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

**Jeffrey S Berger, MD, MS**[°], **David L Brown, MD**[1], **Gregory L Burke, MD, MSc**[2], **Albert Oberman, MD, MPH**[3], **John B Kostis, MD**[*], **Robert D Langer, MD, MPH**[^], **Nathan D Wong, PhD**[†], and **Sylvia Wassertheil-Smoller, PhD**[ǂ]

[°]Duke University Medical Center, Durham, NC; University of Pennsylvania, Philadelphia, PA

[1]SUNY-Stony Brook School of Medicine, Stony Brook, NY

[2]Wake Forest University School of Medicine, Winston-Salem, NC

[3]University of Alabama, Birmingham, AL

[*]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ

[^]University California San Diego, San Diego, CA

[†]University of California Irvine, Orange, CA

[ǂ]Albert Einstein College of Medicine, Bronx, NY

## Abstract

Corresponding Author: Jeffrey S. Berger, MD, MS, Duke Clinical Research Institute, Duke University Medical Center, Department of Internal Medicine, DUMC 31007, Durham, NC 27710.

Conflict of Interest Disclosures
None

**Bullet Point Summary**

1. Among postmenopausal women with stable cardiovascular disease, aspirin use was reported in 46% of the population.
2. Among aspirin users, 30% were on 81mg and 70% were on 325mg.
3. Under-utilization was most pronounced in African Americans and women with Medicaid insurance.
4. After multivariate adjustment, aspirin use was associated with a significantly lower risk of all-cause (HR 0.86, [0.75-0.99], P=0.04) and cardiovascular related mortality (HR 0.75, [0.60-0.95], P=0.01).
5. Aspirin use was not associated with a significant lowering of the composite (myocardial infarction, stroke or cardiovascular death) (HR 0.90, [0.78-1.04], P=0.14).
6. Compared with 325mg, use of 81mg was not significantly different for all-cause mortality, cardiovascular events or any individual endpoint.

Clinical Summary
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 325mg) and clinical outcomes. In this cohort, aspirin use was low in this cohort of women with stable cardiovascular disease. Forty six percent reported taking aspirin, of whom 30% were on 81mg and 70% were on 325mg. This under-utilization was most pronounced in African Americans and women with Medicaid insurance. After multivariate adjustment, aspirin use was associated with a significantly lower risk of all-cause (HR 0.86, [0.75-0.99], P=0.04) and cardiovascular related mortality (HR 0.75, [0.60-0.95], P=0.01), but no significant lowering in a composite of myocardial infarction, stroke or cardiovascular death (HR 0.90, [0.78-1.04], P=0.14). Compared with 325mg, use of 81mg was not significantly different for all-cause mortality, cardiovascular events or any individual endpoint.

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**Background—**Despite compelling evidence that aspirin reduces fatal and non-fatal 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 325mg) and clinical outcomes among postmenopausal women with stable cardiovascular disease.

**Methods—**Women with cardiovascular disease (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).

**Results—**Among 8928 women with stable cardiovascular disease, 4101 (46%) reported taking aspirin, of whom 30% were on 81 and 70% were on 325mg. 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 HR 0.86, [0.75-0.99], P=0.04) and cardiovascular related mortality (adjusted HR 0.75, [0.60-0.95], P=0.01) compared with no aspirin. Aspirin use was associated with a lower risk of cardiovascular events (adjusted HR 0.90, [0.78-1.04], P=0.14) which did not meet statistical significance. Compared with 325mg, use of 81mg was not significantly different for all-cause mortality, cardiovascular events or any individual endpoint.

**Conclusions—**After multivariate adjustment, aspirin use was associated with significantly lower risk of all-cause mortality, specifically cardiovascular mortality, among postmenopausal women with stable cardiovascular disease. No significant difference was noted between 81 and 325mg of aspirin. Overall, aspirin use was low in this cohort of women with stable cardiovascular disease.

## Keywords

Aspirin; Dose; Women; Cardiovascular Disease; Observational Study

Randomized studies of patients with cardiovascular disease 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 cardiovascular disease has not been fully evaluated. Among 278 trials included in the Antiplatelet Trialists' Collaboration, 34 evaluated a population with stable cardiovascular disease (prior myocardial infarction, stroke/transient ischemic attack, or stable angina), and only 6 trials evaluated low-dose aspirin (50-325mg) versus placebo/control, some of which excluded or only included a minority of women[5].

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 75-150mg and 160-325mg[1, 2]. A more recent analysis of the same data among unstable patients documented a greater benefit with lower doses of aspirin[8]. Consistent with the uncertainty of optimal aspirin dose, guidelines tend to differ[4, 9]. The AHA/ACC guidelines for secondary prevention recommend aspirin (75-162mg) in all patients unless contraindicated. The recent AHA guidelines for cardiovascular disease prevention in women support aspirin (75-325mg) in women with established cardiovascular disease. Despite the increased recent attention to aspirin dose, little is known about aspirin dose in women with stable cardiovascular disease.

The purpose of this study was three-fold. First, to define the utilization of aspirin among post-menopausal women with cardiovascular disease in the Women's Health Initiative (WHI) Observational Cohort. Second, to determine the association between aspirin use, all-cause mortality and other cardiovascular events. Finally, to evaluate the relationship between aspirin dose (81 vs. 325mg) and clinical outcomes.

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# Methods

## Study Population

As described elsewhere[10], the WHI has clinical trial and observational study (OS) components. The latter component is on ongoing, nationwide, prospective cohort study of post-menopausal women of diverse races and ethnicities and is designed to examine the association between clinical, socio-economic, behavioral, and dietary risk factors and the subsequent incidence of several health outcomes. The WHI-OS cohort consists of 93,676 women between 50-79 years of age enrolled at 40 clinical centers throughout the US between 1994-1998. 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[11].

Among WHI-OS participants, 8928 had a history of stable cardiovascular disease, defined by one or more of the following conditions at baseline: previous myocardial infarction, previous stroke/transient ischemic attack, previous or current angina, and 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 anti-inflammatory (NSAID) pain pills (including prescription drugs), or acetaminophen tablets or capsules?” Those individuals who reported using aspirin at least three times a week 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 was validated by checking pill bottle labels and prescription records during the interview process. For the current analysis women reporting 81mg, 325mg and no aspirin (as the reference category) were included. Women who reported use of 120-300mg (n=86, 0.9%) or > 325mg (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 (Standard Deviation, 1.6 years; Range, 0.1-9.3 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, electrocardiogram, 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 MI. Confirmation of self-reported nonfatal MI was based on adjudication by trained physicians of documentation of new chest pain syndromes accompanied by characteristic evolution of electrocardiographic changes or clear evidence of 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 $X^2$ statistics for categorical variables and *t* test or ANOVA, as appropriate, for continuous

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variables. Aspirin use was related to all-cause mortality and cardiovascular endpoints 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 and NSAID use, and history of myocardial infarction, transient ischemic attack, 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[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 non-using 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 non-aspirin 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 81mg to a user of 325mg. We were able to match 1036 users of 81mg to 1036 users of 325mg. 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 (SAS).

### 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 post-menopausal women with cardiovascular disease, 4101 (46%) reported taking aspirin. Of the aspirin users, 1224 (30%) were on 81mg and 2877 (70%) were on 325mg. Among women with a history of myocardial infarction, transient ischemic attack, 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 [2.68-3.55]), hypercholesterolemia (1.27 [1.10-1.46]), treated hypertension (1.18 [1.05-1.33]), previous MI (1.18 [1.04-1.33]), prior transient ischemic attack (1.41 [1.23-1.61]), statin treatment (1.40 [1.19-1.65]) and beta blocker therapy (1.54 [1.36-1.74]). Demographic predictors of aspirin

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use included increasing age per year (1.02 [1.01-1.03]) and college education (1.25 [1.01-1.55]). Negative predictors of aspirin use included African American race (0.70 [0.59-0.83]), Medicaid insurance (0.59 [0.45-0.77]), increasing BMI (0.98 [0.98-0.99]) and NSAID use (0.86 [0.76-0.97]).

Women who were older and more educated were more frequently on 81mg. A history of myocardial infarction, prior revascularization, beta blocker use and increasing BMI were predictors for 325mg. 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% lowering in the risk of all cause mortality (HR 0.86 [0.75-0.99]) (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 non-significant decrease in cardiovascular events (HR 0.90 [0.78-1.04]). However, aspirin was associated with a 25% significantly lower risk of cardiovascular mortality (HR 0.75 [0.60-0.95]).

### 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, beta-blocker use and NSAID 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 between the ages 50 to 59, 60 to 69, and 70 to 79, the hazard ratios 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

In order 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 5,292 patients. These patients were well matched on the basis of baseline characteristics with no significant differences between users and non-users 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% vs. 11.5%, P=0.045). Aspirin use was associated with a lower composite of cardiovascular adverse events, which was not statistically significant (10.1% vs. 11.3%, P=0.142). For the individual endpoints, 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 81mg to 1036 users of 325mg. 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 81mg and 325mg patients.

## Discussion

This analysis produced 3 major findings. First, is the observation that only 46% of women with preexisting cardiovascular disease reported aspirin use. A regression model identified clinical, demographic and socioeconomic factors as positive and negative predictors for use of therapy.

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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 325mg of aspirin.

## Aspirin Use

In total, 46% of postmenopausal women with cardiovascular disease were on 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 cardiovascular disease[13-22].

Prior studies[14-23] demonstrated a wide range of aspirin utilization (25-80%). Studies in community settings such as this one have demonstrated lower rates[21, 22] compared to studies in the hospitalized or post-hospitalization period[14, 16-20]. The present study is unique because it focuses on postmenopausal women with cardiovascular disease. 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 US.

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 African American 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 cardiovascular disease [24, 25], higher education was associated with use of aspirin. The lower utilization of aspirin among African Americans and patients with Medicaid insurance is consistent with the observation that minorities and socio-economically disadvantaged populations receive less aggressive treatment of cardiovascular disease[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.

## Efficacy of Aspirin

Previous analyses demonstrated that anti-platelet therapy prevents adverse events across many patients 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 anti-platelet medications and when grouping stable and unstable cardiovascular disease. There is little data on aspirin in women with stable cardiovascular disease.

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 cardiovascular disease. Subsequently, we performed a propensity analysis to further adjust for potential confounders and selection biases[12, 13], which demonstrated a similar lowering in the risk of death. No subgroup of women except those on current HRT 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 HRT may have been due to chance. Alternatively, by inhibiting the post menopausal hormone-induced increase in C-reactive protein[28] or thrombosis risk[29], aspirin may be additionally protective in this population.

This study also noted a non-significant decrease in the composite of cardiovascular adverse events. In subgroup analyses, older women were noted to have the greatest benefit with aspirin

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use (P for interaction = 0.02), a finding consistent with the Women's Health Study[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 events7. Second, data from primary prevention studies suggest that aspirin may not be effective in reducing the risk of myocardial infarction in women[30, 31]. Third, our data may be consistent with the non significant effect of aspirin for preventing cardiovascular events in women without cardiovascular disease as noted in the Women's Health Study[30]. Finally, several studies have suggested a reduced effect of aspirin among women compared to men[32, 33].

Our study is unique because it focused on a population of postmenopausal women with cardiovascular disease. Previous randomized trials of aspirin that included women[34, 35] were unable to find any significant effect of aspirin use on mortality. However, women were under-represented in trial enrollment and therefore the studies were underpowered. Two previous observational analyses[36, 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 cardiovascular disease, 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 US, 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 while observing no differences in effectiveness[6, 39-41]. Other reports have presented conflicting results. Quinn et al. demonstrated a decreased rate of myocardial infarction with a higher dose (325mg) of aspirin[42] while other studies found that a lower dose (81mg) is associated with a lower risk of cardiovascular complications7, 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 325mg 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 confounding around aspirin use[12, 13]. Second, there is a potential for aspirin use to be under reported 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, non-prescription and all over the counter medications at study enrollment. Third, there is a potential that participants were on other anti-platelet or anti-thrombotic 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.

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### Conclusions

While 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 cardiovascular disease. No significant difference in dose (81 vs. 325mg) was noted for any of the clinical outcomes measured. In addition, aspirin use was very low among women with cardiovascular disease. This under-utilization was most pronounced in African Americans and women with Medicaid insurance.

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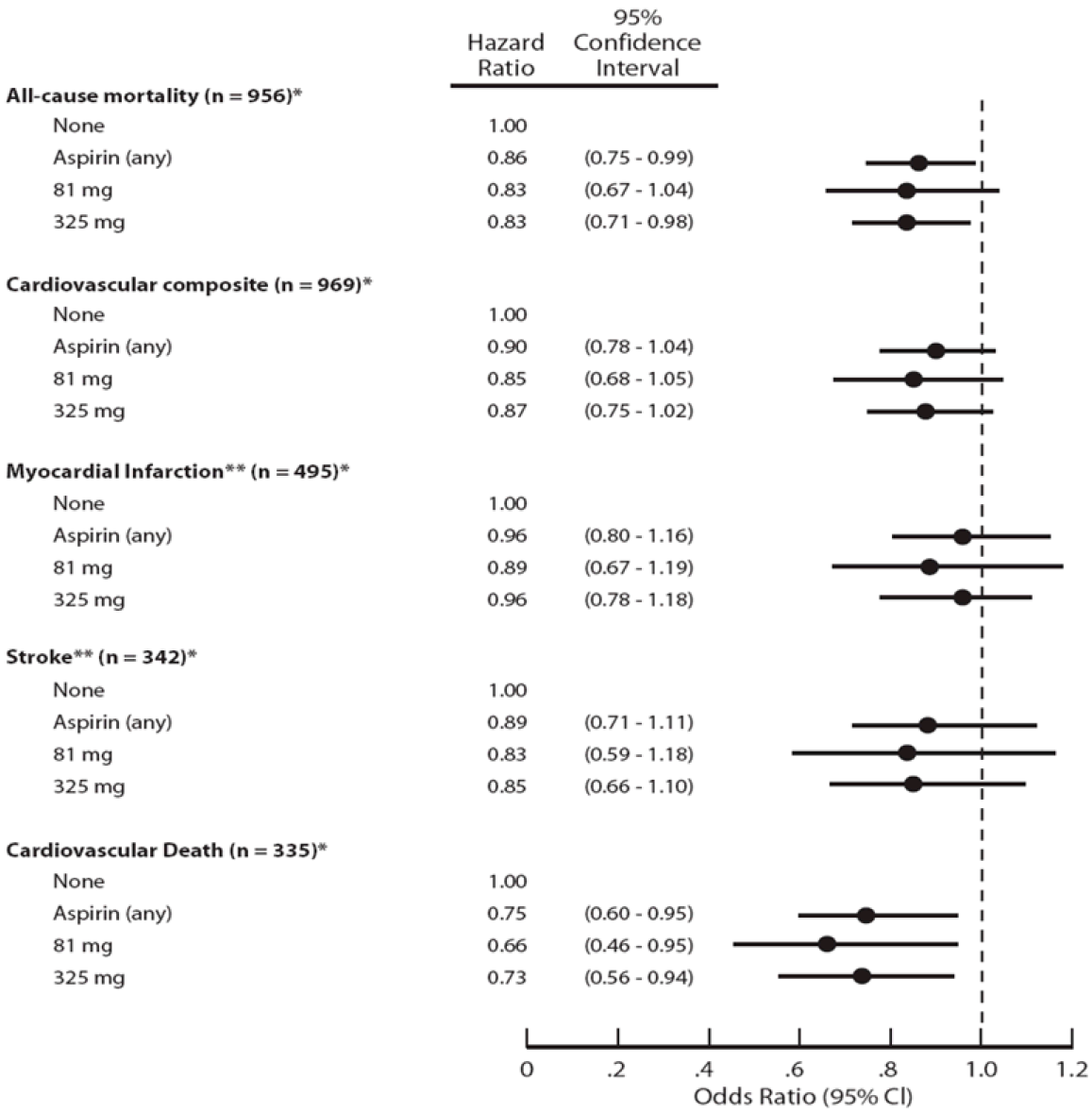


* Adjusted for age, race, education, last medical visit within 1 year, insurance status, hormone replacement therapy, history of myocardial infarction, transient ischemic attack, stroke, angina, peripheral artery disease, coronary revascularization, diabetes, hypertension, smoking status, body mass index, statin use, B-Blocker use and NSAID use.

** Fatal and non-fatal

**Figure 1. Adjusted Cox Proportional Hazards Analyses of Time to Adverse Outcomes among Women with Cardiovascular Disease (n=8,928)**

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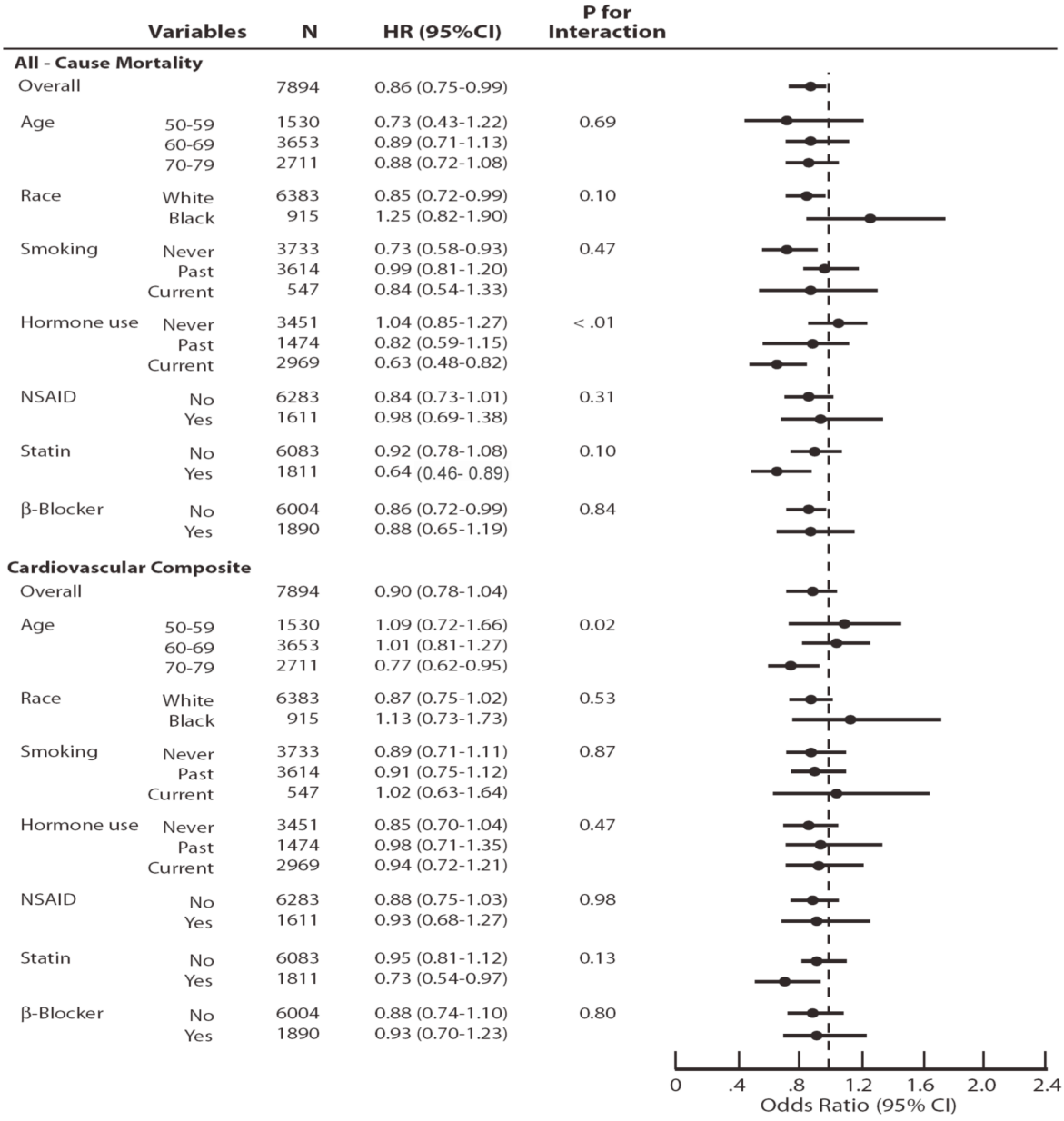


**Figure 2. Subgroup Analyses According to Aspirin Use**

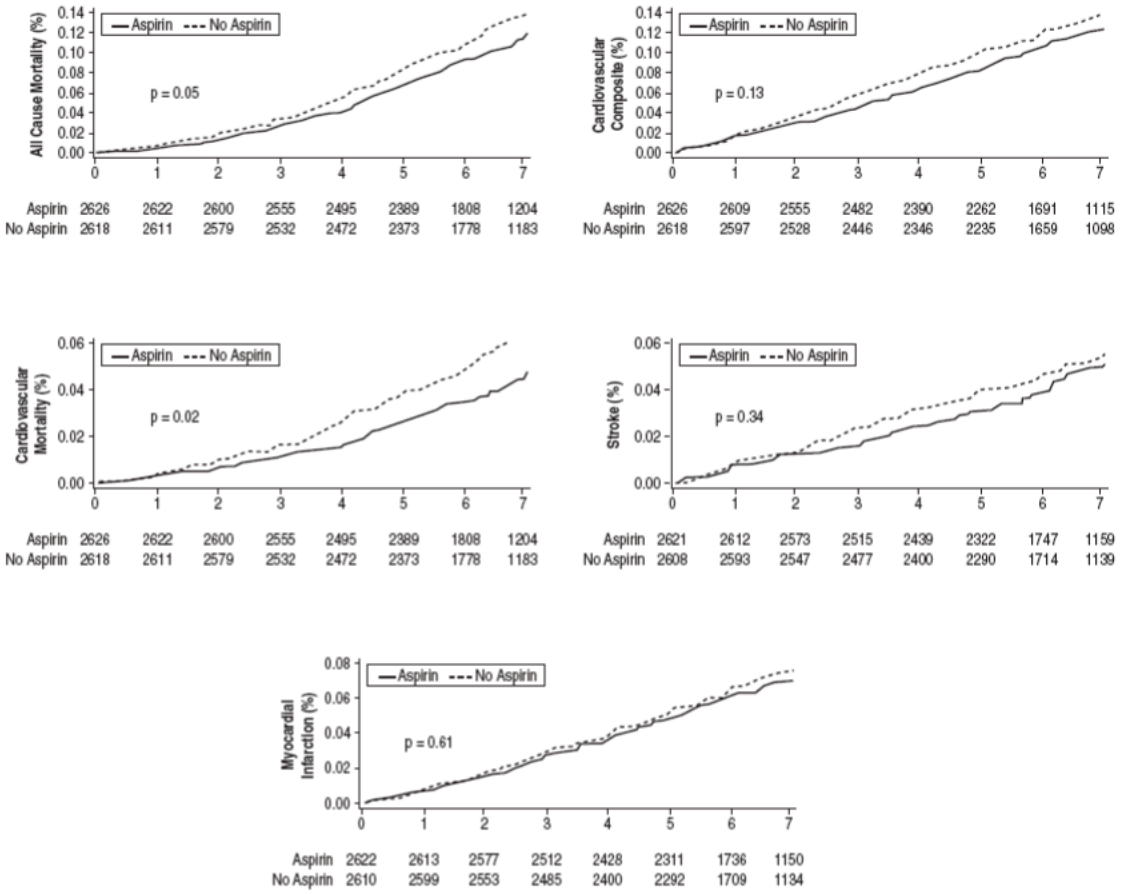


**Figure 3. Clinical Outcomes According to Aspirin Use**



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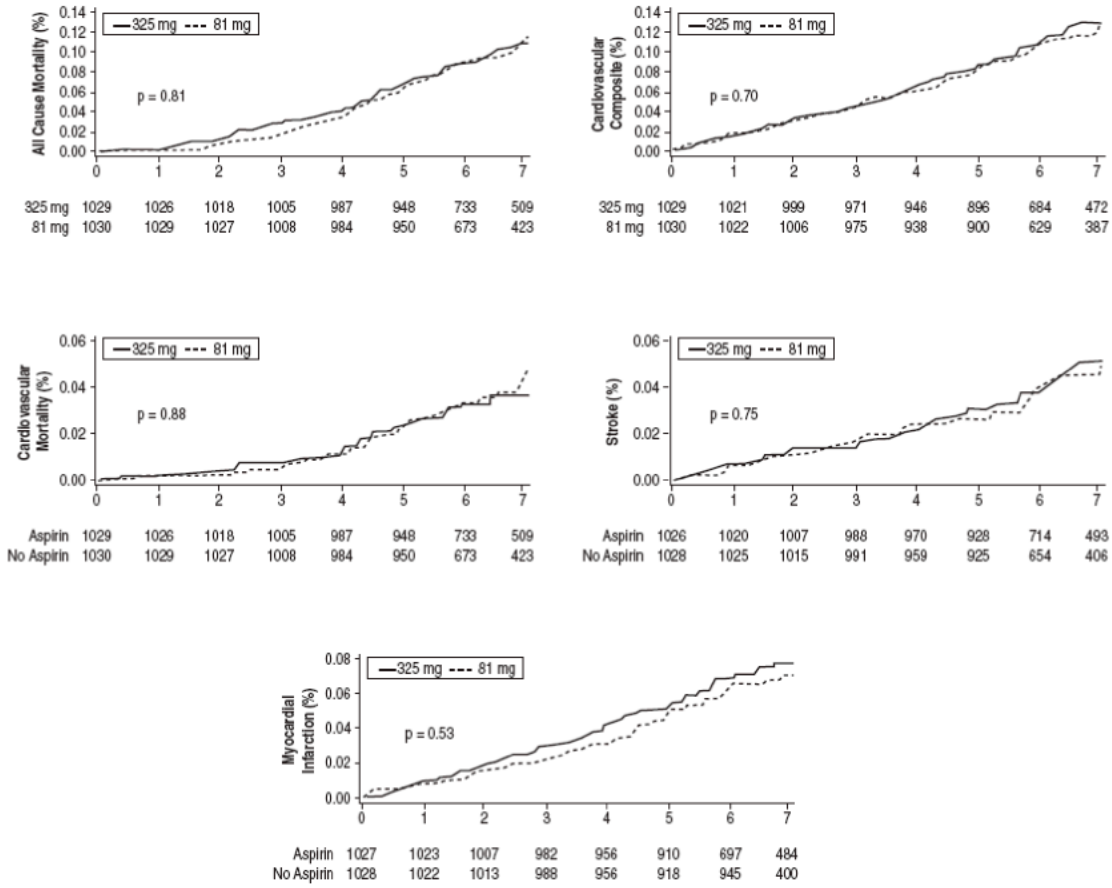


**Figure 4. Clinical Outcomes According to Aspirin Dose**

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## Table 1
**Baseline Differences for Women With Cardiovascular Disease According to Aspirin Dose**

| | No aspirin (n=4,827) | 81mg (n=1,224) | 325 mg (n=2,877) | P value |
|---|---|---|---|---|
| **Demographics (%)** | | | | |
| Age ± SD | 66 ± 7 | 68 ± 6 | 68 ± 7 | <0.001 |
| Age | | | | <0.001 |
| ≤60 | 23 | 12 | 15 | |
| >60 | 77 | 88 | 85 | |
| Race/Ethnicity | | | | <0.001 |
| White | 75 | 83 | 84 | |
| Black | 16 | 9.0 | 9.8 | |
| Other | 9.6 | 7.8 | 5.8 | |
| BMI ($kg/m^2$) ± SD | 29 ± 6 | 28 ± 6 | 28 ± 6 | <0.001 |
| BMI | | | | <0.001 |
| <25 | 28 | 34 | 38 | |
| 25-30 | 38 | 35 | 27 | |
| >30 | 31 | 30 | 32 | |
| **Clinical History (%)** | | | | |
| Diabetes | 15 | 14 | 16 | 0.334 |
| Hypertension | 58 | 60 | 63 | <0.001 |
| Systolic BP ± SD | 132 ± 19 | 132 ± 19 | 133 ± 19 | 0.022 |
| Diastolic BP ± SD | 75 ± 10 | 72 ± 10 | 73 ± 10 | <0.001 |
| Hypercholesterolemia | 28 | 45 | 43 | <0.001 |
| Stroke | 16 | 13 | 15 | 0.052 |
| TIA | 24 | 27 | 25 | 0.032 |
| Angina | 63 | 60 | 57 | <0.001 |

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| | No aspirin (n=4,827) | 81mg (n=1,224) | 325 mg (n=2,877) | P value |
|---|---|---|---|---|
| Myocardial infarction | 21 | 26 | 31 | <0.001 |
| Percutaneous revascularization | 6.3 | 17 | 21 | <0.001 |
| Bypass surgery | 5.1 | 13 | 16 | <0.001 |
| PAD | 8.3 | 8.1 | 9.3 | 0.301 |
| CHF | 6.4 | 5.3 | 5.8 | 0.250 |
| Hormone use ever | | | | 0.006 |
| Past user | 27 | 27 | 26 | |
| Current user | 39 | 44 | 41 | |
| **Social History** | | | | |
| Smoking | | | | 0.013 |
| Never smoked | 48 | 47 | 46 | |
| Past smoker | 44 | 47 | 47 | |
| Current smoker | 7.9 | 5.7 | 7.0 | |
| >7 alcoholic drinks/wk | 8.0 | 10 | 10 | <0.001 |
| Last medical visit w/in 1 year | 89 | 93 | 92 | <0.001 |
| Any Insurance | 96 | 98 | 97 | 0.001 |
| Medicaid | 5.5 | 2.3 | 2.9 | <0.001 |
| Medicare | 54 | 63 | 62 | <0.001 |
| Military / VA | 2.9 | 2.2 | 3.0 | 0.389 |
| Region | | | | <0.001 |
| Northeast | 22 | 26 | 25 | |
| South | 28 | 22 | 24 | |
| Midwest | 21 | 20 | 24 | |

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| | No aspirin (n=4,827) | 81mg (n=1,224) | 325 mg (n=2,877) | P value |
|---|---|---|---|---|
| | | | | |
| West | 29 | 32 | 28 | |
| Education | | | | <0.001 |
| < high school diploma | 10 | 6.5 | 8.5 | |
| high school – college | 61 | 58 | 61 | |
| ≥ college graduate | 29 | 36 | 30 | |
| **Medications** | | | | |
| NSAIDs | 22 | 19 | 18 | 0.001 |
| Beta blockers | 18 | 28 | 31 | <0.001 |
| Statins | 15 | 31 | 30 | <0.001 |

CVD, cardiovascular disease; BMI, body mass index; BP, blood pressure; TIA, transient ischemic attack; PAD, peripheral artery disease; CHF, congestive heart failure; VA, veterans affairs; NSAID, non-steroidal anti inflammatory drug.

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## Table 2
## Clinical Outcomes According to Aspirin Use and Dose

| | No aspirin (n=4,827) | 75-81mg (n=1,224) | 325 mg (n=2,877) | P value |
|---|---|---|---|---|
| **Clinical outcomes (%)** | | | | |
| All-cause mortality | 10.9 | 9.9 | 10.7 | 0.566 |
| Cardiovascular composite* | 10.3 | 11.0 | 11.7 | 0.186 |
| Myocardial infarction | 5.5 | 6.5 | 7.3 | 0.005 |
| Stroke | 4.3 | 4.1 | 4.5 | 0.818 |
| Cardiovascular mortality | 4.3 | 4.0 | 4.3 | 0.876 |

*myocardial infarction/stroke/cardiovascular mortality