Low-dose enteric-coated aspirin does not inhibit thromboxane B2 and prostaglandin E2: data-derived hypothesis formulation


Background: All usual daily doses of plain aspirin inhibit thromboxane B2 (TXB2) as well as prostaglandin E2 (PGE2). The role of 81-mg enteric-coated aspirin (ECA) is controversial. Method: In a randomized, double-blind trial, 37 patients (25 men and 12 women) with chronic stable coronary disease taking ECA 81 mg at baseline were assigned to plain aspirin 81, 162.5, 325, 650 or 1300 mg daily for 12 weeks. At baseline and 12 weeks, blood was tested for TXB2 and PGE2. Results: All doses of plain aspirin produced virtually identical reductions in TXB2 and PGE2. For all doses combined, the mean ratio of the 12-week to baseline value was 0.03 for TXB2 (p < 0.001) and 0.63 for PGE2 (p < 0.001). Conclusion: These data indicate that ECA 81 mg daily does not inhibit TXB2 and PGE2, markers of acute and systemic responses to aspirin. Randomized trials designed a priori to test this hypothesis are necessary.

Keywords: enteric-coated aspirin • lack of platelet inhibition • low dose
These mechanisms seem sufficient to explain the risks as well as the benefits of aspirin on clinical cardiovascular disease events. With respect to risks, gastrointestinal side effects and bleeding are well known and have been well described [7–10]. Although a causative relationship for gastrointestinal side effects seems apparent only at ≥325 mg daily, there has been an increasing tendency to prescribe 81 mg daily. There is also an increasing tendency to prescribe 81 mg ECA as an alternative attempt to decrease gastrointestinal side effects and bleeding. Low-dose ECA has been increasingly used despite some suggestions that this dose and formulation may not produce adequate, or in some instances any, platelet inhibition [11]. A randomized trial was designed and conducted to test the effects of various doses of plain aspirin from 81 to 1300 mg daily, on NO as well as platelet and inflammatory biomarkers, specifically TXB2, and PGE2, at 12 weeks. The population studied were patients with chronic stable coronary disease, all of whom had been taking 81 mg ECA for at least one year. The circumstances afforded us a unique opportunity to contribute relevant data to the formulation of – but not to test – the hypothesis that low-dose ECA does not inhibit two markers of acute and systemic response to aspirin.

Method

The protocol was approved by the Institutional Review Board at Florida Atlantic University (FL, USA). All patients were recruited from two private cardiology practices. After explaining the protocol and obtaining written, informed consent for participation in a randomized, double-blind trial, 37 secondary prevention patients (25 men, 12 women) aged 46–80 years inclusive, with chronic stable coronary disease. The registration number was NCT00272337. This trial was funded as an investigator-initiated project by the Division of Medicine, as Principal Investigator. The trial was designed, conduct, analysis, interpretation, preparation, and writing of the final manuscript for publication.

Table 1. Baseline characteristics of randomized daily dose of aspirin treatment groups.

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Randomized daily dose of aspirin treatment groups</th>
<th>p-value†</th>
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<tbody>
<tr>
<td>81 mg (n = 8)</td>
<td>162 mg (n = 7)</td>
<td>325 mg (n = 7)</td>
</tr>
<tr>
<td><strong>Mean age ± SD (yrs)</strong></td>
<td>61.8 ± 9.7</td>
<td>67.8 ± 8.0</td>
</tr>
<tr>
<td><strong>Mean height ± SD (inches)</strong></td>
<td>68.3 ± 3.5</td>
<td>68.7 ± 3.7</td>
</tr>
<tr>
<td><strong>Mean weight ± SD (lb)</strong></td>
<td>218.9 ± 37.7</td>
<td>192.4 ± 30.0</td>
</tr>
<tr>
<td><strong>Mean BMI ± SD (kg/m²)</strong></td>
<td>33.3 ± 3.6</td>
<td>28.6 ± 3.2</td>
</tr>
<tr>
<td><strong>Caucasian (n; %)</strong></td>
<td>8 (100)</td>
<td>6 (85.7)</td>
</tr>
<tr>
<td><strong>ACE inhibitor (n; %)</strong>*</td>
<td>2 (25)</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td><strong>Diuretic (n; %)</strong>*</td>
<td>2 (25)</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td><strong>Other lipid lowering (n; %)</strong>*</td>
<td>7 (87.5)</td>
<td>7 (100)</td>
</tr>
<tr>
<td><strong>Statin (n; %)</strong></td>
<td>8 (100)</td>
<td>7 (100)</td>
</tr>
<tr>
<td><strong>Calcium blocker (n; %)</strong>*</td>
<td>2 (25)</td>
<td>5 (71.4)</td>
</tr>
</tbody>
</table>

Table 1. Baseline characteristics of randomized daily dose of aspirin treatment groups.

**Role of the funding source**

This trial was funded as an investigator-initiated grant by Bauer to the Charles E Schmidt College of Medicine at Florida Atlantic University, with Charles Hennekens the Sir Richard Doll Research Professor of Medicine, as Principal Investigator. The trial was registered on the ClinicalTrials database as ‘Aspirin dose and atherosclerosis in patients with heart disease’. The registration number was NCT00273387. The funding source, Bauer, had no role in the design, conduct, analysis, interpretation, preparation of the manuscript or any decision about whether, or where, to submit the manuscript for publication.

Results

Despite the relatively small sample size, randomization achieved a fairly balanced distribution of baseline characteristics by treatment group (Table 1). Among the notable baseline characteristics were mean age of 64 years and mean BMI of 30.6. In addition, the vast majority of these patients with chronic stable coronary disease were being treated, according to guidelines, with statins (85%), angiotensin converting enzyme inhibitors (54%) and β-adrenergic blockers (75%). Of the 37 randomized patients, 33 (one missing data point) accepted each 81 mg dose and had complete baseline and follow-up data for TXB2 and PGE2 after 12 weeks. In addition, there were no statistically significant differences between any of the doses for TXB2 or PGE2, either at baseline or week 12; we therefore combined the data across all daily doses (Table 2).

**Conclusion**

In a randomized, double-blind trial of 37 patients with chronic stable coronary disease, who had been taking ECA 81 mg at baseline for at least 1 year prior, it was found that plain aspirin, at all doses in the usual range employed in clinical practice – including 81, 162.5, 325, 650 and 1300 mg – produced significant reductions in TXB2 and PGE2, after 12 weeks. These data contribute to the formulation of the hypothesis that daily administration of low dose ECA does not inhibit TXB2 or PGE2. These findings are comparable with several previous observations [11–16]. In one study, ECA 50 mg was not very efficient at inhibiting the arachidonic acid conversions to thromboxane as well as inhibiting in vitro platelet function [17]. A small, second trial showed that poor response was associated with high body weight, as well as ECA 100 mg on alternate days [18]. In another trial of 71 healthy volunteers, equivalent doses of the ECA were not as effective as plain aspirin [19]. Finally, some investigators also showed poor response was associated with noncompliance, high body weight and use of ECA [20]. In the present trial, the mean BMI was 30.6, therefore the average patients were obese and, in addition, the sample size was too small to detect any association with even higher BMI.

There are several limitations that merit mention. First, the findings were unexpected and had not been hypothesized in advance. In fact, the trial was designed to test various doses of plain aspirin on NO [10], as well as platelet and inflammatory biomarkers. Thus, the
Nonfatal MI, nonfatal stroke or vascular death. The benefits are also similar regardless of age, gender or history of hypertension or diabetes. In indirect comparisons of these trials, the benefits in reducing important vascular events by approximately 25% are similar across a wide range of doses, from 75 mg to <150 mg of aspirin daily. Data from only three randomized trials of small sample size show that doses of >75 mg/day yield only approximately a 13% reduction, a finding that does not achieve statistical significance (\( p = 0.05 \)). As one would expect, the 10-year risk of a first coronary heart disease event in the WHS was very low; approximately 2.5%.

In a landmark clinical investigation of patients with stable coronary disease by their private cardiologists, as measured by self reports by the patients to their health professionals taking aspirin 100 mg every other day \( \times 2 \) among those assigned placebo; relative risk: 0.66; 95% CI: 0.65–0.67. In the meta-analysis, of amongst 55,580 apparently healthy individuals (11,466 women), there were far fewer end points than in the 287 trials of secondary prevention with 212,000 patients. Nonetheless, aspirin had a statistically significant different from zero. In the meta-analysis, of amongst 55,580 apparently healthy individuals (11,466 women), there were far fewer end points than in the 287 trials of secondary prevention with 212,000 patients. Nonetheless, aspirin had a statistically significant different from zero. In the meta-analysis, of amongst 55,580 apparently healthy individuals (11,466 women), there were far fewer end points than in the 287 trials of secondary prevention with 212,000 patients. Nonetheless, aspirin had a statistically significant different from zero. In the meta-analysis, of amongst 55,580 apparently healthy individuals (11,466 women), there were far fewer end points than in the 287 trials of secondary prevention with 212,000 patients. Nonetheless, aspirin had a statistically significant different from zero. In the meta-analysis, of amongst 55,580 apparently healthy individuals (11,466 women), there were far fewer end points than in the 287 trials of secondary prevention with 212,000 patients. Nonetheless, aspirin had a statistically significant different from zero.

Table 2. No significant differences for thrombosome B2 and prostaglandin E2 between all clinically relevant doses of aspirin at 12 weeks compared with 81 mg enteric-coated aspirin daily at baseline.

<table>
<thead>
<tr>
<th>Mean 12-week</th>
<th>Randomized daily dose of aspirin (mg)</th>
<th>TXB2 (ng/ml)</th>
<th>PGE2 (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 12-week</td>
<td>81 mg</td>
<td>162 mg</td>
<td>325 mg</td>
</tr>
<tr>
<td>baseline of TXB2 (ng/ml)</td>
<td>0.04</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>baseline of PGE2 (ng/ml)</td>
<td>0.62</td>
<td>0.69</td>
<td>0.57</td>
</tr>
<tr>
<td>p-values = 0.15 for all comparisons.</td>
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</tbody>
</table>

The issue of dose and formulation of aspirin also has relevance to the primary prevention of cardiovascular disease [15]. In that regard, prior to the Women’s Health Study (WHS), five randomized trials of aspirin and their meta-analysis had been published [16]. The daily doses used in these trials ranged from 75 to 500 mg. In the meta-analysis, of amongst 55,580 apparently healthy individuals (11,466 women), there were far fewer end points than in the 287 trials of secondary prevention with 212,000 patients. Nonetheless, aspirin had a statistically significant different from zero.

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Randomized trials of sufficient size designed a priori to test these hypotheses are necessary and should include various doses of generic and branded plain aspirin as well as equivalent doses of ECA.

Future perspective

These findings contribute important relevant information to the hypothesis that 81 mg ECA daily does not inhibit TXB2, and PGE2, markers of acute and systemic responses to aspirin. Randomized trials of sufficient size designed a priori to test these hypotheses are necessary and should include various doses of generic and branded plain aspirin, as well as equivalent doses of ECA. If this hypothesis is correct, the next 5–10 years may see a paradigm shift toward the utilization of higher doses of ECA in the treatment and prevention of CVD. It is also plausible that greater utilization of 325 mg daily may occur if the randomized data in prevention of colon polyps as well as colon cancer are added to the benefit-risk considerations for daily aspirin use.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal studies.
experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Financial & competing interests disclosure
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References


