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Antiplatelet therapy for transient ischaemic attack and minor ischaemic stroke

Transient ischaemic attacks carry an increased risk of large ischaemic stroke in the 90 days after an event. Patients need to be seen within 24 hours in a dedicated clinic to start secondary prevention. This editorial reviews evidence for consideration of early dual antiplatelet therapy after a transient ischaemic attack.

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Transient ischaemic attack and acute ischaemic stroke have been historically managed differently. Transient ischaemic attacks are defined as brief episodes of neurological dysfunction, resulting from focal cerebral ischaemia, with symptoms lasting less than 24 hours (Easton et al, 2009). However, there is evidence that a large proportion of patients with transient ischaemic attacks show injury on brain imaging, suggesting they form part of the same clinical spectrum as 'minor' acute ischaemic strokes. Patients with transient ischaemic attacks and those with minor ischaemic stroke (defined as National Institute of Health Stroke Scale (NIHSS) ≤3) carry a similar higher risk of subsequent large ischaemic stroke (3–15%) in the 90 days after an event. A meta-analysis (Giles and Rothwell, 2007) identified significant study heterogeneity for the large range of risk, but risks reported over different durations of follow up were highly correlated (0–7 days vs 8–90 days, r=0.89, P<0.0001) giving higher early post-event risk. Although a further large registry-based study (Amarenco et al, 2016) reported overall lower risk ranging from 4–6% event rate at 3–12 months post-event, the risk is big enough to address and optimise therapies. Aspirin reduces the risk of early recurrent stroke by 12% (95% confidence interval 3–20%), leading to several guidelines recommending early administration of aspirin (CAST (Chinese Acute Stroke Trial) Collaborative Group, 1997; Royal College of Physicians, 2016). Adding clopidogrel to aspirin reduces the risk of recurrent cardiovascular events by 20% (95% confidence interval 10–28%). An outstanding question remains, regarding appropriate antiplatelet combination regimens and their efficacy in various clinical scenarios.

The CHANCE trial (Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events) by Wang et al (2013) included 5170 ethnic Chinese patients with high-risk transient ischaemic attack or minor ischaemic stroke, and showed that the addition of clopidogrel to aspirin reduced the relative risk of recurrent stroke at 90 days by 32% (8.2% vs 11.7% (aspirin alone), hazard ratio 0.68, 95% confidence interval 0.57–0.81, absolute risk reduction 3.5%) with no significant difference in moderate to severe haemorrhage or haemorrhagic stroke between the groups. The numbers needed to treat for dual antiplatelet therapy in this study were 29 to prevent one stroke event for a 90-day period. A similar dual therapy study (Johnston et al, 2018) in a multicentre population (POINT study – Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) of 4881 patients showed significantly fewer ischaemic stroke events (4.6% vs 6.3%) in the clopidogrel plus aspirin group compared to the aspirin alone group. This trial was stopped by the trial data safety monitoring team because of clear efficacy in reducing stroke events, after 84% of the planned recruitment had taken place. The efficacy between the two trials were consistent although the risk of haemorrhage was significant in POINT compared to CHANCE. Nevertheless, it is worth noting that most bleeds in these trials were non-fatal and were not intracranial haemorrhages.

Clopidogrel and aspirin, taken together as dual antiplatelet therapy, increase the risk of major bleeding by 38% (95% confidence interval 13–67%). An individual patient data analysis (Hilkens et al, 2018) from six randomised clinical trials (Clopidogrel vs Aspirin in Patients at Risk of Ischaemic Events [CAPRIE], Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management, and Avoidance [CHARISMA], Second European Stroke Prevention Study [ESPS-2], European/Australasian Stroke Prevention in

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Key points

- The highest risk of recurrent stroke occurs in the initial hours to days after the first event.
- Prompt review in a transient ischaemic attack clinic within 24 hours to aid early correct diagnosis and treatment initiation with appropriate therapies can reduce the risk of further ischaemic events.
- There is evidence for benefit of early (within 24 hours) initiation and short-term (0–21 days) dual antiplatelet therapy (aspirin and clopidogrel) for patients with high-risk transient ischaemic attack or non-cardioembolic, non-disabling ischaemic stroke.
- Ticagrelor is not superior to aspirin, and has a similar to worse bleeding profile.
- Triple therapy (aspirin+clopidogrel+dipyridamole) is not recommended because of the increased risk of bleeding with no additional benefit.
- Further studies are needed to evaluate other antiplatelets or combination strategies in specified patient sub-groups.

Reversible Ischaemia Trial [ESPRIT], Management of Atherothrombosis With Clopidogrel in High-Risk Patients [MATCH], and Prevention Regimen for Effectively Avoiding Second Strokes [PRoFESS]), which included 45 195 patients, showed dual antiplatelet therapy is associated with high early risks (incidence of 5.8 and 4.9 per 100 person-years in the first 30 days) of major and gastrointestinal bleeding. This risk declined after the first month in the studied trial cohorts.

Ticagrelor therapy was studied in around 900 patients and was not found to be superior to aspirin in reducing the rates of stroke, myocardial infarction or death at 90 days (Johnston et al, 2016). Triple antiplatelet therapy with clopidogrel, aspirin and dipyridamole is not recommended because of severe bleeding (adjusted commons odds ratio 2.54, 95% confidence interval 2.05–3.16, $P<0.0001$) as studied in the TARDIS trial (Bath et al, 2018).

A pooled analysis (Pan et al, 2019) of POINT and CHANCE, which can provide more precise estimates of treatment outcomes, identified the benefit of dual antiplatelet therapy to be optimal within the first 21 days after minor ischaemic stroke or high-risk transient ischaemic attack. Another meta-analysis (Hao et al, 2018), which pooled FASTER trial data along with those from POINT and CHANCE, also identified that use of dual antiplatelets (aspirin and clopidogrel) for 21 days was associated with a reduction in stroke recurrence. The American Heart Association (Powers et al, 2018) has incorporated this result into its 2018 guidelines. It will be interesting to see if the Royal College of Physicians UK will recommend this in its next update. The National Institute of Health and Care Excellence did not include dual antiplatelets in its 2019 update.

Conclusions

UK clinicians should consider incorporating recent evidence on the benefits of using dual antiplatelet therapy with aspirin and clopidogrel for the first 21 days, into their local policies, based on their patient population. Although the case for use of dual antiplatelets is strong enough to be included in local treatment policies, clinicians will have to be aware of limitations to the generalisability of these studies in certain groups of patients. Indeed the trials reported above involved large patient cohorts, who were screened according to inclusion criteria, with specific age ranges, ethnicities, and excluding certain patient groups. For example, it is likely that patients with evidence of cerebral microbleeds or a history of brain or systemic bleeding, will encounter more harm with dual antiplatelet therapy. Clinicians will have to consider all these points and tailor their therapy appropriately. In parallel, they will need to identify other causes of stroke, such as atrial fibrillation, which may warrant treatment with anticoagulation.

Conflicts of interest

E Rounis declares no conflicts. D Kalladka has recruited patients into the POINT trial and is a collaborating author.

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