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Antiplatelet therapy for transient ischaemic attacks and acute minor strokes: current best practice and future

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Abstract

In patients presenting with transient ischaemic attacks and acute minor noncardioembolic ischemic strokes (NIHSS score ≤3) who did not receive intravenous alteplase, treatment with dual antiplatelet therapy with aspirin and clopidogrel, started within 24 hours of symptom onset and continued for 21 days is effective in reducing a recurrent ischemic stroke up to 90 days from the symptom onset. However, as the long-term risk of major disabling bleeding with aspirin-based antiplatelet treatment is higher in patients aged 75 years or older, routine co-prescription of proton pump inhibitor should be encouraged.

Key words: antiplatelet, stroke, transient-ischaemic-attack, prevention, dual-antiplatelet

Introduction

A significant percentage (15-26%) of strokes are preceded by transient ischaemic attacks (TIA) or minor strokes.[1] Recurrent strokes following TIA or minor stroke is highest in the first 48 hours through the first week.[2-6] Early assessment and initiation of preventive treatment at emergency TIA clinics have shown to reduce the early recurrence of stroke at 90-days by about 80% in EXPRESS (Effect of urgent treatment of transient ischaemic attack and minor stroke on the early recurrent stroke) and SOS-TIA studies.[7,8] Therefore, starting secondary prophylaxis measures as soon as possible is very important.

What is the evidence behind current antiplatelet regimen?

Aspirin is the most effective treatment that has evidence to have reduced recurrent disabling ischemic strokes in patients with noncardioembolic ischaemic stroke during the first 90 days.[9-12] Time-course analysis of acute stroke trials had observed, 60-70% reduction in risk and severity of early recurrent stroke with early initiation of aspirin following TIA and ischaemic stroke.[13] Furthermore, the benefit of aspirin is highest within the first 6 weeks and it gradually wanes off by 12 weeks and the benefits become less clear beyond 90 days.[13] The benefit of aspirin is more when initiated following mild to moderate strokes than major stroke.[13] Therefore, early initiation of aspirin, preferably within

Practice points

- Patients presenting with transient ischaemic attacks and acute minor (non-cardioembolic) ischemic strokes should receive dual antiplatelet therapy with aspirin and clopidogrel for 21 days.
- Minimum of aspirin (preferably aspirin and clopidogrel) should be started within 24 hours of symptom onset.
- Routine co-prescription of proton pump inhibitors with aspirin-based antiplatelet treatment is encouraged in patients aged 75 years or older in order to reduce major bleeding complications.

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24-48 hours had been the guideline for long.[14,15] However, long term low dose aspirin increases the risk of bleeding episodes[12] and the risk is highest in patients above 75 years of age. More than 50% of the bleeds in above 75-year-olds are upper gastrointestinal bleeds.[16] Aspirin-induced gastrointestinal bleeds are reduced 70-90% by proton-pump inhibitors (PPIs)[17] and PPIs are superior to H2 receptor blockers in preventing the bleeds.[18]

Dual antiplatelet therapy with aspirin and modified-release dipyridamole in ischaemic strokes and TIA was studied in two major studies: the ESPS-2 (European Stroke Prevention Study 2)[19] and the ESPRIT (European/Australasian Stroke Prevention in Reversible Ischemia Trial).[20] Even though the studies were positive in their primary endpoints, the use was limited due to nearly 40% of patients developing significant headache as a side effect.

Dual antiplatelet therapy with aspirin and clopidogrel in acute ischaemic strokes or TIA was studied in two major trials. The CHANCE (Clopidogrel with aspirin in acute minor stroke or transient ischaemic attack) trial studied aspirin vs aspirin and clopidogrel combination administered within 24 and continued for 21 days following TIA or minor stroke and demonstrated that aspirin and clopidogrel combination was more effective in reducing recurrent strokes at 90 days without a significant increase in bleeding risk.[21] However, the POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) trial observed that early initiation of aspirin and clopidogrel combination vs aspirin, given for 90 days caused 25% increased risk reduction of recurrent strokes but at the expense of 0.5% increased risk of bleeding.[22] Later, a pooled analysis confirmed that the benefits of dual antiplatelet therapy is confined to the first 21 days after minor ischaemic stroke or high-risk TIA.[23] Therefore, it is now recommended to treat TIA and minor strokes (NIHSS score ≤3 and of noncardioembolic origin who did not receive IV alteplase) with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours of symptom onset and to be continued for 21 days.[14]

Clopidogrel is a platelet P2Y12 receptor blocker. It is a prodrug which needs to be activated in the liver by CYP2C19. As clopidogrel needs to be activated in the liver it is ineffective in patients who are carriers of CYP2C19 loss-of-function alleles. This allele is reported to be present in 15-60% of Asians depending on the ethnic group.[24,25] Unlike clopidogrel, the newer P2Y12 receptor blocker, ticagrelor has a direct action and does not need activation in the liver.[26,27] Ticagrelor is a quick-acting, predictable (as not dependent on CYP2C19 gene polymorphism) and reversible platelet inhibitor unlike clopidogrel. In addition, there is an antidote to ticagrelor being developed in phase II trials.[28] Therefore, ticagrelor is now being studied in clinical trials for secondary prevention of TIA and strokes.

What are the antiplatelet regimens expected in future?

SOCRATES (Acute Stroke Or Transient IsChaemic Attack TReated With Aspirin or Ticagrelor and Patient OutcomES) trial studied aspirin vs ticagrelor started within 24 hours of the index event in secondary prevention of stroke and it showed that ticagrelor was not superior to aspirin in reducing recurrent cardiovascular events (myocardial infarction (MI), stroke and death) at 90 days.[29] Therefore, ticagrelor is not recommended over aspirin in the early management of acute ischaemic strokes in current AHA/ASA guidelines.[14] Even though ticagrelor in SOCRATES trial did not show benefit in achieving the primary outcome of reducing recurrent MI, stroke or death, a stratified analysis, showed benefit in the reduction of all stroke.[29] Later, subgroup analyses of SOCRATES trial showed that ticagrelor was substantially more efficacious in large artery disease[30] and in patients with a background history of aspirin use.[31]

Dual antiplatelet therapy with aspirin and ticagrelor was compared with aspirin and clopidogrel in the small, unblinded Chinese study PRINCE (Platelet Reactivity in Acute Non-disabling Cerebrovascular Events), and it was observed that aspirin and ticagrelor combination is superior in reducing platelet reactivity at 90 days.[32] THALES (The acute stroke or transient ischaemic attack treated with ticagrelor and ASA for prevention of stroke and death) trial studied aspirin vs aspirin and ticagrelor combination treatment started within 24 hours and continued for 30 days in mild to moderate (NIHSS<5) stroke patients over 40 years of age. The results were that the aspirin and ticagrelor combination was superior to aspirin in reducing stroke or death (1.1%) but at the expense of increased rate of severe bleeding (0.4%).[29]

As for current and emerging strategies, CHANCE-II trial is in progress comparing dual antiplatelet therapy with aspirin and clopidogrel vs aspirin and ticagrelor given for 21 days following acute TIA/stroke and will hopefully bring new recommendations in future (ClinicalTrials.gov no: NCT04078737).

Conclusion

Therefore, in conclusion, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started

within 24 hours after symptom onset and continued for 21 days is recommended in patients presenting with TIA or minor noncardioembolic ischaemic stroke (NIHSS score ≤3) who did not receive IV alteplase, as the current best practice of secondary prevention.

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Conflict of Interest

No conflict of Interest.

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