Thrombolytic therapy for ischemic stroke—A review. Part II—Intra-arterial thrombolysis, vertebrobasilar stroke, phase IV trials, and stroke imaging

Peter D. Schellinger, MD; Jochen B. Fiebach, MD; Alexander Mohr, MD; Peter A. Ringleb, MD; Olav Jansen, MD; Werner Hacke, MD, PhD

Objective: Intra-arterial thrombolytic therapy for carotid and vertebrobasilar stroke may result in a more rapid clot lysis and higher recanalization rates than can be achieved with intravenous thrombolysis and thus may warrant the more invasive and time-consuming therapeutic approach. We present an overview of all hitherto completed trials of intra-arterial thrombolytic therapy for carotid and vertebrobasilar artery stroke including recommendations for therapy and a meta-analysis. Furthermore, new imaging techniques such as diffusion- and perfusion-weighted magnetic resonance imaging and their impact on patient selection are discussed. Finally, phase IV trials of thrombolysis in general and cost efficacy analyses are presented.

Data Sources: We performed an extensive literature search not only to identify the larger and well-known randomized trials but also to identify smaller pilot studies and case series. Trials included in this review, among others, are the PROACT I and PROACT II studies and the Cochrane Library report.

Conclusion: Intra-arterial thrombolytic therapy of acute M1 and M2 occlusions with 9 mg/2 hrs pro-urokinase significantly improves outcome if administered within 6 hrs after stroke onset. Seven patients need to be treated to prevent one patient from death or dependence. Vertebrobasilar occlusion has a grim prognosis and intra-arterial thrombolytic therapy to date is the only life-saving therapy that has demonstrated benefit with regard to mortality and outcome, albeit not in a randomized trial. New magnetic resonance imaging techniques may facilitate and improve the selection of patients for thrombolytic therapy. Presently, thrombolytic therapy is still underutilized because of problems with clinical and time criteria, and lack of public and professional education to regard stroke as a treatable emergency. If applied more widely, thrombolytic therapy may result in profound cost savings in health care and reduction of long-term disability of stroke patients. (Crit Care Med 2001; 29:1819–1825)

Key Words: thrombolysis; ischemic stroke; review; intra-arterial lysis; intravenous lysis; vertebrobasilar stroke; diagnostic imaging; diffusion magnetic resonance imaging; perfusion magnetic resonance imaging; computed tomography

Stroke is the third most common cause of death in the industrialized nations, after myocardial infarction and cancer, and the single most common reason for permanent disability (1). Up to 85% of all strokes are of ischemic origin and most are the result of blockage of a cerebral artery by a blood clot (2). Occlusion of a brain vessel leads to a critical reduction in cerebral perfusion and, within minutes, to ischemic infarction (see also Part I of this review). Therefore, the underlying rationale for the introduction and application of thrombolytic agents is the lysis of an obliterating thrombus and subsequent reestablishment of cerebral blood flow by cerebrovascular recanalization (3). The delivery of thrombolytic agents locally, at or within the occluding thrombus, has the advantage of providing a higher concentration of the particular thrombolytic agent where it is needed while minimizing the concentration systemically. Hence, local intra-arterial thrombolysis has the potential for greater efficacy with regard to arterial recanalization rates and greater safety with regard to lower risk of hemorrhage. The technique involves performing a cerebral arteriogram, localizing the occluding clot, navigating a microcatheter to the site of the clot, and administering the lytic agent at or inside the clot with or without mechanical dissolution of the thrombus. Grade of vessel occlusion is usually assessed with the Thrombolysis in Myocardial Infarction (TIMI) score, where TIMI 0 is complete occlusion, TIMI 1 minimal perfusion, TIMI 2 partial flow (recanalization), and TIMI 3 complete flow (recanalization) (4). The agents most commonly used or which are under investigation are urokinase, recombinant tissue plasminogen activator (rt-PA; alteplase), and pro-urokinase, all of which are usually administered at a lower dose than used in the intravenous treatment of acute ischemic stroke.

Early trials of intra-arterial thrombolysis for acute ischemic stroke

Results of several case series on local thrombolysis in the carotid artery territory have been promising, although not convincing (5–19). For recombinant rt-PA (rt-PA), doses ranged between 10 and 80 mg; for urokinase, doses usually ranged up to 1.5 million units. Time from symptom onset to treatment in the smaller series has been for the most part within 6 hrs, but not within 3 hrs or even 4 hrs of symptom onset with regard to the mean or median. The reported complete or partial recanaliza-
zation rates vary substantially between <50% (11) and >90% (16, 19). When combining the results of these case series, complete clot lysis is reported for 67 of 174 patients (39%). Partial clot lysis with partial recanalization is reported for 62 of the same 174 patients (36%). The combined partial or complete recanalization rate for these patients was 75%, clearly higher than that demonstrated in the angiography-based intravenous studies (approximately 55%). Each of these intra-arterial case series differs from all of the others with regard to thrombolytic agent, baseline neurologic deficit, angiographic anatomy, time-to-treatment, outcome, and method of neurologic evaluation at follow-up. Accordingly, conclusions regarding efficacy are not possible. The most feared complication of local intra-arterial therapy for stroke, as for intravenous thrombolytic therapy, is intracranial hemorrhage (ICH). Symptomatic ICH based on the case series is estimated to be 4%, which is lower than that reported for any intravenous thrombolysis series. However, this rate is also lower than that reported in the Prolyse in Acute Cerebral Thromboembolism (PROACT) I and II trials, in which 24-hr computed tomography (CT) scans were performed on all patients. Other complications of intra-arterial thrombolysis include arterial intracranial embolization, subarachnoid hemorrhage, arterial perforation, secondary embolization, hemorrhagic infarction, groin hematoma, and retroperitoneal hematoma. These complications occur infrequently, certainly in <5% for all the series in toto. One drawback of intra-arterial contrast to intravenous thrombolysis is the considerable time delay to angiography, and from initiation of angiography to clot lysis (5, 6, 19). There are only a few data at present to support the combined use of intravenous and intra-arterial thrombolysis with rt-PA (19a). Usually, 0.6 mg/kg with a 10% to 20% bolus and continuous infusion up to a maximum of 60 mg rt-PA are administered; when angiography is started, the infusion is stopped. The rest of the dose up to 90 mg maximum is given intra-arterially. The underlying rationale for this approach is the reduction of any delay for thrombolysis, while still having the higher recanalization rate and proven larger time window for therapy with the intra-arterial approach. However, this protocol should at present be limited to further clinical investigations and cannot be recommended as a routine procedure.

**PROACT I**

PROACT I was a randomized phase II trial of recombinant pro-urokinase (rpro-UK) vs. placebo in patients with angiographically documented proximal middle cerebral artery occlusion (20). Angiography was performed after exclusion of ICH by CT. Patients displaying TIMI grade 0 or 1 occlusion of the M1 or M2 middle cerebral artery were randomized 2:1 to receive rpro-UK (6 mg) or placebo over 120 mins into the proximal thrombus face. Recanalization efficacy was assessed at the end of the 2-hr infusion and symptomatic ICH at 24 hrs. A total of 105 patients underwent angiography; 65 of these (no occlusion [n = 25], no M1 or M2 occlusion [n = 36], time interval >6 hours [n = 2], complications [n = 2]) were excluded from randomization. Among the 40 treated patients, 26 received rpro-UK and 14 placebo at a median of 5.5 hrs from symptom onset. Recanalization was significantly associated with rpro-UK (p = .0085) and TIMI 3 recanalization was achieved in five rpro-UK patients, as opposed to none of the placebo patients. ICH occurred in 15.4% of the rpro-UK–treated patients and 7.1% of the placebo-treated patients (nonsignificant); all patients with rpro-UK and early CT signs of >33% suffered ICH. In patients who received high-dose adjuvant heparin, the recanalization rate was 81.8%; in the low-dose heparin group (dose was lowered for reasons of safety by the safety committee) it was 40% (p = .0255). Mortality was lower in the rpro-UK group, albeit not significantly.

**PROACT II**

PROACT II, a randomized, controlled, multicenter, open-label clinical trial with blinded follow-up, aimed to determine the clinical efficacy and safety of intra-arterial rpro-UK in patients with acute stroke of <6 hrs’ duration caused by middle cerebral artery (MCA) occlusion (21). Eligible patients had new focal neurologic signs attributable to the MCA territory, allowing initiation of treatment within 6 hrs after symptom onset, a minimum National Institutes of Health Stroke Scale (NIHSS) score of 4 points, and exclusion of ICH on CT. Patients with these criteria underwent angiography and were randomized (2:1) to either treatment with 9 mg rpro-UK/2 hrs plus the PROACT I lower dose of heparin (2000 IU bolus, 500 IU/hour continuous infusion) or heparin alone. Mechanical disruption of the clot was not permitted. After 1 hr (4.5 mg rpro-UK), a control angiogram was performed and, if the clot had partially or even completely dissolved, the rest of the rpro-UK dose was administered. The primary outcome was the rate of patients with a modified Rankin scale (MRS) of ≤2 at 90 days. Secondary outcomes included MCA recanalization (TIMI 2 and 3), the frequency of symptomatic ICH, and mortality. Of 12,323 patients screened in 54 centers, only 474 (4%) underwent angiography at a median of 4.5 hrs after stroke onset. 294 of which demonstrated angiographic exclusion criteria, leaving 121 rpro-UK and 59 control patients with a median baseline NIHSS of 17 points for intention to treat (ITT) analysis. Forty percent of rpro-UK patients and 25% of control patients had a MRS of ≤2 (absolute benefit 15%, relative benefit 58%, number needed to treat = 7; p = .04). Mortality was 25% for the rpro-UK group and 27% for the control group (p = .8). The recanalization rate was 66% for the rpro-UK group and 18% for the control group (p < .001); TIMI 3 recanalization rates were 19% and 2%, respectively (p < .003). All other secondary outcomes were nonsignificant. Early ICH occurred in 35% vs. 13% of patients (p = .003); at 10 days the rates were 68% and 57% (p = .23). Early symptomatic ICH occurred only in patients with NIHSS scores >11 within 24 hrs in 10.2% of rpro-UK patients and 2% of control patients (number needed to harm = 12; p = .06).

The results of PROACT II did not suffice for Food and Drug Administration approval. Another study of intra-arterial pro-urokinase for acute stroke within 6 hrs has been initiated (PROACT III) (Anthony Furlau, personal communication).

**RECOMMENDATIONS FOR INTRA-ARTERIAL THROMBOLYSIS**

Intra-arterial thrombolytic therapy of acute M1 and M2 occlusion with 9 mg/2 hrs significantly improves outcome if administered within 6 hrs after stroke onset. Seven patients need to be treated in order to prevent one patient from death or dependence. The higher rate of symptomatic ICH (10.2% in PROACT II vs. 8.8% in European Cooperative Acute Stroke Study (ECASS II), 6.4% in National Institute of Neurologic Disorders
and Stroke [NINDS] and 7.2% in Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke [ATLANTIS]] is very well explained by the far larger baseline severity of stroke in PROACT II (NIHSS of 17 in PROACT II vs. 11 in ECASS II and ATLANTIS, and 14 in NINDS). According to the Cochrane meta-analysis, combining PROACT I and II data (34), there is a 0.55 odds ratio (OR) (confidence interval [CI] 0.31–1.00) for death or disability, an OR of 2.39 (CI 0.88–6.47) for early symptomatic ICH (7–10 days), and an OR of 0.75 (CI 0.4–1.42) for death from all causes at follow-up. Although recanalization rates may be superior with intra-arterial (66%) than with intravenous (=55%) thrombolysis and may even be increased by careful mechanical disruption of a thrombus, in addition to the lytic effect of the drug, a limited availability of centers with 24-hr-a-day, 7-days-a-week interventional neuroradiology service may restrict the use of this therapy. On the other hand, the clinically more severe strokes may benefit even more from an intra-arterial than an intravenous approach. Furthermore, the time to eventual recanalization may be substantially shorter with intra-arterial thrombolysis. Another intra-arterial pro-UK trial (PROACT III), which is partly stroke magnetic resonance imaging (MRI) based, to reduce the rate of screening angiography and optimize patient selection is underway.

THROMBOLYTIC THERAPY FOR VERTEBROBASILAR INFARCTION

Vertebral basilar distribution cerebral infarction has been of particular interest to centers experienced with local intra-arterial thrombolysis. Six large case series (19, 22–26) have been published since 1986. The great majority of the more than 120 patients treated were administered intra-arterial urokinase locally; a few patients were given rt-PA. Treatment was almost always delayed such that no patients were reported in these series as having been treated within 3 hrs of symptom onset. The median time from the beginning of treatment to the time of recanalization was reported to be 120 mins (19). For the total group, the complete or partial recanalization rate approximates 70%; in reality, the rate probably is somewhat lower, as partial or complete recanalization is usually not achieved in 100% of patients, as reported by Zeumer et al. (19). Mortality of vertebral basilar thromboembolism is high, with overall rates of approximately 70% to 80%. Successful recanalization, however, was associated with a survival rate of 55% to 75%, as opposed to 0% to 10% in persistent or untreated basilar artery occlusion (23, 25). Two thirds of the survivors after recanalization had a favorable outcome; all survivors in the untreated group were moderately disabled. Other authors reported an overall mortality of 75% in 13 patients, although ten of these had experienced recanalization (24), non-recanalization lead to death in all patients (n = 3). The authors concluded that recanalization of the vertebrobasilar system is necessary but not sufficient for effective treatment of vertebralbasilar occlusive disease (24). To address the potential risks and potential benefits of intra-arterial thrombolysis for vertebral basilar artery occlusion more fully, a randomized trial (The Australian Urokinase Stroke Trial) is planned but has not been started to date because of expected low recruitment numbers (27). Grond et al. (28) reported one small case series of 12 consecutive patients in whom they investigated whether early intravenous thrombolysis could also effectively be applied in acute vertebralbasilar ischemic stroke. Patients with clinically diagnosed moderate to severe vertebralbasilar ischemic stroke with clearly determined symptom onset were treated with intravenous rt-PA within 3 hrs after symptom onset, following a protocol similar to that of the NINDS study. On admission, seven patients exhibited moderate to severe brainstem symptoms without impairment of consciousness and five patients had impairment of consciousness, of whom two were comatose. Of 12 patients, 10 had a favorable outcome after 3 months, defined as full independence (Barthel index score of 100) or return to premorbid condition. One patient had a poor outcome with complete dependence resulting from stroke patients with angiographically proven MCA occlusion (38–41). More recent studies have reported incidences of early CT signs of infarction between 53% and 92% within the first 6 hrs for all acute stroke patients (32–34, 37, 38, 42). In patients with a M1-segment occlusion, the incidence of a parenchymal hypodensity is reported to be
with parenchymal hypodensity without hypodensity, 23% in patients brain hemorrhage (33). According to benefit but increased the risk for a fatal patients with a large area of hypodensity (<33% of the MCA territory), treatment increased the chance of a good clinical outcome, whereas rt-PA in patients with a large area of hypodensity (>33% of the MCA territory) had no benefit but increased the risk for a fatal brain hemorrhage (33). According to ECASS I, mortality was 13% in patients without hypodensity, 23% in patients with parenchymal hypodensity <33% of the MCA territory, and 49% in patients with an early hypodensity exceeding 33% of the MCA territory (44). Although several studies have shown the usefulness of early CT findings in selecting patients before intravenous thrombolytic therapy, other studies demonstrated that physicians, including general radiologists and neurologists, do not uniformly achieve a sufficient level of sensitivity for identifying CT contraindications for thrombolytic therapy (45). However, radiologists can be trained to recognize early infarct signs on CT and the positive effect of being trained to read CT scans of hyperacute stroke patients has recently been demonstrated in a large trial (34). CTA can provide additional information on stenoses or occlusions in the basal arteries of the brain (46), as nonionic contrast material does not affect infarction volume or worsen the symptoms of cerebral ischemia (47). In addition to the assessment of a major vessel occlusion, CTA has the potential to deliver information about the quality of the collateral circulation as contrast enhancement in arterial branches beyond the occlusion occurs in those patients (46, 48). Volume CT scanners may produce images that can be used to construct functional maps of cerebral blood volume, cerebral blood flow, or time to peak enhancement, utilizing a first-pass curve of a contrast bolus (49). In a recent study, perfusion CT was performed within 6 hrs of symptom onset in 32 patients with acute stroke symptoms and showed a good correspondence in 81% of the patients with single photon emission computed tomography (SPECT) (50). However, at present only one slice and not images of the whole brain can be obtained.

The need for an all-around diagnostic tool with which all the important pathophysiologic aspects of hyperacute stroke can be investigated is evident. Such a method must answer five decisive questions: 1) Where and how large is the actual area of irreversible ischemic brain damage? 2) How old is the infarction? 3) Is there tissue at risk and how much tissue is at risk? 4) Is there a vessel occlusion and where is it? 5) Is an ICH or another underlying, nonischemic disease present? Presently, the decision to initiate intravenous rt-PA treatment is based on clinical findings and CT scanning. The reported diagnostic yield of CT within 3 hrs after symptom onset does not adequately meet these criteria (51). The advent of new MRI techniques such as perfusion- (PWI) and diffusion- (DWI) weighted imaging has revolutionized diagnostic imaging in stroke (52–57). DWI may delineate infarcted brain tissue in <1 hr after symptom onset, probably within minutes (58), although there is cumulating evidence that in the very early stage of stroke there may be reversible DWI changes (59, 60), whereas PWI defines the area of cerebral hypoperfusion. The absolute volume difference or ratio of PWI and DWI reveals the ischemic tissue potentially at risk of irreversible infarction (61, 62). MRA can reliably assess the cerebral vessel status (63). Stroke MRI further allows a definitive diagnosis of ICH within the first hours of stroke (64–66) and possibly also that of subarachnoid hemorrhage (67). Several studies have reported early findings of stroke MRI within the first 6–12 hrs, demonstrating the feasibility and practicability of this method in the setting of acute stroke and thrombolytic therapy (53, 56, 61, 68–72). In essence, the presence of a vessel occlusion according to magnetic resonance angiography is associated with a PWI/DWI mismatch, the stroke MRI setting that defines the ideal candidate for thrombolysis (70, 73). In addition, there are five studies that clearly demonstrate that early recanalization achieved by thrombolysis results in significantly smaller infarcts and a significantly better clinical outcome (60, 61, 70, 72, 74). Although presently limited by a low availability, the utility of stroke MRI is likely to lie in the early identification of those patients in whom outcome and final infarct size, ultimately the patient’s fate, have not yet been determined. Furthermore, cost effectiveness is likely as there is no need for CT or Doppler ultrasound in the hyperacute stage of stroke. With an increasing distribution and “around the clock” availability of stroke MRI, the identification of patients more suitable for thrombolytic therapy, and those who are not, may lead to an increased benefit and a reduction in complications in patients receiving thrombolytic therapy (70). Furthermore, the rather strictly defined therapeutic window may be qualified and individualized according to the findings in each individual patient.

PHASE IV TRIALS OF INTRAVENOUS THROMBOLYSIS AND COST ASPECTS

There are no phase IV trials of intraarterial thrombolysis. After Food and Drug Administration approval of rt-PA for intravenous thrombolytic therapy in June 1996, the rate of thrombolysis remained fairly constant until the end of 1998 (75). At most centers where thrombolysis is performed, the NINDS protocol is used; many of these centers also use the ECASS-CT criteria of early infarction. Overall it is estimated that 1% of all ischemic stroke patients and 2% of the time-eligible patients (3-hr window) are treated with rt-PA—a rather low rate. Also, the reported outcome and complication rates seem to be similar to the NINDS trial in most instances. In Cologne, approximately 22% of the patients who arrive within 3 hrs after symptom onset (5% of all ischemic stroke patients) receive thrombolysis (76). This rate was achieved after a cooperation between emergency caregivers, internists, and neurologists was initiated and the referral system optimized. The average door-to-needle-time in Cologne is 48 mins. The rates of total, symptomatic, and fatal ICH were 11%, 5%, and 1%, respectively. Of these patients, 53% recovered to a fully independent functional state. Recently, the same group published their data on long-term follow-up after thrombolytic therapy, where 150 patients treated within 3 hrs were reevaluated after 12 months (77). After 12 months, 41% of the patients had an MRS score of ≤1 and 52% of ≤2. The stroke recurrence rate (6.6%/year, transient ischemic attack 3.3%/year) was consistent with that of population-based studies (78). These results are nearly identical to the late follow-up outcome analysis published by
Kwiatkowski et al. (79) in 1999. In Houston, 30 patients were treated prospectively after the NINDS protocol (80). Six percent of all patients hospitalized with ischemic stroke received intravenous rt-PA at the university hospital and 1.1% at the community hospitals. The respective rates of total, symptomatic, and fatal ICH were 10%, 7%, and 3%, and 37% of patients recovered to fully independent function. The average door-to-needle-time was 1 hr and 40 mins.

Two very recent studies presented divergent results: Albers et al. (81) reported the STARS (Standard Treatment with Alteplase to Reverse Stroke) study results, a phase IV trial mandated by the Food and Drug Administration. STARS was a prospective, multicenter study of consecutive patients, who received intravenous rt-PA according to NINDS criteria. Outcome measurement was the MRS at 30 days. Here, 389 patients received rt-PA within 2 hrs and 44 mins, and the median baseline NIHSS score was 13. The 30-day mortality rate was 13%; 35% of patients had very favorable outcomes (MRS = 1), and 43% were functionally independent (MRS = 2) at day 30. Another 3.3% of the patients experienced symptomatic ICH, which was fatal in seven. Asymptomatic ICH was seen in 8.2%. Protocol violations were reported for 32.6% of the patients and consisted mostly of treatment after 3 hrs (13.4%) mainly because of a doorto-needle-time of 1 hr and 36 mins, treatment with anticoagulants within 24 hrs of rt-PA administration (9.3%), and rt-PA administration despite systolic blood pressure exceeding 185 mm Hg (6.7%). The authors conclude that favorable clinical outcomes and low rates of symptomatic ICH can be achieved using rt-PA for stroke treatment, while the time effort for emergency evaluation may leave room for logistic improvement. Another study by Katzan et al. (82) yielded different results. Twenty-nine hospitals in the metropolitan area of Cleveland, OH, prospectively assessed the rate of rt-PA use, rate of ICH, and outcomes in 3,948 stroke patients. Seventy patients (1.8%) admitted with ischemic stroke received rt-PA; Sixteen patients (22%) experienced ICH; 11 of these patients (15.7%) had a symptomatic ICH (of which 6 were fatal), and 50% had deviations from national treatment guidelines. In-hospital mortality was significantly higher (p < .001) among patients treated with rt-PA (15.7%) than in patients not receiving rt-PA (5.1%). The fact that blood pressure guidelines were followed in only 47.8% and that the baseline NIHSS was only documented in 40% of the patients illustrates that intravenous thrombolysis, although an effective therapy, should be performed at experienced centers only and may explain the substantially higher rate of mortality and ICH in this study compared with those of other investigators. Unpublished data from Canada and Germany confirm the impression that the efficacy and risk of thrombolytic therapy seen in the controlled trials can be matched or even improved in the clinical setting.

The costs associated with intravenous thrombolytic therapy will be a factor in determining the extent of its utilization. Fagan et al. (83) analyzed data from the NINDS study and the medical literature were used to estimate the health and economic outcomes associated with using rt-PA in acute stroke patients. A Markov model was developed to compare the costs per 1,000 patients treated with rt-PA compared with the costs per 1,000 untreated patients. In the NINDS rt-PA Stroke Trial, the average length of stay was significantly shorter in rt-PA–treated patients than in placebo-treated patients (10.9 vs. 12.4 days; p = .02) and more rt-PA patients were discharged to home than to inpatient rehabilitation or a nursing home (48% vs. 36%; p = .002). The Markov model estimated an increase in hospitalization costs of $1.7 million and a decrease in rehabilitation costs of $1.4 million and nursing home costs of $4.8 million per 1,000 treated patients with a >90% probability of cost savings. The estimated impact on long-term health outcomes was 564 (CI 3–850) quality-adjusted life-years saved over 30 yrs of the model per 1,000 patients, which makes a net cost savings to the healthcare system likely. With growing experience and better training of emergency medicine personnel, internists, and neurologists throughout all stroke services, the efficacy of intravenous thrombolytic therapy with rt-PA may even improve and the time window may be routinely extended to 6 hrs after symptom onset.

CONCLUSION AND FUTURE PROSPECTS

Intra-arterial thrombolysis with rpro-UK is safe and effective within 6 hrs after stroke onset, leading to a significantly higher rate of functional independence, also in patients with more severe baseline stroke symptoms. For vertebrobasilar artery thrombosis, intra-arterial thrombolysis, although not proven in randomized trials, if successful, may dramatically reduce mortality and disability, and therefore is the therapy of choice within 6 hrs but eventually up to 12 hrs after symptom onset. The adjunctive use (and also the optimal time point of use) of antithrombotic agents is still controversial and at present no recommendation can be given with regard to concomitant administration of heparin or antiplatelet agents in the setting of thrombolytic therapy. Improvements in early diagnostic evaluation of patients, particularly in MRI techniques, allow a better patient selection and possibly a qualification of the presently rigid therapeutic time frame. However, at present, thrombolytic therapy is still underutilized. Among the major problems are that relatively few candidates meet the clinical and time criteria. Educating the general public to regard stroke as a treatable emergency and training emergency caregivers in the use of thrombolysis may decrease these problems. Healthcare institutions should be made aware of the potential in long-term cost savings, once stroke management is optimized and thrombolysis is more widely available. Patients and their relatives should be informed not only about the hazards of thrombolytic therapy but also about its potential benefit and thus the risk of not being treated.

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