Optimizing thrombolysis in acute ischaemic stroke
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CHAPTER 8

SUMMARY AND GENERAL DISCUSSION
INTRODUCTION

With the introduction of intravenous thrombolysis (IVT) almost twenty years ago, acute ischaemic stroke has changed from a desperate condition into a treatable emergency. Despite its modest capacity to prevent poor outcome, IVT with alteplase (or recombinant tissue plasminogen activator, rt-PA) is still the only effective acute treatment so far. In daily care, however, only a small proportion of ischaemic stroke patients is actually treated with IVT. Considering the major burden of stroke for individuals and society, amplifying the benefits of acute stroke treatment is a clinical and research priority. This thesis describes two approaches that aim to optimize the yields of IVT in routine care: aspirin as add-on therapy for IVT and the reduction of treatment delays. After reviewing the effects of these strategies, we discuss future perspectives at the end of this chapter.

PART I: ANTIPLATELET THERAPY AND INTRAVENOUS THROMBOLYSIS

The rationale of acute stroke treatment is to restore reperfusion by recanalization of an occluded cerebral artery. Early recanalization is closely correlated to long-term clinical outcome. Since the overall recanalization rate with IVT is only 46%, add-on therapies might enhance this rate and thereby improve outcome. Given the time-sensitivity of IVT, these additional therapies must be readily available and easy to administer. In cardiology, the addition of aspirin to IVT substantially decreased mortality after myocardial infarction. This finding was explained by the prevention of early reocclusion after initial recanalization, attributed to concurrent platelet activation.

Animal studies investigating whether concomitant antiplatelet agents would enhance IVT in embolic stroke models are scarce. Two studies in the early 1990s found no effect of aspirin in addition to IVT on infarct volume or reperfusion, while it increased the incidence of cerebral haemorrhage. Other studies investigated the effect of antiplatelet therapy prior to IVT. Aspirin pre-treatment in rabbits treated with IVT reduced the ability of clot lysis. The researchers speculated that an aspirin-induced loss of endothelial prostacyclin production...
explained the clot lysis antagonism. In a murine stroke model, pre-treatment with aspirin had no effect on cerebral haemorrhage compared to IVT alone, whereas pre-treatment with cilostazol, a phosphodiesterase inhibitor, had a protective effect on cerebral haemorrhage. This effect was attributed to a reduced matrix metalloproteinase-9 activity, which suppressed the microvasculature disruption.

Chapter 2 summarizes the rationale for the combination of antiplatelet therapy and IVT from a clinical perspective. Transcranial Doppler (TCD) studies demonstrated that early reocclusion occurred in 14–34% of the patients treated with IVT, and that reocclusion was predictive of early neurological deterioration and poor outcome. Observational studies reported less early neurological deterioration and a better outcome in patients using aspirin prior to IVT, despite an increased risk of symptomatic intracranial haemorrhage (SICH). The Multicenter Acute Stroke Trial-Italy investigated aspirin and IVT with streptokinase in a 2x2 factorial design. Streptokinase was associated with higher early mortality rates, mainly due to haemorrhagic transformation of cerebral infarctions, with the highest risk for patients who additionally received aspirin. However, of the survivors in this combination group, the proportion of patients with a favourable outcome, defined as a modified Rankin scale (mRs) score of 0–2, was 65% compared to 53% in the streptokinase only group. Since the commonly used alteplase is associated with less SICH compared to streptokinase, it was expected that the compensatory antithrombotic effect of aspirin would outweigh the small increase of SICH. We therefore hypothesized that the immediate addition of aspirin to alteplase would be beneficial in patients with ischaemic stroke.

Chapter 3 contains the results of a multicenter randomised open-label trial that investigated the effect of 300 mg aspirin within 90 minutes after IVT in antiplatelet-naïve ischaemic stroke patients. Primary endpoint of the Antiplatelet therapy in combination with Rt-PA thrombolysis in Ischaemic Stroke (ARTIS) trial was a favourable outcome, defined as mRs score of 0–2 at 3 months follow-up. After enrolling 642 patients (322 aspirin, 320 standard treatment), the trial was prematurely stopped by the Data Safety Monitoring Board because of an increased SICH rate in the aspirin group, without any prospect of a beneficial
effect on the primary endpoint. Fourteen (4.3%) patients in the aspirin group compared to five patients (1.6%) in the standard treatment group had a SICH (relative risk [RR] 2.78, 95% confidence interval [CI] 1.01–7.63). The decision to stop the trial was based on a small number of patients, and the SICH rate was low in both the aspirin and the standard treatment group compared to reported rates of 2.4–8.9% in other randomised IVT trials. Nevertheless, the reported SICH were considered clinically relevant as SICH was more often the cause of poor outcome in the aspirin group compared to the standard treatment group (11 versus 1 patients, p<0.01). At 3 months, 174 (54.0%) patients in the aspirin group versus 183 (57.2%) patients in the standard treatment group had a favourable outcome (RR 0.94, 95% CI 0.82–1.09). Although the premature termination of the trial has reduced the precision of the primary endpoint, the observed trend of a worse outcome in the aspirin group makes a missed beneficial effect highly unlikely. These results demonstrate that the addition of aspirin in the acute phase cannot be recommended and support the current guidelines that advise to start antiplatelet therapy 24 hours after IVT.

The lack of effect of aspirin on the primary outcome of ARTIS can be interpreted in two ways: either the trial was based on a fundamentally incorrect hypothesis, or aspirin has an antithrombotic effect which has not been detected in a long-term follow-up endpoint. Early neurological deterioration (END) is recognized as an expression of progressive ischaemic stroke and stroke recurrence, besides SICH, and occurred less likely while on aspirin. From this point of view, chapter 4 contains a post hoc analysis of the ARTIS trial to explore the effect of aspirin in the acute phase. END was defined as a worsening of ≥4 points on the National Institutes of Health Stroke Scale (NIHSS) within 24 hours after IVT and was classified as due to SICH (END\textsubscript{SICH}) or due to cerebral ischaemia (END\textsubscript{CI}). Of the per-protocol population of 613 patients (290 aspirin, 325 standard treatment), 31 patients (5.1%) experienced END (14 END\textsubscript{SICH}; 17 END\textsubscript{CI}). In the univariate analysis, aspirin increased the risk of END\textsubscript{SICH} (OR 4.20, 95% CI 1.16–15.24) but not of END\textsubscript{CI} (OR 1.02, 95% CI 0.39–2.68). After adjustment for other explanatory variables of SICH in a multinomial model, aspirin remained significantly associated with END\textsubscript{SICH} (OR 6.00, 95% CI 1.17–30.74), without an effect on
ENDCI (OR 0.86, 95% CI 0.27–2.73). Besides the association with \( \text{END}_{\text{SICH}} \), there was no evidence of early benefit from the addition of aspirin from this post-hoc analysis. These findings do not support the hypothesis that addition of aspirin to IVT enhances recanalization.

ARTIS was the first clinical trial investigating the addition of aspirin to IVT in ischaemic stroke. One other antiplatelet agent has been investigated as add-on therapy for IVT. In a randomised phase II trial, the glycoprotein IIb/IIa inhibitor eptifibatide in combination with low-dose alteplase was compared with standard treatment of full-dose alteplase. Although SICH was not increased in patients treated with the combination of eptifibatide and alteplase, there was a trend towards a worse outcome in the combination group, which was explained by the low dosage of alteplase used. When eptifibatide was added to a higher dose of alteplase in a larger follow-up study, there was trend towards a better outcome in the combination group compared to standard treatment group. These results have to be interpreted with caution since this study was designed for safety and used an unequal treatment allocation. A phase II trial investigating eptifibatide in combination with a full-dose of alteplase is currently ongoing.

After the commencement of the ARTIS trial more clinical data has become available that focus on antiplatelet therapy prior to IVT in acute ischaemic stroke. Two TCD studies investigated the relation between prior use of antiplatelet drugs and vessel patency after IVT. In a retrospective analysis of 284 patients treated with IVT by Ibrahim and co-workers, complete recanalization was observed less frequently in patients on aspirin compared patients with no previous antiplatelet therapy: 16 (22%) versus 68 (39%) patients (\( p=0.02 \)). There was no difference in rates of reocclusion and SICH between the groups. Patients with antiplatelet therapy had less often a favourable outcome (39% versus 53%), whereas after adjustment, no correlation between antiplatelet use and outcome was found. Contrary to these findings, a smaller study of 146 consecutive patients treated with IVT demonstrated that partial or complete recanalization occurred more often in patients with prior antiplatelet therapy than in antiplatelet-naïve patients: 30 (54%) versus 28 patients (30%), and the association remained significant after adjustment. Although these conflicting results can be partially explained by
TCD assessment at varying points in time and the use of different recanalization scales, the effect of aspirin on vessel patency remains uncertain. Larger, prospective studies are needed to determine the effect of aspirin and other antiplatelet agents on vessel status.

Additional clinical data on the association between prior antiplatelet therapy and IVT originates from randomised trials and observational registries. Meta-analyses found around a doubling of the odds for SICH from use of any antiplatelet agent before IVT. Dual antiplatelet treatment, in particular the combination of aspirin and clopidogrel, has a higher risk of SICH compared to monotherapy. Despite this risk, prior antiplatelet therapy does not negatively affect the net clinical benefits of IVT. None of the studies in a recent review and meta-analysis found that prior antiplatelet therapy was associated with a poor outcome. The previous observed association with favourable outcome was however not confirmed by other studies. Nevertheless, patients on antiplatelet therapy still benefit from IVT when their outcome is compared to patients on antiplatelet therapy not treated with IVT. Prior use antiplatelet therapy should therefore not be a contraindication for IVT.

PART II: REDUCING TREATMENT DELAYS

As the benefits of IVT rapidly decrease as time progresses, the most efficient way to improve the efficacy of IVT is to avoid unnecessary treatment delay. This thesis has translated the concept of ‘time is brain’ into three strategies that might contribute to a rapid start of treatment after hospital arrival. First, in chapter 5, we show that an important reduction of the in-hospital delay can be achieved by the implementation of a multidisciplinary stroke protocol based on pre-notification, collective stroke team warning and streamlining of in-hospital procedures. In this single centre before-and-after study, the median door-to-needle time (DNT) decreased from 75 minutes in the pre-intervention period (100 patients) to 28 minutes in the post-intervention period (373 patients, p<0.001.) As a consequence of the reduced DNT, patients were treated sooner after symptom onset (158 versus 105 minutes, p<0.001). The proportion of patients with a
favourable outcome, defined as a mRs of 0–2, increased from 38.9% to 52.3% (OR 1.72, 95% CI 1.09–2.73), while SICH and mortality rates were not different between the two periods.

Comparable multifaceted intervention protocols have been described, with DNTs varying between 20 and 74 minutes.\textsuperscript{37-42} The lowest DNT is reported in Helsinki, where in the final year a median DNT of 20 minutes was achieved by “doing as much as possible before the patient has arrived while doing as little as possible after the patient has arrived at the hospital”.\textsuperscript{40} The large-scale Get With the Guidelines registry containing data of 71,169 patients treated with IVT from 1030 US hospitals showed that the achieved 10-minutes reduction of the DNT from 77 to 67 minutes resulted in a lower in-hospital mortality and an improved functional status at discharge.\textsuperscript{37} Functional outcome at 3 months was lacking in all but one small study, which showed no difference after reduction of the DNT.\textsuperscript{38} However, all these studies including ours are limited by a before-and-after design, not excluding the influence of external factors such as the extension of time window for IVT to 4.5 hours in 2008, or the change in study population over time.

Besides treating patients earlier when IVT is more beneficial, rapid treatment can also increase the absolute number of patients treated with IVT in the highly undertreated stroke population. We have shown that the annual number of IVT treated patients has increased from a median 17 to 55 patients in our hospital, although data on acute ischaemic stroke referrals in the pre-intervention period was unavailable precluding rate calculations. Other studies found an absolute increase of IVT rates between 2.7% and 7.8% after a comparable intervention.\textsuperscript{37,38,41} Notwithstanding these advances, treatment within a few hours will remain a challenge in clinical practice, since arrival in the hospital outside the time window remains the main reason to withhold IVT.\textsuperscript{43,44}

A potential drawback of cutting treatment delays is the limitation of initial diagnostic work-up in suspected stroke, while conditions that mimic acute ischaemic stroke are common. The concern of insufficient assessment and therefore a greater chance of complications is not be supported by our findings, but the number of patients who finally turned out to have an alternate diagnosis than
stroke increased from 0 (0.0%) to 14 (3.5%, p=0.05). Thus, the need for speed has be to balanced against the need for diagnostic accuracy. Therefore, as a second strategy that can contribute to rapid treatment initiation, chapter 6 investigates the safety of IVT in patients with a stroke mimic. From an international database containing 5518 patients treated with IVT, 100 patients (1.8%, 95% CI 1.5–2.2) with a stroke mimic were retrospectively identified. Compared to patients with a final diagnosis of ischaemic stroke, patients with a stroke mimic were younger, more often female, and had less cardiovascular comorbidities except smoking and a history of ischaemic stroke or transient ischaemic attack. The proportion of SICH in patients with a stroke mimic was 1.0% (95% CI 0.0–5.0) compared to 5.5% (95% CI 4.9–6.1) in true stroke patients, and mortality was 2.1% (95% CI 0.3–7.3) in patients with a stroke mimic versus 14.4% (95% CI 13.4–15.3) in true stroke patients. Consistent with these findings, other studies, identified through a systematic literature review, univocally suggested that IVT in stroke mimics was safe as well. The incidence of 1.8% in our series, which is the largest to date, was in the lower range of 1.4–15.5% reported by these studies. It has been suggested that incorporating diffusion-weighted magnetic resonance imaging (MRI) criteria into the definition of a stroke mimic could identify additional cases because a negative MRI would raise the suspicion of a stroke mimic. On the contrary, MRI has a false-negative rate of 17% (and 27% for patients presenting within 3 hours of symptom onset) leading to an overestimation of the proportion of stroke mimics. Moreover, using a clinical definition of a stroke mimic has increased the external validity of our study since in many hospitals a noncontrast computed tomography scan is the only imaging modality directly available. The results of our study support the idea that the benefit of rapid treatment in patients with acute stroke symptoms likely outweighs the risk of IVT-related complications. Nevertheless, we should keep in mind that the rate of stroke mimics among patients treated with IVT should be as low as possible. Prospective studies are therefore warranted to identify and validate prognostic variables in order to distinguish stroke mimics from true strokes in the acute phase.

In chapter 5 we have also shown that uncertainty about eligibility of IVT was the main contributor to a DNT exceeding 30 minutes. Therefore, determination
of the effect of IVT in subgroups of stroke patients in whom eligibility is uncertain is a third strategy that can contribute to a rapid treatment decision. In chapter 7, we focus on the safety of thrombolysis in patients with a stroke due to carotid artery dissection (CAD). Besides the risk of SICH, thrombolysis may cause expansion of the intramural haematoma leading to distal embolization or vessel occlusion. Through a systematic review of the literature, we identified 180 patients with a CAD-related stroke treated with thrombolysis (121 IVT, 59 intra-arterial thrombolysis), described in 14 case series and 22 case reports. From an individual patient data analysis, the pooled SICH rate was 3.1% (95% CI 1.3–7.2) and mortality was 8.1% (95% CI 4.9–13.2). At a median follow-up period of 3 months, 41.0% (95% CI 31.4–51.4) had an excellent outcome (mRs 0–1). There were no differences for the subgroup treated with IVT, and the results were similar to matched controls from the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register. Since this meta-analysis was based solely on retrospective, uncontrolled series and case reports, there is a risk of publication bias leading to an underestimation of the true risks. Although excluding the case reports did not change our findings, this bias might still have influenced the results. Taking this limitation into account, it can be concluded that IVT should not be withheld in the dissection-related stroke, thereby avoiding the need for more advanced imaging before the start of IVT.

However, although IVT does not seem to harm patients with a dissection-related stroke, the net clinical benefit is still uncertain as randomised trials in this subgroup of stroke patients are lacking. After completion of our meta-analysis, a few more studies have been published that provide further insight into the efficacy of thrombolysis in dissection-related stroke. In contrast to our findings, these studies found a worse recovery after thrombolysis (mainly IVT) in stroke due to CAD compared to stroke of other aetiologies. In addition, there appears to be a lack of benefit from thrombolysis (mainly IVT) when disability and mortality rates were compared to patients with a CAD who were not treated with thrombolysis. This can be explained by the high frequency of vessel occlusion in dissection-related stroke, including tandem occlusion of the carotid and middle cerebral artery. Clot localization is one of the factors that affects recan-
alization rates after IVT, with proximal sites of occlusion being more resistant to IVT than distal sites and associated with higher disability rates. In dissection-related stroke with a proximal occlusion and no response to IVT, thrombectomy by an endovascular procedure can be considered.

FUTURE PERSPECTIVES

Endovascular treatment
Analogous to the development of acute treatment for myocardial infarction, numerous endovascular techniques have been described for acute ischaemic stroke. These endovascular techniques comprise local administration of a thrombolytic drugs (intra-arterial thrombolysis) or mechanical recanalization by means of balloon angioplasty, stent placement or clot retrieval (Figure 8.1). Compared to a recanalization rate of 46% for IVT, endovascular treatment achieves recanalization in 63–84%.

In 2013, results of three randomised trials investigating endovascular treatment in acute ischaemic stroke were published. Contrary to the expectations of the medical field, all these trials failed to show superiority of (adjunctive) endovascular treatment over IVT (alone). However, these studies were limited by several factors, including the lack of confirmation of large vessel occlusion before randomisation and wide use of Merci retrievers for mechanical revascularization. Current stent retrievers, which temporarily restore blood flow and capture the thrombus, have been shown to achieve higher recanalization rates associated with better outcome compared to the Merci retrievers. Another concern regarding the relevance of these trials was the significant delay between the onset of symptoms and initiation of treatment when the odds for recovery have already been reduced. This delay reflects the complex logistics needed to transfer the patient to a stroke centre and to mobilize the interventional team. Nevertheless, these trials confirmed once more the relationship between early recanalization and favourable clinical outcome. Additional trials are needed that overcome the above mentioned limitations. Recently, the Multicenter Randomised Clinical trial of Endovascular treatment for Acute ischaemic stroke in the Netherlands
**Summary and general discussion**

(MR CLEAN) finished enrolment after inclusion of 500 patients with an anterior circulation stroke. In this study (adjunctive) endovascular therapy was compared with standard IVT treatment and results are expected in October 2014. The current BASilar artery International Cooperation (BASICS) study investigates the effect of additional endovascular treatment after IVT within 6 hours after symptom onset in patients with basilar artery occlusion. Both studies require confirmation of large-vessel occlusion before randomisation, and stent retrievers are widely used. Hopefully, these results will contribute to a proper selection of patients who would benefit from an (adjunctive) endovascular intervention. As a prerequisite for successful endovascular treatment, each intervention centre

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**Figure 8.1:** Different approaches of endovascular treatment in stroke due to large vessel occlusion. Adapted with permission from JNS Publishing group, Neurosurg Focus 2014;36:E5: doi:10.3171/2013.10.FOCUS13374.
should come to an agreement with regional hospitals on logistic procedures in order to treat patients within an appropriate time window.

New thrombolytic agents
Awaiting the results of these and future intervention trials, IVT is currently the mainstay of acute stroke treatment. Considering the poor recanalization rates and risk of SICH associated with alteplase, there is a high need for thrombolytic agents with a better risk-benefit profile. Third generations thrombolytic agents have a greater fibrin specificity and therefore potentially a lower risk of SICH. Among these, tenecteplase was superior to alteplase on recanalization and clinical endpoints in a phase IIb study,\textsuperscript{66} and is currently investigated in a phase III trial.\textsuperscript{67} Desmoteplase, also a third generation agent, has been investigated in two dose-escalation studies and one phase III trial.\textsuperscript{68-70} In the latter, safety was confirmed without efficacy, while a post-hoc analysis showed that in patients with a high-grade stenosis or occlusion, desmoteplase improved favourable outcome at 3 months.\textsuperscript{71} Currently, a placebo controlled trial is randomising patients with a high-grade stenosis or occlusion within 3–9 hours of symptom onset.\textsuperscript{72}

Centralization and ambulance-based thrombolysis
In the Netherlands, most hospital are equipped to perform IVT. However, there is an ongoing debate for concentration of acute stroke treatment in designated stroke centres as hospitals with higher volumes of thrombolysis of IVT activity are considered to have shorter treatment delays.\textsuperscript{73} On the other hand, patients may have to travel further when IVT facilities are restricted to a few stroke centres only. In addition, with its ease of use without the need for advanced imaging, IVT treatment does not necessarily have to be restricted to these stroke centres. For example, IVT has been shown be safe in less experienced centers.\textsuperscript{74,75} In a study that compared a centralized model to a decentralized model in two regions in the northern part of the Netherlands, the DNT was shorter in a centralized model but onset-to-treatment times were similar.\textsuperscript{76} Instead of using IVT volume as selection criterion, distances between hospitals in the region and DNTs should be taken into account for deciding which hospitals are allowed to perform IVT.
Besides cutting in-hospital delays, reduction of the time before arrival is another important objective to improve the benefits of time-dependent IVT. Especially in rural areas with long distances to the nearest hospital with IVT facilities, a promising strategy is treatment at the emergency site by using a specialized ambulance equipped with a small CT scanner and point-of-care laboratory. This approach has been investigated in a small randomised trial of 100 acute stroke patients. The alarm-to-treatment decision time was 35 minutes in the ambulance group compared to 76 minutes in the hospital group. In a larger randomised study of 518 patients treated with IVT, ambulance-based IVT reduced in the alarm-to-treatment time from 77 to 52 minutes without an increase of adverse events. While this policy is promising, the optimal setting and the cost-effectiveness of on-site IVT have to be investigated before this concept can be implemented in clinical practice. In particular, whether the stroke physician can be replaced by a telemedicine connection to the stroke centre to reduce costs needs further investigation.

CONCLUSION

IVT is the mainstay of acute stroke treatment while there is an ongoing need for further optimization of the risk-benefit ratio of IVT with a central role for reducing treatment delays. The addition of aspirin does not contribute to the benefits of IVT. Future research will show whether more fibrin-selective thrombolytic agents will improve outcome after IVT. Adjunctive endovascular treatment combines the advantages of a rapid treatment of IVT with a higher likelihood of recanalization by an endovascular intervention and might be beneficial in patients with persistent proximal occlusion after IVT. A streamlined chain between emergency site and angiography suite is a prerequisite as time is the most important determinant of successful acute stroke treatment.
REFERENCES


34. Diener HC, Foerch C, Riess H, Rother J, Schroth G, Weber R. Treatment of acute ischaemic stroke with thromboly-


49. Saver JL, Barsan WG. Swift or sure?: The acceptable rate of neurovascular mimics among IV tPA-treated patients. *Neurology* 2010;74:1336–1337.


55. Saqqur M, Uchino K, Demchuk AM, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to in-


73. Zorgverzekeraars Nederland. Kwaliteits-


