Acta Neurol. Belg., 2010, **110**, 157-162

Original articles

The Belgian experience with intravenous thrombolysis for acute ischemic stroke

P. Vanacker[1], V. Thijs[2], A. Peeters[3], B. Bruneel[4], P. Laloux[5], P. Druwé[6], P. De Deyn[7], N. Ahmed[8], N. Wahlgren[8], G. Vanhooren[1] for the Belgian SITS-collaboration group

[1]Department of Neurology, AZ Sint-Jan Brugge-Oostende, Brugge, Belgium; [2] Department of Neurology, UZ Leuven, Leuven, Belgium; [3]Department of Neurology, CHU Saint-Luc, Brussel, Belgium; [4]Department of Neurology, AZ Groeninghe, Kortrijk, Belgium; [5]Department of Neurology, CHU Mont-Godinne, Yvoir, Belgium; [6]Department of Emergency Medecine, AZ Sint-Vincentius, Antwerpen, Belgium; [7]Department of Neurology, AZ Middelheim, Antwerpen, Belgium; [8]Department of Clinical Neurosciences, Karolinska Institutet, Stockholm, Sweden

Abstract

Purpose: We report the Belgian results of the Safe Implementation of Thrombolysis in Stroke – International Stroke Thrombolysis Register (SITS-ISTR). This prospective observational register evaluates the safety and efficacy of intravenous thrombolysis with rtPA (recombinant tissue Plasminogen Activator) for ischemic stroke in routine clinical practice.

Methods: We compared the baseline characteristics, treatment delay, rate of symptomatic intracerebral hemorrhage and functional outcome at 90 days after treatment between patients enrolled in centres in Belgium and the non-Belgian SITS-registry population. We performed a multivariate analysis to adjust for differences in demographic and baseline characteristics.

Results: 743 patients were enrolled in 42 centers in Belgium between December 2002 and December 2007. These patients were older, had more severe stroke were more frequently female and more frequently had hyperlipidemia and atrial fibrillation. The median stroke onset-to-treatment delay was 140 min vs. 145 min.

More patients died and were disabled 3 months after the stroke. A slight, non-significant, increase of symptomatic intracerebral hemorrhage (SICH) as per SITS protocol was observed (2,4 vs. 1,6%, p = 0.15).

After adjustment for differences in baseline characteristics, functional independence (mRS $\leq$ 2) at 3 months (OR 0.95, 95% CI 0.86-1.05, p = 0.31) was not different from non-Belgian patients, nor was the rate of SICH. However mortality at 3 months in Belgian patients was slightly higher (OR 1.15, 95% CI 1.02-1.29, p = 0.02).

Conclusion: Intravenous thrombolysis for ischemic stroke is safe and effective in the routine clinical use in Belgium. The higher mortality we observed is not related to a higher rate of SICH.

Key words: acute stroke; intravenous thrombolysis; Safety Implementation of Thrombolysis in Stroke Monitoring Study; register.

Introduction

Intravenous thrombolytic therapy with alteplase is an effective treatment for acute ischemic stroke in clinical trials although intracerebral hemorrhage is a concern(1, 2). Before widespread implementation of a new therapeutic agent with potentially harmful effects, registries can provide important information whether the findings from clinical trials can be translated into routine clinical practice and whether a new therapy is safe in the real-life situation. SITS-ISTR, an open worldwide, prospective and observational register (3) was initiated form Karolinska Institute in Sweden to evaluate the safety in clinical practice of alteplase for acute ischemic stroke. From 2002 till 2006 a subset of data as per SITS-MOST protocol (Safe Implementation of Thrombolysis in Stroke-Monitoring study) was used by EMEA (European Medicins Agency) to approve the use of intravenous thrombolysis with rtPA for acute ischemic strokes with an onset of less than 3 hours in Europe. (4) In our study we report the Belgian experience of the Safe Implementation of Thrombolysis in Stroke study (SITS-ISTR) which also includes the SITS-MOST data. Although patients older than 80 years were excluded from SITS-ISTR per protocol, registration of all iv-thrombolysis procedures, including the treatment of octogenarians, was expected in SITS-ISTR. At the start of the register, intravenous thrombolysis and specialized acute stroke care was not widespread in Belgian general hospitals. Due to new data, in practice, the time window for intravenous thrombolysis has recently been extended from 3h to 4.5 hours after stroke onset with still an acceptable good safety and efficacy profile (5, 6, 7).

Methods & Materials

All Belgian patients recruited for the SITS-ISTR between December 2002 and December 2007 were included in this study. The registry design, methodology and data management have been described before (8).

The SITS registry records baseline and demographic characteristics, cardiovascular risk factors, medication, baseline NIHSS (National Institute of Health Stroke Scale) score, initial imaging and rt-PA dose. Only the SITS-MOST protocol contained primary and secondary outcome parameters with emphasis on safety. The SITS-ISTR register, by itself, didn't postulate outcome endpoints. The primary outcome measures for SITS-MOST were SICH per SITS/MOST protocol and death within 3 months. SICH was evaluated using different definitions used in clinical trials in the past. The clinical assessment by using the modified Rankin Score at 3 months was the other primary endpoint. A secondary outcome of SITS-MOST was functional independence (mRS 0-2) while additional outcome measures were complete recovery (mRS 0-1) and SICH per ECASS and per NINDS protocol.

All participating centers agreed to include consecutive patients treated with intravenous thrombolysis in the given period. Registration of off label use of thrombolysis was permitted. Data collection was done by the local investigators and anonymized data storage was performed by the SITS international collaboration group on servers in Sweden. As SITS-ISTR was a registry of a regular treatment, not an interventional clinical trial no systematic, formal informed consent was obtained. Patients (or their representatives) signed a privacy protection form. In all patients the treatment was discussed on beforehand and patients gave a more informal informed consent. The researchers of the Karolinska Institutet (Stockholm, Sweden) performed a multivariable analysis comparing the main outcomes between the Belgian cohort and the non-Belgium SITS-ISTR cohort. This multivariate analysis was used to adjust for imbalances in baseline and demographic characteristics (age, gender, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, congestive heart failure, previous stroke, independence before current stroke (defined as modified Rankin Score 0-1), smoking, aspirin treatment at stroke onset, signs of current infarction in the baseline imaging study, patients treated in centres with previous thrombolysis experience, baseline NIHSS, blood pressure and blood glucose and stroke onset to treatment time) (9).

Results

Of the total of 16049 patients included in SITS-ISTR between December 2002 and December 2007, 743 (4,6%) patients were treated in 42 Belgian stroke centers. There were seven high volume centres with more than 25 patients registered. The number of registered patients and recruiting centers diminished steadily after having reached a peak in 2004 (Fig. 1).

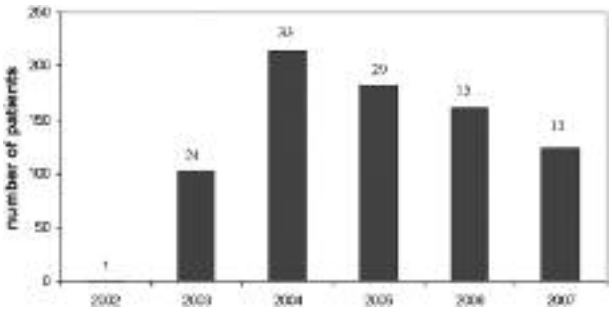

Fig. 1. — Distribution of the patient inclusions (x-axis) and number of registering centres in the period 2002-2007 (top numbers).

The demographic and baseline characteristics of the Belgian cohort in comparison with the non-Belgian cohort are shown in Table 1 and Table 2. The median age of the Belgian SITS-ISTR participants was higher (71 vs. 67y). Belgian participants were more frequently female (47 vs. 41%, $p < 0.01$) and they more frequently had a history of hyperlipidemia (42 vs. 34%, $p < 0.01$) and atrial fibrillation (30 vs. 26%, $p < 0.01$). More Belgian patients were already disabled before thrombolysis (20 vs. 8%, $p < 0.01$).

The median NIHSS score at stroke onset in the Belgian SITS-ISTR patients was higher (14 vs. 12). Forty-five percent of the Belgian participants had a NIHSS of more than 14 in comparison with 38% of the non-Belgians. At baseline there was a higher proportion of current infarction on initial imaging (26 vs. 21%, $p < 0.001$The median onset-to-treatment delay of the Belgian patients was 140 vs. 145 minutes., with a median door-to-needle time of 75 vs. 66 minutes and a median door-to-brain imaging time of 31 vs. 25 min.) The glucose levels, lipid levels and blood pressure were similar between both groups. A cardioembolic origin was more frequent in (42 vs. 36%, $p < 0.001$) (Fig. 2).

The clinical endpoints are shown in Table 3. A moderate, non significant increase of SICH as per NINDS protocol was observed (9.5 vs. 7.5%, $p = 0.05$). In Belgium, 48 patients met the ECASS criteria for SICH (6,9% vs. 5.2%, $p = 0.05$). Seven-

Table 1

Demographic characteristics of the Belgian vs. non-Belgian cohort

	Belgian SITS-ISTR (n = 743)	**Non-Belgian SITS-ISTR (n = 15306)**	**P-value**
Mean age (years, range)	71 (10-98)	67 (14-97)	
Female	(351/743) 47%	(6258/15306) 41%	< 0,001
Independence (mRS 0-1) before stroke	(570/712) 80%	(13559/14809) 92%	< 0,001
Hypertension	(277/727) 62%	(5752/14959) 62%	0,85
Diabetes Mellitus	(110/737) 15%	(2625/15050) 17%	0,78
Hyperlipidaemia	(279/663) 42%	(4585/13459) 34%	< 0,001
Current smoking	(134/694) 19%	(3362/14244) 24%	0,02
Previous smoking	(137/694) 20%	(2466/14244) 17%	0,02
Previous stroke >3 months before	(99/738) 13%	(1920/15066) 13%	0,59
Artrial fibrillation	(222/730) 30%	(3814/14913) 26%	0,004
Congestive heart failure	(61/724) 8%	(1204/14962) 8%	0,71
Antihypertensive	(407/741) 55%	(7327/15167) 48%	< 0,001
Aspirin at stroke onset	(265/740) 36%	(4585/15123) 30%	0,002

Table 2

Baseline characteristics of the Belgian vs. non-Belgian cohort

	Belgian SITS-ISTR (n = 743)	**Non-Belgian SITS-ISTR (n = 15306)**	**P-value**
Current infarct at baseline imaging	(190/734) 26%	(3183/15146) 21%	< 0,001
Blood glucose (mmol/L)	126 (40-212)	130 (38-222)	NS
Median NIHSS score (Q25-75)	14 (9-19)	12 (8-17)	NS
Systolic blood pressure (mm Hg, 95% CI)	152 (108-196)	151 (109-193)	NS
Diastolic blood pressure (mm Hg, 95% CI)	81 (51-111)	83 (57-109)	NS
Median stroke onset to treatment time (range)	140 (35-420)	145 (10-600)	NS

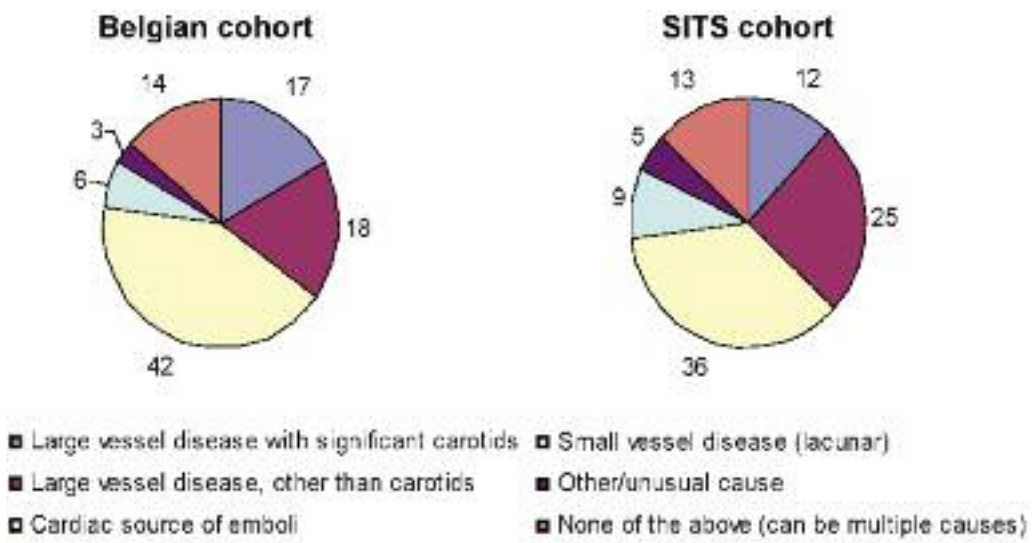

Fig. 2. — The different subgroups of strokes in the Belgian and non-Belgian cohort.

Table 3

Both the unadjusted as adjusted outcome measures of the Belgian and non-Belgian SITS-ISTR patients after a multivariable analysis with adjustment of the outcome results for the baseline and demographic characteristics

	Unadjusted Belgian SITS-ISTR (n = 743)	**Unadjusted Non-Belgian SITS-ISTR (n = 15306)**	**P-value for unadjusted data**	**Adjusted Belgian SITS-ISTR (Odd ratio, 95% CI)**	**P-value for adjusted data**
Primary outcome measures					
SICH per SITS/MOST	(17/724) 2,4%	(246/14982) 1,6%	0,15	1,15 (0,87-1,52)	0,33
Mortality (3 months)	(143/626) 23%	(1895/13208) 14,0%	< 0,001	1,15 (1,02-1,29)	0,02
Secondary outcome measures					
SICH per Cochrane/NINDS	(68/715) 9,5%	(1125/14948) 7,5%	0,05	1,08 (0,94-1,25)	0,29
SICH per ECASS	(48/701) 6,9%	(761/14746) 5,2%	0,05		
mRS 0-2 (3 months)	(269/619) 44%	(6953/13037) 53%	< 0,001	0,95 (0,86-1,05)	0,31
mRS 0-1 (3 months)	(181/619) 29,%	(4925/13037) 38%	< 0,001		

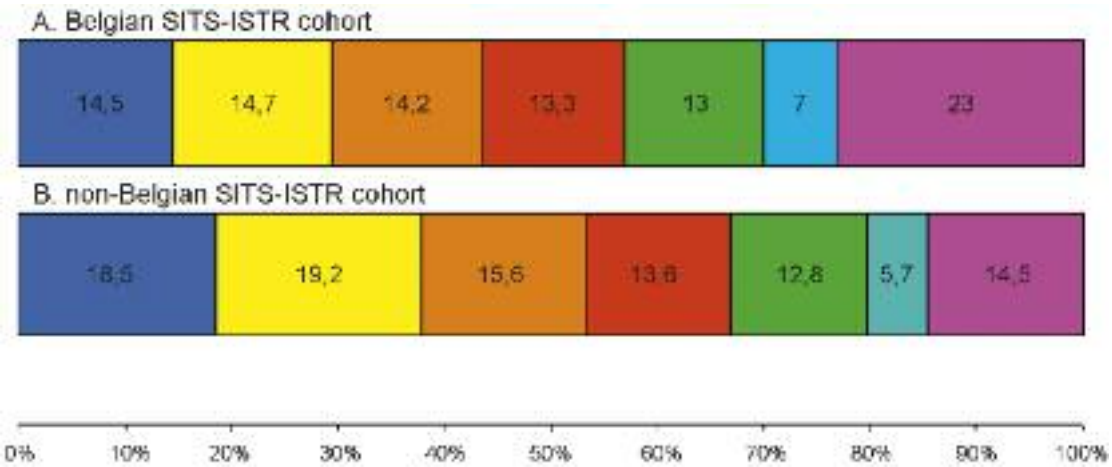

Fig. 3. — Functional (in)dependence (modified Rankin Score) after 3 months for the unadjusted Belgian and non-Belgian SITS-ISTR patients.

teen patients in Belgium (2.4%) met the SITS-ISTR criteria for symptomatic intracerebral haemorrhage. The corresponding SICH rate in the entire SITS-ISTR cohort was 1.6%. (p = 0.15). Mortality (at 3 months) was higher (23% compared to 14% (p < 0.01)). Belgian patients less frequently reached independence (mRS ≤ 2) for activities of daily living (43.5 vs. 53.3%, p < 0.001), as well as good clinical outcome (mRS ≤ 1) at 3 months (29.2 vs 37.8%, p < 0.001).

Because of imbalances in the baseline and demographic characteristics of both groups, a multivariable analysis was performed. After correction for this imbalance, mortality in Belgian patients, at 3 months after stroke, was still slightly higher (OR 1.15, 95% CI 1.02-1.29, p = 0.02), although there was no statistical difference in SICH rates (OR 1.15, 95% CI 0.87-1.52, p = 0.33). Functional independence at 3 months (OR 0.95, 95% CI 0.86-1.05, p = 0.31) was no longer statistically different in Belgium compared to whole of the database.

Discussion

Thrombolytic treatment for acute ischemic stroke was implemented successfully in routine clinical practice in a large number of Belgian hospitals. From the total numbers of registered patients and the evolution in time of the numbers of registered thrombolysis procedures (Fig. 1) it should be clear that the register did not cover all thrombolysis procedures in the given timeframe in Belgium.

The thrombolysed population in Belgium was different from the rest of the database population

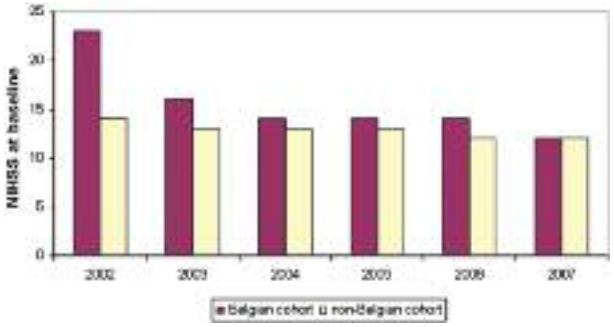

Fig. 4. — Time distribution of the severity of strokes by using the mean NIHSS at baseline for the period 2002-2007. The mean NIHSS at baseline in 2002 is not representative due to the low number of patients.

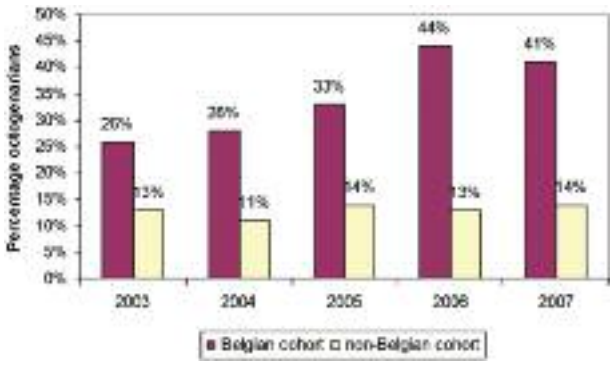

Fig. 5. — Time distribution of the proportion of octogenarians in the Belgian and non-Belgian cohort.

in several aspects. Patients treated in Belgium were more severely affected at baseline. This can be explained by three hypotheses. First of all, the difference was most obvious during the first years of the register. The reluctance to treat minor strokes has diminished (Fig. 4) although we have no hard data to proof this. The median NIHSS at baseline decreased over the years for both the Belgian and non-Belgian cohort, but this effect was more pronounced in Belgium. Secondly, the proportion of low volume stroke centres that registered data, decreased (Fig. 1). The data of the United Kingdom SITS-ISTR substudy demonstrated that there was no major difference in outcome between 'low-throughput' and 'high-throughput' centers (10). At last, the proportion of octogenarians was higher in the Belgian cohort across the whole study period and this trend increased over the years. At the start of the register in 2002, there was some limited evidence that octagenarians had a similar risk to develop SICH in comparison with younger patients (11). During the following years, the number of centers treating octagenarians increased, as more statistic evidence became available (12). As a recent systematic review showed that octagenarians had a similar immediate functional outcome as younger patients, the use of rt-PA in this group of patients, although still being off-label use, can be defended (13) (Fig. 5).

Although the non-adjusted analysis suggested differences in functional outcome and SICH rate between the Belgian and non-Belgian population, analyses corrected for imbalances in prognostic factors revealed similar rates of SICH, functional independence and good outcome. The increased mortality therefore can not be attributed to excess SICH. There is no ready explanation for the increased mortality. This may possibly explained by the relative underdevelopment of stroke unit care, in Belgium (14, 15). Other, unmeasured factors like co morbidity or frailty may explain the excess mortality as well as differences in end of life practice or this may just be due to chance as many hypotheses were tested. Given the lack of data on the exact causes of death these reasons remain entirely speculative.

Despite the elevated mortality rates at 3 months, all the primary and secondary outcome results are in line with the rates in clinical trial experience of intravenous thrombolysis (7). We compared our data with two cohort studies (STARS: Standard Treatment with Alteplase to Reverse Stroke (16) and CASES: Canadian Alteplase for Stroke Effectiveness Study (17)). The CASES study had a similar mortality rate at 3 months (22.3 vs. 22.8%), although the rate of excellent clinical outcomes was higher (37% vs. 29.2%). Also, the STARS multicenter study had less SICH (3,3% vs. 9,5%) but used a different and more restrictive definition (STARS: SICH = symptomatich hemorrhage on a follow-up scan within 3 days; vs. CASES: SICH = clinical neurologic decline in first 24h with a new hemorrhage on CT) for SICH. Although, the clinical outcome was assessed at 30 instead of 90 days, patients in the STARS study more frequently had an excellent clinical outcome (35% vs. 29.2%) and there were fewer deaths (13% vs. 22,8%). Both the STARS as the CASES register did not perform a multivariable analysis to correct for their baseline and demographic characteristics.

In conclusion, the Belgian cohort of the SITS-ISTR demonstrated that intravenous thrombolysis for ischemic stroke is safe and effective in the routine clinical use in Belgium at least in the centres having taken part in this registration.

Acknowledgements

We thank all the Belgian SITS-ISTR investigators and their centres for participation (AZ Sint Jan, Brugge-Oostende; UZ Gasthuisberg, Leuven; AZ Sint Blasius,

Dendermonde; AZ Heilige Familie, Reet; AZ Algemeen Ziekenhuis, Aalst; AZ Sint Lucas, Brugge; AZ Waasland, Sint Niklaas; AZ Sint Vincentius, Antwerpen; AZ Jan Palfijn, Gent; AZ Jan Ypermanziekenhuis, Ieper; Regionaal ziekenhuis H. Hart, Leuven; AZ Heilig Hart, Tienen; Sint Andries Ziekenhuis, Tielt; AZ Klina, Brasschaat; AZ Virga jesse Ziekenhuis, Hasselt; AZ Groeninge, Kortrijk; AZ Sint Lucas, Gent; Imeldaziekenhuis, Bonheiden; AZ Middelheim, Antwerpen; UZ, Brussel; AZ Vezalius, Tongeren; AZ Sint Trudo, Sint Truiden; AZ Maria Middelares, Gent; AZ Stuivenberg, Antwerpen; AZ Jan Portaels, Vilvoorde; AZ Damiaan, Oostende; UZ Gent, Gent; AZ Sint Rembert, Torhout; CHU Mont-Godinne, Yvoir; CHU St. Luc, Woluwe; CHU Hopital Erasme, Bruxelles; Clinique Saint-Jean, Bruxelles; Hôpital Civil, Charleroi; CH Reine Fabiola, Montignies; CHA, Libramont; Hôpital Tivoli, La Louviere; CHR Tournai, Tournai; Hôpital de Jolimont, Jolimont; Cliniques de l'Europe, Bruxelles; CH du Bois de l Abbaye, Waremme; Centre Hospitalier Peltzer, Verviers; CHU Brugmann, Bruxelles; Cliniques Saint-Joseph, Liége). Further on, we also thank the patients who participated in SITS-ISTR. The SITS-ISTR register was funded by an unrestricted grant from Boehringer-Ingelheim GmbH (Ingelheim, Germany). The data collection and analysis was performed, independent of Boehringer-Ingelheim, by Uppsala Clinical Research (Uppsala, Sweden).

REFERENCES

1. Wardlaw JM, Murray V, Berge E, Del Zoppo GJ. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2009;4:CD000213.
2. Hacke W, Donnan G, Fieschi C, Kaste M, Van Kummer R. *et al*. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS and NINS rt-PA stroke trials. Lancet. 2004; 363:768-74.
3. SITS-ISTR (Safe Implementation of Treatments in Stroke – International Stroke Thrombolysis Register). Available at http://www.acutestroke.org. Accessed December 2, 2009.
4. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M. *et al.*; SITS-MOST investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet. 2007;369:275-82.
5. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A. *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317-29.
6. Lansberg MG, Bluhmki E, Thijs VN. Efficacy and safety of tissue plasminogen activator 3 to 4.5 hours after acute ischemic stroke: a metaanalysis. Stroke. 2009;40:2438-41
7. Wahlgren N, Ahmed N, Davalos A, Hacke W, Millan M. *et al*. Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy Investigators. Thrombolysis with alteplase 3-4,5h after acute ischaemic stroke (SITS-ISTR): an observational study. Lancet. 2008;372:1303-9.
8. Toni D, Lorenzano S, Puca E, Prencipe M. The SITS-MOST registry. Neurol Sci. 2006;27:S260-262.
9. Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E. *et al*. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy Investigators. Stroke. 2008;39:3316-22.
10. Lees KR, Ford GA, Muir KW, Ahmed N, Dyker AG. *et al*. Thrombolytic therapy for acute stroke in the United Kingdom: experience from the Safe Implementation of Thrombolysis in Stroke (SITS) register. Q J Med. 2008;101:863-9.
11. Tanne D, Gorman MJ, Bates VE, Scott E, Kasner *et al*. and the tPA Stroke Survey Group. Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke in Patients Aged 80 Years and Older: The tPA Stroke Survey Experience. Stroke, 2000; 31:370-5.
12. Rubiera M, Ribo M, Santamarina E, Maisterra O, Delgado-Mederos R. *et al*. Is it time to reassess the SITS-MOST criteria for thrombolysis? A comparison of patients with and without SITS-MOST exclusion criteria. Stroke, 2009; 40:2568-71.
13. Engelter ST, Bonati LH, Lyrer PA. Intravenous thrombolysis in stroke patients of > 80 versus < 80 years of age – a systematic review across cohort studies. Age Ageing, 2006; 35: 572-80.
14. Saposnik G, Fang J, O'Donnell M, Hachinski V, Kapral MK, et al. Investigators of the Registry of the Canadian Stroke Network (RCSN) for the Stroke Outcome Research Canada (SORCan) Working Group. Escalating levels of access to in-hospital care and stroke mortality. Stroke, 2008, 39:2522-30.
15. Zhu HF, Newcommon NN, Cooper ME, Green TL, Seal B. *et al*. Calgary Stroke Program. Impact of a stroke unit on length of hospital stay and in-hospital case fatality. Stroke. 2009;40:18-23.
16. Albers GW, Bates VE, Clark WM, Bell R, Verro P. *et al*. Intravenous Tissue-Type Plasminogen Activator for Treatment of acute stroke. The Standard Treatment with Alteplase to Reverse Stroke (STARS) study. JAMA. 2000;283:1145-50.
17. Hill MD, Buchan AM, for the Canadian Alteplase for Stroke Effectiveness Study (CASES) investigators. CMAJ. 2005;172:307-12.

Peter Vanacker
AZ Sint-Jan Brugge-Oostende AV
Ruddershove 10
B-8000 Brugge, Belgium
peter.vanacker@azbrugge.be