Effect of Aspirin on Vascular and Nonvascular Outcomes

Meta-analysis of Randomized Controlled Trials

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Background: The net benefit of aspirin in prevention of CVD and nonvascular events remains unclear. Our objective was to assess the impact (and safety) of aspirin on vascular and nonvascular outcomes in primary prevention.

Data Sources: MEDLINE, Cochrane Library of Clinical Trials (up to June 2011) and unpublished trial data from investigators.

Study Selection: Nine randomized placebo-controlled trials with at least 1000 participants each, reporting on cardiovascular disease (CVD), nonvascular outcomes, or death were included.

Data Extraction: Three authors abstracted data. Study-specific odds ratios (ORs) were combined using random-effects meta-analysis. Risks vs benefits were evaluated by comparing CVD risk reductions with increases in bleeding.

Results: During a mean (SD) follow-up of 6.0 (2.1) years involving over 100,000 participants, aspirin treatment reduced total CVD events by 10% (OR, 0.90; 95% CI, 0.85-0.96; number needed to treat, 120), driven primarily by reduction in nonfatal MI (OR, 0.80; 95% CI, 0.67-0.96; number needed to treat, 162). There was no significant reduction in CVD death (OR, 0.99; 95% CI, 0.85-1.15) or cancer mortality (OR, 0.93; 95% CI, 0.84-1.03), and there was increased risk of nontrivial bleeding events (OR, 1.31; 95% CI, 1.14-1.50; number needed to harm, 73). Significant heterogeneity was observed for coronary heart disease and bleeding outcomes, which could not be accounted for by major demographic or participant characteristics.

Conclusions: Despite important reductions in nonfatal MI, aspirin prophylaxis in people without prior CVD does not lead to reductions in either cardiovascular death or cancer mortality. Because the benefits are further offset by clinically important bleeding events, routine use of aspirin for primary prevention is not warranted and treatment decisions need to be considered on a case-by-case basis.


Methods

We searched the electronic databases PubMed and Cochrane Library from their inception to June 2011 using terms related to aspirin, coronary heart disease (CHD), CVD, cancer, nonvascular events, all-cause mortality, clinical trials, and primary prevention, without restriction to
end points, and details were provided of disease (PAD) were recorded as the main ease, heart failure, and peripheral arterial comes (CHD, stroke, cerebrovascular dis-
up during which CHD and/or CVD out-
ous CHD or stroke, ie, primary prevention inclusion criteria were randomized lists for additional studies. Our predefined
mented by hand-searching their reference
studies) and had at least 1 year of follow-

phy trials testing aspirin and cardiovascular outcomes or cancer outcomes
66 Citations were related to relevant primary prevention trials testing aspirin and cardiovascular outcomes or cancer outcomes
445 Articles were excluded because they were reviews or not clinical trials
14 Citations were excluded because they overlapped between databases
44 Citations tested interventions other than aspirin and therefore were excluded
11 Citations were excluded because they were not placebo-controlled trials
8 Citations were excluded because they ascertained outcomes not relevant to this meta-analysis
77 Citations were excluded because they were not primary prevention trials
17 Studies were excluded because they were not randomized controlled trials
2 Studies were identified and included through hand-searching reference lists of other citations

12 Original publications were related to aspirin in primary prevention of cardiovascular disease
54 Citations were follow-up publications related to original trials and therefore were excluded

ASPREE was ongoing study and was therefore excluded; PACE and LASAF were excluded because they did not fulfill inclusion criteria
9 Original trials were included in our meta-analysis: PHS,2,21 BDS,26 HOT,14 PPP,26 TPT,11 WHS,8 POPADAD,7 JPAD,8 and AAA9

Figure 1. Details of literature review. See Abbreviations footnote in the Table for a list of the trial names. ASPREE indicates Aspirin in Reducing Events in the Elderly; LASAF, Low-Dose Aspirin, Stroke, Atrial Fibillation; and PACE, Prevention With Low-Dose Aspirin of Cardiovascular Disease in the Elderly.

any language (Figure 1). This was supple-

bleeding events. As data on cancer and other nonvascular outcomes were generally unavailable in primary trial reports, we obtained relevant information from (1) subsequent trial reports that had published information on nonvascular events13; (2) a recent individual-participant data meta-analysis of aspirin in mixed popu-
ations1 (ie, including both primary and secondary prevention populations) and using numbers provided therein to derive data on additional end points like noncancer, nonvascular death; (3) investigators of individual studies (2 studies [Hypertension Optimal Treatment Trial [HOT]14 and Physicians’ Health Study [PHS]15] provided previously unpublished data on cancer). As nonvascular outcomes were generally reported as fatal events, risk estimates were calculated for cancer and other nonvas-
cular mortality rather than incidence. Trials that enrolled subjects with pre-existing PAD were eligible for inclusion if they had been asymptomatic for this condition and had no history of CVD. Trials of second-
ary prevention or mixed primary and sec-
dry prevention,16 pilot studies,17 and studies comparing aspirin with other an-
tiplatelet agents instead of placebo18 were excluded. In case of multiple publications from the same source, we used informa-
tion from the primary trial report unless stated otherwise. Thus, 9 trials involving 102 621 participants were eligible for the meta-analysis.

Three authors (S.W., R.S., and S.N.) independently abstracted the data (including demographic characteristics, number of participants and events, mean [or median] follow-up duration, and risk esti-
mates), and discrepancies were resolved through discussion (S.R.K.S. and K.K.R.). For studies that reported combined clinical end points and at least 1 subsidiary end point (eg, total CHD and either non-
fatal MI or fatal CHD but not both), the number of events for the missing end point were calculated by simple subtraction (or addition, as relevant), assuming that these events did not overlap. Our primary ef-
cacy end points were total CHD and total cancer mortality, with the secondary ef-
cacy end points being subtypes of vas-
cular disease, total CVD events, cause-
specific death, and all-cause mortality. Because definitions for major bleeding events varied across studies, and since participant-level data were unavailable to allow reclassification according to standard criteria,19,20 we defined a category of clinically “nontrivial” bleeding (fatal bleeding from any site; cerebrovascular or retinal bleeding; bleeding from hollow viscous; bleeding requiring hospitalization and/or transfusion; or study-defined ma-

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lulated ORs would closely approximate reported HRs. Because individual studies differed with regard to various characteristics, heterogeneity was quantified using the I² statistic, and potential sources of heterogeneity were explored by subgroup analyses and metaregression. The I² statistic measures the proportion of overall variation in effect estimates that is attributable to between-study heterogeneity. Subgroup analyses involved grouping studies according to predefined characteristics and calculating stratum-specific ORs using random-effects meta-analysis. As analyses involved aggregate (and not individual-participant) data, it was not possible to study effect-modification by various participant-level characteristics. Metaregression was used instead to explore heterogeneity, using trial-level information. Crude event rates for aspirin and control groups were calculated using data on number of events and mean follow-up time (when mean follow-up was unavailable, median duration was used instead). To contextualize net benefit due to aspirin treatment, we compared rates of any statistically meaningful associations (CVD or nonfatal MI) with rates of bleeding. Mean baseline event rates for the combined study population were estimated by pooling study-specific control event rates for each outcome using random-effects meta-analysis. Numbers needed to treat (NNT) and harm (NNH) were derived by applying pooled ORs to the mean baseline event rates for the combined study population. Values of NNT and NNH provided herein represent the number of persons that need to be treated with aspirin to prevent 1 event. Quality of follow-up time (when mean follow-up was unavailable, median duration was used instead) to avert or incur, respectively, 1 event. Mean baseline event rates for the combined study population were estimated by applying pooled ORs to the mean baseline event rates for the combined study population. Values of NNT and NNH provided herein represent the number of persons that need to be treated with aspirin for 6 years (the overall mean follow-up time in this study) to avert or incur, respectively, 1 event. Quality of studies was evaluated using a Delphi scoring system, which is based on the following: adequacy of randomization; allocation concealment; balance between randomized groups at baseline; a priori identification of inclusion criteria; presence or absence of blinding; use of intention-to-treat analyses; and reporting of point estimates and measures of variability for main outcomes. Potential publication bias was investigated using funnel plots and the Egger test. All P values reported are 2-sided; P < .05 was considered statistically significant. Statistical analyses were performed using Stata (version 10.1) software (StataCorp).

RESULTS

STUDY POPULATION

Nine good-quality randomized controlled trials of aspirin for primary prevention of CVD including 102 621 participants were eligible (Figure 1; Table; and eTable 1 [http://www.archinternmed.com]).

Most studies were conducted in Western populations and tended to include occupational groups (mainly health professionals) and patients with high cardiovascular risk. The I² statistic measures the proportion of overall variation in effect estimates that is attributable to between-study heterogeneity. Subgroup analyses involved grouping studies according to predefined characteristics and calculating stratum-specific ORs using random-effects meta-analysis. As analyses involved aggregate (and not individual-participant) data, it was not possible to study effect-modification by various participant-level characteristics. Metaregression was used instead to explore heterogeneity, using trial-level information. Crude event rates for aspirin and control groups were calculated using data on number of events and mean follow-up time (when mean follow-up was unavailable, median duration was used instead). To contextualize net benefit due to aspirin treatment, we compared rates of any statistically meaningful associations (CVD or nonfatal MI) with rates of bleeding. Mean baseline event rates for the combined study population were estimated by applying pooled ORs to the mean baseline event rates for the combined study population. Values of NNT and NNH provided herein represent the number of persons that need to be treated with aspirin for 6 years (the overall mean follow-up time in this study) to avert or incur, respectively, 1 event. Quality of studies was evaluated using a Delphi scoring system, which is based on the following: adequacy of randomization; allocation concealment; balance between randomized groups at baseline; a priori identification of inclusion criteria; presence or absence of blinding; use of intention-to-treat analyses; and reporting of point estimates and measures of variability for main outcomes. Potential publication bias was investigated using funnel plots and the Egger test. All P values reported are 2-sided; P < .05 was considered statistically significant. Statistical analyses were performed using Stata (version 10.1) software (StataCorp).

FOLLOW-UP AND EVENTS

Over a mean (SD) follow-up of 6.0 (2.1) years (approximately 700 000 person-years at-risk) in 9 studies, 2169 CHD events were accrued, of which 1540 were nonfatal MI and 592 were fatal CHD events. One study did not register any fatal MI events in the aspirin group, hence, 0.5 events were added to both treatment groups to calculate ORs. Other major outcomes included stroke (n = 1504); total CVD events (n = 4278); CVD death (n = 1285); nonvascular death (n = 2587); cancer death (n = 1512, 8 studies); non-cancer, nonvascular death (n = 983, 8 studies); all-cause mortality (n = 3895); total bleeding events (n = 40 712); and nontrivial bleeding events (n = 10 049). Pooled event rates per 1000 person-years of follow-up in people randomized to aspirin vs placebo were 4.1 vs 5.1 for nonfatal MI; 1.9 vs 1.9 for fatal MI; 7.0 vs 8.1 for total CHD; 3.8 vs 4.0 for stroke; 12.8 vs 14.1 for total CVD events; 3.9 vs 4.0 for CVD mortality; 6.6 vs 7.2 for non-CVD death; 5.3 vs 5.9 for cancer death; 3.1 vs 3.2 for noncancer, nonvascular death; 11.0 vs 11.7 for all-cause mortality; 36.0 vs 21.2 for total bleeding events; and 9.7 vs 7.4 for nontrivial bleeding events. Losses to follow-up in individual studies are summarized in eTable 2.

EFFECTS OF ASPIRIN ON VASCULAR AND NONVASCULAR OUTCOMES

Aspirin treatment was associated with a significant 10% reduction in risk of total CVD events (OR, 0.90; 95% CI, 0.85-0.96), largely owing to a 20% reduction in risk of nonfatal MI (OR, 0.86; 95% CI, 0.74-0.91) (Figure 2). There was no beneficial effect on fatal MI (OR, 0.96; 95% CI, 0.83-1.09), stroke (OR, 0.94; 95% CI, 0.84-1.06), or CVD death (OR, 0.98; 95% CI, 0.85-1.15). Modest, but nonsignificant, reductions were observed for total CHD (OR, 0.86; 95% CI, 0.74-1.01), total nonvascular mortality (OR, 0.92; 95% CI, 0.85-1.00), and all-cause mortality (OR, 0.94; 95% CI, 0.88-1.00), although there was no convincing evidence of benefit with regard to cancer mortality (OR, 0.93; 95% CI, 0.84-1.03). By contrast, there was a 70% excess risk of total bleeding events (OR, 1.70; 95% CI, 1.17-2.46) and a higher than 30% excess risk of nontrivial bleeding events (OR, 1.31; 95% CI, 1.14-1.50) in people receiving aspirin (eTable 3 contains details of definitions for bleeding). Qualitatively similar findings were observed in analyses restricted to studies of daily aspirin use (ie, after excluding Women’s Health Study [WHS] and PHS), except that the risk of nontrivial bleeding was even higher in these studies (OR, 1.48; 95% CI, 1.17-1.86; eFigure 1). Considerable heterogeneity was observed for the ORs for major efficacy and safety end points (Figure 2 and eFigure 2), which could not be explained by reported characteristics (Figure 3 and eFigures 3-5). The risk of CVD events in people treated with aspirin was, however, lower at an older age (eFigure 6), and that of nontrivial bleeding was somewhat higher at a younger age and at higher systolic blood pressure (eFigure 5). Contrary to previous reports, we did not find any statistically significant sex differences in treatment effect for total CVD events (eFigure 7). Lastly, no significant heterogeneity between studies was observed for nonvascular, cancer, and all-cause mortality (P > .10; Figure 2).

SENSITIVITY ANALYSES

The effect of aspirin on nonfatal MI or total CVD events was unrelated to
Table. Characteristics of Individual Trials Contributing to the Current Analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>Location</th>
<th>Year</th>
<th>No. of Participants</th>
<th>Age, Mean (SD), y</th>
<th>Male, %</th>
<th>Diabetes, %</th>
<th>Smokers, %</th>
<th>SBP, Mean (SD), mm Hg</th>
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<tr>
<td>BDS24</td>
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<td>5139</td>
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<td>US</td>
<td>1989</td>
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<td>100</td>
<td>2</td>
<td>11</td>
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<tr>
<td>HOT14</td>
<td>Multiple</td>
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<td>61.5</td>
<td>53</td>
<td>8</td>
<td>16</td>
<td>170</td>
</tr>
<tr>
<td>TPT25</td>
<td>UK</td>
<td>1998</td>
<td>5085</td>
<td>57.5</td>
<td>100 NS</td>
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<td>139</td>
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<tr>
<td>PPP26</td>
<td>Italy</td>
<td>2001</td>
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<td>WHS13</td>
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<td>2005</td>
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<td>13</td>
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<tr>
<td>POPADAD7</td>
<td>Scotland</td>
<td>2008</td>
<td>1276</td>
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<td>44</td>
<td>100</td>
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<td>145</td>
</tr>
<tr>
<td>JPAD8</td>
<td>Japan</td>
<td>2008</td>
<td>2539</td>
<td>64.5</td>
<td>55</td>
<td>100</td>
<td>21</td>
<td>135</td>
</tr>
<tr>
<td>AAA9</td>
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<td>2010</td>
<td>3350</td>
<td>61.6</td>
<td>28</td>
<td>3</td>
<td>32</td>
<td>147.5</td>
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<tr>
<td><strong>Total or Mean (SD)</strong></td>
<td></td>
<td></td>
<td>102,621</td>
<td>57.3 (4.1)</td>
<td>46</td>
<td>8</td>
<td>16</td>
<td>138 (17)</td>
</tr>
</tbody>
</table>

Abbreviations: AAA, Aspirin for Asymptomatic Atherosclerosis Trial; BDS, British Doctors Study; HOT, Hypertension Optimal Treatment Trial; JPAD, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes Trial; NS, not stated; PHS, Physicians’ Health Study; POPADAD, Prevention of Progression of Arterial Disease and Diabetes Trial; PPP, Primary Prevention Project; SBP, systolic blood pressure; TPT, Thrombosis Prevention Therapy Trial; WHS, Women’s Health Study.

Comparative Merits of Aspirin

The net benefit due to aspirin treatment (expressed as a difference between absolute event rates in the placebo and aspirin treatment arms) for both nonfatal MI and total CVD events increased proportionately with background event rates for these outcomes, although the benefit appeared to be more modest for CVD than nonfatal MI (Figure 4). Such benefits were offset by increased rates of nontrivial bleeding, even though for nonfatal MI there was a suggestion that at high baseline event rates there may be net benefit in favor of aspirin prophylaxis. The NNT to avoid 1 nonfatal MI event over 6 years was 162 (NNT was 120 to avert 1 CVD event over the same period). By comparison, the NNT for nonvascular death was 292 (247 for cancer death), and at least 1 nontrivial bleeding event was caused for every 73 persons treated with aspirin for approximately 6 years.

Comment

This meta-analysis provides the largest evidence to date regarding the wider effects of aspirin treatment in primary prevention and contextualizes the relevance of aspirin prophylaxis by comparing CVD risk reduction against concomitant el-
evaluation in risk of bleeding. Unlike previous studies, the findings reported herein do not suggest a protective role for aspirin against cancer mortality in people at low-to-moderate risk for CVD events. Available data also suggest that the principal cardiovascular effect of aspirin in primary prevention is on nonfatal MI with no real benefit with regard to fatal MI, stroke, or CVD death. Even these benefits are considerably offset by an elevated risk of bleeding (NNT for nonfatal MI of 73). Although our data failed to conclusively identify subgroups of participants likely to benefit from aspirin treatment, the results nevertheless suggest an increased risk of nontrivial bleeding in individuals receiving daily (vs alternate day) aspirin treatment, with a particularly unfavorable risk to benefit ratio for individuals at lower baseline CVD risk. Since it may be argued that events such as MI are potentially more serious compared with bleeding, both patients and physicians should carefully consider the relative merits of daily aspirin treatment in primary prevention.

However, modest, nonsignificant reductions in nonvascular death and all-cause mortality were observed, with questionable benefits regarding cancer mortality. Although recent evidence suggests that aspirin reduces mortality from certain cancers, this is based on information from both primary and secondary prevention studies. As background event rates for cancers and other chronic diseases may be different for participants with pre-
Figure 4. Comparison of risk vs benefit due to aspirin treatment for primary prevention of cardiovascular disease. A, Plot of absolute risk difference in relation to background (ie, placebo) event rate for main outcomes. B, Plot comparing absolute number of nontrivial bleeding events caused vs absolute number of nonfatal MI events averted. C, Plot comparing absolute number of nontrivial bleeding caused vs absolute number of total CVD events averted. In each of the panels, data points and associated labels correspond to individual studies, while straight lines represent fitted values. In panel A, the x-axis represents the background (ie, placebo) event rate for each of the outcomes of interest (nonfatal MI, total CVD, and nontrivial bleed), whereas the y-axis shows risk difference for these outcomes (total number of events averted in case of nonfatal MI and total CVD, as against total number of adverse events caused in case of nontrivial bleeding). In panels B and C, the x-axis shows the absolute number of events averted for nonfatal MI or total CVD, respectively, in each study plotted against the absolute number of nontrivial bleed events caused in the same studies. See Abbreviations footnote in the Table for a list of the trial names and reference citations.
vention advocate widespread use of aspirin in people at increased risk for CVD. Others have even suggested regular prophylaxis in people above a certain age, either singly or in combination with other agents. However, such strategies require closer scrutiny because aspirin cannot be compared with either statins or blood pressure–lowering agents with regard to its effects on CVD death. Hence, based on our findings of a marginal benefit on nonfatal MI, a nonsignificant effect on cancer death, and a significantly increased risk of clinically relevant bleeding, it is perhaps timely to re-appraise existing guidelines for aspirin use in primary prevention. Our data additionally highlight the need for more robust evidence in specific subgroups of participants, since current guidelines are based on limited evidence in different subgroups. Future studies should therefore aim to assess the impact of low-dose, alternate-day aspirin treatment on both vascular and nonvascular outcomes, especially in specific subgroups of individuals and within diverse populations. Also, owing to the relatively short mean follow-up duration reported in this meta-analysis, longer-term studies may be warranted to clarify the precise role of aspirin in cancer prevention.

Despite obvious advantages, there are important limitations to our analyses. First, we were unable to harmonize outcome definitions across studies (especially for outcomes with high heterogeneity such as bleeding) and were further unable to quantify precisely the effect of aspirin treatment in clinically relevant subgroups. Nonetheless, we combined bleeding episodes that were unlikely to be trivial and conducted subgroup analyses using available summary information. Second, as data on cancer incidence were generally unavailable from published reports, we were only able to assess the relationship between aspirin treatment and cancer mortality. Although this may have somewhat underestimated this association, it may have in fact been beneficial for study validity because estimates based on mortality, rather than incidence, are less likely to be affected by ascertainment bias.

Third, the effect of aspirin on cancer mortality could be evaluated using information from only 8 of 9 studies. Nevertheless, these results are fairly robust because the majority of primary prevention trials of aspirin were included in our analyses. Fourth, as we studied the effect of aspirin on multiple outcomes, some of the associations may be due to chance alone. However, as the risk estimates were largely consistent with previous reports, the scope of any artifactual associations is likely to be limited. Lastly, as most studies were performed in occupational groups in Western populations, findings of this meta-analysis may not be entirely generalizable.

In conclusion, we found rather modest benefits of aspirin treatment on nonfatal MI and total CVD events in primary prevention, while the effect on cancer mortality was nonsignificant. Because the benefits of aspirin treatment were accompanied by a significant increase in risk of bleeding, further study is needed to identify subsets of participant having favorable ratio to benefit for aspirin use in primary prevention and/or involving more high-risk participants. In the absence of such information, a reappraisal of current guidelines appears to be warranted, particularly in countries where a large number of otherwise healthy adults are prescribed aspirin, since a significant proportion of them may develop bleeding complications.

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Author Contributions: Drs Seshasai and Ray had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Seshasai and Ray. Acquisition of data: Seshasai, Wijesuriya, Sivakumaran, Nethercott, and Ray. Analysis and interpretation of data: Seshasai, Wijesuriya, Sivakumaran, Nethercott, Erqou, Satter, and Ray. Drafting of the manuscript: Seshasai and Ray. Critical revision of the manuscript for important intellectual content: Seshasai, Wijesuriya, Sivakumaran, Nethercott, Erqou, Satter, and Ray. Statistical analysis: Seshasai and Erqou. Study supervision: Seshasai, Satter, and Ray.

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REFERENCES

Aspirin Therapy in Primary Prevention

To Use or Not to Use?

The use of aspirin in medicine dates as far back as Hippocrates who found analgesic effects for the extract (salicin) of white willow bark. 1 Aspirin irreversibly inactivates platelet cyclooxygenase, preventing platelets from synthesizing thromboxane A2, a potent vasoconstrictor and promoter of platelet aggregation. Aspirin also has anti-inflammatory and vasodilatory effects that may be important.


33. British Cardiac Society; British Hypertension Society; Diabetes UK; HEART UK; Primary Care Cardiovascular Society; Stroke Association. JBS 2: Joint British Societies’ guidelines on prevention of cardiovascular disease in clinical practice. Heart. 2005;91(Suppl 5):v5-s2.


INVITED COMMENTARY