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RESEARCH

Time to treatment with recombinant tissue plasminogen activator and outcome of stroke in clinical practice: retrospective analysis of hospital quality assurance data with comparison with results from randomised clinical trials

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Abstract

Objective To study the time dependent effectiveness of thrombolytic therapy for acute ischaemic stroke in daily clinical practice.

Design A retrospective cohort study using data from a large scale, comprehensive population based state-wide stroke registry in Germany.

Setting All 148 hospitals involved in acute stroke care in a large state in southwest Germany with 10.4 million inhabitants.

Participants Data from 84 439 patients with acute ischaemic stroke were analysed, 10 263 (12%) were treated with thrombolytic therapy and 74 176 (88%) were not treated.

Main outcome measures Primary endpoint was the dichotomised score on a modified Rankin scale at discharge ("favourable outcome" score 0 or 1 or "unfavourable outcome" score 2-6) analysed by binary logistic regression. Patients treated with recombinant tissue plasminogen activator (rtPA) were categorised according to time from onset of stroke to treatment. Analogous analyses were conducted for the association between rtPA treatment of stroke and in-hospital mortality. As a co-primary endpoint the chance of a lower modified Rankin scale score at discharge was analysed by ordinal logistic regression analysis (shift analysis).

Results After adjustment for characteristics of patients, hospitals, and treatment, rtPA was associated with better outcome in a time dependent pattern. The number needed to treat ranged from 4.5 (within first 1.5 hours after onset; odds ratio 2.49) to 18.0 (up to 4.5 hours; odds ratio 1.26), while mortality did not vary up to 4.5 hours. Patients treated with rtPA beyond 4.5 hours (including mismatch based approaches) showed a significantly better outcome only in dichotomised analysis (odds ratio 1.25, 95% confidence interval 1.01 to 1.55) but the mortality risk was higher (1.45, 1.08 to 1.92).

Conclusion The effectiveness of thrombolytic therapy in daily clinical practice might be comparable with the effectiveness shown in randomised clinical trials and pooled analysis. Early treatment was associated with favourable outcome in daily clinical practice, which underlines the importance of speeding up the process for thrombolytic therapy in hospital and before admission to achieve shorter time from door to needle and from onset to treatment for thrombolytic therapy.

Introduction

Intravenous administration of recombinant tissue type plasminogen activator (rtPA) is the approved treatment for acute ischaemic stroke up to the 4.5 hour time window after the onset of stroke.[1-4] Randomised clinical trials of rtPA indicated that the chance to achieve a better outcome with treatment is strongly time dependent and declines throughout the first 4.5 hours after stroke onset. In a pooled analysis of individual patient data from

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Appendix: Supplementary tables A-C

the eight major rtPA trials, 1273 (out of 1849) patients were treated within 4.5 hours.[4] This analysis showed the effectiveness of thrombolytic therapy, with a number needed to treat of between 4.5 and 14.1 (odds ratio 2.6 to 1.3) to reach a score of 0 or 1 on a modified Rankin scale after three months.[4] For the 576 patients treated after than 4.5 hours after onset the analysis failed to show a significant benefit of thrombolytic therapy, despite a non-significant trend towards a better outcome (number needed to treat 21.7, 95% confidence interval for odds ratio 0.9 to 1.6) and an increase in mortality of borderline significance, whereas the third international stroke trial (IST-3) suggested some clinical efficacy up to six hours, also associated with a signal of increased mortality.[5] A subsequent pooled analysis of the previous trials with the individual patient dataset from the third international stroke trial (IST-3) (the stroke thrombolysis trialists collaboration (STTC)) confirmed the time dependency of the treatment effect and the increased mortality risk over time in randomised clinical trials.[5]

The inclusion and exclusion criteria used in randomised controlled trials excluded important patient groups for various reasons, depending on general approval regulations by health authorities or specific concepts developed and approved by local ethics committees. This includes patients beyond the upper age limit, with pre-existing disabilities or any other factors that could independently influence patient outcome, while in routine clinical practice, these patients are usually not excluded from treatment. In addition, randomised controlled trials were mostly conducted at dedicated stroke centres with extensive experience in the management of new treatment protocols. Non-randomised studies yielded mixed results regarding the association between time to treatment with rtPA and reduction in disability and might be prone to selection bias because they were carried out at selected hospitals or lacked of a group of patients not treated with rtPA.[6-10]

To further evaluate the effects of rtPA in a large practice based study we analysed the consecutive and prospective stroke database of Baden-Wuerttemberg, a federal state with 10.4 million inhabitants in southwestern Germany. This comprehensive database documents the clinical parameters, diagnostic investigations, and outcomes of all patients with stroke admitted to hospital and treated in the federal state of Baden-Wuerttemberg.[11] We investigated the time dependent effect on early outcome and mortality in patients treated and not treated with rtPA and compared the findings with those of published randomised controlled trials and meta-analyses, hypothesising a time dependent effect of thrombolytic therapy in daily clinical practice at various levels of stroke care with a magnitude comparable with that observed in randomised controlled trials.

Methods

Study design and setting

We performed a retrospective cohort study using data from a large scale comprehensive population based and state-wide stroke registry in Germany. Since the year 2000, the state of Baden-Wuerttemberg has implemented a three level system for the treatment of acute stroke with local or regional stroke units and comprehensive stroke centres. A consecutive and prospective database of all stroke patients admitted to hospital was started in 2005. All hospitals are legally required (German Social Code V, §112) to implement this database for all patients aged ≥18 admitted to a hospital with the diagnosis of stroke (according to their ICD-10 (international classification of diseases, 10th revision) code). Participation is independent of the structure and process qualification of individual hospitals and departments.[11] Data covering a period of five years from 1 January 2008 to 31 December 2012 were available for our analysis.

Eligibility criteria and study size

We included all patients with the final diagnosis of acute ischaemic stroke based on ICD-10 code (I63.0-I63.5, I63.8, I63.9, I64, I67.0) admitted to a hospital within seven days after stroke onset in 2008-12. Data from the years 2006-07 were excluded because documentation of relevant factors (such as National Institutes of Health stroke scale at admission) was not mandatory at that time. We excluded patients undergoing intra-arterial thrombolytic therapy or interventional embolectomy (fig 1⇓) and patients with missing modified Rankin score at discharge. Patients with missing data for parameters considered in the regression model were not included in this analysis (see table 1⇓); baseline data of included and excluded patients are in appendix table A.

Variables

The documentation included demographic data (age, sex); medical history; time of stroke onset (in the case of unknown exact time we applied standardised predefined categories concerning the time the patient was last seen well); route to hospital admission; hospital admission time; admission to general ward, stroke unit, or intensive care unit; admission to neurology or internal medicine; nature and timing of diagnostic procedures; rtPA treatment including timing; treatment complications; discharge information; and hospital mortality. Stroke severity was measured with the National Institutes of Health stroke scale.[12] The modified Rankin score was documented at admission and at discharge, and a premorbid score was estimated at admission. Data on hospital structure (such as size, stroke cases/year, and level of care in a three level stroke concept or general hospital without qualified stroke care) and type and timing of imaging are available for all hospitals. Detailed descriptive results on the documentation have been published elsewhere.[11] Data privacy laws in Germany do not allow follow-up visits to patients who have not consented to them. As the database was not primarily designed for scientific evaluations, no consents for follow-up were collected.

Data sources/measurement

All the data we used were collected by the Office for Quality Assurance in Hospitals (GeQiK). Documentation forms are commonly filled out by the treating hospital physicians or trained study nurses. The data management system is included in electronic medical records or in the electronic patient management systems. Data are submitted electronically to the Office for Quality Assurance in Hospitals. To ensure high rates of inclusion and documentation, reimbursement of hospitals for stroke care depends partly on transmission of the relevant data. In practice the current inclusion rate is over 98% of all patients with stroke admitted to hospital. Plausibility checks of incoming data are performed routinely; raw data are checked in random samples. If a hospital does not meet the requirements concerning the rate of data transmission, consistency of data transmitted, or other quality aspects, a structured dialogue is initiated to improve documentation and transmission rates.

Potential bias

Selection bias is minimised in this study because of the mandatory documentation of all stroke patients, which is also

independent of their type of health insurance. A small fraction of patients were treated by outpatient services (often patients with a high modified Rankin score living in nursing homes, but over 95% of stroke patients in Germany were admitted to hospital) and were therefore not included in this database.[13] As thrombolytic therapy is not delivered for ambulatory patients with stroke, we cannot draw any conclusions about outpatient stroke care. Data quality is checked on a regular basis for each hospital based on random samples of documentation, and extensive plausibility checks were conducted before data analysis. Nevertheless, as data were collected in routine clinical practice, they are unlikely to fulfil standards applied in carefully planned and conducted clinical trials. We compared characteristics of patients with missing values on the modified Rankin scale at discharge (main outcome parameter) with patients with complete datasets to assess a potential source of bias.

Statistical analysis

The primary endpoint was the dichotomised modified Rankin score at discharge: "favourable outcome" (modified Rankin score 0 or 1) or "unfavourable outcome" (score 2-6). We used binary logistic regression analysis to assess the association between outcome and rtPA treatment. In a first model we coded the treatment variable as dichotomous (treatment *v* no treatment). In a second model treatment was differentiated according to time from stroke onset to treatment with (0-90, 91-180, 181-270, and ≥271 minutes). In both models, we calculated odds ratios representing the chance of a favourable clinical outcome in the rtPA group compared with the group without rtPA treatment, with adjustment for potential confounders (sex, age, premorbid modified Rankin score, National Institutes of Health stroke scale at admission, diabetes, previous stroke, atrial fibrillation, ventilation, level of stroke care (stroke centre, regional stroke unit, local stroke unit, no stroke unit), pneumonia, pulmonary embolism and thrombosis, length of hospital stay). Analogous analyses were conducted to model the association between treatment and mortality.

The number need to treat for one additional patient with a favourable outcome in the rtPA group was calculated from adjusted odds ratios as described elsewhere.[14] Because it has been shown that the modified Rankin score at day 10 can serve as a good proxy for day 90 outcome, we compared our findings with results observed in the pooled analysis.[15]

As a co-primary endpoint the chance of a lower modified Rankin score at discharge was analysed by ordinal logistic regression analysis (shift analysis) to assess the potential effect of rtPA treatment over the whole range of the outcome variable (modified Rankin score 0-6). This approach is statistically more efficient than, and generally preferable to, dichotomised and other collapsed approaches.[16 17] It is, however, based on the strong assumption of proportional odds between the categories. Ordinal logistic regression analysis was considered sensible here because in clinical practice (as opposed to the published clinical trials) substantial proportions of patients have a premorbid modified Rankin score ≥2 and thus cannot realistically achieve a modified Rankin score of 0 or 1, which was the primary endpoint. Treatment variables and confounder adjustment were handled analogously to the binary models.

We reanalysed the dataset under inclusion of the patients with missing values (but without patients treated with intra-arterial approaches) using a conservative imputation strategy for missing values; for the outcome modified Rankin score at discharge, we carried forward the last observation (that is, modified Rankin score at admission), assuming no treatment effect of rtPA, and imputed the group specific median of this variable for the other missing values (mainly National Institutes of Health stroke scale).

All statistical tests were two sided, and P values of <0.05 were considered to be significant. The analyses were carried out with SAS 9.3 (SAS Institute, Cary, NC).

Results

The complete dataset included 109 284 patients with acute ischaemic stroke treated in hospitals in Baden-Wuerttemberg from January 2008 to December 2012. We excluded 1684 patients who were treated with intra-arterial approaches (because of the possible impact of therapy on outcome; these patients will be reported separately). Of the 107 600 patients remaining, 23 161 patients had missing values (fig 1⇓). Among the latter were 6886 patients with a missing modified Rankin score at discharge and 16 275 patients with an incomplete dataset of key parameters for consideration in the multivariate regression models (most commonly missing National Institutes of Health stroke scale at admission). The primary analysis is based on 84 439 patients with acute ischaemic stroke treated in 148 hospitals in Baden-Wuerttemberg (49 of them with a certified dedicated stroke unit).

Table 1 shows the baseline characteristics of the patients.⇓ Because of the large sample size, even small differences between groups are significant, although they might not be clinically relevant. In the total cohort, 41 092 (49%) were women, and the mean age was 73.5 (SD 12.6). Over a third (30 776; 36%) of the patients were aged over 80, and treatment with rtPA would be considered off label according to the European labelling, but in accordance with guidelines from the European Stroke Organisation (ESO).[18] About a quarter (20 149; 24%) of patients had a pre-existing modified Rankin score of 2 or higher. Table A in the appendix provides baseline characteristics of the included and excluded patients.

The mean rate of thrombolytic therapy (of all patients with acute ischaemic stroke) was >12%, with a constant increase over time. The state-wide thrombolysis rate in 2012 was 14%. Of the 10 263 patients who received rtPA, time from onset to treatment was <90 minutes in 16%, 90-<180 minutes in 62%, 180-270 minutes in 16%, and >270 min (maximum 12 hours) in 7%. The mean time to treatment for patients receiving rtPA was 140 minutes (SD 69.1). The main independent predictors for outcome and mortality, apart from treatment, were premorbid modified Rankin score, National Institutes of Health stroke scale at admission, age, diabetes, atrial fibrillation, ventilation, and length of hospital stay.

Onset to treatment time ≤4.5 hours

The primary endpoint (modified Rankin score at discharge 0-1 *v* 2-6; fig 2⇓) showed that treatment with rtPA was associated with an overall favourable early outcome (P<0.001). The odds ratio decreased from 2.5 for treatment within 90 minutes (95% confidence interval 2.1 to 2.9) to 1.3 in for treatment within 3.0-4.5 hours (1.1 to 1.5), leading to a number needed to treat of between 4.5 and 18.0 (table 2⇓).

The adjusted in-hospital mortality was not higher in the groups treated up to 4.5 hours after stroke onset; there was also a non-significant trend towards reduced mortality (after adjustment) with an odds ratio of 0.85 (95% confidence interval 0.7 to 1.1) for a time from onset to treatment of up to 90 minutes compared with the group not treated with rtPA (table 3⇓).

Regarding mortality, we found no differences in the subgroups. The main factors associated with in hospital mortality were older age, pulmonary embolism, pneumonia, atrial fibrillation, higher National Institutes of Health stroke scale, and higher premorbid modified Rankin score.

In ordinal logistic regression analysis, the chance of a lower modified Rankin score at discharge was significantly increased with rtPA treatment, and the magnitude of the effect was larger with shorter time to treatment (fig 3⇓, table 4⇓).

Onset to treatment time >4.5 hours

The modified Rankin score at discharge (0-1 *v* 2-6; odds ratio 1.25, 95% confidence interval 1.01 to 1.55) showed a positive effect of thrombolytic therapy in selected patients in clinical practice (fig 2⇓). About 43% (308 of 721) of patients treated after 4.5 hours were assessed by magnetic resonance imaging as the primary imaging modality, while other hospitals used perfusion computer tomography, suggesting that a mismatch paradigm was used for selection of patients. The confidence intervals of the odds ratio are wider than in the 3.0-4.5 hour cohort (because of the smaller sample size), but the odds ratio is comparable with the odds ratio from the pooled analysis of clinical trials (1.25 *v* 1.22), with an estimated number needed to treat of 18.6 versus 21.4 (table 2⇓). The number needed to treat for the 3.0-4.5 hour cohort and the >4.5 hour cohort, in which thrombolytic therapy is offered to only a highly selected subgroup of patients, are comparable with the results of the present study. On the downside, the adjusted in-house mortality for the group >4.5 hours was, as in the pooled analysis of randomised controlled trials, significantly higher (1.45, 1.08 to 1.92; fig 4⇓).

Sensitivity analysis

Sensitivity analysis (with a conservative imputation of missing values in baseline and outcome data) showed similar results (see appendix table B). Because of the imputation that assumed no treatment effect for patients with missing modified Rankin scores at discharge, the estimated treatment effect was, as expected, smaller. As in the main analysis, however, rtPA treatment was associated with better outcome and followed a time-dependent pattern.

Discussion

Principal findings

Thrombolytic therapy in patients with ischaemic stroke in an unselected clinical cohort shows a benefit/risk ratio similar to that in previously reported randomised controlled trials, and, in agreement with a pooled analysis of thrombolytic therapy, there is a clear association between shorter time from onset to treatment and better functional outcome. The time dependent odds ratio for favourable early outcome in routine clinical practice is close to the values found in the pooled analysis of randomised controlled trials, suggesting a similar magnitude of treatment effect, although in our study we could provide outcome data only at 10 days, not 90 days. Thrombolytic therapy beyond the 4.5 hour time window seems to be effective in clinical practice for selected patients, who were selected in almost 50% by mismatch imaging, but is still associated with a significant increase in mortality, which is in line with the findings of the pooled analysis.[4 5] The state-wide thrombolysis rates were >12% for the whole observation period and 14% for 2012, which are among the highest population based rates published so far.

Findings in comparison with other analysis

The pooled analysis of trials of recombinant tissue plasminogen activator (rtPA), with 1273 patients treated in the 4.5 hour time window (and 527 patients beyond the 4.5 hour time window), suggested that the treatment effect is time dependent, with a high association between earlier treatment and favourable outcome (modified Rankin score of 0 or 1).[4 5] These analyses were based on selected patients and centres, and the transferability and generalisability of these findings to routine clinical practice might be limited. Previous smaller non-randomised studies in clinical settings reported inconsistent results, probably because of the limited power conferred by the sample sizes involved.[6-8] A recent study reported a clear relation between time from onset to treatment and outcome in patients treated with intravenous rtPA in clinical practice but did not investigate differences between treated and untreated patients.[6 19] Accordingly, Saver's study incorporated the premorbid functional status but did not report the modified Rankin score as a functional outcome parameter.[19] The SITS registry reported a lower rate of good outcome after thrombolytic therapy in the 3-4.5 hour time window compared with <3 hours but did not perform a comparison with a group of patients not treated with rtPA.[20] The registry contains a high proportion of dedicated stroke centres, so the representativeness of these data is uncertain.[21]

In clinical practice, thrombolytic therapy provides a higher chance of improved early outcome in all patients with acute ischaemic stroke, including those with pre-existing disabilities. Although patients with a pre-existing modified Rankin score of 2 or higher have a smaller potential benefit from thrombolytic therapy, because it is not possible that they will have an outcome after stroke that is better than their pre-existing disability, but still benefit from thrombolysis when compared with patients not treated.[17] Mortality in patients treated with rtPA was comparable with mortality observed in pooled analyses of randomised controlled trials (fig 4⇓).

Our results support the relation between short time to treatment and better functional outcome in everyday clinical practice. This is the first analysis to confirm the association between time to treatment and good functional outcome in a population based state-wide cohort from hospitals with different levels of stroke expertise and levels of specialisation in a state with a population of more than 10 million inhabitants.

After adjustment for imbalances, the magnitude of the association between time from onset to treatment and improved functional outcome in our study within the first 4.5 hours after stroke onset is almost identical to that seen in the pooled analyses (fig 2⇓).

More than 700 patients were treated with rtPA beyond the 4.5 hour time window (up to 12 hours after stroke onset). In this cohort the apparent improvement in outcome was outweighed by increased mortality. Unlike the third international stroke trial (IST-3), in which patients were included on the basis of plain computed tomography, most of our patients were selected with mismatch based approaches.[5 22] Our finding is in line with the pooled analysis, in which a non-significant trend for a favourable outcome was also counterbalanced by a borderline increase in mortality.[4] A recent analysis of the SITS-ISTR register found comparable effectiveness of thrombolytic therapy in those treated within 3.0-4.5 hours and within 4.5-6.0 hours but did not report increased mortality in patients treated beyond 4.5 hours, contrary to the first results from the STTC-trialists-analysis of mortality.[5 10] These findings emphasise the importance of a randomised controlled trial of intravenous

rtPA treatment beyond the 4.5 hour time window selected with modern imaging protocols. We believe that especially because of the increased mortality in this group, patients beyond the 4.5 hour time window should be preferentially treated in clinical trials with the aim of improving patient selection for thrombolytic therapy.

The observed state-wide thrombolysis rate of 14% is among the highest population based rate of thrombolysis published so far.[17 23 24] This is probably because of the inclusion of patients aged over 80 or with pre-existing disability or beyond the 4.5 hour time window in the group who received thrombolysis. As it has been shown that implementation of processes and structures for thrombolytic therapy increases the rate of thrombolysis,[25] the state-wide stroke unit certification system with 49 stroke units for a population of slightly over 10 million inhabitants could have contributed to that rate.[23]

Limitations

Several potential limitations should be considered in interpreting the results of our analysis. First of all, the consecutive and prospective data were collected from all hospitals in Baden-Wuerttemberg. The accuracy of results depends on the accuracy of data input at all locations. Because of the scale of coverage (a whole state), the source data could not be checked as a whole. Predefined logic and range checks are carried out, and regular data reports including assessment of data quality are sent to each hospital. The documentation is performed by the treating physician or by a trained study nurse. This probably ensures a high level of correctness of data. In our setting, with consecutive and prospective documentation of all in-hospital cases (with an actual documentation rate of more than 98%), selection bias is small but might nevertheless be present. While this could be considered a limitation, it also has the benefit of looking at real-life data with all their advantages and weaknesses. For this analysis we excluded patients with missing outcome data (modified Rankin score at discharge) and with missing data in the explanatory variables used in regression models (mainly missing National Institutes of Health stroke scale). We found no evidence for substantial selection bias in a sensitivity analysis with conservatively imputed values. The estimated treatment effect was, as expected, slightly lower than estimated in the main analysis but consistent with the pattern observed in the main analysis. Nevertheless, we cannot completely exclude any selection bias. Moreover, we could not adjust for other potentially influential factors associated with outcome after thrombolytic therapy (like blood glucose, infarct signs on imaging at admission, diastolic blood pressure at admission) because those were not collected in the state-wide database, and we cannot completely exclude other residual confounding.

A further limitation is that the outcome parameter reported in this group was the modified Rankin score at discharge (at a mean of days), while the clinical trials had the modified Rankin score at three months as an outcome parameter. The modified Rankin score at day 10, however, has been shown to be a good proxy for outcome at 90 days (r=0.81).[15] Thrombolytic therapy does not have an impact on differences in the modified Rankin score at 10 and 90 days; the performed comparison of a treated and an untreated group in our study minimises the potential impact on the findings.[15] A life table plot of the updated pooled analysis of the STTC trialists shows a trend toward increased mortality in the first 10 days after stroke onset, but an absolute parallel course of mortality up to the 90 day follow-up, confirming that day 10 data can serve as a proxy for day 90 data.[5] We believe, especially because of the consecutive inclusion and the comparison of a treated and an untreated group for this analysis, that this limitation does not invalidate the overall findings of this analysis.

Finally, the cohort of patients treated with thrombolytic therapy beyond the 4.5 hour time window is relatively small. The treatment of these 721 patients was not standardised, and the confidence interval is wider than that of the 3.0-4.5 hour cohort because of the smaller sample. Comparability with the group of patients treated beyond the 4.5 hour time window in the randomised controlled trials is limited because maximum time from onset to treatment in the trials was six hours, while in our database, almost 400 patients were treated beyond six hours after stroke onset.

Conclusion and policy implications

To summarise, in this database covering the whole population (over 10 million inhabitants) of one of the German federal states earlier treatment of stroke is associated with a better outcome. This is the first analysis to show the effectiveness and safety of thrombolytic therapy in everyday clinical practice from a whole state treated at hospitals with different levels of stroke expertise. The treatment effect of thrombolytic therapy in clinical practice and mortality of patients treated with rtPA was similar to that observed in randomised controlled trials and the pooled analysis. Our findings support the usefulness of initiatives to raise public awareness of stroke symptoms and especially to shorten the time from onset to treatment.

We thank all those who provided data. A list of the participating hospitals in Baden-Wuerttemberg can be found at www.geqik.de/fssa2011.php.

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Contributors: CG designed the study, analysed data, and wrote the paper. CS planned and performed the statistical analysis. BR, CS, TS, HW, RK, and PR were involved in planning of analysis and in interpretation of data. IB and SR were involved in preparation of source data, MGH and WH jointly supervised the research and revised the paper. The “AG Schlaganfall” was involved in interpretation of data and revised the paper. WH is guarantor.

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Competing interest: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: CG holds a scholarship from the Nachwuchsakademie Versorgungsforschung (a health service research body) for a programme in Baden-Wuerttemberg. RK received speaker’s honorariums from Boehringer Ingelheim, Pfitzer, and Philips Healthcare, and received funding from the Federal Ministry of Education and Research (BMBF), Germany. He is a member of the editorial board of the journal

What is already known on this topic

Pooled analyses of randomised clinical trials of recombinant tissue plasminogen activator have shown a time related decreasing benefit/risk ratio within an onset to treatment time of up to 4.5 hours

Study populations included in randomised controlled trials were limited and highly selected, so generalisability and transferability to clinical practice remained to be confirmed

What this study adds

Thrombolytic therapy in patients with ischaemic stroke in an unselected clinical cohort shows a clear association between shorter time from onset to treatment and better functional outcome

The benefit/risk ratio in this analysis of clinical practice was similar to that observed in a pooled analysis of randomised controlled trials, suggesting a similar magnitude of treatment effect

Thrombolytic therapy beyond the 4.5 hour time window seems to be associated with a significant increase in mortality in clinical practice; patients with a prolonged time from onset to treatment should be included in actual or future randomised controlled trials

Cerebrovascular Diseases. IB is the project leader at GeQiK. PR is the national coordinator of the SITS-registry and has received lecture fees and travel compensation for talks regarding thrombolysis and acute stroke treatment from Boehringer-Ingelheim, Ferrer, Paion, Bayer, Sanofi. MGH was the first chair of the Stroke Quality Assurance Committee and the lead author of the quality assessment questionnaire. WH was the first chair of the stroke unit working group in the state of Baden-Wuerttemberg and initiated the SU certification process. He was the chair of the stroke unit working group when the quality assessment was started. He was also the chair of the ECASS 1-3 studies and was compensated for his time by Boehringer Ingelheim, for which he is a consultant.

Ethical approval: This study was approved by the ethics committee of the Medical Faculties, University of Heidelberg (S339-2012) and by the board of the GeQiK.

Transparency statement: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing: Statistical code is available from the corresponding author.

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Tables

Table 1| Characteristics of patients with stroke according to treatment with tissue plasminogen activator (rtPA). Figures are numbers (percentage) of patients unless stated otherwise

	Treatment with intravenous rtPA		
Characteristics	**Yes (n=10 263)**	**No (n=74 176)**	**All patients (n=84 439)**
Women	4774 (46.5)	36 318 (49.0)	41 092 (48.7)
Mean (SD) age (years)	72.2 (12.7)	73.7 (12.5)	73.5 (12.6)
Time from stroke onset to admission (hours):			
<3	9086 (88.5)	18 185 (24.5)	27 271 (32.3)
3-4.5	350 (3.4)	3911 (5.3)	4261 (5.0)
>4.5-6	54 (0.5)	2803 (3.8)	2857 (3.4)
Unclear (3-6 hours)	396 (3.9)	9584 (12.9)	9980 (11.8)
3-6	800 (7.8)	16 298 (22.0)	17 098 (20.2)
>6	377 (3.7)	39 693 (53.5)	40 070 (47.4)
Premorbid modified Rankin score:			
0	7395 (72.1)	45 644 (61.5)	53 039 (62.8)
1	1 170 (11.4)	10 081 (13.6)	11 251 (13.3)
2	791 (7.7)	8866 (12.0)	9657 (11.4)
3	632 (6.2)	6290 (8.5)	6922 (8.2)
4	236 (2.3)	2640 (3.6)	2876 (3.4)
5	39 (0.4)	655 (0.8)	694 (0.8)
Mean (SD) NIHSS	10.2 (6.5)	6.0 (6.6)	6.5 (6.7)
Comorbidities:			
Diabetes	2365 (23.0)	20 931 (28.2)	23 296 (27.6)
Previous stroke	1727 (16.8)	19 686 (26.5)	21 413 (25.4)
Atrial fibrillation	3430 (33.4)	20 743 (28.0)	24 173 (28.6)
Level of stroke care:			
Stroke centre	4246 (41.4)	17 630 (23.8)	21 876 (25.9)
Regional stroke unit	1876 (18.3)	14 380 (19.4)	16 256 (19.3)
Local stroke unit	3297 (32.1)	29 960 (40.4)	33 257 (39.4)
No stroke unit	844 (8.2)	12 206 (16.5)	13 050 (15.5)
Ventilation required	630 (6.1)	2426 (3.3)	3056 (3.6)
Complications:			
Pneumonia	846 (8.2)	3820 (5.1)	4666 (5.5)
Thrombosis or pulmonary embolism	38 (0.4)	222 (0.3)	260 (0.3)
Mean (SD) length of hospital stay (days)	11.2 (7.9)	10.0 (7.6)	10.1 (7.6)

NIHSS=National Institutes of Health stroke scale.

Table 2| Outcomes measured by score on modified Rankin scale (mRS) of treatment in patients with stroke after treatment with tissue plasminogen activator (rtPA) in observational analysis compared with clinical trial data

	Present observational analysis			Pooled analysis of clinical trials[4]			
				No (%) with mRS score 0-1 at 90 days			
Time from onset to treatment (mins)	No (%) with mRS score 0-1 at discharge after intravenous rtPA*	Adjusted OR† (95% CI)	NNT for mRS 0-1	Intravenous rtPA	Placebo	Adjusted OR‡ (95% CI)	NNT for mRS 0-1
0-90	378/1245 (30.4)	2.49 (2.12 to 2.92)	4.5	67/161 (41.6)	44/151 (29.1)	2.55 (1.44 to 4.52)	4.5
91-180	1464/4838 (30.3)	1.86 (1.71 to 2.02)	6.4	127/303 (41.9)	91/315 (28.9)	1.64 (1.12 to 2.40)	9.0
181-270	370/1230 (30.1)	1.26 (1.08 to 1.46)	18.0	361/809 (44.6)	306/811 (37.7)	1.34 (1.06 to 1.68)	14.1
>270§	172/721 (23.9)	1.25 (1.01 to 1.55)	18.6	215/575 (37.4)	193/542 (35.6)	1.22 (0.92 to 1.61)	21.4
Any¶	2966/10 263 (29.0)	1.70 (1.59 to 1.81)	7.7	770/1849 (41.6)	634/1820 (34.8)	1.40 (1.20 to 1.63)	12.6

*Control group 27 998/74 176 (37.7%) without rtPA treatment.

†Adjusted for sex, age, premorbid mRS, National Institutes of Health stroke scale (NIHSS), diabetes, previous stroke, atrial fibrillation, ventilation, pneumonia, thrombosis or pulmonary embolism, level of stroke care, and length of hospital stay.

‡Adjusted for time from onset to treatment, NIHSS, age, categorised diastolic blood pressure at admission, previous hypertension, previous stroke, and interaction of age and NIHSS.

§Includes mismatch approaches between 4.5 hours and 12 hours (721 patients) in observational analysis. In pooled analysis of clinical trial data time from onset to treatment was 270-360 min.

¶Includes 2229 patients with intravenous rtPA in observational analysis for whom time from onset to treatment could not be unambiguously determined.

Table 3| Mortality in patients with stroke after treatment with tissue plasminogen activator (rtPA) in observational analysis compared with clinical trial data

Time from onset to treatment (mins)	Present observational analysis		Pooled analysis of clinical trials[4]		
	No (%) of deaths during hospital stay after intravenous rtPA*	Adjusted OR† (95% CI)	No (%) of deaths within 90 days		Adjusted OR‡ (95% CI)
			Intravenous rtPA	Placebo	
0-90	104/1245 (8.4)	0.85 (0.67 to 1.08)	31/151 (18.6)	30/161 (20.5)	0.78 (0.41 to 1.48)
91-180	403/4838 (8.3)	0.99 (0.87 to 1.13)	49/315 (16.8)	51/303 (15.6)	1.13 (0.70- to 1.82)
181-270	84/1230 (6.8)	0.99 (0.76 to 1.28)	82/811 (11.0)	89/809 (10.1)	1.22 (0.87 to 1.71)
>270§	81/721 (11.2)	1.45 (1.08 to 1.92)	55/542 (15.0)	86/575 (10.2)	1.49 (1.00 to 2.21)
Any¶	900/10 263 (9.6)	1.05 (0.96 to 1.16)	217/1820 (13.9)	257/1849 (11.9)	1.19 (0.96 to 1.·47)

*Pooled analysis of randomised clinical trials of alteplase for acute stroke.

*Control group 4125/74 176 (5.6%) without rtPA treatment.

†Adjusted for sex, age, premorbid mRS score, National Institutes of Health stroke scale (NIHSS), diabetes, previous stroke, atrial fibrillation, ventilation, pneumonia, thrombosis or pulmonary embolism, level of stroke care, and length of hospital stay.

‡Adjusted for NIHSS score at baseline (grouped) and diastolic blood pressure (grouped) and age.

§Includes mismatch approaches between 4.5-12 hours (721 patients) in observational analysis. In pooled analysis of clinical trial data time from onset to treatment was 270-360 min.

¶Includes 2229 patients with intravenous rtPA in observational analysis for whom time from onset to treatment could not be unambiguously determined.

Table 4| Chance of lower score on modified Rankin scale at discharge* in patients with stroke according to intravenous treatment with tissue plasminogen activator (rtPA)

Treatment and time between onset and treatment	No of patients	Adjusted OR† (95% CI)
No intravenous rtPA	74 176	1.00 (reference)
Intravenous rtPA (mins):		
0-90	1245	1.37 (1.24 to 1.51)
91-180	4838	1.18 (1.12 to 1.25)
181-270	1230	1.15 (1.04 to 1.27)
>270‡	721	0.92 (0.81 to 1.06)
Any	10 263	1.17 (1.13 to 1.22)

*See appendix table C for distribution of patients regarding score.

†Adjusted for sex, age, premorbid modified Rankin score, National Institutes of Health stroke scale, diabetes, previous stroke, atrial fibrillation, ventilation, pneumonia, thrombosis or pulmonary embolism, level of stroke care, and length of hospital stay.

‡Includes mismatch approaches between 4.5-12 hours (721 patients).

Figures

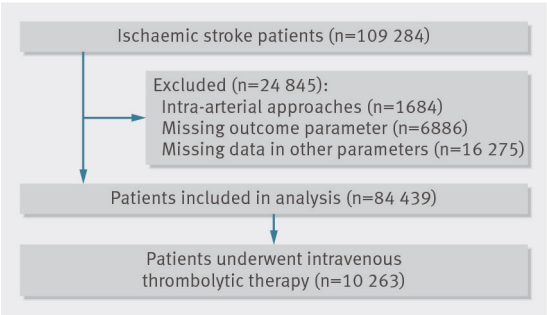

Fig 1 Flow chart of inclusion of patients in study of treatment with recombinant tissue plasminogen activator and outcome of stroke in clinical practice

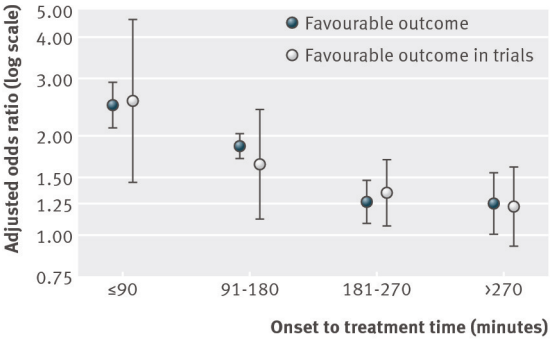

Fig 2 Odds ratio for favourable outcome (score 0-1 on modified Rankin scale) with time to treatment with recombinant tissue plasminogen activator after onset of stroke in binary logistic regression analysis and comparisons with trials (pooled analysis of randomised clinical trials of alteplase for acute stroke[4])

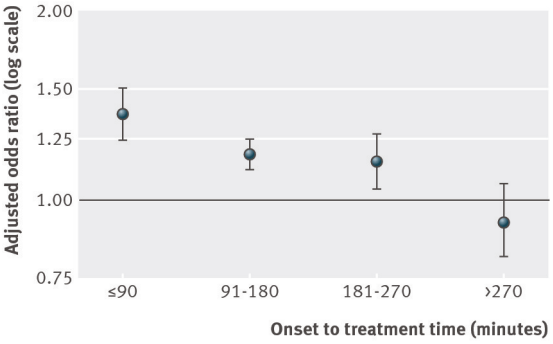

Fig 3 Odds ratios for lower score on modified Rankin scale with time to treatment with recombinant tissue plasminogen activator after onset of stroke in ordinal logistic regression analysis

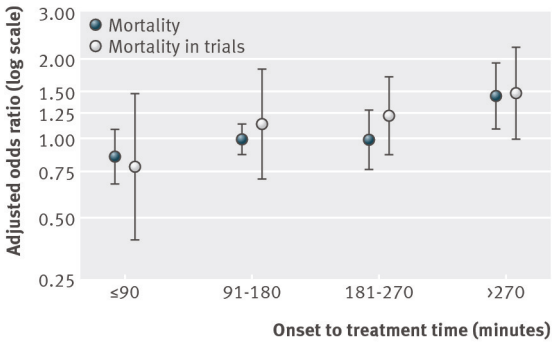

Fig 4 Odds ratio for mortality with time to treatment with recombinant tissue plasminogen activator after onset of stroke and comparisons with pooled analysis of randomised clinical trials of alteplase for acute stroke[4]