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Intravenous thrombolysis in Acute Ischaemic Stroke: A systematic review and meta-analysis to aid decision making in patients over 80 years of age.

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1. The title.

Intravenous thrombolysis in Acute Ischaemic Stroke: A systematic review and meta-analysis to aid decision making in patients over 80 years of age.

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Intravenous thrombolysis in Acute Ischaemic Stroke: A systematic review and meta-analysis to aid decision making in patients over 80 years of age.

Abstract

Introduction: Patients ≥ 80 years of age are increasingly receiving intravenous thrombolysis for acute ischaemic stroke (AIS) despite lack of firm evidence. This systematic review assesses safety and efficacy of intravenous thrombolysis with Alteplase in ≥ 80 vs. < 80 year old patients with AIS.

Methods: The existing literature was systematically analysed for outcome measures of mortality, functional recovery by modified Rankin scale (mRS) and symptomatic intracranial haemorrhage (SICH) at three months following intravenous thrombolysis with Alteplase in < 80 and ≥ 80 years old patients with AIS. Statistical tests were performed for heterogeneity and publication bias. A detailed sensitivity analysis was performed and Forest plot was constructed for each of the outcome measures.

Results: Thirteen studies were identified. The overall odds ratio (OR) was 2.77 (95% CI 2.25 – 3.40) for death, 0.49 (95% CI 0.40 – 0.61) for achieving favourable outcome and 1.31 (95% CI 0.93 – 1.84) for SICH in ≥ 80 years old patients, compared to those <80 years old. The total number of events contributing to the estimates of effect for each outcome was: death 199, favourable outcome 141 and SICH 49.

Conclusion: Patients ≥ 80 years, appear to have a lower probability of gaining favourable outcome and a higher mortality rate as compared to patients < 80 years old; however, the rate of SICH is not significantly increased. This supports recruitment of patients aged ≥ 80 into ongoing trials comparing thrombolysis with control. For patients who refuse or can not be randomised, it provides information on risks and benefits of using Alteplase off-licence.

Introduction

The safety and efficacy of intravenous (IV) thrombolysis with Alteplase, a reverse transcriptase Plasminogen Activator (tPA), licensed for use in a select population with acute ischemic stroke (AIS) is well established [1]. In the United Kingdom about 30,000 people over 80 have AIS each year but they do not receive tPA because of their age and concern of causing symptomatic haemorrhage. The elderly (over 80 years) population have previously been subject to discrimination in trials of thrombolytic therapies. There have been attempts to justify their inclusion on the basis of data from non-randomised monitoring cohorts; Thrombolysis in the above 80 year old group is increasing and the SITS-MOST (Safe Implementation of Thrombolysis and Monitoring Study) database currently documents approximately 4000 such patients in 450 centres across 33 countries [2]. The question that clinicians are increasingly facing is: what is the safety and efficacy of IV thrombolytic therapy in the elderly population? The ongoing International Stroke Trial-3 (IST-3) [3] is likely to present its findings in April 2012 but until then stroke physicians need some information to help patients unable or unwilling to be part of thrombolysis trials to make an informed choice regarding off-licence use of alteplase. To try and help until such trials report we have performed a systematic review of current literature. The last systematic review published in 2006 by Engelter [4] had a limited look at outcomes of IV thrombolysis in stroke patients of ≥ 80 versus < 80 years of age. Since then more evidence has become available that we have analysed in this paper to reach a clinical bottom line. We believe this analysis is timely and justifies the continuation of trials that seek to obtain information on the balance of risk and benefit to populations presently excluded from treatment.

Methods

Methodology of systematic review

The existing literature was systematically searched by two independent authors (PB and DS) using *National Information Resources* facility for Medline (1950 onward), Embase (1980 onwards) and

CINAHL (1981 onwards) databases until September 2010 for various terms related to "acute isch(a)emic stroke" and "thrombolysis" using thesaurus mapping and truncation as appropriate to maximise the scope of search. Following PICOS strategy was used to search the various databases. Population: elderly patients ≥ 80 years old thrombolysed for AIS; Intervention: thrombolysis with tPA (Alteplase); Comparison: patients <80 years old thrombolysed for AIS; Outcomes: death, functional recovery by modified Rankin scale (mRS) and symptomatic intracranial haemorrhage (SICH) at three months; tudy design:comparative observational cohort studies; non-comparative case series, isolated case reports, reviews and comments were excluded. The leading journals and bibliographies of selected articles were hand searched. The studies satisfying inclusion and exclusion criteria were then individually appraised by PB and DS. Any disagreement was resolved by mutual discussion involving PG.

Statistical analysis

For each outcome of interest (SICH, mRS, and mortality at 3 months), a separate fixed-effects meta-analysis was performed utilizing the Mantel-Haenszel method in order to calculate an overall summary measure [5].

For all fixed-effects meta-analyses, it was assumed that the true effect sizes were the same for all studies, and any difference observed was simply due to sampling variation. A χ^2 test of heterogeneity (Q) was applied in each case to assess the fixed effects assumption. A 10% significance level was used for the test of heterogeneity.

For each of the outcomes of interest, forest plots were produced to show the effect sizes (odds ratios) for each of the relevant studies with an overall summary estimate (odds ratio) generated from the meta-analysis. Corresponding 95% confidence intervals (95% CI) were shown alongside the

odds ratios. Publication bias was investigated for each meta-analysis using funnel plots with standard error on the y-axis and effect size on the x-axis.

In meta-analyses of observational studies, biased effect sizes for individual studies are an unfortunate possibility and therefore any biases in individual studies are likely to propagate into the overall summary measure. Therefore, Egger *et al.* suggest that exploring the possible sources of heterogeneity between observational study results should be an important feature of meta-analyses of observational studies [6]. We believe a non-significant test result of heterogeneity is not enough in order to have confidence in the overall summary measure since these tests often lack power so low levels of heterogeneity may still exist in practice. In addition, a hypothesis test provides no substitute for a thorough comparison of the studies. Therefore, with this in mind, in our systematic review we carefully assessed heterogeneity between studies and also tested the stability of the overall summary measure by performing a thorough sensitivity analysis for each meta-analysis.

The statistics software used was the '*Metafor*' package [7] in the R statistics software [8].

Results

Results of systematic review:

The systematic search returned thirteen comparative cohort observational studies that appeared to answer the question, making it the most comprehensive review to date. Two papers [9, 10] used similar methodology but calculated in-hospital death and/ or disability at discharge rather than at three months; hence only data on SICH was taken from them to maintain uniformity of analysis. One study [11] was alleged to have been included in a larger national multi-centre study [12] in a

previous review [4]. We included this study and performed a sensitivity analysis to investigate the effect of this study on the overall summary estimates.

All studies had well defined methodology and collected data prospectively. Ringleb [13] and Mouradian [11] followed their local and national protocols. Subsequent sensitivity analysis excluding these studies revealed very little change in the overall summary odds ratios. The majority of authors attempted to compare most of the known, potentially confounding, baseline characteristics of the two populations except Ringleb [13]and Berrouschot [14] who compared only few characteristics such as baseline NIHSS, sex and time to treatment. Four authors [12,13,15,16) did not mention if they included consecutive thrombolysed patients but it appears from their results that they did. Seven authors (table 1) mentioned protocol violations and amongst them Tanne [10] had protocol violations significantly different between the two groups. Losses to follow up were accounted for in two studies at three months. It was not considered relevant for Tanne [10] and Chen [9] as the outcome measures of death and disability were calculated at discharge. The individual characteristics of the studies are tabulated in table 1 and details of each study including results are mentioned in table 2. Uyttenboogaart [17] performed multivariate analysis to adjust for possible confounders and eight other studies [10-12, 14-16, 18, 19, 21] performed logistic regression analysis to adjust for the differences in important baseline characteristics and to identify predictors of favourable and/or poor outcomes. Our analysis showed that there was little evidence to suggest publication bias in funnel plots for the three outcomes (figure 1).

a) Death at 3 months

Mortality at three months was reported by eleven studies. Results by Mouradian [11] were excluded from the meta-analysis as they reported only stroke related deaths at three months. The combined

(fixed) OR as represented by a diamond at the bottom of the plot (figure 2), was calculated to be 2.77, 95% CI 2.25 – 3.40 from ten studies suggesting an increased likelihood of death at three months in the thrombolysed over 80 group. Including Mouradian [11] in the analysis did not change the results significantly with the odds ratio being 2.80 (95% CI 2.29 – 3.43).

The test for heterogeneity gave a Q score of 11.98 on 9 degrees of freedom. This corresponds to a p-value of 0.21, which is non-significant at the 10% level. Therefore, there is insufficient evidence of any heterogeneity between studies.

Sensitivity analysis performed to adjust for minor variations amongst the studies showed little change in the overall summary odds ratio and our conclusions remained the same in each case. When the Gomez-Choco [19] paper was removed however, the overall summary estimate of the odds ratio increased by 0.15, but our overall conclusions did not change.

b) Functional outcome at 3 months

Analysis was performed on eight studies that reported favourable outcome as mRS 0 – 1. Three studies were not included in the statistical analysis [11, 15, 19] as they reported favourable outcome as 0 – 2. The combined (fixed) odds ratio was calculated to be 0.49 (95% CI 0.40 – 0.61) suggesting that patients over 80 are not as likely to achieve favourable outcome as patients less than 80 years old thrombolysed for AIS.

The test for heterogeneity gave a Q score of 6.54 on 7 degrees of freedom. This corresponds to a p-value of 0.48, which is non-significant at the 10% level. Therefore, there is insufficient evidence of any heterogeneity between studies.

A sensitivity analysis was performed which showed very little change in the overall summary odds ratio and our conclusions remained the same.

We considered performing a meta-analysis of favourable outcome as mRS 0-2. That is, we only included the Toni [15], Gomez-Choco [19] and Mouradian [11] papers. However, the test for heterogeneity resulted in a Q-statistic of 5.49 on 2 degrees of freedom with a corresponding p-value of 0.06. Therefore, the test was significant at the 10% level, and it was considered invalid to combine the results.

c) Incidence of symptomatic intracranial haemorrhage (SICH)

Studies were noted to have employed two different definitions of SICH. Five studies [10,13,16,17 and 20] used definition as utilised by NINDS stroke study group [22] where a haemorrhage was considered symptomatic if it was not seen on an previous CT scan and there had subsequently been a decline in neurological status. Eight [9,11,12,14, 15,18, 19 and 21] used definition as utilised by ECASS III trial [23] where SICH was defined as an intracranial bleed on CT scan with a decrease in the NIHSS score of 4 or more points.

The combined (fixed) OR, of all studies, was calculated to be 1.31, 95% CI 0.93 – 1.84 suggesting no significant difference in the risk of SICH between the two age groups.

The test for heterogeneity gave a Q score of 6.41 on 12 degrees of freedom. This corresponds to a p-value of 0.89, which is non-significant at the 10% level. Therefore, there is insufficient evidence of any heterogeneity between studies.

A thorough sensitivity analysis was performed by sequentially removing individual studies that had minor variations and it showed very little change in the overall summary odds ratio and our overall conclusions remained the same.

Discussion

The question whether thrombolysis is safe and effective in the elderly population aged over 80 years requires an adequately powered randomised controlled trial (RCT) such as the ongoing IST-3 [24]. Various studies, appraised in this review, attempted to obtain indirect evidence to answer the question by comparing their experience of off-licence use of IV thrombolysis in patients over 80 years of age with those in younger patients.

In the absence of an RCT such comparative cohort observational studies are the next most appropriate research design to be considered as patients over 80 years old are increasingly being provided thrombolysis as treatment for AIS.

The mean proportion of over 80 patients achieving favourable outcome of 0-1 was found to be 26.7% (range 16.1 – 43.5%; standard deviation of 8.1) on pooled analysis of the data from the eleven studies included in this review..

The estimate of effect on SICH is more problematic to assess and has lowest power because of two separate definitions across studies and small number of events. The confidence intervals are also

wide and can not exclude either a small reduction or an increase in incidence of SICH. However regardless of these two different definitions there was no significant difference noted amongst the two groups.

Systematic reviews of observational studies have the inherent weakness that in the absence of randomisation they are particularly prone to biases; for example, selection bias. It is not unreasonable to suppose that many (if not all) of the studies in the meta-analysis suffer from this kind of bias whereby only those elderly patients who seem particularly healthy or suitable are entered in the study cohort, while those in the younger age group are selected less carefully. If this is true, then this will help to mask an increased risk of SICH for the older age group if it exists. The pooled analysis of appraised studies in this review shows case fatality ranging from 6.1% to 45.2% (mean 28.3%; standard deviation of 12.0) in the thrombolysed ≥ 80 group. Given these data are from reasonably representative samples of hospital patients, there must be a considerable, but variable, amount of case selection (selection bias) in the included cohorts. For these reasons, the results provide no substitute for a randomised control trial. Moreover, if confounding bias is present such that there are one or more variables related to both age group and SICH which are not consequences of either, they can serve to distort the relationship between age group and SICH. The confounding variables which induce a negative association between age group and SICH are of particular interest since these will minimise any existing relationship between the variables. Some authors used logistic regression analysis to adjust for confounders, and this method is to be recommended. However, unadjusted-for confounders may still remain.

Publication bias may be an additional cause of bias whereby authors may be less willing to publish results which show a significant difference in SICH if it is against their a priori beliefs. However, the funnel plots did not suggest any evidence of publication bias for each of the outcomes in this meta-analysis.

Another potential bias is caused by loss to follow-up and/or protocol violations; especially differential loss to follow-up between the age groups. If those in the <80 age group are followed-up less rigorously for example, and if loss to follow-up is mainly caused by greater health or mobility, then the proportion of patients in the <80 age group associated with SICH or mortality will be biased upwards and this could contribute to a non-significant result. Unfortunately, only Parnetti [21] and Meseguer [18] described and compared losses to follow up.

In some studies, small numbers of elderly patients over 80 may cause problems, not only because it suggests selection bias, but also because the sample size itself means that there may be low power to detect differences which are clinically significant. This means that the Type II error rate would be high. This is also likely to be a feature of poorly designed and conducted studies. Therefore, in order to have any confidence in non-significant results it is especially important that studies are well-conducted.

One important weakness which was not mentioned in any of the studies except Engelter [16] is that of the disadvantage associated with using the dichotomization of <80 years and ≥ 80 years. The motivation for this is clear, since the NINDS study did not include many patients over 80, but it still seems unsatisfactory that an 80 year old patient should be treated any differently to a 79 year old. In reality, the relationship between age and outcome is likely to be gradual as calculated by Berrouschot [14] and any dichotomization of a continuous variable such as age is likely to result in a loss of power to detect a significant association. This is especially the case for example, if probability of SICH increases only very slightly for patients 80-85 years and then increases more substantially after this. The problems associated with the dichotomization provides another reason why an RCT in the elderly population is better than any comparison between two age groups <80 and ≥ 80 for tPA treated patients.

Conclusion

Elderly patients, thrombolysed for AIS, appear to have a lower probability of gaining favourable outcome and a higher mortality rate compared to younger patients less than 80 years of age. However, the rate of SICH is not significantly worse in the ≥80 year olds when compared to younger patients.

These data support the rationale for recruiting patients aged over 80 into ongoing trials comparing thrombolysis with control. For patients who refuse or cannot be randomised, this meta-analysis provides useful information on the potential risks and benefits of using Alteplase off-licence.

Table 1: Characteristics of appraised studies

Studies	Centre	Prospective data collection	Protocol	Protocol violations	Losses to follow up
Toni (15)	Multi, Italy	√	NINDS	Described (p=0.59)	Not described
Uyttenboogaart (17)	Single, Netherlands	√	NINDS	Not described	Not described
Gómez-Choco (19)	Single, Spain	√	NINDS	Not described	Not described
Meseguer (18)	Single, France	√	NINDS	Described (p=1.0)	Described
Ringleb (13)	Single, Germany	√	Local	Not described	Not described
Mouradian (11)	Single, Canada	√	National	Not described	Not described
Berrouschot (14)	Multi, Germany	√	NINDS	Described (p=0.67)	Not described
Engelter (16)	Multi, Switzerland	√	NINDS	Described (p=0.43)	Not described
Sylaja (12)	Multi, Canada	√	NINDS	Described (p=0.26)	Not described
Oostenbrugge (20)	Single, Netherlands	√	NINDS	Not described	Not described
Parnetti (21)	Single, Italy	√	NINDS + EUSI	Described (no difference detected)	Described
Tanne (10)	Multi, USA	√	NINDS	Described (p=0.03)	none
Chen (9)	Single, USA	√	NINDS	Not described	none

NINDS: National Institute of Neurological Diseases and Stroke
EUSI: European Stroke Initiative recommendations for stroke management – update 2003

Table 2: Results of individual studies

Studies	Patients (%)	Baseline characteristics	SICH (%)	Favourable outcome	Mortality at 3 months
Toni • ≤80 • >80	• 207 • 41 (16.5%)	More females, diabetics, AF, patients on anti-platelets in >80 group	• 10 (4.8%) • 2 (4.8%) ➢ p=1.0	*(mRS 0 – 2)* • 121 (58.5%) • 18 (44%) ➢ Not significant	• 22 (10.6%) • 14 (34.1%) ➢ *p<0.001*
Uyttenboogaart • <80 • ≥80	• 111 • 31 (22%)	Older patients had longer time to treatment and had fewer lacunar strokes	• 4(3.6%) • 3(9.7%) ➢ P=0.176	• 40(36.0%) • 5 (16.1%) ➢ *P=0.004*	• 14 (12.6%) • 14 (45.2%) ➢ *P<0.001*
Gómez-Choco • ≤80 • >80	• 108 • 49 (31.2%)	Older patients were more often on anti-platelets and had longer 'time to rtPA'	• 6(5.5%) • 3(6%) ➢ p≥0.05	*(included mRS 2)* • 39(37%) • 12(25%) ➢ p≥0.05	• 11(10%) • 3(6%) ➢ p≥0.05
Meseguer • <80 • ≥80	• 107 • 22 (17%)	More females, less smokers, higher baseline NIHSS and cardio-embolic source in elderly	• 8(7.5%) • 3(13.6%) ➢ P=0.40	• 40(37.4%) • 6(27.3%) ➢ P=0.37	• 12(11.2%) • 6(27.3%) ➢ P-value n.a.
Ringleb • <80 • ≥80	• 378 • 90 (19%)	More females and higher SGL in elderly group. Longer time to treatment in MRI selection	• 20(5.3%) • 6(6.7%) ➢ P>0.05	• 158(41.8%) • 17(18.9%) ➢ P value n.a.	• 48(12.7%) • 26(28.9%) • *P<0.001*
Mouradian • <80 • ≥80	• 65 • 31	Higher incidence of CHF and HTN in elderly. More elderly	• 4(6.2%) • 3(9.7%)	mRS 0-2 • 38(58.5%) • 5(16.1%)	CVA related deaths • 7(10.8%) • 10(32.3%)

		patients had higher baseline NIHSS	➢ P=0.69	➢ *P<0.001*	➢ *P=0.01*
Berrouschot • <80 • ≥80	• 190 • 38 (16%)	Only baseline NIHSS compared p=0.115	• 5(2.6%) • 1(2.6%) ➢ P=1.0	• 89(46.8%) • 10(26.3%) ➢ *P=0.021*	• 10(5.3%) • 8(21.1%) ➢ *P=0.004*
Engelter • <80 • ≥80	• 287 • 38 (12%)	More females, higher SBP, cardio-embolic source and AF in elderly group	• 24 (8%) • 5 (13%) ➢ P=0.36	• 107 (37%) • 11 (29%) ➢ P=0.37	• 35 (12%) • 12 (32%) ➢ *P=0.005*
Sylaja • <80 • ≥80	• 865 • 270 (23.8%)	More females, higher incidence of HTN, AF, IHD, CHF, higher pre-treatment SBP and baseline NIHSS in ≥80 group and less smoker and cholesterol	• 40 (4.6%) • 12 (4.4%) ➢ P=1.0	• 40.2% • 25.9% ➢ *P=0.001*	• 18.2% • 35.3% ➢ *P=0.001*
Oostenbrugge • <80 • ≥80	• 139 • 45 (24%)	More females, higher incidence of IHD and CHF in ≥80 group and were less often smokers	• 4 (2.9%) • 5 (11.1%) OR 4.2 (95%CI:1.08-16.46)	• 62 (45%) • 12 (27%) OR 2.2 (95%CI:1.06-4.46)	Not available
Parnetti		Higher			

• <80 • ≥80	• 49 • 23 (30.5%)	incidence of previous stroke and anti-platelet therapy in ≥80 group	• 1 (2%) • 1 (4.3%) ➢ p>0.05	• 20 (40.8%) • 10 (43.4%) ➢ p>0.05	• 4 (8.2%) • 3 (13.0%) ➢ p>0.05
Tanne • <80 • ≥80	• 159 • 30 (15.8%)	Higher incidence of diabetes and current smokers in <80 and higher pre-treatment systolic BP in elderly	• 10 (6%) • 1 (3%) ➢ P=0.99	Not calculated at three months	Not calculated at three months
Chen • <80 • ≥80	• 127 • 56 (44.1%)	More females and cardio-embolic strokes in elderly group	• 8 (6.3%) • 4 (7.1%) ➢ P=0.90	Not calculated at three months	Not calculated at three months

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Figure 1: Funnel plots to assess possible publication bias corresponding to meta-analyses performed for SICH, mortality at three months and functional outcome on mRS respectively.

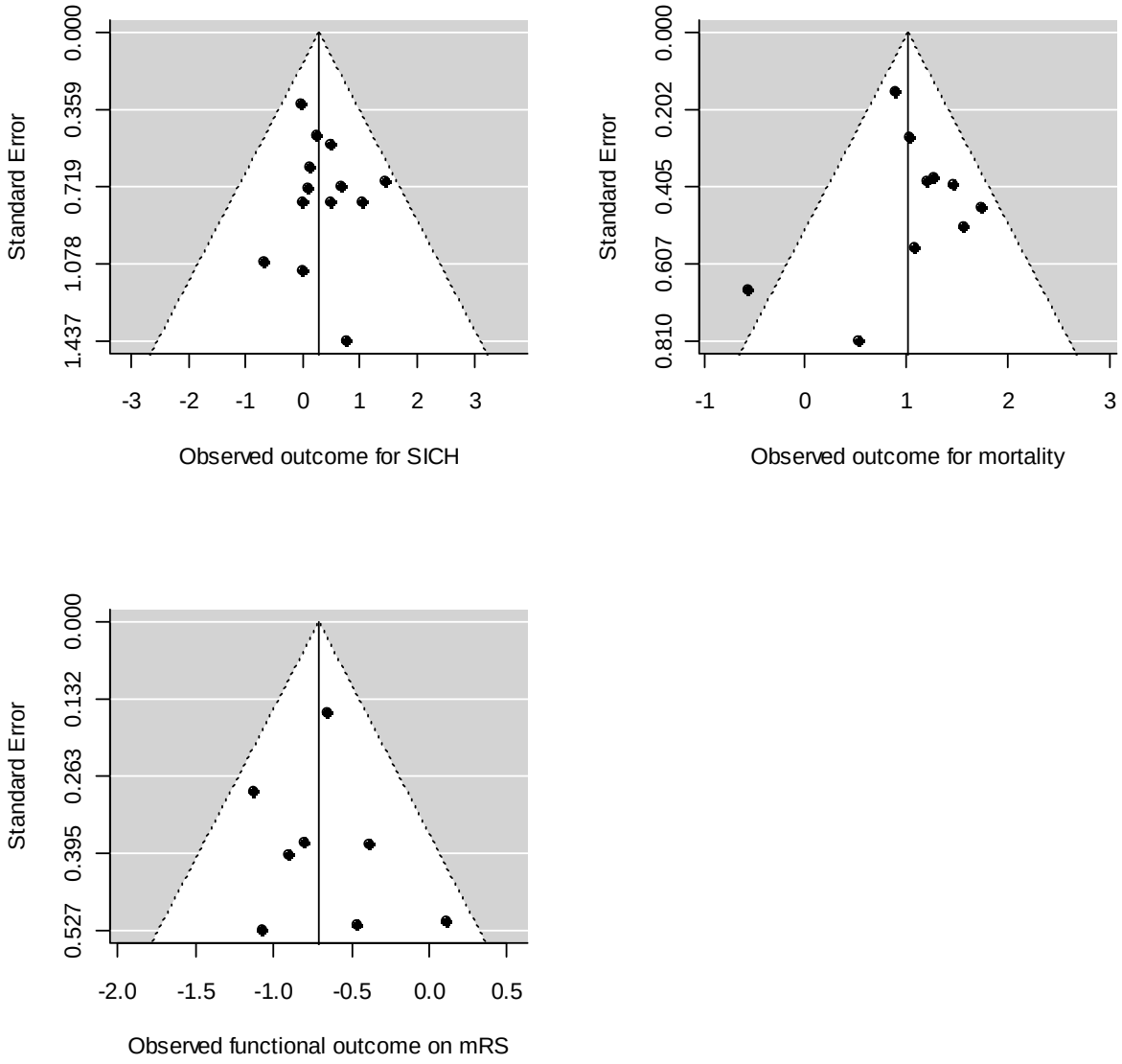
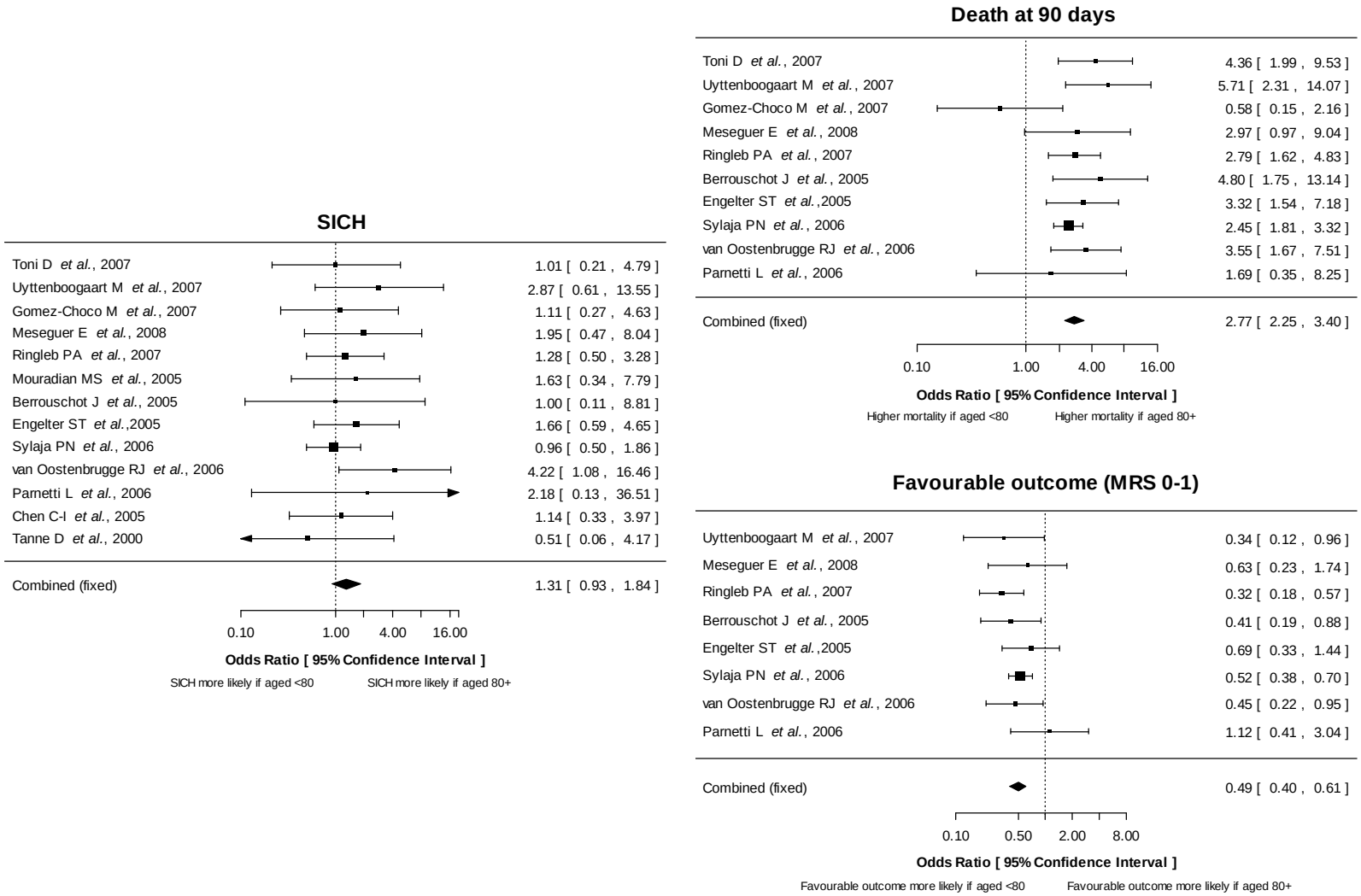
Figure 2: Forest plots showing effect of age group on SICH, risk of death at three months/ 90 days and probability of favourable outcome - odds ratio (fixed effects) meta-analysis plots. Right hand side of plot corresponds to an increased risk for patients ≥ 80 years old relative to those <80 years.