

Antiplatelets and Anticoagulants in Ischemic Stroke/Transient Ischaemic Attack: A Practice Survey Among Singapore Neurologists

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Abstract

Purpose: Evidence-based stroke clinical practice guidelines provide guidance as how to best manage patients with cerebrovascular disease. Where there are grey zones, the clinician decides what she/he feels is the most appropriate in that circumstance. This study was performed to determine how adult neurologists in Singapore would use antiplatelets(AP) and anticoagulants(AC) for their ischemic stroke patients in various settings where the evidence is uncertain.

Methods: A standardised questionnaire was sent to adult neurologists in Singapore. The questions evaluated their preferred AP, use of heparin prior to initiating warfarin, target INR and INR monitoring, and their preferred treatments in 6 different clinical scenarios.

Results: A total of 31/33 neurologists responded (93.9%). For long term secondary prevention, 71.0% preferred aspirin only, 22.6% clopidogrel/ticlopidine only, 6.5% aspirin plus dipyridamole. Anticoagulation with warfarin was initiated with a heparin bolus by 45.2%. AC were preferred by 80.6% for stroke in evolution, 80.6% for presumed basilar artery thrombosis, 54.8% for crescendo TIAs. For patients awaiting CEA, 58.1% preferred AP, 32.3% AC. For patients on preferred AP developing another cerebrovascular event with no new underlying cause, 48.4% would change AP, 25.8% would add another AP. For patients on adequate AC for non-cardioembolism developing another cerebrovascular event, 54.8% would add anti-platelet, 19.4% would increase AC.

Conclusions: The widespread use of aspirin for long-term secondary prevention is similar to other countries. The variation in the use of antithrombotic agents in other settings may reflect the lack of sufficient evidence to guide therapy in the various specific stroke patient management scenarios.

Keywords: neurologist, practice, antiplatelet, anticoagulant, stroke, cerebrovascular disease.

Acta Neurol Taiwan 2022;31:154-160

INTRODUCTION

Stroke is a major cause of death and disability

world-wide⁽¹⁾. The many clinical trials, particularly those performed in the last decade, have provided valuable and much needed answers to some of the important questions

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Received February 18, 2022. Revised February 15, 2022.

Accepted March 15, 2022.

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in stroke secondary prevention. It is well-established that antiplatelet agents (AP) are effective in reducing the risk of recurrent ischemic stroke⁽²⁾; anticoagulants (AC) are useful in the secondary prevention of ischemic stroke in those with non-valvular atrial fibrillation^(3,4), and carotid endarterectomy (CEA) or stenting (CAS) reduces recurrent stroke risk in selected patients with moderate or severe symptomatic carotid stenosis^(5,6).

However, the trials have not satisfactorily resolved all anti-thrombotic issues in stroke secondary prevention. What therapeutic regimen the patient actually receives will ultimately depend on the clinical setting, drug availability, published evidence, and the preference of the treating physician, guided by current clinical practice guidelines.

Singapore is a small tropical island city-state of 5.7 million people⁽⁷⁾. Stroke is our fourth leading cause of death⁽⁸⁾, and a leading cause of disability. The number of admissions to our hospitals for stroke has been steadily increasing, and is expected to continue to rise with the greying of the population⁽⁹⁾. Stroke comprises 54.9% of the inpatient and 17.3% of the outpatient workload of our neurologists⁽¹⁰⁾. With the establishment of stroke units in all hospitals⁽¹¹⁾, even more patients with stroke will come under the care of our neurologists. This prospective study was thus performed to determine how Singapore neurologists would use AP and AC in the management of their patients with ischemic stroke.

METHODS

Neurologists in Singapore were identified by reviewing the list of specialists registered with the Singapore Medical Council⁽¹²⁾. Paediatric neurologists and those who are not actively practising neurology were excluded.

A standard questionnaire was used. The questions investigated the neurologist's practice characteristics, number of stroke patients seen, preferred AP, use of bolus heparin, and target International Normalised Ratio (INR) for patients with non-cardioembolic stroke. Six brief clinical scenarios were presented covering stroke in evolution, crescendo transient ischemic attacks (TIAs), presumed basilar artery thrombosis, pre-CEA, and recurrent cerebrovascular events while already on appropriate treatment with AP or AC.

The forms were mailed or faxed out to the doctor's practice address. Those who did not respond within 2 weeks were contacted by phone, fax or mail 3 more times. The cut-off date for receipt of responses was 2 months after the first mail or fax.

The data was analysed using the Statistics Package for Social Sciences (SPSS) for Windows. Means, medians and ranges were determined for continuous variables.

RESULTS

Respondent characteristics

A total of 31 out of 33 neurologists participated, giving a response rate of 93.9%. 77.4% worked in government, government-restructured or university hospitals, while 22.6% were solo private practices – no-one worked in both sectors. Their mean number of years of neurology practice was 13.3 yr (+/- 7.0), median 12.0 yr, range 3.0 to 30.0 yr. The mean number of stroke patients seen per week was 24.8, median 23, range 3 to 51.

Neuroimaging

All but 1 (96.8%) would send the patient for a brain scan before starting AP or AC.

Antiplatelet regimens

After initial treatment, for long term secondary prevention of non-cardioembolic stroke, the preferred regimen was aspirin only (71.0%), 22.6% preferring clopidogrel/ticlopidine only, 6.5% aspirin + dipyridamole (A+D).

Anticoagulants

For patients to be given warfarin, 45.2% would initiate intravenous heparin infusion with a bolus dose of intravenous heparin. One neurologist used exclusively LMWH.

The target INR for patients with a non-cardioembolic stroke was variable: 74.3% aimed for INR in the range 2.0 to 3.0, 9.6% aimed below 2.0, and 16.2% exceeded 3.0.

The frequency of INR monitoring also varied widely: 25.8% would monitor it at intervals of 8 weeks, 22.6% at 4 weeks, 19.4% at 12 weeks, 12.9% at 6 weeks, and 3.9% each at 2, 3, 14, 18 and 20 weeks. (Fig. 1)

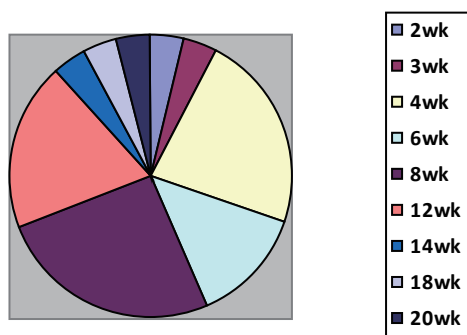


Fig 1: Interval of International Normalised Ratio (INR) monitoring

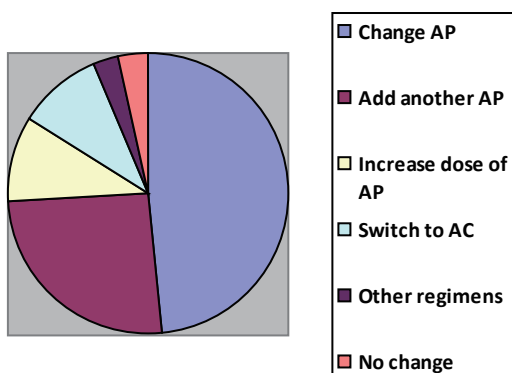


Fig 2: New regimen for recurrent ischaemic event while already on preferred antiplatelet (Key: AP = antiplatelet; AC = anticoagulant)

Clinical scenarios

Both in patients with stroke in evolution, and in patients with presumed basilar artery thrombosis, 80.6% preferred AC alone, 9.7% AC+AP, 6.5% AP alone, and 3.2% other regimens.

In patients with crescendo TIAs, 54.8% preferred AC alone, 22.6% AP alone, 19.4% AP+AC, and 3.2% other regimens.

In patients who are awaiting CEA, 58.1% preferred AP, 32.3% AC, 3.2% AP+AC, and 6.4% other regimens.

In patients who were already on their preferred AP and who then developed another cerebrovascular event due to the same mechanism, 48.4% changed to another AP, 25.8% added another AP, 9.7% increased the dose of the AP, 9.7% switched to AC, 3.2% used other regimens. 3.2% would not alter their treatment regimen. (Fig. 2)

In patients who were on already on AC in the

preferred INR range and who then developed another cerebrovascular event due to the same mechanism, 54.8% would add anti-platelet, 19.4% increase AC dose; 19.4% would not alter their treatment regimen.

DISCUSSION

This study, for the first time, presents information on the varying practice in the treatment of stroke specifically among Asian neurologists, in this case among neurologists in Singapore. The preferred long-term anti-platelet is aspirin, almost half would initiate heparin infusion with a bolus, target INR for most was 2.0 to 3.0 with widely varying monitoring intervals, AC was preferred for stroke in evolution, presumed basilar artery thrombosis and crescendo TIAs, AP while awaiting CEA, and varied responses on subsequent anti-thrombotic regimens if there is a recurrence of cerebral ischaemia.

Antiplatelets

After initial treatment, for long term secondary prevention of non-cardioembolic stroke, the recommended long-term antiplatelet regimen include aspirin, clopidogrel or aspirin plus dipyridamole⁽¹³⁾; trifusal (not available in Singapore) may also be used⁽¹⁴⁾. 71% of our neurologists preferred aspirin only, 22.6% clopidogrel/ticlopidine only, 6.5% aspirin plus dipyridamole. This compares with a publication in 1999 showing 99% of US physicians preferring aspirin⁽¹⁵⁾. In older studies, aspirin was the most widely used AP in New Zealand (94%, A+D 2%, D 1%)⁽¹⁶⁾, Hungary (92%, clopidogrel 4%, A+D 4%)⁽¹⁷⁾, Taiwan (64.8%, ticlopidine 13.3%, A+D 0.6%)⁽¹⁸⁾, Australia⁽¹⁹⁾ and Switzerland⁽²⁰⁾. A study published in 1998 comparing leading stroke experts in North America (NA) and Western Europe (WE), 96% and 94% respectively reported prescribing aspirin; in WE 4% chose A+D and 1 respondent ticlopidine⁽²¹⁾. In an international survey of stroke experts from all continents published in 1997, 93.4% chose aspirin, 3% ticlopidine, 1.5% A+D⁽²²⁾.

Anticoagulants

It is suggested that routine bridging therapy prior to anticoagulation therapy with oral anticoagulants be avoided; however, the quality of the evidence is low and the strength of recommendation weak⁽²³⁾. Slightly less

than half of Singapore neurologists gave a bolus dose of intravenous heparin when commencing heparin infusion for anticoagulation, similar to the 39% to 49% of US physicians reported in older studies^(24,25). Nearly 75% of Singapore neurologists aimed for INR in the 2 to 3 range, with 16.2% exceeding 3. The international survey of stroke experts showed that 86% aimed for INR 2-3, with 19.5% targeting a lower INR for patients older than 75 years⁽²²⁾. In a comparative study on the use of warfarin for primary stroke prevention in patients with atrial fibrillation, 65% of North American and 46% of Western European stroke experts used INR targets of 2 to 3; however 18% and 46% respectively exceeded 3⁽²¹⁾. The higher ranges in Western Europe may be related to the higher INR targets used in primary and secondary stroke prevention trials in atrial fibrillation patients conducted in Western Europe⁽³⁾.

The frequency of INR monitoring varied considerably in Singapore, with 29.0% monitoring at least monthly. In the US, 80% of physicians monitor at least monthly, compared with 58% in the UK^(15,26).

Brain imaging

Brain imaging is part of the routine investigation for suspected stroke^(13,14). However, in patients thought to have had a TIA and planned brain imaging is delayed in the face of further ischaemic events, antiplatelet monotherapy may be started, though the quality of the evidence is low and the strength of recommendation weak⁽²⁷⁾. All but 1 Singapore neurologist performed a brain scan before commencing antithrombotics; in Hungary, 69% await imaging⁽¹⁷⁾. This contrasts with publications in the 1990s from the UK^(28,29), where only 10 to 27% of consultant physicians caring for stroke patients would withhold aspirin till a scan is done, but up to 51% always await a brain scan before commencing full heparinisation. This was attributed in part to the lack of widespread easy availability of brain scan facilities in the UK.

Clinical scenarios

Urgent anticoagulation for halting neurological worsening is not recommended⁽³⁰⁾. More than 80% of Singapore neurologists prescribed AC for patients with evolving stroke. This contrasts with older studies showing 90 to 94% of US neurologists⁽³¹⁾, 25% of Hungarian⁽¹⁷⁾ and 20% of Latin American neurologists⁽³²⁾. It is also used

in Australia and Sweden^(19,33). Approximately 70% of US neurologists⁽²⁵⁾ ranked heparin as useful for the prevention of stroke progression.

The optimal medical management of patients with stroke and nonocclusive, intraluminal thrombosis of vertebrobasilar arteries remains uncertain⁽³⁰⁾, though benefit has been reported⁽³⁴⁾. More than 80% of Singapore neurologists would prescribe AC for presumed basilar thrombosis, similar to 74 to 75% of US neurologists⁽³¹⁾. This is also practised in Australia⁽¹⁹⁾. 57% of US neurologists⁽²⁵⁾ ranked AC as useful for basilar artery occlusion, 21% in Hungary⁽¹⁷⁾.

In the absence of guidance for the management of crescendo TIAs, slightly less than half of Singapore neurologists would prescribe AC for such patients. AC also is preferred in this setting in Sweden⁽³³⁾ and is prescribed by 73% to 77% of US neurologists⁽³¹⁾ for such patients, and 4% in Hungary⁽¹⁷⁾.

The usefulness of anticoagulation of patients with severe carotid stenosis is not well established⁽³⁰⁾. Antiplatelets are preferred^(13,14,30). For patients awaiting CEA, 58.1% of Singapore neurologists would prescribe AP, 32.3% AC. In a study of US physicians published in 1996⁽³⁵⁾, among the neurologists, 30% prescribed AC always or often for patients with recent TIA or minor stroke and symptomatic carotid stenosis exceeding 70% and no contraindications to surgery. This compared with 3.7% of these neurologists reporting that they seldom or never used AP for these patients. AC is used by some neurologists in Australia⁽¹⁹⁾.

When already patient on AP suffers a recurrent event, treatment strategies include no change, change to another AP, add another AP or use AC⁽¹⁴⁾. For those already on aspirin, the effectiveness of increasing the dose or changing to another anti-platelet is not well established⁽¹³⁾. For a patient on AP suffers a recurrent event while on the preferred AP, 48.4% of Singapore neurologists would change to another AP, 25.8% would add another AP, 9.7% would increase the dose of the first AP; 3.2% no change. In Hungary, 49% would change AP, 35% would add another AP, 8% would increase AP dose, 8% no change⁽¹⁷⁾. In case of recurrence of cerebral ischemia despite treatment, approximately one third of responding experts from NA and WE reported increasing the dose of their favorite agent first (36% and 30%, respectively), whereas

57% and 61%, respectively, immediately proceeded with their second-choice agent; 40% and 37% respectively reported combining different drugs at some time⁽²¹⁾. The international expert survey showed 59.6% preferred to change medication, 29.5% would instead increase the dose of current medication; 45.3% would try a combination of drugs at some time⁽²²⁾. In a recent meta-analysis of 5 cohort studies, strategies of addition of and switching another antiplatelet agent showed benefit versus continued aspirin monotherapy⁽³⁶⁾.

For those on AC and already in the target range of INR, 54.8% of Singapore neurologists would add an AP, 19.4% would increase the INR to a higher level, 19.4% would not change treatment. Among stroke experts in the US⁽²¹⁾, 57% changed drug, and 36% increased the dose in patients with recurrent events, similar to Western European experts' 61% and 36% respectively. 40% and 37% respectively on North American and Western European stroke experts⁽²¹⁾ combined different drugs at some time in the search for an effective therapy, especially aspirin with warfarin. In a very recent US survey, 83% would routinely change therapy to a DOAC for patients experiencing ischemic stroke while on warfarin⁽³⁷⁾.

Possible reasons for practice differences

There are a number of possible reasons why the preferences of Singapore neurologists may differ from other countries. It may be due to clinician factors eg. how the available trial and other data was interpreted, the training the neurologist had (local vs overseas and which country), the number of patients treated, the proportion of stroke vs other neurological illnesses managed, the influence of key opinion leaders. There may also be differences in the practice settings eg. proportion in public service vs private practice, ready availability of facilities such as scan machines and rapid reporting of laboratory tests like INR. There may also be differences in patient factors eg patients preferences, cost and availability of medications, who pays for medication and consultations (patients vs public funds vs insurance).

Limitations

There are a few limitations to this study. Only neurologists were surveyed. Second, the number of neurologists surveyed is small, numbering 31. However,

there are only 33 neurologists in our small country, of whom all but 2 participated in our study – the data thus would accurately reflect the practice in Singapore. Third, the study depends on recollection for some questions and the preferred practice of the participant for the others, instead of a prospective study of all patients seen with case records review. However, the method used in this study is similar to most of the previous publications on this issue. Fourthly, some of the studies referenced are older studies – unfortunately only a few relevant studies were published in the last 5 years^(36,37).

CONCLUSIONS

This study provides valuable insights into the variation in the use of antithrombotic agents by Singapore neurologists for ischemic stroke where the evidence for or against a specific intervention are not compelling. While AP, particularly aspirin, remain the most widely used drug for secondary stroke prevention, there is a varying practice with regards to the use of AC, particularly in the differing clinical scenarios. This reflects the lack of sufficient evidence from the clinical trials performed so far to clearly delineate the correct therapy in these patients. It is hoped that future therapeutic trials in stroke would provide this much needed information so that the most appropriate treatment may be offered to our patients, based on the best possible evidence.

Acknowledgements

The author would like to thank all participants of the study.

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