Thrombolysis and clinical outcome in patients with stroke after implementation of the Tyrol Stroke Pathway: a retrospective observational study

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See appendix for a list of the project teams

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Summary

Background Intravenous thrombolysis for ischaemic stroke remains underused worldwide. We aimed to assess whether our statewide comprehensive stroke management programme would improve thrombolysis use and clinical outcome in patients.

Methods In 2008–09, we designed the Tyrol Stroke Pathway, which provided information campaigns for the public and standardised the entire treatment pathway from stroke onset to outpatient rehabilitation. It was commenced in Tyrol, Austria, as a long-term routine-care programme and aimed to include all patients with stroke in the survey area. We focused on thrombolysis use and outcome in the first full 4 years of implementation (2010–13).

Findings We enrolled 4947 (99%) of 4992 patients with ischaemic stroke who were admitted to hospitals in Tyrol; 675 (14%) of the enrollees were treated with alteplase. Thrombolysis administration in Tyrol increased after programme implementation, from 160 of 1238 patients (12·9%, 95% CI 11·1–14·9) in 2010 to 213 of 1266 patients (16·8%, 14·8–19·0) in 2013 ($p_{trend\ 2010–13}<0·0001$). Differences in use of thrombolysis in the nine counties of Tyrol in 2010 (range, 2·2–22·6%) were reduced by 2013 (12·1–22·5%). Median statewide door-to-needle time decreased from 49 min (IQR 35–60) in 2010 to 44 min (29–60) in 2013; symptomatic post-thrombolysis intracerebral haemorrhages occurred in 28 of 675 patients (4·1%, 95% CI 2·8–5·9) during 2010–13. In four Austrian states without similar stroke programmes, thrombolysis administration remained stable or declined between 2010 and 2013 (mean reduction 14·4%, 95% CI 10·9–17·9). Although the 3-month mortality was not affected by our programme (137 [13%] of 1060 patients in 2010 *vs* 143 [13%] of 1069 patients in 2013), 3-month functional outcome significantly improved (modified Rankin Scale score 0–1 in 375 [40%] of 944 patients in 2010 *vs* 493 [53%] of 939 in 2013; score 0–2 in 531 [56%] patients in 2010 and 615 [65%] in 2013; $p_{trend\ 2010–13}<0·0001$).

Interpretation During the period of implementation of our comprehensive stroke management programme, thrombolysis administration increased and clinical outcome significantly improved, although mortality did not change. We hope that these results will guide health authorities and stroke physicians elsewhere when implementing similar programmes for patients with stroke.

Funding Reformpool of the Tyrolean Health Care Fund.

Introduction

According to the World Stroke Organization campaign, one in six people will have a stroke during their lifetime.[1] Alteplase (recombinant tissue plasminogen activator) is the only approved drug for patients with acute ischaemic stroke and is recommended as first-line treatment within 4·5 h of stroke onset.[2] There is compelling scientific evidence of its efficacy from randomised controlled trials and their meta-analysis.[3] Its safe applicability in the routine clinical setting is supported by analyses of data from large-scale thrombolysis registries.[4] Over the past decade initiatives have prompted the elimination of specific barriers to the delivery of stroke thrombolysis, mainly at the hospital level, and resulted in increased thrombolysis administration.[5–14] Likewise, far-reaching quality assurance programmes like the American Heart Association's Get With The Guidelines-Stroke have improved guideline adherence and have also led to increased use of alteplase.[15] Nevertheless, almost two decades after the first positive trial,[16] 12 years after approval in the European Union, 15 years after approval in Canada, and 18 years after approval in the USA, intravenous thrombolysis for stroke remains underused worldwide. Proportions of patients with acute stroke receiving thrombolysis have been reported for several countries and states (mainly from Europe and North America) and varied between 1·7% and 10·4%.[15,17–22] True percentages are likely to be even lower because none of the surveys had full coverage (enrolment of about 10% to 85% of all patients with stroke in these countries)[19] and

many excluded groups of patients who were less likely to receive thrombolysis, such as patients with recurrent stroke[19] or those older than 80 years.[18]

We investigated whether a multifaceted statewide routine-care disease management programme targeting all relevant aspects of stroke care, from disease onset to rehabilitation, would increase thrombolysis administration and improve clinical outcome in patients.

Methods

Patients and study design

The survey area of Tyrol, a state in western Austria (appendix), has a population of about 850 000, including temporary guests (tourists and seasonal workers). Tyrol is located in the Alps, Central Europe's main mountain range, and comprises a few urban areas in the central Inn Valley surrounded by sparsely populated rural areas. These regional characteristics result in difficult transport conditions and geographical remoteness (appendix). All patients with stroke in this region from mid-2009 (July 1) onwards entered the Tyrol Stroke Pathway (figure 1; how to enter and navigate within the electronic Tyrol Stroke Pathway is explained in the appendix), which we designed in 2008–09, and were guided through it until 3 months after the stroke; patients in the outpatient rehabilitation programme and requiring rehabilitative services beyond the 3-month follow-up visit stayed in the pathway for a maximum of 6 months. The pathway included patients with ischaemic stroke (including those with transient symptoms but with CT or MRI evidence of acute infarction)[23] or intracerebral haemorrhage. The Tyrol Stroke Pathway was implemented and maintained as a sustained component of routine patient care in the entire survey area by the Tyrolean Health Care Fund, which is funded by the Tyrol Government and the health insurance carriers. Ethics committee approval and patients' written informed consent were not required under Austrian law, because this project relies on a retrospective analysis of routine hospital data (appendix).

Procedures

The Tyrol Stroke Pathway covers all eight hospitals in the state (three of which have a stroke unit that admits patients with acute stroke; two of which have inpatient rehabilitation facilities), prehospital emergency response services, and general practitioners and health-care providers outside the hospitals (appendix). The Tyrol Stroke Pathway comprised four consecutive phases: prehospital, hospital, inpatient rehabilitation, and outpatient rehabilitation. Briefly, the two main components of the prehospital phase are a broad information campaign for the public (appendix) and efforts to reduce prehospital delays and ensure appropriate information transfer (appendix). One emergency medical service protocol and one triage algorithm for patients with suspected stroke, involving referral guidelines for thrombolysis and a prenotification system, were implemented. According to the algorithm, patients with stroke who might be suitable for thrombolysis are directed to one of four hospitals offering thrombolysis therapy (three with a stroke unit and one without a stroke unit) and the other patients with stroke are directed to hospitals close to their homes. The programme is not intended to establish routine intravenous thrombolysis in the smaller hospitals. The hospital and inpatient rehabilitation phases are aimed at standardising all aspects of inpatient stroke care in Tyrol. We formed local multidisciplinary stroke teams to advance day-to-day management of patients with stroke, identify specific local barriers, and coordinate educational activities. All hospitals have immediate access (24 h per day, 7 days per week) to neuroimaging and CT prioritisation for patients with stroke. The stroke neurologists are in-house or available for telephone consultation 24 h per day, 7 days per week, using a competence platform (a telephone hotline for contacting stroke specialists and neuroradiologists to provide real-time decision support and teleradiological reporting). The purpose of the final phase is to establish quality-controlled outpatient rehabilitation in the pilot county Landeck with subsequent and ongoing rollout to other counties in the state.

The electronic pathway is prominently placed on the starting pages of the hospital intranets, is easily accessible from all hospital computers, and can be accessed from outside through a password-secured interface. The electronic pathway contains up-to-date material required for best stroke care along with educational material (guidelines, less formal standards, and educational videos for the National Institutes of Health Stroke Scale [NIHSS] and Gugging Swallowing Screen),[24] and information for the public (folders, posters, video clips, and home page links; more details are provided in the appendix).

International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) discharge codes for the primary diagnosis were restricted to I61.× (intracerebral haemorrhage) and I63.× (ischaemic stroke); other codes (I65.× to I67.×) and G46.× were used as additional diagnoses and I64 was judged to be inappropriate. Stroke teams in each hospital obtained and entered patient-level data for clinical characteristics—including baseline NIHSS, timing of diagnostic procedures, treatment strategies, adherence to selected quality measures, comorbidities, complications, inhospital mortality, and discharge destination—in a three-page form embedded in the electronic patients' records (appendix). As standard, the pages for acute stroke care were completed on admission and the remainder of the form was completed as part of the discharge process. If ICD-10 stroke codes were entered as the primary discharge diagnosis, the electronic systems to enable discharge of patients were locked until after completion of all documentary requirements and no empty fields were allowed. Data quality was assured by automatic plausibility checks, fill-in helps (precise variable definitions),

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See **Online** for appendix

For the **Tyrol Stroke Pathway** see http://schlaganfallpfad.uki.at/english/01_ENGLISH_Pfadbeschreibung_TP1-TP4_2013.pdf

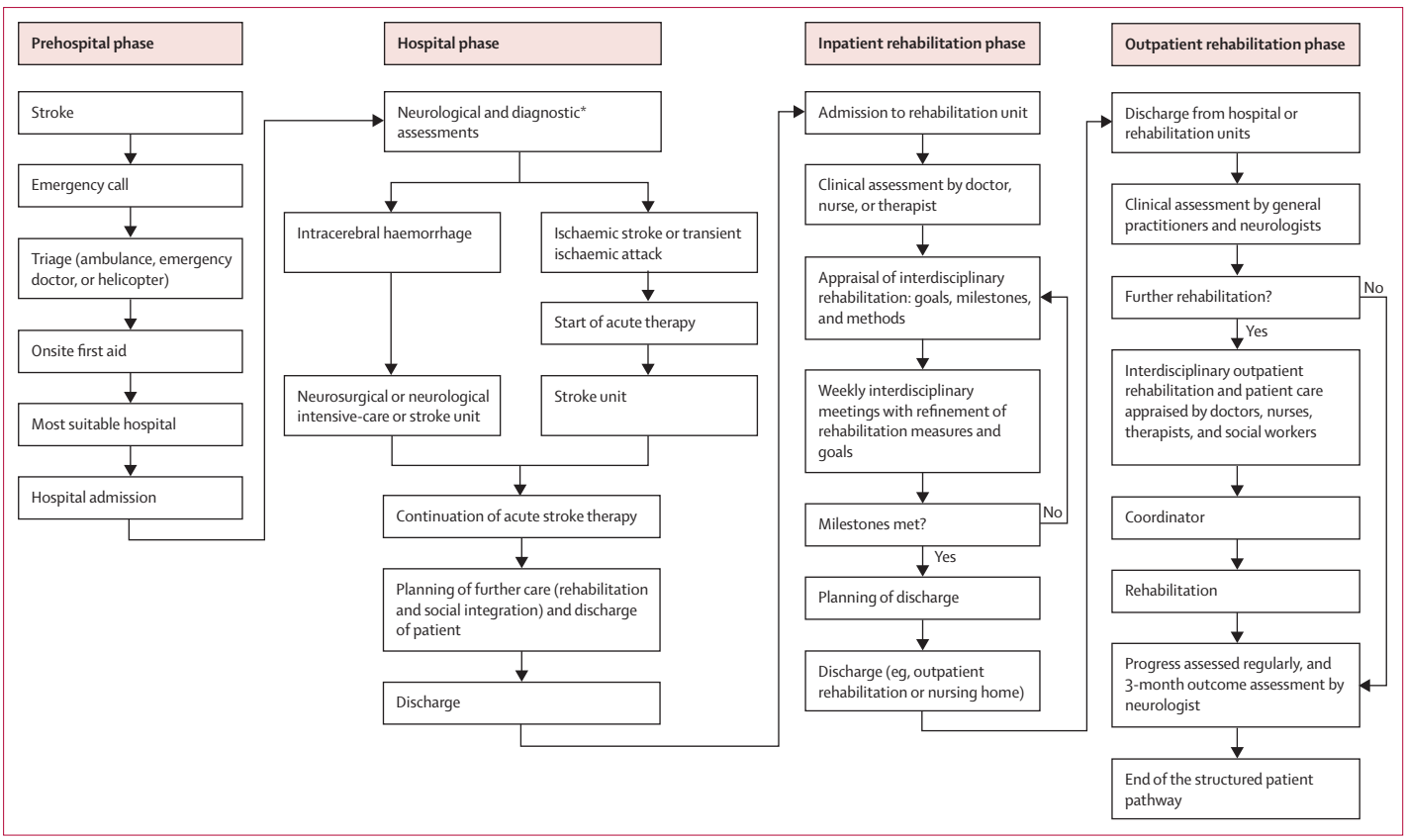

Figure 1: **Four consecutive phases of the Tyrol Stroke Pathway**
*Standard operating procedures include CT or MRI, sonography, electrocardiography, and blood tests.

continuously updated guidelines for correct completion of the form, full data monitoring (to resolve incongruencies within and between various data sources, check key data, and ensure completeness), and discussion of yearly data reports with each hospital.

Mortality at 3 months, and 6 months after stroke onset was assessed by linking the database with the National Register of Deaths. Functional outcome was assessed 3 months after the stroke with the modified Rankin Scale (mRS; appendix). These assessments were restricted to permanent residents of Tyrol. For the current analysis, data from eight of the nine counties in Tyrol were used. Information about thrombolysis administration was retrieved for other Austrian states from the Documentation and Information Systems for Analyses in Health Care, a platform for routine health-care data in Austria, and for stroke units from the Austrian Stroke Unit Registry[9,25] (appendix). The analysis of stroke units did not include the hospitals in Tyrol.

Statistical analysis

Thrombolysis administration percentages with 95% CIs were calculated as the number of acute stroke cases in the catchment area in which intravenous thrombolysis was given divided by the overall number of ischaemic strokes (appendix). We did not include patients receiving endovascular stroke treatment unless they had undergone previous intravenous thrombolysis for the same stroke (appendix). In sensitivity and subsidiary analyses, we applied a more stringent stroke definition (first-ever strokes only with an NIHSS on admission >0) or focused on subgroups defined by sex, stroke severity (NIHSS <4, 4–10, 11–20, or >20), admission delay (onset-to-door time <1·5 h, 1·5–3·0 h, 3·0–4·5 h, >4·5 h, or unclear onset), and age at stroke onset (<70 years, 70–80 years, or >80 years). Proportions and trends in proportions were compared with the χ^2 test or χ^2 test for trend (degrees of freedom 3, if not otherwise specified) for categories. Multivariable logistic regression analysis was used to test independent effects of the calendar year (time trend) and alteplase treatment on clinical outcome after adjustment for age (in years), sex, and NIHSS (continuous scale, $\log_e$ transformed). All tests were two-tailed and significance was assessed at the 0·05 level. Analyses were done with R (version 3.1.0).

Role of the funding source

Representatives of the Tyrolean Health Care Fund (Reformpool) were members of the steering committee and contributed to programme design and implementation,

and data monitoring and analysis. The funder had no role in defining the medical content of the programme, gathering data, or writing this report. The academic review board (JS, SK, JW, TG, HR, SP, HS, GB, EW, JG, KB, and MB; appendix) made the decision to submit the report for review. The scientific project leaders (SK [corresponding author] and JW) and the statistician (HR) for the Tyrolean Health Care Fund had full access to the data.

Results

During the survey (2010–13), 4992 patients with ischaemic stroke were admitted to Tyrol's hospitals and 4947 (99%) were enrolled in the Tyrol Stroke Pathway, had complete assessment of their baseline characteristics, and were the study population for our analyses (appendix). 675 (14%) of 4947 patients were treated with alteplase.

The incidence of ischaemic stroke in Tyrol was stable during the survey: 116 cases and 33 cases per 100 000 person-years for first-ever events and recurrent events, respectively (149 per 100 000 person-years overall; appendix). In the survey area, hospital admission for patients with stroke was near complete (appendix). Table 1 shows the patients' characteristics. Mean age, male-to-female ratio, and stroke severity remained stable during the survey period (appendix), and the numbers of patients with stroke who were treated at stroke units, neurological departments (standard wards), or internal medicine and other departments were similar in 2010 and 2013 (table 2). Overall, diagnostic work-up (door-to-needle time, time performance of CT or MRI, time performance of vessel imaging, and performance of transthoracic or transoesophageal echocardiography) of patients with stroke improved, and the frequency of pneumonia and the regional heterogeneity in providing speech or dysphagia therapy declined (table 2). Efforts to increase knowledge at population level about stroke improved the accuracy of recognition of stroke symptoms (appendix); however, this improvement did not translate into a decline in admission delays to hospital (patients arriving at hospital within 4·5 h of symptom onset, 517 [42%] of 1238 in 2010 *vs* 505 [40%] of 1266 in 2013).

Before the initiation of the Tyrol Stroke Pathway, 82 of 1237 patients with ischaemic stroke received intravenous thrombolysis (6·6%, 95% CI 5·3–8·2) in 2007. The number almost doubled to 160 of 1238 patients (12·9%, 11·1–14·9) in 2010, after implementation of the Tyrol Stroke Pathway was completed (figure 2A), and further increased in 2013 to 213 of 1266 patients (16·8%, 14·8–19·0; $p_{trend\ 2010–13}<0·0001$). In 2010, among 196 patients arriving within 4·5 h with an NIHSS of at least 4 and age 80 years or younger, 106 were treated with alteplase (54·1%, 46·8–61·2), with an increase to 134 of 211 patients (63·5%, 56·6–70·0) in 2013 ($p_{trend\ 2010–13}=0·020$). The median door-to-needle time decreased from 49 min (IQR 35–60) in 2010 to 44 min (29–60) in 2013 ($p_{trend\ 2010–13}=0·03$). The range of proportions of patients receiving thrombolysis across the nine counties of Tyrol narrowed over the study period (2010, 2·2–22·6%; 2013, 12·1–22·5%; figure 3). During 2010–13, symptomatic intracerebral haemorrhage occurred in 28 of 675 patients with ischaemic stroke (4·1%, 95% CI 2·8–5·9) who received thrombolysis and 68 patients died in hospital (10·1%, 7·9–12·6).

Clinical outcome data during follow-up were obtained for 3720 (98%) of 3798 patients with stroke who were permanent residents of eight of the nine counties in Tyrol. 3-month excellent functional outcomes (mRS 0–1) and good functional outcomes (mRS 0–2) improved over 2010–13 (mRS 0–1, 375 of 944 patients, 39·7% [95% CI

	Patients
Female sex	2301 (47%)
Age (years)	75 (66–83)
National Institutes of Health Stroke Scale (score)	4 (2–10)
Diabetes	940 (19%)
Previous stroke	1023 (21%)
Onset-to-door time of less than 3 h	1680 (34%)
CT or MRI within 1 h of admission to hospital	3464 (70%)
Transthoracic or transoesophageal echocardiography	2238 (45%)
Ultrasound, CT angiography, or magnetic resonance angiography of carotid and vertebral arteries within 24 h*	3513 (82%)

Data are number (%) or median (IQR). Diabetes and previous stroke were coded as unknown in 51 (1%) and 192 (4%) of the patients, respectively, because they could not be reliably assessed. *Percentages refer to 4285 patients who underwent ultrasound, CT angiography, or magnetic resonance angiography of carotid and vertebral arteries.

Table 1: **Characteristics of the 4947 patients with ischaemic stroke in Tyrol during 2010–13**

	2010 (n=1238)	2013 (n=1266)	p value
Type of stroke care			0·15
Stroke unit	717 (58%)	798 (63%)	
Neurological department	261 (21%)	241 (19%)	
Internal medicine and other departments	260 (21%)	227 (18%)	
Stroke incidence, per 100 000 person-years (95% CI)	150·4 (141·5–159·8)	149·3 (140·5–158·6)	0·88
Ultrasound, CT angiography, or magnetic resonance angiography of carotid and vertebral arteries within 24 h	869 (79%)*	917 (85%)†	0·0006
CT or MRI within 1 h of admission to hospital	820 (66%)	918 (73%)	0·0004
Transthoracic or transoesophageal echocardiography	501 (40%)	589 (47%)	0·0026
Pneumonia	100 (8%)	63 (5%)	0·0022
Speech or dysphagia therapy (number [%], range in the nine counties of Tyrol)	733 (59%, 16–68)	847 (67%, 49–78)	<0·0001
Door-to-needle time in patients given intravenous thrombolysis (min; median, IQR)	49 (35–60)	44 (29–60)	0·030

Data are number (%), unless otherwise indicated. *Denominator is 1098 patients. †Denominator is 1080 patients.

Table 2: **Changes in stroke incidence and performance measures of adequate stroke care in patients during 2010 and 2013**

36·6–42·8] in 2010 *vs* 493 of 939 patients, 52·5% [49·0–55·3] in 2013, $p_{trend\ 2010–13}$<0·0001; mRS 0–2, 531 of 944 patients, 56·3% [53·1–59·5] in 2010 *vs* 615 of 939 patients, 65·5% [62·5–68·5] in 2013; $p_{trend\ 2010–13}$<0·0001; figure 2B) and these findings remained significant after adjustment for age, sex, NIHSS, and thrombolysis therapy ($p_{trend\ 2010–13}$<0·0001 for both mRS categories). Differences in functional outcome between regions in 2010 were reduced by 2013 (appendix). The percentages of patients treated with alteplase who had excellent and good clinical outcomes at 3 months (mRS 0–1, 162 of 473 patients, 34·2% [29·9–38·5] and mRS 0–2, 226 of 473 patients, 47·8% [43·3–52·2]) were within the ranges of those reported in randomised controlled trials and in thrombolysis registries (appendix). Patients receiving alteplase were more likely to achieve excellent or good outcome at 3 months than patients who did not receive alteplase after adjustment for age, sex, NIHSS, and calendar year (multivariable odds ratio for mRS 0–1 2·4, 95% CI 1·8–3·1, and mRS 0–2 2·4, 1·8–3·2, p<0·0001 for both mRS categories).

Unlike functional outcome, mortality remained unaffected by our programme: 137 (13%) of 1060 patients had died at 3 months and 170 (16%) at 6 months in 2010 versus 143 (13%) of 1069 at 3 months and 165 (15%) at 6 months in 2013 (log-rank p=0·44 for difference in the survival curves).

We used a broad definition of stroke, which in addition to the standard clinical criteria allowed for the inclusion of patients with transient symptoms (<24 h) and CT or MRI evidence of acute infarction, thus complying with the recent update of the stroke definition by the American Heart Association and American Stroke Association.[23,26] When more stringent criteria were applied for the ascertainment of acute stroke (first-ever strokes with an NIHSS >0), the proportion of people who received thrombolysis increased to 131 of 791 patients (16·5%, 95% CI 14·0–19·3) in 2010 to 177 of 869 (20·4%, 17·7–23·2) in 2013 ($p_{trend\ 2010–13}$<0·0001; figure 2A). Increases in thrombolysis treatment were noted in both sexes and most subgroups of patients (figure 4), but thrombolysis use remained low in patients with mild symptoms (NIHSS <4; figure 4C) and unclear time of onset of stroke and stroke after 4·5 h (figure 4B). Helicopter transport was strived for when the expected duration of ground transport exceeded 45 min and patients who were transported by helicopter were more likely to receive alteplase than were those who had ground transport (appendix). Improvement in clinical outcome was evident in most subgroups and occurred in patients receiving alteplase (mRS 0–2, 40 of 104 patients, 38·5%, 95% CI 29·1–47·6, in 2010 and 93 of 157 patients, 59·2%, 51·5–66·9, in 2013; $p_{trend\ 2010–13}$=0·0006) and in those not receiving alteplase (mRS 0–2, 491 of 840 patients, 58·5%, 55·2–61·8, in 2010 and 522 of 782 patients, 66·8%, 63·5–70·1, in 2013; $p_{trend\ 2010–13}$<0·0001).

In the eight other Austrian states, changes in thrombolysis administration between 2010 and 2013 were heterogeneous (appendix) and the spread of proportions of people receiving thrombolysis was wider by the end of the survey period than at the start. In four states with ongoing integrative comprehensive stroke care programmes, delivery of alteplase increased by a mean of 28·0% (95% CI 24·3–30·7) from 2010 to 2013, whereas in four states without such programmes proportions of patients receiving thrombolysis fell by a mean of 14·4% (10·9–17·9; figure 2C). In patients with stroke treated at Austria's stroke units, thrombolysis administration fell slightly between 2010 (1311 [17%] of 7705 patients) and 2013 (1373 [16%] of 8328 patients; appendix).

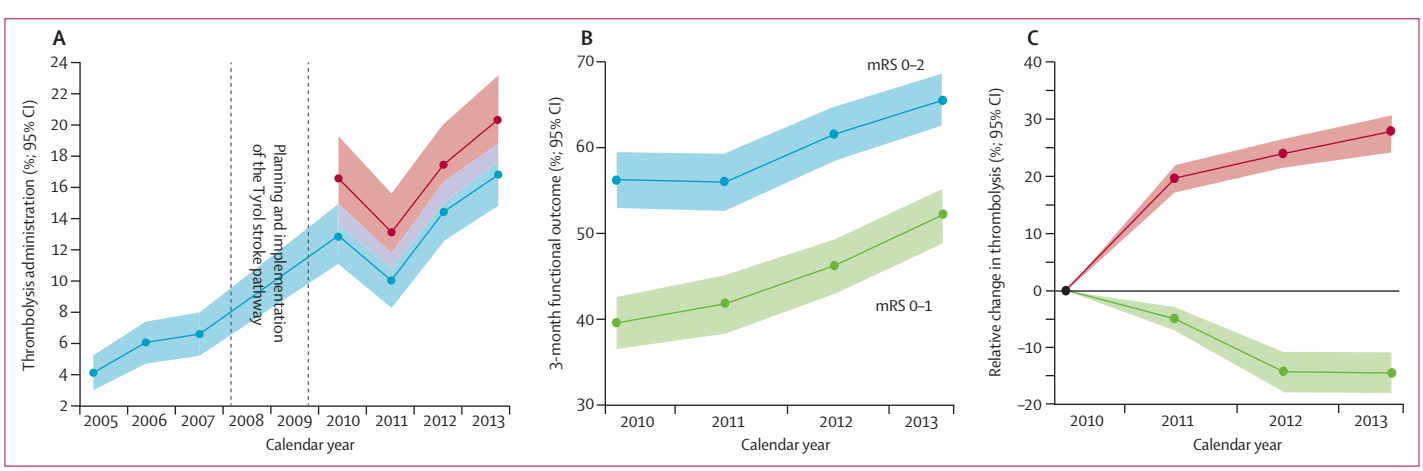

Figure 2: **Changes in thrombolysis administration and clinical outcome**
(A) Tyrol-wide trends in thrombolysis administration in all patients with ischaemic stroke (main analysis, in blue) and in the subgroup of patients with first-ever strokes and an NIHSS score greater than 0 (subsidiary analysis, in red). Data for 2005, 2006, and 2007 were included to allow estimation of long-term trends. (B) Tyrol-wide trends in excellent and good clinical outcome (3-month mRS 0–1 [in green] and 0–2 [in blue], respectively). (C) Changes in the rates of alteplase treatment for patients with ischaemic stroke in four Austrian states with ongoing integrative comprehensive stroke care programmes (in red) and four states without such programmes (in green). NIHSS=National Institutes of Health Stroke Scale. mRS=modified Rankin Scale.

Discussion

With implementation of the Tyrol Stroke Pathway, thrombolysis administration in Tyrol increased from 2010 to 2013 (figure 2A), despite the challenging transport conditions in the mountainous survey area. Subsidiary analyses of first-ever strokes with an NIHSS greater than 0 showed thrombolysis use to be 20·4% in 2013 (figure 2A), close to the postulated maximum for this particular subgroup of 25%.[27] Increased thrombolysis was not associated with more symptomatic intracerebral haemorrhage, the most feared complication of alteplase (4·1%, 95% CI 2·8–5·9, for 2010–13 *vs* 7·3%, 6·7–7·9, in the SITS-MOST registry[4] and 6·8%, 6·3–11·6, in pooled randomised controlled trials[3]). A continuous gain in thrombolysis administration was noted in most patient subgroups (figure 4), and the initial high variability in thrombolysis use across Tyrol's nine counties was reduced, indicating similar access to and quality of acute stroke therapy throughout the entire state (figure 3). The only two large subgroups of patients with stroke who had low percentages of thrombolysis were those with unclear timing of symptom onset (figure 4), corresponding to the absence of supportive evidence from randomised controlled trials in this clinical setting, and those with minor strokes (NIHSS <4). Data from meta-analyses and stroke registries have suggested efficacy of alteplase in selected patients with minor stroke.[3,25]

Sustained increase in thrombolysis administration was only one of various achievements that improved patient care (table 2). Implementation of the programme was followed by a significant increase in the likelihood of good clinical outcome at 3 months (figure 2B) with almost two-thirds of patients achieving a good outcome in 2013 throughout Tyrol. Similar proportions have been noted in networks of specialised stroke units, but data at a state level have not been published so far.[28] Potential reasons for this success, apart from the comprehensiveness of the programme, are the multidisciplinary approach supported by all health-care professions, the yearly feedback visits by members of the steering committee to the hospitals resulting in continuous improvements, and the broad acceptance of the programme (appendix). However, there was no reduction in mortality, which should be interpreted in the context of an overall low mortality of less than 15% in the first 3 months.

Theoretically, the patterns we noted might be attributable to independent time trends and circumstances unrelated to the implementation of the Tyrol Stroke Pathway. This interpretation, however, is unlikely to be correct because of the close temporal relation between the start of the programme and the rise in thrombolysis use, consistent changes in most subgroups, the high proportion of thrombolysis finally achieved, and the divergences with Austrian states that did not have similar initiatives (figure 2C). Moreover, worth consideration is the fact that there was no centralisation of stroke care or infrastructure advancement in Tyrol during the study period.

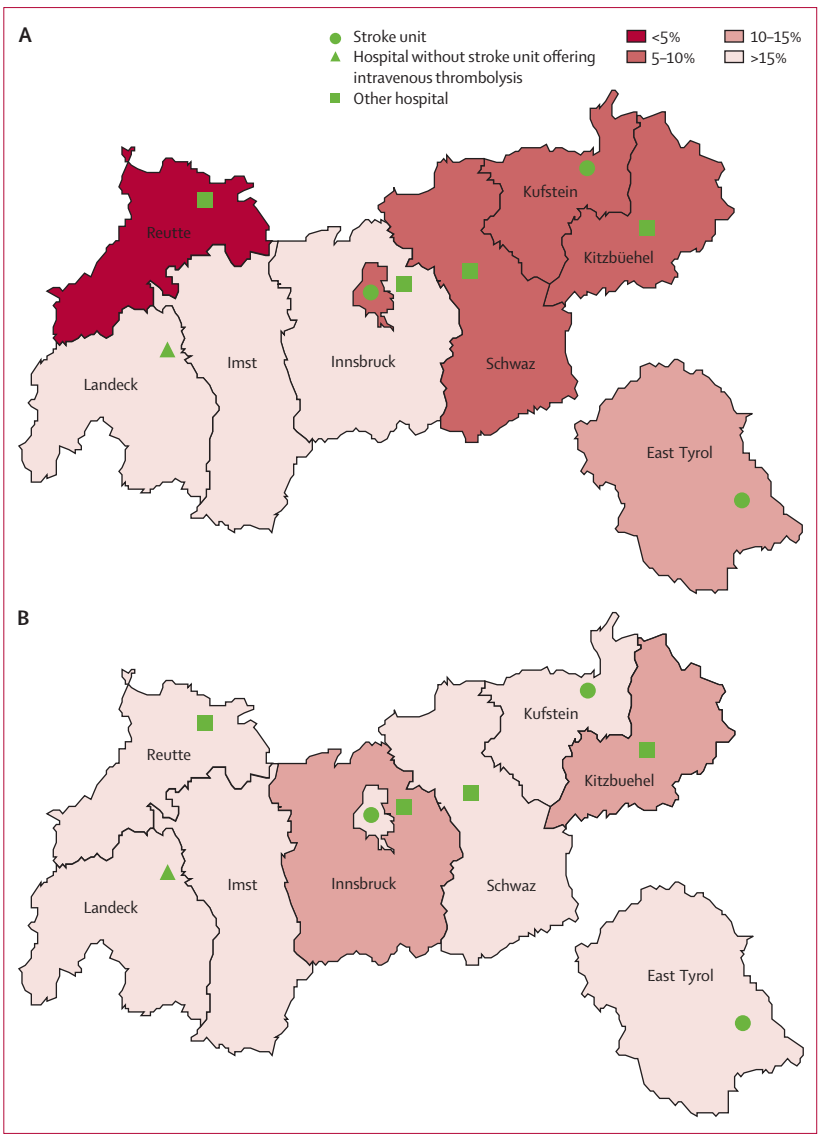

Figure 3: **Thrombolysis administration in the nine counties of Tyrol in 2010 (A) and 2013 (B)**

Almost 20 years after the results of the first randomised controlled trial suggested efficacy of intravenous thrombolysis in patients with stroke, there is still a substantial discrepancy between the estimated 25% of patients potentially eligible and the proportion actually treated.[27] The proportions of patients with stroke who receive thrombolysis worldwide range from 1·7% to 10·4%,[17–19,21,22] and recent reports of longitudinal studies showed increases in the US hospitals taking part in the Get With The Guidelines programme (4·0% in 2003 to 7·0% in 2011),[15] in Massachusetts, USA (6·7% in 2005 to 10·4% in 2008),[22] Hesse, Germany (2·5% in 2003 to 8·4% in 2009),[21] and Rhineland-Palatinate, Germany (1·9% in 2001 to 4·7% in 2006),[29] but a

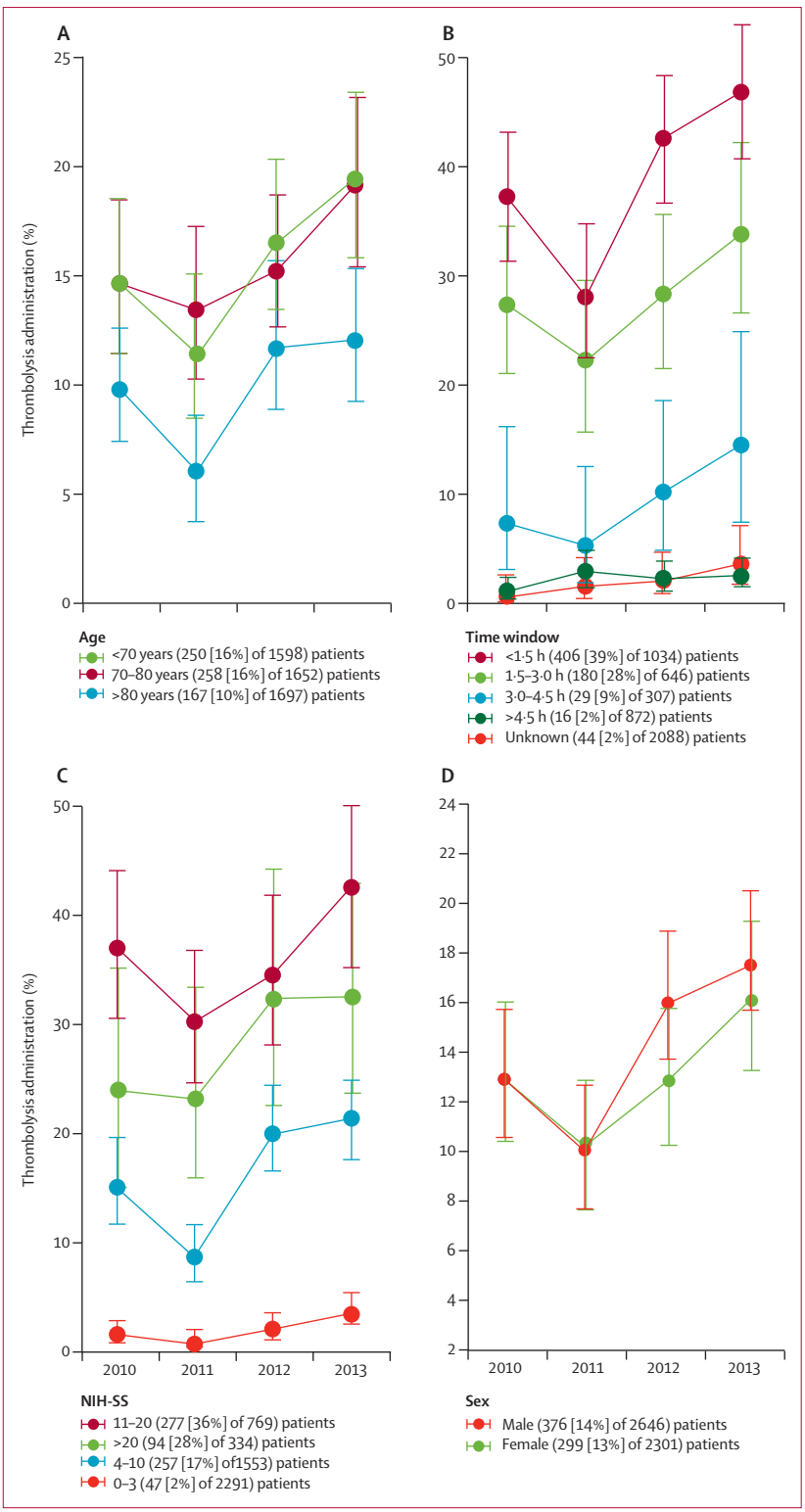

Figure 4: **Changes in thrombolysis administration in subgroups of patients with ischaemic stroke**
(A) Age strata (<70 years, 70–80 years, and >80 years). (B) Time window (onset-to-door time <1·5 h, 1·5–3·0 h, 3·0–4·5 h, >4·5 h, and unclear onset including wake-up strokes). (C) Stroke severity-strata according to the National Institutes of Health Stroke Scale at admission to hospital (<4, 4–10, 11–20, and >20). (D) Men and women. Error bars indicate 95% CI.

maximum proportion in Sweden of 8–9% from 2008 onwards.[18] Higher percentages of thrombolysis use have been reported in individual stroke centres, stroke units, and regional networks (eg, southeast Bavaria, 15·5%),[30] and large urban areas like Bern in Switzerland (13%)[31] and Helsinki in Finland (16%),[7] but the evaluation in Bern did not include the smaller hospitals, Helsinki's initiative was restricted to first-ever strokes, and TEMPiS in Bavaria included 56% of patients with stroke in the region (panel).

In Tyrol, we used a comprehensive approach (figure 1) to tackle the problem of undertreatment. The Tyrol Stroke Pathway covers almost all aspects of stroke care from symptom onset to rehabilitation, and stroke awareness campaigns, standardisation of diagnostic procedures and therapy, establishment of multidisciplinary stroke teams, broad educational activities for health-care professionals, uniform documentation of quality indicators, and several targeted interventions to improve stroke care (appendix). The electronic Tyrol Stroke Pathway was implemented in the whole of Tyrol as a routine standard and was generally accepted (appendix). There were no missing data for the patients enrolled, so the study population comprises a largely unselected cohort of patients with ischaemic stroke.

To the best of our knowledge, our initiative is the only one that can claim near full coverage of all patients with stroke within the survey area, whereas other high-quality programmes achieved coverage of between 20% and about 85%.[19] Moreover, we considered all patients with stroke including elderly patients and recurrent events; the recurrent strokes accounted for roughly a fifth of all strokes. Importantly, our programme comprises full data monitoring with labour-intensive review and resolution of all data incongruences at the medical record level and the availability of 3-month outcome data. However, our study also has limitations. Our findings are not necessarily applicable to low-income countries because our programme was launched in hospitals with western European standards of providing imaging 24 h a day throughout the week and offering access to stroke units. Moreover, the Tyrol Stroke Pathway has now been active for 4·5 years, so long-term efficacy and its applicability to other states remain to be established. Also, it was not feasible to control adherence to all of the many protocol criteria. Instead, we monitored adherence to selected key criteria and analysed processes of patient care at a hospital level in the event that standards for quality indicators were not met.

Recent advances in endovascular stroke therapy are intriguing but are without proof of efficacy and are suitable for selected patients only, whereas broad programmes like ours could provide benefit to all patients with ischaemic stroke. The prospect of a disability-reducing intervention is particularly attractive

Panel: Research in context

Systematic review

We searched PubMed for relevant articles published before Oct 1, 2014. Our search strategy is detailed in the appendix, and combined free and MeSH search terms related to stroke and thrombolysis (eg, "thrombolysis", "rt-PA", and "alteplase"), and study design (eg, "registry", "initiative", "organisational model", and "implementation"), without language restrictions. We scanned backward and forward citations of identified studies and reviews (snowballing technique) for any additional relevant articles. Of the 1109 records retrieved from PubMed, 1020 were excluded because they did not specifically address organisational models of stroke care (with an interventional character) and did not provide information about alteplase delivery. 89 records were included in the discussion and interpretation of the findings reported in this study. We identified two block-randomised prehospital, two-cluster randomised hospital-based, and one pioneer quasi-experimental intervention trial, which reported substantial[10,11] but temporary[11] or slight[6,32,33] effects on thrombolysis administration. With the challenges and limitations of undertaking randomised trials of routine stroke care, most interventions monitored changes in thrombolysis use and other quality measures after programme implementation, several did have suitable comparator groups, and a few targeted whole countries or states. Specific strategies facilitated the administration of alteplase including the establishment of stroke networks,[13,14,19,34] centralised stroke care,[5] stroke code protocols and prenotification systems,[7,35] emergency helicopters,[9] prehospital thrombolysis,[10,33] telemedicine support,[12,30,36] and programmes to minimise inhospital delays.[7]

Interpretation

To our knowledge, the Tyrol Stroke Pathway is the first routine-care stroke programme to comprise the entire treatment pathway from stroke onset to outpatient rehabilitation and to accomplish near 100% coverage of patients with stroke in an entire state. Use of this programme achieved high thrombolysis administration rates and significant improvement in clinical outcome. The results show that thrombolysis administration rates in patients with acute ischaemic stroke as high as 16·8% are feasible at a state level and might guide health authorities and stroke physicians in implementing similar programmes.

from both a public health and the patient's perspective; hence, our findings might encourage health authorities and stroke physicians elsewhere to initiate similar programmes.

Contributors

SK and JW interpreted the data and wrote the manuscript, and were assisted by MK, TT, RP, and KW. TG, JS, HR, AT, HK, NT, SK, and JW formed the steering committee. HR and SK analysed the data. SK, JW, and HR take full responsibility for this research. Together with JS and TG, they headed and designed the programme, and participated in data acquisition and analysis. AT and HK were responsible for organisation and implementation of the programme and AT established the electronic pathway. NK and SP managed the database, did full data monitoring, and resolved all data incongruences. PW, SK, and JW did the systematic literature review. The other authors participated in data gathering and were engaged in the various working teams during the planning and implementation phases (concept and design). All authors have critically reviewed the final draft of the manuscript and have given final approval for the version submitted. Additionally, all authors are accountable for the parts of the work they did and all are part of the Tyrol Stroke Team (group authorship).

Declaration of interests

AT and HK have received honoraria for establishing the electronic pathway and for programme implementation. These honoraria were part of the project budget (Reformpool project) provided by the Tyrolean Health Care Fund. The other authors declare no competing interests.

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