CHAPTER 10

General discussion

Despite advances in prevention and treatment, ischemic stroke remains a common and debilitating global healthcare problem.[1,2] 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 translate these evidence-based recommendations into clinical practice appropriately. This thesis focuses on improving the quality of care for ischemic stroke and TIA patients through measures that can easily be implemented in their daily care. The first part of this thesis **(Chapters 2 and 3)** describes how short door-to-needle times can be achieved by following an optimized intravenous thrombolysis protocol. The second part of the thesis **(Chapters 4 to 9)** focuses on the quality of long-term secondary prevention after ischemic stroke or TIA. In the final chapter, we discuss the main findings of this thesis and make recommendations for future research.

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

Timely intravenous thrombolysis significantly improves the clinical outcome in cases of acute ischemic stroke. In a meta-analysis the proportional benefit of intravenous thrombolysis remained statistically significant up to at least 4.5 hours after initial stroke symptoms, yet within this time period the efficacy of treatment decreases over time (the time-is-brain concept).[3]

In **Chapter 2** we demonstrate that in-hospital treatment delay for acute ischemic stroke patients can be reduced relatively easily by introducing an optimized intravenous thrombolysis protocol. However, even with

an optimized intravenous thrombolysis protocol, the door-to-needle time is still frequently extended for avoidable reasons. In **Chapters 3** we identified factors extending the door-to-needle time; and although corrective improvement measures could slightly reduce in-hospital treatment delay for acute ischemic stroke patients, in our opinion room for further improvement is limited. The main challenge now is to consolidate the progress that has been achieved. Furthermore, it is important to record and interpret the door-to-needle time in a more uniform manner.[4] After a patient has undergone intravenous thrombolysis, the door-to-needle time is often estimated based on time observations by one or more care providers. Because all these care providers have a motivation to carry out this treatment as quickly as possible, their estimates may generally be too low. In order to obtain more reliable data and thus to see more clearly whether, and where, time is being lost, it is important to find a more objective way to measure the time needed for this treatment. To this end, we could use a relatively new technique called 'process mining'.[5] This technique utilizes the information technology that is already commonplace in hospitals these days, but until now this information has not been used to improve pathways of care for ischemic stroke and TIA patients. Vast amounts of logistical data in various hospital information systems are recorded on a daily basis, including in the electronic patient record. The electronic patient record includes, for instance, information about the time of arrival at the hospital, the time when additional tests are requested and who requests them, or the time when the patient is admitted to the stroke unit. Care providers can use the information recorded in this way in what are called event logs, a set of traces each containing all the activities executed for a particular process instance, to understand the actual execution of processes such as intravenous thrombolysis. Process mining can help us to discover the actual process model, so that we can check whether a given process is being carried out in accordance with the appropriate guidelines and so that we can find opportunities to further optimize the process.[5]

Collaboration with process mining experts could result in a significant leap forward in the use of this technique within healthcare.

While we effectively reduced the door-to-needle times, the weak link in reducing the total time lapse between symptom onset and intravenous thrombolysis turned out to be prehospital delay or 'symptom-to-door time'. As we describe in **Chapter 3**, about three quarters of the symptom-to-needle time had passed before patients arrived at hospital, and these results are consistent with those reported in previous studies.[6-8] Although prehospital delay is widely recognized as the largest contributor to symptom-to-needle time, there is a scarcity of data on the prehospital phase for ischemic stroke patients.[9] The symptom-to-door time can be divided into three phases: **(1)** the time from stroke onset to the decision to seek medical attention; **(2)** the time from the decision to seek medical attention to the first medical contact; and **(3)** the time between the first medical contact and arrival at the emergency department.[10] To further reduce the symptom-to-needle time, each phase in the symptom-to-door-time must be further studied for potential improvements.[11] Well-known factors that delay the decision to seek medical attention after stroke onset include a lack of knowledge about stroke, difficulty in recognizing stroke symptoms, and a lack of awareness that these symptoms constitute an emergency. A lack of awareness of the existence of an effective treatment was also recently identified as a barrier to seeking medical attention.[12] Furthermore, once the patient makes the decision to seek medical attention, it is important to realize that the emergency medical services must be contacted immediately rather than contacting the general practitioner. This is of particular importance since available evidence suggests that the immediate use of emergency medical services is crucial in reducing the time from the decision to seek medical attention to the first medical contact as well as the time from the first medical contact to arrival at the emergency department.[10,11] Public awareness campaigns, such as the

recent Face-Arm-Speech campaign of the Dutch Heart Foundation, can improve stroke knowledge and could therefore reduce symptom-to-door time.[9,13-16] However, it is still unclear how, and in particular how often, these campaigns are best implemented.

Although intravenous thrombolysis is still the first line of treatment for acute ischemic stroke,[17,18] new intra-arterial treatment options have greatly expanded the treatment arsenal for patients suffering from acute ischemia caused by an intracranial occlusion in the anterior circulation artery. During this treatment, a catheter is inserted via the groin (femoral artery) and the intracranial occlusion is approached from the inside. The catheter is inserted into the occluded blood vessel, after which a microcatheter is used to pass the occlusion. Next, the thrombus is removed using a special catheter. Several independent studies have found that in patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion of the anterior circulation, intra-arterial treatment improves functional outcomes and reduces mortality.[19-22] Thus, intra-arterial treatment should be considered for all acute ischemic stroke patients with a proximal intracranial arterial occlusion of the anterior circulation who are not recanalized after intravenous thrombolysis or who are not eligible for intravenous thrombolysis. This new treatment option appears to have the same time sensitivity as intravenous thrombolysis, so as well as the symptom-to-door time and the door-to-needle time this adds a third time-critical period to the treatment process for acute ischemic stroke patients who are eligible for intra-arterial treatment.[23] We find ourselves in uncharted territory when it comes to the logistics for patients who are eligible for intra-arterial treatment. As any delay in establishing successful recanalization of the intracranial arterial occlusion must be minimized, it is important to look for innovative ways of reducing the time needed between the patient's arrival at the first hospital and access to arterial circulations via the femoral artery, also known as the door-to-groin time. At present, many patients

with an intracranial arterial occlusion of the anterior circulation are treated by means of the 'drip-and-ship' method, whereby intravenous thrombolysis is used as the initial treatment of choice in the nearest community hospital before transporting the patient to an intervention centre.[17] Precious time is likely to be lost due to this transfer between hospitals for patients who are eligible for intra-arterial treatment. By optimizing the care pathway for these patients in both community hospitals (eg by short door-to-needle times, 24-hour availability of CT angiography and immediate transfer on finding an intracranial arterial occlusion) and intervention centres, this delay can be reduced to a minimum. Another possible way of reducing door-to-groin time is to transport all patients with symptoms of an acute ischemic stroke straight to an intervention centre. This is known as the 'mothership' paradigm. One important disadvantage of this approach is the fact that the use of intravenous thrombolysis as a first-line treatment could be delayed for all acute ischemic stroke patients due to longer driving time, while ultimately only a relatively small proportion of patients are eligible for intra-arterial treatment. Another disadvantage is that it could lead to exceeding the capacity of the intervention centre emergency department for two reasons: firstly because all patients who have suffered an ischemic stroke and are eligible for intravenous thrombolysis need to be treated at these centres; and secondly, in the wake of the patients with an acute ischemic stroke there will also be increased numbers of patients with acute neurological symptoms caused by other conditions. Another possible way to improve acute treatment for all acute ischemic stroke patients is to organize a regional mobile neurointervention team which can travel to the patient rather than transporting all patients to an intervention centre. Not only would this potentially reduce the time from onset of symptoms to groin puncture, it could also help to avoid current intervention centres being overwhelmed by the number of patients coming in with acute neurological symptoms. Therefore regional cooperation between all hospitals caring for stroke patients is necessary.

Part 2: Secondary prevention after ischemic stroke and TIA

Secondary prevention is an effective way to reduce the burden of recurrent stroke and other cardiovascular disease.[24,25] 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.[26,27] The exploratory studies **(Chapters 4-6 and 8)** and the review with meta-analyses **(Chapter 9)** 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.

Why do patients who have suffered an ischemic stroke and/or TIA not subsequently achieve the guideline-recommended secondary prevention targets in clinical practice? There are various reasons for this; besides patient-related factors, healthcare provider issues and healthcare delivery processes play a role in this. Past studies have devoted attention primarily to patient-related factors (such as an unhealthy lifestyle and non-adherence to medication instructions), and unfortunately interventions aiming to influence these factors have often had only a limited effect on the quality of secondary prevention. Besides the almost self-evident attention to these patient-related factors, in order to improve the quality of care with regard to long-term secondary prevention it is important to take a critical look at the way this care is organized at present. The results of our survey among Dutch neurologists, described in **Chapter 8,** show that the

way in which this care is currently provided varies from one hospital to another. Many respondents felt that general practitioners should be responsible for this care. This may seem self-evident, as it is generally easier for general practitioners to approach patients, and at the same time they have access to good national guidelines for cardiovascular risk management.[28] In addition, there is increasing substitution of care from specialized secondary healthcare to primary healthcare. However, there is a great deal of room for improvement in the secondary prevention of cardiovascular disease within primary healthcare. For instance, not all patients are regularly tested for their blood pressure and lipid profile, and even when they are tested, in many cases the values of these measurements do not conform to the guideline-recommended values.[29] In addition, disability, reduced cognitive function, post-stroke depression, and fatigue after ischemic stroke and TIA have a significant effect on the quality of care for these patients. There is a lack of expertise in primary healthcare when it comes to the prompt detection and, where possible, treatment of these less visible consequences of ischemic stroke. It is highly questionable whether these patients are better off under primary healthcare alone. Therefore, in our opinion, formal cardiovascular risk management for ambulatory patients without residual symptoms could be provided by general practitioners. However, patients with a disability, cognitive impairment, or other residual symptoms after an ischemic stroke or TIA require personalized care. This could be provided by regional 'stroke prevention teams'. These teams could include nurses and nurse practitioners working in close collaboration with a local general practitioner, pharmacist, and stroke neurologist. Unlike the hospital-based secondary prevention programmes described in **Chapters 4, 5, and 6**, these teams could serve more of a primary care function, as well as visiting patients at home or in a nursing home. This form of care provision is also referred to as 'shared care'.[30] A randomized study of 186 patients who had suffered a stroke found that a multimodal programme that included a shared care component was effective in

modifying a variety of vascular risk factors, namely systolic blood pressure, body mass index, and physical activity.[31] The question of whether this intervention actually resulted in lowered rates of stroke recurrence, readmission to hospital, or death from a vascular cause in the stroke survivors is currently being investigated by the same research group in a larger multicentre randomized controlled trial.[32]

Concerning the way in which care is organized for patients after ischemic stroke or TIA, it is important to realize that we have progressed far beyond the time when information could only be transferred face to face between care provider and patient. New digital possibilities, by means of information technology and with the use of social media, are increasingly entering our consultation room. Although as yet these possibilities only exist sparsely in hospitals, this digital revolution will have a profound impact on how doctors interact with their patients. Some experts even claim that the use of what is known as eHealth will eliminate the consultation room as we know it, because communication between doctors and patients will take place increasingly often by means of electronic devices. In addition, software companies are developing more and more mobile and other applications intended to enable patients to take control of their own health. These new opportunities could contribute to the self-management of behaviourally modifiable risk factors for ischemic stroke and TIA patients. eHealth solutions also make it easier for us as care providers to reach these patients, who then need not always come to hospital for their appointments. This could increase participation in follow-up care programmes for ischemic stroke and TIA patients with cognitive, motor, or visual impairments. Despite the fact that eHealth is an extremely promising development, we suggest that the new eHealth applications currently in more widespread use must first be investigated to determine whether they are truly effective. In other words, the rules of evidence-based medicine should also apply to eHealth.[33]

Regarding the initiatives intended to improve the quality of long-term secondary prevention after an ischemic stroke or TIA, it is important for future studies to meet a number of conditions. Since lifestyle interventions are typically complex, the most important thing, as we describe in **Chapter 9**, is that future randomized controlled trials investigating the effects of these interventions on preventing cardiovascular events, mortality, and modifiable risk factors should include a detailed description of all therapy-related characteristics of the intervention (e.g. timing of intervention, intensity, total duration, and use of behavioural change techniques). In the review and meta-analysis described in **Chapter 9** we found that longer-lasting interventions and interventions that include a cardiovascular fitness programme as well as behavioural change techniques were effective in reducing systolic blood pressure. Regarding other endpoints, we found no effect of lifestyle interventions on cardiovascular events, mortality, diastolic blood pressure, or total cholesterol. Multiple lines of evidence suggest that exercise-based cardiac rehabilitation in patients following myocardial infarction is not only effective in reducing systolic blood pressure, but also leads to reductions in mortality and reinfarction and has favourable effects on cardiovascular risk factors, including smoking, body weight, and lipid profile.[34,35] Although ischemic stroke, TIA, and myocardial infarction share risk factors and pathologic mechanisms, comprehensive secondary prevention programmes of this nature have not yet been implemented for ischemic stroke or TIA patients. Whether or not such programmes are also effective in reducing mortality and recurrent strokes in these patients will need to become clear from future research. Despite the similarities in risk factors and pathologic mechanisms, there are also differences between these patients in terms of both psychosocial characteristics (cognition, depression, anxiety, and fatigue) and physical performance. In **Chapter 6** we describe how an exercise-based post-stroke care programme is safe and feasible in the acute phase after a minor 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 stroke or TIA to prevent cognitive decline. 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 the available knowledge on the effectiveness of cardiovascular fitness programmes among patients who have suffered a TIA or ischemic stroke. Currently all 120 patients have completed the follow-up period and we will start analysing the results soon.

In the studies described so far, we measured quality of care by determining the degree to which our patients achieved the treatment goals recommended by the guidelines (**Chapters 4 to 6**). We used this as a surrogate outcome for cardiovascular risk, because it involves uncontested measures for reducing cardiovascular risk. It would be more reliable to determine the actual risk of ischemic stroke or TIA or mortality. However, even in the case of these outcomes, it is uncertain whether they truly measure the added value that our treatment has for patients. Value-based healthcare may provide better insight into the actual quality of the care provided. Value-based healthcare is a method focused on maximizing the quality of healthcare and reducing its costs. This method defines 'value' as the total benefit gained by a patient divided by the cost of achieving this outcome.[36] An important condition for the use of value-based healthcare is whether results have been defined that are meaningful for patients. In order to enable the assessment of healthcare value in ischemic stroke and TIA patients, an international working group, the International Consortium for Health Outcomes Measurement (ICHOM), has defined a minimum recommended set of consensus patient-centred outcomes, the ICHOM Standard Set for stroke. This list of outcomes includes mortality, a new stroke after admission, questions about motor functioning, and even more importantly patients' judgements about their own health, ie

patient-reported outcome measures.[37] By recording these outcomes and using them for benchmarking purposes, medical personnel can learn from one another and exchange best practices. This could benefit the quality of secondary prevention and could reduce the costs of care for patients who have experienced an ischemic stroke or TIA.

To conclude, there are plenty of opportunities to improve the quality of care relating to acute treatment of stroke and secondary prevention after an ischemic stroke or TIA. Currently we are making insufficient use of the tools that we have at our disposal to achieve this. The measures described in the discussion in this thesis, such as the use of process mining, the creation of stroke prevention teams, the use of eHealth, and the use of value-based healthcare, could optimize the quality of care for patients after an ischemic stroke or TIA. The point is not to simply develop a new, expensive, or complicated treatment; but rather to apply measures which have been recognized for years as being effective in increasing the likelihood that our patients will have a future without new cardiovascular events.

REFERENCES

1. Feigin VL, Lawes CMM, Bennett DA, et al. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 2009;8:355–369.

2. Go AS, Mozaffarian D, Roger VL, et al. Executive summary: heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation 2014;129:399–410.

3. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014;384:1929–1935.

4. Kruyt ND, Nederkoorn PJ, Dennis M, et al. Door-to-needle time and the proportion of patients receiving intravenous thrombolysis in acute ischemic stroke: uniform interpretation and reporting. Stroke 2013;44:3249–3253.

5. Rojas E, Munoz-Gama J, Sepúlveda M, et al. Process mining in healthcare: A literature review. J Biomed Inform 2016;61:224–236.

6. Meretoja A, Weir L, Ugalde M, et al. Helsinki model cut stroke thrombolysis delays to 25 minutes in Melbourne in only 4 months. Neurology 2013;81:1071-1076

7. Meretoja A, Strbian D, Mustanoja S, et al. Reducing in-hospital delay to 20 minutes in stroke thrombolysis. Neurology 2012;79:306–313.

8. Köhrmann M, Schellinger PD, Breuer L, et al. Avoiding in hospital delays and eliminating the three-hour effect in thrombolysis for stroke. Int J Stroke 2011;6:493–497.

9. Yperzeele L, Van Hooff R-J, De Smedt A, et al. Prehospital stroke care: limitations of current interventions and focus on new developments. Cerebrovasc Dis 2014;38:1–9.

10. Bouckaert M, Lemmens R, Thijs V. Reducing prehospital delay in acute stroke. Nat Rev Neurol 2009;5:477–483.

11. Fassbender K, Balucani C, Walter S, et al. Streamlining of prehospital stroke management: the golden hour. Lancet Neurol 2013;12:585–596.

12. Le Bonniec A, Haesebaert J, Derex L, et al. Why Patients Delay Their First Contact with Health Services After Stroke? A Qualitative Focus Group-Based Study. PLoS ONE. 2016;11:e0156933.

13. Hodgson C, Lindsay P, Rubini F. Can mass media influence emergency department visits for stroke? Stroke 2007;38:2115–2122.

14. Mellon L, Doyle F, Rohde D, et al. Stroke warning campaigns: delivering better patient outcomes? A systematic review. Patient Relat Outcome Meas 2015;6:61–73.

15. Flynn D, Ford GA, Rodgers H, et al. A time series evaluation of the FAST National Stroke Awareness Campaign in England. PLoS ONE 2014;9:e104289.

16. Bray JE, Mosley I, Bailey M, et al. Stroke public awareness campaigns have increased ambulance dispatches for stroke in Melbourne, Australia. Stroke 2011;42:2154–2157.

17. Goyal M, Yu AYX, Menon BK, et al. Endovascular Therapy in Acute Ischemic Stroke: Challenges and Transition From Trials to Bedside. Stroke 2016;47:548–553.

18. Mokin M, Snyder KV, Siddiqui AH, et al. Recent Endovascular Stroke Trials and Their Impact on Stroke Systems of Care. J Am Coll Cardiol 2016;67:2645–2655.

19. Berkhemer OA, Fransen PSS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372:11–20.

20. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid

endovascular treatment of ischemic stroke. N Engl J Med 2015;372:1019–1030.

21. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372:2285–2295.

22. Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372:1009–1018.

23. Fransen PSS, Berkhemer OA, Lingsma HF, et al. Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial. JAMA Neurol 2016;73:190–196.

24. Rothwell PM, Algra A, Amarenco P. Medical treatment in acute and long-term secondary prevention after transient ischaemic attack and ischaemic stroke. Lancet 2011;377:1681–1692.

25. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2014;45:2160–2236.

26. Billinger SA, Arena R, Bernhardt J, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2014;45:2532–2553.

27. Sarikaya H, Ferro J, Arnold M. Stroke prevention--medical and lifestyle measures. Eur Neurol 2015;73:150–157.

28. Landelijke werkgroep 'Cardiovasculair risicomanagement'. NHG-Standaard 'Cardiovasculair risicomanagement' (tweede herziening). Huisarts Wet 2012; 55:14-28.

29. Nielen MMJ, Hek K, Korevaar JC, et al. Cardiovasculair risicomanagement in de huisartsenpraktijk. In: Van Dis I, Buddeke J, Vaartjes I, et al. Hart- en vaatziekten in Nederland 2015, cijfers over heden, verleden en toekomst. Den Haag: Hartstichting;2015:69-79.

30. Orton P. Shared care. Lancet 1994;344:1413–1415.

31. Joubert J, Reid C, Barton D, et al. Integrated care improves risk-factor modification after stroke: initial results of the Integrated Care for the Reduction of Secondary Stroke model. J Neurol Neurosurg Psychiatr 2009;80:279–284.

32. Joubert J, Davis SM, Hankey GJ, et al. ICARUSS, the Integrated Care for the Reduction of Secondary Stroke trial: rationale and design of a randomized controlled trial of a multimodal intervention to prevent recurrent stroke in patients with a recent cerebrovascular event, ACTRN = 12611000264987. Int J Stroke 2015;10:773–777.

33. Franklin NC, Lavie CJ, Arena RA. Personal health technology: A new era in cardiovascular disease prevention. Postgrad Med 2015;127:150–158.

34. Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. Am Heart J 2011;162:571–584.

35. Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. Am J Med 2004;116:682–692.

36. Porter ME. What is value in health care? N Engl J Med 2010;363:2477–2481.

37. Salinas J, Sprinkhuizen SM, Ackerson T, et al. An International Standard Set of Patient-Centered Outcome Measures After Stroke. Stroke 2016;47:180–186.