Journal Club: Dual antiplatelet treatment in TIA and high-risk ischemic CVA, a review of the POINT trial

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Full citation

– Trial: Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med* 2018;379(3):215-25.
– Protocol: Johnston SC, Easton JD, Farrant M, et al. Platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trial: rationale and design. *Int J Stroke* 2013;8(6):479-83.

Abstract links:
– https://www.nejm.org/doi/full/10.1056/NEJMoa1800410
– https://www.ncbi.nlm.nih.gov/pubmed/23879752
Article type: Double-blind, randomized control trial
Ratings: Methods – 4/5 Usefulness – 4/5

INTRODUCTION

Background

Patients have an increased risk for stroke after a transient ischemic attack (TIA) or stroke. This is the first large, international randomized controlled trial (RCT) to look at clopidogrel and aspirin for secondary prevention.

Objectives

The primary efficacy objective was the risk of major ischemic events. The primary safety objective was the risk of major hemorrhage.

METHODS

Design

RCT with $n = 4881$

Setting

ED patients from 269 international sites.

Subjects

- Inclusion criteria: adults with high-risk TIA ($ABCD^2 \geq 4$) or minor ischemic stroke [National Institute of Health Stroke Scale (NIHSS) ≤ 3] presenting within 12 hours of symptoms.
- Exclusion criteria: patients whose only symptom was numbness, visual changes, or vertigo; patients on thrombolytics in the previous week; patients who were candidates for thrombolysis, endovascular treatment, or required anticoagulation for atrial fibrillation or cardiovascular disease; patients requiring nonsteroidal anti-inflammatory drugs (NSAIDs) for more than seven days.

Intervention

The treatment group received clopidogrel (600 mg, then 75 mg daily) and aspirin (50–325 mg as decided by the treating physician). The control group received only the aspirin and a placebo.

MAIN RESULTS

There was a decreased risk of major ischemic events in the treatment group (hazard ratio [HR] = 0.75, 95% confidence interval [CI] 0.59–0.95; $p < 0.02$) but an increased risk of major hemorrhage (HR = 2.32, 95% CI 1.1–4.87; $p < 0.02$). The authors estimated that dual-antiplatelet treatment (DAPT) would prevent 15 events per 1,000 patients and cause 5 major hemorrhages per 1,000 patients.

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The secondary analyses looking at specific ischemic and bleeding events were "exploratory" only. For ischemia, the only significant difference was for stroke (HR = 0.72, 95% CI 0.56–0.91; $p < 0.01$). For hemorrhagic events, the secondary analysis contradicts the primary one, finding no difference in risk of stroke, symptomatic intracranial hemorrhage, or any other "major hemorrhage." There was a difference in minor hemorrhage (HR = 3.12).

Looking at the timing of events, the control group's increased risk of ischemic events was only statistically significant during the first seven days of treatment (HR = 0.74, 95% CI 0.55–0.99; $p < 0.04$); The treatment group's increased risk of hemorrhage was statistically significant only after seven days (HR = 2.69, 95% CI 1.05–6.86; $p < 0.04$).

APPRAISAL

Strengths

- Randomized using a 1:1 permuted-block design with good demographic similarity between groups. The intention-to-treat analysis had 93% trial completion in both arms.
- Included an international population (though 83% of patients were American). The trial had many exclusion criteria but did include patients with diabetes, heart disease, and hypertension.

Limitations

- While described as a double-blind trial, the authors did not describe blinding of the researchers and clinicians.
- The trial was halted early at 84% enrolment because it passed the safety threshold for bleeding, and there was a 29% non-adherence rate (though the discontinuation rates were similar in both arms). Aspirin doses were variable, but this was also similar between groups.
- The ischemic HR CI was wide, and the *a priori* incidence of secondary strokes was uncertain; thus, our estimate of the treatment effect must also be imprecise. The secondary analyses had methodological flaws that invalidated the results.

CONTEXT

Since 2007, several studies have evaluated DAPT for secondary prevention. The CHANCE trial (2013), comparing clopidogrel with aspirin, demonstrated an HR of 0.68.[1] However, as it included only Chinese patients, its external validity was limited. The SOCRATES trial (2016),[2] comparing aspirin with ticagrelor, demonstrated no difference in ischemic events. The THALES trial, another ticagrelor trial, is underway. In 2018, both the AHA/ASA and CAEP recommended considering DAPT for 21 days in certain patients.[3,4]

BOTTOM LINE

Despite some methodological flaws, this study was well designed to measure its primary objectives. It supports the hypothesis that DAPT reduces the risk of secondary ischemic events but that treatment is associated with an increased risk of bleeding. From a secondary analysis, it appears that DAPT has a greater benefit and lower risk in the first 21 days.

This study strengthens the AHA recommendations for secondary stroke prevention. More research is needed to narrow the CI for the treatment effect and to look specifically at drug dosing and timing and drugs' influence on specific bleeding and ischemic events.[5]

Keywords: Drugs and pharmacology, emergency medicine, neurology, stroke/TIA

Competing interests: No competing interests or funding sources to report.

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