Aspirin following PCI: too much of a good thing?

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This editorial refers to ‘Effects of aspirin dose on ischaemic events and bleeding after percutaneous coronary intervention: insights from the PCI-CURE study’1, by S.S. Jolly et al., on page 900

There is only one cardiovascular medication with a 4-fold difference in the ‘routine’ daily dose approved by regulatory bodies, recommended by guideline committees, and suggested by clinicians.1 That medication is acetylsalicylic acid (ASA), or aspirin. When considering any drug routinely used in the treatment of the patient with cardiovascular disease—statins, thienopyridines, angiotensin-converting enzyme (ACE) inhibitors, β-blockers—are there any in which a 4-fold difference in dose would not be expected to lead to significant differences in efficacy, safety, and tolerability? Yet with aspirin, the most widely used drug worldwide for cardiovascular disease prevention, the choice of dose is frequently based more on habit than on science. In fact, market research suggests that, among US cardiologists, approximately two-thirds recommend a 325 mg daily dose; most of the remainder recommend 81 mg per day.2

With respect to its use specifically during percutaneous coronary interventions (PCIs), aspirin has a long history of being taken for granted. Although Andreas Gruentzig utilized (somewhat fortuitously) aspirin during the first initial coronary angioplasty ever performed, its antithrombotic efficacy was thought by investigators to be so minimal, compared with heparin, that several placebo-controlled trials were later carried out, primarily to see if it might reduce restenosis.3 In fact, randomized trials of aspirin were later carried out, primarily to see if it might reduce restenosis.3,4 What these investigators surprisingly found was that aspirin did not reduce restenosis; instead, they found that aspirin, administered at the time of a PCI, was associated with an extraordinary, ~75% reduction in the relative risk of acute thrombotic events compared with placebo. Next, the hypothesis was tested that aspirin might be of no benefit after the initial PCI was completed.5 However, once again, aspirin-treated patients experienced a remarkably large, ~80%, relative reduction in myocardial infarction and other thrombotic events in the following 6 months, compared with placebo.

While these placebo-controlled trials unequivocally established the benefits of aspirin during and following a PCI, they provided no information as to whether one dose was better than others. If a ‘correct’ dose were to be based on what daily dose would be necessary to inactivate platelet cyclo-oxygenase-1 (COX-1) maximally, doses of 30 mg daily, at least as studied in healthy individuals, would be most appropriate.6 Even in patients with chronic stable angina undergoing pacing-induced ischaemia, 50 mg/day normalized thromboxane production, and prevented an increase in thromboxane production during ischaemia.7 However, if doses as small as 30–50 mg/day are effective from a pharmacodynamic standpoint, then how is it that doses as high as 325 mg/day have come to be so commonly recommended and utilized? Historically, nearly 100 years ago, the makers of Bayer Aspirin found that 5 grains (~325 mg) was the optimal amount to form into a difficult counterfeit pill—and it was the first pharmaceutical agent supplied in pill form. From an antiplatelet perspective, the 81 mg ‘children’s’ aspirin was similarly, arbitrarily, determined to be a quarter of the ‘adult’ dose. Fast forward over half a century, and these doses originally chosen to treat fevers, aches and pains became the routine doses of aspirin used in cardiovascular medicine. However, while it is still often stated that 325 mg is recommended by the guidelines because that was the dose mandated in PCI clinical trials, a quick review of landmark PCI trials over the last 30 years indicates that this has not always necessarily been true. Table 1 is an admittedly partial list of PCI trials that permitted doses <325 mg; many others did as well, including trials in which drug-eluting stents were placed.

The study of Jolly et al.,8 a post hoc observational analysis of a post-randomization subgroup analysis of the landmark CURE trial, is one of almost half a dozen analyses of large, randomized trials designed to identify the optimal dose of aspirin in terms of both efficacy and safety.9 Interestingly neither the earlier trials nor the study of Jolly et al. found even a trend towards a reduction in their primary ischaemic endpoint in those patients who received higher doses of aspirin. What makes the PCI-CURE analysis unique, however, is its focus on a primarily stented population, a population in whom appropriate antiplatelet therapy is so critical to reduce not only procedural complications but also post-procedural thrombotic events. PCI involving stent procedures has been the last remaining stronghold for the assumption that when it comes to aspirin, more must be better.
Table 1: Protocol-mandated aspirin dose in select landmark trials in percutaneous coronary intervention

<table>
<thead>
<tr>
<th>Trial</th>
<th>Years performed</th>
<th>Design</th>
<th>No. of patients</th>
<th>Aspirin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAVEAT 12</td>
<td>1991–1992</td>
<td>Directional atherectomy vs. balloon angioplasty</td>
<td>1072</td>
<td>≥160 mg pre-procedure then 325 mg daily for 1 month</td>
</tr>
<tr>
<td>BENESTENT 13</td>
<td>1991–1993</td>
<td>Scent vs. balloon angioplasty</td>
<td>520</td>
<td>230–500 mg daily</td>
</tr>
<tr>
<td>STRESS 14</td>
<td>1991–1995</td>
<td>Antiplatelet vs. anti-coagulant therapy after stenting</td>
<td>410</td>
<td>325 mg daily</td>
</tr>
<tr>
<td>STRESS 15</td>
<td>1994–1996</td>
<td>Stent vs. balloon angioplasty</td>
<td>1965</td>
<td>100 mg twice daily</td>
</tr>
<tr>
<td>SIRIUS 16</td>
<td>1996</td>
<td>Stent vs. balloon angioplasty</td>
<td>238</td>
<td>≥100 mg daily</td>
</tr>
<tr>
<td>SPIRIT III 21</td>
<td>2005–2006</td>
<td>Everolimus-eluting vs. paclitaxel-eluting stent</td>
<td>1002</td>
<td>≥80 mg daily for a maximum of 6 months</td>
</tr>
</tbody>
</table>

The clinical implications of the PCI-CURE analysis, in light of multiple similar analyses in admittedly different patient populations but with similar conclusions, appear relatively straightforward. In all cardiovascular disease patient populations, including recently stented patients, there is no evidence that greater antithrombotic efficacy is achieved when daily doses of aspirin >100 mg are utilized. On the other hand, it is clear that increasing doses of aspirin increase the risk of bleeding. Despite the large volume of retrospective analyses supporting the use of lower aspirin doses, adequately powered, prospective trials directly comparing aspirin doses are still required to bring clarity to the matter. The ongoing Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent EvNTs/Optimal Antiplatelet Strategy for InterventionS (CURRENT/OASIS-7) trial will evaluate ~25 000 patients who will be randomized to a short course (~3 weeks) of 75–100 mg of aspirin vs. 300–325 mg of aspirin (in addition to high or routine doses of clopidogrel) and will be the first, and quite possibly the only, trial to do so.

The results of the study of Jolly et al., and their consistency with prior studies, should also give us reason to pause in the midst of the deluge of aspirin ‘resistance’ studies, which almost uniformly conclude that higher doses of aspirin are required in as many as 50% of patients in order to overcome aspirin resistance. Such conclusions can only be reconciled with the clinical data with one of two hypotheses: (i) a large proportion of patients achieve greater inhibition of platelet COX-1 with higher doses of aspirin as reflected by ex vivo platelet function testing, but these high doses produce a pro-ischaemic effect in vivo (possibly related to increased inhibition of vascular prostacyclin); or (ii) current platelet function tests designed to determine an individual’s response to aspirin (and there are many, and they do not always correlate with one another) are measuring something unrelated to aspirin’s clinical efficacy.

Either way, it is clear that we have a way to go before we fully understand the science behind platelet function testing. Until we do, and perhaps even after, it is wise to be guided by clinical data rather than historical precedent or surrogate endpoints such as platelet function testing. The clinical data to date consistently remind us that when it comes to aspirin, you can certainly never have too much of a good thing.

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References


