of radiologists' professional time would be \$495 (salary plus benefits at approximately \$248 per hour [benefits at approximately 33% of salary⁵²] for 2 hours⁵³; Table 15). We assumed that the cost of training would be incurred only in year 1. We assumed that the workload of using the imaging would be minimal. We assumed that using automated CT perfusion imaging would be included as part of a radiologist's routine work, so we excluded professional fees for using the imaging to select eligible stroke patients.

Installing automated CT perfusion imaging at a hospital would include a one-time manufacturer fee for implementation, optimization, and training, and the costs of the radiologists' time for training. Because some hospitals have already installed automated CT perfusion imaging, we assumed that these one-time costs would be incurred at 6 MT hospitals and 25 referral hospitals.

Table 15: Costs of Radiologists' Time for Training, Stroke Treatment, and Patient Transfer

Description	Cost ^a	Source
Radiologists' Time for Training on Automated CT Perfusion Imaging (Year 1 Only)		
Cost of 2 hours of professional time per radiologist	\$495	Neuvoo ⁵³
Cost per MT hospital (12 radiologists)	\$5,940	—
Cost per referral hospital (8 radiologists)	\$3,960	—
First-Year Health Care Costs for Patients With Ischemic Stroke, Excluding the Cost of Automated CT Perfusion Imaging^a		
MT and standard medical care ^b	\$73,481	HQO ⁵
Standard medical care only ^b	\$67,944	HQO ⁵
Costs for Between-Hospital Patient Transfers^c		
Cost of a one-way between-hospital patient transfer	\$901	Robinson et al ⁵⁴
Cost of a two-way between-hospital patient transfer	\$1,802	Robinson et al ⁵⁴
Proportion of avoidable transfers when automated CT perfusion imaging is available in referral hospitals	38.5%	Albers et al ¹⁰

Abbreviations: CT, computed tomography; HQO, Health Quality Ontario; MT, mechanical thrombectomy; MT hospital, a hospital that provides mechanical thrombectomy, tPA treatment, and CT perfusion; tPA, tissue plasminogen activator.

^aAll costs are in 2019 CAD.

^bFor patients with acute ischemic stroke presenting at 6 to 24 hours after stroke symptom onset, standard medical care often includes Aspirin and standard deep vein thrombosis prevention therapy.¹⁰

^cThese costs were used in the scenario analyses.

First-Year Health Care Costs for Patients With Ischemic Stroke

Various costs are incurred after using automated CT perfusion imaging in patients with ischemic stroke. These costs include mechanical thrombectomy, standard medical care, other hospitalization-related costs, and the long-term costs related to post-stroke functional ability (functional independence or dependence). The long-term health outcomes (e.g., survival and disability) for mechanical thrombectomy at 6 to 24 hours after stroke symptom onset were not available, so it was difficult to capture long-term costs. For simplicity, we limited health care costs to the first year after a stroke. In general, the average health care costs for stroke in the first year are much higher than in subsequent years.⁵

Our previous economic evaluation of mechanical thrombectomy plus intravenous thrombolysis versus intravenous thrombolysis alone at 0 to 6 hours after stroke symptom onset included the costs of emergency services, mechanical thrombectomy, hospitalizations, rehabilitation, physician services, diagnostics, and medications. That evaluation showed that mechanical thrombectomy led an additional cost of \$5,537 in the first year (mechanical thrombectomy plus intravenous thrombolysis: \$73,481; intravenous thrombolysis alone: \$67,944).⁵ For simplicity, we assumed that excluding the extra cost of automated CT perfusion imaging, the costs of mechanical thrombectomy plus intravenous thrombolysis and intravenous thrombolysis alone at 0 to 6 hours after stroke symptom onset would be the same as mechanical thrombectomy plus standard medical care and standard medical care alone at 6 to 24 hours after stroke symptom onset (see Table 15).

Costs for Between-Hospital Patient Transfer

We included the costs of between-hospital patient transfers in our scenario analyses (see Table 15). Automated CT perfusion imaging could reduce unnecessary between-hospital transfers for patients. For instance, in a referral hospital (which offers CT perfusion imaging but not mechanical thrombectomy), automated CT perfusion imaging could help select patients who are eligible for mechanical thrombectomy at 6 to 24 hours and should be transferred to MT hospitals. Using automated CT perfusion imaging would help avoid the transfer of patients who do not meet the eligibility criteria for mechanical thrombectomy. However, few published studies have reported on how many unnecessary transfers can be avoided as a result of using automated CT perfusion imaging.

We used the DEFUSE 3 trial¹⁰ to approximate avoidable transfers. In this trial, 296 patients consented to participate (Figure S1, Consort Diagram), but 114 were excluded (100 did not meet imaging criteria, seven did not meet clinical criteria, and seven did not meet imaging and clinical criteria). The trial used several imaging techniques to exclude patients, but for simplicity we assumed that all excluded cases were identified using automated CT perfusion imaging. We estimated that for every 100 patients eligible for mechanical thrombectomy at 6 to 24 hours after stroke symptom onset, automated CT perfusion imaging would identify 63 patients ($100 \times [114 / (296 - 114)]$) who were not eligible for mechanical thrombectomy (38.5% of patients assessed would not be eligible for mechanical thrombectomy).

There is limited research on the overall cost of between-hospital transfers. A study in Ontario showed that the total cost of land transfers was \$283 million in 2005 CAD (\$362 million in 2019 CAD after Consumer Price Index adjustment) for nearly 400,000 patient transfers.⁵⁴ This would equate to an average cost of \$901 in 2019 CAD per person for a one-way between-hospital patient transfer. For patients who were eligible for mechanical thrombectomy, we assumed a one-way transfer from a referral hospital to an MT hospital (i.e., a minimal transfer scenario). For patients who were not eligible for mechanical thrombectomy, two-way transfers would be incurred (CorHealth Ontario, email communication, October 2019), including one transfer from a referral hospital to an MT hospital, and another from the MT hospital to the referral hospital or a hospital closest to home that could best meet the patient's needs. In scenario analyses 4-1, 4-2, 4-3, 4-4, and 4-5, we considered different types of patient transfers.

Analysis

In this analysis, we focused on the use of automated CT perfusion imaging to aid in the selection of stroke patients for mechanical thrombectomy at 6 to 24 hours after stroke symptom onset. We calculated the annual budget impact for the next 5 years. We also calculated the number of unnecessary between-hospital patient transfers and possible cost savings as a result of using automated CT perfusion imaging. Cost components considered in the reference case and scenario analyses are described in Table 16. Estimates for unnecessary between-hospital patient transfers are presented in Table 17.

Reference Case

We included the cost of purchasing automated CT perfusion imaging (RAPID CT perfusion) and the associated costs of implementation and radiologists' time for training in MT hospitals and referral hospitals.

Scenario Analyses

There were considerable uncertainties of the number of hospitals to be funded, the volume of mechanical thrombectomies at 6 to 24 hours, the downstream costs (up to 1 year) after mechanical thrombectomy, and potential patient transfers avoided. We explored these costs in the following scenario analyses:

- Scenario 1-1: To purchase automated CT perfusion imaging (RAPID CT perfusion) for 11 MT hospitals only
- Scenario 1-2: To purchase automated CT perfusion imaging (RAPID CT perfusion) from the perspective of an MT hospital
- Scenario 1-3: To purchase automated CT perfusion imaging (RAPID CT perfusion) from the perspective of a referral hospital
- Scenario 2-1: To purchase the entire RAPID neuroimaging platform, including automated CT perfusion imaging (RAPID CT perfusion), for MT hospitals and referral hospitals
- Scenario 2-2: To purchase the entire RAPID neuroimaging platform, including automated CT perfusion imaging (RAPID CT perfusion) for 11 MT hospitals only
- Scenario 2-3: To purchase automated CT perfusion imaging (RAPID CT perfusion) with 25% discounting for MT hospitals and referral hospitals
- Scenario 2-4: To purchase automated CT perfusion imaging (RAPID CT perfusion) with 25% discounting for MT hospitals only
- Scenario 3-1: To purchase automated CT perfusion imaging in MT and referral hospitals (reference case) and first-year health care costs for target patients at an annual increase rate of 15% for mechanical thrombectomy cases. Although some MT hospitals have started to offer mechanical thrombectomy at 6 to 24 hours after stroke symptom onset, we expected that the current volume of mechanical thrombectomy during this extended time window would be small. In the current scenario, we assumed that hospitals provided standard medical care for these patients
- Scenario 3-2: Similar to scenario 3-1, but we assumed an annual increase rate of 5% for mechanical thrombectomy cases (instead of 15%)
- Scenario 3-3: To purchase automated CT perfusion imaging in MT hospitals only, including the first-year health care costs of target patients at an annual increase rate of 15% for mechanical thrombectomy cases
- Scenario 3-4: Similar to scenario 3-3, but we assumed an annual increase rate of 5% for mechanical thrombectomy cases (instead of 15%)
- Scenario 4-1: To examine the cost difference between funding automated CT perfusion imaging in both MT and referral hospitals and funding it in MT hospitals only. This analysis included the cost of between-hospital transfers for patients who were eligible or ineligible (unnecessary transfers) for mechanical thrombectomy. We have illustrated the between-hospital patient transfers in Figure 4. If automated CT perfusion imaging were available in referral hospitals, together with other criteria, only patients eligible for mechanical thrombectomy beyond 6 hours would be transferred. If hospitals did not have automated CT perfusion imaging, they would have to transfer more patients to MT hospitals for evaluation (including plausibly eligible but actually ineligible patients). Thus, without automated CT perfusion imaging, additional patients would be transferred. Because treatment with mechanical thrombectomy at 6 to 24 hours for eligible patients is a relatively new practice in Ontario, we have no statistics on how many patients

receiving mechanical thrombectomy in the extended time window come from referral hospitals. We assumed that 60% of mechanical thrombectomy cases in the extended time window would be transferred from referral hospitals (e.g., 52 in year 1), and the remaining 40% would come to MT hospitals directly (no transfer) or be transferred from emergency departments of other (non-referral) hospitals (Table 17). Based on the DEFUSE 3 trial¹⁰ and assuming that the number of patients receiving mechanical thrombectomy would increase by 15% per year, we estimated that there would be 33 (year 1) to 57 (year 5) unnecessary transfers over the next 5 years (Table 17). We assumed that using automated CT perfusion imaging to evaluate eligibility for mechanical thrombectomy at referral hospitals (before transfer) or MT hospitals (after transfer) would not change the total volume of mechanical thrombectomy procedures or first-year health care costs. Therefore, we considered only the costs of automated CT perfusion imaging and patient transfers from referral hospitals

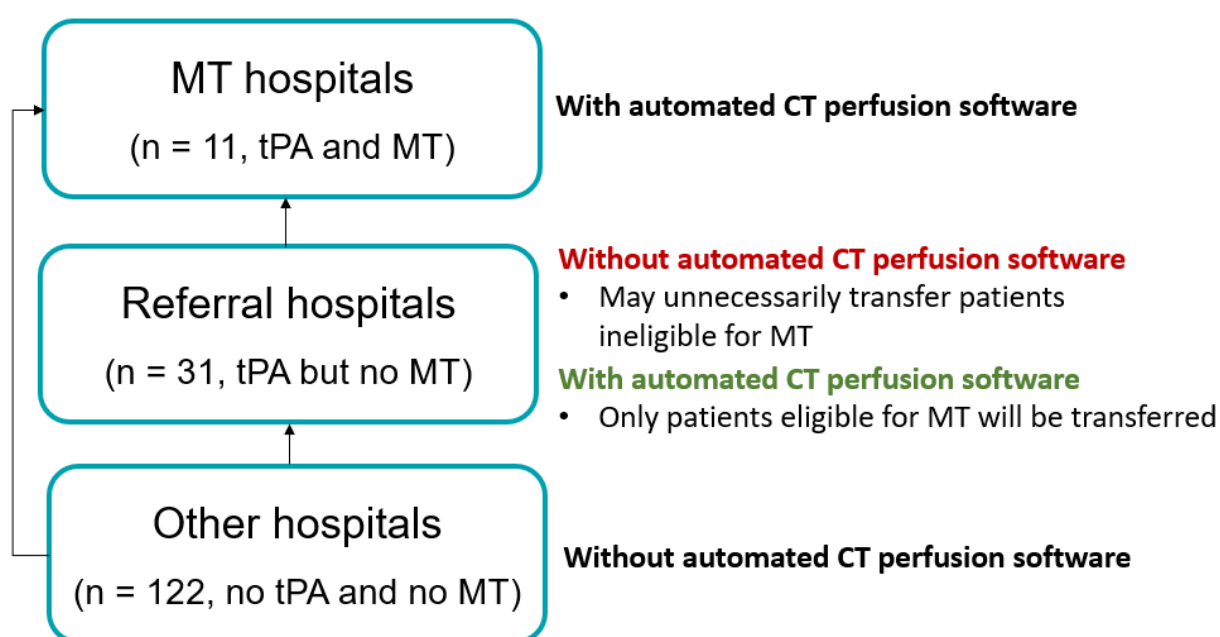


Figure 4: Between-Hospital Stroke Transfer for Mechanical Thrombectomy, From Referral Hospitals to MT Hospitals^a

Abbreviations: CT, computed tomography; MT, mechanical thrombectomy; tPA, tissue plasminogen activator.

^aMT hospitals provide mechanical thrombectomy, tPA treatment, and CT perfusion; tPA hospitals administer tPA and perform CT perfusion; other hospitals do not provide mechanical thrombectomy or tPA treatment, and may or may not have CT perfusion capacity.

- Scenario 4-2: Similar to scenario 4-1, but we assumed an annual increase rate of 5% for mechanical thrombectomy cases (instead of 15%; Table 17)
- Scenario 4-3: Similar to scenario 4-1, but we assumed twice as many unnecessary transfers as in scenario 4-1 (Table 17)
- Scenario 4-4: Similar to scenario 4-2, but we assumed twice as many unnecessary transfers as in scenario 4-2 (Table 17)
- Scenario 4-5: To include hospitalized patients with ischemic stroke and patients who presented at the emergency department but were not hospitalized. We used other parameters to estimate

potential patient transfers avoided by using automated CT perfusion imaging. We assumed that mechanical thrombectomy at 6 to 24 hours after stroke symptom onset would be fully funded for all eligible patients. Only patients who presented at the referral hospital would be associated with avoidable transfers:

- There were 21,434 cases of ischemic stroke in 2018/19 in Ontario (based on most responsible diagnosis; data source: Discharge Abstract Database and National Ambulatory Care Reporting System, Canadian Institute for Health Information; CorHealth Ontario, email communication, September 2019)
- Of those, 7,451 (34.8%) patients presented at referral hospitals (CorHealth Ontario, email communication, September 2019)
- Among patients who presented at referral hospitals, 1,496 (20.1%) arrived within 6 to 24 hours after stroke symptom onset (CorHealth Ontario, email communication, September 2019)
- We estimated that about 11.5% of ischemic stroke patients arriving at 6 to 24 hours after stroke symptom onset would be eligible for mechanical thrombectomy. A recent study reported that 9.2% of all patients with stroke presenting in this time window were eligible for mechanical thrombectomy.⁵⁵ Assuming that 80% of all strokes are ischemic and the remaining 20% are hemorrhagic, and that the distribution of arrival time is the same for ischemic and hemorrhagic stroke, we calculated that 11.5% of ischemic stroke patients arriving at 6 to 24 hours after stroke symptom onset would be eligible for mechanical thrombectomy ($9.2\% \div 80\% = 11.5\%$)
- For patients with ischemic stroke presenting at 6 to 24 hours after stroke symptom onset but ineligible for mechanical thrombectomy, we estimated that 50% could be excluded based on clinical and other imaging criteria (e.g., CT and CTA). For example, clinicians can use neuroimaging performed by CT and/or CTA to identify patients with acute ischemic stroke due to large-vessel occlusion, include those who are potentially eligible for mechanical thrombectomy,^{56,57} and exclude those who are not eligible. We assumed that the remaining 50% could be excluded only with automated CT perfusion imaging, and those would be potentially avoidable patient transfers if automated CT perfusion imaging were available in referral hospitals

Table 16: Hospital Groups and Cost Components in Reference Case and Scenario Analyses

Scenario	Intervention and Comparator	Hospital Groups ^a	Cost Components		
			Automated CTP Imaging	First-Year Health Care	Patent Transfer
Reference case	Automated CT perfusion imaging	MT and referral hospitals	Yes	No	No
	No automated CT perfusion imaging	MT and referral hospitals	No	No	No
Scenario 1-1: 11 MT hospitals	Automated CT perfusion imaging	MT hospitals	Yes	No	No
	No automated CT perfusion imaging	MT hospitals	No	No	No
Scenario 1-2: MT hospital perspective	Automated CT perfusion imaging	An MT hospital	Yes	No	No
	No automated CT perfusion imaging	An MT hospital	No	No	No
Scenario 1-3: referral hospital perspective	Automated CT perfusion imaging	A referral hospital	Yes	No	No
	No automated CT perfusion imaging	A referral hospital	No	No	No
Scenarios 2-1 and 2-3: different prices for automated CT perfusion imaging, MT and referral hospitals	Automated CT perfusion imaging	MT and referral hospitals	Yes	No	No
	No automated CT perfusion imaging	MT and referral hospitals	No	No	No
Scenarios 2-2 and 2-4: different prices for automated CT perfusion imaging, MT hospitals only	Automated CT perfusion imaging	MT hospitals	Yes	No	No
	No automated CT perfusion imaging	MT hospitals	No	No	No
Scenarios 3-1 and 3-2: include treatment costs	Automated CT perfusion imaging and MT	MT and referral hospitals	Yes	Yes (MT)	No
	No automated CT perfusion imaging and medical care	MT and referral hospitals	No	Yes (medical care)	No
Scenarios 3-3 and 3-4: include treatment costs	Automated CT perfusion imaging and MT	MT hospitals	Yes	Yes (MT)	No
	No automated CT perfusion imaging and medical care	MT hospitals	No	Yes (medical care)	No
Scenarios 4-1 to 4-5: automated CT perfusion imaging cost vs. transfer cost	Automated CT perfusion imaging in MT and referral hospitals	Transfer from referral hospitals to MT hospitals	Yes (for referral hospitals)	No	Yes
	Automated CT perfusion imaging in MT hospitals, but not in referral hospitals	Transfer from referral hospitals to MT hospitals	No (for referral hospitals)	No	Yes

Abbreviations: CT, computed tomography; MT, mechanical thrombectomy; tPA, tissue plasminogen activator.

^aMT hospitals provide mechanical thrombectomy, tPA treatment, and CT perfusion; tPA hospitals administer tPA and perform CT perfusion; other hospitals do not provide mechanical thrombectomy or tPA treatment, and may or may not have CT perfusion capacity.

Table 17: Target Population, Transfer of Patients With Ischemic Stroke From Referral Hospitals to MT Hospitals, Scenario 4^a

	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario 4-1: Transfer From Referral Hospitals to MT Hospitals (15% Annual Increase in MTs)					
Total MTs at 6 to 24 hours, n	86	99	114	131	150
MTs at 6 to 24 hours transferred from referral hospitals (60% of cases), n	52	59	68	79	90
Between-hospital patient transfers if referral hospitals do not have automated CT perfusion imaging, n	85	96	111	129	147
Unnecessary transfers	33	37	43	50	57
Scenario 4-2: Transfer From Referral Hospitals to MT Hospitals (5% Annual Increase in MTs)					
Total MTs at 6 to 24 hours, n	86	90	95	99	104
MTs at 6 to 24 hours transferred from referral hospitals (60% of cases), n	52	54	57	59	62
Between-hospital patient transfers if referral hospitals do not have automated CT perfusion imaging, n	85	88	93	96	101
Unnecessary transfers	33	34	36	37	39
Scenario 4-3: Transfer From Referral Hospitals to MT Hospitals (15% Annual Increase in MTs), Twice as Many Unnecessary Transfers					
Between-hospital patient transfers if referral hospitals do not have automated CT perfusion imaging, n	118	133	154	179	204
Unnecessary transfers	66	74	86	100	114
Other parameters the same as scenario 4-1	—	—	—	—	—
Scenario 4-4: Transfer From Referral Hospitals to MT Hospitals (5% Annual Increase in MTs), Twice as Many Unnecessary Transfers					
Between-hospital patient transfers if referral hospitals do not have automated CT perfusion imaging, n	118	122	129	133	140
Unnecessary transfers	66	68	72	74	78
Other parameters the same as scenario 4-2	—	—	—	—	—
Scenario 4-5: Transfer From Referral Hospitals to MT Hospitals, Including Both Inpatients and Cases From the Emergency Department					
Patients with ischemic stroke who present at referral hospitals at 6 to 24 hours, n	1,571	1,649	1,732	1,818	1,909
Patients with ischemic stroke who are eligible for MT at 6 to 24 hours, n	181	190	199	209	220
Patients with ischemic stroke who are ineligible for MT at 6 to 24 hours, n	1,390	1,459	1,533	1,609	1,689
Ineligibility can be determined by clinical and other imaging criteria, n	695	730	767	805	845
Unnecessary transfers (ineligibility can be determined only by automated CT perfusion imaging), n	695	729	766	804	844

Abbreviations: CT, computed tomography; MT, mechanical thrombectomy; tPA, tissue plasminogen activator.

^aMT hospitals provide mechanical thrombectomy, tPA treatment, and CT perfusion; tPA hospitals administer tPA and perform CT perfusion; other hospitals do not provide mechanical thrombectomy or tPA treatment, and may or may not have CT perfusion capacity.

Internal Validation

The secondary health economist conducted a formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Results

Reference Case Analysis

Table 18 presents the projected annual costs associated with publicly funding automated CT perfusion imaging over the next 5 years. To fund 42 MT and referral hospitals, the 5-year budget impact would be approximately \$5.0 million: \$1.3 million in year 1 and \$0.9 million per year in subsequent years.

Table 18: Budget Impact Analysis Results, Reference Case

Scenario	Budget Impact, \$ ^{a,b}				
	Year 1	Year 2	Year 3	Year 4	Year 5
Reference Case: To Fund Automated CT Perfusion Imaging at 11 MT Hospitals and 31 Referral Hospitals^c					
Current scenario	0	0	0	0	0
New scenario	1,342,890	906,000	906,000	906,000	906,000
Automated CT perfusion imaging	906,000	906,000	906,000	906,000	906,000
Implementation/optimization/training (one-time fee) ^d	302,250	0	0	0	0
Radiologists' time for training (first year) ^d	134,640	0	0	0	0
Budget impact	1,342,890	906,000	906,000	906,000	906,000

Abbreviations: CT, computed tomography; MT, mechanical thrombectomy; tPA, tissue plasminogen activator.

^aAll values in 2019 Canadian dollars.

^bNumbers may appear inexact because of rounding.

^cMT hospitals provide mechanical thrombectomy, tPA treatment, and CT perfusion; tPA hospitals administer tPA and perform CT perfusion; other hospitals do not provide mechanical thrombectomy or tPA treatment, and may or may not have CT perfusion capacity.

^dBecause some hospitals have already installed automated CT perfusion imaging, we applied a one-time fee for implementation, optimization, and training on automated CT perfusion imaging by the manufacturer and the costs of radiologists' time for training in 6 MT hospitals and 25 referral hospitals.

Scenario Analysis

Table 19 presents the results for scenarios 1 to 3. To fund automated CT perfusion imaging in 11 MT hospitals, the annual budget impact would be approximately \$0.4 million in year 1 and decrease to \$0.3 million in subsequent years. If the cost of mechanical thrombectomy were included, the total budget increase would be higher than for the reference case, because the first-year health care costs for mechanical thrombectomy are higher than for standard medical care.

Table 19: Budget Impact Analysis Results, Scenario Analyses, Scenarios 1 to 3

Scenario	Budget Impact, \$ ^{a,b,c,d}				
	Year 1	Year 2	Year 3	Year 4	Year 5
Reference Case: To Fund Automated CT Perfusion Imaging at 11 MT Hospitals and 31 Referral Hospitals					
Budget impact	1,342,890	906,000	906,000	906,000	906,000
Scenario 1-1: To Fund Automated CT Perfusion Imaging at 11 MT Hospitals Only					
Budget impact	380,140	286,000	286,000	286,000	286,000
Scenario 1-2: To Purchase Automated CT Perfusion Imaging From the Perspective of an MT Hospital^e					
Budget impact	41,690	26,000	26,000	26,000	26,000
Scenario 1-3: To Purchase Automated CT Perfusion Imaging From the Perspective of a Referral Hospital^e					
Budget impact	33,710	20,000	20,000	20,000	20,000
Scenario 2-1: To Purchase Neurovascular Imaging Platform, Including Automated CT Perfusion Imaging, for MT and Referral Hospitals^{e,f}					
Budget impact	1,727,490	1,210,000	1,210,000	1,210,000	1,210,000
Scenario 2-2: To Purchase Neurovascular Imaging Platform, Including Automated CT Perfusion Imaging, for MT Hospitals Only^{e,f}					
Budget impact	467,240	357,500	357,500	357,500	357,500
Scenario 2-3: To Purchase Automated CT Perfusion Imaging With 25% Discounting for MT and Referral Hospitals^e					
Budget impact	1,040,828	679,500	679,500	679,500	679,500
Scenario 2-4: To Purchase Automated CT Perfusion Imaging With 25% Discounting for MT Hospitals Only^e					
Budget impact	294,015	214,500	214,500	214,500	214,500
Scenario 3-1: To Include Costs of Automated CT Perfusion Imaging in MT and Referral Hospitals, and First-Year Stroke Management Costs (MT Cases: Annual Increase of 15%)					
Current scenario	5,843,165	6,726,434	7,745,590	8,900,635	10,191,566
New scenario	7,662,267	8,180,632	9,282,849	10,532,028	11,928,169
Automated CT perfusion imaging	1,342,890	906,000	906,000	906,000	906,000
First-year health care	6,319,377	7,274,632	8,376,849	9,626,028	11,022,169
Budget impact	1,819,102	1,454,198	1,537,258	1,631,393	1,736,603
Scenario 3-2: To Include Costs of Automated CT Perfusion Imaging in MT and Referral Hospitals, and First-Year Stroke Management Costs (MT Cases: Annual Increase of 5%)					
Current scenario	5,843,165	6,114,940	6,454,659	6,726,434	7,066,153
New scenario	7,662,267	7,519,302	7,886,707	8,180,632	8,548,037
Automated CT perfusion imaging	1,342,890	906,000	906,000	906,000	906,000
First-year health care	6,319,377	6,613,302	6,980,707	7,274,632	7,642,037
Budget impact	1,819,102	1,404,362	1,432,049	1,454,198	1,481,885
Scenario 3-3: To Include Costs of Automated CT Perfusion Imaging in MT Hospitals Only, and First-Year Stroke Management Costs (MT Cases: Annual Increase of 15%)					
Current scenario	5,843,165	6,726,434	7,745,590	8,900,635	10,191,566
New scenario	6,699,517	7,560,632	8,662,849	9,912,028	11,308,169
Automated CT perfusion imaging	380,140	286,000	286,000	286,000	286,000
First-year health care	6,319,377	7,274,632	8,376,849	9,626,028	11,022,169
Budget impact	856,352	834,198	917,258	1,011,393	1,116,603

Scenario	Budget Impact, \$ ^{a,b,c,d}				
	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario 3-4: To Include Costs of Automated CT Perfusion Imaging in MT Hospitals Only, and First-Year Stroke Management Costs (MT Cases: Annual Increase of 5%)					
Current scenario	5,843,165	6,114,940	6,454,659	6,726,434	7,066,153
New scenario	6,699,517	6,899,302	7,266,707	7,560,632	7,928,037
Automated CT perfusion imaging	380,140	286,000	286,000	286,000	286,000
First-year health care	6,319,377	6,613,302	6,980,707	7,274,632	7,642,037
Budget impact	856,352	784,362	812,049	834,198	861,885

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; MT, mechanical thrombectomy; tPA, tissue plasminogen activator.

^aAll costs in 2019 Canadian dollars.

^bNumbers may appear inexact because of rounding.

^cAll analyses were conducted from the perspective of Ontario Ministry of Health, except for scenarios 1-2 and 1-3.

^dMT hospitals provide mechanical thrombectomy, tPA treatment, and CT perfusion; referral hospitals administer tPA and perform CT perfusion but refer eligible patients to MT hospitals for mechanical thrombectomy.

^eThe cost of the current scenario is zero.

^fThe RAPID neuroimaging platform includes the Alberta Stroke Program Early CT Score (ASPECTS), CT angiography, CT perfusion, and MRI diffusion and perfusion.

We compared the cost of patient transfers with the cost of purchasing automated CT perfusion imaging for referral hospitals (Table 20). We estimated that the cost for a two-way between-hospital patient transfer was \$1,802, and the cost of an imaging licence was \$20,000 per year per referral hospital (for two connected scanners). If automated CT perfusion imaging avoided more than 11 unnecessary two-way transfers for a referral hospital, purchasing it would lead to cost savings. From the perspective of the health care system, automated CT perfusion imaging would lead to cost savings if the 31 referral hospitals purchased licences, and would further avoid more than 344 unnecessary two-way transfers per year.

However, because the volume of unnecessary transfers was relatively small (see Table 17), the cost of purchasing automated CT perfusion imaging was ultimately much greater than the cost of patient transfers shown in scenarios 4-1 to 4-4. In scenario 4-5, we estimated a higher number of avoidable transfers, from 695 in year 1 to 844 in year 5. In this case, purchasing automated CT perfusion imaging in referral hospitals would lead to cost savings, from 0.3 million in year 1 to 0.9 million in year 5.

Table 20: Budget Impact Analysis Results, Scenario Analyses, Scenario 4

Scenario	Budget Impact, \$ ^{a,b}				
	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario 4-1: Transfer From Referral Hospitals to MT Hospitals (MT 15% Annual Increase)					
Cost of transfer when referral hospitals do not have automated CT perfusion imaging	106,318	119,833	138,754	161,279	183,804
Total costs when referral hospitals have automated CT perfusion imaging	1,009,602	673,159	681,268	691,179	701,090
Automated CT perfusion imaging	962,750	620,000	620,000	620,000	620,000
Patient transfer	46,852	53,159	61,268	71,179	81,090
Cost difference	903,284	553,326	542,514	529,900	517,286
Scenario 4-2: Transfer From Referral Hospitals to MT Hospitals (MT 5% Annual Increase)					
Cost of transfer when referral hospitals do not have automated CT perfusion imaging	106,318	109,922	116,229	119,833	126,140
Total costs when referral hospitals have automated CT perfusion imaging	1,009,602	668,654	671,357	673,159	675,862
Automated CT perfusion imaging	962,750	620,000	620,000	620,000	620,000
Patient transfer	46,852	48,654	51,357	53,159	55,862
Cost difference	903,284	558,732	555,128	553,326	549,722
Scenario 4-3: Similar to Scenario 4-1, but Twice as Many Unnecessary Transfers					
Cost of transfer when referral hospitals do not have automated CT perfusion imaging	165,784	186,507	216,240	251,379	286,518
Cost difference ^c	843,818	486,652	465,028	439,800	414,572
Scenario 4-4: Similar to Scenario 4-2, but Twice as Many Unnecessary Transfers					
Cost of transfer when referral hospitals do not have automated CT perfusion imaging	165,784	171,190	181,101	186,507	196,418
Cost difference ^d	843,818	497,464	490,256	486,652	479,444
Scenario 4-5: Including Inpatient Transfers and Transfers From the Emergency Department					
Cost of transfer when referral hospitals do not have automated CT perfusion imaging	1,415,471	1,484,848	1,559,631	1,637,117	1,719,108
Total costs when referral hospitals have automated CT perfusion imaging	1,125,831	791,190	799,299	808,309	818,220
Automated CT perfusion imaging	962,750	620,000	620,000	620,000	620,000
Patient transfer	163,081	171,190	179,299	188,309	198,220
Cost difference	-289,640	-693,658	-760,332	-828,808	-900,888

Abbreviations: CT, computed tomography; MT, mechanical thrombectomy.

^aAll costs in 2019 Canadian dollars.

^bNumbers may appear inexact because of rounding.

^cTotal costs when referral hospitals had automated CT perfusion imaging in scenario 4-3 were the same as scenario 4-1.

^dTotal costs when referral hospitals had automated CT perfusion imaging in scenario 4-4 were the same as scenario 4-2.

Discussion

Publicly funding automated CT perfusion imaging would be associated with an increased cost to the province. The magnitude of the budget increase is directly linked to the number of licences purchased. The health benefits of using automated CT perfusion imaging are based on the volume of mechanical thrombectomy procedures that can be performed 6 to 24 hours after stroke symptom onset.

Cost of Imaging Versus Cost of Patient Transfer

We have provided rough estimates of the number of unnecessary patient transfers that could be avoided using automated CT perfusion imaging in scenarios 4-1 to 4-5. Scenario 4-5 showed potential cost savings when mechanical thrombectomy was fully funded for all eligible patients at 6 to 24 hours after stroke symptom onset. The parameters for this scenario included patients who were hospitalized for ischemic stroke and patients who presented at the emergency department (no inpatient care), so the number of ischemic stroke cases in this scenario was higher than the estimates in Table 13 (which included only patients hospitalized for ischemic stroke). As well, scenarios 4-1 to 4-4 were based on clinical trials in hospitalized ischemic stroke.¹⁰ Clinical trials can apply strict criteria for patient selection, but in clinical practice some criteria may not be easily implemented; for this reason, scenario 4-5 had a much higher number of avoidable transfers.

Other Applications for Automated CT Perfusion Imaging

We assumed the main reason for purchasing automated CT perfusion imaging would be to aid in the selection of patients with acute ischemic stroke for mechanical thrombectomy at 6 to 24 hours after stroke symptom onset. However, automated CT perfusion imaging can be used for a variety of other applications, including selecting patients for mechanical thrombectomy less than 6 hours after stroke symptom onset, and intravenous thrombolysis with alteplase treatment at more than 4.5 hours after stroke symptom onset.⁵⁸ If additional patients were treated, this could change the budget impact. The cost of automated CT perfusion imaging is paid for via an annual (unlimited use) licence. Therefore we expect the cost to use the software on additional patients to be marginal. However, using automated CT perfusion imaging may change patients' management. If it is used in more patients, the costs associated with management may change (i.e., either increase or decrease) and this would alter the budget impact.

Strengths and Limitations

Our study had the following strengths:

- Our key parameters and main assumptions were verified by experts in Ontario
- We provided estimates of economic implications, considering the avoidance of unnecessary between-hospital patient transfers with automated CT perfusion imaging
- Various analyses covered many possible scenarios, and cost estimates can be easily extended for further analysis

The following limitations should be noted when interpreting the findings of this analysis:

- The volume of mechanical thrombectomy at 6 to 24 hours may not entirely reflect the medical need
- Our estimates for the volume of mechanical thrombectomy cases conducted at 6 to 24 hours after stroke symptom onset, first-year health care costs for stroke management, and the cost of patient transfers may be inaccurate because of a lack of reliable data
- Stroke management practice may not be the same across Ontario hospitals; our analysis did not capture potential variability
- Between-hospital patient transfers are associated with non-financial burdens for the health care system; our analyses focused only on cost
- We did not include tele-stroke management costs. Neurologists from MT hospitals could provide remote interpretation and consultations for patients at referral hospitals. It is possible that automated CT perfusion imaging could reduce tele-stroke management costs

Conclusions

We estimate that publicly funding automated CT perfusion imaging for hospitals that provide mechanical thrombectomy and referral hospitals in Ontario would lead to additional costs of approximately \$1.3 million in year 1 and approximately \$0.9 million per year in subsequent years. Some automated CT perfusion imaging costs could be offset by avoiding unnecessary between-hospital patient transfers.

PATIENT PREFERENCES AND VALUES

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat the health condition. It includes the effect of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).⁵⁹⁻⁶¹ Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Automated CT Perfusion Imaging

For the current health technology assessment, the Patient and Public Partnering team at Ontario Health determined the scope and direction of patient and public engagement using a formal needs assessment. The purpose of this needs assessment was threefold:

- To determine if obtaining lived-experience information about automated computed tomography (CT) perfusion imaging would be of value in understanding the impact of this technology
- If lived-experience information was of value, to determine goals and objectives for patient engagement to obtain this information
- To scope out the optimal engagement activity

To complete the needs assessment, we completed background research on the topic in question, which included reviewing the clinical review plan and consulting clinical experts. As we refined the needs assessment, we consulted with lived-experience advisors on the Ontario Health Technology Advisory Committee.

Through this consultation and the needs assessment, we determined that lived-experience information related to patient preferences and values for automated CT perfusion imaging would not be needed to evaluate this technology, for several reasons:

- *Patient preferences and values in decision-making:* For a health technology assessment, patient engagement can often illuminate the context for patient preferences related to a technology and how patients make decisions surrounding its use. We felt that it was unlikely that patient preferences and choices about automated CT perfusion imaging would affect whether it was used or not as clinical experts suggested that patients currently have no direct input or influence on decision-making when it comes to the use (or non-use) of this type of technology in their care.
- *Direct effect on patients:* A number of health technology assessments involve devices or procedures that directly interact and affect a patient's physical state. For example, a device can be inserted or worn, or a procedure can be performed that can cause or relieve symptoms. Direct patient engagement to determine preferences and values for these treatments can illuminate

among other things the outcomes most desired by patients and provide insights into their own decision-making framework for their health care. For automated CT perfusion imaging, the imaging itself does not directly affect the patient's physical state. It is an adjunctive diagnostic tool used by a physician, often without a patient's awareness. Because of this, the types of patient insights and preferences informative for some health technologies such as how the technology feels, is used, or directly affects their quality of life are not relevant for automated CT perfusion imaging.

- *Patient outcomes:* A key component of health technology assessment is evaluating the impact of the technology on important patient outcomes. Direct patient engagement can often provide information about which outcomes are most important and relevant to patients. For automated CT perfusion imaging, the clinical evidence reported in this HTA evaluated functional independence and mortality after treatment with MT in the 6- to 24-hour period after stroke (where eligibility for MT was determined by automated CT perfusion imaging). Through consultation, we felt that functional independence and mortality would be relevant and important outcomes to patients who have experienced a stroke. Therefore, we did not undertake further direct patient engagement.

After careful consideration of these factors as a result of the needs assessment and through consultations, the Patient and Public Partnering team concluded that that direct patient engagement would provide low value and impact for this project.

CONCLUSIONS OF THE HEALTH TECHNOLOGY ASSESSMENT

Automated CT perfusion imaging has an acceptable sensitivity and specificity for detecting brain areas that have been affected by stroke. Misclassification of patients for mechanical thrombectomy may occur in 7% of cases when automated computed tomography (CT) perfusion imaging is used. The results of randomized controlled trials that used automated CT perfusion imaging to select patients for mechanical thrombectomy showed that patients who underwent mechanical thrombectomy had significantly less disability at 90 days compared with patients who did not undergo mechanical thrombectomy.

We also estimated that mechanical thrombectomy using automated CT perfusion imaging to select patients was likely to be cost-effective for patients presenting at 6 to 24 hours after stroke symptom onset. Publicly funding automated CT perfusion imaging for selected hospitals in Ontario would lead to additional costs of \$1.3 million in year 1 and \$0.9 million per year in subsequent years.

ABBREVIATIONS

CBF	Cerebral blood flow
CI	Confidence interval
CT	Computed tomography
CTA	CT angiography
DWI	Diffusion-weighted imaging
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
IQR	Interquartile range
MRI	Magnetic resonance imaging
mRS	modified Rankin Scale
NCCT	Non-contrast computed tomography
NIHSS	National Institute of Health Stroke Scale
rCBF	Relative cerebral blood flow
SD	Standard deviation
Tmax	Time to maximum tissue contrast density
tPA	tissue plasminogen activator

GLOSSARY

Anterior circulation of the brain	The blood supply to the anterior (front) part of the brain. It includes the anterior cerebral artery and the middle cerebral artery.
Budget impact analysis	A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).
Cost-effective	A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.
Cost-effectiveness analysis	Used broadly, “cost-effectiveness analysis” may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, “cost-effectiveness analysis” may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.
Discounting	Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.
Ischemic stroke	An ischemic stroke is type of stroke caused by a blockage in a blood vessel in the brain, causing severely reduced blood flow (ischemia).

Ministry of Health perspective	The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).
Penumbra	In patients with an acute ischemic stroke, the penumbra is the tissue that surrounds the infarcted area (dead tissue). In the penumbra, the blood flow is not completely stopped, but is too low for tissues to survive for a long period. This area is at risk for further damage unless blood flow is restored quickly.
Quality-adjusted life-year (QALY)	The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.
Recanalization	Recanalization in acute ischemic stroke is the reopening of a blocked artery.
Reference case	The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.
Reperfusion	Reperfusion is the restoration of blood flow to organs or tissues.
Thrombolysis	Thrombolysis is a treatment to dissolve a blood clot in a blood vessel and improve blood flow.
Scenario analysis	A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.

APPENDICES

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: April 5, 2019

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <March 2019>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 27, 2019>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2019 Week 13>, Ovid MEDLINE(R) ALL <1946 to April 04, 2019>

Search strategy:

-
- 1 *Stroke/ (123966)
 - 2 (((stroke or strokes or CVA or CVAs) adj4 (acute or isch?em*)) or (acute adj2 isch?em*) or AIS).ti,ab,kf. (248289)
 - 3 ((cerebrovascular or cerebro vascular or cerebral vascular) adj2 (accident* or infarct*) adj2 (acute or isch?em*)).ti,ab,kf. (1879)
 - 4 exp Brain Ischemia/ (268660)
 - 5 ((brain or cerebral or intracerebral or arachnoid or subarachnoid or intracranial or cranial) adj2 (infarct* or isch?em*)).ti,ab,kf. (147280)
 - 6 (((occlus* or block* or infarct* or clot* or terminat*) adj4 (large vessel* or large arter* or carotid or cerebr* or MCA or ACA) or LVO).ti,ab,kf. (115518)
 - 7 or/1-6 (554158)
 - 8 ((automate* or automatic or software* or cloud* or map*) adj4 perfusion adj4 (CT or comput* tomograph* or imag*)).ti,ab,kf. (1106)
 - 9 (RAPID* adj3 (software* or automate* or automatic or platform* or processing or postprocessing)).ti,ab,kf. (12113)
 - 10 (((Syngo* or Brilliance* or Philips* or Intellispace*) adj3 software*) or AW Volumeshare*).ti,ab,kf. (863)
 - 11 (viz* adj2 (AI or LVO)).ti,ab,kf. (4)
 - 12 iSchemaView*.ti,ab,kf. (14)
 - 13 (DAWN or DEFUSE).ti,ab,kf. (9679)
 - 14 or/8-13 (23665)
 - 15 Perfusion Imaging/ (23946)
 - 16 (perfusion adj3 (imag* or volume* or analys#s)).ti,ab,kf. (39506)
 - 17 exp Stroke/dg [Diagnostic Imaging] (9733)
 - 18 exp Brain Ischemia/dg [Diagnostic Imaging] (11187)
 - 19 Tomography, X-Ray Computed/ (397907)
 - 20 ((compute* adj2 tomograph*) or CAT scan* or (CT adj3 (scan* or perfusion or contrast*)) or CTP).ti,ab,kf. (825948)
 - 21 ((target or clinical or core or map*) adj3 mismatch*).ti,ab,kf. (2132)

- 22 ((cerebral blood flow* or cerebral blood volume*) adj4 map*).ti,ab,kf. (1527)
- 23 early CT score*.ti,ab,kf. (1105)
- 24 or/15-23 (1097953)
- 25 Software/ (147047)
- 26 Image Processing, Computer-Assisted/ (180531)
- 27 (software* or automate* or semiautomate* or automatic or semiautomatic or machine learn* or postprocess* or post process* or (image* adj2 (process* or analys#s))).ti,ab,kf. (908221)
- 28 or/25-27 (1104016)
- 29 24 and 28 (72477)
- 30 or/14,29 (94922)
- 31 7 and 30 (3329)
- 32 exp Animals/ not Humans/ (15935431)
- 33 31 not 32 (2345)
- 34 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congresses.pt. (5076128)
- 35 33 not 34 (2164)
- 36 limit 35 to english language [Limit not valid in CDSR; records were retained] (2013)
- 37 36 use medall,cctr,coch,clhta,cleed (1383)
- 38 *cerebrovascular accident/ (137742)
- 39 (((stroke or strokes or CVA or CVAs) adj4 (acute or isch?em*)) or (acute adj2 isch?em*) or AIS).tw,kw. (250548)
- 40 ((cerebrovascular or cerebro vascular or cerebral vascular) adj2 (accident* or infarct*) adj2 (acute or isch?em*)).tw,kw. (2198)
- 41 brain ischemia/ (174777)
- 42 ((brain or cerebral or intracerebral or arachnoid or subarachnoid or intracranial or cranial) adj2 (infarct* or isch?em*)).tw,kw. (155409)
- 43 blood vessel occlusion/ (8650)
- 44 *middle cerebral artery occlusion/ (8686)
- 45 (((occlus* or block* or infarct* or clot* or terminat*) adj4 (large vessel* or large arter* or carotid or cerebr* or MCA or ACA)) or LVO).tw,kw. (118204)
- 46 or/38-45 (518848)
- 47 ((automate* or automatic or software* or cloud* or map*) adj4 perfusion adj4 (CT or comput* tomograph* or imag*)).tw,kw,dv. (1117)
- 48 (RAPID* adj3 (software* or automate* or automatic or platform* or processing or postprocessing)).tw,kw,dv. (12150)
- 49 (((Syngo* or Brilliance* or Philips* or Intellispace*) adj3 software*) or AW Volumeshare*).tw,kw,dv. (946)
- 50 (viz* adj2 (AI or LVO)).tw,kw,dv. (4)
- 51 iSchemaView*.tw,kw,dv. (15)
- 52 (DAWN or DEFUSE).tw,kw,dv. (9758)
- 53 or/47-52 (23876)
- 54 (perfusion adj3 (imag* or volume* or analys#s)).tw,kw,dv. (40595)
- 55 x-ray computed tomography/ (399683)
- 56 *computer assisted tomography/ (112195)
- 57 ((compute* adj2 tomograph*) or CAT scan* or (CT adj3 (scan* or perfusion or contrast*)) or CTP).tw,kw,dv. (839703)
- 58 ((target or clinical or core or map*) adj3 mismatch*).tw,kw,dv. (2173)
- 59 brain perfusion/ (22837)

- 60 (blood flow velocity/ or brain blood volume/) and brain mapping/ (495)
 61 ((cerebral blood flow* or cerebral blood volume*) adj4 map*).tw,kw,dv. (1532)
 62 early CT score*.tw,kw,dv. (1100)
 63 or/54-62 (1142503)
 64 software/ (147047)
 65 *image analysis/ (10880)
 66 image processing/ (191148)
 67 imaging software/ (16822)
 68 (software* or automate* or semiautomate* or automatic or semiautomatic or machine learn* or postprocess* or post process* or (image* adj2 (process* or analys#s))).tw,kw,dv. (926089)
 69 or/64-68 (1140793)
 70 63 and 69 (79697)
 71 or/53,70 (102274)
 72 46 and 71 (3264)
 73 (exp animal/ or nonhuman/) not exp human/ (10216901)
 74 72 not 73 (3120)
 75 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. (10289515)
 76 74 not 75 (2190)
 77 limit 76 to english language [Limit not valid in CDSR; records were retained] (2044)
 78 77 use emez (871)
 79 37 or 78 (2254)
 80 79 use medall (1279)
 81 79 use emez (871)
 82 79 use coch (0)
 83 79 use cctr (104)
 84 79 use clhta (0)
 85 79 use cleed (0)
 86 remove duplicates from 79 (1647)

Economic Evidence Search

Search date: April 23, 2019

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <March 2019>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 17, 2019>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2019 Week 16>, Ovid MEDLINE(R) ALL <1946 to April 22, 2019>

Search strategy:

-
- 1 *Stroke/ (124314)
 - 2 (((stroke or strokes or CVA or CVAs) adj4 (acute or isch?em*)) or (acute adj2 isch?em*) or AIS).ti,ab,kf. (250238)

- 3 ((cerebrovascular or cerebro vascular or cerebral vascular) adj2 (accident* or infarct*) adj2 (acute or isch?em*)).ti,ab,kf. (1886)
- 4 exp Brain Ischemia/ (270362)
- 5 ((brain or cerebral or intracerebral or arachnoid or subarachnoid or intracranial or cranial) adj2 (infarct* or isch?em*)).ti,ab,kf. (148018)
- 6 (((occlus* or block* or infarct* or clot* or terminat*) adj4 (large vessel* or large arter* or carotid or cerebr* or MCA or ACA)) or LVO).ti,ab,kf. (116176)
- 7 or/1-6 (557255)
- 8 ((automate* or automatic or software* or cloud* or map*) adj4 perfusion adj4 (CT or comput* tomograph* or imag*)).ti,ab,kf. (1121)
- 9 (RAPID* adj3 (software* or automate* or automatic or platform* or processing or postprocessing)).ti,ab,kf. (12184)
- 10 (((Syngo* or Brilliance* or Philips* or Intellispace*) adj3 software*) or AW Volumeshare*).ti,ab,kf. (872)
- 11 (viz* adj2 (AI or LVO)).ti,ab,kf. (4)
- 12 iSchemaView*.ti,ab,kf. (15)
- 13 (DAWN or DEFUSE).ti,ab,kf. (9736)
- 14 or/8-13 (23817)
- 15 Perfusion Imaging/ (24090)
- 16 (perfusion adj3 (imag* or volume* or analys#s)).ti,ab,kf. (39759)
- 17 exp Stroke/dg [Diagnostic Imaging] (9799)
- 18 exp Brain Ischemia/dg [Diagnostic Imaging] (11249)
- 19 Tomography, X-Ray Computed/ (400028)
- 20 ((compute* adj2 tomograph*) or CAT scan* or (CT adj3 (scan* or perfusion or contrast*)) or CTP).ti,ab,kf. (831057)
- 21 ((target or clinical or core or map*) adj3 mismatch*).ti,ab,kf. (2163)
- 22 ((cerebral blood flow* or cerebral blood volume*) adj4 map*).ti,ab,kf. (1536)
- 23 early CT score*.ti,ab,kf. (1115)
- 24 or/15-23 (1104141)
- 25 Software/ (148764)
- 26 Image Processing, Computer-Assisted/ (181164)
- 27 (software* or automate* or semiautomate* or automatic or semiautomatic or machine learn* or postprocess* or post process* or (image* adj2 (process* or analys#s))).ti,ab,kf. (915267)
- 28 or/25-27 (1111710)
- 29 24 and 28 (73001)
- 30 or/14,29 (95580)
- 31 7 and 30 (3364)
- 32 exp Animals/ not Humans/ (15934207)
- 33 31 not 32 (2387)
- 34 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congresses.pt. (5091537)
- 35 33 not 34 (2205)
- 36 limit 35 to english language [Limit not valid in CDSR; records were retained] (2054)
- 37 economics/ (251524)
- 38 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (814237)
- 39 economics.fs. (418103)

- 40 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmaco-economic* or pharmaco-economic*).ti,ab,kf. (864516)
- 41 exp "costs and cost analysis"/ (570294)
- 42 (cost or costs or costing or costly).ti. (258413)
- 43 cost effective*.ti,ab,kf. (317149)
- 44 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*).ab,kf. (208250)
- 45 models, economic/ (12447)
- 46 markov chains/ or monte carlo method/ (78681)
- 47 (decision adj1 (tree* or analy* or model*).ti,ab,kf. (41047)
- 48 (markov or markow or monte carlo).ti,ab,kf. (125777)
- 49 quality-adjusted life years/ (38658)
- 50 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (71066)
- 51 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (115434)
- 52 or/37-51 (2491681)
- 53 36 and 52 (38)
- 54 53 use medall,coch,cctr,clhta (20)
- 55 36 use cleed (0)
- 56 or/54-55 (20)
- 57 *cerebrovascular accident/ (138592)
- 58 (((stroke or strokes or CVA or CVAs) adj4 (acute or isch?em*)) or (acute adj2 isch?em*) or AIS).tw,kw. (252497)
- 59 ((cerebrovascular or cerebro vascular or cerebral vascular) adj2 (accident* or infarct*) adj2 (acute or isch?em*)).tw,kw. (2206)
- 60 brain ischemia/ (176033)
- 61 ((brain or cerebral or intracerebral or arachnoid or subarachnoid or intracranial or cranial) adj2 (infarct* or isch?em*)).tw,kw. (156175)
- 62 blood vessel occlusion/ (8744)
- 63 *middle cerebral artery occlusion/ (8750)
- 64 (((occlus* or block* or infarct* or clot* or terminat*) adj4 (large vessel* or large arter* or carotid or cerebr* or MCA or ACA)) or LVO).tw,kw. (118868)
- 65 or/57-64 (522097)
- 66 ((automate* or automatic or software* or cloud* or map*) adj4 perfusion adj4 (CT or comput* tomograph* or imag*).tw,kw,dv. (1132)
- 67 (RAPID* adj3 (software* or automate* or automatic or platform* or processing or postprocessing)).tw,kw,dv. (12221)
- 68 (((Syngo* or Brilliance* or Philips* or Intellispace*) adj3 software*) or AW Volumeshare*).tw,kw,dv. (955)
- 69 (viz* adj2 (AI or LVO)).tw,kw,dv. (4)
- 70 iSchemaView*.tw,kw,dv. (16)
- 71 (DAWN or DEFUSE).tw,kw,dv. (9815)
- 72 or/66-71 (24028)
- 73 (perfusion adj3 (imag* or volume* or analys#s)).tw,kw,dv. (40845)
- 74 x-ray computed tomography/ (401804)
- 75 *computer assisted tomography/ (112511)
- 76 ((compute* adj2 tomograph*) or CAT scan* or (CT adj3 (scan* or perfusion or contrast*)) or CTP).tw,kw,dv. (844819)
- 77 ((target or clinical or core or map*) adj3 mismatch*).tw,kw,dv. (2204)

- 78 brain perfusion/ (22973)
 79 (blood flow velocity/ or brain blood volume/) and brain mapping/ (497)
 80 ((cerebral blood flow* or cerebral blood volume*) adj4 map*).tw,kw,dv. (1541)
 81 early CT score*.tw,kw,dv. (1109)
 82 or/73-81 (1148697)
 83 software/ (148764)
 84 *image analysis/ (10976)
 85 image processing/ (191781)
 86 imaging software/ (17128)
 87 (software* or automate* or semiautomate* or automatic or semiautomatic or machine learn* or postprocess* or post process* or (image* adj2 (process* or analys#s))).tw,kw,dv. (933213)
 88 or/83-87 (1148745)
 89 82 and 88 (80267)
 90 or/72,89 (102978)
 91 65 and 90 (3300)
 92 (exp animal/ or nonhuman/) not exp human/ (10245822)
 93 91 not 92 (3156)
 94 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. (10368227)
 95 93 not 94 (2218)
 96 limit 95 to english language [Limit not valid in CDSR; records were retained] (2072)
 97 Economics/ (251524)
 98 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (126997)
 99 Economic Aspect/ or exp Economic Evaluation/ (446648)
 100 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (890042)
 101 exp "Cost"/ (570294)
 102 (cost or costs or costing or costly).ti. (258413)
 103 cost effective*.tw,kw. (329342)
 104 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*).ab,kw. (219093)
 105 Monte Carlo Method/ (62770)
 106 (decision adj1 (tree* or analy* or model*)).tw,kw. (44848)
 107 (markov or markow or monte carlo).tw,kw. (130828)
 108 Quality-Adjusted Life Years/ (38658)
 109 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (74892)
 110 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (136007)
 111 or/97-110 (2134482)
 112 96 and 111 (129)
 113 112 use emez (22)
 114 56 or 113 (42)
 115 114 use medall (20)
 116 114 use emez (22)
 117 114 use coch (0)
 118 114 use cctr (0)
 119 114 use clhta (0)
 120 114 use cleed (0)
 121 remove duplicates from 114 (33)

Grey Literature Search

Performed: April 24–May 1, 2019; updated September 11–12, 2019

Websites searched:

HTA Database Canadian Repository, Alberta Health Evidence Reviews, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Université de Québec-Université Laval (CHU), Health Technology Assessment Database, Epistemonikos, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Council of Australian Governments Health Technologies, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, Health Technology Wales, Oregon Health Authority Health Evidence Review Commission, Veterans Affairs Health Services Research and Development, ClinicalTrials.gov, PROSPERO, EUnetHTA, Tuft's Cost-Effectiveness Analysis Registry

Keywords used:

automated perfusion, perfusion software, automatic software, perfusion imaging, postprocessing, post processing, RAPID software, mismatch, viz.ai, cerebral blood volume, cerebral blood flow

Clinical results (included in PRISMA): 11

Economic results (included in PRISMA): 13

Ongoing clinical trials (ClinicalTrials.gov): 4

Ongoing HTAs (PROSPERO/EUnetHTA): 3

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias^a Among Diagnostic Accuracy Studies (QUADAS-2 Tool)

Author, Year	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Siegler et al, 2019 ³³	Low	Low	Low	Low	Low	Low	Low
Hoving et al, 2018 ³¹	Low	Low	Low	Low	Low	Low	Low
Haussen et al, 2016 ³⁰	Low	Low	Low	Low	Low	Low	Low
Benson et al, 2015 ²⁸	Low	Low	Low	Low	Low	Low	Low
Campbell et al, 2015 ³²	Low	Low	Low	Low	Low	Low	Low
Gueskens et al, 2015 ²⁹	Low	Low	Low	Low	Low	Low	Low

Abbreviation: QUADAS, Quality Assessment of Diagnostic Accuracy Studies.

^aPossible risk of bias levels: low, high, unclear.

Table A2: Risk of Bias^a Among Randomized Controlled Trials (Cochrane Risk-of-Bias Tool)

Author, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Incomplete Outcome Data	Selective Reporting	Other Bias
Albers et al, 2018 ¹⁰	Low	Low	Low ^b	Low	Low ^c	Low
Nogueira et al, 2018 ¹¹	Low	Low	Low ^b	Low	Low ^c	Low
Campbell et al, 2015 ³⁷	Low	Low	Low ^b	Low	Low ^c	Low
Saver et al, 2015 ⁶	Low	Unclear ^d	Low ^b	Low	Low ^c	Low

^aPossible risk of bias levels: low, high, and unclear.

^bIt was impossible to blind participants, but the assessors were blinded to the treatment assignment.

^cReported all clinical outcomes selected for this review.

^dNo description of allocation concealment.

Table A3: GRADE Evidence Profile for Automated CT Perfusion Imaging

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Diagnostic Accuracy: Identifying the Infarct Core and Estimating Volume							
1 (meta-analysis) ^{31a}	No serious limitations	No serious limitations	Serious limitations (-1) ^c	No serious limitations	Undetected	NA	⊕⊕⊕ Moderate
3 (observational) ^{28-30b}	No serious limitations	No serious limitations	Serious limitations (-1) ^c	No serious limitations	Undetected	NA	⊕⊕⊕ Moderate
Diagnostic Accuracy: Misclassification Rate							
2 (observational) ^{32,33b}	No serious limitations	No serious limitations	Serious limitations (-1) ^c	No serious limitations	Undetected	NA	⊕⊕⊕ Moderate
Clinical Utility: Mortality							
5 (RCTs) ^{6,10,11,37,43d}	No serious limitations	No serious limitations	Serious limitations (-1) ^e	No serious limitations	Undetected	NA	⊕⊕⊕ Moderate
Clinical Utility: Functional Independence							
6 (RCTs) ^{6,10,11,37,43,44d}	No serious limitations	No serious limitations	Serious limitations (-1) ^e	No serious limitations	Undetected	NA	⊕⊕⊕ Moderate
Clinical Utility: Intracranial Hemorrhage							
4 (RCTs) ^{6,10,11,37d}	No serious limitations	No serious limitations	Serious limitations (-1) ^e	No serious limitations	Undetected	NA	⊕⊕⊕ Moderate

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.

^aEvidence for this outcome begins at high quality because it is based on a meta-analysis of individual patient data from RCTs.

^bEvidence for this outcome begins at high quality because diagnostic studies start at high quality and the trials compared the diagnostic accuracy with an appropriate reference standard.

^cThere was uncertainty about the effect of diagnostic accuracy on patient clinical outcomes.

^dEvidence for this outcome begins at high quality because it is based on well-conducted RCTs.

^eClinical outcomes are indirect evidence for diagnostic accuracy.

Appendix 3: Selected Excluded Studies—Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary Reason for Exclusion
Austein F, Riedel C, Kerby T, Meyne J, Binder A, Lindner T, et al. Comparison of perfusion CT software to predict the final infarct volume after thrombectomy. <i>Stroke</i> . 2016;47(9):2311-7.	Compared two or more automated imaging platforms
Bivard A, Levi C, Spratt N, Parsons M. Perfusion CT in acute stroke: a comprehensive analysis of infarct and penumbra. <i>Radiology</i> . 2013;267(2):543-50.	Compared two or more automated imaging platforms
Churilov L, Liu D, Ma H, Christensen S, Nagakane Y, Campbell B, et al. Multiattribute selection of acute stroke imaging software platform for extending the time for thrombolysis in emergency neurological deficits (EXTEND) clinical trial. <i>Int J Stroke</i> . 2013;8(3):204-10.	Compared two or more automated imaging platforms
Fahmi F, Marquering HA, Streekstra GJ, Beenen LF, Velthuis BK, VanBavel E, et al. Differences in CT perfusion summary maps for patients with acute ischemic stroke generated by 2 software packages. <i>Am J Neuroradiol</i> . 2012;33(11):2074-80.	Compared two or more automated imaging platforms
Kamalian S, Kamalian S, Maas MB, Goldmacher GV, Payabvash S, Akbar A, et al. CT cerebral blood flow maps optimally correlate with admission diffusion-weighted imaging in acute stroke but thresholds vary by postprocessing platform. <i>Stroke</i> . 2011;42(7):1923-8.	Compared two or more automated imaging platforms
Kudo K, Sasaki M, Yamada K, Momoshima S, Utsunomiya H, Shirato H, et al. Differences in CT perfusion maps generated by different commercial software: quantitative analysis by using identical source data of acute stroke patients. <i>Radiology</i> . 2010;254(1):200-9.	Compared two or more automated imaging platforms
Tsurukiri J, Ota T, Jimbo H, Okumura E, Shigeta K, Amano T, et al. Thrombectomy for stroke at 6-24 hours without perfusion CT software for patient selection. <i>Journal Stroke Cerebrovasc Dis</i> . 2019;28(3):774-81.	Used MRI for patient selection
Zussman BM, Boghosian G, Gorniak RJ, Olszewski ME, Read KM, Siddiqui KM, et al. The relative effect of vendor variability in CT perfusion results: a method comparison study. <i>Am J Roentgenol</i> . 2011;197(2):468-73.	Compared two or more automated imaging platforms

Appendix 4: Eligibility Criteria in DEFUSE 3 and DAWN Trials

DEFUSE 3¹⁰

- Patients with occlusion in the proximal middle cerebral artery or internal carotid artery
- Infarct core < 70 mL
- Target mismatch ratio ≥ 1.8
- Absolute volume of penumbra ≥ 15 mL

DAWN¹¹

- Patients with occlusion in the first segment of the middle cerebral artery or internal carotid artery or both, on computed tomography angiography or magnetic resonance angiography
- Mismatch between the severity of clinical deficit and the infarct volume, which was defined according to the following criteria:
 - Patients ≥ 80 years of age, National Institute of Health Stroke Scale (NIHSS) ≥ 10 , infarct volume < 21 mL
 - Patients < 80 years of age, NIHSS ≥ 10 , infarct volume < 31 mL
 - Patients < 80 years of age, NIHSS ≥ 20 , infarct volume 31–50 mL

Appendix 5: Crude Estimate of the Cost-Effectiveness of Mechanical Thrombectomy Using Automated CT Perfusion Imaging to Select Patients

We approximated the cost-effectiveness of mechanical thrombectomy with automated computed tomography (CT) perfusion imaging, compared with standard medical care alone, for patients with acute ischemic stroke 6 to 24 hours after onset of stroke symptoms from the perspective of Ontario Ministry of Health.

Mechanical thrombectomy refers to the mechanical thrombectomy procedure plus standard medical care (intravenous thrombolysis for patients at 0 to 6 hours, and Aspirin and standard deep vein thrombosis prevention for 6 to 24 hours). Our previous economic evaluation of mechanical thrombectomy at 0 to 6 hours after onset of stroke symptoms showed that, compared with intravenous thrombolysis alone, mechanical thrombectomy led to 0.21 additional quality-adjusted life-years (QALYs) and cost an additional \$2,520 over a 5-year time horizon.^{5,46} The corresponding incremental cost-effectiveness ratio (ICER) was \$11,990 per QALY gained.

Using the modified Rankin Scale (mRS), the treatment effect of mechanical thrombectomy at 6 to 24 hours compared to standard medical care alone was greater than the treatment effect of mechanical thrombectomy at 0 to 6 hours compared to medical care alone.⁴⁵ The mRS is a 6-point scale that measures functional independence and is the scale most commonly used in stroke clinical trials (0 indicates no symptoms; 5 indicates severe disability).

- Compared with usual care, mechanical thrombectomy at 0 to 6 hours after stroke symptom onset led to a higher proportion (19 percentage points) of patients with mRS scores 0 to 2 (i.e., functional independence) at 90 days (mechanical thrombectomy 46% vs. intravenous thrombolysis 27%)
- Compared with standard medical care, the proportion of patients with an mRS score of 0 to 2 following mechanical thrombectomy at 6 to 24 hours after stroke symptom onset was 32 percentage points higher at 90 days (mechanical thrombectomy 47% vs. standard medical care 15%)

Thus, mechanical thrombectomy at 6 to 24 hours after stroke symptom onset would lead to QALYs gained equal or greater than the 0.21 found for mechanical thrombectomy at 0 to 6 hours after stroke symptom onset.

Excluding the cost of automated CT perfusion imaging, we assumed that the incremental cost of mechanical thrombectomy at 6 to 24 hours compared to standard medical care would be the same as mechanical thrombectomy at 0 to 6 hours compared to usual care (\$2,520). Our budget impact analysis projected the number of mechanical thrombectomy cases over the next 5 years to be 474 (86 in year 1 and an annual increase of 5%) to 580 (86 cases in year 1 and annual increase of 15%) at 6 to 24 hours after stroke symptom onset. Over the next 5 years, to fund automated CT perfusion imaging in 11 hospitals that provide mechanical thrombectomy and 31 hospitals that would refer patients to hospitals that provide mechanical thrombectomy would cost \$5.0 million. The costs of automated CT perfusion imaging per patient undergoing mechanical thrombectomy would be \$8,564 (for 580 mechanical thrombectomy cases in 5 years) to \$10,479 (for 474 mechanical thrombectomy cases in 5 years). Based on these assumptions, we approximated the incremental cost of mechanical thrombectomy following automated CT perfusion imaging to be \$11,084 to \$12,999.

The ICER for mechanical thrombectomy with automated CT perfusion imaging compared to standard medical care would be less than \$53,000 ($\$11,084 \div 0.21$) or \$62,000 ($\$12,999 \div 0.21$), depending on the volume of mechanical thrombectomy cases. Thus, mechanical thrombectomy using automated CT perfusion imaging to select patients is likely to be cost-effective in Ontario.

In addition, a cost–utility study⁶² showed that mechanical thrombectomy up to 24 hours after the onset of acute ischemic stroke symptoms was cost-effective (ICER for mechanical thrombectomy within 12 hours: \$1,564 USD; ICER for mechanical thrombectomy within 16 hours: \$5,253 USD; ICER for mechanical thrombectomy within 24 hours: \$3,712 USD), but authors did not explicitly mention automated CT perfusion imaging in the article. However, given the low ICERs found in this study and the QALYs gained of 1.6 per patient, even adding the cost of automated CT perfusion imaging for the mechanical thrombectomy group (assuming that the number of mechanical thrombectomies carried out per imaging licence at 6 to 24 hours after stroke symptom onset was not particularly low), mechanical thrombectomy performed up to 24 hours after stroke symptom onset would be still cost-effective.

Appendix 6: Hospitalizations for Ischemic Stroke in Ontario, 2013 to 2017

Table A4: Hospitalizations for Ischemic Stroke in Ontario by ICD Code, 2013 to 2017

ICD-10-CA Code ^a	Hospitalizations for Ischemic Stroke, n				
	2013	2014	2015	2016	2017
I630	118	165	172	217	216
I631	130	161	220	208	161
I632	470	506	513	542	654
I633	379	408	429	542	554
I634	1,006	1,148	1,253	1,518	1,750
I635	3,492	4,039	4,524	4,488	4,830
I636	18	20	20	25	17
I638	532	598	520	493	585
I639	4,918	5,193	5,309	5,144	5,307
H341	17	10	9	14	14
Total	11,080	12,248	12,969	13,191	14,088
% Increase, relative to preceding year	NA	10.5%	5.9%	1.7%	6.8%

Abbreviation: ICD-10-CA, International Statistical Classification of Diseases and Related Health Problems 10th Revision, Canada.

^aDischarge Abstract Database, 2017, IntelliHealth Ontario.⁴⁹

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