Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Stroke Association
A Division of American Heart Association

Outcomes of Intravenous Thrombolysis After Dissemination of the Stroke Code and Designation of New Referral Hospitals in Catalonia: The Catalan Stroke Code and Thrombolysis (Cat-SCT) Monitored Study

Sònia Abilleira, Antoni Dávalos, Ángel Chamorro, José Álvarez-Sabín, Aida Ribera, Miquel Gallofré and on behalf of the Catalan Stroke Code and Thrombolysis Study Group (Cat-SCT)

Stroke published online May 12, 2011;
DOI: 10.1161/STROKEAHA.110.605030
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

Outcomes of Intravenous Thrombolysis After Dissemination of the Stroke Code and Designation of New Referral Hospitals in Catalonia

The Catalan Stroke Code and Thrombolysis (Cat-SCT) Monitored Study

Sònia Abilleira, MD, PhD; Antoni Dávalos, MD, PhD; Ángel Chamorro, MD, PhD; José Álvarez-Sabín, MD, PhD; Aida Ribera, BSc, PhD; Miquel Gallofré, MD, PhD; on behalf of the Catalan Stroke Code and Thrombolysis Study Group (Cat-SCT)

Background and Purpose—From 2006, the Stroke Code system operates throughout Catalonia with full coverage. The objective of this study was to determine safety and effectiveness of intravenous thrombolysis in routine practice through a monitored study (Catalan Stroke Code and Thrombolysis [Cat-SCT]) and to assess outcomes according to hospitals' previous experience.

Methods—We conducted a prospective, multicenter, observational, monitored study of recombinant tissue plasminogen activator-treated patients declared to the Cat-SCT by all treating hospitals in Catalonia (n=13, of which 6 were newly designated) over a 12-month period. Consecutive recruitment and quality of data were assured through comprehensive quality control. We estimated rates of outcome measures for the potential final sample (after inclusion of undeclared cases) and compared them with those reported for the actual sample. Symptomatic intracranial hemorrhage, mortality, and favorable outcome (modified Rankin Scale score 0 to 1) at 3 months were also evaluated according to hospitals' previous experience using multilevel logistic regression.

Results—We analyzed 488 patients with a median age of 72 years (interquartile range: 63, 77), 57.2% males, with a baseline National Institutes of Health Stroke Scale score of 13 (interquartile range: 8, 19), and stroke to treatment time of 150 minutes (interquartile range: 120, 180 minutes). Symptomatic intracranial hemorrhage (Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy definition) was observed in 3.3% patients. Ninety-day mortality was 16.6% and 38.5% showed a favorable outcome at 3 months. External monitoring set inclusion losses at <5%. A sensitivity analysis including undeclared cases did not show significant changes in main outcomes. Inexperienced hospitals achieved similar outcomes, except for a higher rate of favorable outcome at 3 months.

Conclusions—Health planning applied to acute stroke care and based on dissemination of the Stroke Code system and designation of new referral hospitals showed intravenous thrombolysis safe and effective in routine practice, even among inexperienced hospitals. (***Stroke*. 2011;42:00-00.)**

Key Words: acute stroke ■ outcomes ■ thrombolysis ■ tPA

In Catalonia (population as of 2009: 7.6 million inhabitants; area: 32 000 km^2), stroke causes >12 000 hospital admissions per year, representing 2% of all admissions to acute care hospitals.[1] Acute stroke care is provided through a network of 48 publicly financed, acute care hospitals distributed across the territory according to demographic criteria; larger hospitals are located in and around the capital (Barcelona), whereas middle- and small-sized hospitals cover the rest of the

Received October 7, 2010; final revision received January 7, 2011; accepted January 10, 2011.

From the Stroke Programme (S.A.), Catalan Agency for Health Information, Assessment and Quality (CAHIAQ), Barcelona, Spain; CIBER Epidemiología y Salud Pública (CIBERESP; S.A., A.R.), Spain; The Cat-SCT Steering Committee (A.D., A.C., J.A.-S.), Barcelona, Spain; the Cardiovascular Epidemiology Unit (A.R.), Hospital Vall d'Hebron, Barcelona, Spain; and the Stroke Programme (M.G.), Health Department, Generalitat de Catalunya, Barcelona, Spain.

The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.605030/DC1.

The Catalan Stroke Code and Thrombolysis Study Group are: J.J. Baiges and M. Garcés (H. Verge de la Cinta, Tortosa); A. Pellisé, X. Ustrell, and R. Marés (H. Joan XXIII, Tarragona); J. Sanahuja and F. Purroy (H. Arnau de Vilanova, Lleida); J. Saura (Fundació Althaia Hospital, Manresa); M. Aguilar (H. Mútua de Terrassa); D. Cánovas (H. de Sabadell); J. Serena, M. Castellanos, and Y. Silva (H. Dr Josep Trueta, Girona); A. Dávalos, N. Pérez de la Ossa, M. Millán, and M. Gomis (H. Germans Trias i Pujol, Badalona); J. Roquer, A. Ois, and A. Rodríguez-Campello (H. del Mar, Barcelona); J. Martí-Fàbregas, S. Martínez-Ramírez, and R. Delgado-Mederos (H. de la Santa Creu i Sant Pau, Barcelona); A. Chamorro, V. Obach, and A. Cervera (H. Clínic i Provincial, Barcelona); J. Álvarez-Sabín, C.A. Molina, M. Ribó, and M. Rubiera (H. Vall d'Hebron, Barcelona); F. Rubio and P. Cardona (H. Universitari de Bellvitge, l'Hospitalet); and S. Abilleira, A. Ribera, and M. Gallofré (Stroke Programme).

Correspondence to Sònia Abilleira, MD, PhD, Stroke Programme, Catalan Agency for Health Information, Assessment and Quality (CAHIAQ), Roc Boronat 81-95, 2a planta, 08005 Barcelona, Spain. E-mail sabilleira@aatrm.catsalut.cat

***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.110.605030**

territory where demographic density is much lower. In 2004, the Health Department of the Autonomous Government of Catalonia created the Stroke Programme as 1 of the branches of the Master Plan for Diseases of the Circulatory System. One of the main objectives of the Stroke Programme was the design of a regionwide model for early evaluation, diagnosis, and treatment of patients with acute stroke based on a pre-existing Stroke Code (SC) system. The main purpose of the SC system is to favor recombinant tissue-type plasminogen activator (rtPA) administration among candidates by facilitating early recognition of stroke and speeding up the transfer of acute patients to referral hospitals (RHs) where immediate assessments can be performed. Our territory-based model disseminated the SC system, operated already by a few hospitals since the late 1990s and beyond,[2–5] to the whole Catalan territory by drawing a map with 10 healthcare areas within which 13 RHs operate the SC through a local stroke network composed by community hospitals, the emergency medical system, and primary care. This regionwide SC system was fully operative as of May 2006.

The main objectives of this study were to determine safety and effectiveness of intravenous thrombolysis in routine practice after dissemination of the SC system throughout Catalonia and to establish whether newly designated RHs with no previous expertise in thrombolysis performed according to standards. Because all new RHs had been designated according to availability of pre-established technical and professional requirements, we hypothesized that results of intravenous rtPA in routine practice in terms of safety and effectiveness would be comparable to previously published outcomes. Moreover, because we were aware of the potential selection bias linked to unmonitored studies, we assessed safety and effectiveness of thrombolysis in routine practice through a monitored study to estimate the occurrence and magnitude of such bias.

Methods

Study Design and Participating Hospitals

Catalan Stroke Code and Thrombolysis (Cat-SCT) was an observational, prospective study that involved all publicly financed RHs in Catalonia with capacity to assess SC patients and administer alteplase among candidates (n=13). RHs were considered experienced (n=7) or inexperienced (n=6) depending on whether they had begun to administer intravenous rtPA before or after the spread of the SC system, respectively. Thus, RHs that started delivering rtPA in mid-2006, since the dissemination of the SC system by the Stroke Programme, were considered nonexperts. Additionally, 2 community hospitals that operated a telestroke network in connection with 2 experienced RHs were also involved.

All participating hospitals were encouraged to enrol consecutive treatments performed over a 12-month period (October 2007 to October 2008). Inclusion criteria were ≥18-year-old patients with ischemic stroke treated with intravenous rtPA. Treatments administered in combination to any rescue therapy were excluded from this analysis. At each site, designated local investigators were in charge of identifying patients with stroke treated with rtPA, requesting the informed consent, and collecting in-hospital and follow-up data. During the admission, cases were declared to a Web-based registry that satisfied all legal requirements for protection of personal data. Approval was obtained from the Ethics Committee at Institut de Recerca Hospital Universitari Vall d'Hebron (Barcelona, Spain).

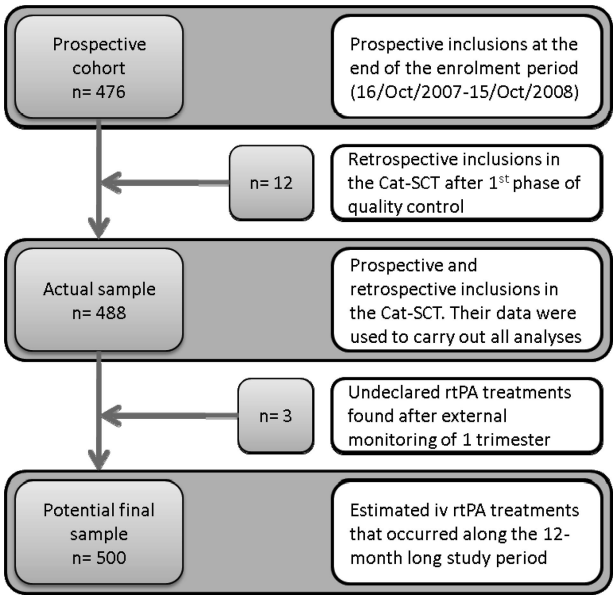

Figure. Flow chart of the quality control carried out in this study.

Outcome Measures

The primary outcome measures for the Cat-SCT were symptomatic intracerebral hemorrhage (SICH), death, and favorable outcome (defined as a modified Rankin Scale score 0 to 1) after 3 months. SICH was defined according to the Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST) protocol[6] as any local or remote parenchymal hemorrhage Type 2 on the 22 to 36 hour post-treatment imaging scan, combined with a neurological deterioration of ≥4 points on the National Institutes of Health Stroke Scale from baseline, or from the lowest National Institutes of Health Stroke Scale value between baseline and 24 hours, or leading to death. Mortality and functional status at 3 months were recorded through face-to-face or telephone follow-up visits performed by local investigators. Whenever a patient was lost to follow-up, survival was retrospectively assessed by study coordinators through official population registries or contact with the patient's family. Secondary outcome measures were functional independence at 3 months (modified Rankin Scale score 0 to 2), death within 7 days and incidence rates of SICH by the European Cooperative Acute Stroke Study definition (any hemorrhage plus a neurological deterioration of ≥4 points on the National Institutes of Health Stroke Scale from baseline or from the lowest National Institutes of Health Stroke Scale value after baseline to 7 days or leading to death).[7]

Quality Control in the Cat-SCT

At the end of the enrollment period, we carried out a comprehensive quality control to assess exhaustiveness or consecutive recruitment and quality of data (Figure). In a first step, local stroke databases from all treating hospitals were crosschecked against the central database. Undeclared rtPA treatments retrieved this way were retrospectively included in the Cat-SCT to result in the actual sample (prospective+retrospective inclusions), which was then used to calculate outcomes reported in this article. Second, heads of medical records services among all treating hospitals were requested to produce a local list of all stroke admissions occurred between January 1, 2008, and March 31, 2008, according to predefined International Classification of Diseases, 9th Revision diagnostic codes (431, 432, 433.x1, 434, 436). Discharge and mortality reports from all listed cases were then revised by external monitors in the search of patients treated with intravenous rtPA. International Classification of Diseases, 9th Revision codes corresponding to intravenous thrombolysis (99.10) were discarded as a method for identifying rtPA-treated patients because in a previous stage, we had detected a very low coding rate, similar to what others have described.[8] All cases identified through this process were labeled

Table 1. Baseline Characteristics of Patients in the Cat-SCT, SITS-MOST, and Pooled RCTs

	Cat-SCT (n=488)	Experienced RHs (n=372)	Inexperienced RHs (n=116)	SITS-MOST (n=6483)	Pooled Analysis (rtPA; n=464)
Age, y	72 (63–77)	73 (64–78)	68.5 (59–75)	68 (59–75)	69.6 (61.3–75.4)
Sex, female	209 (42.8)	164 (44.1)	45 (38.8)	2581 (39.8)	186 (40.1)
Baseline NIHSS	13 (8–19)	13 (7.25–19)	14 (9.25–18)	12 (8–17)	13 (8–18)
Pre-stroke mRS 0–1	437/480 (91)	332 (90.5)	105 (92.9)	5899/6337 (93.1)	. . .
OTT, min	150 (120–180)	155 (120–185)	140 (100–164.5)	140 (115–165)	140 (90–168)
DTN, min	61.5 (47–81.7)	61 (46–80)	63 (50–86)	68 (30)	. . .
Hypertension	287 (58.8)	219 (58.9)	68 (58.6)	3710/6318 (58.7)	277 (59.7)
Diabetes mellitus	97 (19.9)	74 (19.9)	23 (19.8)	1020/6374 (16.0)	98 (21.1)
Dyslipidemia	164 (33.6)	130 (34.9)	34 (29.3)	1967/5661 (34.8)	. . .
Previous stroke	65 (13.3)	48 (12.9)	17 (14.7)	643/6395 (10.1)	64 (13.8)
Atrial fibrillation	96 (19.7)	70 (18.8)	26 (22.4)	1507/6306 (23.9)	96 (20.7)
Coronary heart disease	80 (16.4)	65 (17.5)	15 (12.9)	. . .	. . .
Congestive heart failure	27 (5.5)	20 (5.4)	7 (6.0)	467/6339 (7.5)	61 (13.2)
Stroke subtype					
Atherothrombotic	79 (16.5)	49 (13.2)	30 (25.9)	2279 (35.2)	. . .
Cardioembolic	198 (41.3)	150 (40.3)	48 (41.4)	2270 (35.0)	. . .
Small vessel disease	26 (5.4)	16 (4.3)	10 (8.8)	535 (8.3)	. . .
Unusual	9 (1.9)	7 (1.9)	2 (1.7)	1171 (18.1)*	. . .
Undetermined	168 (35.0)	145 (39.0)	23 (19.8)	228 (3.5)†	. . .

Data are: median (interquartile range), mean (SD), or no. (%).

Cat-SCT indicates Catalan Stroke Code and Thrombolysis; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy; RCTs, randomized controlled trials; RHs, referral hospitals; rtPA, recombinant tissue-type plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; OTT, onset-to-treatment time; DTN, door-to-needle time.

*Labeled "other" in the SITS-MOST.

†Labeled "unknown" in the SITS-MOST.

as declared or undeclared thrombolyses according to their previous inclusion in the central database. Quality of data included at each study site was ensured through external monitoring of patients treated along one fourth of the total recruitment period. Before and during the recruitment period, local collaborators had been warned that a quality control would take place at the end of the study. A registry users' guide and a help line were available along the recruitment period.

Statistical Analyses

We used percentages to describe discrete variables and means (SD) or medians (interquartile range) to describe continuous variables. The proportion and 95% CIs of SICH, mortality, and favorable outcome at 3 months were calculated and compared with those in the SITS-MOST[6] and the pooled results from randomized controlled trials (active group).[9]

The effect of hospitals' previous experience on outcomes after intravenous thrombolysis was assessed using multilevel logistic regression analysis. We built 1 model for each outcome variable and added hospitals' previous experience as an explanatory variable adjusting for other baseline variables to take possible differences in the case mix between hospitals into account. Variables for adjustment were selected on the basis of clinical plausibility and a statistical significance for bivariate associations set at a probability value <0.2. All treatments delivered at community hospitals through telestroke were allocated to the experienced group.

To determine the presence of a potential selection bias, we estimated the rates of primary outcome measures for the potential final sample (=actual sample+4*[undeclared treatments detected by the quality control]) and compared it with the rates in the actual sample. All statistical analyses were done using STATA software. The level of significance was set at 0.05.

Results

We studied 488 intravenous thrombolyses included in the actual sample, of which 12 were retrospective inclusions. Three hundred seventy-two of 488 thrombolyses were delivered at experienced RHs (thrombolysis rate: 7.0% of acute ischemic stroke admissions), whereas the remaining 116 treatments were administered at inexperienced RHs (thrombolysis rate: 4.7% of acute ischemic stroke admissions). Numbers of thrombolyses ranged from 10 to 98 across RHs. Seventeen treatments were performed through telestroke. Along the recruitment period, another 34 patients with ischemic stroke received endovascular reperfusion therapies, of which 15 were bridging therapies. Median age of our series was 72 years (IQR: 63, 77), and 279 (57.2%) were males. Compared with patients in the SITS-MOST, those in our study were 4 years older. Accordingly, sex distribution showed a higher percentage of females in our series. Baseline National Institutes of Health Stroke Scale was similar across the Cat-SCT, the SITS-MOST, and the pooled analysis of RCTs, whereas the onset-to-treatment time was longer in the Cat-SCT (Table 1). Deviations from the SITS-MOST eligibility criteria, particularly of age and time criteria, were detected in 166 (34%) patients, most of who had been treated at experienced RHs (Table 2).

As for the primary outcome measures, 16 of 488 (3.3%) patients developed a SICH and 180 of 468 (38.5%) patients achieved a favorable functional outcome. Up to 79 of 468 (16.9%) died within the first 90 days. Overall, outcomes in our series resembled those shown by the pooled analysis of RCTs very much but when compared with the SITS-MOST, patients in the Cat-SCT displayed a significantly higher death rate at 3 months (Table 3). We also analyzed the influence of RHs' previous experience on outcomes (Table 4; http://

Table 2. Protocol Violations

Unmet Criteria	Cat-SCT (n=488)	Inexperienced RHs (n=116)	Experienced RHs (n=372)
1 criterion	138 (83.1)	11 (91.7)	127 (82.5)
Age >80 y	43 (25.9)	4 (33.3)	39 (25.3)
OTT >3 h	76 (45.8)	2 (16.7)	74 (48.1)
NIHSS ≥25	3 (1.8)	0 (0)	3 (1.9)
Previous stroke and diabetes	16 (9.6)	5 (41.7)	11 (7.1)
2 criteria	26 (15.7)	1 (8.3)	25 (16.2)
Age >80 y+OTT >3 h	18 (10.8)	1 (8.3)	17 (11.0)
Age >80 y+NIHSS ≥25	1 (0.6)	0 (0)	1 (0.6)
Age >80 y+[previous stroke+diabetes]	3 (1.8)	0 (0)	3 (1.8)
OTT >3 h+NIHSS ≥25	1 (0.6)	0 (0)	1 (0.6)
OTT >3 h+[previous stroke+diabetes]	2 (1.2)	0 (0)	2 (1.2)
NIHSS ≥25+[previous stroke+diabetes]	1 (0.6)	0 (0)	1 (0.6)
3 criteria	2 (1.2)	0 (0)	2 (1.3)
Age >80 y+OTT >3 h+NIHSS ≥25	2 (1.2)	0 (0)	2 (1.2)
Any criteria	166 (100)	12 (100)	154 (100)

Numbers express no. (column %).

Cat-SCT indicates Catalan Stroke Code and Thrombolysis; RH, referral hospitals; OTT, onset-to-treatment time; NIHSS, National Institutes of Health Stroke Scale.

stroke.ahajournals.org). Newly designated RHs were at least as safe and effective as experienced RHs. After adjusting for several prognostic factors, we observed non significant trends of higher SICH and mortality rates in experienced centers, whereas chances of achieving a favorable outcome at 3 months were significantly higher for patients treated at inexperienced RHs.

After auditing one fourth of the total study period, we detected 3 cases that had not been declared to the Cat-SCT registry, which together with 12 undeclared cases returned by the first step of the quality control, and retrospectively included in the Cat-SCT, set the overall loss at 4.8% (Figure). The estimated rates of primary outcomes in the potential final sample of 500 patients did not differ significantly from the rates observed in the actual sample (Table 5). Regarding the accuracy of outcome measures, death at 7 days had an almost perfect agreement, whereas post-rtPA CT and outcome at 90 days showed moderate agreement. Sources of disagreement were investigated and found to be related to external monitors reporting missing data when local investigators had reported death or a particular score on the modified Rankin Scale, thus suggesting that quality of original data provided by stroke clinicians was good, whereas that of external auditors was improvable.

Table 3. Outcomes of Intravenous Thrombolysis in the Cat-SCT, the SITS-MOST, and the Pooled RCTs

	Cat-SCT (n=488)	SITS-MOST (n=6483)	Pooled RCTs (n=464)
SICH (SITS-MOST)	3.3 (1.7–4.9)	1.7 (1.4–2.0)	*
SICH (ECASS II)	4.9 (3.0–6.8)	4.6 (4.1–5.1)	*
7-d death rate	10.8 (7.9–13.4)	6.5	*
3-m death rate	16.6 (13.3–19.9)	11.3 (10.5–12.1)	17.3 (14.1–21.1)
mRS 0–1 at 3 mo	38.5 (34.1–42.9)	39.9	*
mRS 0–2 at 3 mo	50.6 (46.1–55.2)	54.8 (53.5–56.0)	49.0 (44.4–53.6)

Numbers express proportions and 95% CI.

Cat-SCT indicates Catalan Stroke Code and Thrombolysis; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy; RCTs, randomized controlled trials; SICH, symptomatic intracerebral hemorrhage; ECASS, European Cooperative Acute Stroke Study; mRS, modified Rankin Scale.

*Not reported.

Table 4. Effect of Previous Experience of Referral Hospitals on Outcomes of Intravenous Thrombolysis (OR for the Outcome at Experienced RHs Versus Newly Designated RHs)

	OR (95% CI)	*P*
SICH (SITS-MOST)*	5.15 (0.65–41)	0.121
SICH (ECASS II)*	2.52 (0.7–9.1)	0.159
7-d death rate†	1.72 (0.7–4.23)	0.239
3-mo death rate†	1.46 (0.71–3)	0.303
mRS 0–1 at 3-m‡	0.54 (0.31–0.92)	0.023
mRS 0–2 at 3-m‡	0.72 (0.41–1.26)	0.248

All models adjusted for age, sex, onset-to-treatment time, baseline National Institutes of Health Stroke Scale.

RHs indicates referral hospitals; SICH, symptomatic intracerebral hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy; ECASS, European Cooperative Acute Stroke Study; mRS, modified Rankin Scale; rtPA, recombinant tissue-type plasminogen activator.

*Also adjusted for diabetes, antiplatelet treatment and atrial fibrillation.

†Also adjusted for previous stroke, pre-morbid mRS, and comorbid conditions (coronary heart disease, congestive heart failure, diabetes, atrial fibrillation, hypertension).

‡Also adjusted for pre-morbid mRS, blood glucose control pre-rtPA, dyslipidemia, and antiplatelet treatment.

Discussion

This study shows how an initiative launched by the autonomous health administration, and based on the dissemination of the SC system throughout Catalonia, facilitated the delivery of intravenous thrombolysis in routine practice at the same time as ensuring safety and effectiveness. The results of this study add more evidence to previous knowledge about

Table 5. Variation of Main Outcomes According to Pre-/Postquality Control Inclusions

	Actual Sample (n=488)	Sample Before Retrospective Inclusion (n=476)	Potential Final Sample (Estimated n=500)*
SICH (ECASS II)	31 (6.4)	32 (6.7)	35 (7)
SICH (SITS-MOST)	20 (4.1)	20 (4.2)	20 (4)
7-d death rate	53 (10.8)	53 (11.1)	57 (11.4)
3-m death rate	81 (16.6)	81 (17)	85 (17)
mRS 0–1 at 3 mo	188 (38.5)	182 (38.2)	196 (39.2)
mRS 0–2 at 3 mo	247 (50.6)	239 (50.2)	255 (51)

Numbers express no. (%).

SICH indicates symptomatic intracerebral hemorrhage; ECASS, European Cooperative Acute Stroke Study; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy; mRS, modified Rankin Scale.

*Estimated sample size: n=actual sample (= 488)+[undeclared treatments detected by external audit (n=3)]*4.

the reproducibility in clinical practice of outcomes achieved with intravenous rtPA in an experimental setting. However, in our opinion, remarkable contributions of this study are first, it evaluates the impact of health planning on acute stroke care in Catalonia, whereby the SC system was disseminated to cover the whole territory from May 2006. Because the SC dissemination meant designation of new RHs with no previous expertise in thrombolysis, we wanted to assess whether thrombolysis was being delivered safely and effectively. Second, by undertaking a rigorous quality control, we can assure that the results of this study certainly reflect real-world practice, a pivotal feature seldom guaranteed by observational studies.[10]

Worldwide thrombolysis rates remain low despite the very many efforts done.[8,11] Poor recognition of stroke and a delayed alert on the patient's side play a crucial role by stopping patients from benefits of early admission.[12] At the hospital level, certain features of in-hospital organization, particularly clinical leadership, shared goals concerning door-to-needle time and thrombolysis rates and feedback, also contribute to enlarge the numbers of patients with stroke treated with rtPA.[13] At the prehospital level, organization of stroke networks that clearly identify RHs and establishment of referral circuits for patients with acute stroke are of utmost importance, mainly for territories with a public health system and a myriad of differently resourced hospitals. Although local prehospital and in-hospital organization is well known to have an impact on thrombolysis rates of single centers,[2,3,14] from a wider territorial perspective, prehospital organization according to principles of territorial equity is also necessary.[5,15,16] This is what we pursued by implementing a sectoring model with 10 SC areas and 13 RHs.[17] These areas work independently and were designed on the basis of 3 main criteria: first, a minimum volume of stroke admissions at each potential RHs that ensured the proper development of the learning curve for intravenous thrombolysis; second, a resident population within the extended catchment areas of designated RHs that would make affordable the estimates of incident SC patients within the area; and third, isochrones of up to 60 minutes from each geographic point within a SC area and its RH. In addition, RHs had to comply with the specific technical and professional requirements for RHs described in our Clinical Practice Guidelines for Stroke[18] and ascertained through local visits by members of the Stroke Programme. Once the RHs and their catchment areas were established, circuits among community hospitals, primary care, and the RHs were defined. The emergency medical system played a role as either the transporter of patients from any of the levels to the RH or as a primary source of SC patients. Neurologists from new RHs who otherwise had no previous experience with intravenous rtPA delivery were asked to undertake short training periods at experienced RHs under the supervision of stroke experts, after which they organized the acute stroke team within their own RHs. In the understanding that responsibilities of health managers follow a logical sequence that goes from planning to evaluation through implementation, we designed and promoted this monitored study to assess the results of our territorial model of acute stroke care.

Our data show that intravenous thrombolysis is just as safe and effective in clinical practice as in major trials.[9,19] However, when compared with the SITS-MOST,[6] our data show a significant increase in long-term mortality. Possible explanations for this finding are: (1) a difference in median age of 4 years between the SITS-MOST and the Cat-SCT (older patients in the Cat-SCT); (2) a slightly worse previous functional status and slightly higher comorbidity burden among patients included in the Cat-SCT; (3) a 10-minute delay of median onset-to-treatment time for patients in the Cat-SCT; and (4) more rigorous quality control in the Cat-SCT. The differences observed in terms of age, comorbidity, and onset-to-treatment time, however, did not evenly apply to the whole cohort and mainly affected patients recruited at experienced hospitals (Table 1). Routine practice in experienced centers and physicians show a relaxation of rules because well-established label contraindications for rtPA use are questioned on the grounds of experience.[20] In our study, newly designated centers made a much more careful selection of rtPA candidates, whom with very few exceptions fulfilled SITS-MOST criteria (Table 2). This finding is in contrast with existing evidence showing more protocol violations and higher mortality in inexperienced centers.[21,22] Despite a more accurate patient selection, however, inexperienced RHs did not perform systematically and significantly better across the series of outcomes measured, except for a higher proportion of patients with a modified Rankin Scale score 0 to 1 at 3 months (Table 4). Moreover, using any protocol violation as a covariate in the multivariate model did not produce any significant change in terms of outcomes compared between experts and nonexperts (data not shown). Thus, protocol violation was not an independent predictor of outcome in our study, suggesting that some other factors play a role (ie, differences in the process of care). However, we believe these findings are not conclusive because the study was not designed to answer this particular question. Although this study cannot confirm nor exclude that differences in outcomes are due to differences in protocol violations, we still believe it necessary to be cautious in selecting patients eligible for rtPA, particularly among experienced hospitals where indication for thrombolysis is frequently made on the basis of radiological mismatch and regardless of the onset-to-treatment time delay. In our study, the proportion of patients treated beyond the 3-hour and 4.5-hour time window were 20.3% (experienced: 25.8%; inexperienced: 2.6%) and 3.9% (experienced: 5.1%; inexperienced: 0%), respectively. In the light of these results as well as existing evidence,[23,24] thrombolysis beyond the 4.5-hour time window should be cautiously administered in clinical trials only.

This study has some limitations. We analyzed data on 488 patients with stroke treated with intravenous rtPA along 1 year across Catalan hospitals, of which 116 (23.8%) were treated at newly designated hospitals with no previous experience. The trends in favor of safer and more effective treatments at inexperienced RHs are somehow disturbing and need further attention. A longer recruitment period would likely clarify this issue at the same time as offering additional information about changes in rtPA benefits over time. Furthermore, we cannot preclude an effect of unmeasured differences in the case mix of patients treated at experienced and inexperienced RHs on the outcomes. Because we only audited one fourth of the recruitment period, we cannot establish the absence of a selection bias with absolute certainty. However, because the sensitivity analysis showed no distortions, we estimate the magnitude of such

bias small. Finally, the methods used for determining the accuracy of data (retrospective review of case records of all stroke admissions treated with rtPA along one fourth of the study period) are improvable. However, a detailed review of the sources of disagreement revealed that those administering thrombolysis provided reliable data. In other words, quality of the original data provided by stroke clinicians was good, whereas that of external auditors was improvable.

In summary, this study shows that health policies that prioritize planning of acute stroke care from a territorial perspective may encourage the use of evidence-based therapies. Accordingly, since SC dissemination across Catalonia, we have observed a gradual increase of intravenous thrombolysis rates, which represented 8.1% of all acute ischemic stroke admissions in 2009. Because thrombolysis carries the potential of harm, we believed it necessary to assess and monitor the outcomes of this particular health planning. Whether this model has external validity and can be applied to other regions or countries with independent health administrations will depend on social and geographic similarities as well as the characteristics of their national health system.

Acknowledgments

We thank Sílvia López-Aguilà for statistical assistance. We especially thank Gaietà Permanyer-Miralda for critical review of the article and all the support offered to the Stroke Programme. We are also indebted to the patients willing to participate in this study and all local collaborators contributing to data collection.

Sources of Funding

This study was funded by grants from the TV3 Marató Foundation (06/2810) and the Catalan Agency for Health Technology, Assessment and Research (050/03/06).

Disclosures

A.D. receives fees as a scientific advisor from Boehringer Ingelheim and Lundbeck. J.A.-S. receives fees as a scientific advisor from Boehringer Ingelheim.

References

1. Activity of the Healthcare and Social-Healthcare Network of Catalonia 2006. Report on Registers of the Minimum Basic Data Set (CMBD). Barcelona: Servei Català de la Salut (Departament de Salut, Generalitat de Catalunya); 2007 (cited July 13, 2010). Available at: http://www10.gencat.cat/catsalut/archivos/publicacions/estad_sanitaries/xarxa_sanitaria_2006_ang.pdf. Accessed May 4, 2011.
2. Belvis R, Cocho D, Marti-Fabregas J, Pagonabarraga J, Aleu A, Garcia-Bargo MD, Pons J, Coma E, Garcia-Alfranca F, Jimenez-Fabrega X, Marti-Vilalta JL. Benefits of a prehospital stroke code system. Feasibility and efficacy in the first year of clinical practice in Barcelona, Spain. *Cerebrovasc Dis*. 2005;19:96–101.
3. Álvarez-Sabin J, Molina C, Montaner J, Arenillas J, Pujadas F, Huertas R, Mourino J, Ribo M, Santamarina E, Quintana M. Clinical benefit following the implementation of a specialized urgent stroke care system [in Spanish]. *Med Clin (Barc)*. 2004;122:528–531.
4. Alvarez-Sabin J, Molina C, Abilleira S, Montaner J, Garcia F, Alijotas J. 'Stroke code.' Shortening the delay in reperfusion treatment of acute ischemic stroke [in Spanish]. *Med Clin (Barc)*. 1999;113:481–483.
5. de la Ossa NP, Sanchez-Ojanguren J, Palomeras E, Millan M, Arenillas JF, Dorado L, Guerrero C, Abilleira S, Davalos A. Influence of the stroke code activation source on the outcome of acute ischemic stroke patients. *Neurology*. 2008;70:1238–1243.
6. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V, Lees KR, Roine RO, Soinne L, Toni D, Vanhooren G. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet*. 2007;369:275–282.
7. Hacke W, Kaste M, Fieschi C, von KR, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan G, Schneider D, ez-Tejedor E, Trouillas P. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998;352:1245–1251.
8. Kleindorfer D, Lindsell CJ, Brass L, Koroshetz W, Broderick JP. National US estimates of recombinant tissue plasminogen activator use: ICD-9 codes substantially underestimate. *Stroke*. 2008;39:924–928.
9. Hacke W, Donnan G, Fieschi C, Kaste M, von KR, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC Jr, Kwiatkowski T, Levine SR, Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, Albers G, Bluhmki E, Wilhelm M, Hamilton S. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004;363:768–774.
10. Ferreira-Gonzalez I, Marsal JR, Mitjavila F, Parada A, Ribera A, Cascant P, Soriano N, Sanchez PL, Aros F, Heras M, Bueno H, Marrugat J, Cunat J, Civeira E, Permanyer-Miralda G. Patient registries of acute coronary syndrome: assessing or biasing the clinical real world data? *Circ Cardiovasc Qual Outcomes*. 2009;2:540–547.
11. Rudd AG, Hoffman A, Grant R, Campbell JT, Lowe D. Stroke thrombolysis in England, Wales and Northern Ireland: how much do we do and how much do we need? *J Neurol Neurosurg Psychiatry*. 2011;82:14–25.
12. Mosley I, Nicol M, Donnan G, Patrick I, Dewey H. Stroke symptoms and the decision to call for an ambulance. *Stroke*. 2007;38:361–366.
13. van Wijngaarden JD, Dirks M, Huijsman R, Niessen LW, Fabbricotti IN, Dippel DW. Hospital rates of thrombolysis for acute ischemic stroke: the influence of organizational culture. *Stroke*. 2009;40:3390–3392.
14. Abdullah AR, Smith EE, Biddinger PD, Kalenderian D, Schwamm LH. Advance hospital notification by EMS in acute stroke is associated with shorter door-to-computed tomography time and increased likelihood of administration of tissue-plasminogen activator. *Prehosp Emerg Care*. 2008;12:426–431.
15. Gladstone DJ, Rodan LH, Sahlas DJ, Lee L, Murray BJ, Ween JE, Perry JR, Chenkin J, Morrison LJ, Beck S, Black SE. A citywide prehospital protocol increases access to stroke thrombolysis in Toronto. *Stroke*. 2009;40:3841–3844.
16. Riopelle RJ, Howse DC, Bolton C, Elson S, Groll DL, Holtom D, Brunet DG, Jackson AC, Melanson M, Weaver DF. Regional access to acute ischemic stroke intervention. *Stroke*. 2001;32:652–655.
17. Gallofre M, Abilleira S, Tresserras R, de la Puente ML. The Stroke Programme of Catalonia. *Med Clin (Barc)*. 2009;133:589–593.
18. Guía de Práctica Clínica del Ictus. Catalunya 2007. Barcelona: Agència d'Avaluació de Tecnologia i Recerca Mèdiques; 2007 (cited November 2010). Available at: www.gencat.cat/salut/depsalut/pdf/gp05ictuspacientses.pdf. 2008. Accessed January 5, 2011.
19. Graham GD. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. *Stroke*. 2003;34:2847–2850.
20. Meretoja A, Putaala J, Tatlisumak T, Atula S, Artto V, Curtze S, Happola O, Lindsberg PJ, Mustanoja S, Piironen K, Pitkaniemi J, Rantanen K, Sairanen T, Salonen O, Silvennoinen H, Soinne L, Strbian D, Tiainen M, Kaste M. Off-label thrombolysis is not associated with poor outcome in patients with stroke. *Stroke*. 2010;41:1450–1458.
21. Heuschmann PU, Berger K, Misselwitz B, Hermanek P, Leffmann C, Adelmann M, Buecker-Nott HJ, Rother J, Neundoerfer B, Kolominsky-Rabas PL. Frequency of thrombolytic therapy in patients with acute ischemic stroke and the risk of in-hospital mortality: the German Stroke Registers Study Group. *Stroke*. 2003;34:1106–1113.
22. Heuschmann PU, Kolominsky-Rabas PL, Roether J, Misselwitz B, Lowitzsch K, Heidrich J, Hermanek P, Leffmann C, Sitzer M, Biegler M, Buecker-Nott HJ, Berger K. Predictors of in-hospital mortality in patients with acute ischemic stroke treated with thrombolytic therapy. *JAMA*. 2004;292:1831–1838.
23. Lees KR, Bluhmki E, von KR, Brott TG, Toni D, Grotta JC, Albers GW, Kaste M, Marler JR, Hamilton SA, Tilley BC, Davis SM, Donnan GA, Hacke W, Allen K, Mau J, Meier D, del Zoppo G, De Silva DA, Butcher KS, Parsons MW, Barber PA, Levi C, Bladin C, Byrnes G. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. 2010;375:1695–1703.
24. Mishra NK, Albers GW, Davis SM, Donnan GA, Furlan AJ, Hacke W, Lees KR. Mismatch-based delayed thrombolysis: a meta-analysis. *Stroke*. 2010;41:e25–e33.