Title Page

**Antiplatelet Therapy for Transient Ischemic Attack and Minor Stroke**

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**Non-standard Abbreviations and Acronyms**

| | |
|---|---|
| CHANCE | Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events |
| CHANCE-2 | Clopidogrel With Aspirin in High-risk Patients With Acute Non-disabling Cerebrovascular Events II |
| CI | Confidence interval |
| COMPASS | Cardiovascular Outcomes for People Using Anticoagulation Strategies |
| HR | Hazard ratio |
| PLATO | PLATelet inhibition and patient Outcomes |
| POINT | Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke |
| SOCRATES | The Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes |
| THALES | Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and Aspirin for Prevention of Stroke and Death |
| TIA | Transient ischemic attack |

Transient ischemic attack (TIA) and minor stroke account for 30%-50% of all cerebral ischemic events around the world.[1, 2] In the acute setting, mono antiplatelet therapy (aspirin) is better than none for prevention of recurrent stroke [3, 4], and dual antiplatelet therapy with aspirin and clopidogrel was superior to aspirin alone as seen in the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) [5] and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) [6] trials (**Table 1**). However, CYP2C19 genetic resistance to clopidogrel is present in 25-33% of individuals [7] and although there are functional tests such as P-selectin expression [8] that detect high residual platelet reactivity, they are not used routinely. Therefore, an adenosine diphosphate-receptor antagonist without genetic resistance, e.g. ticagrelor, might offer advantages.

The Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial [9] was the first phase III trial of ticagrelor in acute TIA/minor stroke but failed to show superiority over aspirin at preventing stroke, a finding similar to other mono-antiplatelet therapy comparisons [10, 11]. However, a pre-specified subgroup analysis of SOCRATES reported that ticagrelor was more effective than aspirin in patients with ipsilateral atherosclerotic stenosis ≥50%.[12]

To test this secondary finding and, since previous dual versus mono antiplatelet therapy trials have been positive [5, 6], the Acute Stroke or Transient Ischemic Attack

Treated with Ticagrelor and Aspirin for Prevention of Stroke and Death (THALES) trial [13] compared ticagrelor plus aspirin with aspirin alone in preventing stroke or death in patients with a minor acute non-cardioembolic ischemic stroke (NIHSS ≤5) or TIA (either high risk or presence of ipsilateral atherosclerotic stenosis ≥50%) and without thrombolysis or thrombectomy (**Table 1**). With 11,016 enrolled patients, THALES found that aspirin plus ticagrelor was superior to aspirin alone for preventing the primary outcome of stroke or death by 30 days (5.5% *vs.* 6.6%, hazard ratio [HR]: 0.83, 95% confidence interval [CI]: 0.71-0.96) and stroke alone (HR 0.81, 95% CI: 0.69–0.95) but not death. An increase in severe bleeding was seen with aspirin plus ticagrelor (0.5% *vs.* 0.1%, HR 3.99, 95% CI: 1.74-9.14), with this mainly driven by increased intracranial but not fatal bleeding; the increase in bleeding was present from 5 days after randomisation.[14]

Several questions remain to be answered regarding THALES. First, the exclusion of patients receiving reperfusion therapy (inevitable because of the 24 hour inclusion window) makes interpretation of the results difficult for those patients with large vessel occlusion (the proportion of these is so far unreported). Second, the loading dosage of aspirin was much higher than in CHANCE and POINT and this may have contributed to increased bleeding (as also seen in the PLATelet inhibition and patient Outcomes (PLATO) trial in patients with an acute coronary syndrome [15]). Although POINT also found an increased risk of major hemorrhage with aspirin and clopidogrel given for 90 days, a pooled analysis of CHANCE and POINT revealed that the

treatment effect of aspirin and clopidogrel was mostly achieved in the first 21 days without an increased risk of severe bleeding.[16] Hence, an analysis of severe bleeding by time from randomisation is needed to determine the optimal duration for aspirin plus ticagrelor. THALES has not yet reported results for the subgroup of patients with ipsilateral atherosclerotic stenosis ≥50%, important since 3 months of aspirin plus clopidogrel are recommended for symptomatic severe intracranial stenosis.[17] Third, aspirin may not be the most appropriate comparator for trials in acute TIA and minor stroke. Whether aspirin plus ticagrelor is superior to aspirin plus clopidogrel remains unknown. In indirect comparisons, aspirin and ticagrelor in THALES had a significantly lower rate of stroke (5.14% vs. 6.54%, P=0.002 ) and ischemic stroke (5.00% vs. 6.30%, P=0.004 ) than aspirin plus clopidogrel in both CHANCE and POINT but with similar moderate to severe bleeding rates (0.65% vs. 0.60%, P=0.727). Further randomized clinical trials are warranted to directly compare aspirin plus ticagrelor with aspirin plus clopidogrel in patients with minor stroke or high-risk TIA.

Dual antiplatelet therapy is better than monotherapy but triple antiplatelet therapy (aspirin, clopidogrel, dipyridamole) was not better still due to increased bleeding.[18] Ticagrelor is already licensed for acute coronary syndrome[15] and presumably will become available for use after minor stroke and TIA. However, it should not be used long term since other dual combinations are safe, e.g. aspirin plus cilostazol [19], and aspirin plus dipyridamole[20].

Whether THALES should lead to a change in practice to using aspirin and ticagrelor first line, or just as an option in high risk patients who fail aspirin plus clopidogrel or those with clopidogrel resistance, remains unclear. The Clopidogrel With Aspirin in High-risk Patients With Acute Non-disabling Cerebrovascular Events II (CHANCE-2) trial (NCT04078737) is testing dual therapy in those with clopidogrel resistance. The THALES regime may be most relevant in non-cardioembolic ischemic stroke patients with NIHSS 4-5 or with ipsilateral atherosclerotic stenosis ≥50%. The changeover from the THALES regime to maintenance therapy will depend on patient characteristics and national guidelines; possible strategies include monotherapy with aspirin,[3, 4] clopidogrel or cilostazol alone, or combinations of aspirin and dipyridamole [20] or aspirin and cilostazol.[19] The combination of aspirin and rivaroxaban, as tested in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial is not relevant since it did not enroll patients with recent stroke. Many questions remain beyond the THALES trial and a pooled analysis of individual patient data from CHANCE, POINT and THALES will provide more evidence for dual antiplatelet therapy in patients with minor stroke or high-risk TIA in future.

**Disclosures**

PMB is Stroke Association Professor of Stroke Medicine and an emeritus NIHR Senior Investigator. He has received honoraria from DiaMedica, Moleac, Nestle,

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**Table 1.** Summary of milestone trials of dual antiplatelet therapy in minor stroke and high risk transient ischemic attack

| | CHANCE [5] | POINT [6] | THALES [13,14] |
|---|---|---|---|
| Country (publication year) | China (2013) | 10 countries (2018) | 28 countries (2020) |
| Sample size | 5,170 | 4,881 | 11,016 |
| Onset to randomization | ≤24 h | ≤12 h | ≤24 h |
| Definition of minor stroke | NIHSS ≤3 | NIHSS ≤3 | NIHSS ≤5 |
| Definition of high-risk TIA | $ABCD^2$ ≥4 | $ABCD^2$ ≥4 | $ABCD^2$ ≥6 |
| Additional inclusion criteria | -- | -- | Ipsilateral atherosclerotic stenosis ≥50% |
| Dosage | Clopidogrel: d1: 300mg; d2-d90: 75 mg/d;<br><br>Aspirin: d1: 75-300 mg; d2-d21: 75 mg/d; | Clopidogrel: d1: 600mg; d2-d90: 75 mg/d;<br><br>Aspirin: d1-d90: 50-325 mg/d; | Ticagrelor: d1:180mg; d2-d30: 90mg/d;<br><br>Aspirin:d1:300-325mg; d2-d30 75-100mg/d |
| Dual antiplatelet treatment | 21 days | 90 days | 30 days |
| Follow-up duration | 90 days | 90 days | 30 days |
| Primary outcome | Stroke<br><br>HR 0.68 (0.57-0.81) | Ischemic stroke, myocardial infarction, and ischemic vascular death HR 0.75 (0.59-0.95) | Stroke or death<br><br>HR 0.83 (0.71-0.96); |
| Safety outcome | Severe bleeding<br><br>HR 0.94 (0.24-3.79) | Major hemorrhage<br><br>HR 2.32 (1.10-4.87) | Severe bleeding<br><br>HR 3.99 (1.74-9.14) |