Thrombolysis for the Treatment of Acute Ischemic Stroke

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Abstract: Objective: Thrombolytic therapy for acute ischemic stroke was implemented into clinical routine 4 years ago. Unfortunately, at present less than 2% of eligible patients receive thrombolytic therapy. We present an overview of all hitherto completed trials of intravenous and intraarterial thrombolytic therapy for carotid and vertebrobasilar artery stroke including recommendations for therapy and diagnostic procedures and their impact on patient selection and meta-analyses. New imaging techniques such as MRI diffusion- and perfusion-weighted 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 NINDS study, ECASS I and II, and ATLANTIS A and B, PROACT I and II and two large meta-analyses, including the Cochrane Library report. In addition, we inclue our own experience with more than 500 thrombolysis patients over the past 20 years where appropriate. Conclusion: Intravenous thrombolytic therapy with rt-PA has demonstrated a significant benefit and have proven to be safe for patients who can be treated within 3-6 hours after symptom onset. This benefit is at the cost of an increased rate of symptomatic intracranial hemorrhage without a significant effect on overall mortality. In general, the benefit of thrombolysis decreases and the risks increase with progressing time after symptom onset. Intra-arterial thrombolytic therapy significantly improves outcome if administered within 6 hours after stroke onset. 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 MRI-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 healthcare and reduction of long-term disability of stroke patients.

Key words: Thrombolysis, ischemic stroke, review, intra-arterial lysis, intravenous lysis, vertebrobasilar stroke, diagnostic imaging, diffusion MRI, perfusion MRI, CT

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Introduction

Up to 85% of all strokes are of ischemic origin and mostly due to blockage of a cerebral artery by a blood clot. After introduction of thrombolytic therapy for the treatment of acute myocardial infarction in the early 1990s, major trials for the evaluation of this new therapeutic approach to ischemic stroke were initiated. Occlusion of a brain vessel leads to a critical reduction in cerebral perfusion and, within minutes, to ischemic infarction with a central infarct core of irreversibly damaged brain tissue and a more or less large area of hypoperfused but still vital brain tissue (the ischemic penumbra), which can be salvaged by rapid restoration of blood flow. 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. 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). The agents most commonly used or which are under investigation are urokinase, t-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.

Randomized Trials of Intravenous Thrombolysis

The first anecdotal report of thrombolytic therapy for ischemic stroke dates back to the early 1960s. Three trials in the early 1980s investigated the effect of low-dose intravenous urokinase for the therapy of acute ischemic stroke. These trials are different from others for several reasons, such as a late time-point of inclusion (up to 5 or 14 days after stroke onset, respectively), the exclusion of presumed cardioembolic stroke, application of low doses of urokinase given daily for a period of several days, and the lack of assessment of clinical outcome except death and intracerebral hemorrhage (ICH).

Early Randomized Trials of Intravenous Thrombolysis for Acute Ischemic Stroke

In the early 1990s three small trials of intravenous thrombolysis with rt-PA were carried out, two of them in Japan. These trials, though not large enough to prove the efficacy, very well demonstrated the feasibility of early thrombolytic therapy and also suggested a reasonable degree of safety and a potential benefit. All these trials were blinded or double-blinded, randomized, and placebo-controlled. Mori et al randomized 31 patients with acute carotid artery territory stroke to treatment with either 20 or 30 mega-international units (MIU) duteplase (equivalent to 40 or 60mg rt-PA) or placebo given intravenously for 60 minutes in a time window of 6 hours after stroke onset. Baseline and postfusion angiography demonstrated complete or partial reperfusion in 50% of patients treated with 30 MIU duteplase, 44% of those treated with 20 MIU duteplase, and 17% in the control group. Patients treated with 30 MIU duteplase showed earlier and better clinical improvement than those treated with placebo, there was one parenchymal hemorrhage in each group. Yamaguchi and colleagues randomized 98 patients into two treatment arms (20 MIU duteplase or placebo over 60 minutes) within 6 hours. According to immediate posttreatment angiography, recanalization rates were significantly better in the treatment group than in patients receiving placebo (21% versus 4%). In the
treatment group, 16% of the patients experienced a marked clinical improvement as opposed to 6% in the placebo group; the rates of ICH, however, were similar in the two groups. The smallest randomized trial reported was that of Haley et al, who performed a pilot study with a time window to treatment of 3 hours in preparation for the NINDS rt-PA trial. Twenty patients received 0.85 mg rt-PA within 90 minutes, another 7 patients within 91 to 180 minutes after stroke onset. Six patients in the 90-minutes group improved by 4 or more NIH stroke scale (NIHSS) points at 24 hours compared with 1 patient in the placebo group (P < 0.05). There was no difference in the 91-to-180-minutes group, and one fatal ICH occurred in the placebo group.

**The Streptokinase Trials**

One pilot study and three large trials investigated the efficacy of streptokinase for acute ischemic stroke. In summary, all of the trials using streptokinase for acute ischemic stroke were prematurely stopped due to a high rate of early death, mostly due to ICH, and because of a lack of benefit at outcome in a meta-analysis as well. In the streptokinase trials together there were 92 (95% CI 65 to 120) additional fatal ICH per 1,000 treated patients (OR 6.03, 95% CI 3.47 to 10.47). The higher bleeding rate may be due to pharmacological properties of streptokinase other than, for instance, rt-PA, additional anticoagulation (MAST-E), a rather small fraction of patients treated within 3 hours, and a rather high dose of 1.5 MU, which is identical to the dose used in myocardial infarction (MI), whereas the rt-PA studies (see below) chose approximately two thirds the dose used in MI. Other side effects of streptokinase are a decrease in systolic blood pressure of more than 20 mmHg in 33% (only 6% in the placebo group) as well as anaphylaxis in 2.2% of the patients. Therefore, intravenous administration of streptokinase, outside the setting of a clinical investigation, is dangerous and not indicated for the management of patients with ischemic stroke.

**The rt-PA Trials**

In 1995, the results of the ECASS I and NINDS trials of intravenous rt-PA for acute ischemic stroke were published and followed by ECASS II in 1998 and ATLANTIS in 1999. These 4 trials randomized a total of 2,657 patients to treatment with placebo (N = 1,316 patients) or intravenous rt-PA (N = 1,341 patients) within 0 to 3 hours (NINDS), 3 to 5 hours (ATLANTIS), or 0 to 6 hours (ECASS I and II) after symptom onset. All four studies required a baseline CT scan to exclude ICH, and except for the NINDS study all others also established CT exclusion criteria such as major early signs of infarction. All trials used the 0.9 mg/kg body weight dose up to a maximum of 90 mg rt-PA, except ECASS I, in which 1.1 mg/kg up to a maximum dose of 100 mg was given. Ten percent of the total dose was given as a bolus; the rest was infused over 1 hour in all 4 trials.

**NINDS**

The NINDS trial (National Institute of Neurological Disorders and Stroke) randomized 624 patients (312 each placebo and intravenous rt-PA) within a time window of 3 hours after stroke symptom onset. Half of the patients were treated within 0 to 90 minutes, the other half within 91 to 180 minutes. The trial had two parts. Part 1 (in which 301 patients were enrolled) tested whether t-PA demonstrated a clinical effect, as indicated by an improvement of 4 points over baseline values in the NIHSS score or the resolution of the neurologic deficit within 24 hours of the onset of stroke (primary endpoint). Part 2 (in which 333 patients were enrolled) used a global test statistic to assess clinical outcome at 3 months, according to scores on the BI, MRS, Glasgow Outcome Scale (GOS), and NIHSS, evaluating each single score and all four as a combined endpoint. A good outcome was defined as a NIHSS score of ≤ 1, GOS = 1, BI ≥ 95, and MRS ≤ 1. The median baseline NIHSS score was 14 (rt-PA group) versus 15 (placebo group). There was no significant difference between the drug treatment and placebo group in the percentages of patients with neurologic improvement at 24 hours (rt-PA 47% versus placebo 57%; RR 1.2, P = 0.21), although a post hoc analysis comparing the median NIHSS scores at 24 hours showed a median of 8 in the rt-PA-treated group ver-
sus 12 in the placebo group (P<0.02). Furthermore, a benefit was observed for the t-PA group at 3 months for all four outcome measures. In part 2, the long-term clinical benefit of t-PA predicted by the results of part 1 was confirmed in all single scores as well as in the global test: BI (50% vs 38%, OR 1.6 (1.1–2.5), P = 0.026); MRS (39% vs 26%, OR 1.7 (1.1–2.5), P = 0.019); GOS (44% vs 32%, OR 1.6 (1.1–2.5), P = 0.025); NIHSS (31% vs 20%, OR 1.7 (1.0–2.8), P = 0.033); and combined endpoint (OR 1.7 (1.2–2.6), P = 0.008). For every 100 patients treated with rt-PA, an additional 11 to 13 will have a favorable outcome as compared to 100 not treated with rt-PA. The combined analysis of all 624 patients of part 1 and 2 together yielded results which were nearly identical to those of part 2 alone; interestingly, however, outcome did not vary by stroke subtype at baseline, meaning that patients with small vessel disease benefited as well as patients with, for instance, cardioembolic stroke. Symptomatic ICH within 36 hours after the onset of stroke occurred in 6.4 percent of patients given t-PA but only in 0.6 percent of patients given placebo (P<0.001). Nevertheless, severe disability and death were higher in the non-treated group (mortality at 3 months: t-PA 17% versus placebo 21%, P = 0.30). After publication of the NINDS trial in 1996, rt-PA received FDA approval for the treatment of acute ischemic stroke in a time window of 3 hours. ECASS I, a prospective, multicenter, randomized, double-blind, placebo-controlled trial, recruited 620 patients for treatment either with 1.1 mg/kg rt-PA or placebo within 6 hours after stroke symptom onset. Anticoagulants, neuroprotectants, and rheologic therapy were prohibited during the first 24 hours. Patients with a severe deficit (hemiplegia, forced head and eye movement, impairment of consciousness), with only mild or improving stroke symptoms, or CT signs of early infarction exceeding 33% of the middle cerebral artery (MCA) territory were excluded. Primary endpoints included a difference of 15 points in the BI and 1 point in the MRS at 90 days in favor of rt-PA. Secondary endpoints included combined BI and MRS, Scandinavian Stroke Scale (SSS) at 90 days, and 30-day mortality. Tertiary endpoints included early neurologic recovery (SSS) and duration of in-hospital stay. In anticipation of a substantial number of protocol violations due to the first time early CT signs of infarction were being used as an inclusion criterion, the investigators prospectively specified a target population (TP) analysis in addition to the primary intention to treat (ITT) analysis, which was performed at the end of the trial. The median NIHSS score at baseline was 13 (rt-PA patients) and 12 (placebo group), respectively. ECASS I was the first trial of thrombolysis to use CT exclusion criteria. In spite of these predefined parameters there were 109 protocol violations in ECASS I (17.4%), 66 (11%) of which were CT protocol violations and 52 (8.4%) of these due to maldetection of early infarct signs. There was no difference in the primary endpoints in the ITT analysis, while the TP analysis revealed a significant difference in the MRS (but not BI) in favor of rt-PA-treated patients (P = 0.035). Of the secondary endpoints, the combined BI and RS showed a difference in favor of rt-PA-treated patients (P < 0.001). Neurologic recovery at 90 days was significantly better for rt-PA-treated patients in the TP (P = 0.03). There was a non-significant trend towards a higher mortality rate at 30 days (P = 0.08) and a significant increase in parenchymal ICH (19.8% versus 6.5%, P < 0.001). There was a significant inverse relationship between protocol violation in rt-PA patients and 7-day-survival. A post hoc analysis of the ECASS I 3-hour cohort (N = 87 patients) did not reveal a significant difference between rt-PA and placebo group outcomes.

ECASS II

The results of ECASS I and NINDS led to the design of ECASS II, which was conducted from October 1996 to January 1998 in 108 centers in 16 countries in Europe, New Zealand and Australia. A total of 800 patients (409 rt-PA, 391 placebo) were randomized to treatment with either 0.9 mg/kg rt-PA or placebo within 6 hours (stratified into a 0-to 3-hour and a 3-to 6-hour group) after stroke symptom onset. The primary endpoint was the MRS at 90 days, dichotomized for favorable (score 0–1) and unfavorable (score 2–6) outcome. Analysis were by ITT and an 8% abso-
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The ATLANTIS study began in 1991 and originally was designed to assess efficacy and safety of thrombolytic therapy with rt-PA within 0–6 hours after stroke symptom onset. In 1993 the time window was changed due to safety concerns to 0–5 hours and re-started as part B (ITT), only to be further modified in 1996 to a 3–5 hour window (TP) after rt-PA had been approved by the FDA. Part A enrolled 142 patients (22<3 hours; 46>5 hours). The primary endpoint was an improvement of 4 or more points on the NIHSS at 24 hours and day 30; secondary endpoints included functional outcome (BI and MRS) at days 30 and 90. There was a significant improvement at 24 hours in the rt-PA group (40% versus 21%, P=0.02); this effect, however, was reversed at day 30 (60% versus 75%, P=0.05). Rt-PA significantly raised the rate of symptomatic ICH (11% versus 0%, P<0.01) and mortality at 90 days (23% versus 7%, P<0.01). The primary endpoint for part B was a NIHSS score of ≤1 at 90 days; secondary endpoints were outcome at days 30 and 90 according to BI, MRS, and GOS. An ITT population of 613 acute ischemic stroke patients was enrolled, with 547 of these treated as assigned within 3 to 5 hours of symptom onset (TP). There were no differences on any of the primary (34% versus 32%, P=0.65) or secondary functional outcome measures; however, there was a significant difference in the rate of major neurologic recovery (complete or ≥11 NIHSS points improvement: 44.9% versus 36%, P=0.03), which did not affect overall outcome. Treatment with rt-PA significantly increased the rate of symptomatic ICH (7.0% versus 1.1% P<0.001). As in ECASS II (median baseline NIHSS: 11 points), the median baseline NIHSS score was substantially lower than in the NINDS trial (10 versus 14 points), which (as in ECASS II) may have led to a better than expected outcome in the placebo group. In contrast to ECASS II, ATLANTIS was negative for the alternate outcome measurement independence (MRS 0–2) versus dependence or death (MRS 3–6) (rt-PA 54% versus placebo 56%, P=0.75). The authors conclude that...
thrombolysis with r-PA for acute ischemic stroke later than 3 hours after symptom onset cannot be recommended.

Meta-analyses

A search of the literature revealed 2 large meta-analyses. The first meta-analysis by Hacke et al in 1999 covered the NINDS study and both ECASS trials, with a total of 2,044 patients included (1,034 rt-PA patients versus 1,010 placebo patients). The authors assessed the benefit of rt-PA dichotomized the outcome into dependent versus independent or dead (MRS 0–2 versus 3–6) and favorable versus unfavorable (MRS 0–1 versus MRS 2–6). Risk in these three trials can be defined as ICH and mortality. Differences between the trials such as the dose of rt-PA (1.1 mg/kg in ECASS I versus 0.9 mg/kg in NINDS and ECASS II) and the therapeutic time window (3 hours in NINDS versus 6 hours in ECASS I and II) were taken into account. ICH occurred significantly more often in patients receiving rt-PA (144/1,034 versus 43/1,010; OR 3.23, CI 2.39–4.37), and was slightly less increased in the 3-hour time window and at the lower dosage (41/393 versus 15/389; OR 2.68, CI 1.56–4.62). These was no significant difference in mortality between rt-PA and placebo (OR 1.07, CI 0.84–1.36) but a slight trend towards a lower mortality in the 0.9 mg/kg and 3-hour group (OR 0.91, 0.63–1.32). Rt-PA, on the other hand, led to a 37% reduction in death and dependence regardless of dose and time window (OR 0.63, CI 0.53–0.76). If treated with the lower dose and within 3 hours the chance of an unfavorable outcome was reduced by 45% (OR 0.55, CI 0.30–0.97). For every 1,000 patients treated there are 90 fewer patients who are dead or disabled but 96 hemorrhages more than expected with placebo. Conversely, for 1,000 patients treated with 0.9 mg/kg and within 3 hours, there are 65 additional ICH and 140 fewer patients dead or disabled. The NNT for all doses and time windows is 11; for the 3-hour and 0.9 mg/kg group it is 7. These numbers are far better than the NNT for thrombolysis in myocardial infarctions, which is 30–40.

Wardlaw et al included in their Cochrane Library meta-analysis all randomized trials of thrombolysis regardless of time window, dosage, administration route, and substance. Seventeen trials with a total of 5,216 patients (2,889 of which were from rt-PA trials) were included. The 17 trials were NINDS, ECASS I and II, ATLANTIS A and B (with preliminary data), PROACT I and II (with preliminary data), ASK, MAST-E, MAST-I, and the early trials by Abe, Atarashi, Haley, Mori, Morris, Ohtomo, and Yamaguchi. The main objectives were to show that thrombolytic therapy reduces the risk of late death, increases the risk of early and fatal ICH, and that the benefit at outcome (reduction of death and dependence) offsets any early hazard. Symptomatic and fatal ICH were significantly more common as a result of thrombolytic therapy (symptomatic ICH: OR 3.53, CI 2.79–4.45, P < 0.000001; fatal ICH: OR 4.15, CI 2.96–5.84). This translates into 70 additional instances of symptomatic ICH for patients receiving thrombolysis and 29/1,000 (OR 3.2) additional instances of fatal ICH in rt-PA patients but 92/1,000 (OR 6.03) additional ICH in those patients receiving streptokinase as opposed to placebo. Despite this, thrombolytic therapy, administered up to 6 hours after ischemic stroke, significantly reduced death or dependence at the end of follow-up (55.2% versus 59.7%, OR 0.83, CI 0.73 to 0.94, P = 0.0015), which is equivalent to 44 fewer patients being dead or dependent per 1,000 treated (CI 15–73). For patients treated with rt-PA only, the OR was 0.79 (CI 0.68–0.92, P = 0.001) or 57 deaths/dependence prevented per 1,000 patients treated (CI 20–93). An alternative endpoint analysis yields similar results for favorable versus unfavorable outcome (OR 0.79 for all patients and 0.76 for rt-PA patients). When treatment was given within 3 hours after stroke onset, there was an even better risk reduction for dependency or death (55.2% versus 68.3%, OR 0.58, CI 0.46 to 0.74, P = 0.00001) or 126 fewer dead or dependent patients per 1,000 treated. The difference of benefit of rt-PA in the 0–3 hour window or 3–6 hour window was nonsignificant but showed a trend towards better improvement with early therapy (OR 0.7 versus 0.76). The authors conclude that the significant increase in early death and
fatal and nonfatal symptomatic ICH are offset by the significant reduction of disability in survivors. Therapy with rt-PA is associated with less risk and more benefit than with other substances. Recently, Brott presented a new metaanalysis of the NINDS, ECASS I and II and ATLANTIS studies in San Antonio at the ASA meeting\(^a\). They quadrantized the time interval to treatment in 90 minute intervals (0–90; 91–180; 181–270; 271–360) and analyzed the ratio of patients with a favorable outcome (mRS 0–1) in 2,776 patients. They found a significant correlation of outcome with time from symptom onset. The odds ratios for the favorable outcome were 2.83, 1.53, 1.4 and 1.16 respectively with the last OR missing statistical significance. The lower confidence interval intersects with 1.0 at 285 minutes after symptom onset. Most interestingly the significant effect in favor of rt-PA is mainly on the cost of patients in the mRS range from 2–5 but there is no difference in death (mRS 6). Thus the negative correlation of time loss with outcome again is established ("Time is Brain).\

**Phase IV Trials of Intravenous Thrombolysis and Cost Aspects**

There are no phase IV trials of intraarterial thrombolysis. After FDA approval of rt-PA for intravenous thrombolytic therapy in June 1996, the rate of thrombolysis remained fairly constant until the end of 1998\(^3\). 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. Despite of Level I evidence in favor of thrombolysis, it is estimated that overall only 1% of all ischemic stroke patients and 2% of the time eligible (3-hour window) are treated with rt-PA, a rather low rate. This is due to several facts such as persisting doubts, fear of hemorrhage, or inadequate reimbursement. The reported outcome and complication rates seem to be similar to the NINDS trial in most instances. The CASES registry in Canada has registered more than 1,000 rt-PA-treated patients with a median NIH-SS of 15, a symptomatic ICH rate of 4.6% and a rate of 46% independent patients (mRS 0–2). In Cologne, approximately 22% of the patients that ar-

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\(^a\) Kwiatkowski et al in 1999. In Houston, 30 patients were treated prospectively after the NINDS protocol\(^4\). Six percent of all patients hospitalized with ischemic stroke received intravenous t-PA at the university hospital and 1.1% at the community hospitals. The 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 hour 40 minutes.

Two very recent studies presented divergent results: Albers et al reported the STARS (Standard Treatment with Alteplase to Reverse Stroke) study results, a phase IV trial mandated by the Food and Drug Administration\(^5\). 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 hours 44 minutes, 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 7. Asymptomatic ICH was seen in 8.2%. Protocol violations were reported for 32.6% of the patients and consisted mostly of
treatment after 3 hours (13.4%) mainly due to a door-to-needle-time of 1 hour 36 minutes, treatment with anticoagulants within 24 hours of tPA administration (9.3%), and tPA 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 tPA for stroke treatment, while the time effort for emergency evaluation may leave room for logistic improvement. Another study by Katzan et al. yielded different results. Twenty-nine hospitals in the metropolitan area of Cleveland, Ohio, 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 < 0.001) among patients treated with tPA (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, though 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 to other investigators. Unpublished data from Canada and Germany and our own data 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 analyzed data from the NINDS study and the medical literature were used to estimate the health and economic outcomes associated with using tPA in acute stroke patients. A Markov model was developed to compare the costs per 1,000 patients treated with tPA 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 tPA-treated patients than in placebo-treated patients (10.9 versus 12.4 days; P = 0.02) and more tPA patients were discharged to home than to in-patient rehabilitation or a nursing home (48% versus 36%; P = 0.002). 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 greater than 90% probability of cost savings. The estimated impact on long-term health outcomes was 564 (CI 3 to 850) quality-adjusted life-years saved over 30 years of the model per 1,000 patients, which makes a net cost savings to the health care 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 hours after symptom onset.

### 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. For 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 hours, but not within 3 hours or even 4 hours of symptom onset with regard to the mean or median. The reported complete or partial recanalization rates very substantially between less than 50% and more than 90%. 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 neurological deficit, angiographic anatomy, time-to-treatment, outcome, and
method of neurological evaluation at follow-up. Accordingly, conclusions regarding efficacy are not possible. The most feared complication of local intraarterial therapy for stroke, as for intravenous thrombolytic therapy, is ICH. Symptomatic ICH based on the case series is estimated to be 4%, which is lower than that reported for any intravenous thrombolytic series. However, this rate is also lower than that reported in the PROACT I and II trials, in which 24-hour 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 less than 5% for all the series in toto. One drawback of intraartrial in contrast to intravenous thrombolysis is the considerable time delay to angiography, and from initiation of angiography to clot lysis. There are limited data (Phase I and II) data only at present to support the combined use of intravenous and intra-arterial thrombolysis with rt-PA. A protocol of the Bridging group uses 0.6mg/kg with a 10% to 20% bolus and continuous infusion up to a maximum of 60mg rt-PA; when angiography is started, the infusion is stopped. The rest of the dose up to 90 mg maximum is given intraarterially. 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. Preliminary data in a phase II trial suggest besides of a reasonable safety profile efficacy of this technique. The final data have not been reported in written form yet. It has to be noted that the combination of i.v. and i.a. therapy utilizes the time saving i.v. route and the higher and faster recanalization rates of the i.a. approach. However, this protocol should be limited to clinical investigations and is not based on any study results, and thus cannot be recommended as a routine procedure.

**PROACT I**

PROACT I was a randomized phase II trial of recombinant pro-urokinase (rpro-UK) versus placebo in patients with angiographically documented proximal middle cerebral artery occlusion. 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 (6mg) or placebo over 120 minutes into the proximal thrombus face. Recanalization efficacy was assessed at the end of the 2-hour infusion and symptomatic ICH at 24 hours. A total of 105 patients underwent angiography; 65 of these (N = 25: no occlusion, N = 36: no M1 or M2 occlusion, N = 2: time interval >6 hours, N = 2: complications) were excluded from randomization. Among the 40 treated patients, 26 received rpro-UK and 14 placebo at a median of 5.5 hours from symptom onset. Recanalization was significantly associated with rpro-UK (P = 0.0085) and TIMI 3 recanalization was achieved in 5 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 (non-significant); 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 = 0.0255). 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 intraarterial rproUK in patients with acute stroke of less than 6 hours' duration caused by MCA occlusion. Eligible patients had new focal neurological signs attributable to the MCA territory, allowing initiation of treatment within 6 hours after symptom onset, a minimum 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 rproUK/2 hours plus the PROACT I lower dose of heparin (2,000 IU bolus, 500IU/hour continuous infusion) or heparin alone. Mechanical disruption
of the clot was not permitted. After 1 hour (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 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 hours 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 ITT analysis. Further, 40% of rpro-UK patients and 25% of control patients had a MRS of 2 or less (absolute benefit 15%, relative benefit 58%, number needed to treat = 7; P = 0.04). Mortality was 23% for the rpro UK group and 27% for the control group (P = 0.8). The recanalization rate was 66% for the r-proUK group and 18% for the control group (P < 0.001); TIMI 3 recanalization rates were 19% and 2%, respectively (P < 0.003). All other secondary outcomes were nonsignificant. Early ICH occurred in 33% versus 13% of patients (P = 0.003); at 10 days the rates were 68% and 57% (P = 0.23). Early symptomatic ICH occurred only in patients with NIHSS scores >11 within 24 hours in 10.2% of r-pro UK patients and 2% of control patients (number needed to harm = 12; P = 0.06).

The results of PROACT II did not suffice for FDA approval. Another study of intra-arterial pro-urokinase for acute stroke within 6 hours is planned but due to funding problems still a matter of debate (PROACT III).

Recommendations for Intraarterial Thrombolysis

Intra-arterial thrombolytic therapy of acute M1 and M2 occlusion with 9mg/2 hours significantly improves outcome if administered within 6 hours after stroke onset. Seven patients need to be treated in order to prevent 1 patient from death or dependence. The higher rate of symptomatic ICH (10.2% in PROACT II versus 8.8% in ECASS II, 6.4% in NINDS and 7.2% in ATLANTIS) is very well explained by the far larger baseline severity of stroke in PROACT II (NIHSS of 17 in PROACT II versus 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 OR (CI 0.31~1.00) for death or disability, an OR of 2.39 (CI 0.88~6.47) for early symptomatic ICH (7 to 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 hour a day-7 days 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.

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 have been published since 1986. The early and first series by Bruckmann and Hacke retrospectively investigated the clinical-angiologic data and the clinical outcome in 66 patients with angiographically demonstrated thrombotic vertebrobasilar artery occlusions who received either local intra-arterial thrombolytic therapy (urokinase or streptokinase) (43 patients) or conventional therapy (antiplatelet agents or anticoagulants) (22 patients). Recanalization in patients who received thrombolytic therapy correlated significantly with clinical outcome: in 19 of 43 patients, recanalization was demonstrated angiographically, while in 24 patients the occlusion persisted. All patients without recanalization died, but 14 of the 19 patients displaying recanalization survived (p = 0.000007), 10 with a favorable clinical outcome. Only three of the 22 patients who received conventional therapy survived, all with a moderate clinical deficit. When we compared the treatment groups, highly sig-
nificant differences in both outcome quality \((p = 0.017)\) and survival \((p = 0.005)\) were found to depend on establishing recanalization. These data support the concept that technically successful thrombolysis of vertebrobasilar artery occlusions is associated with beneficial clinical outcome. The great majority of the more than 120 patients (from all studies) 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 hours of symptom onset. The median time from the beginning of treatment to the time of recanalization was reported to be 120 minutes\(^{40}\). 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\(^{40}\). Mortality of vertebrobasilar thromboembolism is high, with overall rates of approximately 70\%–80\%. Successful recanalization, however, was associated with a survival rate of 55\% to 75\%, as opposed to 0\%–10\% in persistent or untreated basilar artery occlusion\(^{63,65}\). 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\(^{46}\), 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 vertebrobasilar occlusive disease\(^{60}\). 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\(^{65}\). Grond et al reported one small case series of 12 consecutive patients in whom they investigated whether early intravenous thrombolysis could also effectively be applied in acute vertebrobasilar ischemic stroke\(^{66}\). Patients with clinically diagnosed moderate to severe vertebrobasilar ischemic stroke with clearly determined symptom onset were treated with intravenous rt-PA within 3 hours after symptom onset, following a protocol similar to that of the NINDS study. On admission, 7 patients exhibited moderate to severe brainstem symptoms without impairment of consciousness and 5 patients had impairment of consciousness, of whom 2 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 due to reocclusion after primarily successful thrombolysis, and 1 patient died of severe brainstem infarction and additional space-occupying parietal hemorrhage. Unfortunately, basilar artery occlusion was not demonstrated with any means such as Doppler ultrasound, CT or MR angiography, or digital subtraction angiography. The utility of Doppler ultrasound and CTA in the diagnosis of vertebrobasilar occlusion, however, has been studied and demonstrated by Brandt et al\(^{66}\), who showed a greater than 90\% sensitivity and specificity for CTA but only 30\% for Doppler ultrasound.

In summary, the natural disease course of vertebrobasilar occlusion has a grim prognosis. Neuroradiological intervention with intra-arterial thrombolysis to date is the only life-saving therapy that has demonstrated benefit with regard to mortality and outcome, albeit not in a randomized trial. However, sufficient data are available to justify intra-arterial thrombolytic therapy in the light of mortality and disability in these patients. The time window for thrombolysis in the posterior circulation has not been established but may be up to and even exceed 12 hours, although Fox et al. Suggest a time window of more than 10 hours to be associated with a poor prognosis\(^{66}\). Presence or absence of vertebrobasilar vessel occlusion can be safely, noninvasively, and rapidly established by CT (or MR) angiography before a neuroradiological intervention is initiated. The data for intravenous thrombolysis in vertebrobasilar obstruction are too scarce for any recommendation to be made, but warrant further study.
Diagnostic Imaging and Thrombolytic Therapy

In spite of discouraging reports that CT cannot demonstrate ischemic tissue changes during the first 12 hours after symptom onset, it has been generally accepted in the academic stroke community that CT can demonstrate early infarct signs within the first 2 to 6 hours after stroke. The reported sensitivity of early CT findings ranges from 12% to 92%, depending on the infarct signs, the exact time window of the investigated population, and on the authors.

The most common early infarct sign is a frequently subtle gray matter and/or cortical hypodensity. Other early infarct signs include the loss of the insular ribbon, sulcal effacement due to early edema in 12% to 41% of stroke patients, and the hyperdense middle cerebral artery sign (HMCAS) in 40 to 60% of patients with angiographically proven MCA occlusion. More recent studies have reported incidences of early CT signs of infarction between 53% and 92% within the first 6 hours for all acute stroke patients. In patients with a M1-segment occlusion, the incidence of a parenchymal hypodensity is reported to be 68% within the first two hours but increases to 89% in the third hour after symptom onset and up to 100% thereafter, and there is an association between the size of early hypodensities and the risk of a secondary hemorrhage, and clinical outcome, as early parenchymal hypodensity of more than 50% of the MCA territory is associated with a mortality of 85%. ECASS I and II showed that in patients with a small area of hypoattenuation (<33% of the MCA-territory), treatment increased the chance of a good clinical outcome, while rt-PA in patients with a large area of hypoattenuation (>33% of the MCA-territory) had no benefit but increased the risk for a fatal brain hemorrhage. According to ECASS I, mortality was 13% in patients without hypodensity, 23% in patients with parenchymal hypodensity less than 33% of the MCA territory, and 49% in patients with an early hypodensity exceeding 33% of the MCA territory. While 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. 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. CT angiography (CTA) can provide additional information on stenoses or occlusions in the basal arteries of the brain, as nonionic contrast material does not affect infarction volume or worsen the symptoms of cerebral ischemia. In addition to the assessment of 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. Volume CT scanners may produce images which 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. In a recent study, perfusion CT was performed within 6 hours of symptom onset in 32 patients with acute stroke symptoms and showed a good correspondence in 81% of the patients with SPECT. However, at present only one slice and not images of the whole brain can be obtained.

The need for an allround 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 h after symptom onset does not adequately meet these criteria. The advent of new MRI techniques such as perfusion- (PWI) and diffusion- (DWI) weighted imaging has revolutionized diagnostic imaging in stroke. DWI may delineate infarcted brain
tissue in less than 1 h after symptom onset, probably within minutes\textsuperscript{90}, although there is cumulating evidence that in the very early stage of stroke there may be reversible DWI changes\textsuperscript{39-46}, while PWI defines the area of cerebral hypopERSION. The absolute volume difference or ratio of PWI and DWI reveals the ischemic tissue potentially at risk of irreversible infarction\textsuperscript{35,96}. MRA can reliably assess the cerebral vessel status\textsuperscript{92}. Stroke MRI further allows a definitive diagnosis of ICH within the first hours of stroke\textsuperscript{92,100} and possibly also that of subarachnoid hemorrhage\textsuperscript{91}. Several studies have reported early findings of stroke MRI within the first 6 to 12 hours, demonstrating the feasibility and practicality of this method in the setting of acute stroke and thrombolytic therapy\textsuperscript{87,90,95,102,103,106}. In essence, the presence of a vessel occlusion according to MRA is associated with a PWI/DWI mismatch, the stroke MRI setting that defines the ideal candidate for thrombolysis. 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\textsuperscript{94,95,100,106,108}. 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\textsuperscript{101}. Furthermore, the rather strictly defined therapeutic window may be qualified and individualized according to the findings in each individual patient.

Conclusion, Recommendations and Future Prospects for Thrombolysis

Overall, thrombolysis with 0.9 mg/kg rt-PA for acute ischemic stroke within 6 hours leads to a clinically significant effect in favor of treated patients but is associated with an excess rate of symptomatic ICH, which does, however, not take effect on mortality. Intravenous rt-PA (0.9 mg/kg; maximum of 90 mg) is therefore the recommended treatment within 3 hours after stroke symptom onset. Thrombolytic therapy should be performed in centers experienced with the procedure. The benefit from the use of intravenous rt-PA for acute ischemic stroke beyond 3 hours from onset of symptoms is lower, but definitely present in selected patients. Also, the European Stroke Initiative (EUSI) recommendations state that thrombolytic therapy is the therapy of choice within 3 hours and in selected patients up to 6 hours after stroke onset\textsuperscript{90}. 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. Intravenous rt-PA is not recommended when the time of onset of stroke cannot be ascertained reliably: this includes patients in whom strokes are recognized upon awakening. Intravenous administration of streptokinase for acute ischemic stroke is dangerous and not indicated. Data on the efficacy of any other intravenously administered thrombolytic drugs are not available such that a recommendation could be provided. Intra-arterial thrombolysis with recombinant pro-urokinase is safe and effective within 6 hours 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 but eventually up to 12 hours 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 qualifi-
Intravenous rt-PA has been approved with restrictions for stroke patients in Germany since August 2000 and without restrictions from 2001 on in South America. The mutual recognition procedure, however, did not result in a Europe-wide approval of rt-PA. Finally, approval for rt-PA within 3h has been given Europe-wide after an arbitration procedure, where evidence and expert reports have been reviewed and reevaluated. Preliminary restrictions for patients older than 75 years or with regular pre-stroke use of platelet inhibitors were not based on any data and thus not understood by these authors and have been amended in the revised version of the approval. However, another trial named ECASS III has been demanded by the European authorities and are currently in the planning phase. The protocol will be finished by the end of 2002. ECASS III will be a randomized, placebo-controlled trial in the 3–4h time window with approximately 300 patients per study arm. Furthermore in analogy to the CASES registry, a European rt-PA for ischemic stroke registry called SITS-MOST where every patient treated with rt-PA within 3 hours has to be reported will be compulsory. SITS-MOST is internet based and will be located in Stockholm. A stroke-MRI based study on the efficacy of recombinant desmoteplase (DSPA, derived from saliva of the vampire bat Desmodus rotundus) for treatment of stroke in the 3–9h time window has paused recruitment after 47 patients due to safety concerns (DIAS = Desmoplatin in Acute ischemic Stroke) but will resume activity in a new dose finding protocol. A pilot trial with tenecteplase (TNK) for acute ischemic stroke is planned. DEFUSE (USA) and EPITETH (Australia) are two studies that perform MRI based thrombolysis with rt-PA in the 3–6h time window, data are currently not available. IST 3 is a large thrombolysis trial planned to include thousands of patients in a randomized fashion with the uncertainty principle. This means that physicians, who want to treat their patients with rt-PA should do so, those that do not want to treat a specific patient should not. Only, when not being sure whether to treat or not they should randomize the patient. We believe that the Cleveland area experience has clearly demonstrated that physicians, who do not know whom to treat and whom not to treat should keep their hands from rt-PA as there will be an abundance of hemorrhagic complications. The benefits of arterial recanalization may be supplemented by neuronal protection (first protocol drafts underway), particularly when the two strategies are used simultaneously, and if they can be used very early following symptom onset. A very interesting approach is the ultrasound enhanced recanalization under treatment with rt-PA. These are intravascular devices (EKOS, EPAR, Angiojet), until present no data are available. Clot lysis facilitation with transcranial ultrasound is another option. Two trials are underway: TRUMBI is an international trial, CLOTBUST is an oligocentric trial headed by the university clinic at Houston, Texas. Preliminary unpublished data (AV Alexandrov, Grotta JC) showed a significantly higher rate of early (meaning during infusion time) recanalization (10/22) in patients treated with rt-PA and ultrasound as opposed to rt-PA alone (3/22). Further data are pending.

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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