Intravenous thrombolysis for acute ischaemic stroke in the elderly: data from the Baden-Wuerttemberg stroke registry

B. Reuter\textsuperscript{a,b}, C. Gumbinger\textsuperscript{c}, T. Sauer\textsuperscript{a}, H. Wiethölter\textsuperscript{d}, I. Bruder\textsuperscript{e}, S. Rode\textsuperscript{e}, P. A. Ringleb\textsuperscript{c}, R. Kern\textsuperscript{a}, W. Hacke\textsuperscript{e} and M. G. Hennerici\textsuperscript{c} Stroke Working Group of Baden-Wuerttemberg\textsuperscript{*}

\textsuperscript{a}Department of Neurology, Universitätsmjizin Mannheim, University of Heidelberg, Mannheim; \textsuperscript{b}Department of Neurology, University Hospital Freiburg, University of Freiburg, Freiburg; \textsuperscript{c}Department of Neurology, University of Heidelberg, Heidelberg; \textsuperscript{d}Department of Neurology, Bürgerhospital, Stuttgart; and \textsuperscript{e}Office for Quality Assurance in Hospitals (GeQiK), Baden-Wuerttembergische Hospital Association, Stuttgart, Germany

Keywords: acute stroke, age, epidemiology of stroke, stroke unit concept, thrombolytic therapy

Background and purpose: In Europe intravenous thrombolysis (IVT) for ischaemic stroke is still not approved for patients aged >80 years. However, elderly patients are frequently treated based on individual decision making. In a retrospective observational study a consecutive and prospective stroke registry in southwest Germany was analysed.

Methods: The data registry collected 101,349 patients with ischaemic stroke hospitalized from January 2008 to December 2012. Of these, 38,575 (38\%) were aged 80 years and older and 10,286 (10.1\%) underwent IVT. Favourable outcome at discharge was defined as modified Rankin Scale (mRS) \leq 1 or not worse than prior to stroke. Multiple logistic regression models stratified by 10-year age groups were used to assess the relationship between IVT and mRS at discharge, adjusted for patient characteristics, admitting facility and length of hospital stay.

Results: The highest IVT rate was 15\% in patients aged <50 years, with a continuous decline down to 8\% in patients aged \geq 90 years. Adjusted odds ratios and 95\% confidence intervals for patients 80–89 years of age were 2.20 (1.95–2.47) (P < 0.0001) and 1.25 (0.88–1.78) (P = 0.21) for patients \geq 90 years of age, compared to patients of the same age decade not treated with IVT.

Conclusions: The evidence from routine hospital care in southwest Germany indicates that IVT is an effective treatment also for aged patients with ischaemic stroke in an age range between 80 and 89 years. Although no clear evidence for the effectiveness of IVT beyond 90 years was found, treatment should also be carefully considered in these patients. High age should not discourage from treatment.

**Introduction**

Currently the only evidence-based approved pharmacetical treatment option for acute ischaemic stroke is intravenous thrombolysis (IVT) with administration of recombinant tissue plasminogen activator (rtPA). Despite modifications of time frames, nowadays IVT in Europe still lacks approval for stroke patients older than 80 years [1–4]. Whilst this restriction was reasonable for the preceding clinical trials aiming for highly homogeneous study populations, as a consequence more than one-third of all stroke patients was...
considered ineligible for treatment [5]. IVT is frequently and successfully performed off-label in the elderly population based on individual decision making, as communicated in several observational studies [6–12]. However, overall efficacy and safety in patients older than 80 years lacked statistical evidence until large registries like the combined analysis of the Safe Implementation of Treatments in Stroke (SITS) and Virtual International Stroke Trials Archive (VISTA) as well as following meta-analyses observed a positive benefit to harm ratio [13–17]. The Third International Stroke Trial (IST-3) provides the highest level of evidence for this age cohort [2]. Although both community and university driven hospitals participate in SITS and IST-3 thereby representing all facets of clinical practice it is believed that a confirmation in a hospital-based stroke registry with mandatory participation is of value.

Data from a large consecutive stroke registry were used to investigate the age-dependent effectiveness of IVT. This registry documents the clinical parameters, diagnostic work-up and outcomes of hospitalized stroke patients in the federal state of Baden-Württemberg (BW) in southwestern Germany [5].

Methods

A retrospective observational study based on a large-scale hospital-based stroke registry was conducted. The study was approved by the ethics committee of the Medical Faculty, University of Heidelberg (S339-2012).

Setting

Baden-Württemberg has approximately 10.8 million inhabitants and 142 hospitals involved in acute stroke care [18]. In 1998 BW implemented a structured three-level medical concept for the treatment of stroke [5]. Since 2005 this concept has been monitored by a consecutive and prospective stroke database. Hospitals involved in acute stroke care are statutorily required to contribute. Therefore the database includes hospitals with stroke care under the responsibility of the departments of internal medicine and neurology, consisting of general wards, stroke units and intensive care units. Stroke patients ≥18 years of age and hospitalized within 7 days after stroke onset are registered. Based on consistency monitoring the overall inclusion rate to this database is >98% of all hospitalized stroke patients in BW [5]. Reasons for not being admitted to a hospital for acute stroke care might be previous severe disability. Over 95% of all stroke patients in Germany are expected to be hospitalized and thus included in this database [19]. Data covering a period of 5 years, from 1 January 2008 to 31 December 2012, were analysed in the present study. The patient cohort was divided into age-stratified subgroups (18–49, 50–59, 60–69, 70–79, 80–89 and ≥90 years of age).

Eligibility criteria and study size

From January 2008 to December 2012, 108 933 out of 173 555 hospitalized stroke patients were discharged with an ICD-10 diagnosis of ischaemic stroke (Fig. 1). Subsequent exclusion criteria were endovascular treatment, acute ischaemic stroke during in-hospital stay, and transfer to other hospitals after diagnostic work-up in emergency departments only. Furthermore, \( n = 19 \, 636 \) ischaemic stroke patients were not primarily included in our outcome analysis because of incomplete data with missing National Institutes of Health Stroke Scale (NIHSS) scores at admission \( (n = 15 \, 255) \) and/or modified Rankin Scale (mRS) scores at discharge \( (n = 4910) \), leaving 81 713 patients suitable for our primary statistical analysis. Missing documentation of adjustment or endpoint variables ranged between 10% (<50 years) and 22% (≥90 years) for NIHSS at admission with an age-dependent

![Figure 1 Study cohort selection flow diagram.](image)
increase, and 4%–5% for mRS at discharge, the latter independent of age. Patient characteristics and procedural parameters are described in detail and the effect of IVT on disability and performance in daily activities is assessed. A secondary sensitivity analysis for all 101,349 patients was conducted by imputation of missing values to identify any substantial differences.

Variables

Documentation includes patient demographic data, medical history, way of hospital admission, hospital admission time, level of hospital care, admitting department and ward, nature and timing of diagnostic procedures, IVT, in-hospital complications, discharge information and hospital mortality. Stroke severity was measured using the NIHSS score at admission and the mRS score, documented as an estimated premorbid mRS at admission and at discharge.

The following binary outcome variables were considered to measure the clinical effectiveness of thrombolysis (all assessed at discharge from hospital): (i) mRS ≤1 or not worse than prior to the index stroke as the primary outcome parameter; (ii) mRS ≤1; (iii) mRS ≤2; (iv) mRS as ordinal outcome variable ('shift analysis'); and (v) in-hospital mortality, respectively, as secondary outcome parameters [20].

Statistical analysis

Standard descriptive statistics were first used to explore differences in patient characteristics, stroke care and clinical outcomes across age groups. Multiple logistic regression models were then used to assess the association between IVT and binary clinical outcomes. For the ordinal outcome mRS at discharge an ordinal logistic regression analysis ('shift analysis') was applied. The models were fitted both stratified and unstratified by age group and were adjusted for patient characteristics (pre-stroke and admission mRS scores, NIHSS score, prior stroke event, diabetes, atrial fibrillation), admitting facility and length of hospital stay. For unstratified analyses of the total study cohort, adjustment was also performed for age.

Sensitivity analyses were conducted with imputed values in the case of missing NIHSS scores at admission and mRS at discharge. For the NIHSS score, the median age and treatment group specific score was imputed and for the mRS at discharge the mRS at admission was carried forward. This strategy was deemed conservative by the authors as it implies no treatment effect for observations with incomplete data.

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

Results

Patient baseline characteristics

Out of 101,349 ischaemic stroke patients, 32,576 (32%) were aged 80–89 years and 5999 (6%) ≥90 years. Patient characteristics are shown in Table 1. The age-dependent gender ratio showed a majority of males in the age groups <80 years, whereas older patients were mostly females. The percentage of patients previously having suffered an ischaemic or haemorrhagic stroke was 11% in stroke patients <50 years and showed a continuous increase up to 30% in stroke patients ≥80 years of age. In accordance with this finding, prior to acute stroke 89% of patients <50 years of age were free of any disability with an mRS of 0, compared to 34% of those aged ≥90 years. The frequency of the comorbid disorders arterial hypertension, diabetes mellitus, hypercholesterolaemia and atrial fibrillation showed an age-dependent increase.

Procedural parameters

Procedural parameters are presented in Table 2. Aged stroke patients were more frequently admitted to a hospital by paramedic or emergency physician assistance and tended to present earlier in emergency departments, probably due to higher stroke severity rates were highest in patients <50 years at 15%, compared to 11% in patients 80–89 years and 8% in the age group ≥90 years (Table 2). In-hospital complications were strongly associated with age, except for deep vein thrombosis and pulmonary embolism with a generally low frequency of <1%.

Effectiveness and mortality

After adjustment for patient, hospital and treatment characteristics IVT was associated with a better functional outcome in stroke patients 80–89 years of age, whilst stroke patients ≥90 years of age showed a non-significant trend towards better outcome [mRS ≤1 or
Patients, NIHSS, median (IQR) 

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age group</th>
<th>&lt;50 years</th>
<th>50–59 years</th>
<th>60–69 years</th>
<th>70–79 years</th>
<th>80–89 years</th>
<th>≥90 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>4977 (5)</td>
<td>8523 (8)</td>
<td>16 307 (16)</td>
<td>32 967 (33)</td>
<td>32 576 (32)</td>
<td>5999 (6)</td>
<td></td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>2021 (41)</td>
<td>2569 (30)</td>
<td>5505 (34)</td>
<td>14 689 (45)</td>
<td>20 611 (63)</td>
<td>4655 (78)</td>
<td></td>
</tr>
<tr>
<td>Pre-stroke mRS score, n (%)</td>
<td>4445 (89)</td>
<td>6940 (81)</td>
<td>12 064 (74)</td>
<td>21 095 (64)</td>
<td>15 385 (47)</td>
<td>20 298 (34)</td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>1306 (42)</td>
<td>3936 (72)</td>
<td>8064 (83)</td>
<td>18 234 (88)</td>
<td>18 114 (89)</td>
<td>3520 (87)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>1050 (54)</td>
<td>2789 (51)</td>
<td>5471 (56)</td>
<td>11 646 (56)</td>
<td>10 143 (50)</td>
<td>1619 (40)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>158 (9)</td>
<td>643 (8)</td>
<td>2679 (16)</td>
<td>9233 (28)</td>
<td>13 885 (43)</td>
<td>3091 (52)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>483 (10)</td>
<td>1831 (22)</td>
<td>4774 (29)</td>
<td>10 444 (32)</td>
<td>9447 (29)</td>
<td>1310 (22)</td>
<td></td>
</tr>
<tr>
<td>Prior stroke event, n (%)</td>
<td>533 (11)</td>
<td>1466 (17)</td>
<td>3654 (22)</td>
<td>8994 (27)</td>
<td>9794 (30)</td>
<td>1768 (30)</td>
<td></td>
</tr>
</tbody>
</table>
| IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

A = Information was missing for N = 15 255 patients.

B = Information was not routinely documented over the entire study period and is therefore missing for N = 37 744 patients.

Table 1 Patient characteristics

not worse than prior to the index stroke; 80–89 years, adjusted odds ratio (aOR) 2.20, 95% confidence interval (95% CI) 1.95–2.47 (P < 0.0001); ≥90 years, aOR 1.25, 95% CI 0.88–1.78 (P = 0.21); Table 3. This effect was consistent for most but not all secondary positive functional outcome parameters at discharge, estimated by binary or ordinal logistic regression analyses with mRS ≤1 [80–89 years, aOR 2.36, 95% CI 2.07–2.72 (P < 0.0001); ≥90 years, aOR 1.44, 95% CI 0.90–2.30 (P = 0.13); Table S1] and shift analysis [80–89 years, aOR 1.60, 95% CI 1.48–1.72 (P < 0.0001); ≥90 years, aOR 1.11, 95% CI 0.91–1.36 (P = 0.30); Table S2]. When favourable outcome was defined as mRS ≤2, stroke patients ≥90 years of age also showed a significant benefit [80–89 years, aOR 1.90, 95% CI 1.69–2.14 (P < 0.0001); ≥90 years, aOR 1.61, 95% CI 1.13–2.31 (P = 0.009); Table 4]. Overall mortality was higher in those receiving IVT at 9% compared to 5%; however, this difference was not significant after adjustment for confounders (aOR 1.06, 95% CI 0.97–1.16, P = 0.19; Table 5). Age-stratified analyses revealed a borderline significant association between IVT and mortality for those 80–89 years of age (aOR 0.14, 95% CI 1.00–1.30, P = 0.05) but not for those ≥90 years (aOR 1.21, 95% CI 0.97–1.61, P = 0.18).

In sensitivity analyses with imputation in the case of missing values for the NIHSS score (n = 15 255) and the mRS score at discharge (n = 4910), very similar results to the primary analyses were observed (Tables S3 and S4).

Discussion

Although in violation of a formal restriction, IVT for elderly patients is a common finding in daily clinical routine in southwest Germany. Our results support preliminary evidence that IVT within 4.5 h of onset is an effective treatment for ischaemic stroke patients older than 80 years. In binary logistic regression analysis with definition of an mRS ≤1 or not worse than prior to the index stroke as a favourable outcome parameter, the aOR of patients between 80 and 89 years showed a significantly positive and almost equally effective response to IVT compared to younger stroke patients (Table 3). IVT in patients ≥90 years of age showed a positive trend, but no clear evidence for effectiveness. These results were very reliable in ordinal logistic regression analysis (shift analysis) or binary logistic regression analysis with mRS ≤1 as secondary outcome parameter (Tables S1 and S2). However, after statistical calculation with a mRS ≤2 as the favourable outcome parameter, patients aged ≥90 years demonstrated a significantly positive response to IVT (Table 4).

The results provided by our analysis and representing daily clinical routine are comparable to those presented by the combined analysis of SITS and VISTA [13]. The IST-3 trial and two meta-analyses by Wardlaw et al. from 2012 and Emberson et al. from 2014 showed a generally beneficial effect for those aged >80 years, but did not distinguish between stroke patients 81–90 years and ≥90 years of age [2,3,17,21].
Hospital mortality was higher in the old and showed a borderline significant association with IVT in the age group 80–89 years after adjustment for stroke severity and comorbidities. This is contrary to the results provided from previous observational stroke registries, which reported no higher mortality in the treatment cohort ≥80 years of age at days 30–90 after stroke [13,22]. The IST-3 trial revealed that a higher 7-day mortality in the treatment group was more than counterbalanced by a lower mortality in the following 7 days to 3 months [2]. This time-dependent finding might also account for the overall higher mortality in the rtPA treatment group in our study.

Several age-dependent differences in baseline parameters, the mode of hospital admission and level of stroke care were noticed. Regarding the pre-stroke mRS, 90% of the youngest age cohort 18–50 years were free of any disability. This number strongly declined with increasing age, with only half of patients aged 80–89 years and one-third of the ≥90 years of age patients having an mRS of 0 prior to stroke. This observation is of importance for the definition of clinical endpoints in future clinical trials with elderly patients. Stroke patients ≥80 years of age should therefore have a generally higher chance of being selected for IVT. However, the faster onset to door-time seemed to be counterbalanced by a lower chance of being treated in hospitals of high level stroke care, departments of neurology and specialized stroke units.

Several limitations of our study have to be addressed. Despite the fact that the source of our analysis is a stroke registry with subsequent methodological limitations, the main restriction is a missing
long-term outcome parameter. Nevertheless, it was previously demonstrated that the short-term mRS at discharge can serve as a sufficient proxy for long-term outcome [23]. Furthermore, the mRS at discharge in our analysis corresponds quite well with the 3-month outcome data derived from SITS/VISTA [13]. Secondly, our study suffered from a relevant proportion of missing stroke severity or functional scores, with 15.1% for NIHSS at admission and 4.8% for mRS at discharge. To avoid a substantial selection bias and thus over-interpretation of our results, a conservative procedure with imputation of missing parameters was performed under the assumption of no rtPA-related treatment effect and the results were comparable to our primary analysis. Thirdly, concerning in-hospital complications, our analysis is not able to provide any information about secondary intracerebral haemorrhage. However, according to SITS-ISTR higher age was not found to be associated with an increased risk for secondary symptomatic intracerebral haemorrhage (SITS-MOST definition) [13]. Fourthly, the small fraction of stroke patients who receive outpatient

<table>
<thead>
<tr>
<th>Age group</th>
<th>Thrombolytic therapy</th>
<th>No thrombolytic therapy</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 years</td>
<td>667 (49)</td>
<td>3622 (65)</td>
<td>2.25 (1.79, 2.82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>50–59 years</td>
<td>1042 (42)</td>
<td>6202 (58)</td>
<td>2.44 (2.04, 2.93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>60–69 years</td>
<td>1835 (37)</td>
<td>11 867 (55)</td>
<td>2.03 (1.77, 2.33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>70–79 years</td>
<td>3499 (32)</td>
<td>23 213 (50)</td>
<td>2.23 (2.01, 2.47)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>80–89 years</td>
<td>2849 (25)</td>
<td>22 509 (39)</td>
<td>2.20 (1.95, 2.47)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥90 years</td>
<td>394 (15)</td>
<td>4014 (32)</td>
<td>1.25 (0.88, 1.78)</td>
<td>0.21</td>
</tr>
<tr>
<td>Overall</td>
<td>10 286 (32)</td>
<td>71 427 (48)</td>
<td>2.18 (2.05, 2.31)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio.

Numbers do not add up to group totals in Table 1 due to missing values in the outcome variable.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Thrombolytic therapy</th>
<th>No thrombolytic therapy</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 years</td>
<td>667 (65)</td>
<td>3622 (82)</td>
<td>1.69 (1.31, 2.18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>50–59 years</td>
<td>1042 (61)</td>
<td>6202 (76)</td>
<td>1.94 (1.60, 2.36)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>60–69 years</td>
<td>1835 (54)</td>
<td>11 867 (71)</td>
<td>1.73 (1.50, 2.00)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>70–79 years</td>
<td>3499 (45)</td>
<td>23 213 (64)</td>
<td>1.87 (1.68, 2.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>80–89 years</td>
<td>2849 (32)</td>
<td>22 509 (46)</td>
<td>1.90 (1.69, 2.14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥90 years</td>
<td>394 (17)</td>
<td>4014 (30)</td>
<td>1.61 (1.13, 2.31)</td>
<td>0.009</td>
</tr>
<tr>
<td>Overall</td>
<td>10 286 (45)</td>
<td>71 427 (60)</td>
<td>1.84 (1.73, 1.96)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio.

Numbers do not add up to group totals in Table 1 due to missing values in the outcome variable.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Thrombolytic therapy</th>
<th>No thrombolytic therapy</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 years</td>
<td>9/712 (1)</td>
<td>31/3760 (1)</td>
<td>0.83 (0.37, 1.83)</td>
<td>0.64</td>
</tr>
<tr>
<td>50–59 years</td>
<td>22/1098 (2)</td>
<td>78/6486 (1)</td>
<td>0.91 (0.53, 1.58)</td>
<td>0.75</td>
</tr>
<tr>
<td>60–69 years</td>
<td>97/1954 (5)</td>
<td>293/12 393 (2)</td>
<td>1.23 (0.94, 1.62)</td>
<td>0.13</td>
</tr>
<tr>
<td>70–79 years</td>
<td>297/29384 (8)</td>
<td>977/24 419 (4)</td>
<td>1.02 (0.87, 1.20)</td>
<td>0.80</td>
</tr>
<tr>
<td>80–89 years</td>
<td>435/3146 (14)</td>
<td>2073/23 683 (9)</td>
<td>1.14 (1.00, 1.30)</td>
<td>0.05</td>
</tr>
<tr>
<td>≥90 years</td>
<td>94/466 (20)</td>
<td>614/4193 (15)</td>
<td>1.21 (0.91, 1.61)</td>
<td>0.18</td>
</tr>
<tr>
<td>Overall</td>
<td>954/11 160 (9)</td>
<td>4066/74 934 (5)</td>
<td>1.10 (1.01, 1.21)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.

Numbers do not add up to group totals in Table 1 due to missing values in the outcome variable.

Table 3 Outcome mRS score ≤1 or no worse than prior to the index stroke at discharge

Table 4 Outcome mRS ≤2 at discharge

Table 5 Outcome in-hospital mortality
treatment only for various reasons such as severe dementia or malignant disease are not registered in the database. This comprises <5% of all annual stroke patients in BW [5].

In conclusion, data from a stroke registry which covers approximately 10.8 million inhabitants in Germany are provided. The epidemiological, procedural and outcome parameters of 101 349 ischaemic stroke patients hospitalized between 2008 and 2012 were analysed. Ischaemic stroke patients 80–89 years of age showed a correspondingly favourable functional outcome compared to younger stroke patients when receiving IVT. This comes at the cost of a borderline significant higher mortality in patients 80–89 years of age. Patients ≥90 years of age showed a non-significant trend towards favourable outcome. In this age group mortality was not higher after IVT. Our data were consistent for different statistical models to evaluate favourable functional outcome, i.e. mRS ≤1 or not worse than prior to the index stroke as our primary outcome parameter, mRS ≤1 and ordinal logistic regression ‘shift analysis’ as secondary outcome parameters, respectively. Under the definition of mRS ≤2 as favourable outcome parameter also patients aged >90 years demonstrated a significantly positive outcome after IVT. Our data confirm the evidence derived from international stroke registries and controlled stroke trials and reflect daily clinical practice in central Europe. If otherwise eligible, ischaemic stroke patients should be treated with IVT regardless of age.

Acknowledgements
The authors wish to thank Christian Stock, Institute of Medical Biometry and Informatics, University of Heidelberg, for the fundamental statistical support and all collaborators in the hospitals of Baden-Wuerttemberg for providing data. A complete list of the 144 hospitals can be found at http://www.geqik.de/fs-sa2011.php. The study was supported by an internal grant from the Department of Neurology, Medical Faculty Mannheim, Ruprecht-Karls Universität Heidelberg, Germany. The sources of funding did not influence the study design, the collection, analysis and interpretation of data, the writing of the report, and the decision to submit the article for publication.

Disclosure of conflicts of interest
All authors declare no support from any organization for the submitted work. CG holds a scholarship from the Nachwuchsakademie Versorgungsforschung (a health service research body) for a programme in Baden-Wuerttemberg. R.K. has received speaker’s honoraria from Boehringer Ingelheim that were unrelated to this study, Pfizer and Philips Healthcare. P.R. has received lecture fees and travel compensation from Boehringer-Ingelheim that were unrelated to this study, Ferrer, Paion, Bayer and Sanofi. W.H. reported honoraria from Johnson & Johnson and Bayer and advisory board fees from Boehringer Ingelheim that were unrelated to this study. M.G.H. has received research grant support from Boehringer Ingelheim and Bayer that were unrelated to this study. No other relationships or activities are disclosed that could appear to have influenced the submitted work.

Supporting Information
Additional Supporting Information may be found in the online version of this article:
Table S1. Outcome mRS score 0–1 at discharge (binary logistic regression analysis).
Table S2. Outcome mRS score at discharge (ordinal logistic regression analysis, ‘shift analysis’).
Table S3. Characteristics of included and excluded patients.
Table S4. Comparison of outcome in binary and ordinal logistic regression models without inclusion of patients with missing endpoint variables.

References
7. Berrouschot J, Rother J, Glahn J, Kucinski T, Fiehler J, Thomalla G. Outcome and severe hemorrhagic compli-
cations of intravenous thrombolysis with tissue plasminogen activator in very old (≥ 80 years) stroke patients. *Stroke* 2005; 36: 2421–2425.


