**Aspirin Therapy in Women**

**Back to the ABCs**

Samia Mora, MD, MHS

Comprehensive risk-factor management is the cornerstone of therapy in women and men with known cardiovascular disease (CVD). Therapeutic interventions can be summarized in an “ABC” format (Table).\(^1\)\(^2\)\(^3\) CVD death rates have declined in men and older women during the past decade.\(^4\) By contrast, there has been a significant rise in CVD deaths among younger women.\(^5\) Evidence-based therapies, including aspirin use, have been believed to account for half of the decline in CVD death rates, whereas improvement in risk factors, including lower cholesterol and blood pressure, accounts for the other half.\(^6\)

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The use of aspirin in medicine dates at least as far back as Hippocrates, who found analgesic effects for the extract (salicin) of white willow bark.\(^7\) Aspirin irreversibly inactivates platelet cyclooxygenase, preventing platelets from synthesizing thromboxane A\(_2\), a potent vasoconstrictor and promoter of platelet aggregation. Aspirin also has anti-inflammatory and vasodilatory effects that may be important.

Over the past 3 decades, aspirin has been shown to decrease the risk of CVD events and mortality in clinical trials of men and women with CVD.\(^8\) The latest meta-analysis by the Antiplatelet Trialists’ collaboration in 2002 analyzed \(\sim 135,000\) patients with CVD. Compared with placebo, antiplatelet therapy (mostly aspirin) resulted in a relative risk reduction of about one quarter for CVD events, one third for nonfatal myocardial infarction, one quarter for stroke, and 15% for CVD mortality.\(^9\) Antiplatelet therapy reduced the relative risk of ischemic stroke by 30% but increased the relative risk of hemorrhagic stroke by 22%.\(^9\) Because ischemic stroke was more common than hemorrhagic stroke, the absolute benefit was greater than the absolute risk of antiplatelet therapy, with a net relative risk reduction of total stroke by 22%. In 3 trials (\(N=3570\)) that directly compared a dose \(\geq 75\) mg daily versus \(< 75\) mg, there was no statistically significant difference between the doses. Aspirin doses of 75 to 150 mg had as much benefit as higher doses (160 to 1500 mg). Insufficient data were available on those treated with \(< 75\) mg to provide definitive recommendations on the use of \(< 75\) mg daily.\(^9\)

One limitation of the 2002 meta-analysis is the lack of sex-specific or age-specific subgroup data. In the previous 1994 meta-analysis by the Antiplatelet Trialists, sex-specific data were analyzed from 29 trials with \(\sim 40,000\) men and \(\sim 10,000\) women with known CVD.\(^8\) Women derived as much benefit as did men from aspirin.\(^8\)

In patients without known CVD, the picture is less clear. In the primary prevention setting, aspirin reduces the risk of myocardial infarction but not stroke in men, and reduces the risk of stroke but not myocardial infarction in women.\(^10\)\(^11\) There has been little or no benefit for aspirin in reducing death (CVD or all cause) in men or women without known CVD. Aspirin did not prevent CVD in asymptomatic Japanese patients with diabetes in the primary prevention setting unless they were age 65 or older.\(^12\) Guidelines recommend using aspirin for primary prevention in higher risk men and women who have increased event rates and a greater benefit-to-risk ratio.\(^13\)

In this issue of *Circulation: Cardiovascular Quality and Outcomes*, Berger et al\(^14\) examined aspirin use and dose in relation to clinical outcomes in 8928 postmenopausal women with known CVD followed up for 6.5 years in the Women’s Health Initiative (WHI) Observational Study. After controlling for potential confounders, women who reported taking aspirin had lower rates of all-cause mortality compared with women who did not take aspirin (hazard ratio 0.73; 95% confidence interval 0.60 to 0.89). Women who took aspirin at lower doses had a similar benefit compared with women who took aspirin at higher doses (hazard ratio 0.74; 95% confidence interval 0.59 to 0.93).

### Table. ABCs of CVD Therapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>A</th>
<th>Antiplatelet agents</th>
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<tbody>
<tr>
<td>B</td>
<td>Antianginal agents</td>
<td></td>
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<tr>
<td>C</td>
<td>ACEI/ARBs</td>
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<tr>
<td>D</td>
<td>Blood pressure control</td>
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<td>E</td>
<td>Cholesterol management</td>
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<td>F</td>
<td>Cigarette smoking cessation</td>
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<td>G</td>
<td>Diet/weight management</td>
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<td>H</td>
<td>Diabetes prevention/management</td>
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<tr>
<td>I</td>
<td>Exercise/rehabilitation</td>
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<tr>
<td>J</td>
<td>Ejection fraction</td>
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</tr>
<tr>
<td>K</td>
<td>Fish ((\omega-3)) oils</td>
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</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.
aspirin at least 3 times a week had significant risk reductions in all-cause death (14%) and CVD death (25%) compared with nonusers. There was also a 10% risk reduction in composite CVD events (including nonfatal myocardial infarction) that did not reach statistical significance. An aspirin dose of 81 mg was comparable with 325 mg for preventing clinical events in 2072 women who were matched on risk factors and other potential confounders.

Although the present WHI study is an observational study, it adds to previous findings from randomized clinical trials. The use of propensity scores to control for confounding may not completely balance unmeasured confounders as would randomization in a clinical trial, but it may reduce confounding when determinants of drug use are multifactorial, as in the case of aspirin. The magnitude of the benefit associated with aspirin use was similar to the estimates obtained from meta-analyses of clinical trials, as was the consistency of benefit with lower versus higher doses of aspirin for preventing clinical outcomes.

Finally, the most striking finding of this WHI study is the low use of aspirin and other proven therapies in community women with known CVD (1994–1998). Less than 1 in 2 women in the study were taking aspirin, and rates were lower in black women and those with Medicare insurance. Statin and β-blocker use in the study was even lower than aspirin, with <1 in 4 women taking statins or β-blockers, a rate similar to their use of nonsteroidal anti-inflammatory drugs.

We learned from the WHI and Heart and Estrogen/Progestin Replacement Study randomized clinical trials that estrogen and progestereone therapy did not confer cardiovascular protection and may increase CVD risk in postmenopausal women. An observational study is that lifesaving therapies, including aspirin, β-blockers, and statins, continue to be substantially underused in postmenopausal women with known CVD. Our greatest challenge remains the wider implementation of the ABCs of CVD treatment and prevention in both men and women.

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Disclosures
None.

References


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