Title of the Project:

Outcome after stroke-thrombolysis >80 years in the 3-4.5h compared to 3h: An observational study

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Contribution

N. Ahmed designed the study and write the first draft of the manuscript in close collaboration with GA Ford, KR Lees and D Toni. PA Ringleb, C. Bladin and D. Collas were coordinator for top recruiting center and contributed to the manuscript by their comments. N Ahmed had full access to all the data in the study, conducted and is responsible for the statistical analysis. and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Abstract

Objective: We determined outcomes and risks of intravenous thrombolysis (IVT) in patients with acute ischemic stroke (AIS) over 80-years within 3hr compared to >3-4.5hr recorded in the SITS International Stroke Thrombolysis registry.

Methods: 14,240 (Year 2003-2015) patients >80 years with AIS were treated with IVT ≤4.5h of stroke onset (3,558 in >3-4.5hr). Of these 8658 (2157 in >3-4.5hr) were treated otherwise according to the European Summary of product criteria (EU-SmPC) for alteplase. Outcomes were 3-month functional independence (modified Rankin scale 0–2), mortality, and symptomatic intracerebral hemorrhage (SICH)/SITS. Results were compared between the >3-4.5hr and <=3hr patients.

Results: Median age was 84 years, 61% female in both groups. Median NIHSS was 12 vs. 14 in the >3-4.5hr and <=3hr respectively. Three-month functional independence was 34% vs. 35%, adjusted odds ratio (aOR, 95% CI) 0.78 (0.69-0.89, p<0.001). Mortality 31% vs. 32%, aOR 1.10 (0.97-1.25, p=0.13), SICH/SITS 2.7% vs. 1.6%, aOR 1.72 (1.25-2.35, p=0.001). In EU-SmPC compliant patients: Three-month functional independence was 36 vs. 37%, aOR 0.79 (0.68-0.92, p=0.002). Mortality 29% vs. 29.6%, aOR 1.10 (0.95-1.28, p=0.20). SICH/SITS 2.7% vs. 1.6%, aOR 1.62(1.12-2.34, p=0.01).

Conclusions: In this observational study, unselected patients >80-years treated with IVT after 3h versus earlier had a slightly higher rate of SICH but similar unadjusted functional outcome but poorer adjusted outcome. The absolute difference between the treatment groups is small and elderly patients should not be denied IVT in the later time window solely for age without other contraindications.

Main text:

Introduction

Pooled analysis of randomized controlled trials (RCTs) of intravenous thrombolysis (IVT) for acute ischemic stroke has shown that patients >80 years treated with IVT versus control derived equal benefit compared to patients 18-80 years. Within the >3-4.5h window the effect was significant for younger patients (OR 1.26 [1.04-1.54]) but was not independently significant for the more elderly; however, the elderly sample was smaller and showed a greater point estimate (OR 1.36 [0.87-2.14]).[1] Effectiveness of IVT diminished as the treatment delay increased across the first 6 hours without a corresponding increase in the relative risk of symptomatic intracerebral hemorrhage (SICH).[1] Real world registry experience supports these RCT data in patients >80 years treated within 3h.[2,3] The SITS-ISTR (Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register)-VISTA analysis demonstrated benefit of IVT in patients >80 years compared to control and found no difference in the slope of benefit versus treatment delay for younger versus elderly patients,[3] a finding that was confirmed in the RCT dataset.[4]

The European guideline[5] recommends use of IVT within 4.5h of symptom onset also in the elderly, but North American guidance does not recommend IVT in the >3-4.5h window in patients >80 years.[6] Most European regulatory agencies have not approved marketing of IVT with Actilyse for use in ischemic patients >80 years, whereas the American regulatory agency supports promotion of IVT in patients >80 years within 3h of symptom onset.

About 30% of admitted ischemic stroke patients are older than 80 years[7,8] but about 2/3 of overall stroke-related morbidity and mortality occurs in patients >80 years old.[9,10] A large proportion of these elderly patients are possible candidates for thrombolysis. Divergent recommendations from professional bodies and regulatory agencies may have a negative impact on IVT treatment in elderly populations.

We used the SITS-ISTR to determine the outcomes and risks of IVT that are achieved in routine practice in patients >80 years in the >3-4.5h compared to within 3h time window.

Methods:

Study design:

This is an observational study based on retrospective analysis of a prospective registry.

Patient selection:

Figure 1 shows the flow diagram for patient selection. In the primary analysis, we included unselected ischemic stroke patients over 80 years who were treated with intravenous alteplase within 4.5 hours of symptoms onset and registered in SITS-ISTR between 2003 and 2015.[11] Patients treated with mechanical thrombectomy, unknown or missing stroke onset to treatment time were excluded from the analysis. In

the sensitivity analysis, we only included patients treated in compliance with the other European Summary of Product Characteristics criteria (EU SmPC). European licence restrictions of intravenous alteplase in acute ischemic stroke described in the EU SmPC.[12] In light of these, the following data were collected in the SITS-ISTR, and we excluded them from the sensitivity analysis: 1) Severe stroke as assessed clinically (e.g. NIHSS>25) and/or by appropriate imaging techniques, 2) Administration of heparin within the previous 48 hours and a thromboplastin time exceeding the upper limit of normal for laboratory, 3) Patients with any history of prior stroke and concomitant diabetes, 4) Prior stroke within the last 3 months, 5) Systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg, or aggressive management (IV medication) necessary to reduce BP to these limits, 6) Blood glucose <50 or > 400 mg/dl (<2.7 or > 22.2 mmol/L), 7) Patients receiving oral anticoagulants, e.g. warfarin sodium.

We collected baseline and demographic characteristics including stroke severity using the National Institutes of Health Stroke Scale (NIHSS), and pre-stroke disability using the modified Rankin Scale (mRS), medication at stroke onset, risk factors, NIHSS at 2, 24 hours and 7 days following treatment, brain imaging prior to IVT treatment and follow up CT brain imaging at 24-36 hours and any other extra imaging scans to assess for hemorrhagic transformation, and mRS at 3 months.

Ethical considerations and source data verification

The need for ethical approval or patient consent for participation in SITS-ISTR varied among participating countries, but approvals were obtained in countries that required this; other countries approved the register for conduct as an anonymized audit. The current study is a

part of the SITS-Monitoring Study II which is approved by the Ethics Committee of the Karolinska Institute in Stockholm, Sweden.

The SITS International Coordination Office performed regular online monitoring of the SITS-ISTR data and checked individual patient data on a regular basis to handle errors or inconsistencies. For a sample of patients included in SITS-MOST (n=6483)[8], source data were verified on-site by monitors under the supervision of their national coordinator.

Outcome measurements

Main outcome measurements	
Functional independence at 3 months	*modified Rankin Scale Score (*mRS) score of ≤2 at 3 months
Symptomatic intracerebral hemorrhage (SICH) per the SITS-MOST[13]	a local or remote parenchymal hemorrhage type 2 on the 22- to 36-h post-treatment imaging scan or earlier if clinically indicated, combined with a neurological worsening of ≥4 points in the NIHSS score between baseline and 24 h, or leading to death.
SICH per the ECASS-2[14]	Any intracerebral hemorrhage on any post-treatment imaging scans combined with NIHSS worsening ≥4 points between baseline and 7days (ECASS definition).
For comparison with other published work, we also analyzed the following outcomes	
No/ minimal disability	*mRS s*core 0 or 1 at 3 months

SICH per the NINDS[15]	Any intracerebral hemorrhage on any post-treatment imaging scans combined with any decline in neurologic status as measured by NIHSS between baseline and 7days.
Death	*Death within 3 months*
Hemorrhagic transformation (HT)	was categorized using the ECASS trial definitions.[14]

All evaluations of imaging studies and neurological status were performed according to clinical routine by the local sites. All definitions of SICHs were adjudicated by the SITS International Coordination Office based on the clinical and imaging data entered by the investigators in the registry.

Statistical analysis

In the primary analysis, patients over 80yrs were divided into two groups according to stroke onset to treatment time (OTT): IVT initiated within 3h (the early cohort) and in the >3-4.5h (the later cohort). Descriptive statistics for the baseline and demographic data were contrasted according to the early and the later cohort per OTT. Unknown or missing values were excluded from the denominator when calculating proportions. Hemorrhagic transformations, SICH, neurological status until day 7 or discharge and 90 day mortality and disability (mRS) were compared between the two groups. We performed multivariable logistic regression analyses to examine if the outcomes differ between the two OTT groups after adjusting for baseline imbalances. Unknown or missing values were excluded from the multivariable analysis. We performed sensitivity analysis for patients treated in compliance with the other European Summary of Product Characteristics criteria (EU SmPC). The following variables were entered into the multivariable model as a predictor for outcome parameters based on

their statistical significance in the univariate analysis at 10% level and known clinical importance to predict outcome even if p>0.10: age, sex, baseline NIHSS, history of DM, hypertension, smoking, previous stroke within 3m, atrial fibrillation and pre-stroke mRS, signs of current infarction, hyperdense artery sign, systolic blood pressure and plasma glucose. Hospital arrival to treatment time was not included in the model due to collinearity with onset to treatment time. P-values less then 5% were regarded as statistical significance. All analyses were performed using STATISTICA software, version 13.

Results:

Between January 2003 and December 2015, 14240 patients over 80 years with acute ischemic stroke treated with IVT within 4.5h of symptom onset were recorded in the SITS-ISTR. These patients were recorded from 45 countries across 595 centers and 94% (n=13370) were from European countries. Patients treated within the 3-4.5h time window were registered from 38 countries across 399 clinical centers.

Baseline and demographic characteristics of patients over 80 years treated with IVT within 3-4.5h are compared with ≤3h of symptom onset in **Table 1**. In the later cohort, median time for IVT initiation was longer (83 minutes since stroke onset and 25 minutes since hospital arrival) and median stroke severity was lower (by 2 points as measured by NIHSS score) compared to the early cohort.

Figure 2 (**Table e-1**) shows the extent of hemorrhage found on any post-IVT imaging scans. The overall rate of HT was 19.1% vs. 16.1% (p=0.0001) in the later compared to the early time window. Patients who received IVT in the later cohort had slightly higher local type of hemorrhages compared to the early cohort (p=0.0001 for overall difference between the groups). When tested within each hemorrhage type separately, HI1 (p=0.03) and PH2

(p<0.0001) appeared statistically significant between the groups. There was no difference regarding remote hemorrhages between later and early cohorts (p=0.5). In patients treated within EU SmPC criteria, overall rate of HT was 18.1% vs. 15.7% (p=0.01), any PHs was 9.6% vs. 8.1% (p=0.03), any local hemorrhages 16.1% vs. 13.6% (p=0.005), remote hemorrhages 3.5% vs. 3.7% (p=0.52) in the later compared to the early time window respectively.

In Table 2 main outcome results were compared between early and later cohorts. Patients >80 years treated in the later time window had a higher frequency of SICH in the univariate analysis and higher adjusted odds ratio in the multivariable analysis compared to patients treated earlier. Patients >80 years treated in the later time window had a similar rate of functional outcome in the univariate analysis but had a lower odds ratio for functional independence in the multivariable analysis compared to patients treated in the early time window. Mortality at 3 months did not differ statistically significantly between the early and later time windows in the univariate or multivariate analysis.

Figure 3 shows the distribution of mRS at 3-months categorized by stroke onset to treatment time

Patients compliant with the other European Summary of Product Characteristics criteria (EU SmPC)

In the Table e-2, baseline and demographic characteristics of patients over 80 years treated with IVT in compliance with the other EU SmPC criteria were compared between early and

later cohorts.

In the Table 3 main outcome results were compared between later and early cohorts for patients in compliance with the other EU SmPC criteria. Results were similar for the EU SmPC cohort as for the unselected cohort described above but the overall outcomes in the EU SmPC cohort were better than the unselected cohort in both time windows.

Patients with missing 3 months mRS

In the **Table e-3 (supplementary),** baseline and demographic characteristic of patients for missing 3m outcome data were compared between the early and later time window. There was no statistically significant difference between the early and later time window patients with regard to baseline characteristics except for higher frequency of previous stroke >3m earlier (16% vs. 12%, p=0.01), oral antihypertensive treatment (72% vs. 68%, p=0.03), plasma glucose (6.8 vs. 6.6 mmol/L, p=0.047), longer hospital arrival to treatment time (82 vs. 59 min, p<0.001) and lower NIHSS (11 vs. 13, p<0.001) score in the later compared to early time window respectively.

Discussion:

This study with a large number of acute ischemic stroke patients over 80 years old treated with IVT showed slightly higher frequency and adjusted odds ratio (aOR) of SICH in the later time window (>3-4.5h) compared to earlier time window (<=3h). The overall rate of hemorrhagic transformations (HTs) was also higher in the later compared to earlier time window. We did not detect a difference in SICH or overall HT rates between early and later

cohorts in our first SITS >3-4.5h publication among the patients aged up to 80 years.[16] The current study findings are consistent with a subsequent analysis of SITS in a larger cohort of EU SmPC-compliant patients aged up to 80 years, which found higher rates of SICH per SITS in the >3-4.5h compared to 3h time window.[17] In a recent prospective study, SICH per ECASS 2 (aOR 1.46, p=0.05) and NINDS (aOR 1.35, p=0.07) were borderline significantly higher in the later time window compared to early time window. [18]

In the pooled analysis of RCTs, there was no hint that HTs and SICH rates increase in the later treatment window (>3h) compared to earlier time window (<=3h). The overall fatal intracranial hemorrhage rate was higher (3.6% vs. 2.3%) in the >80 years compared to <=80 years. The smaller pooled analysis population has not published an analysis of patients older than 80 years and treated >3h.[1] We do not know if the higher HTs and SICH in the >3-4.5h time window observed in our study applies only for IVT treated patients or is a natural phenomenon in control and IVT treated patients, as we lack a control group.

Post-thrombolysis imaging scans were performed 81 minutes later from stroke onset (25.6h in the 3h vs. 26.9h in the >3-4.5h) in our study cohort which may have contributed slightly higher rates of visible HTs in the later than early cohort. A possible relation between onset to assessment time and SICH rate that is independent of treatment was apparent in the control group of the pooled RCT, published by STTC.[4] The absolute incidence of SITS-MOST hemorrhage was 0.4% <3h, 0.6% >3-4.5h and 0.7% >4.5h, though the small numbers do not permit reliable estimation, and stratification by age groups was not performed.

In the unadjusted analysis, frequency of functional outcome (mRS 0-2 and mRS 0-1) and mortality at 3 months was similar between the >3-4.5h and ≤3h time windows. In the multivariable analyses, adjusted odds ratios were significantly lower for functional outcome (mRS 0-2 and mRS 0-1) at 3 months in the >3-4.5h compared to ≤3h but odds ratio for mortality did not differ significantly between the groups. The difference between unadjusted and adjusted analysis for functional outcome at 3 months could partly be explained by less severe stroke in the >3-4.5h group (2 points lower median NIHSS) compared to the 3h group. However, patients treated in the >3-4.5h time window had some higher prevalence of characteristics associated with worse outcome specifically higher pre-stroke functional dependency, DM, previous smoking, anti-hypertensive treatment, signs of current infarction in the imaging scans, plasma glucose. Most importantly longer stroke onset to treatment time is one of the powerful predictors of poor outcome after thrombolysis and yet defines the distinction between the 3-4.5h versus <= 3h cohorts. Pre-stroke disability may have been underestimated. The reliability of premorbid mRS assessment may be questioned, when undertaken rapidly in elderly patients who are less likely to have reliable witnesses on hand and when treatment options may be known to be influenced by admission of disability; delay in reaching hospital after acute stroke may be associated with such premorbid disability. These and other unidentified imbalances may have contributed poor outcome despite our efforts to achieve appropriate statistical adjustment for imbalances in the multivariable analyses.

In the sensitivity analysis for patients treated according to the other EU SmPC, the results are similar compared to unselected population. The current study results in EU SmPC patients are in line with previous SITS publications where we compared outcome between early and later time window in patients ≤80 years who were compliant with the EU SmPC.[16-19] There, the outcomes were poorer among patients treated in the later time window. It is also important to

note that the statistical significance will be heavily driven by the large sample size. Although SICH rate was higher in the later than early time window, the absolute difference between the groups was small (ranging between 1.1% and 1.8% depending on the definition of SICH): these differences may not be clinically significant, since elderly patients generally have poor outcome if untreated.

Our study has several limitations. Important limitations are observational design and lack of a control group without IVT treatment. There are some baseline imbalances between the groups which may bias the study results. The statistically significant baseline differences between the groups are probably not clinically relevant since they differ in the range 1-3% and became statistically significant due to the large sample size. Baseline stroke severity was 2 points lower and hospital arrival to treatment time was 25 minutes longer in the later group than early group. Although we performed multivariable analysis to adjust for recorded baseline differences, this may not account for all imbalances, or may overemphasize the observed imbalances. A final limitation is the extent of missing data, in particular 3 months outcome data which were missing for about 25% of patients. We analyzed baseline and demographic characteristics of these patients with missing data. We did not detect any major imbalance in the nature or extent of messiness between the later and earlier time windows, and the affected patients appear similar to patients with known outcomes. Nevertheless, this is a major source of potential bias that warrants extremely cautious interpretation of the findings.

Ischemic stroke patients over 80 years treated with IVT in the later time window had slightly higher SICH and had similar unadjusted functional outcome but poorer outcome when adjusted for baseline imbalances in unselected patients compared to patients treated within 3h.

The absolute difference between the treatment groups is small and elderly patients should not be denied IVT in the later time window solely for age without other contraindications. Caution is required to interpret these results that come from an observational, uncontrolled registry; similar findings were previously reported for patients aged <=80 years.

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Table 1 Baseline and clinical characteristics of patients over 80 years by stroke onset to treatment time category

Baseline and demographic variables Data median (IQR) for continuous or ordinal variables or percentage % (n/N) for proportions	**OTT <=3h,** n=10682	**OTT >3-4.5h** n= 3558	**p-value**
Age (years)	84 (82-87)	84 (82-87)	0.17
Sex (female)	61% (6564/10682)	61% (2188/ 3558)	0.96
Independence (mRS 0-1) before stroke	76% (7560/ 9906)	74 % (2452/ 3303)	0.02
Hypertension	77% (8021/ 10463)	78% (2732/ 3500)	0.09
Diabetes Mellitus	18% (1913/ 10464)	21% (727/ 3504)	0.001
Hyperlipidemia	29% (2939/ 10028)	28% (973/ 3426)	0.32
Atrial fibrillation	39% (4027/ 10368)	36% (1259/ 3479)	0.005
Congestive heart failure	14% (1457/10339)	14% (494/ 3464)	0.81
Previous stroke>3m earlier	14% (1421/ 10350)	14% (497/ 3475)	0.40
Previous stroke<=3m	2.1% (204/ 9905)	1.6% (54/ 3394)	0.09
History of transient ischemic attack	8.4% (600/7136)	8.3% (240/2902)	0.85
Any history of Smoking	16% (1545/9799)	14.4% (480/3327)	0.07
Aspirin at stroke onset	45% (4704/10412)	44% (1529/ 3475)	0.23
Dipyridamole	2.3 (240/10463)	2.3% (79/3499)	0.95
Anti-hypertensive, oral	70% (7279/10430)	74% (2565/ 3481)	<0.001
Anticoagulants, oral	4.5% (434/ 9603)	5.0% (161/ 3191)	0.24
Blood glucose (mmol/L)	6.7 (5.8-8.1)	6.9 (5.9-8.4)	<0.001

Weight in kg	70 (60-78)	70 (60-78)	0.51
rt-PA dose in mg	63 (54-70)	63 (54-70)	0.55
NIHSS excluding distal motor function	14 (8-19)	12 (7-18)	<0.001
Systolic blood pressure (mm Hg)	156 (140-170)	158 (140-171)	0.08
Diastolic blood pressure (mm Hg)	80 (70-90)	80 (70-90)	0.001
Signs of current infarction at imaging	18% (1803/10108)	20% (685/ 3433)	0.006
Hyperdense artery sign	22.2% (2214/9961)	18.4% (610/3309)	<0.001
Door to treatment time (minutes)	60 (42-82)	85 (55-122)	<0.001
Stroke onset to treatment time (minutes)	132 (105-158)	215 (195-240)	<0.001

Table 2 Proportion (%) and adjusted odds ratio (OR) of main outcomes in patients over 80 years treated in the early compared to the later time window

Outcomes	**OTT<=3h % (n/N)**	**OTT 3-4.5h % (n/N)**	**Absolute difference of %**	**p-value**	**Adjusted OR[1] (95% CI)**	**p-value**
SICH per SITS-MOST	1.6% (161/10127)	2.7% (90/ 3364)	1.1%	0.0001	1.72 (1.25-2.35)	0.0007
SICH per ECASS-2	5.4% (534/ 9988)	7.1% (235/ 3321)	1.7%	0.0002	1.43 (1.18-1.74)	0.0003
SICH per NINDS	8.0% (801/ 10044)	9.8% (326/ 3331)	1.8%	0.001	1.34 (1.13-1.58)	0.0006
Functional Independence at 3 months	34.8% (2838/8151)	34.0% (903/ 2654)	0.8%	0.46	0.78 (0.69-0.89)	0.0001
No/ minimal disability at 3 months	23.4% (1903/ 8151)	22.5% (596/ 2654)	0.9%	0.36	0.80 (0.69-0.91)	0.001
Mortality at 3 months	32.2% (2688/8340)	31.4% (854/ 2721)	0.8%	0.41	1.10 (0.97-1.25)	0.13

[1] Early time window (<=3h) is the reference group. Multivariable analysis adjusted for age, sex, baseline NIHSS, history of DM, hypertension, smoking, previous stroke within 3m, atrial fibrillation and pre-stroke mRS, signs of current infarction, hyperdense artery sign, systolic blood pressure and plasma glucose.

Table 3 Proportion (%) and adjusted odds ratio (OR) of main outcomes in patients over 80 years treated in the early time window compared to patients treated in the later time window compliant with the EU SmPC

Outcomes	**OTT<=3h % (n/N)**	**OTT 3-4.5h % (n/N)**	**Absolute difference of %**	**p-value**	**Adjusted OR[2] (95% CI)**	**p-value**
SICH per SITS-MOST	1.6% (97/ 6278)	2.7% (55/ 2075)	1.1%	0.001	1.62 (1.12-2.34)	0.01
SICH per ECASS-2	5.1% (314/ 6208)	6.7% (138/ 2052)	1.6%	0.004	1.38 (1.09-1.75)	0.007
SITS per NINDS	7.7% (478/ 6230)	9.4% (194/ 2058)	1.7%	0.01	1.27 (1.04-1.55)	0.02
Functional Independence at 3 months	37.1% (1887/ 5088)	36.0% (601/ 1670)	1.1%	0.42	0.79 (0.68-0.92)	0.002
No/ minimal disability at 3 months	25.4% (1291/ 5088)	24.3% (406/ 1670)	1.1%	0.39	0.78 (0.67-0.92)	0.003
Mortality at 3 months	29.6% (1538/ 5194)	29.0% (495/ 1707)	0.6%	0.63	1.10 (0.95-1.28)	0.20

[2] Early time window (<=3h) is the reference group. Multivariable analysis adjusted for age, sex, baseline NIHSS, history of DM, hypertension, smoking, previous stroke earlier than 3m, atrial fibrillation and pre-stroke mRS, signs of current infarction, hyperdense artery sign, systolic blood pressure and plasma glucose.

Figure legends

Figure 1 Study flow diagram for patient selection. OTT= Stroke onset to treatment time, mRS= modified Rankin Scale, SICH= Symptomatic Intracerebral Hemorrhage, EU SmPC= European Summary of Product Criteria

Figure 2 Proportions (%) of hemorrhagic transformation on post-thrombolysis imaging scans in patients older than 80 years treated in the early and later time window. HI (Hemorrhagic Infarct), PH (Primary Intracerebral Hemorrhage), PHr (Remote Primary Intracerebral Hemorrhage), EU SmPC (European Summary of Product Criteria), OTT (Onset to thrombolysis treatment time)

Figure 3 shows the distribution of mRS (modified Rankin Scale) at 3-months in all patients over 80 years and in patients over 80 years treated according to other EU SmPC (European Summary of Product Criteria) categorized by stroke onset to treatment time

Figure 1

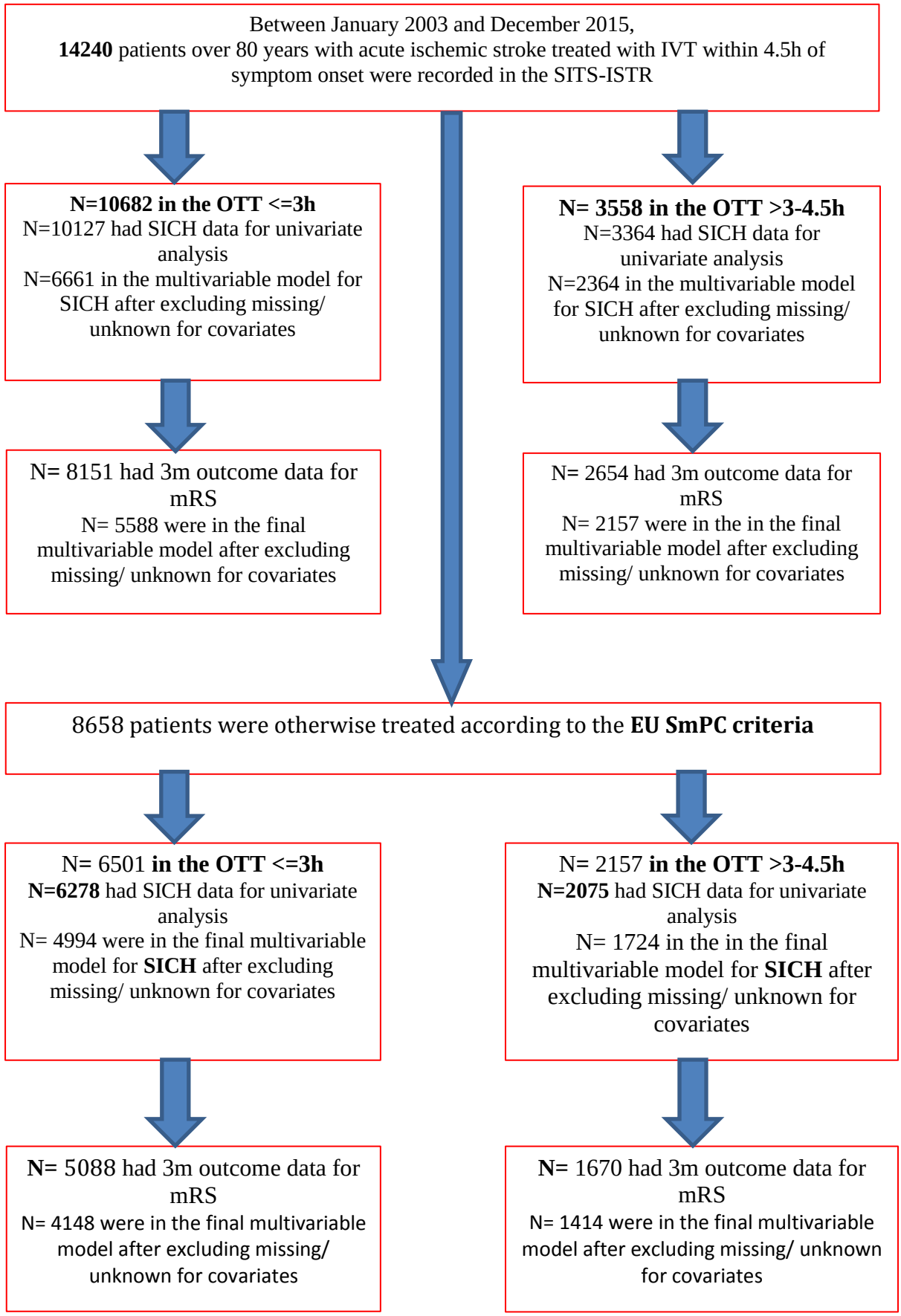
Between January 2003 and December 2015,
14240 patients over 80 years with acute ischemic stroke treated with IVT within 4.5h of symptom onset were recorded in the SITS-ISTR
N=10682 in the OTT <=3h
N=10127 had SICH data for univariate analysis
N=6661 in the multivariable model for SICH after excluding missing/ unknown for covariates
N= 3558 in the OTT >3-4.5h
N=3364 had SICH data for univariate analysis
N=2364 in the multivariable model for SICH after excluding missing/ unknown for covariates
N= 8151 had 3m outcome data for mRS
N= 5588 were in the final multivariable model after excluding missing/ unknown for covariates
N= 2654 had 3m outcome data for mRS
N= 2157 were in the in the final multivariable model after excluding missing/ unknown for covariates
8658 patients were otherwise treated according to the **EU SmPC criteria**
N= 6501 **in the OTT <=3h**
N=6278 had SICH data for univariate analysis
N= 4994 were in the final multivariable model for **SICH** after excluding missing/ unknown for covariates
N= 2157 **in the OTT >3-4.5h**
N=2075 had SICH data for univariate analysis
N= 1724 in the in the final multivariable model for **SICH** after excluding missing/ unknown for covariates
N= 5088 had 3m outcome data for mRS
N= 4148 were in the final multivariable model after excluding missing/ unknown for covariates
N= 1670 had 3m outcome data for mRS
N= 1414 were in the final multivariable model after excluding missing/ unknown for covariates

Figure 2

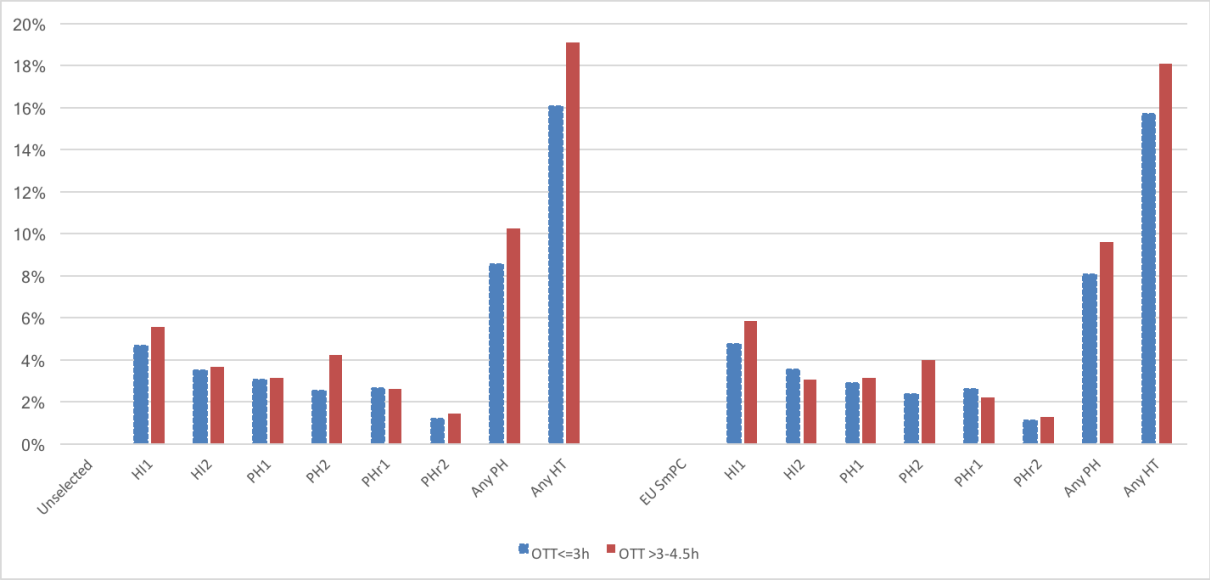

Figure 3