Aspirin and Other Antiplatelet Agents in the Secondary and Primary Prevention of Cardiovascular Disease

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Aspirin permanently inhibits cyclooxygenase-dependent platelet aggregation.1–8 Even low dose aspirin (e.g., 80 mg/day) will, within a few days, inhibit platelet cyclooxygenase so completely that little further effect on this mechanism of platelet aggregation would be expected at higher daily doses of the drug.3,6,8 Although, if antiplatelet therapy is to be started during an acute vascular event, such as MI, then a somewhat higher loading dose (at least 160 mg) might be preferred to ensure a rapid antithrombotic effect.

During the past 20 years, there have been reports from observational epidemiologic studies of aspirin as well as a number of randomized trials. Taken as a whole, the case-control and cohort studies suggest that aspirin may reduce the incidence of cardiovascular disease by about 20%.9–12 Which, if true, would be clinically worthwhile and would have an important impact on public health. Unfortunately, however, the amount of uncontrolled confounding inherent in such observational studies could be about as great as the postulated benefit.13 In general, reliable assessment of such modest benefits can be derived only from large randomized trials.14

Aspirin and Other Antiplatelet Therapy

For Secondary Prevention

In secondary prevention among patients who already have a history of stroke, TCI, MI, or unstable angina, 25 randomized trials of various antiplatelet agents (aspirin, dipyridamole [Persantine], sulfinpyrazone [Anturane], or sulocidil, either alone or in combination) had been completed by 1988. These trials included a total of approximately 29,000 individuals, 18,000 with a history of MI (10 trials),15–27 9,000 with a history of stroke or TCI (13 trials),28–42 and 2,000 with unstable angina (two trials).43,44 Taken separately, these trials were too small to yield statistically stable results, and, moreover, data-dependent emphasis on some trials and not others might be biased. Taken together, however, an overview, or meta-analysis, of all their results can yield a more statistically stable estimate (i.e., one with less variability due to chance fluctuations in the data) of the effects of antiplatelet therapy and can avoid biases arising from overemphasis on just a few of the trials.

In the recent overview,46 the three main types of endpoints analyzed separately were nonfatal MI, nonfatal stroke, and total cardiovascular death (International Classification of Disease, 9th Revision, 390–459, 530–539, and 798–799, which includes not only all forms of cardiac or vascular disease but also deaths from peptic ulcers or from unknown causes), together with a combined category of vascular events (i.e., any of the three main types of end points). Overall, the proportional reductions were greater in nonfatal MI and in nonfatal stroke than in cardiovascular death, but, for each of the three separate end points, the reduction observed among those allocated to antiplatelet treatment was highly significant (p<0.0001). As expected in these high-risk populations, the proportion of deaths attributed to noncardiovascular causes was small and was not significantly affected by antiplatelet therapy. Therefore, total mortality was also very significantly improved (p<0.0001). For statistical stability, the comparisons of different trial results are based primarily on all vascular events, not just vascular

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TABLE 1. Overview of 25 Trials of Antiplatelet Therapy in the Secondary Prevention of Cardiovascular Disease

<table>
<thead>
<tr>
<th>End point</th>
<th>Prior MI (10 trials)</th>
<th>Recent UA (2 trials)</th>
<th>Cardiac history (MI/UA) (12 trials)</th>
<th>Prior cerebrovascular disease (stroke/TCI) (13 trials)</th>
<th>Any history (stroke/TCI/MI/UA) (25 trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI</td>
<td>31±5</td>
<td>35±17</td>
<td>31±5</td>
<td>35±12</td>
<td>32±5</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>42±11</td>
<td></td>
<td>40±10</td>
<td>22±7</td>
<td>27±6</td>
</tr>
<tr>
<td>Total vascular death</td>
<td>13±5</td>
<td>37±19</td>
<td>14±5</td>
<td>15±7</td>
<td>15±4</td>
</tr>
<tr>
<td>Any vascular event</td>
<td>22±4</td>
<td>36±13</td>
<td>26±3</td>
<td>22±5</td>
<td>25±3</td>
</tr>
</tbody>
</table>

Values are percentage ±SD.

Patients with prior vascular disease at entry into therapy. Figures represent reduction in risk among those assigned antiplatelet therapy. MI, myocardial infarction; UA, unstable angina; TCI, transient cerebral ischemia.

deaths, and the overview demonstrated a highly significant 25% reduction in the risk of ever developing a subsequent important vascular event (i.e., nonfatal MI, nonfatal stroke, or vascular death) during the scheduled trial treatment period (Table 1). When these data were grouped according to the characteristics of the study populations at entry, there were similar risk reductions among patients with previous cerebrovascular disease (stroke or TCI) and among patients with previous coronary disease (MI or unstable angina). When all available trials were considered, for subsequent nonfatal MI, the reduction in risk was 32±5% (p<0.00001) and was similar in size and highly significant in both coronary and cerebral disease trials. For subsequent nonfatal stroke, the corresponding reduction in risk was 27±6% (p<0.00001), again, with a significant reduction in both types of trials. Finally, for total cardiovascular mortality, there was a statistically significant 15±4% reduction in risk for all trials combined, reflecting reductions of 15% and 14% for the cerebrovascular and coronary disease trials, respectively (Table 1).

Because there was no obvious large difference among the effects of antiplatelet therapy in the different types of trials, information from all trials was combined to provide both direct and indirect comparisons of the effects of the three main different types of antiplatelet therapy that were tested (Table 2). The direct comparisons were derived from separate overviews of data from individual trials that specifically tested either aspirin versus sulfinpyrazone or aspirin versus a combination of aspirin with dipyridamole, whereas the indirect comparisons involved comparing four risk reductions derived from the four overviews of trials testing each specific regimen against no treatment. As shown in Table 2, each of the four main types of antiplatelet therapy was significantly better than no treatment, and there were no significant differences among these four types. Specifically, these trials provided no good evidence that dipyridamole plus aspirin is any more effective than aspirin alone because the indirect comparison between the two risk reductions is not significant, and the overview of the direct comparisons indicates no difference whatsoever (279/1,597 vs. 275/1,597). Thus, the primary use of alternative antiplatelet therapies (sulfinpyrazone, in particular) may be among those allergic to aspirin. Further, there was no evidence that doses of 900–1,500 mg of aspirin daily were any more effective in avoiding cardiovascular events than a lower dose of 300 mg, or one standard aspirin tablet, per day. This observation is pharmacologically plausible because doses even lower than 300 mg/day would have been sufficient to produce virtually complete inhibition of cyclooxygenase-

| Table 2. Direct and Indirect Comparisons Between Various Antiplatelet Therapies* |
|---------------------------------|------------------|------------------|
|                                 | Difference in favor of aspirin (%±SD) | Difference in favor of antiplatelet therapy (%±SD) |
| Direct comparisons† (total events/patients) | | |
| Aspirin vs. sulfinpyrazone32,45,47 (54/346 vs. 74/357) | 28±17 | . . . |
| Aspirin vs. aspirin + dipyridamole17,18,30,31,36,48 (275/1,597 vs. 279/1,597) | 2±9 | . . . |
| Indirect comparisons‡ | | |
| Aspirin (900–1,500 mg/day vs. 0.0 mg/day) | . . . | 23±4 |
| Aspirin (300 mg/day vs. 0.0 mg/day) | . . . | 24±8 |
| Sulfinpyrazone vs. nothing | . . . | 17±8 |
| Aspirin + dipyridamole vs. nothing | . . . | 31±5 |

*From Table 1; for the combined end point of important vascular events.
†Reductions in risk of suffering an important vascular event (stroke/MI/vascular death), derived from separate overviews of the trials testing these two antiplatelet regimens against each other.
‡Reductions in risk of suffering an important vascular event, derived from comparing these four results from general overview of trials testing each specific agent vs. no treatment. Test for heterogeneity between four risk reduction: χ²=3.5 on 3 df, p=NS.
TABLE 3. Results From the Second International Study of Infarct Survival (ISIS-2): Events in the First 5 Weeks After Suspected MI*  

<table>
<thead>
<tr>
<th>End point</th>
<th>Aspirin (162 mg/day for 1 month) (n=8,587)</th>
<th>Placebo (1 tablet/day for 1 month) (n=8,600)</th>
<th>Reduction in risk (%±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal* reinfarction in hospital</td>
<td>83</td>
<td>170</td>
<td>50±9</td>
</tr>
<tr>
<td>Nonfatal* stroke in hospital</td>
<td>27</td>
<td>51</td>
<td>46±17</td>
</tr>
<tr>
<td>Vascular mortality</td>
<td>804</td>
<td>1,016</td>
<td>23±4</td>
</tr>
<tr>
<td>Nonvascular mortality</td>
<td>1</td>
<td>7</td>
<td>†</td>
</tr>
<tr>
<td>Any vascular event</td>
<td>914</td>
<td>1,237</td>
<td>23±4</td>
</tr>
</tbody>
</table>

*With discharge alive (total numbers suffering reinfarction, including those who died—156 aspirin vs. 284 placebo; total suffering stroke—47 aspirin vs. 81 placebo).
†Nonvascular death was not a prospectively stated endpoint of this study.

dependent platelet aggregation. However, direct evidence of the effects of aspirin in doses lower or less frequent than 300 mg/day is not available from these trials of secondary prevention.

For Evolving Myocardial Infarction

Because low-dose aspirin confers a moderate degree of protection for individuals with a previous history of MI and unstable angina (Table 1), it was hypothesized that aspirin therapy could be effective if started during the first few hours of an evolving MI. To test this (and also to assess the role of intravenous streptokinase in treating evolving MI) ISIS-251 (the Second International Study of Infarct Survival) randomized a total of 17,187 patients with suspected acute MI to either a single dose of 1.5 million units of streptokinase intravenously over about 60 minutes, or 162 mg oral aspirin daily for 1 month, or both, or neither. All arms of the trial were placebo controlled.

Five weeks after randomization, there were 804 vascular deaths in the two aspirin-allocated groups and 1,016 among the two groups allocated to placebo (Table 3), yielding a highly significant 23% reduction in risk among those taking aspirin. A significant mortality reduction was produced by aspirin not only among patients who were to receive no heparin (288 vs. 347 deaths) and among patients who were to receive subcutaneous heparin (338 vs. 431 deaths) but also among those who were to receive intravenous heparin (178 vs. 238 deaths, p<0.001), showing that even intravenous heparin is not a sufficient antithrombotic treatment in acute MI. Whether or not heparin has been given, therefore, aspirin can save lives in acute MI. (The converse question of whether, if aspirin is given, heparin is also necessary is currently being addressed by the Gruppo Italiano per lo Studio della Streptokinasi nelli infarto Miocardico (GISSI-2) and ISIS-3 trials.) In ISIS-2, there were no significant differences between the aspirin and placebo groups for major bleeds (31 vs. 33) and no evidence of any adverse effect on nonvascular deaths (one aspirin vs. seven placebo, p>0.05). With respect to total reinfarction, fatal or not, there were 156 reported events in the aspirin group compared with 284 among those on placebo. This difference was highly statistically significant. Finally, 47 strokes were confirmed in the aspirin group compared with 81 in placebo, a reduction that was also statistically significant (p=0.003). The protective effect of aspirin against reinfarction and stroke included both fatal and nonfatal events (Table 3), and was seen whether or not streptokinase was given.

Strokes were subdivided according to whether or not the event was confirmed as hemorrhagic, as well as by the probable severity of any residual impairment. Although fibrinolytic treatment with agents such as streptokinase does not appear to have any significant effect on the overall incidence of stroke, this may merely reflect a balance between risks and benefits on strokes of differing etiologies. Specifically, fibrinolytic treatment may prevent some occlusive strokes, and does appear to cause some hemorrhagic strokes (about one or two per 1,000 patients treated) within the first 24-48 hours after treatment. There was, in ISIS-2, a nonsignificant tendency for aspirin to aggravate this early fibrinolytic hazard, but even if this effect is real, it is outweighed by the protective effects of aspirin against occlusive stroke and against stroke, as a whole.

Table 4 compares the ISIS-2 results on short-term antiplatelet treatment of suspected acute MI with the overview of the results on long-term antiplatelet treatment of patients with a history of MI. The general pattern is quite similar, with very definite reductions in each of the three types of vascular events from both short-term and long-term treatment.

For Primary Prevention

The definite protective effects of aspirin among high-risk individuals who already have a history of vascular disease raise, but do not address directly, the possibility that aspirin might also be protective in the primary prevention of cardiovascular disease among low-risk individuals with no known history of vascular disease. At present, only two randomized trials of the primary prevention of occlusive
vascular disease with aspirin have been published (Table 5), the US Physicians' Health Study and the British Doctors' Trial. The US Physicians' Health Study is a double-blind, placebo-controlled trial of 325 mg of aspirin taken every other day, conducted among 22,071 US male physicians initially aged 40–84 years. A 2×2 factorial design was utilized, that allowed the simultaneous testing of the effects of β-carotene supplementation on risks of cancer. For the combined end point of all important vascular events (nonfatal MI, nonfatal stroke, or cardiovascular death), there was a statistically significant 18±7% reduction among those on aspirin. There was a highly significant 44% reduction in the overall risk of MI. Most of the infarcts that were prevented were, however, nonfatal (129 vs. 213) and, although there was a conventionally significant reduction in the number of deaths that were definitely attributed to MI by the end points committee (10 vs. 26), there was no difference in the numbers of deaths attributed to “other ischemic heart disease” (24 vs. 25) and a nonsignificant excess of “sudden death, cause unknown” (22 vs. 12), some of which may have been due to coronary artery occlusion) and of stroke deaths (10 vs. seven). Thus, the reduction in total cardiovascular mortality was not significant (2±15%), although the standard deviation is too large for this finding to be reliable evidence of lack of benefit. There appeared to be a slightly increased risk of total stroke among those taking aspirin (19±15%), but this was not statistically significant, and did not become significant even if attention was restricted to the small subgroup of hemorrhagic strokes (23 vs. 12). There was no significant difference in nonvascular mortality (124 vs. 133).

The British Doctors' Trial randomized 5,139 male British physicians initially aged 50–78 years. It tested 500 mg of aspirin daily using an open design, where the control group was merely asked to avoid aspirin and all products containing aspirin rather than to take a placebo. There was no significant difference for the combined end point of important vascular events, for MI, for stroke, or for total vascular mortality. When strokes were subdivided by etiology, as well as by the severity of any residual disability for nonfatal events, the only conventionally significant result was an increased risk of disabling strokes among those in the aspirin group, and even that was not clearly significant (p=0.05). Even if this apparent excess is at least partly real, it is difficult to know whether it reflects more severe strokes among those taking aspirin (perhaps because hemorrhagic strokes are particularly hazardous), or some bias introduced by the subjective nature of the assessment of residual impairment, which was done through self-reports, without placebo control.

### Table 5. Aspirin in Primary Prevention (US Physicians' Health Study and British Doctors' Trial Results)

<table>
<thead>
<tr>
<th>End point</th>
<th>US Physicians' Health Study</th>
<th>British Doctors' Trial</th>
<th>Overview of both trials</th>
<th>Difference between two trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduction (%±SD)</td>
<td></td>
<td></td>
<td>Statistical tests</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>39±9</td>
<td>3±19</td>
<td>32±8</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>↑19±15</td>
<td>↑13±24</td>
<td>↑18±13</td>
<td>NS</td>
</tr>
<tr>
<td>Total cardiovascular death</td>
<td>2±15</td>
<td>7±14</td>
<td>5±10</td>
<td>NS</td>
</tr>
<tr>
<td>Any vascular event</td>
<td>18±7</td>
<td>4±12</td>
<td>13±6</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

↑, a nonsignificant increase in stroke among aspirin-allocated subjects.

### Figure 1. Overviews of US and UK primary prevention trial results for four end points: odds ratios (aspirin versus control), overall risk reductions, and heterogeneity tests (sum of four heterogeneity χ² tests = 4.9, NS).

For comparability between the two trials, “vascular” deaths include all circulatory causes (9th ICD 390–459), gastric ulcer or hemorrhage (530–535, 578), and sudden or unknown causes (798, 799). For the US trial, this includes the 94.8% of deaths confirmed as of the final report (81 versus 83). We have also added to the US trial all reported and unrefuted vascular deaths to date (9 versus 9), including two in the placebo group, which, as fatal lower GI hemorrhages, had been classified as nonvascular in the final report (ICD 530–535, 578).
These two trials of primary prevention had a number of differences in their design. First, with respect to dosage and frequency of administration, the US study tested one 325 mg tablet every other day, whereas the British trial tested 500 mg of aspirin daily. The US study was double blind and placebo controlled, and the UK trial used a single-blind and open design. In the US trial, 86% in the aspirin group took the drug and 14% in the placebo group reported taking aspirin after 60.2 months of follow-up, resulting in a difference of 72% in the proportions using aspirin. In the British trial, 70% of the aspirin takers took the drug and 2% of those assigned to aspirin avoidance reported taking aspirin, resulting in a difference in the proportions using aspirin of 68% after the first 36 months of a 6-year follow-up, which is similar to the 72% seen in the US study. The most obvious difference between the two studies is in their sample sizes, with 22,071 subjects randomized in the US trial and 5,139 in the British trial. This corresponds to a large difference in the number of nonfatal MIs recorded in the two studies, but because the British doctors were older, the numbers of deaths in the two trials were similar.

An early overview of these two trials of primary prevention showed an overall 33% reduction in nonfatal MI that was highly significant (p < 0.0002) but no significant difference in total or cardiovascular mortality. That overview was based on only preliminary data from the US trial, but a repeat analysis, based on final data, gives virtually identical results, in particular, a 32% reduction in the odds of suffering a first nonfatal MI (Table 5, Figure 1).

**Side Effects**

Although the beneficial effects of aspirin on cyclooxygenase-dependent platelet aggregation may be approximately equivalent over a dose range of at least 100–1,500 mg daily, some of the main side effects are dose related. 57 The recently completed UK-TIA trial tested two daily dosages of aspirin versus placebo among 2,345 patients with a history of TCI or mild ischemic stroke. 29 It was, therefore, possible to compare directly the frequencies of side effects reported at 300 mg/day and at 1,200 mg/day (Table 6). For each category of symptom, including indigestion, nausea, or heartburn; constipation; and gastrointestinal (GI) bleed; and serious GI bleed (i.e., requiring hospital admission), the percentage of participants reporting it was lowest in the placebo group, somewhat higher in the group receiving 300 mg/day, and highest of all among those receiving 1,200 mg daily. Moreover, for symptoms of GI distress as well as for any GI bleed, the differences between the low- and high-dose groups were statistically significant. In the Physicians’ Health Study, however, which tested a regimen of 325 mg of aspirin on alternate days, such symptoms were reported by 26.1% of the active group and 25.6% of the placebo group, a nonsignificant absolute difference of only 0.5±1% of such symptoms attributable to the aspirin. This very low rate of GI discomfort attributable to aspirin, in the US study, may be partly due to the alternate-day schedule of administration that may allow the gastric mucosa to heal between doses, 58 as well as to a prerandomization run-in that excluded those unable to tolerate the drug. Even with 325 mg on alternate days, however, some gastrotoxicity may remain and, in the Physicians’ Health Study, there was a nonsignificant (0.2±0.2%) excess of peptic ulcer among those allocated aspirin. This gastrotoxicity might be further reduced by the alternate-day use of low-dose enteric-coated (instead of regular, with or without buffering) aspirin, but no results from large-scale, long-term trials of such a regimen are yet available.

**Current Knowledge of Aspirin and Cardiovascular Disease**

For secondary prevention (in patients with previous MI, stroke, or unstable angina), aspirin definitely reduces subsequent MI, stroke, and cardiovascular death and, in 1985, the US Food and Drug Administration approved the prescription labeling of aspirin for the treatment of patients with a previous myocardial infarction or unstable angina. 29 Similarly, for the treatment of suspected evolving MI, a conclusive benefit is seen for all three cardiovascular end points. 51 For primary prevention, aspirin definitely reduces the incidence of MI, but the net effect on stroke and cardiovascular death remains inconclusive due to inadequate numbers of such end points in both the US and British trials.
Unlike many other trials of primary prevention, in which it is necessary to generalize from a higher risk population to one at usual risk, the participants, particularly in the US Physicians’ Health Study, were at far lower risk of cardiovascular disease than the general population.52 Yet, even in this very healthy population, there was still a statistically definite reduction in MI. Taken together with the similar-sized percentage reduction among the high-risk subjects in the secondary prevention trials, a general conclusion that aspirin can reduce the incidence of myocardial infarction by about one third in a wide range of circumstances seems justified.

For women, there is no direct evidence of the role of aspirin in the primary prevention of cardiovascular disease. For secondary prevention, however, both the overview60 and ISIS-251 demonstrated significant protection against the various manifestations of cardiovascular disease in women, as well as men, contrary to earlier suggestions.60 It is, therefore, reasonable to hope that, at least among women who are old enough (e.g., late middle age) to be at appreciable risk of having a first MI, aspirin might be protective. But, even if a reduction in MI among women could be achieved, there is no direct evidence that the net effect on total mortality would be favorable, and the most reliable way to assess this directly would be by a large primary prevention trial among older women.

**Aspirin as an Adjunct to Management of Other Coronary Risk Factors**

It is important to view the protective effects of aspirin against MI in the context of what is already known about the effect of modification of other risk factors for cardiovascular disease. Specifically, regarding blood cholesterol, the trials of 5–7 years of treatment have, in aggregate, shown that a 10% decrease in cholesterol corresponds to an approximate 20% decrease in the incidence of coronary heart disease.61 For blood pressure, overviews of the randomized trials62,63 suggested that a 5- or 6-mm decrease in diastolic blood pressure through pharmacologic therapy among those with mild to moderate hypertension results in about a 10–15% lower risk of coronary heart disease, as well as a 40% reduction in risk of stroke, and observational epidemiologic studies suggest that a long-term difference of 5–6 mm would produce a 20–25% reduction in coronary heart disease. Finally, in middle age, cessation of cigarette smoking yields an approximate 50% decrease in risk of coronary heart disease, perhaps within only a few months of cessation.64 It would be particularly unfortunate if middle-aged smokers took aspirin instead of quitting smoking because, even if aspirin does have some effect on the risk of coronary heart disease in smokers, the reduction in coronary heart disease from quitting smoking would probably exceed any protective effect of aspirin. Further, a continuing smoker will still remain exposed to a major risk factor for stroke,65,66 cancer,66,67 and chronic lung disease.56

Thus, low-dose aspirin should be a possible adjunct, not an alternative, to coronary risk factor management and, in view of its possible side effects, should be prescribed for long-term use only by a physician or other health care provider. For primary prevention, aspirin is unlikely to be of much net benefit in young adults, except perhaps those few with genetic factors that greatly increase their risk. Among middle-aged and older adults, any decision to use aspirin should consider the cardiovascular risk profile of the patient. In most circumstances it would be reasonable to assume that aspirin will reduce nonfatal MI by about one third, with an effect that is still favorable (but probably not as large as one third) on death from coronary heart disease. No such generalization is yet possible, however, regarding the net effect on fatal or nonfatal strokes. In the primary prevention trials, the apparent effect on stroke was not favorable, perhaps because of a small number of hemorrhagic strokes, and the prescription of long-term aspirin might, therefore, be restricted to circumstances where the incidence of MI is expected to be so high that even the moderate reduction that aspirin can be expected to produce is likely to outweigh any possible adverse effect on stroke or other conditions. For secondary prevention, the decision is much easier, for among patients with a history of occlusive stroke, TCI, or coronary artery disease, aspirin definitely reduces the subsequent incidence of both stroke and MI and definitely reduces subsequent mortality. This reduction is particularly clear in acute MI. Indeed, treatment of 100 acute MI patients with 1 month of aspirin, can preclude approximately two deaths and one nonfatal event.51 But, this is also true for patients with unstable angina and for those past the acute phase; indeed, for MI patients, continuation of low dose aspirin for 1 or 2 years could probably preclude another two deaths and three nonfatal events,56 making the total avoided by early and late MI treatment equal to four fatal and four nonfatal events.51 These are substantial benefits from so simple a treatment, and the uncertainties remaining about whether or when to use antiplatelet therapy in primary prevention do not imply uncertainty regarding its value in many types of secondary prevention.

**Acknowledgments**

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