INTRODUCTION

There was no acute treatment for ischaemic stroke until in 1995, the National Institutes of Neurological Disorders and Stroke trial showed that intravenous thrombolysis (IVT) improved the chance to recover with no or minimal disabilities by an absolute 10%. IVT has now been implemented as regular stroke treatment and together with stroke unit admission, the approach on acute stroke management has irreversibly changed.

Notwithstanding these advances, stroke is still the leading cause of long-term disability and ranks fourth as cause of death. The efficacy of IVT to prevent poor outcome is only modest as more than half of the patients remain dependent in activities of daily living or have died 3 months after their stroke despite IVT. In addition, most patients are left untreated due to arrival outside the therapeutic time window of 4.5 hours after stroke onset. The reported IVT rate varies between 1 and 18% worldwide. In the Netherlands, even despite its excellent access to hospital care, the proportion of ischaemic stroke patients treated with IVT was only 6% in 2005, but increased to 14% in 2012. Since only half of the patients who arrive on time at Dutch emergency departments are actually treated with IVT, there is still room for further improvement. Given the major individual and economic burden of stroke, optimizing the efficacy and use of IVT in daily stroke care is therefore imperative.

PATHOPHYSIOLOGY AND TREATMENT OF ACUTE ISCHAEMIC STROKE

Ischaemic stroke, or cerebral infarction, is caused by an atherothrombotic clot occluding a cerebral artery. According to aetiologia, strokes are classified into the following subtypes: large artery atherosclerosis, cardioembolism, small vessel occlusion, stroke due to uncommon causes, or stroke of unknown aetiology. In all cases, the clot hampers cerebral blood flow in the occluded artery and causes the brain tissue in the vascular territory to become hypoxic. Subsequently, a cascade of ischaemic events sets in that finally results in neuronal cell death. In the absence of oxygen supply, cell death expands over time, leading to the irrevers-
ible formation of a cerebral infarct. It is assumed that this infarct core is surrounded by functionally inactive but still viable brain tissue, the so-called penumbra.\textsuperscript{15} Therapeutic interventions in acute stroke aim to salvage the penumbra by timely restoration of the cerebral blood flow, in order to prevent further extension of the infarct core (Figure 1.1).

IVT is a reperfusion therapy and consists of pharmacological dissolution of occluded cerebral arteries by exogenous activation of the fibrinolytic system. The commonly used thrombolytic agent is alteplase (or recombinant tissue plasminogen activator, rt-PA) which induces conversion of the proenzyme plasminogen into the active enzyme plasmin. Plasmin breaks down the fibrin in the clot into soluble degradation products (Figure 1.2). Thrombus disintegration causes further exposure of fibrin to alteplase and the process of recanalization continues until cerebral blood flow is finally restored. However, at the same time, endogenous inhibition of the fibrinolytic system occurs by plasminogen activator inhibitors and $\alpha_2$-antiplasmine, and the degree of recanalization depends on the balance between fibrinolyis and thrombus formation. Besides breaking down fibrin,
plasmin induces degradation of proteins in the basal lamina causing loss of microvascular integrity, which is a prerequisite for the development of intracranial haemorrhage (ICH), the most feared complication of IVT.\footnote{16}

**OPTIMIZING THROMBOLYSIS IN STROKE**

Vessel patency is closely related to clinical outcome in stroke. As several studies showed, recanalization of an occluded cerebral artery was associated with both short-term and long-term improvement, whereas occlusion persistence was prognostic of early neurological deterioration and poor outcome.\footnote{17-21} A meta-analysis showed that IVT achieved recanalization in 46\% within 24 hours compared to a spontaneous recanalization rate of 24\%, explaining the modest effect of IVT on preventing poor outcome.\footnote{20}
A logical strategy to improve the efficacy of IVT would therefore be to increase the recanalization rate. A higher rate can theoretically be achieved by a higher dosage of alteplase, but this was shown to be associated with an unacceptable high rates of ICH and mortality. Another way to enhance the recanalization rate is to prevent reocclusion. From transcranial Doppler studies, reocclusion after initial recanalization was reported in 14–34% of ischaemic stroke patients treated with IVT and was associated with early neurological deterioration. Interestingly, other studies showed that prior use of aspirin was associated with higher rates of recanalization, less early neurological deterioration and a better functional outcome, despite an increase ICH. Since aspirin is cheap, widely available and safe in acute ischaemic stroke, it could be an appropriate add-on therapy for current IVT treatment. There have been no clinical studies investigating the incremental effect of aspirin in conjunction with IVT.

Another strategy to optimize the efficacy of IVT is to reduce treatment delays. From a pooled analysis of IVT trials it has been shown that the benefit of IVT is highly time-dependent. For recovering without disabilities, the number needed to treat is 4.5 when IVT is initiated within the first 1.5 hours after the onset of symptoms, and increases to 14.1 if IVT is started between 3 and 4.5 hours after onset. In addition, the risk of ICH increases as time progresses. It has been shown that for a 30-minutes faster acceleration of treatment, patients have a 8% greater odds of walking independently at discharge, and a 6% greater odds of being discharged to home instead of to an institution. Thus, time is brain. After hospital arrival, a diagnostic work-up is needed to exclude ICH and other contraindications for IVT. Streamlining these in-hospital processes and ensuring that decisions regarding IVT treatment are made swiftly are therefore important goals.

Hence, in a simplistic view, the key in improving outcome after IVT is to achieve highest possible recanalization rates while minimizing the risk of ICH and treatment delays. All before mentioned strategies are summarized according to their risk-benefit profiles in Figure 1.3.
AIM AND OUTLINES OF THIS THESIS

The aim of the present thesis is to investigate two strategies that intend to improve the effectiveness of IVT in acute ischaemic stroke.

The first part of this thesis focuses on antiplatelet therapy as add-on therapy for IVT. Chapter 2 reviews the rationale for combining IVT with antiplatelet therapy. This strategy is investigated in Chapter 3, where we describe the results of the Antiplatelet therapy in combination with Rt-PA Thrombolysis in Ischaemic Stroke (ARTIS) trial. In this multicenter randomised controlled trial, the effect of the addition of 300 mg aspirin to current IVT treatment on functional outcome is investigated in patients with acute ischaemic stroke. The extended trial protocol can be found in Appendix A. In Chapter 4, we explore the short-term effects of the addition of aspirin in a post-hoc analysis of the ARTIS trial.

In the second part of this thesis, we highlight the reduction of treatment delays. In Chapter 5, we present an intervention study aimed to initiate IVT within 30 minutes after patient’s hospital arrival. In this before-and-after study the effect of the implementation of a number of simple strategies to reduce the door-to-needle time is investigated in a single-centre cohort of consecutive IVT patients. In order to contribute to swift decision making, chapter 6 and 7 con-
tain two observational studies in subgroups of patients, in whom doubt about eligibility for IVT exists. Chapter 6 covers the incidence and safety IVT in patients with stroke mimics from an international cohort of patients treated with IVT. Chapter 7 focuses on the safety and outcome of IVT in patients with a dissection-related stroke, identified from a systemic literature search. Due to the initial time strain in acute stroke, there is a risk that patients with a final diagnosis other than stroke, or ‘stroke mimics’ are treated with IVT and thus exposed to the life-threatening complications of IVT. Finally, in Chapter 8, we review the main findings of this thesis and discuss future perspectives on acute stroke treatment.

REFERENCES