Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE)

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Following a TIA or minor stroke, the risk of an additional ischemic stroke is high (~10-20%) in the subsequent 3 months, with many occurring within the first 48hrs. At the time of this trial, aspirin monotherapy in the acute phase following a TIA/minor stroke had been well-established for secondary stroke prevention, though with only modest benefit. However, at least in trials of acute coronary syndrome, dual anti-platelet therapy (DAPT) with aspirin and clopidogrel was effective at reducing subsequent ischemic events following the index event. Unfortunately, similar large-scale trials in acute stroke had failed to show this benefit of DAPT for secondary prevention, though none of these earlier studies assessed the acute, high-risk period after stroke and most included patients with only moderate and severe strokes. As such, the goal of this trial was to assess the efficacy of early DAPT (vs. aspirin alone) in reducing the risk of a recurrent stroke following a high-risk TIA or minor stroke.

Experimental design and statistics: This study was a randomized, double-blind, placebo-controlled trial conducted at 114 centers across China. Inclusion criteria for enrollment included age $\geq$ 40yrs, an acute, minor ischemic stroke (NIHSS $\leq$ 3) or high-risk TIA (ABCD score $\geq$ 4), and the ability to start the study drug within 24hrs after symptom onset. Exclusion criteria are noted below.[1] At the time of the index event, eligible patients were randomly assigned to one of two study groups via a double-blind and double-dummy design. On day 1, both groups were given 75-300mg of aspirin. In the DAPT group, patients also received a loading dose of clopidogrel 300mg on day 1. Thereafter, patients in the DAPT group were given clopidogrel 75mg from days 2 – 90 with aspirin 75mg from days 2 – 21, and a placebo aspirin pill from days 22 - 90 (i.e., DAPT for the first 21d following the index event, then clopidogrel monotherapy to 90d). Patients allocated to the aspirin-only group were given a placebo clopidogrel from days 1 – 90, along with aspirin 75mg monotherapy from days 2 – 90. The primary efficacy outcome was a new ischemic or hemorrhagic stroke (with imaging evidence) at 90 days. The primary safety outcome was a moderate to severe bleeding event. Secondary efficacy outcomes included a new clinical vascular event (stroke, MI, vascular death) analyzed individually and as a composite outcome. Pre-specified subgroup analyses were conducted for the primary efficacy outcome as well. Cox proportional hazard models were used to compare all primary and secondary outcomes.

Results: A total of 5170 patients were enrolled from Oct 2009 to July 2012 (N = 2584 to DAPT; N = 2586 to aspirin alone); baseline characteristics were similar (**Table 1**). Within both groups, the median time from onset of the index event to study drug randomization was 13hrs. Regarding the primary efficacy outcome, a recurrent stroke by 90d occurred in 8.2% of the DAPT group vs. 11.7% of the aspirin-only group (HR: 0.68, $p < 0.001$), with disabling events in 5.2% of the DAPT and 6.8% of the aspirin-only group (HR: 0.75, $p = 0.01$; **Table 2, Fig. 1**). Most recurrent strokes were ischemic, with only 8 hemorrhagic strokes in each group (0.3%). In terms of the primary safety outcome, the rate of any bleeding event was slightly higher in the DAPT (2.3%) vs. aspirin-only group (1.6%), though the rates of moderate or severe bleeding events were the same in both groups (0.3% in both, **Table 2**). Otherwise, the composite outcome of any vascular event at 90d was higher in the aspirin-only vs. DAPT group, but this was largely

[1] **Exclusion criteria:** hemorrhage, other vascular malformations, isolated sensory/visual symptoms or dizziness w/o imaging evidence for an infarct, MRS >2 at the index event, clear indication for A/C, contraindication to DAPT, h/o ICH, oral A/C therapy 10d prior to randomization, GIB or other surgery in prior 3 months, severe co-existing condition that limited life expectancy. Exclusion of isolated sensory/visual symptoms or isolated dizziness/vertigo helped to reduce treatment of stroke/TIA mimics

accounted for by the higher recurrent stroke risk (**Table 2**). Subgroup analyses yielded no significant effects (**Fig. 2**).

Conclusions: Overall, 21d of DAPT followed by clopidogrel monotherapy for at least 90d (vs. aspirin alone for 90d) significantly reduced the 90d risk of recurrent stroke by 32%, when administered within 24hrs after a high-risk TIA or minor stroke. While there was a trend towards more bleeding events with DAPT, the risk of moderate to severe hemorrhage did not differ between treatment groups. Of note, as in Fig. 1, group differences in rates of survival free of stroke diverged most significantly within the first few days following the index event, with similar recurrent rates thereafter, suggesting that DAPT is most effective when administered within at least 24hrs of the index event. Otherwise, a limitation here was the use of a patient population restricted to China, where stroke etiologies are often due to intracranial atherosclerotic disease and genetic polymorphisms in this population affect clopidogrel metabolism. This was addressed in the later POINT trial, using a broader patient population. Nonetheless, results from this study have since led to the now common practice of early administration of DAPT for 21d (with anti-platelet monotherapy after) following a minor stroke or TIA.

Additional reading, if interested:

1) Johnston, S.C., et. al., Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA (POINT Investigators). NEJM 2018; 379 (3): 215-225.

Summary created by Elaine Sinclair, D.O.