

CHAPTER 1

General introduction
and outline of the thesis

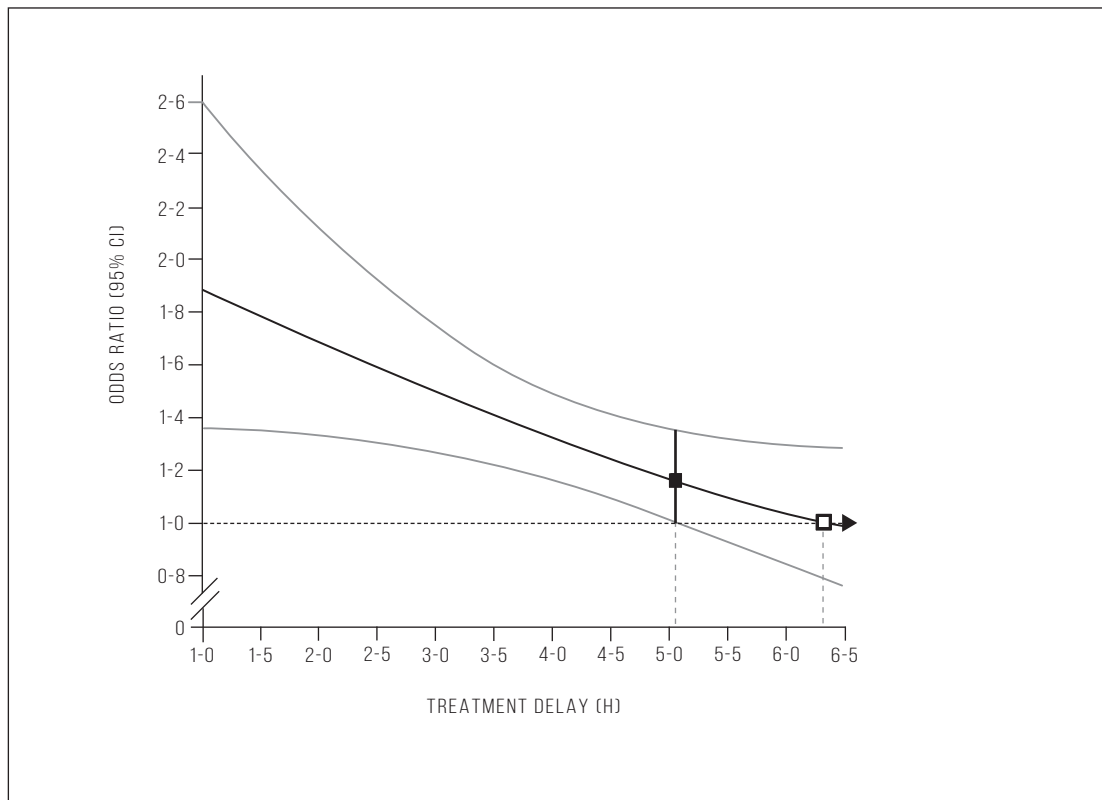
Ischemic stroke and transient ischemic attack (TIA) are both conditions caused by focal ischemia secondary to a blocked cerebral artery. In the latest definitions, the key difference between both conditions is the presence or absence of cerebral infarction. The presence of cerebral infarction, or brain cell death, is based on pathological evidence, imaging abnormalities, or clinical evidence of ischemic injury (symptoms persisting ≥ 24 hours or until death, with other aetiologies being excluded).¹ Whereas in the definition of ischemic stroke the presence of cerebral infarction is required, TIA is defined as a transient episode of neurological dysfunction (symptoms persisting < 24 hours) caused by focal brain ischemia without evidence for cerebral infarction.^{1,2} Based on the TOAST classification scheme, causes for ischemic stroke and TIA can be divided in large-artery atherosclerosis, also called large vessel disease, cardio-embolism, small-vessel disease, stroke of other determined aetiology, and stroke of undetermined aetiology.³

Ischemic stroke is common, and is regarded as a disabling global health-care problem.^{4,5} Despite advances in primary and secondary prevention, 5831 people (2132 men and 3699 women) died as a result of ischemic stroke in the Netherlands in 2012 and 32908 patients (17251 men and 15657 women) were hospitalised for an ischemic stroke in that same year.⁶ Epidemiological data on the incidence of TIA are scarce. In 2000, 2398 patients were hospitalised for a TIA in the Netherlands.⁷ Since not all patients with TIA are hospitalised, and since there is a general lack of recognition of the symptoms associated with TIA by both the public and healthcare professionals this is probably a gross underestimation of the real incidence.

Treatment of acute ischemic stroke

During the last twenty years the treatment of acute ischemic stroke has markedly improved. In 1995 results from the National Institute for Neurological Disorders (NINDS) Recombinant Tissue Plasminogen Activator (rt-PA) Stroke Trial were published. The NINDS trial

demonstrated that treatment with intravenous thrombolysis within 3 hours of the onset of ischemic stroke improved clinical outcome at 3 months.⁸ The implications of this trial have been profound, affecting the emergency management and treatment of stroke patients in general. Intravenous thrombolysis refers to the infusion of thrombolytic agents such as rt-PA in order to dissolve blood clots in blocked cerebral arteries. There is ample evidence from various randomised clinical trials that intravenous thrombolysis significantly improves clinical outcome in acute ischemic stroke, with earlier treatment resulting in an increased likelihood of independent recovery (the “time-is-brain concept”, Figure 1).⁹ In a meta-analysis of individual patient data from these randomized clinical trails the proportional benefit of intravenous thrombolysis remained statistically significant up to at least 4.5 hours after the onset of initial stroke symptoms. For independent recovery,



the Odds ratio is 1.75 when intravenous thrombolysis is initiated within 3 hours after initial stroke symptoms, and decreases to 1.26 when intravenous thrombolysis is initiated between 3 and 4.5 hour after initial stroke symptoms.⁹ In addition, it is estimated that each minute of symptom-to-needle time saved granted on average 1.8 days of extra healthy life.¹⁰ In other words, rapid administration of rt-PA is of paramount importance as it can make the difference between remaining independent or being dependent on others in the near future. Because of the importance of rapid treatment initiation, evidence based guidelines emphasise the importance of initiating intravenous thrombolysis as soon as possible after ischemic stroke onset.¹¹ Still, the time taken from hospital admission to treatment, the so-called door-to-needle time, is often delayed for reasons that could easily be avoided. In addition to this in-hospital treatment

delay, treatment for acute ischemic stroke should already begin in the pre-hospital phase. Although this time period, the so called symptom-to-door time, is widely recognized as the largest contributor to the total treatment delay, data on the pre-hospital phase for ischemic stroke patients are scarce.¹² So, in order to reduce the total time lapse between symptom onset and intravenous thrombolysis, the so-called symptom-to-needle time, the pre-hospital phase must be

FIGURE 1

Effect of timing of alteplase treatment on good stroke outcome (mRS 0–1): “time-is-brain”

Estimates of the effect of timing of alteplase on good stroke outcome as published by Emberson et al.⁹ The solid line is the best linear fit between the log odds ratio for a good stroke outcome for patients given alteplase compared with those given control (vertical axis) and treatment delay (horizontal axis). The white box shows the point at which the estimated treatment effect crosses 1. The black box shows the point at which the lower 95% CI for the estimated treatment effect first crosses 1.⁹
mRS = modified Rankin Scale

further studied for potential improvements as well.

Secondary prevention after ischemic stroke and TIA

Patients with ischemic stroke and TIA have a high risk of recurrent stroke, myocardial infarction, and death from vascular causes.^{13,14} In addition to the high risk of new vascular events, recurrent strokes increase the chance on long-term physical disability and dementia.¹⁵ Therefore, effective secondary prevention is warranted.

Risk factors for recurrent cardiovascular events can be divided into non-modifiable risk factors such as: age, gender, ethnic group and family history and modifiable risk factors. Secondary prevention strategies aim to prevent recurrent events by improving modifiable risk factor control. These strategies can be classified into two major groups: **1)** measures that improve medically modifiable risk factors and **2)** measures that improve behaviorally modifiable risk factors that may be modulated by changes in lifestyle.^{16,17}

Evidence for the effectiveness of secondary prevention strategies after ischemic stroke and TIA is compelling.¹⁸⁻²⁰ The combination of antithrombotic therapy, antihypertensive agents, statins, dietary modification, and exercise could reduce recurrent stroke by 80%.²¹ Therefore, evidence based guidelines emphasize the importance of adequate risk factor assessment and management in ischemic stroke and TIA patients.^{18,22,23} Despite this convincing evidence, secondary prevention in the clinical practice of stroke care is suboptimal.²⁴⁻²⁸

The gap between guidelines and clinical practice

Although there is sufficient evidence for both the benefit of intravenous thrombolysis in acute ischemic stroke and the effectiveness of secondary stroke prevention after ischemic stroke and TIA, health care professionals and organisations fail to appropriately translate these evidence-based recommendations into clinical practice. Several studies report a short median door-to-needle time mainly in large tertiary referral hospitals equipped with a level 1 emergency department, a dedicated stroke team

available round-the-clock, and on-site neurological imaging facilities.²⁹⁻³¹ Yet, the unambitious target of the American Heart Association (a door-to-needle time of 60 min in >80% of the cases)^{11,32} is only met for a minority of patients treated with rt-PA.³³⁻³⁵ In large international stroke registries the percentage of patients treated with a door-to-needle time of less than 60 minutes ranged between 27% and 38%.^{35,36} So it seems that a large number of hospitals are lacking processes of care that could reduce door-to-needle time. The optimisation of these processes of care for acute ischemic stroke patients could save numerous patients per year from a lifetime of disability.

Few studies have focused on the quality of care regarding long-term secondary stroke prevention. The limited data that are available indicate that ischemic stroke and TIA patients often do not receive the recommended interventions.²⁴⁻²⁸ Several studies have attempted to improve the quality of secondary prevention by lifestyle interventions in patients with ischemic stroke or TIA, with until now often disappointing results.³⁷⁻³⁹ These disappointing results can be roughly explained by patient characteristics (eg post-stroke cognitive dysfunction, lack of motivation, and functional limitations) and health care provider issues (beliefs about guidelines, awareness of guidelines, changing routines, and time investment). These results also indicate that there is need for effective strategies to improve the quality of long-term secondary prevention after ischemic stroke and TIA.

Strategies to improve the quality of long-term secondary prevention after ischemic stroke and TIA

As current medical care increasingly focuses on managing chronic diseases, clinicians experience a growing need for effective behaviour change interventions in order to achieve secondary prevention and lifestyle targets. While recent guidelines underline the importance of the behaviourally modifiable risk factors, hitherto evidence for the effectiveness of interventions that modify these risk factors is lacking.³⁹ Some evidence indicates that physical activity has favourable effects on risk factors in ischemic stroke patients.⁴⁰ In patients after myocardial infarction, the role

of physical activity in secondary prevention is well established. It has been demonstrated that cardiac rehabilitation including a physical exercise program has favorable effects on risk factors and reduces mortality.^{41,42} Although ischemic stroke, TIA, and myocardial infarction share risk factors and pathologic mechanisms, such comprehensive secondary prevention programs have not been implemented for ischemic stroke or TIA patients. Interestingly, two previous studies demonstrated a difference in treatment guideline attainment between patients with coronary artery disease and patients with stroke, with the latter group being less likely to achieve the recommended treatment targets.^{25,43} Thus, a secondary prevention program including a physical exercise program after ischemic stroke and TIA, mirroring practice in cardiac rehabilitation, could be a promising method for increasing effectiveness of secondary prevention in these patients. Better use and implementation of effective secondary prevention could not only prevent long-term physical disability and dementia, but also yield significant healthcare savings.

Aim and outline of this thesis

The primary aim of this thesis is to investigate if the quality of care for ischemic stroke and TIA patients can be improved by measures that can easily be implemented in daily care for these patients.

This thesis is divided into two parts. In the first part we describe two studies on how in-hospital treatment for acute ischemic stroke patients can be improved. In **Chapter 2** we report on the results of a study in which the door-to-needle time in intravenous thrombolysis for acute ischemic stroke patients was significantly reduced through the introduction of a standard operating procedure and by creating higher and sustained awareness of the importance of intravenous thrombolysis among all health care professionals involved. In **Chapter 3** we go a step further and investigate patient related and logistic factors that delay door-to-needle time when an optimised intravenous thrombolysis protocol is operational.

The second part of this thesis focuses on the quality of long-term secondary prevention after ischemic stroke and TIA. In **Chapter 4** the effect of a long-

term secondary prevention program in ischemic stroke and TIA patients was investigated. **Chapter 5** reports the potential of motivational interviewing on the attainment of secondary prevention and lifestyle targets in patients with ischemic stroke and TIA. **Chapter 6** describes the results of a pilot study on the safety and feasibility of post-stroke care and exercise after minor ischemic stroke or TIA. In **Chapter 7** we describe the rationale and design of the MoveIT study, a randomised controlled trial of aerobic exercise after minor ischemic stroke or TIA to prevent cognitive decline. The primary aim of this study is to investigate the effect of a physical exercise program on cognition in patients in the acute phase after minor ischemic stroke or TIA, compared with participation in usual care. One of the secondary objectives of this trial is to investigate the effect of a physical exercise program on the attainment of guideline recommended secondary prevention targets. **Chapter 8** reports the results of a web-based survey among Dutch neurologists with a special interest in stroke neurology. This web-based survey contained questions regarding long-term secondary prevention after ischemic stroke and TIA. The aim of this study was to investigate practice variations in long-term secondary stroke prevention in the Netherlands. **Chapter 9** is a systematic review and meta-analysis of the effects of lifestyle interventions to prevent recurrent cardiovascular events after ischemic stroke and TIA. The primary objective of this systematic review and meta-analysis is to determine whether lifestyle interventions focusing on behaviorally modifiable risk factors with or without an exercise program are effective in terms of: preventing recurrent cardiovascular events, reducing mortality, and improving modifiable risk factors associated with cardiovascular disease in patients after ischemic stroke or TIA. Finally, in **Chapter 10**, the main findings of this thesis are discussed and recommendations for future research are given.

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