

S U M M A R Y

Despite advances in prevention and treatment, ischemic stroke remains a common and debilitating global healthcare problem. A general introduction to treatment options for acute ischemic stroke and secondary prevention after ischemic stroke and TIA are given in **Chapter 1**. Although there is ample evidence for both the benefit of intravenous thrombolysis in acute ischemic stroke and the effectiveness of secondary stroke prevention to prevent recurrent ischemic stroke and transient ischemic attack (TIA), care providers frequently fail to appropriately translate these evidence-based recommendations into clinical practice. This thesis focuses on improving the quality of care for ischemic stroke and TIA patients through measures that can be easily implemented in the daily care of these patients.

Part 1: In-hospital treatment delay for acute ischemic stroke patients

The clinical benefit of intravenous thrombolysis in acute ischemic stroke is time dependent. In order to avoid unnecessary treatment delay, it is essential to optimize the in-hospital process of care for acute ischemic stroke patients who are eligible for intravenous thrombolysis. In **Chapter 2** we demonstrate that in-hospital treatment delay for acute ischemic stroke patients can be reduced through the introduction of a standard operating procedure and by creating higher and sustained awareness among healthcare professionals of the importance of this time-driven protocol. In this before-versus-after study, the median door-to-needle time decreased significantly, from 60 minutes in the pre-intervention period to 30 minutes in the immediate post-intervention period; and compared with the immediate post-intervention period there was a further significant decrease to 25 minutes in the late post-intervention period. In addition, the intravenous thrombolysis rate (number of ischemic stroke patients treated with intravenous thrombolysis divided by the total number of ischemic stroke patients) increased significantly across the three study

periods, from 5% in the pre-intervention period to 20% in the late post-intervention period.

Even with an optimized intravenous thrombolysis protocol, as described in **Chapter 2**, the door-to-needle time is still frequently delayed for avoidable reasons. In **Chapter 3** we describe the results of a multicentre, consecutive cohort study of patients treated with intravenous thrombolysis. Despite the short median door-to-needle times in both hospitals (30 and 23 minutes), there was still a delay in door-to-needle time as a result of at least one factor in 63% of patients treated with intravenous thrombolysis. Patients without any delaying factor had a 10-minute shorter median door-to-needle time compared to patients with at least one delaying factor. Multivariable regression analysis showed that patient-related factors independently predicted a delayed door-to-needle time in most cases: uncertainty about symptom onset, uncontrolled blood pressure, fluctuating neurological deficit, other treatment before intravenous thrombolysis, and uncertainty about coagulation or anticoagulation status. The only logistic factor that independently predicted a delayed door-to-needle time was incorrect triage. To the best of our knowledge, this is the first study that prospectively documented factors delaying the door-to-needle time for each individual patient, allowing the identification of independent factors delaying the door-to-needle time.

Part 2: Secondary prevention after ischemic stroke and TIA

In addition to optimizing care for acute ischemic stroke patients, we also aimed to optimize the quality of secondary prevention for patients who have suffered an ischemic stroke or TIA. Currently there is a large gap between guideline recommendations and the utilization of these guideline-recommended secondary prevention measures. Secondary prevention measures can be classified into two major groups: **1)** measures that improve medically modifiable risk factors and **2)** measures that improve behaviourally modifiable risk factors that may be modulated by changes in lifestyle.

In **Chapter 4** the effect of a secondary prevention programme on ischemic stroke and TIA patients was investigated retrospectively. This

programme aimed to improve the quality of secondary prevention and focused on the medically modifiable risk factors. The goal was to achieve the guideline-recommended treatment targets for blood pressure, LDL-cholesterol, and the use of antithrombotic therapy (antiplatelet agents or oral anticoagulants). To this end we used a medication treatment algorithm. We were surprised to find that 31% of the eligible patients did not participate in the programme at all, despite the great deal of effort put into setting up the programme. Of the remaining patients, only 46% completed the full follow-up period of one year. Thirty-seven percent of these patients reached the combined endpoint of optimal medical therapy (the combination of the use of prescribed antithrombotic therapy and achievement of both blood pressure and LDL-cholesterol targets) at their last visit within the secondary prevention programme. This means that in most patients, the medication treatment algorithm used in this study was insufficient to reach the guideline-recommended secondary prevention targets.

Chapter 5 describes the results of a single-centre prospective study on the effect of a motivational interview-based secondary prevention programme on the achievement of guideline-recommended secondary prevention targets after ischemic stroke or TIA. In this study, we used a more multifaceted approach. In addition to a medication treatment algorithm, motivational interviewing was used to influence the behaviourally modifiable risk factors. With this counselling technique, we aimed to motivate patients to attain a healthy and active lifestyle and optimize medication adherence. After one year, 68% of patients reached the primary endpoint for optimal medical therapy. Compared with baseline results, we found a significant increase in the number of patients who achieved the primary endpoint of optimal medical therapy as well as achieving both the blood pressure and LDL-cholesterol targets after one year. In addition, we found a significant change in two behaviourally modifiable risk factors, namely a decrease in the number of active smokers and in waist circumference. During the second year of follow-up, the proportion of patients who reached the primary endpoint fell significantly to 50%. The results of this study, however, still compare favourably with those reported in previous studies.

Some evidence indicates that physical activity has favourable effects

on risk factors in ischemic stroke patients. In **Chapter 6** we describe the results of a prospective, single-blind, randomized controlled pilot study in which we investigated the safety and feasibility of an exercise-based post-stroke care programme in patients in the acute phase after minor ischemic stroke and TIA. In this study, patients were randomly assigned to a multidisciplinary post-stroke care programme with or without an aerobic exercise programme. The multidisciplinary post-stroke care programme used in this study was similar to the multifaceted intervention used in **Chapter 5**. This pilot study demonstrated that an exercise-based post-stroke care programme is safe and feasible in the acute phase after a minor ischemic stroke or TIA. In addition, a significantly larger proportion of patients in the group receiving post-stroke care with exercise reached the composite endpoint of optimal medical therapy as compared to the group receiving post-stroke care without exercise. Larger randomized studies are needed to assess and replicate the effects that post-stroke care that includes an exercise programme has on secondary prevention targets after ischemic stroke or TIA.

In **Chapter 7** we describe the rationale and design of the MoveIT study, a randomized controlled trial of aerobic exercise after minor ischemic stroke or TIA to prevent cognitive decline. The intervention group of this study participates in the MoveIT programme, which consists of a twelve-week aerobic exercise programme and follow-up visits to a specialized physiotherapist every three months for one year. The primary goal of the MoveIT study is to obtain results on cognitive functioning, but we will also investigate whether there are differences in achieving the various guideline-recommended secondary prevention targets. In this way this study will contribute to available knowledge on the effectiveness of cardiovascular fitness programmes among patients who have suffered an ischemic stroke or TIA.

All results of secondary prevention studies mentioned so far in this thesis originated in a single secondary care teaching hospital in Amsterdam. In order to gain more insight into how secondary prevention is implemented in other Dutch hospitals, we distributed a questionnaire among 90 Dutch neurologists with a special interest in

stroke neurology, working in 90 different hospitals. We hypothesized that there are considerable variations in long-term secondary stroke prevention among neurologists in the Netherlands. In **Chapter 8** we describe the results of this survey. As hypothesized, we found considerable practice variation in long-term secondary stroke prevention. We also found considerable variation in the organization of outpatient care after the initial hospital assessment, pharmacologic treatments, and non-pharmacologic strategies. In our survey, we found considerable disagreement among the respondents on who ideally should be responsible for long-term secondary prevention after ischemic stroke and TIA. Half the respondents stated that the general practitioner should hold primary responsibility for long-term secondary stroke prevention, whereas the other half favoured a hospital-based strategy.

In **Chapter 9** we describe the results of a systematic review and meta-analysis of lifestyle intervention studies focusing on behaviourally modifiable risk factors with or without an exercise programme in patients after ischemic stroke and TIA. Twenty-two randomized controlled trials met the predefined inclusion criteria and the main finding of this review and meta-analysis was that lifestyle interventions achieved a significant reduction (3.6 mm Hg) in systolic blood pressure as compared to standard care methods. Furthermore, the subgroup analyses showed that trials with cardiovascular fitness interventions, trials with an intervention that lasted longer than four months and interventions that used more than three behavior change techniques were more effective in reducing systolic blood pressure. Regarding the initiatives that are intended to improve the quality of secondary prevention after an ischemic stroke or TIA, it is important that future studies meet a number of conditions. It is primarily important that future high-quality randomized controlled trial studies investigating the effects of lifestyle interventions on preventing cardiovascular events, mortality, and modifiable risk factors include a detailed description of all therapy-related characteristics of the intervention (eg timing of intervention, intensity, total duration, and the use of behaviour change techniques).

To conclude, the studies presented in this thesis show that quality of

care for ischemic stroke and TIA patients can be improved through measures that can be easily implemented in the daily care of these patients. Regarding intravenous thrombolysis for acute ischemic stroke, room for further reduction of in-hospital treatment delay in our opinion is limited. The main challenge now is to consolidate the progress that has been achieved, to reduce prehospital delay, to record and interpret the door-to-needle time in a more uniform manner, and to look for innovative ways of reducing the door-to-groin time for acute ischemic stroke patients eligible for intra-arterial treatment. The secondary prevention studies in the second part of this thesis have obtained a number of important results: **1)** The treatment targets recommended by the secondary prevention guidelines for ischemic stroke and TIA patients are often not achieved in practice; **2)** Dutch neurologists often differ in their vision of how secondary prevention after ischemic stroke or TIA should be provided in practice; **3)** At present there is a lack of high-quality scientific evidence for the best way to implement patient care after an ischemic stroke or TIA. Because the prevalence of individuals who have experienced an ischemic stroke or TIA is expected to increase in the coming years, there is a need for effective secondary prevention interventions, with the goal of decreasing the cardiovascular risk.