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Clinical Research in Practice: The Journal of Team Hippocrates

Volume 3 | Issue 2 Article 8

2017

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Recommended Citation
WOELKE BJ, ANGELL D, LITOW K. Clopidogrel alone is safer than clopidogrel and aspirin for secondary prevention of acute ischemic stroke.. Clin. Res. Prac. 2017;3(2):eP1344. doi: 10.22237/crp/1498867380

Clinical Research in Practice
The Journal of Team Hippocrates
VOL 3 ISS 2 / eP1344 / AUGUST 29, 2017
doi: 10.22237/crp/1498867380

Clopidogrel alone is safer than clopidogrel and aspirin for secondary prevention of acute ischemic stroke

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ABSTRACT A critical appraisal and clinical application of Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet.* 2004;364(9431):331-337. doi: 10.1016/s0140-6736(04)16721-4

Keywords: *ischemic stroke, secondary prevention, antiplatelet therapy, clopidogrel*

Clinical Context

Our patient is an 85-year-old Hispanic female with a past medical history of hypertension, diabetes mellitus type 2, moderate obesity, chronic left sided Bell's palsy, hyperlipidemia, and coronary artery disease, which was treated with percutaneous coronary intervention and stent placement 10 years ago. She has no history of tobacco, alcohol, or illicit drug use. The patient presented to the emergency department with right-sided weakness and slurred speech. An MRI of the head confirmed that she had suffered a right-sided lacunar stroke. There was no evidence of atrial fibrillation or flutter. Neurology recommended control of her blood pressure, initiation of statin therapy along with dual anti-platelet therapy (DPT), consisting of clopidogrel and aspirin for secondary prevention of cardiovascular events. Our inpatient internal medicine attending was uncertain that this was the optimal treatment and asked us to investigate the evidence for secondary prevention of stroke.

Clinical Question

In patients with ischemic stroke, is aspirin plus clopidogrel superior to clopidogrel alone for secondary prevention of cardiovascular events?

Research Article

Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet.* 2004;364(9431):331-337. doi: 10.1016/s0140-6736(04)16721-4

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ISSN: 2379-4550
http://digitalcommons.wayne.edu/crp

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Related Literature

We started by reviewing Up to Date, which directly addresses the issue of dual anti-platelet therapy versus monotherapy for stroke prevention. This recommendation was supported by four citations[1-4], which included a systematic review and meta-analysis; this was used as the starting point for our PubMed search.[4] The meta-analysis focused on seven randomized, controlled studies[1,5-10]; that included patients with recent history of stroke or transient ischemic attack (TIA); and that compared DPT versus monotherapy. The meta-analysis indicated that DPT was superior to aspirin alone, but not to clopidogrel alone, and that dual anti-platelet therapy was more harmful than clopidogrel. We reviewed the characteristics of the patient populations studied, and of the seven trials only the MATCH trial had a substantial percentage of patients with diabetes (68% vs. 19-40%). We thought this was important consideration for our specific patient. The meta-analysis also scored these seven trials for risk of bias. The MATCH trial was one of two studies that scored low on all types of bias. The MATCH trial compared aspirin plus clopidogrel versus clopidogrel alone. Additionally, only two studies used clopidogrel as the comparator drug. Since the MATCH trial was at low risk of bias, used clopidogrel as a comparator, and included a significant number of patients with diabetes, we felt it was the most relevant study to our patient's clinical context.

Critical Appraisal

The MATCH trial was a large, double-blinded, placebo-controlled study which explored the reduction of secondary vascular events and occurrence of significant bleeding between DPT with aspirin and clopidogrel compared to clopidogrel with placebo. The study methodology is detailed in a separate paper.[12] This study was funded by Sanofi-Synthelabo, one of the patent holders for clopidogrel. The study funders hired the site monitoring and data management companies, had one vote out of 10 on the steering committee, paid study-related expenses to other members of the committee, and performed final statistical analysis. They do note that there was a separate and parallel statistical analysis done independent of the sponsor.

Randomization was accomplished using a centralized computer generated system. There was no mention of block randomization by site. Given that there were 507 sites in 28 countries, the risk of unequal assignment by country was difficult to assess. Baseline characteristics between the two groups were very similar, indicating a successful randomization. Transient ischemic attack was the inclusion criteria in only 21% of patients. Since our patient had an ischemic stroke, the fact that most patients in the study had an ischemic stroke means that the results are more applicable to our patient. The primary efficacy outcome was a composite of ischemic stroke, myocardial infarction, vascular death, or rehospitalization for acute ischemia. The primary safety outcome was life-threatening bleeding. Bleeding was considered life-threatening if it was fatal, resulted in a hemoglobin drop of 5 g/dL, required inotropes for blood pressure support, required four units of red blood cells, or resulted in symptomatic intracranial hemorrhage. These are individual outcomes with varying degrees of severity. This creates the possibility that there are significant changes in one of the less severe outcomes, with less important changes in the more severe outcomes. However, since they are all grouped together, the reader may imply that there are significant changes in the more severe outcomes when in fact there are not.

Reviewing the inclusion and exclusion criteria, our patient would have been eligible to participate and the treatment is available in our practice. Only 4% of cases dropped out or were lost to follow-up. An intention to treat analysis was used. The authors described the study as “double-blind.” They mentioned that a blinded adjudication committee confirmed the reported outcomes. No further details regarding blinding were provided. All patients initiated therapy and were followed at regular intervals in a similar way. Using the SORT criteria[13] this paper is Level 1 evidence and the body of literature supports a Strength of Recommendation A.

The MATCH trial showed no statistically adequate benefit with the addition of aspirin to clopidogrel. The event rate in the clopidogrel monotherapy group was 17% (636/3802). In the dual antiplatelet therapy group, it was 16% (596/3797). We believe this indicates no additional benefit. However, the life-threatening bleeding rate was higher in the aspirin plus clopidogrel group compared to the clopidogrel group alone (3% vs. 1%, $p<0.0001$). The number needed to harm with the addition of aspirin to clopidogrel over 18 months was 77 for life-threatening bleeds. Unfortunately, this was a composite endpoint and details of each individual component were not completely reported. The report indicates that there was no significant difference in fatal bleeding. Effect size seems to be driven by increases in "non-fatal bleeding." No more detail is provided.

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Clinical Application

Dual anti-platelet therapy did not demonstrate a statistically adequate improvement in efficacy, but did increase the rate of life-threatening bleeding. After discussion with the team, we all felt the evidence was conclusive. The attending appreciated the quality of the discussion on rounds. We ultimately discharged the patient on clopidogrel alone.

Take Home Points:

1. Based upon the literature reviewed, clopidogrel alone is safer than dual anti-platelet therapy for the secondary prevention of stroke and can be considered the standard of care.
2. Dual anti-platelet therapy consisting of clopidogrel and aspirin is associated with a statistically significant increase in life threatening bleeds.
3. We can expect diverse opinions from consultants, but being able to examine the primary clinical research ourselves will help us to better care for our patients.

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