Artificial intelligence and cost-effectiveness analyses of radiological imaging in acute ischemic stroke

van Voorst, H.

Publication date
2024

CHAPTER 1

1

General Introduction

This thesis examines the benefits of employing radiological imaging in conjunction with artificial intelligence (AI) and health economic modeling tools to improve the use of radiological imaging in acute ischemic stroke care. The concepts described in this introduction form the foundation for the research we present. First, a global overview of the diagnostic and treatment considerations of a patient presenting with stroke symptoms at an emergency ward is described. Second, we introduce the available radiological imaging modalities and their use in acute ischemic stroke. We conclude by describing recent advancements in the fields of artificial intelligence (AI) and health economic modeling, as well as the structure and objectives of this thesis in relation to the previously covered subjects.

Stroke symptoms and treatment

A drooping face, weakness in the arms or legs, and speech problems are symptoms of a stroke.[1] It is crucial to quickly notify the emergency services when someone experiences such symptoms. Every minute of delay to optimal treatment causes an increase in brain damage.[2] There are two types of stroke, hemorrhagic stroke and ischemic stroke.[2,3] Hemorrhagic stroke is caused by bleeding in or surrounding the brain. Monitoring patients with a hemorrhagic stroke is crucial as an increase in the blood volume in the skull (intracranial) can exert mechanical pressure on the brain tissue and cause secondary damage. If too much intracranial blood accumulates, surgical removal of the blood or opening of the skull to reduce the pressure in the skull is required to prevent further damage.[3] Ischemic stroke is caused by an occlusion of an artery stopping or reducing the blood flow to downstream brain tissue. Such an arterial occlusion is caused by the clotting of blood often referred to as a thrombus. Due to an arterial occlusion, downstream brain tissue is deprived of the supply of oxygen and nutrients causing the death of brain cells [1]. Timely removal of the thrombus prevents further damage to the brain.

Figure 1. Recognize and act FAST on stroke symptoms.
Figure is reprinted with permission from the British Stroke Foundation.,

Two therapeutic options are currently available to remove a thrombus; intravenous thrombolysis (IVT) and endovascular treatment (EVT).[2] IVT consists of delivering a clot-dissolving agent through an intravenous line. IVT is known to result in better outcomes in approximately 1 out of 10 patients with an acute ischemic stroke if given within 3 hours after the onset of the stroke symptoms.[4] Between 3 and 4.5 hours after stroke symptom onset the number of patients benefiting from IVT decreases to 1 out of 19.[4] For occlusions of larger arteries, it is possible to remove the thrombus by accessing it through the arteries with an EVT device. If EVT is provided within 6 hours after the onset of stroke symptoms, approximately 1 out of 8 patients have a better outcome.[5,6] More recent studies also established the benefit of EVT between 6 to 24 hours after symptom onset.[7] Similar to IVT, the benefit of EVT diminishes as time to treatment passes.[8] For patients with stroke, radiological imaging is considered to set the diagnosis, prognosticate patient outcomes, and optimize treatment decisions.[2]

Available radiological imaging techniques

Since the discovery of the X-ray more than a century ago, a wide range of medical imaging modalities have been developed. An X-ray is a beam of electrically charged particles that can be targeted at an object, the particles passing through or next to this object are measured behind the object. By measuring the number of particles passing through an object it is possible to quantify the density of that object in a two-dimensional image.[9] The computerized tomography (CT) scan has been developed as a tomographic extension of multiple X-rays to reconstruct a 3-dimensional representation of the object analyzed. This type of CT is often referred to as a non-contrast enhanced CT (NCCT).[9] After injecting a dense contrast fluid into a patient's bloodstream, it is possible to use CT to visualize blood vessels - this technique is called CT angiography (CTA).[9]

In recent decades, CT perfusion (CTP) has been developed as an extension of CTA. For acquiring a CTP scan, multiple sequential low-dose CT scans are acquired over time while contrast fluid flows through blood vessels and perfuses brain tissue. With CTP analysis software it is possible to estimate the blood flow and thereby also deficits of blood flow. Based on the CTP software claims have been made on the possibility to estimate the extent of damage to brain tissue in the acute stroke setting. Specifically, based on CTP software it is possible to approximate brain tissue with reversible damage (penumbra) and brain tissue with irreversible damage (ischemic core).[9,10]

The main advantages of CT are that it is a quick, affordable, and widely available scanning technique. The disadvantage of CT imaging is that it exposes patients to radiation, which is connected with a slight increase in the risk of cancer among the population. Additionally, contrast fluid can in some instances cause renal dysfunction and may cause an allergic reaction. Magnetic resonance imaging (MRI) is an alternative to CT, MRI employs a high magnetic field, radiofrequency pulses, and encoding gradients to visualize soft tissue.[9] Although MRI is more expensive, more time-consuming, contraindicated in patients with implants, and not always easily available, it provides more comprehensive and accurate measuring and imaging capabilities than CT. Since time is of the essence in acute imaging of patients with stroke symptoms, CT is often preferred over MRI.

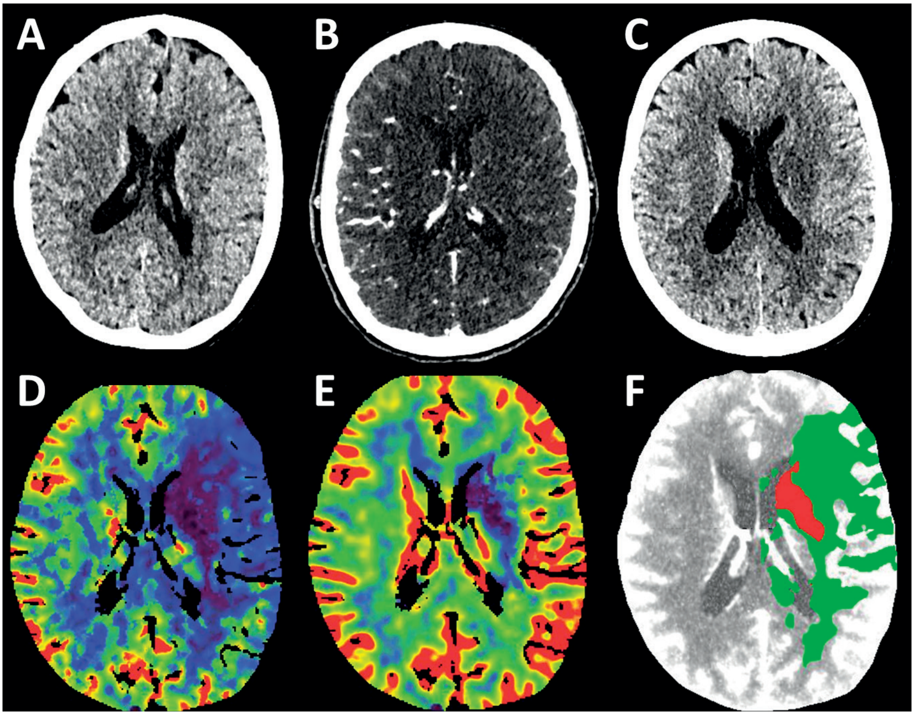

Figure 2. Radiological imaging modalities used in stroke.
A: Baseline NCCT made in the acute setting. B: Baseline CTA with angiographically enhanced arteries and veins. C: Follow-up NCCT one week after the acute ischemic stroke. D: Cerebral blood flow map derived from CTP. E: Cerebral blood volume map derived from CTP. F: The penumbra (green) and ischemic core (red) are derived from CTP.

Radiological imaging in the stroke workflow

When a patient presents at an emergency ward with stroke symptoms, radiological imaging is used in addition to the medical anamnesis, the description of the symptoms and the patient history, and the physical examination by a neurologist to set the diagnosis and consider the optimal treatment.[1] The first step is to assess the presence of a hemorrhagic stroke. NCCT can be used to detect or rule out a hemorrhage in the brain and can sometimes be used to visualize brain damage due to an ischemic stroke.[3] The second step is to assess if there is an occlusion visible in CTA, indicating an ischemic stroke.[2] In the absence of a hemorrhagic or ischemic stroke, further medical examination may be needed by the neurologist to assess if there is another explanation for the symptoms. Since both hemorrhagic and ischemic stroke require fast treatment delivery, timely and accurate diagnosis is crucial in the emergency ward. Furthermore, the presence of ischemic stroke requires a quick administration of IVT. Although the strong thrombolytic properties of IVT are beneficiary to resolving a thrombus, IVT also might cause complications such as hemorrhages.[1,4] IVT-induced hemorrhages can occur anywhere in the body but are most dangerous in the skull (intracerebral hemorrhage). Moreover, if IVT is given to a patient with a hemorrhagic stroke, due to a wrong diagnosis, or to a patient with a high risk of hemorrhagic stroke, the consequences can be fatal.

Arteries can be visualized with CTA and can be used to detect and localize the occluding thrombus. Only occlusions of specific large arteries can be reached in a thrombectomy procedure and are thus suitable for EVT.[2,9] This is in contrast to IVT, which can be administered regardless of the thrombus location. To date, studies have demonstrated the benefit of EVT for patients with an occlusion occurring in the internal and external carotid artery (ICA/ECA), and in the M1- and first part of the M2-segment of the middle cerebral artery (MCA) (Figure 3).

EVT is an invasive procedure and comes with the risk of hemorrhage, thrombus fragmentation, and re-occlusion which can worsen the patient's health.[11–13] Therefore, it might be valuable to select patients that are likely to benefit from EVT. Additionally, EVT can only be performed in specialized stroke hospitals by specialized neuro-interventionists. With a large portion of all stroke patients visiting hospitals without EVT capabilities, selecting patients that do not require EVT would prevent futile patient transfers with an ambulance. The status of collateral circulation visualized with CTA and perfusion parameters measured with CTP have been proposed as candidate metrics to identify patients with a reduced benefit of EVT.[9,10] The collateral circulation is activated in patients with acute ischemic stroke as an alternative supply of blood to the infarcted area affected by an occluded artery. Between patients, the degree of collaterals, and thus the alternative blood supply, can differ considerably. Therefore, poor collaterals are associated with more severe brain damage and a lower benefit of EVT. The actual supply of blood, or rather contrast fluid, to brain tissue is analyzed with CTP. CTP estimates such as the ischemic core volume (ICV), the penumbra volume (PV), and the core-penumbra mismatch ratio (MMR) have been considered in randomized clinical trials (RCTs) and other study settings to identify patients that do and do not benefit from EVT and IVT.[14,15] However, the value of the routine use of CTP in acute ischemic stroke care remains largely unclear.

During an EVT procedure, a 2-dimensional version of a CTA, the digital subtraction angiography (DSA) is used to visualize blood vessels in the brain and the EVT device that is used to extract the thrombus.[16] After the extraction of the thrombus the degree of reperfusion can be measured according to the expanded treatment in cerebral ischemia (eTICI) score.[17] In the days after the acute stroke setting, NCCT or MRI modalities can be used to visualize the brain tissue and the infarcted area.[9] Specifically, if a patient suddenly deteriorates after the acute stroke setting, additional treatment guided by imaging can be indicated. Namely, after an acute ischemic stroke swelling of the brain (edema) or a secondary hemorrhage might occur as a complication. Similar to patients with a primary hemorrhagic stroke, due to edema or a secondary hemorrhage, neighboring brain tissue can experience mechanical pressure and get damaged, requiring the surgical opening of the skull to reduce the pressure inside the skull.

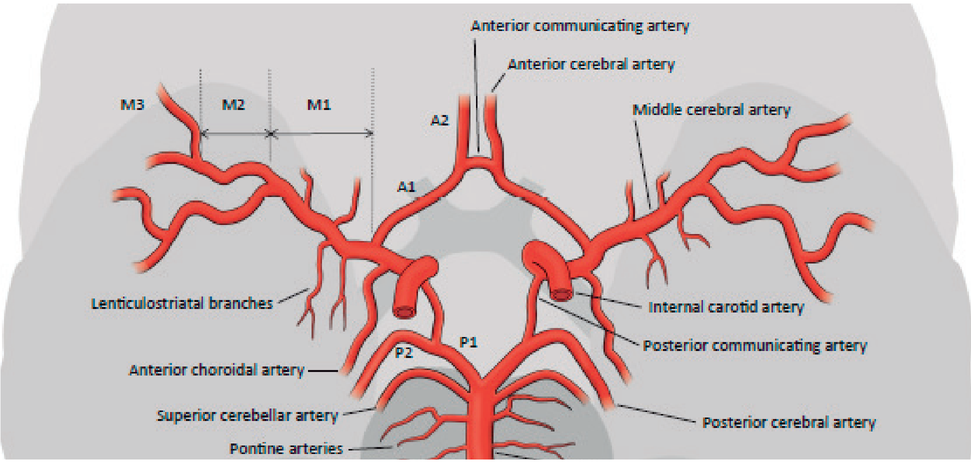

Figure 3. Neurovascular anatomy of the arterial circulation.
This figure is reprinted with permission from the author (reference at the end of this chapter).

Radiologist-lead analysis of imaging in stroke

Radiological images allow for an accurate diagnosis of a hemorrhagic or ischemic stroke by radiologists but can also be used to measure imaging markers to further optimize treatment decisions. To standardize the evaluation and reporting of more subjective imaging markers, radiological scores are developed. In a score, the severity or sub-type of an imaging marker is described by an ordinal ranking score or a nominal sub-classification. However, there are some shortcomings in using radiologist-lead scores in research and clinical practice. First of all, it remains difficult to analyze a risk score statistically. When considering a risk score as a continuous variable, common assumptions of statistical tests including the assumption of a normal distribution are often not fulfilled. Alternatively, the risk score can be converted to a binary variable by thresholding sub-scores resulting in a reduction of information available. Another issue with risk scores is that there is some degree of interrater variability; not every radiologist gives the same score to the same image. This raises a need for developing objective quantitative evaluation metrics, aiming to further improve the medical decision process. In recent years, AI has been suggested to estimate such metrics from data through artificial intelligence.

Definitions of intelligence, learning, artificial intelligence, and machine learning
Oxford Dictionary on intelligence: "the ability to learn, understand and think in a logical way about things"

Oxford Dictionary on learning: "the acquisition of knowledge or skills through study, experience, or being taught"

Marvin Minsky and John McCarthy: "Artificial intelligence is the ability of machines to perform certain tasks, which need the intelligence showcased by humans" [18]

Tom Mitchell: "Learning denotes changes in the system that are adaptive in the sense that they enable the system to do the same task drawn from the same population more efficiently and effectively the next time" [19]

Artificial intelligence
Although the popular language definition of intelligence entails a more abstract form of reasoning, Artificial Intelligence (AI) is often defined more practically as the ability of a machine to execute an originally human-based task. This makes AI multi-interpretable. The multiple interpretations of AI may be explained by two extremes; weak and strong AI. As an example of weak AI, let us consider a public transport chip card. Based on the money charged on the card it is possible to enter through a gate at a train station that allows you to take the train. The system for charging your card, entering through the gate, and deducting money from your card could be seen as an intelligent task as it would otherwise be performed by a human. The computer systems used to perform these tasks are rather rigid and defined by a set of rules that are programmed by a human. Due to this rigid computer model, it is easy to trick a weak AI system. Several hackers have been able to charge the card for free by bypassing the gates and travelling without payment. Strong AI lies on the other end of the AI spectrum. Strong AI is more abstract, and is defined as the ability of a system to reason and have consciousness. In the example of the public transport chip card a strong AI would be able to adapt to the behavior of the hackers bypassing the gate. Although the current state of AI is far from strong AI, in recent decades AI algorithms have evolved from simple rule-based systems to systems that can adapt to specific tasks. In the case of the public transport chipcard: Machine learning and deep learning can be used to track and monitor people (by)passing the public transport gates. Machine learning and deep learning have revolutionized many aspects of our daily life.

Machine learning and Deep learning
Referring to the principles of machine learning defined by Tom Mitchell, algorithms have been developed that use data (experience) to optimize for a specific task (for

example, mortality prediction), based on an evaluation metric (for example the accuracy of mortality prediction).[19,20] Machine learning can be divided into supervised and unsupervised learning algorithms.[20] Supervised learning is optimized for a task that is often defined by a human. Thus, supervised learning requires human readers to add a label to data. Subsequently, the algorithm can be optimized for such a human-based label also referred to as the 'ground truth'. Unsupervised learning does not require explicit human definitions to be optimized. An example of unsupervised learning is a clustering algorithm: based on different patient characteristics it is possible to automatically create groups (clusters) of patients with similar characteristics or phenotypes.

Due to the vast improvement in computer hardware and the increased availability of large datasets in the last decades, it became possible to develop new algorithms and improve existent algorithms. Specifically, artificial neural networks (NN) were already described decades ago but have contributed to the recent rise of interest in AI and deep learning research.[21] An NN consists of layers that pass and transform information before a prediction is made. Each layer consists of nodes representing some form of information described by numbers. A node in the input layer could contain numerical information describing patient characteristics, or each pixel in a 2D image or voxel in a 3D CT or MRI scan. The information of each layer is passed on to the next layer by multiplying values of each node with a weight specific for the node in the next layer. In a fully connected layer, each node in the network receives information from all the nodes in the previous layer. An NN is built by stacking several fully connected layers. At the top of the NN a final output layer is placed to convert the numbers from the last fully connected layer to a prediction. Depending on the task of the NN, the final output layer could be tailored for classification, regression, or another task. An NN can be optimized using a loss function. A loss function generally quantifies the difference between a target label, also referred to as the 'ground truth', and the predicted output. Optimization of an NN is based on the reduction of the loss in an iterative process called gradient descent. Initially, all the weights of the NN are set to random values. Due to these random weight values the forward passing of information for the prediction results in a high loss; a large difference between the predicted value and the actual ground truth. Subsequently, the partial derivative of the loss with respect to each weight in the NN is computed. A partial derivative describes the partial effect that each weight in the NN contributed to the loss. Based on these partial derivatives the weights are adjusted to reduce the loss. This process of optimizing the weights based on the partial derivative with respect to the loss is called backpropagation. Repeating forward propagation (prediction and loss computation) and backpropagation leads to a reduction of the loss referred to as gradient descent. Several gradient descent algorithms, also called optimizers, have been proposed to expedite and minimize the loss.[21]

NNs come with several shortcomings that could not be resolved for a long time and made NNs a rather unpopular algorithm. Due to the large number of weights, optimization of NNs is computationally expensive; it demands a lot of calculations from a computer. Furthermore, when using too many weights, NNs are prone to overfitting. Overfitting implies that a model has a high performance on the data used for optimization (training) but a low performance on unseen data; the model does not generalize to unseen data. Overfitting generally occurs if too many weights are present in an NN or if too few not representative data points are used during training.[21]

Convolutional neural networks (CNNs) use less weights than fully connected NN and are therefore computationally less demanding, easier to optimize, and can have more layers in the network without overfitting. The sparsity in weights is achieved by only considering adjacent nodes in a layer to pass information. Adjacent weights are selected by using a kernel with a specific size that moves over the data. A kernel is a matrix of weights used to pass information through to the next layer. **Figures 4 and 5** provide a visual description of a fully connected and convolutional neural network layer.

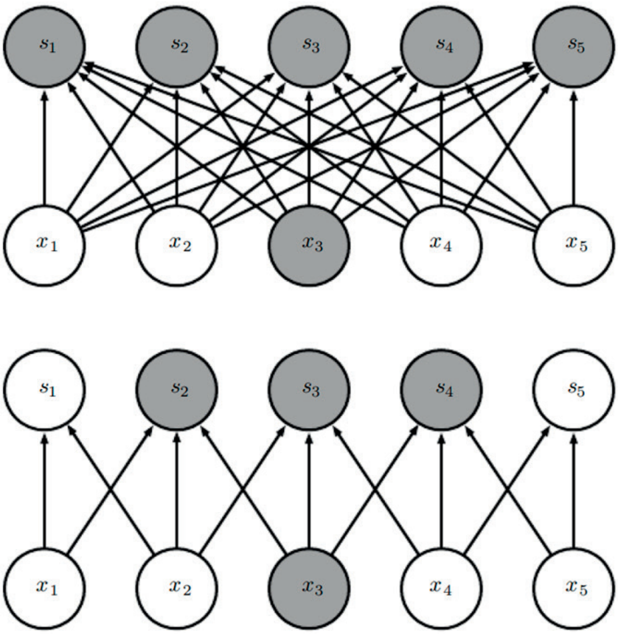

Figure 4. Two examples of connections between two neural network layers.
Each connection between nodes with a line represents a weight that is multiplied by the input value of the node and summed up with other activated nodes. Top: A fully connected neural network layer has connections between all nodes. Bottom: A convolutional neural network is sparser in connections between layers; it only has a connection between spatially adjacent nodes defined by a specific kernel size (3 in the example). This figure is reprinted with permission from the publisher.

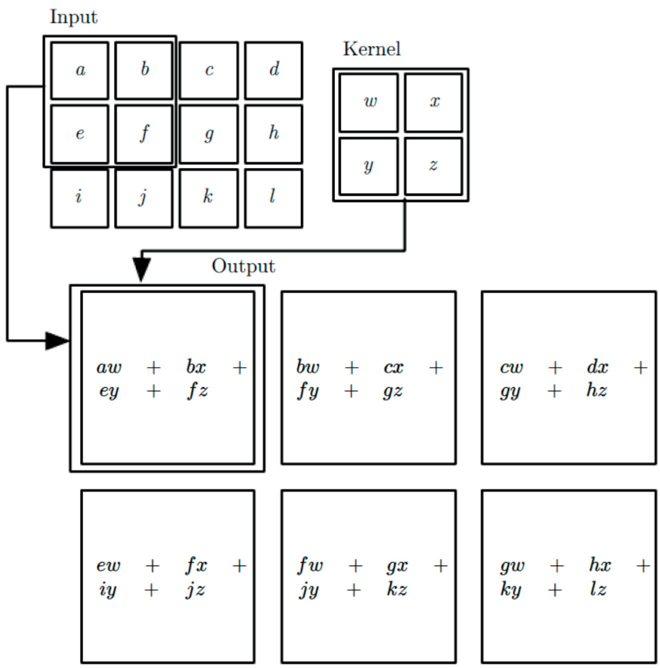

Figure 5. A schematic representation of a convolution operation on an image.
Input: The nodes in a 2-dimensional image are arranged in a grid form. Each symbol from a to l represents a pixel value. The kernel in this example has a size of 2x2 with weights w to z. The output of the convolution operation is the multiplication of the kernel weights with each pixel value of the underlying image followed by a summation. This operation is repeated each step the kernel is moving as a sliding window over the image. During the training of a convolutional neural network, the kernel weights are optimized. In a fully connected layer, the size of the kernel would be equal to the size of the image. This figure is reprinted with permission from the publisher.

Although the sparsity of convolution layers has its benefits in terms of optimization and computational requirements, it might result in an oversimplified model and a small receptive field. A small receptive field implies that only local values in an image are considered by a CNN. For example, if a CNN would be used to predict the presence of an infarcted region in an NCCT scan of the brain, only local voxel values would be considered and not the difference with contralateral regions of the brain. By stacking multiple convolution layers the receptive field can be increased. Furthermore, a fully connected layer on top of a CNN can combine information from separate receptive fields. This stacking of layers is the origin of the name deep learning.[21]
Stacking multiple layers in a network would imply repeated multiplication with weights which could result in very large or very small numbers. Propagating these very large or small numbers through the network can result in exploding or vanishing gradients during backpropagation, complicating the optimization of the network. To reduce this

effect after each layer a normalization is performed to standardize all the output values to a set range. Adding a non-linear activation function such as a rectified linear unit (ReLu) after the normalization enables the estimation of more complex relationships in an NN or CNN. To further improve CNNs skip connections, different normalization techniques, and activation functions have been proposed.

CNNs were initially used for classifying images but their use was rapidly expanded to other tasks. Specifically, the segmentation of lesions in medical images has been studied extensively. Due to its ability to achieve high segmentation performance, the UNet is among the most used models for medical image segmentation.[22] Generative Adversarial Networks (GANs) were developed to generate new images.[23] In image-to-image translation images from a specific domain are transformed to visually appear as images from another domain. For example, with image-to-image translation using a GAN an image made in summer can be converted to an image made in winter by adding snow. GANs consist of two types of networks which can be either NNs or CNNs. A generator network is used to transform or generate an image, a discriminator classifies if the presented image is a generated or original. By iteratively optimizing the generator and discriminator networks, the classification loss of the discriminator provides feedback to optimize the generator network. In this thesis, we optimize GANs to perform image-to-image translation.[23–25]

The unity of medical decision making: Evidence-based medicine

Several forms of information have been presented in this thesis: some statements are presented as facts, others are described as observations, and sometimes uncertain terms such as "might", "is claimed to", and "could" are used. These nuances are made to emphasize differences in the level of scientific evidence that is available for such a statement. To structure the level of medical scientific evidence, several guidelines have been developed of which the Oxford Centre for Evidence-Based Medicine "Levels of evidence" is among the most used.[26] These levels of evidence are used to rank scientific research based on the quality of the study design and its results. The Oxford guidelines distinguish between five forms of research: treatment, prognosis, diagnosis, economic and decision analysis, and differential diagnosis-focused research. **Figure 5** describes the order of treatment-focused research. The highest achievable level of evidence in a single study collecting patient data is the randomized controlled trial (RCT). In an RCT, patients are assigned to different treatment regimens based on a random chance. By using this random element, we assume that the groups with each treatment regime are comparable and that the population of patients in either arm would have had the same outcome as that in the other arm (on average) if the corresponding treatment regime had been followed. A meta-analysis is a combination of all available (highest level of evidence) analyses on that specific topic. Based on the different levels of evidence, recommendations are made in scientific guidelines for medical practice. This enables medical practitioners to guide their decisions based on ordered scientific evidence instead of subjective opinions based on perceptions that would otherwise lead to lawlessness. The concepts of evidence-based medicine are especially important in the field of AI. Namely, in recent years several commercial AI products have been made available for clinicians and initial AI studies in radiological imaging have created high expectations for clinicians. However, the evidence for implementing AI in clinical practice is often feeble due to a lack of proper validation and prospective evaluation. Evaluation of AI products in external centers or settings that more closely resemble clinical practice has frequently resulted in a considerable drop in performance. As a result, only very few AI innovations in healthcare are evaluated in prospective studies and even less have been recommended in clinical practice guidelines. Even if a new (AI) technology could improve patient outcomes by enhancing the medical decision process, it sometimes remains debatable if the effort of implementing such an intervention has sufficient returns in the long run. Therefore, there is a need to further study new technologies such as AI and to identify potential uses for clinicians. Simulation studies based on existing data might help to understand potential shortcomings in current evidence to develop future studies.

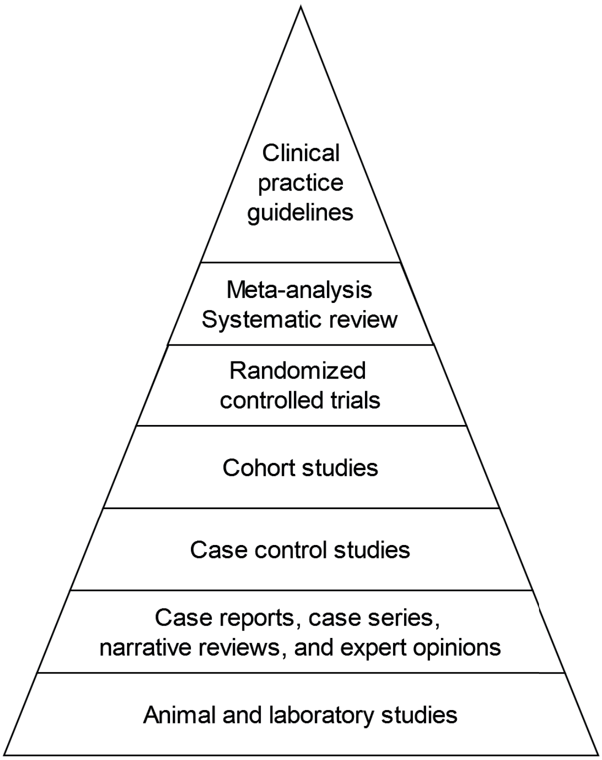

Figure 6. A simplified version of the levels of evidence

Economics

Lionel Robbins: "Economics is the science which studies human behaviour as a relationship between ends and scarce means which have alternative uses." [27]

Medical decision-making using health economic evaluations

Each decision comes with a consequence; a choice to treat with EVT or IVT automatically means that a patient can have both the benefits and suffer from the side-effects of that treatment. Healthcare policy decisions such as treatment decisions are made under the constraint of scarcity. In the setting of health economic analyses, there are two types of scarce goods to consider. First, financial means are used to express healthcare services and indirect financial consequences such as a loss of labor productivity due to a disease. The second scarce good is the years someone lives in good health, often expressed in quality-adjusted life years (QALYs).[28] We would ideally optimize our decisions, given our constraint, to maximize the years of life in good health of a population. To achieve this, the first step is to identify the potential effects of each decision. Subsequently, different healthcare interventions can be compared based on their consequences on our scarce goods. Such an evaluation has become ever-important in recent years with the COVID-19 pandemic and labor shortages in healthcare professions.

Model-based health economic analyses

In the ideal setting, health economic analyses would be studied with an RCT, generating the highest possible evidence. However, an RCT is costly, takes a lot of time, and often has a limited horizon to analyze the effects of a treatment decision. Furthermore, performing an RCT might be unethical; if a promising treatment is withheld or a treatment with many side effects is given at random, harm can be inflicted on patients who participate in a study. Finally, RCTs often have a set end date to analyze while the effects on patients' health continue after such a set date. In acute ischemic stroke research, 90 days after the acute stroke setting is the common endpoint for analyses. Model-based analyses do not come with the downsides of an RCT as analyses are performed using computer simulations. Specifically, a "Markov model" or "health state transition model" is popular for model-based health economic analyses such as cost-effectiveness or cost-utility research.[28] In a Markov model a fixed set of health states are defined in which a patient can be for a set amount of time.

Figure 6 represents a simple Markov model in which all patients can be in the health states healthy, ill, or dead. Over a set amount of time, a year for example, QALYs and costs can be attributed to these health states. Furthermore, the probability of transitioning, getting better, getting ill, or dying, between health states in a set amount of time is required to build a Markov model. A Markov model simulation can be run for several discrete time steps. Subsequently, the total amount of costs and QALYs over all the time steps can be computed. For a decision analysis, multiple models are simulated, one to simulate each different decision for a treatment regime. Subsequently, differences in costs and QALYs over the simulated period between the simulated decisions can be analyzed (**Figure 6**).

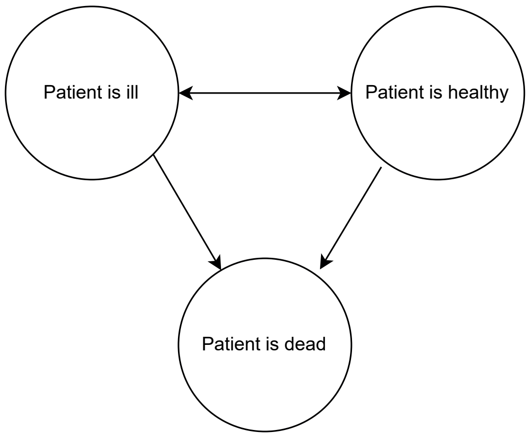

Figure 7. A simplified Markov model.

Besides the use of known parameter settings, model-based analyses could also be used to analyze scenarios with unknown or unlikely parameter settings. By varying model parameters, it is possible to generate answers to "what-if" questions. An example of a what-if question for our simple model could be: "What if the baseline chance of dying every year for healthy and ill patients were higher?" Altering the yearly probability of death could for example be realistic for elderly patients. With such a simulation the value of the treatment decision in the elderly can be analyzed with a model.

Aims and outline of this thesis

In this thesis, we aim to use artificial intelligence and health economic modeling techniques as leverage to improve medical decisions for stroke patients solely using imaging that is already available in standard clinical practice. This thesis is divided into three parts. In Part I (**Chapters 2-5**), we use health economic modeling techniques to simulate the outcome of patients in varying treatment regimens. In Part II (**Chapters 6-8**), we use and compare imaging markers based on manual measurements and AI techniques that can be used to optimize IVT and EVT administration. In Part III (**Chapters 9-10**), we compare supervised with unsupervised segmentation methods in NCCT and CTA using GANs. In **Chapter 11** we discuss the implications of the presented research on clinical practice, AI research, and health economic research in stroke imaging.

Part I: Health economic modeling

As the benefit of EVT diminishes over time,[8] expediting EVT delivery is key to improving patient outcomes. However, it remains unclear what the long-term effects in terms of health and costs are of expediting EVT delivery. In **Chapter 2** we aimed to estimate the effect on patient health and healthcare spending of expediting EVT delivery.

CTP is developed to visualize perfusion deficits in the acute ischemic stroke setting. As a result, CTP measures such as the ischemic core volume and core-penumbra mismatch ratio have been used as inclusion criteria for RCTs comparing EVT with best medical management. The benefit of EVT was larger in RCTs that used CTP-based inclusion criteria.[5] In addition, it has been hypothesized that employing CTP maps rather than just NCCT and CTA will increase the detection of EVT-eligible occlusions. The long-term costs and health effects of these two uses of CTP remain unclear. Therefore, we aimed to evaluate the costs and health effects of using CTP for patient selection for EVT and for detecting EVT-eligible occlusions in Chapters 3-5. In Chapter 3 we describe a protocol for the Cost-effectiveness of CT perfusion for patients with acute ischemic stroke (CLEOPATRA) healthcare evaluation study for analyzing the potential benefits of CTP. In **Chapter 4** we simulate various scenarios to evaluate the potential value of CTP-based EVT patient selection. In **Chapter 5** we describe the costs and health effects of CTP-based screening for EVT-eligible occlusions.

Part II: Outcome prognostication and treatment decisions

Despite the advantages of IVT for treating an occlusion in acute ischemic stroke, IVT comes with a higher risk of hemorrhages that can result in long-term morbidity and mortality.[4] These dangerous side effects were already apparent quickly after the introduction of IVT. As a result, several contraindications for IVT have been established to prevent secondary intracranial hemorrhages in patients with acute ischemic stroke. However, traits that can be drawn from acute stroke imaging are not taken into account. According to earlier studies, both the existence and severity of white matter lesions were linked to an increased risk of cerebral hemorrhages, both naturally occurring and caused by IVT.[29,30] Nevertheless, IVT was also beneficial in patients with severe white matter lesion damage suffering an acute ischemic stroke. With the introduction of EVT, the benefit and safety of using IVT in a subset of patients with white matter lesions has again become a matter of debate. Furthermore, it is yet unknown whether deep learning, as opposed to radiologist-based scoring, could improve the estimation of the hemorrhagic risk related to the white matter lesion burden. In **Chapter 6** we aimed to compare the prognostic value of deep learning-based white matter lesion volume quantification with

the Fazekas scale; a radiological score used in routine clinical practice. Furthermore, we aimed to assess if withholding IVT before EVT based on the white matter lesion improves patient outcomes and reduces the occurrence of intracranial hemorrhages.
Removing the arterial occluding thrombus to achieve reperfusion of brain tissue in as few attempts as possible is the primary goal of EVT. Moreover, the degree of reperfusion that is achieved and the number of attempts to achieve reperfusion have a strong association with patient outcomes and the occurrence of an intracranial hemorrhage.[17,31] Identification of imaging markers that might predict an easy or difficult procedure could be considered by a neurointerventionalist to alter the EVT approach. Several markers describing the occluding thrombus have been derived from routinely acquired radiological images, and are known to be associated with a more difficult procedure. However, the prognostic value of these markers has not yet been compared. In **Chapter 7** we aimed to compare the prognostic value of manually measured thrombus volume and thrombus length regarding EVT procedural and patient outcomes. Furthermore, we aimed to compare if patient and procedural outcomes differed depending on thrombus volume and the EVT device choice. In **Chapter 8** we aimed to assess if radiomic features of a thrombus in NCCT are associated with patient and procedural outcomes.

Part III: Unsupervised segmentation

Supervised deep learning requires manually acquired annotations as ground truth to optimize. Unsupervised deep learning does not require such annotations and might therefore save a lot of time for annotators and enable the use of much larger datasets. In Part III (**Chapters 9 and 10**), we aim to compare the use of supervised deep learning-based stroke lesion segmentation in NCCT (**Chapter 9**) and vessel segmentation in CTA (**Chapter 10**) with generative adversarial networks-based segmentation.

Reuse of figures with permission

Figure 1: Reprinted with permission from the British Stroke Association. The original figure is available online: www.stroke.org.uk/what-is-stroke/what-are-the-symptoms-of-stroke

Figure 2: Deferred consent was received for anonymous use of imaging data. This patient was included in the MR CLEAN No-IV trial.

Figure 3: Reprinted with permission from dr. Simon Jung. The original figure is available online: http://www.neurologie.insel.ch/fileadmin/Neurologie/eng_Stroke_Guidelines_2022_SWS.pdf

Figure 4: Reprinted with permission from MIT press. The original figure is available online: www.deeplearningbook.org

Figure 5: Reprinted with permission from MIT press. The original figure is available online: www.deeplearningbook.org

References

1. Caplan LR. Caplan's stroke. Cambridge University Press; 2016.
2. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Vol. 49, Stroke. 2018. 46–110 p.
3. Greenberg SM, Ziai WC, Cordonnier C, Dowlatshahi D, Francis B, Goldstein JN, et al. 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. Stroke. 2022;53(7):e282--e361.
4. Brunström M, Carlberg B. Thrombolysis in acute stroke. Lancet. 2015;385(9976):1394–5.
5. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016 Apr 23;387(10029):1723–31.
6. Church EW, Gundersen A, Glantz MJ, Simon SD. Number needed to treat for stroke thrombectomy based on a systematic review and meta-analysis. Clin Neurol Neurosurg. 2017;156:83–8.
7. Jovin TG, Nogueira RG, Lansberg MG, Demchuk AM, Martins SO, Mocco J, et al. Thrombectomy for anterior circulation stroke beyond 6 h from time last known well (AURORA): a systematic review and individual patient data meta-analysis. Lancet. 2022;
8. Saver JL, Goyal M, Van Der Lugt A, Menon BK, Majoie CBLM, Dippel DW, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: Ameta-analysis. JAMA - J Am Med Assoc. 2016 Sep 27;316(12):1279–88.
9. Shafaat O, Sotoudeh H. Stroke imaging. 2019;
10. Caldwell J, Heran MKS, McGuinness B, Barber PA. Imaging in acute ischaemic stroke: Pearls and pitfalls. Vol. 17, Practical Neurology. BMJ Publishing Group; 2017. p. 349–58.
11. Oliveira R, Correia MA, Marto JP, Carvalho Dias M, Mohamed GA, Nguyen TN, et al. Reocclusion after successful endovascular treatment in acute ischemic stroke: systematic review and meta-analysis. J Neurointerv Surg. 2022;jnis-2022-019382.
12. Mosimann PJ, Kaesmacher J, Gautschi D, Bellwald S, Panos L, Piechowiak E, et al. Predictors of unexpected early reocclusion after successful mechanical thrombectomy in acute ischemic stroke patients. Stroke. 2018;49(11):2643–51.
13. Van Kranendonk KR, Treurniet KM, Boers AMM, Berkhemer OA, Van Den Berg LA, Chalos V, et al. Hemorrhagic transformation is associated with poor functional outcome in patients with acute ischemic stroke due to a large vessel occlusion. J Neurointerv Surg. 2019;11(5):464–8.
14. Campbell BCV, Majoie CBLM, Albers GW, Menon BK, Yassi N, Sharma G, et al. Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data. Lancet Neurol. 2019;18(1):46–55.
15. Campbell BCV, Ma H, Ringleb PA, Parsons MW, Churilov L, Bendszus M, et al. Extending thrombolysis to 4·5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. Lancet. 2019;394(10193):139–47.
16. Crummy AB, Strother CM, Mistretta CA. The History of Digital Subtraction Angiography. J Vasc Interv Radiol [Internet]. 2018;29(8):1138–41. Available from: https://doi.org/10.1016/j.jvir.2018.03.030
17. Liebeskind DS, Bracard S, Guillemin F, Jahan R, Jovin TG, Majoie CBLM, et al. ETICI reperfusion: Defining success in endovascular stroke therapy. J Neurointerv Surg. 2019;11(5):433–8.

18. Moor J. The Dartmouth College artificial intelligence conference: The next fifty years. Ai Mag. 2006;27(4):87.

19. Michalski RS, Carbonell JG, Mitchell TM. Machine learning: An artificial intelligence approach. Springer Science \& Business Media; 2013.

20. Domingos P. A few useful things to know about machine learning. Commun ACM. 2012;55(10):78–87.

21. Goodfellow I, Bengio Y, Courville A. Deep learning [Internet]. MIT Press; 2016 [cited 2020 Jul 8]. Available from: deeplearningbook.org

22. Ronneberger O, Fischer P, Brox T. U-net: Convolutional networks for biomedical image segmentation. Lect Notes Comput Sci (including Subser Lect Notes Artif Intell Lect Notes Bioinformatics). 2015;9351:234–41.

23. Goodfellow IJ, Pouget-Abadie J, Mirza M, Xu B, Warde-Farley D, Ozair S, et al. Generative adversarial nets. Vol. 3, Advances in Neural Information Processing Systems. 2014. 2672–2680 p.

24. Isola P, Zhu JY, Zhou T, Efros AA. Image-to-image translation with conditional adversarial networks. Proc - 30th IEEE Conf Comput Vis Pattern Recognition, CVPR 2017. 2017;2017-Janua:5967–76.

25. Zhu JY, Park T, Isola P, Efros AA. Unpaired Image-to-Image Translation Using Cycle-Consistent Adversarial Networks. Proc IEEE Int Conf Comput Vis. 2017;2017-Octob:2242–51.

26. OCEBM Levels of Evidence Working Group. The Oxford 2011 Levels of Evidence [Internet]. Oxford Centre for Evidence-Based Medicine. 2011 [cited 2023 Aug 18]. Available from: https://www.cebm.net/

27. Howson S. Lionel Robbins. Cambridge University Press; 2011.

28. Briggs A, Sculpher M, Claxton K. Decision modeling for health economic evaluation. Oup Oxford; 2006.

29. Charidimou A, Pasi M, Fiorelli M, Shams S, Von Kummer R, Pantoni L, et al. Leukoaraiosis, Cerebral Hemorrhage, and Outcome after Intravenous Thrombolysis for Acute Ischemic Stroke: A Meta-Analysis (v1). Stroke. 2016;47(9):2364–72.

30. Kaesmacher J, Kaesmacher M, Maegerlein C, Zimmer C, Gersing AS, Wunderlich S, et al. Hemorrhagic Transformations after Thrombectomy: Risk Factors and Clinical Relevance. Cerebrovasc Dis. 2017;43(5–6):294–304.

31. Maros ME, Brekenfeld C, Broocks G, Leischner H, McDonough R, Deb-Chatterji M, et al. Number of Retrieval Attempts Rather Than Procedure Time Is Associated with Risk of Symptomatic Intracranial Hemorrhage. Stroke. 2021;(May):1580–8.