Aspirin to Prevent Cardiovascular Disease: The Association of Aspirin Dose and Clopidogrel With Thrombosis and Bleeding

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Background: The optimal aspirin dose for the prevention of cardiovascular events remains controversial.

Objective: To assess the incidence of and risk factors for adverse clinical outcomes by investigator-determined aspirin dose in a primary prevention trial.

Design: Post hoc observational analyses of data from a double-blind, placebo-controlled, randomized trial.

Setting: Outpatient.

Patients: 15 595 patients with cardiovascular disease or multiple risk factors.

Intervention: Clopidogrel, 75 mg/d, or placebo, with aspirin, 75 to 162 mg/d, as selected by the investigators.

Measurements: Incidence of the composite outcome of myocardial infarction, stroke, or cardiovascular death (efficacy end point), and incidence of severe or life-threatening bleeding (safety end point), at a median of 28 months (interquartile range, 23 to 31 months) of follow-up.

Results: Daily aspirin doses were categorized as less than 100 mg (75 or 81 mg) ($n = 7180$), 100 mg ($n = 4961$), and greater than 100 mg (150 or 162 mg) ($n = 3454$). The hazard of the primary efficacy end point was the same regardless of dose (adjusted hazard ratio, 0.95 [95% CI, 0.80 to 1.13] for 100 mg vs. less than 100 mg, and 1.0 [CI, 0.85 to 1.18] for greater than 100 mg vs. less than 100 mg). The hazard of the primary safety end point also did not depend on dose (adjusted hazard ratio, 0.85 [CI, 0.57 to 1.26] for 100 mg vs. less than 100 mg and 1.05 [CI, 0.74 to 1.48] for greater than 100 mg vs. less than 100 mg). In patients also receiving clopidogrel, daily aspirin doses greater than 100 mg seemed to be non–statistically significantly associated with reduced efficacy (adjusted hazard ratio, 1.16 [CI, 0.93 to 1.44]) and increased harm (adjusted hazard ratio, 1.30 [CI, 0.83 to 2.04]).

Limitation: The analysis was post hoc, and aspirin use was not randomized or blinded.

Conclusion: Daily aspirin doses of 100 mg or greater were associated with no clear benefit in patients taking aspirin only and possibly with harm in patients taking clopidogrel. Daily doses of 75 to 81 mg may optimize efficacy and safety for patients requiring aspirin for long-term prevention, especially for those receiving dual antiplatelet therapy.

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Aspirin is the most widely used drug worldwide for the prevention of thrombotic cardiovascular events. Of note, the doses of aspirin used most often clinically or recommended in guidelines are based not on the results of trials designed to identify the most efficacious or safest dose, but on a combination of historical precedents and trials in which specific doses of aspirin were mandated by protocol. This practice has led to a wide range in aspirin doses (75 to 325 mg/d) recommended by the U.S. Food and Drug Administration (1) for the management of cardiovascular disease in various populations. Although as little as 30 mg of aspirin daily is needed to fully inhibit platelet thromboxane production (2), doses more than 10 times higher than this are routinely used in long-term prevention of cardiovascular disease.

Because aspirin has been used clinically for more than a century and is a mainstay of therapy for patients who have or are at risk for atherosclerotic disease and other common ailments, its risks are often underappreciated. However, given that more than one third of U.S. adults are estimated to take aspirin daily for cardiovascular disease (3), even a very small incidence of hemorrhagic complications places a large number of people at risk. Consistent with this is a recent analysis of hospitalizations for adverse drug effects that found aspirin to be one of the most common causal agents (4). The gastrointestinal tract is the leading source of bleeding events in aspirin-treated patients because of inhibition of gastroprotective prostacyclins, with an excess risk for upper gastrointestinal complications of 5 cases per 1000 aspirin users per year (5). Prospective evaluation of aspirin-treated patients with coronary artery disease identified an incidence of upper gastrointestinal bleeding of 1.5% per year, with substantial associated morbidity (6). Because inhibition of gastric prostacyclin is dose-dependent and not maximal until a daily dose of about 1300 mg is reached

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Context

The optimal aspirin dose for prevention of cardiovascular events is unknown.

Contribution

This post hoc analysis of CHARISMA trial data suggests no overall differences in efficacy or safety by aspirin dose. However, in the subgroup of patients randomly assigned to clopidogrel, there was a hint of reduced efficacy and increased harm with higher doses.

Caution

Patients were not randomly assigned to aspirin dose.

Implication

Lower aspirin doses (75 to 81 mg/d) may optimize efficacy and safety for patients requiring aspirin for long-term prevention, especially those taking clopidogrel.

—*The Editors*

(4), minimizing the dose of aspirin to that needed to fully inhibit platelet thromboxane production would probably offer the greatest potential benefit with the lowest possible risk.

In several observational studies of large prospective trials, lower doses of aspirin (<162 mg/d) have been associated with the lowest incidence of thrombotic events (7, 8) and a trend toward fewer bleeding events (8). These favorable trends in efficacy and safety were confirmed in the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial (9) of dual antiplatelet therapy with clopidogrel plus aspirin versus placebo plus aspirin. On the basis of these results, the design of the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) trial (10), which randomly assigned 15 603 patients at high risk for atherothrombotic events to clopidogrel or placebo in conjunction with aspirin, mandated a daily aspirin dose of 75 to 162 mg.

We performed a post hoc analysis of associations between investigator-determined daily aspirin dose and thrombotic and hemorrhagic outcomes in the prospective CHARISMA trial.

METHODS

The design, methods, and primary results of the CHARISMA study are reported elsewhere (10). In brief, CHARISMA was a multicenter, double-blind, randomized, placebo-controlled trial of long-term clopidogrel (75 mg/d) treatment versus placebo in patients 45 years or older who had established atherosclerotic disease or were asymptomatic but at high risk because of a combination of risk factors. All patients also received low-dose aspirin therapy, which was limited by protocol to between 75 and 162 mg/d. Patients were excluded if they had an established indication for clopidogrel

therapy, such as a recent acute coronary syndrome or stent implantation. Clinical follow-up was done at 1, 3, and 6 months and every 6 months thereafter until the end of the trial. The actual dose of aspirin being taken was confirmed at each evaluation. The ethics committee at each of the 768 participating hospitals worldwide, as well as the appropriate national ethics committee for each of the 32 participating countries, reviewed and approved the study protocol. All patients provided written informed consent before enrollment.

The primary efficacy end point was the first occurrence of myocardial infarction, stroke, or cardiovascular death. The primary safety end point was severe or life-threatening bleeding according to the GUSTO-I (Global Utilization of Streptokinase and TPA for Occluded coronary arteries) criteria (11): intracerebral bleeding or bleeding resulting in substantial hemodynamic compromise requiring treatment. A secondary safety end point was the combined incidence of severe or life-threatening bleeding or moderate bleeding by the GUSTO-I criteria, with "moderate" defined as bleeding requiring transfusion but not resulting in hemodynamic compromise (11). Of note, patients believed to be at high risk for bleeding were excluded from enrollment.

Aspirin dose was not randomized; rather, it was selected at the discretion of the treating physician. We prospectively divided patients into 3 major groups according to clear demarcations in aspirin dose at baseline: less than 100 mg/d, represented almost entirely by doses of either 75 or 81 mg/d; 100 mg/d; and greater than 100 mg/d, represented by either 150 or 162 mg/d. We evaluated the relative efficacy and safety of the different doses of aspirin among all patients, and we evaluated the efficacy and safety end points between the treatment (clopidogrel) versus placebo groups by aspirin dose category.

Statistical Analysis

We performed all data analyses on the intention-to-treat population. We performed hypothesis tests by using 2-sided tests at the 5% significance level. Baseline characteristics were compared by using chi-square tests for discrete variables and *t* tests for continuous variables. We calculated cumulative Kaplan–Meier estimates of the event rates and assessed differences in the unadjusted rates of primary efficacy and safety end points across the aspirin groups by using a 2-sided log-rank test. We used log-rank weights to compute a test for trend across aspirin dose categories.

We estimated the treatment effect, measured by the hazard ratio and its 95% CI, by using the Cox proportional hazards model. Multivariable modeling was performed to determine whether aspirin dose was independently associated with the primary efficacy and safety outcomes after controlling for potentially confounding factors. Because patients could have had more than 1 efficacy or safety event, we defined the time to the primary efficacy end point as the first occurrence of myocardial infarction, stroke, or cardiovascular death. We defined the time to the

primary safety end point as the first occurrence of severe or life-threatening bleeding according to the GUSTO-I criteria (11).

We selected variables for inclusion in the models on the basis of differences in baseline characteristics among patients in the 3 aspirin dose categories or their clinical relevance to the outcomes. Covariates included in the multivariable model for the primary efficacy end point were the continuous variables of age, weight, and systolic blood pressure and the categorical variables of sex; race or ethnicity (white or Hispanic vs. other); hypertension; hypercholesterolemia; history of congestive heart failure; previous myocardial infarction; previous stroke; previous transient ischemic attack; diabetes mellitus; atrial fibrillation; peripheral arterial disease; diabetic nephropathy; current smoking; primary (vs. secondary) prevention and past use of statins, nitrates, and antiplatelet agents other than aspirin. We developed models with and without inclusion of interaction terms for randomized treatment assignment by aspirin dose category.

Adjustment variables in the multivariable model for the primary safety end point (GUSTO-I severe or life-threatening bleeding) included age and weight as continuous variables and the categorical variables of stable angina with multivessel disease, sex, race or ethnicity (white or Hispanic vs. other), history of congestive heart failure, previous myocardial infarction, previous stroke, previous transient ischemic attack, diabetes mellitus, atrial fibrillation, peripheral arterial disease, diabetic nephropathy, hypertension, hypercholesterolemia, primary prevention (vs. secondary), and current smoking. We developed models with and without inclusion of interaction terms for randomized treatment assignment by daily aspirin dose category.

To adjust for geographical region without estimating its effect, we used region (categorized as United States, Canada, Western Europe, Eastern Europe, Latin America, Asia and Australia, or Africa) as a stratification variable in models for both end points. We assessed the interaction of aspirin dose and randomized treatment in both models. We calculated and tested the difference between the maximum likelihood ratios with and without 2 interaction terms (randomized treatment assignment by daily aspirin dose of 100 mg and greater than 100 mg). We assessed proportional hazards by multiplying each covariate by the log of the time to the event. A Wald test was performed to test the linear hypotheses of the regression coefficients. The proportional hazards assumption was confirmed for models of both end points. Because patients may have changed aspirin dose throughout the study, we performed secondary analyses for each model by using aspirin dose as a time-dependent covariate. We calculated adjusted event rates of the primary efficacy and safety end points by using Cox proportional hazards models as well.

We made no adjustments for multiple comparisons. All statistical analyses were performed by using SAS software, version 8.2 (SAS Institute, Cary, North Carolina).

Role of the Funding Source

The CHARISMA trial was funded by Sanofi-Aventis and Bristol-Myers Squibb; however, no specific funding was obtained for the current analysis. The design, conduct, and analysis of the present data and manuscript submission were entirely at the discretion of the authors, without input from the sponsors of the CHARISMA trial.

RESULTS
Aspirin Dosing

We recorded the aspirin dose at baseline for 15 595 patients (99.9%). Daily aspirin doses less than 100 mg (75 or 81 mg) were most common (7180 patients), with 4961 patients receiving 100 mg and 3454 patients receiving greater than 100 mg (150 or 162 mg). Differences in baseline demographic characteristics were statistically and clinically significant among the aspirin dose categories, with a higher proportion of patients with known cardiovascular

Table 1. **Baseline Characteristics, by Daily Aspirin Dose at Study Entry**

Characteristic	Baseline Daily Aspirin Dose*			P Value
	<100 mg	100 mg	>100 mg	
Mean age, y	64.7	64.1	63.9	<0.001
Women, %	30.2	30.4	28.1	0.044
Mean body weight, kg	84.3	78.2	81.9	<0.001
Mean systolic blood pressure, mm Hg	138.1	140.8	137.3	<0.001
Race or ethnicity, %				
White	87.2	71.7	77.5	<0.001
Hispanic	4.0	18.2	12.2	<0.001
Black	4.3	0.9	3.9	<0.001
Other	4.5	9.2	6.5	<0.001
Inclusion criteria, %				
Documented vascular disease†	76.6	78.0	84.1	<0.001
Multiple risk factors‡	23.4	22.0	15.9	<0.001
Current smoking, %	21.2	20.1	18.3	0.002
Hypertension, %	72.0	76.9	72.1	<0.001
Hypercholesterolemia, %	78.5	67.9	73.1	<0.001
History of heart failure, %	6.7	4.1	7.1	<0.001
Past myocardial infarction, %	36.2	27.8	40.9	<0.001
Past atrial fibrillation, %	4.3	2.9	3.8	<0.001
Past stroke, %	20.1	29.8	26.4	<0.001
Past transient ischemic attack, %	11.2	12.5	12.8	0.020
Peripheral arterial disease, %	23.5	22.6	20.8	0.009
Diabetes mellitus, %	42.6	42.6	40.0	0.028
Diabetic nephropathy, %	13.4	12.8	11.8	0.060
Past statin use, %	70.8	54.4	67.2	<0.001
Past nitrate use, %	15.3	16.2	18.8	<0.001
Past antiplatelet (other than aspirin) use, %	4.6	5.2	5.2	0.20

* 7180 patients received <100 mg/d, 4961 patients received 100 mg/d, and 3454 patients received >100 mg/d.
† Documented cardiovascular, cerebrovascular, or peripheral arterial disease.
‡ Major risk factors were type 1 or 2 diabetes mellitus requiring drug therapy, diabetic nephropathy, ankle–brachial index <0.9, asymptomatic carotid artery stenosis ≥70%, or ≥1 carotid artery plaque as evidenced by intima–media thickness. Minor risk factors were systolic blood pressure ≥150 mm Hg despite ≥3 months of treatment, primary hypercholesterolemia, current smoking >15 cigarettes daily, or male sex and age ≥65 years or female sex and age ≥70 years. Patients were required to have 2 major, 3 minor, or 1 major plus 2 minor risk factors to meet this criterion for enrollment.

Table 2. Incidence of the Primary Composite Efficacy End Point, Its Components, and Safety End Points, by Baseline Daily Aspirin Dose

End Point	Baseline Daily Aspirin Dose*		
	<100 mg	100 mg	>100 mg
Efficacy			
Primary composite end point			
Cumulative incidence, n (%)†	479 (7.5)	363 (9.7)	262 (11.1)
Hazard ratio (95% CI)‡	1.0 (reference)	0.95 (0.80–1.13)	1.0 (0.85–1.18)
Individual components			
Cardiovascular death			
Cumulative incidence, n (%)†	191 (3.2)	161 (4.2)	113 (4.2)
Hazard ratio (95% CI)‡	1.0 (reference)	1.08 (0.82–1.43)	1.09 (0.85–1.40)
Myocardial infarction			
Cumulative incidence, n (%)†	204 (3.3)	90 (2.0)	91 (5.2)
Hazard ratio (95% CI)‡	1.0 (reference)	0.69 (0.50–0.94)	0.82 (0.62–1.07)
Stroke			
Cumulative incidence, n (%)†	167 (2.6)	169 (4.9)	104 (3.3)
Hazard ratio (95% CI)‡	1.0 (reference)	1.01 (0.77–1.33)	1.06 (0.81–1.38)
Safety			
Severe or life-threatening bleeding§			
Cumulative incidence, n (%)†	101 (1.7)	72 (2.0)	61 (2.2)
Hazard ratio (95% CI)‖	1.0 (reference)	0.85 (0.57–1.26)	1.05 (0.74–1.48)
Severe, life-threatening, or moderate bleeding§			
Cumulative incidence, n (%)†	237 (4.1)	130 (3.4)	120 (4.0)
Hazard ratio (95% CI)‖	1.0 (reference)	0.99 (0.74–1.32)	1.01 (0.80–1.28)

* 7180 patients received <100 mg/d, 4961 patients received 100 mg/d, and 3454 patients received >100 mg/d.
† Cumulative incidences are unadjusted and based on Kaplan–Meier estimates.
‡ Derived from proportional hazards model adjusted for age, weight, and systolic blood pressure (continuous variables) and for sex, race or ethnicity (white or Hispanic vs. other), hypertension, hypercholesterolemia, history of heart failure, previous myocardial infarction, previous stroke, previous transient ischemic attack, diabetes mellitus, atrial fibrillation, peripheral arterial disease, diabetic nephropathy, current smoking, primary prevention (vs. secondary), past use of statins, past use of nitrates, and past use of antiplatelet agents other than aspirin (categorical variables).
§ According to the GUSTO-I (Global Utilization of Streptokinase and TPA for Occluded coronary arteries) criteria.
‖ Derived from proportional hazards model adjusted for age and weight (continuous variables) and for sex, race or ethnicity (white or Hispanic vs. other), hypertension, hypercholesterolemia, history of heart failure, previous myocardial infarction, previous stroke, previous transient ischemic attack, diabetes mellitus, atrial fibrillation, peripheral arterial disease, diabetic nephropathy, current smoking, primary prevention (vs. secondary), and stable angina with multivessel disease (vs. not having stable angina with multivessel disease) (categorical variables).

disease in the group receiving greater than 100 mg/d compared with the other 2 groups (**Table 1**). By the final visit, 95% of patients who began the study taking less than 100 mg/d of aspirin were still taking that dose, whereas 88% of those taking 100 mg/d at baseline were still receiving that dose at the final visit (9% had switched to less than 100 mg/d, and 2% had switched to greater than 100 mg/d). Only 68% of patients taking greater than 100 mg/d initially were taking the same dose at end of follow-up; most of those who changed doses decreased to less than 100 mg/d (26%).

Primary Efficacy End Point and Aspirin Dose

The incidence of the combined primary end point (death, myocardial infarction, or stroke) by the end of follow-up (median, 28 months [interquartile range, 23 to 31 months]) did not differ by aspirin dose (**Table 2**). Increasing daily doses of aspirin seemed to be associated with a trend toward an increased incidence of the primary end point, but this trend was no longer evident after adjustment for baseline characteristics (daily aspirin dose less than 100 mg, 9.4%; dose of 100 mg, 8.9%; and dose greater than 100 mg, 9.2%; P for trend = 0.99).

Among patients randomly assigned to the placebo group, no relationship between aspirin dose and the incidence of the primary end point was observed. Among patients randomly assigned to the clopidogrel group, however, increasing doses of aspirin were associated with an increasing incidence of the primary efficacy end point (P = 0.029 for trend). Compared with clopidogrel-treated patients given less than 100 mg of aspirin daily, patients randomly assigned to receive clopidogrel who also received greater than 100 mg of aspirin daily had significantly higher incidences of the composite primary end point (14.5% vs. 7.4%; P = 0.016), cardiovascular death (5.2% vs. 3.4%; P = 0.043), and stroke (3.6% vs. 2.4%; P = 0.022) but showed no significant difference in the incidence of myocardial infarction (7.4% vs. 3.2%; P = 0.79).

In a multivariable model that did not include an interaction term for treatment assignment, no association was apparent between aspirin dose and the primary efficacy end point (adjusted hazard ratio, 0.95 [95% CI, 0.80 to 1.13] for daily aspirin dose of 100 mg and 1.00 [CI, 0.85 to 1.18] for daily aspirin dose greater than 100 mg, both compared with a daily aspirin dose less than 100 mg). The same was true when we included terms testing for interac-

tion between dose and randomization (adjusted ratios for the placebo group, 1.06 [CI, 0.86 to 1.32] for daily aspirin dose of 100 mg and 0.86 [CI, 0.68 to 1.08] for daily aspirin dose greater than 100 mg; adjusted hazard ratios for the clopidogrel group, 0.82 [CI, 0.65 to 1.04] for daily aspirin dose of 100 mg and 1.16 [CI, 0.93 to 1.44] for daily aspirin dose greater than 100 mg). The P value for the difference between the maximum likelihood ratios for the interaction between randomized treatment assignment and daily aspirin dose was 0.003 ($P = 0.002$ for time-dependent analysis).

Primary Safety End Point and Aspirin Dose

The incidence of severe or life-threatening bleeding tended to increase with greater daily doses of aspirin ($P = 0.20$) (Table 2). Among patients randomly assigned to placebo, we found no relationship between aspirin dose and the incidence of severe or life-threatening bleeding. In patients randomly assigned to clopidogrel, however, the increase noted in the incidence of severe or life-threatening bleeding with daily aspirin doses greater than 100 mg was significantly greater than in those treated with less than 100 mg daily (2.6% vs. 1.7%; $P = 0.040$).

In a multivariable model that did not include an interaction term for treatment assignment, we found no apparent association between daily aspirin dose and the primary safety end point (adjusted hazard ratio, 0.85 [CI, 0.57 to 1.26] for dose of 100 mg and 1.05 [CI 0.74 to
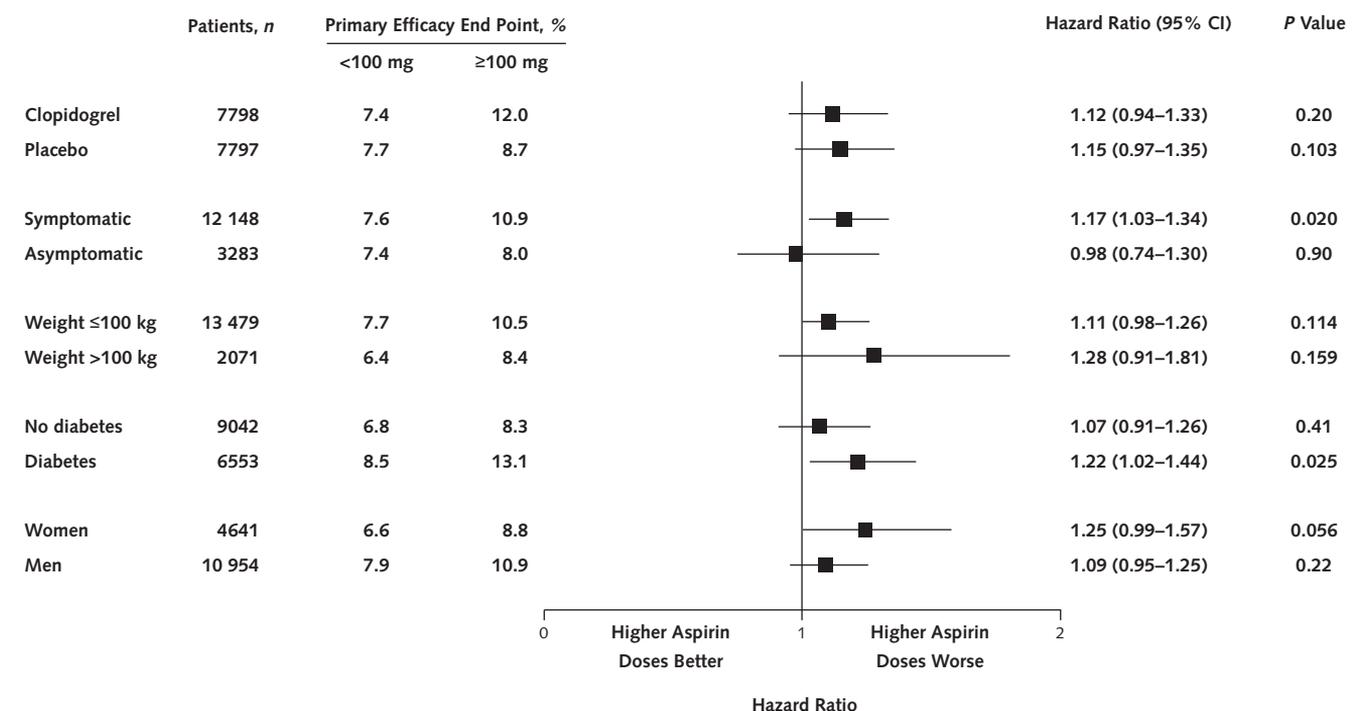
1.48] for dose greater than 100 mg, both compared with a dose less than 100 mg). When we included terms testing for interaction between dose and randomization in the model, the adjusted hazard ratios for the safety end point among placebo recipients were 0.71 (CI, 0.42 to 1.18) for daily aspirin dose of 100 mg and 0.80 (CI, 0.48 to 1.33) for daily aspirin dose greater than 100 mg (compared with a daily aspirin dose of less than 100 mg). Higher daily doses of aspirin seemed to cause greater harm in patients randomly assigned to clopidogrel (adjusted hazard ratio, 0.99 [CI, 0.61 to 1.60] for dose of 100 mg and 1.30 [CI, 0.83 to 2.04] for dose greater than 100 mg). The P value for the interaction between randomized treatment assignment and aspirin dose was 0.31 ($P = 0.48$ for time-dependent analysis).

For the combined incidence of severe life-threatening or moderate bleeding, the aspirin dose categories did not significantly differ for the overall study population (4.1% for dose less than 100 mg/d, 3.4% for 100 mg/d, and 4.0% for greater than 100 mg/d) or for the individual treatment groups (Table 2).

Association Between Aspirin Dose and Primary Efficacy Outcomes in Subgroups

We analyzed efficacy outcomes by aspirin dose category in several subgroups, including those for whom higher doses of aspirin might be more efficacious (Figure) (12, 13). No subgroup seemed to benefit from higher doses; in

Figure. Unadjusted hazard ratios, 95% CIs, and Kaplan–Meier estimates of the primary efficacy end point (cardiovascular death, myocardial infarction, or stroke) in selected daily aspirin dose subgroups.

	Patients, *n*	Primary Efficacy End Point, %		Hazard Ratio (95% CI)	P Value
		<100 mg	≥100 mg		
Clopidogrel	7798	7.4	12.0	1.12 (0.94–1.33)	0.20
Placebo	7797	7.7	8.7	1.15 (0.97–1.35)	0.103
Symptomatic	12 148	7.6	10.9	1.17 (1.03–1.34)	0.020
Asymptomatic	3283	7.4	8.0	0.98 (0.74–1.30)	0.90
Weight ≤100 kg	13 479	7.7	10.5	1.11 (0.98–1.26)	0.114
Weight >100 kg	2071	6.4	8.4	1.28 (0.91–1.81)	0.159
No diabetes	9042	6.8	8.3	1.07 (0.91–1.26)	0.41
Diabetes	6553	8.5	13.1	1.22 (1.02–1.44)	0.025
Women	4641	6.6	8.8	1.25 (0.99–1.57)	0.056
Men	10 954	7.9	10.9	1.09 (0.95–1.25)	0.22

Higher Aspirin Doses Better — Higher Aspirin Doses Worse

Hazard Ratio

fact, treatment with daily aspirin doses of 100 mg or greater was associated with a higher risk for the primary efficacy end point independent of sex, randomized treatment assignment, body weight, or diabetic status. Of interest, in the large subgroups with either symptomatic cardiovascular disease or diabetes mellitus, higher doses of aspirin were associated with significantly worse outcomes, although these differences were no longer significant after adjustment.

DISCUSSION

The results of this post hoc analysis suggest that daily aspirin doses of 100 mg or greater are not associated with clear benefit and may cause harm, and that daily aspirin doses of 75 to 81 mg may provide the optimal balance between efficacy and safety in patients with known cardiovascular events or those who are at risk for events but require aspirin therapy. This may be especially true in the setting of combination antiplatelet therapy with clopidogrel, given that daily aspirin doses greater than 100 mg seemed to be associated with reduced efficacy and increased incidence of severe or life-threatening bleeding in patients also taking clopidogrel, although these associations were no longer significant after adjustment.

These results are consistent with those of several previous post hoc analyses of large randomized trials, including the BRAVO (Blockade of the glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion) study (8), CURE (9), the GUSTO-IIb (Global Use of Strategies To Open occluded coronary arteries) trial (12), and the PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrelin Therapy) study (7). The difference between those analyses and ours is that the maximal daily aspirin dose in the CHARISMA trial was kept at 162 mg, whereas daily doses up to 325 mg were allowed in previous trials. Even with the narrower range of aspirin doses in the CHARISMA trial, the lowest doses still tended to be the most efficacious, as well as the safest. In addition, the median follow-up of 28 months in our analysis is more than twice as long as that in previous analyses, allowing a more realistic evaluation of the efficacy and safety of different aspirin doses for cardiovascular disease prevention.

Despite the consistency of these clinical trial data favoring lower doses of aspirin (albeit mostly via post hoc analyses), the optimal dose for long-term aspirin use in primary and secondary prevention remains controversial. Much of this controversy stems from the unusual path aspirin took in becoming a mainstay of preventive therapy in cardiology. Before being used in a clinical setting as an antiplatelet agent, aspirin had been available over the counter for nearly 100 years as a 325-mg tablet (13). The 81-mg children's version of aspirin has been available since the early 1920s, yet the first suggestion that aspirin be used in cardiology was not until the late 1940s (14). Pharmacodynamic studies suggest that as little as 30 to 50 mg of

aspirin daily is adequate to completely inhibit platelet thromboxane production in healthy volunteers and patients with stable angina (2, 15). The strongest evidence that the clinical benefit of aspirin is tied to its ability to inhibit platelet thromboxane production is the fact that numerous analyses, including ours, show no additional benefit with higher doses of aspirin (16, 17). Yet, current guidelines still recommend that doses up to 10 times higher be used on a daily basis, especially after percutaneous coronary intervention (18).

The most important safety concern about using doses of aspirin that are higher than necessary is aspirin's dose-dependent gastrointestinal toxicity, which does not seem to be maximal until daily doses of about 1300 mg (19). Although all doses of aspirin are toxic to the gastrointestinal tract, minimizing the dose would be expected to reduce the risk for this type of bleeding. Consistent with this hypothesis, the risk for hospital admission for gastrointestinal bleeding in a case–control analysis (20) was lower for patients treated with 75 mg/d of aspirin than for those receiving 300 mg/d. Given that the incidence of aspirin-induced gastrointestinal bleeding is not insignificant, and with such a large population at risk because of daily aspirin exposure, identifying the safest efficacious dose remains critically important. Again, our results and those of many other analyses all support the greater safety of lower doses of aspirin (8, 9, 21).

Because aspirin dose was not randomized in the CHARISMA trial and because baseline risk factors among the different dose cohorts were clearly imbalanced, it is possible that physicians in our study selected higher doses of aspirin for patients at greater risk, which might explain the significant increase in the risks for thrombotic and bleeding events before adjustment for baseline differences. However, a potential physiologic explanation for an association between higher aspirin doses and an increase in thrombotic events may relate to the dose-dependent inhibition of vascular prostacyclins, which act as both vasodilators and platelet inhibitors (22). The clinical importance of this remains poorly understood and controversial. Another potential explanation for the association between increased aspirin doses and the risk for thrombotic events may relate to the recently recognized and still inadequately understood association between bleeding and thrombosis (23). Alternatively, higher doses of aspirin may be less well tolerated, leading to greater degrees of nonadherence and therefore less protection from thrombotic events.

Several ex vivo measures of the antiplatelet effects of aspirin have found a marked dose-response, with increasing doses leading to greater inhibition or increased "responsiveness" (24, 25). Such findings contrast with clinical results, suggesting that ex vivo testing does not fully measure all clinically important actions of aspirin. One potential measure of aspirin responsiveness is urinary thromboxane metabolite levels, which have been shown to correspond to an increased risk for thrombotic events (26) and to decrease

with increasing doses of aspirin (22). A substudy from the CHARISMA trial found an association between lower levels of urinary thromboxane metabolite and better outcomes and an association between higher doses of aspirin and lower levels of urinary thromboxane (27). This finding suggests that higher doses of aspirin might be expected to be associated with better outcomes, but this was not the case. The reason for this is unclear; however, given that both urinary metabolites of thromboxane and prostacyclin are increased in atherosclerosis (28), higher doses of aspirin may inhibit the synthesis of both to a greater degree and lead to an unfavorable balance, although this is highly speculative.

Our analysis has several important limitations. Of primary importance is that aspirin doses were not randomly assigned or blinded. Physicians might have chosen higher aspirin doses for patients who they felt were at a higher risk for future events or who had undergone a more recent invasive procedure, although the latter generally were excluded from enrollment in the CHARISMA trial. Second, we analyzed our results on the basis of baseline aspirin use. Although aspirin dose remained relatively constant during follow-up for the lower-dose cohorts, this tended to change over time in the higher-dose cohorts—perhaps because of gastrointestinal or other toxicity, or simply poor adherence—diminishing our ability to identify differences between the higher- and lower-dose groups. The dose of aspirin that patients were taking when a primary efficacy or safety end point occurred was not recorded. Finally, the use of enteric-coated aspirin preparations was allowed but not captured.

This post hoc analysis of data from the CHARISMA trial indicates that daily aspirin doses of 100 mg or greater are not associated with clear benefit and may cause harm compared with lower doses (75 or 81 mg/d). The rate of severe or life-threatening bleeding according to the GUSTO-I criteria also was lowest in patients receiving the lowest baseline doses of aspirin. Overall, these results suggest that daily aspirin doses no greater than 81 mg optimize efficacy as well as safety in patients receiving aspirin for long-term primary and secondary prevention. This may be especially true in patients receiving dual antiplatelet therapy.

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