Stroke prevention and stroke thrombolysis: quantifying the potential benefits of best practice therapies

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ABSTRACT

Objective: To identify and quantify current deficiencies in primary and secondary stroke prevention, as well as potential gains from optimal employment of thrombolysis.

Design, participants and setting: Observational study of 259 consecutive patients admitted to a tertiary hospital stroke unit from 24 January 2006 to 10 January 2007, with retrospective assessment of prestroke risk factors and therapies to determine stroke preventability, based on relative risk reductions from published meta-analyses of preventive therapies.

Main outcome measures: Numbers of strokes preventable by optimal risk factor modification and numbers of strokes with preventable disability through optimal thrombolysis; characteristics of patients with preventable strokes; contributions of each risk factor to stroke preventability.

Results: 183 patients had a disabling or fatal stroke; 135 patients had at least one suboptimally managed risk factor. On the basis of prespecified stroke preventability weightings, 70 strokes were preventable. The younger the patient, the more likely that the stroke was potentially preventable (relative risk [RR] for age < 60: ⩾ 80 years, 3.10; 95% CI, 1.96–4.92). Smoking, inadequate control of hypertension and suboptimal anticoagulation accounted for nearly 90% of preventable strokes. Patients with target systolic blood pressures of 130 mmHg or lower were more likely to have inadequately controlled hypertension (RR, 4.27; 95% CI, 2.58–7.05). By comparison, disability could have been prevented in four strokes through optimal thrombolysis.

Conclusions: A significant proportion of stroke remains preventable, especially in younger patients, by optimal modification of risk factors, particularly smoking, blood pressure and anticoagulation. Only a small proportion of patients will benefit from best-practice thrombolysis.

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Stroke is common, and frequently fatal or disabling.[1,2] In Australia, stroke is the second leading contributor to disease burden after ischaemic heart disease.[3]

Stroke occurs most commonly in patients with known risk factors. It has been estimated that the proportion attributable to these factors is as high as 80%,[4] implying that stroke is largely a preventable disease. However, as various preventive therapies are now widely employed, it is uncertain whether these estimates still apply.

The effects of ischaemic stroke (the most common kind) can potentially be minimised with thrombolysis.[5] However, thrombolysis rates in Australia are around 3%,[6] and treatment rates, even at centres of excellence, struggle to exceed 10%.[7] There is therefore scope for reducing the effects of stroke by expanding thrombolysis.

We designed The Royal Adelaide stroke disability Prevention Study (TRAPS) to identify and quantify current deficient areas in primary and secondary prevention, as well as to estimate the potential benefits of optimal thrombolysis.

METHODS

We performed an observational stroke unit-based study with retrospective assessment of prestroke therapies. Eligibility for thrombolysis was determined at or shortly after admission.

The Royal Adelaide Hospital serves a local population within metropolitan Adelaide, and is also a tertiary referral centre for adjacent rural areas. Its stroke unit admits all patients with a diagnosis of acute stroke regardless of age or severity, except those requiring neurosurgical intervention (subarachnoid haemorrhage and some with intracerebral haemorrhage) and those transferred from high-level residential care. The study was approved by the Royal Adelaide Hospital Research Ethics Committee.

Information was collected about all consecutive patients with a final diagnosis of stroke who were admitted to the stroke unit from 24 January 2006 to 10 January 2007, except those from whom informed consent could not be obtained. Information about prestroke health status and therapies was obtained from the treating general practitioner or specialist.

1 Relative risk reductions from published studies for modification of designated risk factors for stroke

Risk factor that was modified	Relative risk reduction (95% CI)
Untreated hypertension[9]	30% (26%–32%)
Undertreated hypertension[9]	30%*
Grossly undertreated hypertension[9]	50%*
Untreated high-risk atrial fibrillation[10]	64% (49%–74%)
Aspirin-treated high-risk atrial fibrillation[10]	39% (22%–52%)
Untreated low- to medium-risk atrial fibrillation[10]	22% (6%–35%)
Smoking[16]	66% (50%–75%)
Untreated hypercholesterolaemia[11]	17% (12%–22%)
Untreated antiplatelet indication[12]	25% (22%–28%)
Untreated "normal" blood pressure after stroke[14]	28% (17%–38%)
Untreated symptomatic carotid disease[15]	61% (49%–72%)
Inappropriate hormone replacement therapy[13]	22% (12%–32%)
Subtherapeutic warfarinisation[17]	82%*

* 95% confidence intervals were not provided in the articles cited. ◆

2 Demographic characteristics, prestroke risk factors and therapies, and stroke characteristics and outcomes for 259 patients admitted to Royal Adelaide Hospital stroke unit from 24 January 2006 to 10 January 2007

Variables	Findings
Demographic characteristics	
Median age (years)	75 (IQR, 61–81)
Non-English-speaking background	73 (28%)
Female	114 (44%)
Lives alone	77 (30%)
Lives outside Adelaide	71 (27%)
Identifiable treating doctor	255 (98%)
Prestroke risk factors and therapies	
Hypertension	161 (62%)
Current smoker	45 (17%)
Diabetes	46 (18%)
Atrial fibrillation	53 (20%)
Ischaemic heart disease	42 (16%)
Previous stroke	61 (24%)
Hypercholesterolaemia	77 (30%)
Any preventive therapy	181 (70%)
Antihypertensive therapy	157 (61%)
Warfarin therapy	28 (11%)
Antiplatelet therapy	111 (43%)
Statin therapy	73 (28%)
Stroke characteristics and outcome	
Intracerebral haemorrhage	37 (14%)
Median admission National Institutes of Health stroke scale score	8 (IQR, 4–17)
Fatal stroke	41 (16%)
Median discharge modified Rankin scale	3 (IQR, 2–5)
Disabling stroke (modified Rankin scale, ≥ 4)	123 (47%)

IQR = interquartile range. ◆

Assessment of stroke preventability

We calculated percentage stroke preventability using a previously published method,[8] assuming a multiplicative scale for relative risk reductions of underutilised therapies:

$$RRR = (1 - [RR_1 \times RR_2 \times RR_3 \times RR_n]) \times 100$$

(where RRR represents relative risk reduction, and RR_n represents the relative risk of stroke if $therapy_n$ had been employed).

Factors assessed included untreated or suboptimally treated hypertension,[9] untreated or suboptimally treated atrial fibrillation,[10] indications for statin[11] or antiplatelet therapy but no treatment,[12] inappropriate hormone replacement therapy,[13] untreated "normal" post-stroke blood pressure,[14] untreated symptomatic carotid disease,[15] smoking,[16] and subtherapeutic warfarinisation,[17] (Box 1). Only risk factors with strong data from randomised controlled trial (RCT) meta-analyses or large RCTs were included, except for smoking,[16] which has robust population relative risk data, and for suboptimal anticoagulation, which cannot feasibly be assessed in an RCT but clearly increases stroke risk.[17,18] Studies on the effect of smoking and hypertension on stroke risk have not always reliably distinguished ischaemic and haemorrhagic stroke, and hence the impact of these factors on the preventability of ischaemic and haemorrhagic stroke was not differentially weighted.

Efficacy of hypertension management was assessed by comparing the last two prestroke systolic blood pressure readings with national guidelines.[19] Undertreated hypertension was identified where both readings were more than 10 mmHg above those recommended in guidelines, and grossly undertreated hypertension was identified where both were more than 20 mmHg above. Only systolic pressure was considered.[20] Adequacy of anticoagulation for atrial fibrillation was assessed by comparison with national guidelines,[21] and hypercholesterolaemia with Pharmaceutical Benefits Scheme guidelines applicable in 2006. Hormone replacement therapy was designated inappropriate unless a patient had significant menopausal symptoms refractory to other therapies. Inadequate warfarininsation was defined as subtherapeutic admission and preadmission international normalised ratio (INR) readings or, in the case of periprocedural stroke, a failure to follow national guidelines.[22] All smoking-associated strokes were deemed potentially preventable.

If risk factor modification was considered inadequate, both the patient and treating doctor were asked if there were extenuating circumstances (such as medication side effects). If extenuating factors were identified, the stroke was deemed not preventable.

The total number of potentially preventable strokes was obtained by multiplying the total number of strokes by the average "stroke preventability". The contribution of each risk factor to this total figure was also extracted.

Potential prevention of disability from stroke by thrombolysis was assessed by comparing actual versus potential thrombolysis cases (ie, patients with ischaemic stroke potentially able to reach hospital within 120 minutes of stroke onset with no contraindications). A number needed to treat (NNT) of 8 (95% CI, 5.3–15.3) was derived from a recent meta-analysis,[5] being the number needed to render one patient who had had a stroke minimally symptomatic or asymptomatic (a modified Rankin score of ≤ 1).

Statistical analysis

Categorical variables potentially influencing stroke preventability were assessed by the χ^2 test with two-tailed P values. Variables prospectively hypothesised to be associated with stroke preventability were being male, social isolation, rural address, non-English-speaking background and older age. A post-hoc analysis was conducted of the association between hypertension targets not being reached and whether those targets were standard (140/90 mmHg) or lower (130/85 mmHg or less). Relative risks and 95% CIs were calculated. Analyses were performed with GraphPad Prism, version 5.00

3 Total strokes preventable by optimal management of each risk factor for 135 patients with one or more risk factors

Risk factor	Total patients*	Relative risk reduction	Strokes preventable
Smoking	45	66%†	26.4†
Untreated hypertension	9	30%	2.4
Undertreated hypertension	31	30%	8.3
Grossly undertreated hypertension	26	50%	11.5
Total hypertension-related			22.2
Untreated high-risk atrial fibrillation	3	64%	1.7
Aspirin treated high-risk atrial fibrillation	18	39%	6.2
Untreated low-risk to medium risk atrial fibrillation	0	22%	0
Subtherapeutic warfarinisation	7	82%	5.1
Total atrial fibrillation-related			13.0
Untreated statin indication	6	17%	0.9
Untreated antiplatelet indication	18	25%	4.0
Untreated blood pressure after stroke	11	28%	2.7
Untreated symptomatic carotid	2	61%	1.1
Inappropriate hormone replacement therapy	0	22%	0
Total other			8.7
Strokes preventable (of 259)			70.3

* Some patients had more than one risk factor.

†The percentage contribution of each factor to stroke preventability was adjusted if other risk factors were present and, in these patients, was less than the stated relative risk reduction. ◆

for Windows (GraphPad Software, San Diego, Calif, USA).

RESULTS

Baseline data

During the study period, 306 patients were admitted to the stroke unit; 43 had a diagnosis other than stroke. Four patients did not or could not consent to inclusion in the study, leaving a total of 259 patients who had had a stroke.

Demographic data, risk factor prevalence and therapies, and stroke characteristics are shown in Box 2. Almost all patients identified a treating doctor. Stroke type and mortality, median ages and sex distribution did not differ from recent Australian population-based studies.[2,23] Over 70% of patients were being treated with at least one preventive therapy. The most common previously identified risk factor was hypertension. Most patients with hypertension were being treated, many with polytherapy.

Risk factor modification

Overall, 135 patients (52%) had at least one suboptimally modified risk factor (Box 3), and 10% had two or more. In these patients, average stroke preventability was 52%. Therefore, overall, 70 out of 259 strokes (27%) were preventable.

Nearly 20% of patients were active smokers. Consistent with the assumptions listed in the methods, smoking was the single largest contributor to preventable stroke, contributing to nearly half the total.

At least two recent blood pressure measurements had been recorded for 95% of patients; a quarter were not within the target range. Patients were more likely to have had inadequately controlled hypertension if their target systolic pressure was 130 mmHg or less (patients with diabetes, young-onset hypertension and renal disease;[19] relative risk, 4.27; 95% CI, 2.58–7.05; $P < 0.001$).

Of the 48 patients with ischaemic stroke in the setting of known atrial fibrillation, only 20 had received appropriate therapy. High-risk atrial fibrillation was treated with aspirin or nothing in 21 patients. The remaining seven patients were suboptimally anticoagulated. Warfarin was associated with intracerebral haemorrhage in three cases. Overall, smoking, inadequate blood pressure control and suboptimal use of warfarin accounted for nearly 90% of preventable strokes.

We had hypothesised that the very old were more likely to be treated suboptimally. However, as shown in Box 4, we found the opposite. There was a strong trend for the association of suboptimally managed risk factors with younger age, principally because of the prevalence of smoking and unmet blood pressure targets in this group. Our other hypotheses, that rural address, social isolation, non-English-speaking background and being male might be linked to stroke preventability, were not supported.

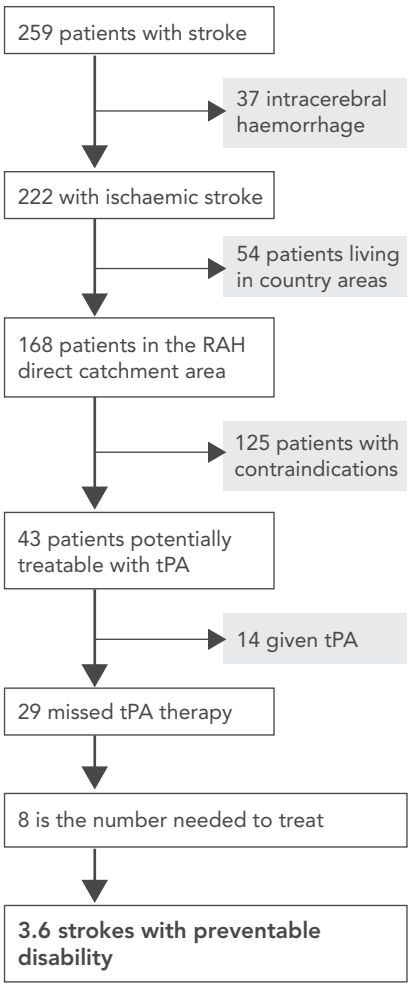
Potential for expanding thrombolysis

Compared with optimal modification of risk factors, fewer strokes were "preventable" with best-practice thrombolysis (Box 5). Roughly a quarter of stroke patients were ineligible for treatment with tissue plasminogen activator because of intracerebral haemorrhage, or were not transferred in time from rural hospitals. Of the remaining 168, 125 had a contraindication to thrombolysis, most commonly because of time-of-onset uncertainty (most often awaking with neurological symptoms) or unavoidable presentation outside the 3-hour window (eg, being found by relatives after a prolonged period). A third of potential thrombolysis (14/42) candidates received treatment. Assuming a number

4 Association of prospectively hypothesised demographic variables with relative risk of potentially preventable stroke

Demographic variable	Relative risk of preventable stroke (95% CI)	*P*
Age group (years)		
< 60: ⩾ 80	3.10 (1.96–4.92)	< 0.0001
60–69: ⩾ 80	2.29 (1.23–4.23)	0.006
70–79: ⩾ 80	1.13 (0.84–1.51)	0.43
Rural address (yes: no)	1.28 (1.01–1.62)	0.051
Non-English-speaking background (yes: no)	1.00 (0.77–1.29)	0.99
Lives alone (yes: no)	1.14 (0.90–1.46)	0.29
Male (yes: no)	1.01 (0.80–1.28)	0.92

5 Potential prevention of disability from stroke with optimal thrombolysis



RAH = Royal Adelaide Hospital.
tPA = tissue plasminogen activator. ◆

needed to treat of 8,[5] disability could potentially have been prevented in four strokes under optimal conditions.

DISCUSSION

Our study demonstrates the continued high prevalence of suboptimally modified risk factors in a hospital-based cohort of consecutive patients admitted with stroke from 24 January 2006 to 10 January 2007 from whom informed consent could be obtained. Although this was a highly treated population (over 70% were being treated with at least one preventative therapy), over half had at least one suboptimally modified risk factor. According to the assumptions outlined in our methods, over a quarter of strokes were preventable. By comparison, best-practice thrombolysis could have prevented disability in a smaller number of strokes.

Estimates of stroke preventability were conservative, as lifestyle factors contributing independently to stroke risk that cannot be readily quantified were not included (eg, obesity,[24] physical inactivity,[25] alcohol consumption[26] and poor diet[24]). Furthermore, statin therapy,[27] therapeutic anticoagulation[18] and angiotensin-converting enzyme inhibition[28] not only prevent stroke, but also lessen stroke severity.

Stroke preventability is difficult to define and quantify, and our finding that a quarter of strokes could be prevented is less than the 80% attributable risk cited in the introduction,[4] and a recently estimated 80% reduction in recurrence risk with best-practice treatments.[8] However, our population was already being treated with a number of preventive therapies, in contrast to patients in both cited articles, in which no therapy, rather than some therapy was assumed. Additionally, one article focused only on secondary prevention, and included dietary and exercise interventions,[8] which are not proven on a population basis for primary stroke prevention. Our study identifies and quantifies the risk factors that remain suboptimally managed in an era of widespread medical therapies and declining smoking habits.

We found that the three suboptimally modified risk factors with the greatest impact were smoking, hypertension and atrial fibrillation. This finding is consistent with a recent population-based study of general practice patients,[29] and broadly consistent with international data.[30] Smoking and suboptimally treated hypertension were more prevalent in younger patients, explaining the higher prevalence of "stroke preventability" in this group. These patients often also had lower blood pressure target values, which could only have been achieved by combination therapy. Hypertension and other risk factors were well managed in older patients, despite the greater prevalence of risk factors, refuting the possibility that therapeutic nihilism or undertreatment among older people may be a significant cause of ischaemic stroke. We did, however, demonstrate a continued reluctance of health practitioners to prescribe warfarin and of patients to take it, also documented elsewhere.[31] It is to be hoped that new data confirming the efficacy and safety of warfarin therapy in older people will help allay persisting concerns.[32]

Our study has several limitations. Most significantly, multiple assumptions were made to reach an estimate of "stroke preventability". In particular, the adequacy of hypertensive therapy was assessed on the last two prestroke readings, which may not be representative of longer-term trends.

As a hospital-based rather than population-based study, minor strokes may have been underrepresented, as well as strokes in nursing home patients. And as our study was set in a tertiary hospital stroke unit, neurosurgical and country referral patterns will have skewed the data. Subarachnoid haemorrhage was not included. Lastly, one investigator collected all the data and assessed the adequacy or otherwise of therapy, raising the possibility of bias.

In summary, in an Australian stroke unit-based cohort of consecutively admitted patients, many strokes were potentially preventable with optimal risk factor management, particularly in younger patients. This population was already being treated with one or more preventive therapies. This may account for the lesser extent of potential stroke reduction predicted by other studies. Nonetheless, tackling the major contributors — smoking, inadequate anticoagulation and hypertension (especially in patients with recommended systolic blood pressure targets of 130 mmHg or less) — would prevent a significant proportion of stroke. Far fewer patients will benefit from optimising thrombolysis.

COMPETING INTERESTS

Timothy Kleinig received funding from Servier (manufacturer of perindopril) to attend the Australasian stroke conference in Perth in 2007.

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