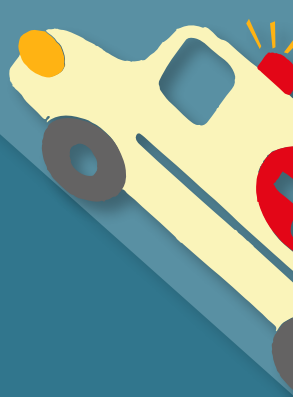
CHAPTER 1

General introduction



From the age of 25 years, the global lifetime risk of stroke is almost 25%.[1] Stroke causes more than 10% of all deaths worldwide and leads to disability among stroke survivors.[2] Suffering a stroke means that a blood vessel in the brain is blocked by a clot (ischemic stroke) or has ruptured (hemorrhagic stroke). Of all strokes, 87% are ischemic.[3] During a stroke the blood supply to specific areas of the brain is interrupted and causes neuronal cell death with a loss of approximately 2 million neurons every minute.[4] Therefore the phrase "time is brain"[5] refers to the importance of starting treatment aimed at restoring blood flow as soon as possible. As such acute stroke treatment is highly time dependent.[6] Timely treatment increases the probability of better patient outcomes, measured as a lower modified Rankin scale (mRS) scores after three months. The mRS is used to assess disability after stroke and ranges from 0 (no symptoms) to 5 (severe disability), whereas 6 indicates death.[7]

Patients suffering acute ischemic stroke can be treated with intravenous thrombolysis (IVT) or endovascular thrombectomy (EVT), in case of large vessel occlusion (LVO). IVT given within 4.5 hours (or within 12 hours based on perfusion imaging) increases the probability of excellent outcome (mRS score of 0 or 1) after three months.[8] For LVO patients EVT should be initiated (groin puncture) within 6 hours (or 24 hours based on perfusion imaging) after onset to increase the probability of functional independence (mRS 0 to 2) after 3 months.[9] Nevertheless, for each additional hour delay from onset to groin puncture (OTG), the probability of regaining functional independence after 3 months declines by 5% to 6%.[6,10,11]

Organization of acute stroke care

To accurately diagnose and distinguish different stroke sub-types in suspected stroke patients and subsequently offer the appropriate treatment, emergency transport to a hospital is needed. The use of neuroimaging is needed to definitively distinguish ischemic strokes from hemorrhagic strokes. Computed tomography (CT) and Magnetic Resonance imaging (MRI) are commonly used imaging modalities.[12] To diagnose ischemic stroke patients with LVO, computed tomography angiography (CTA), magnetic resonance angiography or conventional angiography are used.[13]

Importantly, not every hospital is equipped to offer both reperfusion treatments, IVT and EVT. Hospitals that perform IVT only are known as primary stroke centers (PSCs), whereas hospitals that perform both IVT and EVT are known as comprehensive stroke centers (CSCs). According to most emergency medical services (EMS) protocols, suspected stroke patients are routed to the nearest IVT-capable hospital, which could be a PSC or CSC.

Two main organizational models reflect current practice in transporting LVO patients eligible for EVT. In the so called 'mothership' model the patient is transported directly to a CSC for IVT treatment, and when eligible, also EVT is performed at the same hospital. When patients are routed according to the 'drip-and-ship model', they are first transported to the nearest PSC, receive IVT when indicated and when eligibility for EVT is confirmed, patients are transported a second time by inter-hospital transfer to a CSC. Whether a suspected stroke patient is routed according to the mothership model or the drip and ship model depends mainly on the regional infrastructure of PSCs and CSCs, i.e. the travel distance from symptom onset location to the first available hospital, and the regional protocols used for transporting suspected acute stroke patients. In general, the mothership model is associated with shorter OTG times,[14-17] although regional differences such as the distance from onset location to a certain center are usually not taken into account.

As any practice stroke care organization may be optimized by organizational interventions or other organizational models than the 'mothership' and 'drip-and-ship' model. First the spread of PSCs and CSCs could be re-organized by adding or eliminating CSCs in certain regions. Also, expediting workflow over the whole stroke care pathway is another possible organizational intervention. For example, using a helicopter instead of an ambulance for inter-hospital transfer or using a new in-hospital protocol for workflow improvement. Adaptive routing directly to a CSC using pre-hospital triage scales,[18] telemedicine supported triage,[19] or CT/CTA on scene is another organizational intervention that may be used for optimization of the organization of stroke care. For the latter a Mobile Stroke Unit can be used. This is a specialized ambulance equipped with a CT/CTA scanner, and a telemedicine connection to the hospital.[20] Furthermore, a 'drive the doctor' organizational model is a potential innovation to use within a certain region. Within this model, the neuro-interventionalist is traveling to the PSC for EVT treatment instead of the inter-hospital transfer of the patient to the CSC.[21] **Chapter 2** reviews these organizational models and interventions used to reduce OTG times.

Use of modeling in optimizing regional stroke care

Regional differences are a challenge for a generic (re)organization of acute stroke care. The demand for region specific measures and adaptation therefore prevails. Simulation modeling is a promising approach to facilitate such redesign. With the use of simulation modeling essential components of the acute stroke care can be captured, regional improvements can be identified and subsequently tested.[22] The advantage of simulation modeling compared to Randomized Controlled Trials (RCTs) is that modeling is likely to be less time consuming in obtaining output, less expensive and allows comprehensive and detailed analyses of a wide variety of interventions.

To investigate and optimize IVT in the acute stroke care setting simulation modeling has been used regularly.[23-25] For LVO patients treated with EVT, simulation modeling so far has hardly been used to optimize the organization of care. For these type of patients probabilistic modeling has been applied to identify possibilities for improvement in the organization of EVT treatment.[26-29] For example, these models estimated the probability of functional independence (mRS 0-2) when a pre-hospital triage strategy was used for ischemic stroke patients[28] or to identify the optimal triage and transport strategy for suspected LVO patient.[26] Nevertheless, probabilistic studies are based on population averages and probabilities, instead of using patient-level data to experiment and simulate alternative organizational models. Simulation modeling allows to use patient level data and the inherent randomness reflective of a real-time setting. To identify organizational interventions that reduce OTG in specific regions, a simulation model is therefore useful. **Chapter 3** discusses the design and rationale of simulation modeling for patients eligible for EVT. We describe the datacollection, used as input for the simulation model, steps taken to build the simulation model and how we validated the model. In **Chapter 4** we developed two simulation models reflecting the northern Netherlands region, a mothership model and a drip-and-ship model. Furthermore, we estimate the effect on OTG and change in probability of functional outcome when workflow is expedited for both models in this region. In **Chapter 5** the same baseline model is used for modeling the addition of one or two CSC(s) in the northen Netherlands region. The effect of this intervention is calculated in gains in OTG and the predicted probability of favorable outcome (mRS 0-2). In **Chapter 6** the 'drive the doctor' model is hypothetically implemented in the northern Netherlands. How to design such an organizational model in a certain region is central to this chapter, and, additionally, the effect on OTG is estimated.

Chapters 4, 5, 6 are all based on patients treated in the northern Netherlands region. The question arises whether the developed simulation models could be re-used for another region. In **Chapter 7** therefore we performed an external validation of these previous models thus showcasing the utility and versatility of modeling when adapted to the south-western region of the Netherlands. In addition, we estimate the effect on OTG for several organizational interventions for that specific region.

Economic evaluation of organizational interventions

Using simulation modeling some organizational interventions and/or models might show promising time gains for OTG in specific regions. However, some interventions might be very costly, e.g., require investing in personnel and appliances prior to implementation in a certain region. For example, using an helicopter instead of an ambulance for inter-

hospital transfer may only be cost-effective when OTG is reduced by 60 minutes or more.[30] To study the economic impact of certain interventions or models, in addition to the clinical benefits it is therefore important to also evaluate the balance between costs and effects. The technique and software used in simulation generally does allow costs to be tracked as well as clinical outcomes. Thus, simultaneously assessing the impact of organizational adaptations on time delays, ensuing clinical improvement as well as cost consequences is a real option. In chapter **Chapter 8** a systematic review is presented specifically focused on this option of performing an economic evaluation of organizational interventions, and models that reduce onset to treatment times for both acute stroke treatments, IVT and EVT.

References

1 GBD 2016 Lifetime Risk of Stroke Collaborators. Global, regional, and country-specific lifetime risks of stroke, 1990 and 2016. *New England Journal of Medicine,* 2018, 379.25: 2429-2437.

2 Feigin VL, Norrving B, & Mensah GA. Global burden of stroke. *Circulation research*, 2017, 120.3: 439-448.

3 Tsao CW, Aday AW, Almarzooq ZI, et al., Heart disease and stroke statistics—2022 update: a report from the American Heart Association. *Circulation*, 2022, 145.8: e153-e639.

4 Desai SM, Rocha M, Jovin TG, et al., High variability in neuronal loss: time is brain, requantified. *Stroke*, 2019, 50.1: 34-37.

5 Saver JL. Time is brain—quantified. *Stroke*, 2006, 37.1: 263-266.

6 Saver JL, Goyal M, Van der Lugt AA, et al., Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *Jama*, 2016, 316.12: 1279-1289.

7 Kasner SE. Clinical interpretation and use of stroke scales. *The Lancet Neurology*, 2006, 5.7: 603-612.

8 Berge E, Whiteley W, Audebert H, et al., European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *European stroke journal*, 2021, 6.1: I-LXII.

9 Powers WJ. Acute ischemic stroke. *New England Journal of Medicine*, 2020, 383.3: 252-260.

10 Fransen PS, Berkhemer OA, Lingsma HF, et al., Time to reperfusion and treatment effect for acute ischemic stroke: A randomized clinical trial. *JAMA Neurol.* 2016;73(2):190-196.

11 Mulder MJHL, Jansen IG, Goldhoorn RJB, et al. Time to endovascular treatment and outcome in acute ischemic stroke: MR CLEAN registry results. *Circulation*, 2018, 138.3: 232-240.

12 Yew KS, & Cheng EM. Diagnosis of acute stroke. *American family physician*, 2015, 91.8: 528-536.

13 Smith EE, Kent DM, Bulsara KR, et al., Accuracy of prediction instruments for diagnosing large vessel occlusion in individuals with suspected stroke: a systematic review for the 2018 guidelines for the early management of patients with acute ischemic stroke. *Stroke*, 2018, 49.3: e111-e122.

14 Asaithambi G, Castle AL, Stein LJ, et al., Real-world treatment of large vessel occlusions: combined outcomes of directly presenting and transferredin patients to a stroke center. *Neurol Res.* 2018;40:637–643. doi: 10.1080/01616412.2018.1460700

15 Gerschenfeld G, Muresan IP, Blanc R, et al., Two paradigms for endovascular thrombectomy after intravenous thrombolysis for acute ischemic stroke. *JAMA Neurol*. 2017;74:549–556. doi: 10.1001/jamaneurol.2016.5823
16 Pfaff J, Pham M, Herweh C, et al., Clinical outcome after mechanical thrombectomy in non-elderly patients with acute ischemic stroke in the anterior circulation: primary admission versus patients referred from remote hospitals. *Clin Neuroradiol*. 2017;27:185–192. doi: 10.1007/s00062-015-0463-2
17 Rinaldo L, Brinjikji W, McCutcheon BA, et al., Hospital transfer associated with increased mortality after endovascular revascularization for acute ischemic stroke. *J Neurointerv Surg*. 2017;9:1166–1172. doi: 10.1136/neurintsurg2016-012824
18 Duvekot MHC, Venema E, Rozeman AD, et al. Comparison of eight prehospital stroke scales to detect intracranial large-vessel occlusion in suspected stroke (PRESTO): a prospective observational study. *Lancet Neurol* 2021; 20:213.
19 Demaerschalk BM, Berg J, Chong BW, et al., Whitchurch S. American telemedicine association: telestroke guidelines. *Telemed J E Health*. 2017; 23:376–389. doi: 10.1089/tmj.2017.0006
20 Walter S, Kostopoulos P, Haas A, et al. Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: a randomised controlled trial. *The Lancet Neurology*, 2012, 11.5: 397-404.
21 Seker F, Möhlenbruch MA, Nagel S et al. Clinical results of a new concept of neurothrombectomy coverage at a remote hospital—"drive the doctor". *International Journal of Stroke*, 2018, 13.7: 696-699.
22 Monks T, Pearson M, Pitt M, et al., Evaluating the impact of a simulation study in emergency stroke care. Operations Research for Health Care, 2015, 6: 40-49.
23 Lahr MMH, van der Zee DJ, Luijckx GJ, et al., A simulation-based approach for improving utilization of thrombolysis in acute brain infarction. *Medical care*, 2013, 51.12: 1101-1105.
24 Monks T, Pitt M, Stein K, et al., Maximizing the population benefit from thrombolysis in acute ischemic stroke: a modeling study of in-hospital delays. *Stroke*, 2012, 43.10: 2706-2711.
25 Churilov L, Fridriksdottir A, Keshtkaran M, et al., Decision support in pre-hospital stroke care operations: a case of using simulation to improve eligibility of acute stroke patients for thrombolysis treatment. *Comput Oper Res*. 2013;40:2208–2218.
26 Holodinsky JK, Williamson TS, Demchuk, AM, et al., Modeling stroke patient transport for all patients with suspected large-vessel occlusion. *JAMA neurology*, 2018, 75.12: 1477-1486.
27 Holodinsky JK, Williamson TS, Kamal N, et al., Drip and ship versus direct to comprehensive stroke center: conditional probability modeling. *Stroke*, 2017, 48.1: 233-238.

28 Schlemm L, & Schlemm E. Clinical benefit of improved prehospital stroke scales to detect stroke patients with large vessel occlusions: results from a conditional probabilistic model. *BMC neurology*, 2018, 18.1: 1-5.

29 Kamal N, Wiggam MI, Holodinsky JK, et al., Geographic modeling of best transport options for treatment of acute ischemic stroke patients applied to policy decision making in the USA and Northern Ireland. *IISE Transactions on Healthcare Systems Engineering*, 2018, 8.3: 220-226.

30 Coughlan D, McMeekin P, Flynn D, et al. Secondary transfer of emergency stroke patients eligible for mechanical thrombectomy by air in rural England: economic evaluation and considerations. *Emergency Medicine Journal* 2021, 38.1: 33-39.