Aspirin Use, Dose, and Clinical Outcomes in Postmenopausal Women With Stable Cardiovascular Disease
The Women's Health Initiative Observational Study

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Background—Despite compelling evidence that aspirin reduces fatal and nonfatal vascular events among the overall population in various settings, women have frequently been underrepresented and their data underreported. We sought to evaluate the relationship between aspirin use, dose (81 or 325 mg), and clinical outcomes among postmenopausal women with stable cardiovascular disease (CVD).

Methods and Results—Women with CVD (n=8928) enrolled in the Women’s Health Initiative Observational Study were used for this analysis. The primary outcome was the incidence of all-cause mortality and cardiovascular events (myocardial infarction, stroke, and cardiovascular death).

Among 8928 women with stable CVD, 4101 (46%) reported taking aspirin, of whom 30% were on 81 mg and 70% were on 325 mg. At 6.5 years of follow-up, no significant association was noted for aspirin use and all-cause mortality or cardiovascular events. However, after multivariate adjustment, aspirin use was associated with a significantly lower all-cause (adjusted hazard ratio, 0.86 [0.75 to 0.99]; \( P=0.04 \)) and cardiovascular-related mortality (adjusted hazard ratio, 0.75 [0.60 to 0.95]; \( P=0.01 \)) compared with no aspirin. Aspirin use was associated with a lower risk of cardiovascular events (adjusted hazard ratio, 0.90 [0.78 to 1.04]; \( P=0.14 \)), which did not meet statistical significance. Compared with 325 mg, use of 81 mg was not significantly different for all-cause mortality, cardiovascular events, or any individual end point.

Conclusions—After multivariate adjustment, aspirin use was associated with significantly lower risk of all-cause mortality, specifically, cardiovascular mortality, among postmenopausal women with stable CVD. No significant difference was noted between 81 mg and 325 mg of aspirin. Overall, aspirin use was low in this cohort of women with stable CVD. (Circ Cardiovasc Qual Outcomes. 2009;2:78-87.)

Key Words: aspirin ■ dose ■ women ■ cardiovascular disease ■ drugs ■ mortality ■ observational study

Randomized studies of patients with cardiovascular disease (CVD) provide compelling evidence that antiplatelet therapy reduces morbidity and mortality.1,2 Accordingly, evidence-based guidelines strongly advocate aspirin for the secondary prevention of cardiovascular events.3,4 However, the effect of aspirin in women with stable CVD has not been fully evaluated. Among 278 trials included in the Antiplatelet Trialists’ Collaboration, 34 trials evaluated a population with stable CVD (prior myocardial infarction, stroke/transient ischemic attack [TIA], or stable angina), and only 6 trials evaluated low-dose aspirin (50 to 325 mg) versus placebo/control, some of which excluded women or only included a minority of women.5

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The dose of aspirin used for secondary prevention of adverse cardiac events varies.6,7 A meta-analysis found a similar reduction of cardiac adverse events for doses 75 to

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150 mg and 160 to 325 mg.\textsuperscript{1,2} A more recent analysis of the same data among unstable patients documented a greater benefit with lower doses of aspirin.\textsuperscript{6} Consistent with the uncertainty of optimal aspirin dose, guidelines tend to differ.\textsuperscript{4,9} The American Heart Association/American College of Cardiology guidelines for secondary prevention recommend aspirin (75 to 162 mg) in all patients unless contraindicated. The recent American Heart Association guidelines for CVD prevention in women support aspirin (75 to 325 mg) in women with established CVD. Despite the increased recent attention to aspirin dose, little is known about aspirin dose in women with stable CVD.

The purpose of this study was 3-fold: first, to define the utilization of aspirin among postmenopausal women with CVD in the Women’s Health Initiative (WHI) Observational Cohort; second, to determine the association between aspirin use, all-cause mortality, and other cardiovascular events; and finally, to evaluate the relationship between aspirin dose (81 mg versus 325 mg) and clinical outcomes.

**Summary**

- Among postmenopausal women with stable cardiovascular disease, aspirin use was reported in 46% of the population.
- Among aspirin users, 30% were on 81 mg and 70% were on 325 mg.
- Underutilization was most pronounced in blacks and women with Medicaid insurance.
- After multivariate adjustment, aspirin use was associated with a significantly lower risk of all-cause (hazard ratio, 0.86 [0.75 to 0.99]; \( P = 0.04 \)) and cardiovascular-related mortality (hazard ratio, 0.75 [0.60 to 0.95]; \( P = 0.01 \)).
- Aspirin use was not associated with a significant lowering of the composite end point (myocardial infarction, stroke, or cardiovascular death) (hazard ratio, 0.90 [0.78 to 1.04]; \( P = 0.14 \)).
- Compared with 325 mg, use of 81 mg was not significantly different for all-cause mortality, cardiovascular events, or any individual end point.

**Methods**

**Study Population**

As described elsewhere,\textsuperscript{10} the WHI has clinical trial and observational study (OS) components. The latter component is an ongoing, nationwide, prospective cohort study of postmenopausal women of diverse races and ethnicities and is designed to examine the association between clinical, socioeconomic, behavioral, and dietary risk factors and the subsequent incidence of several health outcomes. The WHI-OS cohort consists of 93 676 women between 50 and 79 years of age enrolled at 40 clinical centers throughout the United States between 1994 and 1998. The study was approved by the institutional review boards of the participating clinical centers, the coordinating center at the Fred Hutchinson Cancer Center, and the National Institutes of Health. Participants gave written informed consent. The design and reliability of baseline measures have been published in detail previously.\textsuperscript{11}

Among WHI-OS participants, 8928 had a history of stable CVD, defined by one or more of the following conditions at baseline:

- previous myocardial infarction
- previous stroke/TIA
- previous or current angina
- a history of coronary revascularization

**Measurement of Exposure**

Aspirin use was assessed from an interview-administered questionnaire. Each participant was asked: “Do you take aspirin pills or powders, ibuprofen pills or tablets, other nonsteroidal antiinflammatory drug pills (including prescription drugs), or acetaminophen tablets or capsules?” Those individuals who reported using aspirin at least three weeks in each of the 2 weeks preceding the interview were considered aspirin users. Details of their aspirin use including type of compound and strength (in milligrams) were recorded. The medication data were validated by checking pill-bottle labels and prescription records during the interview process. For the current analysis, women reporting 81 mg, 325 mg, and no aspirin (as the reference category) were included. Women who reported use of 120 to 300 mg (\( n = 86, 0.9\% \)) or >325 mg (\( n = 208, 2.2\% \)) were excluded from this analysis.

**Follow-Up**

As of February 2004, the mean duration of follow-up was 6.5 years (SD, 1.6 years; range, 0.1 to 9.3 years). Vital status was available for 98.2% of respondents. Participant fatalities were identified through communication with proxy respondents and through National Death Index searches. Deaths caused by coronary disease were confirmed on the basis of death certificates, autopsy reports, circumstances of death, ECG, laboratory test results, and reports from all relevant procedures. Participants are sent annual medical update forms to report the occurrence of any hospitalization and a wide variety of outcomes, including myocardial infarction. Confirmation of self-reported nonfatal myocardial infarction was based on adjudication by trained physicians of documentation of new chest-pain syndromes accompanied by characteristic evolution of electrocardiographic changes or myocyte damage as evidenced by elevated creatine kinase–MB or troponin values. Stroke diagnosis was based on the rapid onset of a persistent neurological deficit attributable to an obstruction or rupture of the arterial system supported by imaging studies when available. The neurological deficit must have lasted more than 24 hours, unless death supervened or there was a demonstrable radiographic lesion compatible with acute stroke.

**Statistical Analysis**

Differences between aspirin users (81 and 325 mg) and nonusers were compared using \( \chi^2 \) statistics for categorical variables and \( t \) test or ANOVA, as appropriate, for continuous variables. Aspirin use was related to all-cause mortality and cardiovascular end points using univariable and multivariable Cox proportional hazard regression analyses with inclusion of clinically plausible interactions. Outcome comparisons were made from Cox proportional hazards analyses and Kaplan-Meier curves.

Important subgroups were prespecified. To examine whether the effect of aspirin varied between subgroups, we constructed Cox models with a group of core variables (age, race, education, last medical visit within 1 year, insurance status, hormone replacement therapy, smoking status, body mass index, statin use, \( \beta \)-blocker use, nonsteroidal antiinflammatory drug use, and history of myocardial infarction, TIA, stroke, angina, peripheral artery disease, coronary revascularization, diabetes, and hypertension), treatment subgroup, and the interaction between subgroup and treatment; we then evaluated the interaction terms one at a time, for statistical significance.

Because aspirin use was not randomly assigned, potential confounding and selection biases were accounted for by developing a propensity score for aspirin use.\textsuperscript{12,13} The propensity for aspirin use was determined without regard to outcome, using multivariable logistic regression analysis. A full nonparsimonious model was developed that included 32 covariates. A propensity score for aspirin use was then calculated from the logistic equation for each patient. We then sought to match each aspirin user to a nonusing patient who had a propensity score that was identical to 5 digits. If this could not
be done, we then proceeded to a 4, 3, 2, or 1 digit match. We were able to match 2646 aspirin-using patients to 2646 unique nonaspirin-using patients.

A second propensity model to evaluate the effect of aspirin dose was created only among aspirin users. In this analysis, we generated separate propensity scores for the use of 81 mg of aspirin. We then sought to match each user of 81 mg to a user of 325 mg. We were able to match 1036 users of 81 mg to 1036 users of 325 mg. Kaplan-Meier methods were then used in these cohorts to estimate the unadjusted event rates, and log-rank tests were used to formally compare the groups.

All analyses were conducted by use of Statistical Analysis Software.

Statement of Responsibility
The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Baseline Characteristics
Among 8928 postmenopausal women with CVD, 4101 (46%) reported taking aspirin. Of the aspirin users, 1224 (30%) were on 81 mg and 2877 (70%) were on 325 mg. Among women with a history of myocardial infarction, TIA, prior revascularization, stroke, and angina, the rate of aspirin use was 54%, 43%, 50%, 71%, and 44%, respectively. Baseline characteristics according to aspirin use and dose are summarized in Table 1.

Predictors of Aspirin Use and Dose
Clinical predictors of aspirin use included prior revascularization (3.08 [2.68 to 3.55]), hypercholesterolemia (1.27 [1.10 to 1.46]), treated hypertension (1.18 [1.05 to 1.33]), previous myocardial infarction (1.18 [1.04 to 1.33]), prior TIA (1.41 [1.23 to 1.61]), statin treatment (1.40 [1.19 to 1.65]), and β-blocker therapy (1.54 [1.36 to 1.74]). Demographic predictors of aspirin use included increasing age per year (1.02 [1.01 to 1.03]) and college education (1.25 [1.01 to 1.55]). Negative predictors of aspirin use included black race (0.70 [0.59 to 0.83]), Medicaid insurance (0.59 [0.45 to 0.77]), increasing body mass index (0.98 [0.98 to 0.99]), and nonsteroidal antiinflammatory drug use (0.86 [0.76 to 0.97]).

Women who were older and more educated were more frequently on 81 mg. A history of myocardial infarction, prior revascularization, β-blocker use, and increasing body mass index were predictors for 325 mg. Race and insurance type were not associated with aspirin dose.

Aspirin Use, All-Cause Mortality, and Cardiovascular Outcomes
During an average of 6.5 years of follow-up, 956 participants (10.7%) died. Table 2 summarizes all outcomes based on aspirin use and dose. After multivariable adjustment, aspirin was associated with a 14% decrease in the risk of all-cause mortality (hazard ratio [HR], 0.86 [0.75 to 0.99]) (Figure 1). A composite of adverse cardiovascular events occurred in 969 (10.8%) women during follow-up. After multivariable adjustment, aspirin was associated with a nonsignificant decrease in cardiovascular events (HR, 0.90 [0.78 to 1.04]). However, aspirin was associated with a 25% significantly lower risk of cardiovascular mortality (HR, 0.75 [0.60 to 0.95]).

Subgroup Analyses
Several characteristics of the participants were examined for possible interaction with the use of aspirin and the risk of all-cause mortality (Figure 2). No significant interaction was observed between age, race, smoking status, statin use, β-blocker use, and nonsteroidal antiinflammatory drug use. Women on current hormonal therapy appeared to have the greatest mortality benefit with aspirin therapy (P for interaction, <0.01). Possible interaction with aspirin use and the composite of adverse cardiovascular events were also assessed (Figure 2). For women of ages 50 to 59, 60 to 69, and 70 to 79 years, the HRs for the composite of adverse cardiovascular events associated with age were 1.09, 1.01, and 0.77, respectively (P for interaction, 0.02).

Aspirin Use in Propensity-Matched Patients
To better adjust for the baseline imbalances between groups, patients were matched on the basis of propensity score for aspirin use in a 1-to-1 fashion. This limited the analysis to 5292 patients. These patients were well matched on the basis of baseline characteristics with no significant differences between users and nonusers of aspirin (data not shown). Figure 3 illustrates survival curves in both groups. Overall, there were 565 deaths (10.7%). Aspirin use was associated with a significantly lower all-cause mortality (9.8% versus 11.5%, P=0.045). Aspirin use was associated with a lower composite of cardiovascular adverse events, which was not statistically significant (10.1% versus 11.3%, P=0.142). For the individual end points, aspirin therapy was associated with a significantly lower cardiovascular mortality with no significant lowering in the risk of myocardial infarction or stroke.

Aspirin Dose in Propensity-Matched Patients
To investigate aspirin dose, a second propensity analysis was performed. We matched 1036 users of 81 mg to 1036 users of 325 mg. Baseline variables were similar between groups (data not shown). Figure 4 illustrates survival curves in both groups. No significant difference in mortality or cardiovascular events was noted between patients with 81- and 325-mg doses.

Discussion
This analysis produced 3 major findings. First is the observation that only 46% of women with preexisting CVD reported aspirin use. A regression model identified clinical, demographic, and socioeconomic factors as positive and negative predictors for use of therapy. Second, aspirin use is associated with a reduction in all-cause and cardiovascular mortality. Third, no significant difference in any clinical outcome is noted between 81 and 325 mg of aspirin.

Aspirin Use
In total, 46% of postmenopausal women with CVD were taking aspirin. Thus, a considerable percentage of women remain at an increased risk for adverse outcomes. Our
findings are consistent with previous reports of underutilization of aspirin among patients with CVD.13–22

Prior studies14–23 demonstrated a wide range of aspirin utilization (25% to 80%). Studies in community settings such as this one have demonstrated lower rates21,22 compared with studies in the hospitalization or posthospitalization period.14,16–20 The present study is unique because it focuses on postmenopausal women with CVD. Because the WHI-OS population is large and diverse and assesses the use of medication in the primary care setting, it provides information of adherence patterns across the United States.

As with other studies,14–16,18–22 aspirin use was not uniform across subpopulations. Positive predictors of aspirin use included increasing age and college education. Independent negative predictors of aspirin use were black race and Medicaid insurance. Although past studies have noted aspirin use was lower in older patients,15,22 this study found a positive association between age and aspirin utilization. Consistent with prior studies on educational status and CVD,24,25 higher education was associated with use of aspirin. The lower utilization of aspirin among blacks and patients with Medicaid insurance is consistent with the observation that minorities and socioeconomically disadvantaged populations receive less-aggressive treatment of CVD.26,27 However, one must be mindful that many differences in treatment may result from unmeasured issues such as differences in patient preferences, communication patterns between clinicians and patients, or clinician practice bias, all of which may influence patterns of care.

Table 1. Baseline Differences for Women With CVD According to Aspirin Dose

<table>
<thead>
<tr>
<th>Demographics</th>
<th>No Aspirin (n=4827)</th>
<th>81 mg (n=1224)</th>
<th>325 mg (n=2877)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66±7</td>
<td>68±6</td>
<td>68±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤60</td>
<td>23</td>
<td>12</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>77</td>
<td>88</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>75</td>
<td>83</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>16</td>
<td>9.0</td>
<td>9.8</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9.6</td>
<td>7.8</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29±6</td>
<td>28±6</td>
<td>28±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤25</td>
<td>28</td>
<td>34</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>25–30</td>
<td>38</td>
<td>35</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>31</td>
<td>30</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>15</td>
<td>14</td>
<td>16</td>
<td>0.334</td>
</tr>
<tr>
<td>Hypertension</td>
<td>58</td>
<td>60</td>
<td>63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>132±19</td>
<td>132±19</td>
<td>133±19</td>
<td>0.022</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>75±10</td>
<td>72±10</td>
<td>73±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>28</td>
<td>45</td>
<td>43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>16</td>
<td>13</td>
<td>15</td>
<td>0.052</td>
</tr>
<tr>
<td>TIA</td>
<td>24</td>
<td>27</td>
<td>25</td>
<td>0.032</td>
</tr>
<tr>
<td>Angina</td>
<td>63</td>
<td>60</td>
<td>57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>21</td>
<td>26</td>
<td>31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percutaneous revascularization</td>
<td>6.3</td>
<td>17</td>
<td>21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bypass surgery</td>
<td>5.1</td>
<td>13</td>
<td>16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAD</td>
<td>8.3</td>
<td>8.1</td>
<td>9.3</td>
<td>0.301</td>
</tr>
<tr>
<td>CHF</td>
<td>6.4</td>
<td>5.3</td>
<td>5.8</td>
<td>0.250</td>
</tr>
<tr>
<td>Hormone use ever</td>
<td></td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Past user</td>
<td>27</td>
<td>27</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Current user</td>
<td>39</td>
<td>44</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Social history</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>0.013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>48</td>
<td>47</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Past smoker</td>
<td>44</td>
<td>47</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>7.9</td>
<td>5.7</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>&gt;7 Alcoholic drinks/week</td>
<td>8.0</td>
<td>10</td>
<td>10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Last medical visit within 1 year</td>
<td>89</td>
<td>93</td>
<td>92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any insurance</td>
<td>96</td>
<td>98</td>
<td>97</td>
<td>0.001</td>
</tr>
<tr>
<td>Medicaid</td>
<td>5.5</td>
<td>2.3</td>
<td>2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medicare</td>
<td>54</td>
<td>63</td>
<td>62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Military/VA</td>
<td>2.9</td>
<td>2.2</td>
<td>3.0</td>
<td>0.389</td>
</tr>
<tr>
<td>Region</td>
<td>&lt;0.001</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>22</td>
<td>26</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>28</td>
<td>22</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>21</td>
<td>20</td>
<td>24</td>
<td></td>
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<tr>
<td>West</td>
<td>29</td>
<td>32</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Clinical Outcomes According to Aspirin Use and Dose

<table>
<thead>
<tr>
<th>Clinical Outcomes, %</th>
<th>No Aspirin (n=4827)</th>
<th>75 to 81 mg (n=1224)</th>
<th>325 mg (n=2877)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>10.9</td>
<td>9.9</td>
<td>10.7</td>
<td>0.566</td>
</tr>
<tr>
<td>Cardiovascular composite*</td>
<td>10.3</td>
<td>11.0</td>
<td>11.7</td>
<td>0.186</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5.5</td>
<td>6.5</td>
<td>7.3</td>
<td>0.005</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.3</td>
<td>4.1</td>
<td>4.5</td>
<td>0.818</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>4.3</td>
<td>4.0</td>
<td>4.3</td>
<td>0.876</td>
</tr>
</tbody>
</table>

*Myocardial infarction, stroke, or cardiovascular mortality.
Efficacy of Aspirin

Previous analyses demonstrated that antiplatelet therapy prevents adverse events across many patient subgroups.1,2,5 Women and men had a 33% and 37% reduction in cardiovascular events, respectively. However, these results were found when combining all antiplatelet medications and when grouping stable and unstable CVD. There is little data on aspirin in women with stable CVD.

In unadjusted analyses, no significant difference was detected between aspirin use and mortality or a composite of cardiovascular events. However, this null effect appeared to be due to the fact that those receiving treatment were at substantially higher risk for recurrence; after full adjustment for confounding variables, we demonstrated that aspirin use was associated with a significantly lower risk of all-cause mortality among women with stable CVD.
Subsequently, we performed a propensity analysis to further adjust for potential confounders and selection biases,\textsuperscript{12,13} which demonstrated a similar lowering in the risk of death. No subgroup of women except those on current hormone replacement therapy had evidence of a risk of all-cause mortality with aspirin that differed significantly from that observed for all women, and the findings related to hormone replacement therapy may have been due to chance. Alternatively, by inhibiting the postmenopausal hormone-induced increase in C-reactive protein\textsuperscript{28} or thrombosis risk,\textsuperscript{29} aspirin may be additionally protective in this population.

This study also noted a nonsignificant decrease in the composite of cardiovascular adverse events. In subgroup analyses, older women were noted to have the greatest benefit with aspirin use ($P$ for interaction, 0.02), a finding consistent with the Women’s Health Study.\textsuperscript{30} Although aspirin use was associated with a significantly lower cardiovascular mortality, no association was noted for myocardial infarction or stroke. Several possible explanations exist. First, aspirin may exert its greatest effect on fatal vascular events.\textsuperscript{7} Second, data from primary prevention studies suggest that aspirin may not be effective in reducing the risk of myocardial infarction in women.\textsuperscript{30,31}

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
\textbf{Variables} & \textbf{N} & \textbf{HR (95\%CI)} & \textbf{P for Interaction} \\
\hline
\textbf{All-Cause Mortality} & & & \\
Overall & 7894 & 0.86 (0.75-0.99) & 0.69 \\
Age & & & \\
50-59 & 1530 & 0.73 (0.43-1.22) & 0.69 \\
60-69 & 3653 & 0.89 (0.71-1.13) & 0.69 \\
70-79 & 2711 & 0.88 (0.72-1.08) & 0.69 \\
Race & & & \\
White & 6383 & 0.85 (0.72-0.99) & 0.10 \\
Black & 915 & 1.25 (0.82-1.90) & 0.10 \\
Smoking & & & \\
Never & 3733 & 0.73 (0.58-0.93) & 0.47 \\
Past & 3614 & 0.99 (0.81-1.20) & 0.47 \\
Current & 547 & 0.84 (0.54-1.33) & 0.47 \\
Hormone use & & & \\
Never & 3451 & 1.04 (0.85-1.27) & <0.01 \\
Past & 1474 & 0.82 (0.59-1.15) & <0.01 \\
Current & 2969 & 0.63 (0.48-0.82) & <0.01 \\
NSAID & No & 6283 & 0.84 (0.73-1.01) & 0.31 \\
Yes & 1611 & 0.98 (0.69-1.38) & 0.31 \\
Statin & No & 6083 & 0.92 (0.78-1.08) & 0.10 \\
Yes & 1811 & 0.64 (0.46-0.89) & 0.10 \\
β-Blocker & No & 6004 & 0.86 (0.72-0.99) & 0.84 \\
Yes & 1890 & 0.88 (0.65-1.19) & 0.84 \\
\hline
\textbf{Cardiovascular Composite} & & & \\
Overall & 7894 & 0.90 (0.78-1.04) & 0.02 \\
Age & & & \\
50-59 & 1530 & 1.09 (0.72-1.66) & 0.02 \\
60-69 & 3653 & 1.01 (0.81-1.27) & 0.02 \\
70-79 & 2711 & 0.77 (0.62-0.95) & 0.02 \\
Race & & & \\
White & 6383 & 0.87 (0.75-1.02) & 0.53 \\
Black & 915 & 1.13 (0.73-1.73) & 0.53 \\
Smoking & & & \\
Never & 3733 & 0.89 (0.71-1.11) & 0.87 \\
Past & 3614 & 0.91 (0.75-1.12) & 0.87 \\
Current & 547 & 1.02 (0.63-1.64) & 0.87 \\
Hormone use & & & \\
Never & 3451 & 0.85 (0.70-1.04) & 0.47 \\
Past & 1474 & 0.98 (0.71-1.35) & 0.47 \\
Current & 2969 & 0.94 (0.72-1.21) & 0.47 \\
NSAID & No & 6283 & 0.88 (0.75-1.03) & 0.98 \\
Yes & 1611 & 0.93 (0.68-1.27) & 0.98 \\
Statin & No & 6083 & 0.95 (0.81-1.12) & 0.13 \\
Yes & 1811 & 0.73 (0.54-0.97) & 0.13 \\
β-Blocker & No & 6004 & 0.88 (0.74-1.10) & 0.60 \\
Yes & 1890 & 0.93 (0.70-1.23) & 0.60 \\
\hline
\end{tabular}
\caption{Subgroup analyses according to aspirin use.}
\end{table}
Third, our data may be consistent with the nonsignificant effect of aspirin for preventing cardiovascular events in women without CVD, as noted in the Women’s Health Study.30 Finally, several studies have suggested a reduced effect of aspirin among women compared with men.32,33

Our study is unique because it focused on a population of postmenopausal women with CVD. Previous randomized trials of aspirin that included women34,35 were unable to identify any significant effect of aspirin use on mortality. However, women were underrepresented in trial enrollment, and therefore the studies were underpowered. Two previous observational analyses36,37 demonstrated reduced mortality rates with aspirin in women with known or suspected coronary disease. The current study extends these previous findings in several respects. First, we included all postmenopausal women with stable CVD, not just women with coronary disease. Second, women enrolled in our study were older than in prior studies. This is important, because many studies have noted that older women are less likely to receive standard-of-care-level treatment.18,19,38 Of note, our study demonstrated that older women had the greatest benefit with aspirin treatment. Third, our cohort was drawn from 40 clinical centers across the United States, representing diverse community practice.

**Aspirin Dose**

The ideal dose of aspirin for the prevention of vascular events has been the subject of much debate.6,7 Studies comparing the dose effect of aspirin noted increased bleeding complications with higher doses, whereas no differences were observed in effectiveness.6,39–41 Other reports have presented conflicting results. Quinn et al42 demonstrated a decreased rate of myocardial infarction with a higher dose (325 mg) of aspirin, whereas other studies found that a lower dose (81 mg) is associated with a lower risk of cardiovascular complications.7,43 No previous study evaluated the optimal aspirin dose among women. In the current study, we observed no significant difference in any clinical outcome among women reporting 81 or 325 mg of aspirin use.

**Limitations**

When interpreting the results of our study, several limitations need to be kept in mind. First, aspirin use was not determined by randomized assignment, and therefore is subject to the inherent limitations in any observational study design. However, recent work has suggested that observational studies, if properly done, may expand the evidence base for therapy.44 Moreover, we used a propensity analysis to minimize the potential for residual con-
founding around aspirin use. Second, there is a potential for aspirin use to be underreported by participants because of its availability at low cost without a prescription. However, this was unlikely a major problem, because all women were asked to bring in prescription, nonprescription, and all over-the-counter medications at study enrollment. Third, there is potential that participants were on other antiplatelet or antithrombotic medications that we did not assess. Fourth, all women studied were postmenopausal and self-enrolled in a cohort study, which may not be generalizable to premenopausal women or women who would not enroll in a clinical study. Other limitations of our study include lack of information about aspirin allergy, duration of treatment, contraindications, and side effects.

Conclusions

Although the influence of unmeasured confounders cannot be ruled out, we found that aspirin therapy was associated with a significantly lower risk of all-cause mortality and cardiovascular mortality, raising the hypothesis that aspirin may improve survival in postmenopausal women with stable CVD. No significant difference in dose (81 mg versus 325 mg) was noted for any of the clinical outcomes measured. In addition, aspirin use was low among women with CVD. This underutilization was most pronounced in blacks and women with Medicaid insurance.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Among 8928 postmenopausal women with stable cardiovascular disease enrolled in the Women's Health Initiative Observational Study, we sought to evaluate the relationship between aspirin use, dose (81 or 325 mg), and clinical outcomes. In this cohort, aspirin use was low in women with stable cardiovascular disease. Forty-six percent reported taking aspirin, of whom 30% were on 81 mg and 70% were on 325 mg. This underutilization was most pronounced in blacks and women with Medicaid insurance. After multivariate adjustment, aspirin use was associated with a significantly lower risk of all-cause (hazard ratio, 0.86 [0.75 to 0.99]; P=0.04) and cardiovascular-related (hazard ratio, 0.75 [0.60 to 0.95]; P=0.01) mortality, but there was no significant lowering in a comosite of myocardial infarction, stroke, or cardiovascular death (hazard ratio, 0.90 [0.78 to 1.04]; P=0.14). Compared with use of 325 mg, use of 81 mg was not significantly different for all-cause mortality, cardiovascular events, or any individual end point.
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