

The Relative Efficacy and Safety of Clopidogrel in Women and Men

A Sex-Specific Collaborative Meta-Analysis

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- Objectives** This study sought to investigate the efficacy and safety of clopidogrel in women and men.
- Background** Previous analyses have shown sex-based differences in response to several antiplatelet medications. Little is known about the efficacy and safety of clopidogrel in women and men.
- Methods** This study performed a meta-analysis of all blinded randomized clinical trials comparing clopidogrel and placebo (CURE [Clopidogrel in Unstable Angina to Prevent Recurrent Events], CREDO [Clopidogrel for the Reduction of Events During Observation], CLARITY-TIMI 28 [Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28], COMMIT [Clopidogrel and Metoprolol in Myocardial Infarction Trial], and CHARISMA [Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance] trials), involving a total of 79,613 patients, of whom 30% were women. The relative efficacy and safety of clopidogrel at reducing cardiovascular events (cardiovascular death, myocardial infarction [MI], or stroke) in women and men was estimated using random-effects modeling.
- Results** Overall, clopidogrel was associated with a highly significant 14% proportional reduction in the risk of cardiovascular events (odds ratio [OR]: 0.86; 95% confidence interval [CI]: 0.80 to 0.93), with no significant differences in treatment effect between women and men. Among the 23,533 women enrolled, there were fewer cardiovascular events in the clopidogrel group compared with the placebo group (11.0% vs. 11.8%; OR: 0.93; 95% CI: 0.86 to 1.01). In women the risk reduction with clopidogrel seemed to be greatest for MI (OR: 0.81; 95% CI: 0.70 to 0.93), with the effects on stroke (OR: 0.91; 95% CI: 0.69 to 1.21) or total death (OR: 0.99; 95% CI: 0.90 to 1.08) not statistically significant. Among the 56,091 men enrolled, there were fewer cardiovascular events in those receiving clopidogrel compared with placebo (7.8% vs. 9.0%; OR: 0.84; 95% CI: 0.78 to 0.91), and the risk reduction was significant for MI (OR: 0.83; 95% CI: 0.76 to 0.92), stroke (OR: 0.83; 95% CI: 0.71 to 0.96), and total death (OR: 0.91; 95% CI: 0.84 to 0.97). Clopidogrel increased the risk of major bleeding in both women (OR: 1.43; 95% CI: 1.15 to 1.79) and men (OR: 1.22; 95% CI: 1.05 to 1.42).
- Conclusions** Clopidogrel reduces the risk of cardiovascular events in both women and men. (J Am Coll Cardiol 2009;54: 1935-45) © 2009 by the American College of Cardiology Foundation

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**Abbreviations
and Acronyms**

- ACS** = acute coronary syndrome
- CI** = confidence interval
- MI** = myocardial infarction
- OR** = odds ratio

Pathological and clinical studies consistently show the importance of platelets in the pathogenesis of atherosclerosis and coronary thrombosis (1–5). Medications aimed at disrupting platelet activity have been shown to reduce cardiovascular morbidity and mortality in a variety of settings (6–8). However, several studies showed a sex-specific response to several antiplatelet medications (9–13).

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It has been previously shown that the response to aspirin for the primary prevention of cardiovascular disease is different between women and men (9). Although a similar protection from cardiovascular events was noted, women derived most of their benefit from a reduction in the risk of stroke, whereas men derived most of their benefit from a reduction in the risk of myocardial infarction (MI). The response to another antiplatelet medication, glycoprotein IIb/IIIa inhibitors, was shown to have a sex-specific response as well (10). However, there are very few data on the effect of clopidogrel in men versus women, even though it is one of the most frequently prescribed drugs.

Several randomized trials have evaluated the effect of clopidogrel on cardiovascular events across a broad spectrum of coronary disease (14–20). Accordingly, the most recent acute coronary syndrome (ACS) guidelines make clopidogrel treatment a class I recommendation with grade A evidence in several different clinical situations (21–23). Unfortunately, many of the clinical trials did not include an adequate number of women to determine whether the benefits were similar in men and women. Trials that did report results in women reported aggregate events (e.g., major cardiovascular events), but did not report specific outcomes such as death, MI, or stroke separately. Ex vivo assessment of the antiplatelet effect of clopidogrel suggests that women are more likely to be hyporesponsive to clopi-

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dogrel than men (24), suggesting a potential clinical difference in the effectiveness of clopidogrel according to sex.

Accordingly, to better understand the impact of sex on the response to clopidogrel, we performed a sex-specific collaborative meta-analysis of clopidogrel therapy for the prevention of cardiovascular events.

Methods

Literature search. This meta-analysis considered randomized clinical trials comparing clopidogrel in combination with aspirin to aspirin alone for the treatment of patients at high risk for cardiovascular events. Comprehensive searches of the Medline and Cochrane Central Register of Controlled Trials databases were performed using Internet-based engines (PubMed and OVID) for studies published between 1999 and May 2007. Search terms included clopidogrel, cardiovascular disease, MI, stroke, percutaneous coronary intervention, and randomized controlled trials, as well as combinations of these terms. Experts in the field were questioned, bibliographies of retrieved articles were searched for other relevant studies, and major scientific meetings were monitored.

Study selection. Trials that met the following criteria were included: 1) prospective, randomized, placebo controlled, open or blinded trials; 2) assignment of participants to clopidogrel treatment and a placebo group; and 3) data on all-cause mortality, cardiovascular death, MI, stroke, and major bleeding. A total of 197 potentially eligible studies were identified, and 131 were excluded based on title and abstract for not fulfilling inclusion criteria on the basis of intervention. On further review, 61 studies were excluded either because of their nonrandomized nature or because they were not placebo controlled (Fig. 1).

Outcomes measures. The clinical end point definitions were similar among the trials. Outcomes examined in the current overview were a composite end point of any major

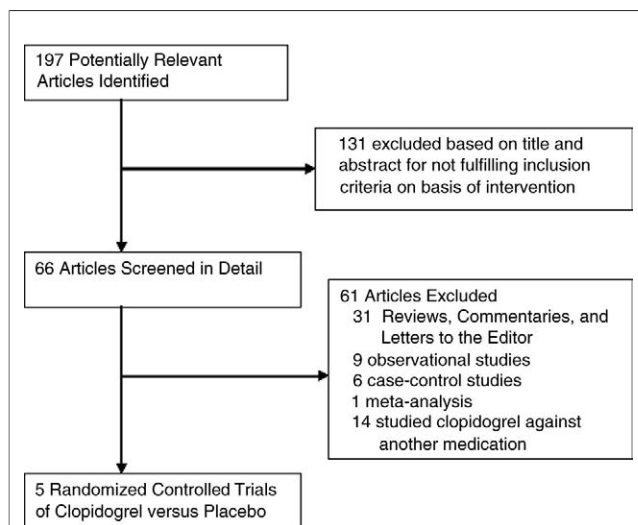


Figure 1 Flow Diagram of the Trial Selection Process

cardiovascular event (cardiovascular mortality, nonfatal MI, or nonfatal stroke), MI (fatal and nonfatal), stroke (fatal and nonfatal), cardiovascular mortality, and all-cause mortality. In the COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) (17), the composite end point included all-cause mortality rather than cardiovascular mortality. We also examined the type of stroke (ischemic vs. hemorrhagic) in all 5 studies. The safety outcome examined was the occurrence of major bleeding as defined by each study.

Statistical analysis. For this collaborative meta-analysis, the principal investigators of each of the included trials supervised the extraction and verified the accuracy of the data from the databases of each trial. Sex-specific data from each trial, which have not been previously published, were combined for this study. The statistical analysis was performed using Stata Statistical Software, release 10 (Stata-Corp, College Station, Texas). Data were analyzed according to the intention-to-treat principle. The Cochrane Q statistic was calculated to assess heterogeneity among the trials for both men and women. However, because the lack of heterogeneity does not necessarily imply homogeneity, a summary odds ratio (OR) was calculated using a random-effects model from the ORs and the 95% confidence intervals (CIs) for each end point in each study using Mantel-Haenszel methods. To test for differences between men and women for each end point, we used a formal test for heterogeneity that is based on the Cochrane Q statistic (25). This test evaluates the degree to which overall heterogeneity can be explained by heterogeneity between subgroups (25). If the p value for the test of heterogeneity is significant ($p < 0.05$), it suggests that the treatment effect differs between groups. In addition, we investigated differences between subgroups using metaregression to explore the relationship between sex and the pooled value for each

outcome measure. The results were nearly identical for each outcome.

The statistical rationale for combining the data has been previously described and used extensively (26). Briefly, the basic principle is that patients allocated to an intervention in a specific trial are only compared with those allocated to the control treatment in the same trial, avoiding direct comparisons of patients across different trials with different designs and lengths of follow-up. These methods provide for combination of information from multiple 2×2 tables, generating a summary OR and its 95% CI as reviewed by Mantel and Haenszel (27) and modified by Yusuf et al. (28). The data were also analyzed using a random-effects model to generate relative risks and 95% CIs. These results did not qualitatively differ from the primary analysis. A value of $p < 0.05$ was judged as statistically significant. Sensitivity analyses were performed for each outcome to assess the contribution of each study to the pooled estimate by excluding individual trials one at a time and recalculating the combined OR for the remaining studies. To assess publication bias, we generated a funnel plot of the logarithm of effect size and compared it with the SE for each trial.

Results

Search results. We identified 5 randomized controlled trials for inclusion (16-20). Women constituted between 20% and 39% of patients enrolled in the trials. In total, 79,613 individuals were enrolled in the 5 trials, of whom 23,522 (30%) were women.

Details of the included studies are shown in Table 1. A broad spectrum of cardiovascular disease was represented by the 5 trials. The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial (20) enrolled patients with a

Table 1 Design of Trials Included in the Meta-Analysis

Trial, Year	n	Patient Population	Female Sex (%)	Clopidogrel Dosage	Clopidogrel Duration	Follow-Up
CURE, 2001	12,562	Patients who presented with acute coronary syndromes without ST-segment elevation	38.5	300-mg loading dose followed by 75 mg/day	3 to 12 months (mean duration of treatment 9 months)	1 yr
CREDO, 2003	2,116	Patients referred for a planned PCI or coronary angiogram	28.6	300-mg loading dose followed by 75 mg once daily*	12 months	1 yr
CLARITY-TIMI 28, 2005	3,491	Patients who presented within 12 h after the onset of an ST-segment elevation MI	19.7	300-mg loading dose followed by 75 mg once daily	Up to and including the day of coronary angiography†	30 days
COMMIT, 2005	45,852	Patients who presented within 24 h of suspected acute MI	27.8	75 mg daily	Hospital discharge or 28 days (median of ≈2 weeks)	Hospital discharge or 28 days (median of ≈2 weeks)
CHARISMA, 2006	15,603	Patients with clinically evident cardiovascular disease or multiple risk factors	29.8	75 mg daily	Median of 28 months, maximum of 35 months	Median of 28 months, maximum of 35 months

*Both groups received 75 mg/day of clopidogrel through day 28. †For patients who did not undergo angiography, study drug was to be administered up to and including day 8 or hospital discharge, whichever came first.

CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; CLARITY-TIMI 28 = Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28; COMMIT = Clopidogrel and Metoprolol in Myocardial Infarction Trial; CREDO = Clopidogrel for the Reduction of Events During Observation; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 2 Characteristics of Women and Men Included in Trials of Clopidogrel Versus Placebo for the Prevention of Cardiovascular Events

	CURE		CREDO		CLARITY		COMMIT		CHARISMA	
	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
n	4,836	7,726	606	1,510	688	2,803	12,759	33,093	4,644	10,959
Demographics										
Age (yrs)	66.5 ± 10.7	62.7 ± 11.4	64.4 ± 10.6	60.6 ± 11.0*	61.6 ± 9.6	56.4 ± 10.2*	66.6 ± 9.7	59.3 ± 11.9*	65.9 ± 10.0	63.6 ± 9.3*
Caucasians	82.4	81.8	85.6	90.1*	91.0	89.0	—	—	89.1	91.0*
BMI (kg/m ²)	27.5 ± 4.5	27.4 ± 3.8	30.0 ± 6.4	30.1 ± 7.4	27.7 ± 5.4	27.4 ± 4.0	—	—	28.9 ± 6.1	28.5 ± 4.8
Clinical history										
Current smoker	14.4	28.4	28.9	32.0	42.0	52.0*	—	—	17.6	21.3*
Hypertension	—	—	76.4	65.9*	56.0	41.0*	51.0	40.0*	81.5	70.2*
SBP (mm Hg)	137.2	132.4	135.0 ± 21.4	132.6 ± 19.9*	132.9 ± 24.2	134.9 ± 22.3	131.1 ± 23.4	127.1 ± 22.1	142.3 ± 20.3	137.3 ± 19.3
DBP (mm Hg)	77.3	76.7	70.1 ± 11.9	74.8 ± 11.8	77.9 ± 14.7	81.5 ± 14.1	81.0 ± 14.4	80.9 ± 14.5	79.0 ± 11.2	78.8 ± 10.7
Hyperlipidemia	48.4	44.5	77.4	76.3	37.0	39.0	—	—	73.8	74.0
Diabetes	25.7	20.7	33.0	23.9*	20.0	16.0*	—	—	45.6	40.5*
Previous MI	25.7	36.2	28.4	37.4*	5.7	10.0*	6.6	9.0*	22.6	39.7*
CVD	59.4	59.3	8.1	5.2*	—	—	—	—	28.6	22.9*
PVD	6.9	9.2	9.8	8.0	4.4	4.1	—	—	—	—
Previous CABG	7.4	13.2	11.8	18.1*	—	—	—	—	11.6	23.2*
Previous PCI	7.3	11.4	22.9	31.1*	2.0	5.6*	—	—	15.1	26.0*
Baseline medication use										
Aspirin	66.3	66.0	28.1	30.5	14.1	16.1	18.2	18.5	90.1	93.7*

Values are presented as mean ± SD or % unless otherwise indicated. *p < 0.05.

BMI = body mass index; CABG = coronary artery bypass graft; CVD = cerebrovascular disease; DBP = diastolic blood pressure; PVD = peripheral vascular disease; SBP = systolic blood pressure; other abbreviations as in Table 1.

non-ST-segment elevation ACS, whereas the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis In Myocardial Infarction 28) (18) and COMMIT (17) trials enrolled patients with an ST-segment elevation MI. The CREDO (Clopidogrel for the Reduction of Events During Observation) (19) trial enrolled patients in whom a percutaneous coronary intervention was planned. Two-thirds of the patients in the CREDO study had a diagnosis of unstable angina or had suffered a recent MI. The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) (16) trial enrolled both patients with established vascular disease ($\approx 80\%$) and patients with multiple risk factors for but without documented vascular disease ($\approx 20\%$). The weighted mean duration of follow-up was 8.3 months. Baseline characteristics of the individuals are presented in Table 2.

Study quality. Randomized treatment allocation sequences were generated in all 5 studies. All 5 trials were placebo-controlled and double-blinded. Treatment in the COMMIT (17) study was randomly assigned according to a 2×2 factorial design; patients were also assigned to metoprolol or placebo; this second randomization will not be considered further here. All 5 trials were partially or completely funded by pharmaceutical companies that make or market clopidogrel. Three of the trials were international (16,18,20), the COMMIT trial was performed solely in China (17), and

the CREDO trial was performed in the U.S. (19). All 5 trials maintained independent clinical events committees to adjudicate the outcomes of interest blinded to treatment assignment. Three of the studies included a 300-mg clopidogrel loading dose at study entry (18-20); all 5 used a daily 75-mg dose of clopidogrel. Aspirin (75 to 325 mg/day in 4 trials and 75 to 162 mg/day in the CHARISMA trial) was administered to patients in all 5 trials. The duration of follow-up ranged from 2 weeks (the COMMIT trial) to 35 months (the CHARISMA trial) and was more than 99% complete in each of the trials.

Major cardiovascular events. A total of 2,680 major cardiovascular events occurred among the 23,533 women enrolled in these trials (Fig. 2), with the event rate being nonsignificantly lower in women allocated clopidogrel compared with those allocated placebo (11.0% vs. 11.8%; OR: 0.93; 95% CI: 0.86 to 1.01).

A total of 4,704 major cardiovascular events occurred among the 56,091 men in these trials, and there was a highly significant 16% reduction in the odds of cardiovascular events among men allocated clopidogrel compared with men allocated placebo (7.8% vs. 9.0%; OR: 0.84; 95% CI: 0.78 to 0.91). There was a weak trend for heterogeneity ($p = 0.092$) that did not reach statistical significance

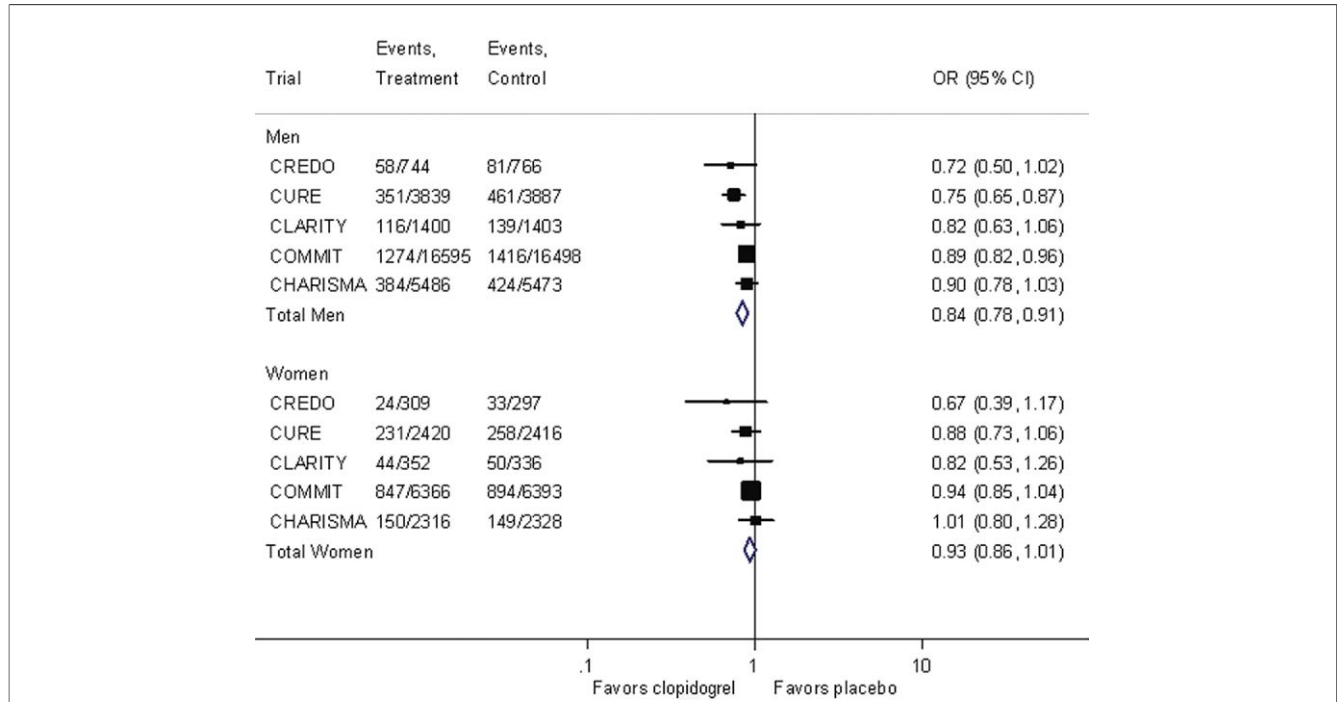


Figure 2 Effect of Clopidogrel Treatment on the Effect of Major Cardiovascular Events

Major cardiovascular events are defined as the composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. Pooled ORs are from a random-effects model. Sizes of data markers are proportional to the amount of data contributed by each trial. CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; CI = confidence interval; CLARITY-TIMI 28 = Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis In Myocardial Infarction 28; COMMIT = Clopidogrel and Metoprolol in Myocardial Infarction Trial; CREDO = Clopidogrel for the Reduction of Events During Observation; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; OR = odds ratio.

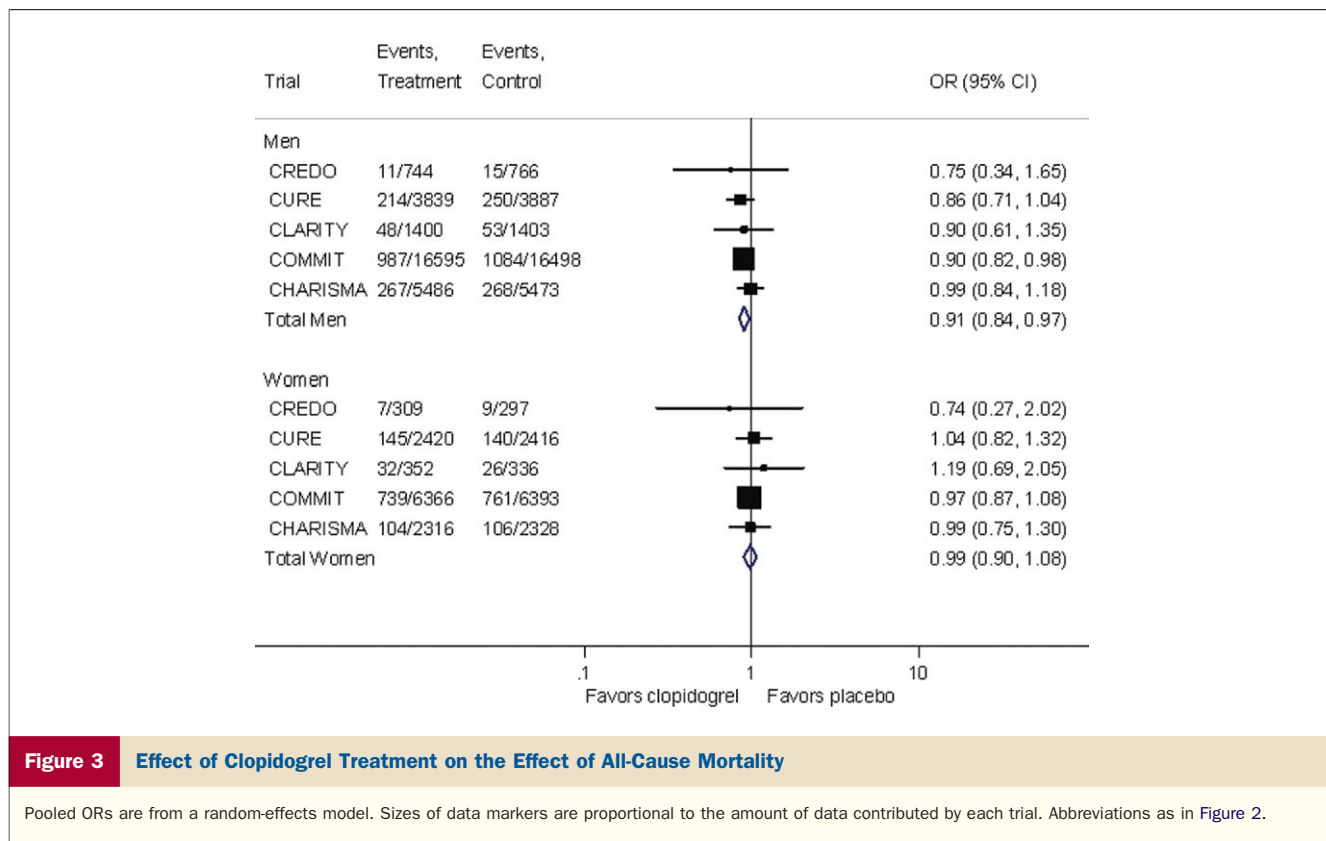


Figure 3 Effect of Clopidogrel Treatment on the Effect of All-Cause Mortality

Pooled ORs are from a random-effects model. Sizes of data markers are proportional to the amount of data contributed by each trial. Abbreviations as in Figure 2.

between women and men for the outcome of major cardiovascular events.

Mortality. Overall, there were 2,069 deaths in 23,522 women (Fig. 3), and this risk was not significantly reduced by allocation to clopidogrel in women (8.7% vs. 8.8%; OR: 0.99; 95% CI: 0.90 to 1.08). Mode of mortality was analyzed in 4 of the 5 trials; no association was noted between clopidogrel allocation and cardiovascular mortality (OR: 1.04; 95% CI: 0.86 to 1.25).

A total of 3,197 deaths occurred in 56,091 men, and allocation to clopidogrel produced a highly significant 9% proportional reduction in the risk of all-cause mortality in men (5.4% vs. 6.0%; OR: 0.91; 95% CI: 0.84 to 0.97). The risk reduction for cardiovascular mortality was almost identical (OR: 0.92; 95% CI: 0.80 to 1.06), although the reduction was not statistically significant. No evidence of statistical heterogeneity in pooled analyses between women and men was detected for all-cause mortality ($p = 0.158$).

MI. There were 766 MIs reported among the 23,533 women (Fig. 4), with the rate being 2.9% in women allocated clopidogrel compared with 3.6% in women allocated placebo (OR: 0.81; 95% CI: 0.70 to 0.93). Each trial reported a decreased risk of MI associated with clopidogrel treatment when analyzed separately.

There were 1,729 MIs reported among the 56,091 men enrolled, and the MI rate was 2.8% in the clopidogrel group compared with 3.4% in the placebo group (OR: 0.83; 95% CI: 0.76 to 0.92). As with women, each trial reported a decreased risk of MI associated with clopidogrel treatment.

There was no evidence of statistical heterogeneity in pooled analyses between women and men for MI ($p = 0.733$).

Stroke. A total of 399 strokes occurred among women in the 5 trials (Fig. 5), and the 9% proportional risk reduction for total stroke with clopidogrel was not statistically significant (1.6% vs. 1.9%; OR: 0.91; 95% CI: 0.69 to 1.21), nor were the separate effects of clopidogrel on ischemic stroke (OR: 0.89; 95% CI: 0.71 to 1.12) or hemorrhagic stroke (1.2% vs. 1.4%; OR: 0.82; 95% CI: 0.29 to 2.32) among women.

A total of 739 strokes occurred among the men. There was a significant decrease in the odds of stroke associated with clopidogrel (OR: 0.83; 95% CI: 0.71 to 0.96). When types of stroke were analyzed separately, there was a significant 16% reduction in ischemic stroke (OR: 0.84; 95% CI: 0.71 to 0.99), with no significant association with hemorrhagic stroke (OR: 0.95; 95% CI: 0.66 to 1.36). There was no evidence of statistical heterogeneity in pooled analyses between women and men for stroke ($p = 0.552$).

Major bleeding. A total of 333 major bleeding events occurred among women (Fig. 6), with the odds being significantly higher among women allocated clopidogrel than among those allocated placebo (1.7% vs. 1.2%; OR: 1.43; 95% CI: 1.15 to 1.79). Each trial reported an increased risk of major bleeding associated with clopidogrel treatment.

Among the men there were a total of 683 major bleeding events recorded, and the rate was significantly higher among men allocated clopidogrel than among men allocated placebo (1.3% vs. 1.1%; OR: 1.22; 95% CI: 1.05 to 1.42).

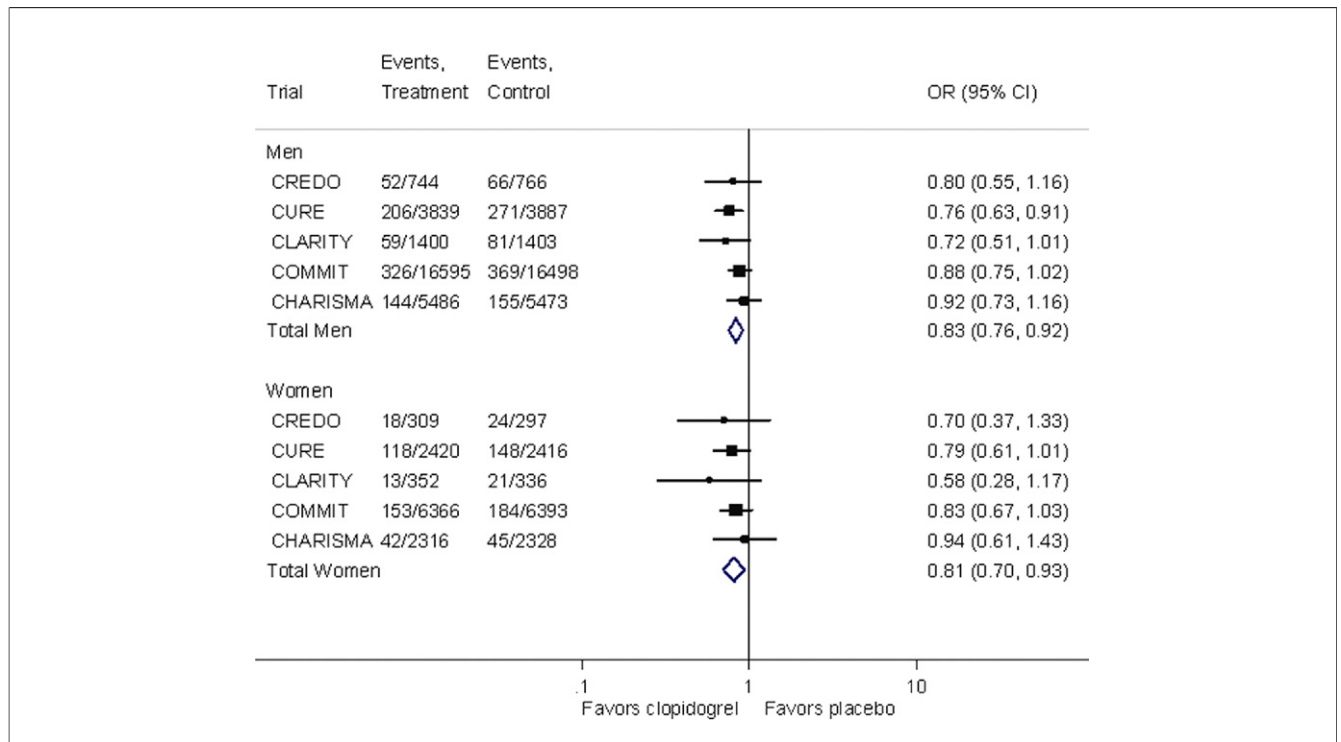


Figure 4 Effect of Clopidogrel Treatment on the Effect of Myocardial Infarction

Pooled ORs are from a random-effects model. Sizes of data markers are proportional to the amount of data contributed by each trial. Abbreviations as in Figure 2.

There was no evidence of statistical heterogeneity in pooled analyses between women and men for major bleeding ($p = 0.243$).

Subgroup analysis. When patients enrolled with an ACS (the CURE, COMMIT, and CLARITY-TIMI 28 trials) are analyzed separately, the efficacy and safety profile in women and men were similar to the results seen in the entire study population (Table 3). In the CHARISMA trial, clopidogrel was associated with an increase in adverse events (including death when analyzed separately) among patients without established cardiovascular disease. We therefore excluded these patients ($n = 3,449$) and evaluated the benefit and risk of clopidogrel only among those with established cardiovascular disease in the CHARISMA trial and the other 4 trials (Table 3). Once again, the efficacy and safety profile in women and men is similar to the results seen in the entire population.

Sensitivity analyses. Deletion of individual studies did not significantly alter the primary outcome. A funnel plot of effect size versus study precision was symmetrical, consistent with a lack of major publication bias. There was no evidence of statistical heterogeneity (as measured by both the Q -test and I^2) between the trials for any of the end points evaluated.

Discussion

In this large study comparing the efficacy and safety of clopidogrel versus placebo between women and men, we

show that clopidogrel reduced the risk of major cardiovascular events in both women and men. In women, the overall effect of clopidogrel was driven by a reduction of MI. In men, however, the effects of clopidogrel on MI, stroke, and all-cause mortality were separately significant. Despite these observations, there was no evidence of statistically significant heterogeneity when the effect of clopidogrel was compared between women and men, indicating that much of the difference between men and women could be explained by play of chance. Regarding major bleeding, there were small but real excess risks with clopidogrel therapy in both men and women.

Benefit of clopidogrel therapy. Platelet inhibition remains a key component in the prevention and treatment of ischemic heart disease (6–8). Treatment with aspirin has been shown to reduce cardiovascular morbidity and mortality in a wide variety of patients and clinical settings (29). Large, randomized trials have shown improved outcomes when clopidogrel is added to aspirin across the spectrum of cardiovascular disease (16–20). In a previous meta-analysis (30), clopidogrel was found to decrease cardiovascular morbidity and mortality. However, there had not previously been a specific analysis of the efficacy and safety of clopidogrel in women compared with men.

In this pooled sex-specific analysis, we found that clopidogrel confers benefit in both women and men. We noted an absolute risk reduction of 0.8% and 0.7% in women for the composite end point and for MI alone, respectively. In

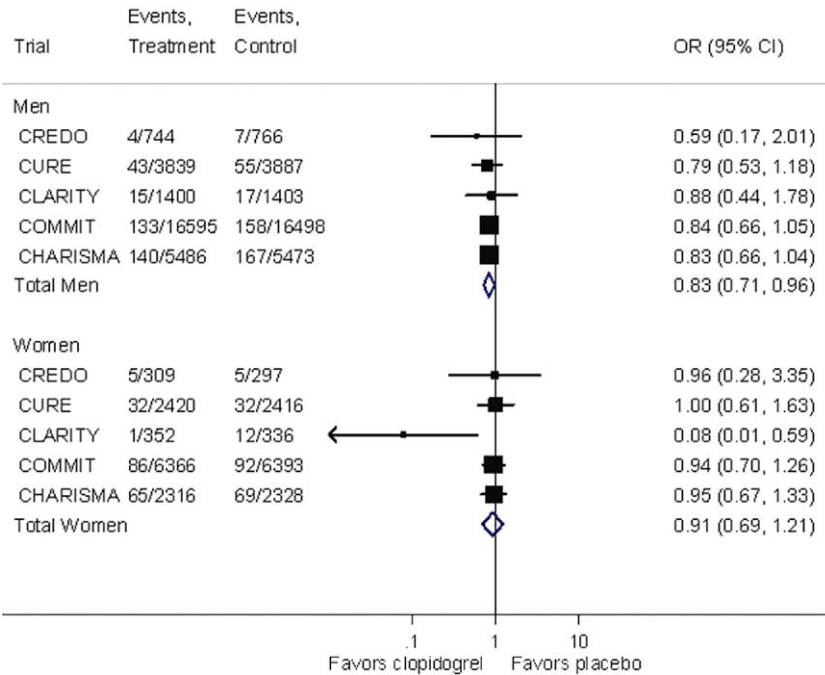


Figure 5 Effect of Clopidogrel Treatment on the Effect of Stroke

Pooled ORs are from a random-effects model. Sizes of data markers are proportional to the amount of data contributed by each trial. Abbreviations as in Figure 2.

other words, an average duration of 8.3 months of treatment with clopidogrel results in an absolute benefit of approximately 8 cardiovascular events and 7 MIs prevented per 1,000 women treated. Among women with ACS, we found an absolute risk reduction of 0.9% in women for the composite end point, corresponding to 9 fewer cardiovascular events per 1,000 women treated with clopidogrel. For men, the absolute risk reduction for the composite and MI end point was 1.2% and 0.6%, respectively, corresponding to approximately 12 fewer cardiovascular events and 6 fewer MIs prevented per 1,000 men treated for an average of 8.3 months. Among men with ACS, we found an absolute risk reduction of 1.3% in men for the composite end point, corresponding to 13 fewer cardiovascular events per 1,000 men treated with clopidogrel.

Safety of clopidogrel therapy. Although effective in preventing further thrombotic events, clopidogrel increases the risk of bleeding. Adding clopidogrel to aspirin therapy resulted in a 43% and 21% increased risk of major bleeding in women and men, respectively. Based on the absolute increase in bleeding of 0.5% and 0.2% in women and men, respectively, the number needed to cause 1 major bleeding event (from an average treatment duration of 8.3 months) with clopidogrel was 200 women and 500 men. In other words, clopidogrel treatment over an average period of 8.3 months results in an absolute increase of approximately 5 major bleeding events per 1,000 women and 2 major bleeding events per 1,000 men. Among those with ACS, in

whom the bleeding risk is believed to be higher, the absolute increase in major bleeding remained 0.5% for women and 0.14% in men.

To better evaluate the balance of benefit versus risk in both groups, we provide the number needed to treat for each individual end point and for a net clinical end point (MI, stroke, cardiovascular death, or major bleeding) in Table 4. Despite no significant difference between women and men, there seems to be a greater benefit for clopidogrel in men. To obtain net clinical benefit over a weighted mean follow-up of 8.3 months, one needed to treat ≈101 men and ≈435 women.

Sex and antiplatelet medications. Several (9–13,31), although not all (32–34), previous studies have reported a sex-specific response to antiplatelet medications. In a sex-specific meta-analysis of aspirin for the primary prevention of cardiovascular disease, aspirin was shown to be effective in reducing cardiovascular events in both women and men (9). However, women derived benefit from a reduction in the risk of stroke, whereas men benefited by a reduction in MI. The increased (≈70%) risk of major bleeding from aspirin was similar between women and men (9). Another class of antiplatelet medication, the intravenous glycoprotein IIb/IIIa inhibitors, was noted to have a significant response by sex. Men, and not women, were noted to have a significant reduction in cardiovascular events, although this difference was largely attributed to patients' baseline risk, as assessed by troponin elevation (10). To date, there is

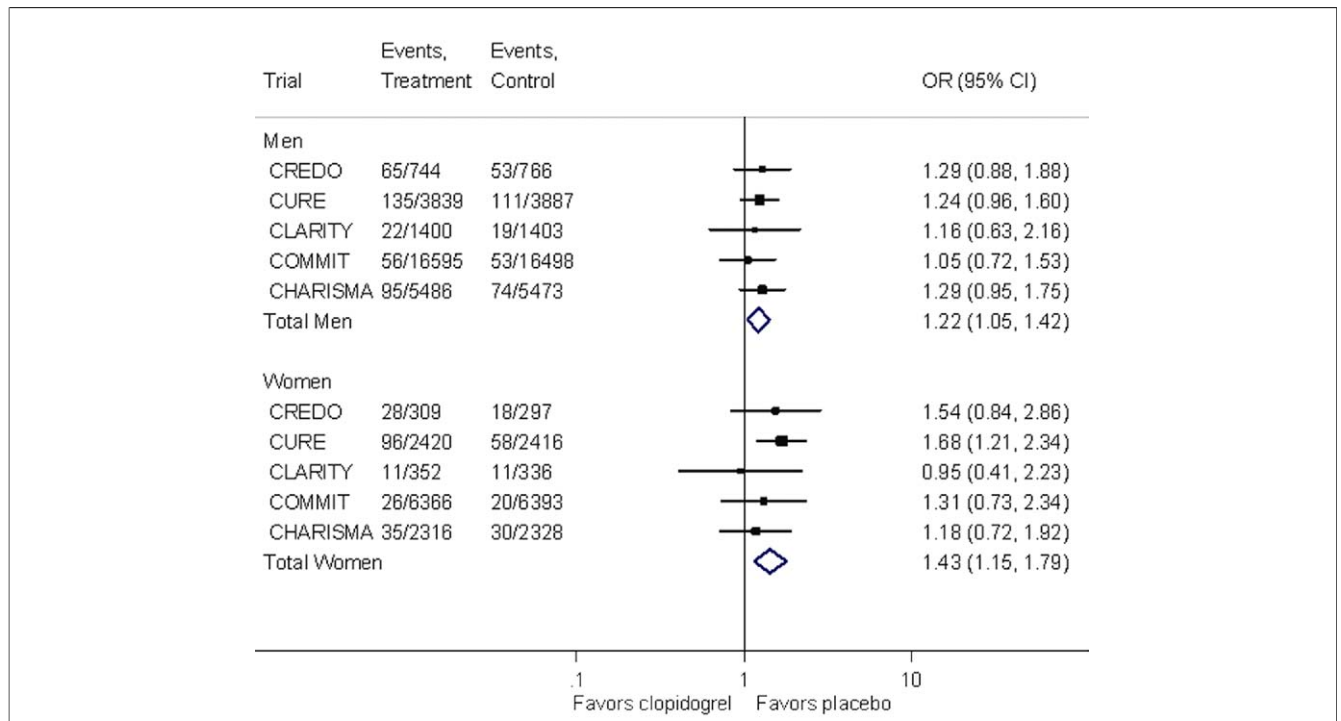


Figure 6 Effect of Clopidogrel Treatment on the Effect of Major Bleeding

Pooled ORs are from a random-effects model. Sizes of data markers are proportional to the amount of data contributed by each trial. Abbreviations as in Figure 2.

no clinical study of clopidogrel in women and men, respectively.

Clopidogrel, a nonreversible platelet antagonist, is a second-generation drug in the class of thienopyridines (35). Although clopidogrel is a more potent antiplatelet agent than aspirin, both drugs have wide ranges of platelet inhibition (36). Several studies have noted increased rates of clinical events among those with decreased platelet inhibition (hyporesponsiveness) to aspirin or clopidogrel (36–42). In response, much attention is focused on identification of these groups with aspirin or clopidogrel hyporesponsiveness. As has been reported with aspirin (43–45), women are also more often found to be hyporesponsive to clopidogrel (24). However, the clinical implication of these findings is uncertain.

The current study shows that both women and men benefit from clopidogrel across a wide spectrum of vascular

disease and clinical presentations. The lack of significant heterogeneity between women and men in their response to clopidogrel for the primary end point and each individual component reinforces this finding. Furthermore, both women and men are at risk for major bleeding from clopidogrel when compared with placebo. Consistent with prior studies (46–49), a numerically increased risk of major bleeding was found among women compared with men; nevertheless, no statistically significant difference existed between the sexes. However, with a greater emphasis being placed on bleeding and its consequences (50), this finding is important and may affect future drug development.

Study limitations. First, as in most meta-analyses, these results should be incorporated with caution because the initial loading dose of clopidogrel and duration of treatment were not uniform. Importantly, these differences did not result in any statistically significant differences in the size of

Table 3 Random-Effects ORs (95% CIs) for Clopidogrel Therapy Versus Placebo in Subgroup Analyses

	Major Cardiovascular Event	All-Cause Mortality	Myocardial Infarction	Stroke	Major Bleeding
Enrollment for ACS					
Women	0.93 (0.85–1.01)	0.99 (0.90–1.09)	0.80 (0.68–0.94)	0.80 (0.45–1.45)	1.50 (1.14–1.97)
Men	0.83 (0.74–0.93)	0.89 (0.82–0.97)	0.82 (0.73–0.91)	0.83 (0.68–1.00)	1.18 (0.96–1.44)
Established CVD					
Women	0.93 (0.85–1.01)	0.98 (0.89–1.07)	0.81 (0.70–0.94)	0.92 (0.67–1.27)	1.43 (1.14–1.79)
Men	0.84 (0.78–0.92)	0.90 (0.83–0.96)	0.82 (0.74–0.90)	0.81 (0.69–0.94)	1.19 (1.02–1.40)

ACS = acute coronary syndromes; CI = confidence interval; CVD = cardiovascular disease; OR = odds ratio.

Table 4

Estimated Number Needed to Treat or Harm With Clopidogrel Versus Placebo in Sex-Stratified Analysis for Each Individual End Point Analyzed

	Clopidogrel (%)	Placebo (%)	Change in Absolute Risk (%)	NNT or NNH
MACE				
Men	7.78	8.99	1.21	83
Women	11.02	11.76	0.74	135
All-cause mortality				
Men	5.44	5.996	0.52	192
Women	8.74	8.85	0.11	909
Myocardial infarction				
Men	2.80	3.36	0.56	179
Women	2.92	3.59	0.67	149
Stroke				
Men	1.19	1.44	0.25	400
Women	1.61	1.95	0.34	294
Major bleeding				
Men	1.33	1.11	0.22	455
Women	1.67	1.16	0.51	196
MACE + major bleeding				
Men	9.11	10.1	0.99	101
Women	12.69	12.92	0.23	435

Major adverse cardiovascular event (MACE): myocardial infarction, stroke, or cardiovascular death. NNH = number needed to harm; NNT = number needed to treat.

the treatment effect between the trials. Furthermore, after removal of the largest trial with the shortest duration of follow-up (the COMMIT trial), the results obtained were nearly identical. Second, we were unable to determine what effect clopidogrel has on particular subgroups of interest. Only an analysis of patient-level data from all of the trials would allow an examination of the benefits of clopidogrel in particular subgroups. Third, among the 5 trials, 4 different definitions of major bleeding were used. Although this should not change the conclusion of the results, these variations in major bleeding definitions make it impossible to determine the true frequency of bleeding using any one of the definitions. Fourth, although no significant differences in benefit or risk from clopidogrel between men and women were observed on heterogeneity analyses, the benefit and risk of clopidogrel was not perfectly homogenous in women and men, and we are unable to rule out with certainty that some difference in benefit and risk might exist. Finally, meta-analysis remains retrospective research that is subject to the methodological deficiencies of the included studies. We minimized the likelihood of bias by developing a detailed protocol before initiating the study, by performing a meticulous search for published and unpublished studies, and by using explicit methods for study selection, data extraction, and data analysis.

Conclusions

This meta-analysis of more than 23,000 women and 56,000 men shows that clopidogrel is effective in reducing cardiovascular events, and this difference is not significantly

different between women and men. Whereas women derived a majority of their cardiovascular benefit by reducing the risk of MI, men had a significant reduction in the risk of MI, stroke, and all-cause mortality. This benefit was consistent across the spectrum of patients with cardiovascular disease and did not differ by clinical presentation.

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