General introduction
Stroke is the leading cause of permanent disability in adults and one of the most frequent causes of death in the Western world\textsuperscript{1}. In addition to this substantial individual suffering, stroke leads to immense societal costs\textsuperscript{2}. Treatment with intravenous tissue plasminogen activator (tPA) or thrombolysis is the most effective treatment for acute ischemic stroke up to 4.5 hours after the onset of stroke symptoms\textsuperscript{3,4}. Within this time window, the benefit of treatment strongly decreases with time (the so-called time-is-brain concept). Neurons are extremely sensitive to hypoxia and die soon when reperfusion cannot be achieved. For every minute a large-vessel stroke remains untreated approximately 1.9 million neurons and 14 billion synapses are lost\textsuperscript{5}. Clinical trials also demonstrate that time is the most important factor for success of treatment. For example, the number needed to treat to achieve a good functional outcome increases from 4.5 when treatment is started within 1.5 hours, to 14.1 if treatment is started by 3.0 – 4.5 hours\textsuperscript{6}. In addition, because of the importance of rapid treatment, it is recommended by international guidelines to complete imaging and clinical evaluation of ischemic stroke patients and initiate tPA treatment (called door-needle-time) within 60 minutes of hospital arrival in those without contraindications\textsuperscript{7}.

Underuse of thrombolysis in acute ischemic stroke

Although thrombolysis is the established treatment for acute ischemic stroke, it remains substantially underused. Of all patients suffering a stroke, currently 1-8\% worldwide\textsuperscript{8,9} and around 11\% (ranging from 4-26\%) within the Netherlands\textsuperscript{10} receive thrombolysis, whereas up to 31\% have been reported in optimized settings\textsuperscript{11}. Reasons for the underuse of thrombolysis are multiple and include, among others, pre-hospital factors and organizational models of acute stroke care\textsuperscript{12,13}.

Pre-hospital delay contributes substantially to underuse of thrombolysis with only 14-48\% arriving at the hospital within 2 hours. This is largely determined by the response of patients and/or bystanders and by that of the Emergency Medical Services (EMS)\textsuperscript{14}. Patients or bystanders may be unaware of stroke symptoms and how to act leading to delay in seeking medical attention. The role of the EMS is important because it is an important predictor for early hospital arrival\textsuperscript{15}. Seemingly, the correct identification of stroke is not trivial, with only 42-83\% of strokes correctly identified by EMS dispatchers\textsuperscript{16-19}.

Organizational models of acute stroke care

Furthermore, patients may greatly benefit from direct transfer to hospitals with stroke expertise thereby bypassing community hospitals that may be located closer to the patient. Previous studies suggest an association between the level of acute stroke care – as offered by designated stroke centers compared to community hospitals – and treatment rates with thrombolysis and patient
outcomes\textsuperscript{20,21}. Within the literature four organizational models can be distinguished: primary and comprehensive stroke centers, telemedicine initiatives, and the mobile stroke unit concept. The performance of these organizational models in terms of clinical outcomes is further discussed in Chapter 2. Centralized stroke care has been associated with better outcome and quality of care. However, until now a direct comparison between organizational models in acute stroke care is lacking. In Chapter 3 a head to head comparison of the proportion of patients treated with tPA between a centralized and decentralized organization model was studied. In Chapter 4 we studied pre-hospital factors contributing to differences in thrombolysis rates between both organizational models.

**Use of simulation models in healthcare**

As thrombolysis remains underused attempts have been made to improve this situation, primarily relying on the use of Randomized Controlled Trials (RCTs) as main research vehicle. While the benefits of RCTs have been clearly established for particular devices or pharmaceuticals, their efficacy in case of complex patient pathways such as thrombolysis may be limited. For example, two recent expensive and time-consuming clinical trials have reported disappointingly low, non-significant increases in thrombolysis of 1.0 – 1.5% in the intervention arm\textsuperscript{22,23}. This warrants the question whether alternative research methods may be applied to study complex systems such as delivery of thrombolysis.

The last decade simulation models have made an entry in healthcare research. Simulation assumes a real world system can be adequately represented by a computer model\textsuperscript{24}. Starting from a validated model, a wide range of scenarios can be tested in a short time aimed at solving barriers identified. Clinical outcomes of scenarios such as treatment rates and time to treatment can also be estimated by simulation. This way simulation allows for testing several important aspects of proposed changes to the care pathway before committing resources\textsuperscript{25}. Simulated factors may include both quantitative (time delay of processes) and qualitative (choice of first responder; i.e. 911 or the general practitioner and diagnostic accuracy) factors. Various studies have shown how simulation models are suitable for assessing highly complex processes. Examples of the use of simulation models include prediction of the prognosis after aortic heart valve replacement before implementation of the therapy\textsuperscript{26}, and length of hospital stay by adverse events and overdiagnosis in case of screening mammography\textsuperscript{27}. Within the stroke literature, simulation models have been used to demonstrate that a national institute of neurological disorders and stroke compliant treatment strategy resulted in a higher proportion of patients treated with thrombolysis while remaining cost-effective\textsuperscript{28}. In addition, studies have been performed investigating the clinical benefit of reducing pre-hospital and in-hospital delays to maximize the population benefit of thrombolysis\textsuperscript{29,30}, and quantifying the population benefit of tPA treatment from an extension from the time window from 3.0 to 4.5 hours\textsuperscript{31}. In Chapter 5 we propose and illustrate a simulation-
based approach for testing interventions along the entire stroke pathway (see Figure 1) aimed at solving observed barriers. In Chapter 6 we used a simulation model to assess the impact of previously identified success factors in a central model when implemented for a decentral model. Both pre-hospital and in-hospital factors were studied. In Chapter 7 we performed a modeling study to assess the effects of centralizing thrombolysis treatment in decentralized stroke care systems on short-term costs and travel time.

**Figure 1:** the acute stroke pathway: key activities.
Aims and outline

In summary the aims of this thesis are:

To review the performance of various organizational models of acute stroke care delivery, and summarized the evidence of their efficacy on improving implementation of thrombolysis (Chapter 2).

To make a direct comparison of the proportion of patients treated with thrombolysis in a centralized versus a decentralized organizational model. This was done by performing a 6-month prospective observational study among 13 hospitals in the North of the Netherlands (Chapter 3).

To investigate whether pre-hospital factors differed between a centralized- and a decentralized organizational model (Chapter 4).

To propose a simulation based approach as a research tool for testing interventions to resolve barriers along the acute stroke pathway (Chapter 5).

To simulate previously identified success factors of centralized stroke care on thrombolysis rates and patient outcome when introduced in the decentral model (Chapter 6).

To perform a simulation study to assess the effects of centralizing thrombolysis treatment in decentralized stroke care systems on short-term costs and effects (Chapter 7).

To provide a general discussion followed by a summary of the results presented in this thesis (Chapter 8 and 9).
References


