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SYSTEMATIC REVIEW

Intravenous thrombolysis in stroke patients of ≥80 versus <80 years of age—a systematic review across cohort studies

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Abstract

Objective: elderly stroke patients were excluded or underrepresented in the randomised controlled trials of intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) applied within 3 h. Cohort studies comparing intravenous rtPA in stroke patients of ≥80 versus <80 years of age were limited by small sample sizes and yielded conflicting results. Thus, we performed a systematic review across all such studies.
Methods: a systematic literature search (PubMed; Science Citation Index) was performed to retrieve all eligible studies. Two reviewers independently extracted data on 'death', 'favourable 3-month outcome (modified Rankin Scale ≤1)' and 'symptomatic intracranial haemorrhage (sICH)'. Across studies, weighted odds ratios (ORs) with 95% confidence intervals (95% CI) were calculated.
Results: six studies were included [n = 2,244 patients; 477 (21%) aged ≥80 years]. Significant differences in baseline characteristics to the disadvantage of older patients were present in all studies. Compared with younger patients, older patients had a 3.09-time (95% CI = 2.37–4.03; $P < 0.001$) higher 3-month mortality and were less likely to regain a 'favourable outcome' (OR = 0.53; 95% CI = 0.42–0.66; $P<0.001$). The likelihood for 'sICH' (OR = 1.22; 95% CI = 0.77–1.94; $P = 0.34$) was similar in both age groups.
Conclusion: intravenous rtPA-treated stroke patients of ≥80 years of age have a less favourable outcome than younger ones. Imbalances in predictive baseline variables to the disadvantage of the older patients may contribute to this finding. Compared with the younger cohort, rtPA-treated stroke patients aged ≥80 years do not seem exceedingly prone to sICH. Thus, there is scope for benefit from thrombolysis for the older age group. Hence, to obtain reliable evidence on the balance of risk and benefit of intravenous rtPA for stroke patients aged ≥80 years, it is safe and reasonable to include such patients in randomised placebo-controlled trials.

Keywords: *thrombolysis, stroke, elderly, ageing, outcome, systematic review*

Introduction

Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) applied within 3 h is efficacious in acute stroke patients [1, 2]. The evidence is less clear for the very elderly, because just 42 patients in the randomised controlled rtPA trials (RCTs) were over 80 years old [2]. In rtPA-treated stroke patients, advancing age is associated with increased in-hospital mortality [3] and increased risk of haemorrhage [4]. However, older stroke patients have a higher stroke mortality [5] without rtPA treatment too and are less likely to recover than younger ones [6, 7]. Thus, stroke patients aged ≥80 years may also benefit from rtPA treatment. More recent or ongoing randomised controlled thrombolysis trials (RCTs) have excluded very old stroke patients (e.g. DIAS and ECASS-3). IST-3 has no upper age limit but uses a different time window (6 h). Thus, the lack of RCT-based data about the usefulness of rtPA within the first 3 h in elderly stroke patients probably will persist in the near future.

Recent cohort studies comparing intravenous rtPA-treated stroke patients aged ≥80 years with those younger than 80 years of age showed inconsistent findings. In some studies, the older patients were less likely to recover favourably [8–11]. In other reports, the odds of favourable outcome were comparable between both the age groups [12–14]. The major limitation of these studies was the small sample size for the elderly group. This shortcoming can be overcome by a systematic review. A systematic assessment across all comparative cohort studies yields more clarity

about the odds for benefits and risks of intravenous rtPA for stroke patients aged ≥80 years compared with younger ones [15, 16]. In addition, the evaluation of potential confounders can disclose important limitations. Thus, until more RCT-based evidence is available, a systematic review can provide information, which may be clinically useful for individual treatment decisions.

Methods

Search strategy

To retrieve all cohort studies and case series comparing intravenous rtPA-treated stroke patients of ≥80 years versus <80 years of age, we searched PubMed (MEDLINE 1966—3 July 2006) and Science Citation Index (last search 3 July 2006). The following MESH search terms were used: 'thrombolytic therapy' and 'cerebrovascular accident' and 'aged, 80 and over' and 'tissue plasminogen activator'. Furthermore, we used the combination of 'thrombolysis', 'stroke' and 'elderly' or 'aged 80 and over' as free search terms. We also reviewed citations from retrieved studies. All abstracts that met our search strategy were reviewed. In addition, Science Citation Index was used to check for all articles that cited the included studies.

We used the following inclusion criteria:

1. Cohort studies comparing outcome of intravenous rtPA-treated stroke patients of ≥80 years versus <80 years of age (i.e. control group).
2. Extractable data stratified according to age groups about mortality, functional outcome as assessed with the modified Rankin Scale (mRS) [17] score after 3 months and symptomatic intracranial haemorrhages (sICH) according to reported definitions.
3. For both age groups, outcome measures and criteria were applied uniformly. We excluded abstracts, case reports, case series with a historical control and reviews without new data.

Quality assessment

The methodological quality was assessed with a checklist, derived from a recent systematic review and modified for the present study [18]. A single rater (S.T.E.) scored the presence or absence of 12 quality criteria (Table 1). Instead of calculating a summary quality score, which has been criticised as misleading [19], we addressed the types of bias potentially present [18].

Characterisation of included studies

The following items were compiled: study type, thrombolysis protocol referred to, criteria used for sICH, main outcome variables, number of included patients, age, median NIH Stroke Scale Score (NIHSS) [20] (mean if median was not available) and median time to treatment in both the groups. Significant differences (i.e. $P<0.05$) in baseline characteristics between both the groups were listed, too.

Data extraction

Two independent reviewers (S.T.E. and L.H.B.) extracted individual data from the included studies. For both the age

Table 1. Summary of the methodological assessment of included studies

	Hypothesis/ objective defined	Study population defined, characterised	Inclusion/ exclusion criteria defined	Consecutive patients	Pre-defined study design	Prospective data collection	Missing data, lost to follow-up quantified	Potentially confounding variables addressed	Outcome assessment at same time	Blinded assessment	Definition of outcome variables	Data analysis/ presentation comprehensible	Total
US-tPA Survey 2000	+	+	+	+	–	–	–	–	–	–	+	+	6/12
Altenburg/Hamburg/ Minden 2005	+	+	+	+	–	+	–	–	+	–	+	+	8/12
Houston 2005	+	+	+	+	–	–	–	+	–	+	+	+	8/12
Switzerland 2005	+	+	+	+	–	+	–	+	+	–	+	+	9/12
Maastricht 2006	+	+	+	+	–	–	–	+	+	–	+	+	8/12
Canada 2006	+	+	+	–	–	+	–	+	+	–	+	+	8/12

Assignment of '+' means quality criterion fulfilled. Assignment of '–' means quality criterion not fulfilled or unclear.

groups, the number of patients with each of the following outcome measures was extracted: (i) death of all cause, as close to 3 months post-stroke as available, (ii) favourable outcome defined as mRS ≤1 after 3 months among all patients and (iii) among survivors and (iv) sICH. Discrepancies were solved by consensus.

Analyses

For each outcome measure, we calculated a weighted estimate of the odds for the older versus the younger age group across studies. Heterogeneity between study results was tested by chi-square tests. For outcome measures without between-study heterogeneity, odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated using the Peto fixed-effect model. In case of significant heterogeneity, the random-effect model was applied. Statistical analyses were performed using the Cochrane Collaboration's Review Manager Computer program (RevMan; Version 4.2.8) [21].

Results

Study population

Among nine cohort studies identified, two were excluded because of the lack of a control group [22] or the age range for the control group (i.e. 76–80 years) [23] diverging from the inclusion criteria, respectively. One single-centre study [9] was excluded, because data overlap with a nationwide study was assumed [11].

Our study population comprised six cohort studies with a total of 2,244 patients, of which 477 (21%) were ≥80 years old. The percentage of patients who were ≥80 years of age varied between studies from 12 [13], 16 [8, 12], 24 [10, 11] to 31% [14].

Quality assessment and characteristics of included studies

The methodological assessment of included studies is summarised in Table 1. All studies but one stated that consecutive patients were included. However, none mentioned the number of missing data or lost to follow-ups. Potentially confounding variables such as the meaning of outcome predictors other than age were mentioned in four studies [10, 11, 13, 14] and quantified in two [10, 14]. Two studies assessed outcome including mortality at discharge rather than at a defined time point [12, 14].

All studies reported on significant differences in baseline characteristics between both groups apart from age. In the older age group, female preponderance was reported in five studies [8, 10, 11, 13, 14], cardioembolic stroke aetiology [13, 14] and atrial fibrillation [11, 13] were more frequent (two studies each), and mean systolic blood pressures were higher (three studies) [11–13]. Fewer protocol violations occurred in one [12] but not in another study [11]. The elderly age group had higher mean NIHSS in one study [11], whereas median or mean NIHSS before thrombolysis did not differ between age groups in three other studies [8, 13, 14]. Mean time-to-treatment times were similar in both the age groups according to all four studies that addressed this issue [10, 11, 13, 14]. The definition of symptomatic ICH was the same for both the age groups within all studies but varied between studies. In four studies, ICH associated with any clinical deterioration meant symptomatic ICH [10–13]. In other studies, symptomatic ICH required an increase of at least 4 NIHSS points [8, 14] (Table 2).

Outcome

Statistically, there was no relevant heterogeneity between study results for all outcome measures (I^2<11%; Figure 1). The OR of 'death (all cause)' among rtPA-treated stroke patients aged ≥80 years was 3.09 (95% CI = 2.37–4.03; P<0.001) compared with younger patients. Within studies, the 3-month mortality rates ranged from 21 [8] to 40% [10] for the older group compared with those ranging from 5 [8] to 18% [11] for the younger cohorts.

For the evaluation of 'favourable outcome after 3 months', two studies had to be excluded for the following reasons: (i) mRS was not determined [14] and (ii) outcome was assessed at discharge rather than after 3 months [12, 14].

On the basis of four studies with a total of 1,872 patients, the older age group was less likely to regain 'favourable outcome' (OR = 0.53; 95% CI = 0.42–0.66; P<0.001) compared with the younger group. Likewise, the likelihood for 'favourable outcome among survivors' (OR = 0.69; 95% CI = 0.53–0.90; P = 0.007) was lower for the older age group, too. Among survivors, 33–44% of the older patients and 33–53% of younger ones had mRS ≤ 1 [8, 10, 11, 13].

For 'sICH', the OR of 1.22 with a 95% CI 0.77–1.94 (P = 0.34) indicated no statistically significant difference between older and younger patients. The percentage of symptomatic ICH varied across studies from 3 to 13% [8, 10–14] (Figure 1).

Discussion

This systematic review across cohort studies comparing intravenous rtPA-treated stroke patients of over and below age 80 years had the following main findings.

1. Stroke patients of ≥80 years receiving rtPA have a substantially higher mortality risk than younger patients and were less likely to recover favourably.
2. The risk of sICH is similar in both the age groups.

Among intravenous rtPA-treated stroke patients, those aged ≥80 years had a 3.09 (95% CI = 2.37–4.03) times higher likelihood to die within the next 3 months compared with younger patients. Without intravenous rtPA, virtually the same OR for '3-month mortality'—3.14 (95% CI = 2.69–3.66)—can be calculated for stroke patients of the same age groups based on the data of the BIOMED study (n = 4,499) [5].

The chance of a favourable outcome was also significantly lower for the older age group. On the basis of data from the BIOMED study, in stroke patients without rtPA, the odds for being discharged home—an assumed surrogate marker for favourable outcome—were significantly lower [OR = 0.42 (95% CI = 0.36–0.48)] for the older age group, too. Thus, these indirect comparisons indicate that age is an

Table 2. Characteristics of included studies

	Study type	Thrombolysis protocol	Main outcome variables	n		Age, median (range)		NIHSS, median (range)		Time to treatment median (min)		Differences in baseline characteristics P < 0.05 (≥80 years versus <80 years)
				≥80 years	<80 years	≥80 years	<80 years	≥80 years	<80 years	≥80 years	<80 years	
US-tPA Survey 2000	Multicentre [13] survey	NINDS	In-hospital mortality Discharge mRS[a] ICH[b] within 36 h	30	159	85 (80–97)	61 (30–79)	–	–	–	–	Less often protocol violations (13 versus 33%) More often treated by stroke specialists (87 versus 66%) Higher mean systolic BP (181 versus 162 mmHg)
Altenburg/ Hamburg/ Minden 2005	Three-centre cohort study	NINDS with modifications ; 22% after 3 h	MRS[a] after 3 months 3-month mortality ICH[c]	38	190	83 (81–85)	65 (57–71)	16 (10–19)	14 (9–17)	–		More women (61 versus 35%)
Houston 2005	Single-centre cohort study	NINDS with minor modifications	In-hospital mortality ICH[c] Discharge disp. Recanalisation 24-h NIHSS	56	127	84 (80–93)	66 (31–79)	18	14	130	120	More women (sex ratio 2.8 versus 0.84) More cardioembolism (61 versus 33%) Less often undetermined aetiology (7 versus 27%)
Switzerland 2005	Multicentre [9] databank-based cohort study	NINDS with minor modifications	3-month mortality mRS[a] ≤1 versus >1 after 3 months ICH[b]	38	287	84 (80–92)	64 (23–79)	14 (5–23)	14 (2–35)	155 (±35.5)	158 (±35.3)	More women (63 versus 33%) More cardioembolism (79 versus 33%) More atrial fibrillation (72 versus 19%) Higher mean systolic BP (171 versus 153 mmHg)

Table 2. *continued*

	Study type	Thrombolysis protocol	Main outcome variables	n		Age, median (range)		NIHSS, median (range)		Time to treatment median (min)		Differences in baseline characteristics P < 0.05
				≥80 years	<80 years	≥80 years	<80 years	≥80 years	<80 years	≥80 years	<80 years	(≥80 years versus <80 years)
Maastricht 2006	Single-centre databank-based cohort study	NINDS with minor modifications	3-month mortality	45	139	84 (80–97)	68 (24–79)	–	–	148 (±36)	140 (±34)	More women (60 versus 35%)
			mRS[a] ≤1 versus >1 after 3 months									Less smokers (7 versus 30%)
			ICH[b]									More ischaemic HD (44 versus 25%)
												More congestive HD (13 versus 4%)
Canada 2006	Multicentre [60] databank-based cohort study	Canadian Stroke Consortium	MRS[a] ≤1 versus >1 after 3 months	270	865	85 mean	66 mean	16 mean ±6.4	14 mean ±6.2	146 mean ±34	150 mean ±39	More women (60 versus 37%)
			ICH[b] (24 h)									Higher mean NIHSS
			Predictors of outcome									More atrial fibrillation (37 versus 18%)
			Complications									Higher mean systolic BP (155 versus 150 mmHg
												More congestive HD (11 versus 6%)
												More pre-rtPA mRS>1 (28 versus 20%)
												Less hyperlipidaemia (10 versus 22%)
												Less smoking (3 versus 19%)

NIHSS indicates NIH Stroke Scale Score; BI means Barthel Index; HD means heart disease; Systolic BP indicates systolic blood pressure before thrombolysis; History of CHF indicates history of congestive heart failure, h means hours.

[a]mRS indicates modified Rankin scale score. Favourable outcome is defined as ≤1. All other scores including 6 (i.e. death) indicate poor outcome. ICH indicates intracranial haemorrhage. Definition of symptomatic ICH varied between studies.

[b]Symptomatic intracranial haemorrhage (ICH) was defined as any CT/MRI-documented haemorrhage that was temporally related to any deterioration in the patient's clinical condition [10–13].

[c]Symptomatic ICH was defined as any intracerebral blood on follow-up CT/MRI, associated with an NIHSS score increased by ≥4 points [8, 14].

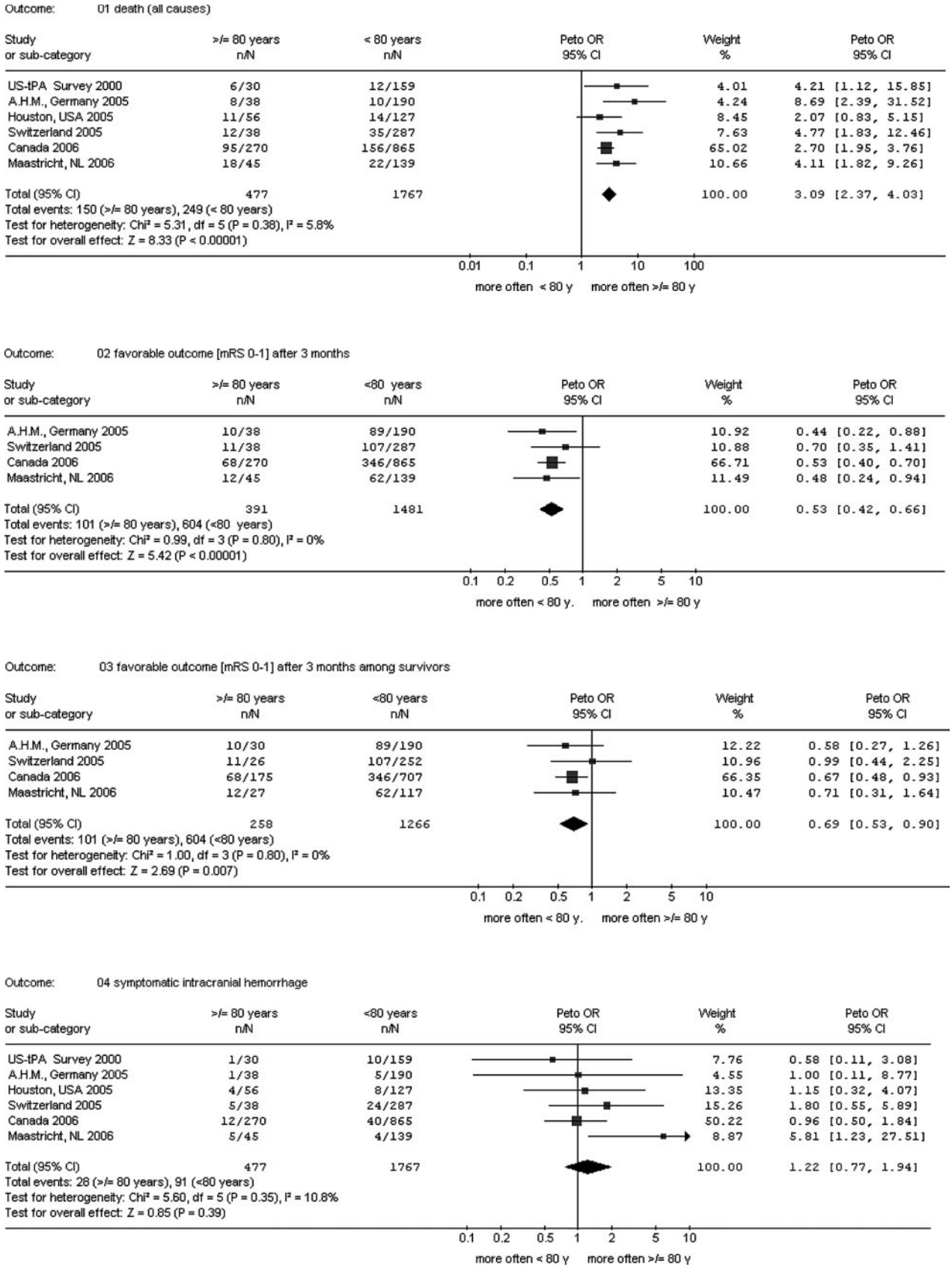

Figure 1. Odds ratios across studies for the outcome events 'death', 'favourable outcome after 3 months', 'favourable outcome among survivors' and 'symptomatic intracranial haemorrhage' of intravenous rtPA-treated stroke patients of ≥80 years of age compared with those of <80 years of age.

outcome predictor in stroke patients treated with rtPA as well as in those without.

The likelihood of sICH did not differ between both the age groups. Advancing age as a continuous variable was a risk factor for sICH in some [4] but not in other randomised placebo-controlled rtPA trials [24]. Our findings clarified that, within an intravenous rtPA population dichotomised in age ≥80 versus <80 years, the risk of sICH is not increased in the older cohort.

The evaluation of potential confounders showed that neither study gave quantified details about missing data. Thus, it remains unknown whether the rate of patients lost to follow-up was equally distributed among both the age groups. Furthermore, two studies had to be excluded from the evaluation of the likelihood for favourable outcome, because outcome measures were assessed at discharge rather than at a pre-defined time point [12, 14]. Such an approach is potentially confounded by differences in length of hospitalisation [25]. For patients with longer lengths of hospitalisation, better functional rating scores become more likely, because patients have more time to recover [25].

All studies reported on significant differences in baseline characteristics to the disadvantages for the older compared to the younger age group. Female sex was overrepresented among the older patients and has been considered an unfavourable outcome predictor [26, 27]. In virtually all studies, older patients were more likely to exhibit cardiac comorbidity or higher blood pressure, which has been reported to predispose to poorer outcome [28] or increase the risk for haemorrhagic transformation. In the largest study [11], stroke severity (i.e. mean NIHSS) as the most important outcome predictor [28] was more pronounced in the older than in the younger age group. Furthermore, pre-stroke disability was more frequent among older than younger patients in this study. These imbalances are likely to contribute to the less favourable outcome among the older age group.

There are several limitations. First, we could not adjust for the aforementioned confounding factors, because this would require individual patient data from each study. The two largest studies [11, 13] performed logistic regression analyses to reveal independent outcome predictors. Both identified stroke severity and glucose level. Age ≥80 years was an additional independent outcome predictor in the Canadian series [11], but not in the Swiss study, in which time to treatment, history of coronary heart disease, glucose level and stroke severity were more important predictive variables than age ≥80 years [13].

Second, methodological quality differed across the studies. Nevertheless, we did not introduce a threshold of a summary quality score, because this has been criticised as potentially misleading [19]. In addition, exclusion of the study with fewest quality criteria achieved would not alter our findings substantially [i.e. $OR_{mortality}$ = 3.05 (95% CI = 2.32–4.00) and OR_{sICH} = 1.30 (95% CI = 0.8–2.11)].

Third, the ORs for favourable outcome defined by an mRS score of 0–1 were based on solely four of the six cohort studies, which may limit the generalisability of the results. Although the sample size for favourable outcome was smaller as for the other outcome variables, the entire population comprised 1,872 patients, which seems large enough for reasonable conclusions.

Fourth, in the older age group, the likelihood for pre-existing disability is higher than that in younger patients. Thus, fewer older than younger patients are likely to achieve mRS of 0–1 simply because of a pre-existing disability of mRS of >1. Thus, favourable outcome defined as return to baseline mRS seems a better outcome than achievement of mRS of ≤1.

Fifth, in between studies, the definitions for sICH varied to some degree, which urges a cautious interpretation of these findings. However, the sICH definitions did not differ within studies. In addition, statistically, the heterogeneity was solely mild (I^2 = 10.8%).

Sixth, only 12–31% of the intravenous rtPA-treated patients were ≥80 years old, whereas this age group accounts for 30–37% of all ischaemic strokes [27, 29]. This discrepancy indicates an unwilling selection bias, as neither study mentioned exclusion criteria exclusively for older patients. The frequency of pre-stroke disability among rtPA-treated older patients was lower (5% [13]; 28% [11, 13]) than that in unselected registries of stroke patients without rtPA (e.g. 45%) [5]. Thus, it is likely that among the older age group, those with the best pre-stroke health received intravenous rtPA. In addition, referral bias to the disadvantages for the older age group seems to be present as shown recently [30]. Interestingly, also in the NINDS trial, patients >80 years of age (13%) were underrepresented [2].

As caveat, the findings of this review must be interpreted as proof neither in favour nor against a beneficial effect of intravenous rtPA for stroke patients aged ≥80 years, because all patients received rtPA. Nevertheless, the findings of this review clarified that in rtPA-treated stroke populations, age of ≥80 years is not associated with an increase in sICH compared with younger ages. Thus, sICH as the major concern of rtPA treatment should not be exceedingly feared in stroke patients aged ≥80 years.

The similar sICH risk in both the age groups and the finding that the magnitude of differences in mortality and favourable outcome between stroke patients aged <80 and ≥80 years old seems comparable to non-thrombolysed populations may lead to the interpretation that older stroke patients are very likely to benefit from rtPA in a way similar to younger ones. On the basis of this interpretation, some physicians may simply treat their patients aged ≥80 years with rtPA as they do with younger patients. This approach is justified soonest for the 80-year olds, who were excluded solely in the ATLANTIS trial [31] but not in ECASS and NINDS [2]. However, this approach is based on indirect comparisons. Therefore, from a methodological and scientific point of view, randomisation in an RCT is the preferable approach.

In conclusion, intravenous rtPA-treated stroke patients of ≥80 years of age have a less favourable outcome compared with younger ones. Imbalances in outcome predictive baseline variables to the disadvantage of the older age group may contribute to this finding. Nevertheless, the similar bleeding risk suggests that bleeding complications are unlikely to outweigh the potential benefit particularly in the

older age group. Thus, there is scope for benefit from thrombolysis for stroke patients aged ≥80 years. Data on this age group from RCTs such as the ongoing IST-3 will hopefully yield more conclusive answers to the question whether (and which) stroke patients aged ≥80 years have a net benefit from intravenous rtPA.

Key points

- A systematic review across cohort studies comparing intravenous thrombolysed stroke patients of over and below age 80 years was performed.
- Stroke patients of ≥80 years receiving intravenous thrombolysis had a three-time higher mortality risk than younger patients and were less likely to recover favourably.
- The risk for symptomatic intracranial haemorrhage was similar in both the age groups.
- Hence, to obtain reliable evidence on the balance of risk and benefit of intravenous thrombolysis for stroke patients aged ≥80 years, it is safe and reasonable to include such patients in randomised placebo-controlled trials.

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Conflict of interest

None.

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