Efficacy and Safety of High Potent P2Y$_{12}$ Inhibitors Prasugrel and Ticagrelor in Patients With Coronary Heart Disease Treated With Dual Antiplatelet Therapy: A Sex-Specific Systematic Review and Meta-Analysis

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***Background*—**Sex differences in efficacy and safety of dual antiplatelet therapy remain uncertain because of the underrepresentation of women in cardiovascular trials. The aim of this study was to perform a sex-specific analysis of the pooled efficacy and safety data of clinical trials comparing a high potent P2Y$_{12}$ inhibitor+aspirin with clopidogrel+aspirin in patients with acute coronary syndrome.

***Methods and Results*—**A systematic literature search was performed. Randomized clinical trials that compared patients following percutaneous coronary intervention/acute coronary syndrome who were taking high potent P2Y$_{12}$ inhibitors+aspirin versus clopidogrel+aspirin were selected. Random effects estimates were calculated and relative risks with 95% CIs on efficacy and safety end points were determined per sex. We included 6 randomized clinical trials comparing prasugrel/ticagrelor versus clopidogrel in 43 990 patients (13 030 women), with a median follow-up time of 1.06 years. Women and men had similar relative risk (RR) reduction for major cardiovascular events (women: RR, 0.89 [95% CI, 0.80–1.00; men: RR, 0.84 [95% CI, 0.79–0.91) (*P* for interaction=0.39). Regarding safety, women and men had similar risk of major bleeding by high-potency dual antiplatelet therapy (RR, 1.18 [95% CI, 0.98–1.41] versus RR, 1.03 [95% CI, 0.93–1.14]) (*P* for interaction=0.20).

***Conclusions*—**The small and statistically insignificant difference in efficacy and safety estimates of high-potency dual antiplatelet therapy between women and men following percutaneous coronary intervention/acute coronary syndrome do not justify differential dual antiplatelet therapy treatment for both sexes. **(*J Am Heart Assoc*. 2020;9:e014457. DOI: 10.1161/JAHA.119.014457.)**

Key Words: coronary artery disease • dual antiplatelet therapy • sex-specific

Current guidelines for the management of patients with coronary artery disease (CAD) recommend the use of dual antiplatelet therapy (DAPT), a combination of aspirin and an oral inhibitor of the platelet P2Y$_{12}$ receptor, to reduce coronary thrombosis and mortality in patients who experienced an acute coronary syndrome (ACS) or who underwent a percutaneous coronary intervention (PCI). Although DAPT is effective in decreasing thrombotic complications in these patients, the therapy increases the risk of bleeding complications. Therefore, risk assessment balancing thrombotic versus bleeding risk is warranted before DAPT is considered.[1]

The next-generation P2Y$_{12}$ inhibitor prasugrel has a more rapid onset of action than clopidogrel, attributable to more efficient metabolic activations,[2] and leads to a higher reduction of ischemic events compared with clopidogrel.[3] Later, ticagrelor was developed, which reversibly inhibits the P2Y$_{12}$ receptor so the effects can be reversed more easily and not be a prodrug, leading to a faster onset of action because it does not require conversion to an active metabolite.[4,5] A large clinical trial also showed higher efficacy of ticagrelor in the reduction of ischemic events and stent thrombosis (ST) compared with clopidogrel.[6]

Therefore, the high potent P2Y$_{12}$ inhibitors ticagrelor or prasugrel in combination with aspirin are currently recommended as first-choice therapy in patients with ACS.[1]

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Accompanying Tables S1 through S6 and Figures S1 through S28 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014457

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Received August 28, 2019; accepted December 19, 2019.

Clinical Perspective

What Is New?

- Women are less likely to be treated with high potent $P2Y_{12}$ inhibitors prasugrel/ticagrelor than men in clinical practice.
- Sex-specific additional risk for cardiovascular end points and bleeding of prasugrel/ticagrelor compared with clopidogrel is lacking.

What Are the Clinical Implications?

- We showed that there are no significant sex differences in efficacy and safety of the high potent $P2Y_{12}$ inhibitors prasugrel/ticagrelor compared with clopidogrel.
- This should lead the way to prescribing guideline-recommended high potent dual antiplatelet therapy in both men and women.

The latest update of the European Society of Cardiology guidelines on DAPT in patients with CAD state that there is "no convincing evidence for a gender-related difference in the efficacy and safety of currently available DAPT type or duration across studies."[1] However, taking into account that the typical women to men ratio in these trials is 1:4, analyses stratified by sex—if published—are underpowered and therefore sex differences in efficacy and safety of DAPT remain uncertain.[7] In addition, registries have shown that women are less likely to be treated with high potent $P2Y_{12}$ inhibitors than men in clinical practice.[8]

Currently, it is more recognized that the efficacy and safety of drugs may differ between men and women. As women have lower body weight, a higher fat/water balance, and a lower clearance in general, as well as different hormonal composition, pharmacokinetics and pharmacodynamics can be affected.[9–11] Therefore, to be able to provide sex- and gender-specific guideline recommendations it is important to verify whether efficacy and safety is equal for specific drugs, especially when these are prescribed to a large number of both male and female patients.

The aim of this study was to perform sex-specific analyses of the pooled efficacy and safety data of trials comparing high potent DAPT prasugrel/ticagrelor against clopidogrel in patients with ACS with or without PCI.

Methods

Our protocol is published on PROSPERO (ID: CRD42018082179).

The authors declare that all supporting data are available within the article (and its online supplementary files).

Literature Search

We developed a search strategy to identify randomized controlled trials (RCTs) investigating the efficacy and safety of aspirin and $P2Y_{12}$ inhibitors compared with aspirin, aspirin+-placebo, or clopidogrel+aspirin in patients with CAD. We performed a systematic literature search in MEDLINE Ovid, EMBASE, and the Cochrane Central Register of Controlled trials (latest search performed: June 2018). For the full search strategies, see Table S1. In addition, reference lists from eligible trials were reviewed to identify potentially relevant trials.

Population

We considered studies of participants who were assigned to DAPT for cardiovascular prevention following PCI with or without coronary stent, or after admission for ACS. Studies focusing on the use of DAPT in patients undergoing coronary artery bypass graft surgery were excluded, as the efficacy and safety of DAPT in these patients is complex and dependent on pretreatment with PCI.[12]

Inclusion and Exclusion Criteria

Studies were eligible if they fulfilled the following criteria: (1) original full-text article; (2) RCT or double-blind, single-blind, or open-label design; (3) DAPT treatment as secondary prevention after either PCI following documented CAD or a diagnosis of CAD with a high risk of events, eg, previous myocardial infarction (MI); (4) DAPT treatment >1 month; (5) analysis on both cardiovascular outcomes and adverse events; (6) ≥50 participants in the intervention and control group; and (7) population age ≥18 years. Language was restricted to English.

For our study, the regimen of DAPT was limited to the following combinations: ticagrelor+aspirin and prasugrel+aspirin versus clopidogrel+aspirin. Studies analyzing the effect of cangrelor and elinogrel were excluded as these are administered intravenously when oral drugs are contraindicated and therefore the duration of use of these agents is generally limited.

Studies were excluded if: (1) the population had cardiovascular disease other than ACS, (2) DAPT was intended as primary cardiovascular prevention, and (3) the population was nonhuman.

If more than 1 published article was available from the same trial, the article with the most detailed information regarding cardiovascular outcomes and adverse events was included.

See Table S2 for the full overview of the inclusion and exclusion criteria.

Data Extraction

A systematic 2-step screening of the literature was performed by 2 independent reviewers (R.B. and L.E.V.). The title and abstract screening was first performed, and then the full-text screening.

DOI: 10.1161/JAHA.119.014457

Table 1. Description of Included Trials in the Meta-Analysis

	Author	Year, Publication	Country	Trial	Year, Baseline	Population*	Age, y	Sample Size, No.	Revascularization*	Follow-Up, Median	Follow-Up Start Related to Event	Intervention	Control	Efficacy End Points	Bleeding Classification	Cochrane Collaboration Tool, Risk of Bias
1	Cannon et al[22]	2007	UK (multicenter trial)	DISPERSE-2[22]	2004	NSTE-ACS	Ticagrelor: 64, clopidogrel 62	948 316 ♀ 632 ♂	PCI	56 d	Not specifically reported	Ticagrelor+ aspirin	Clopidogrel+ aspirin	MI, ACM, stroke, severe recurrent ischemia	TIMI	Low
2	Wallentin et al[6]	2009	United States (multicenter trial)	PLATO[6]	2006	ACS	Ticagrelor: 61, clopidogrel: 61	18 624 5288 ♀ 13 336 ♂	PCI with DES or BMS	279 d	Directly after PCI	Ticagrelor+ aspirin	Clopidogrel+ aspirin	ACM, CVM, MI, CVA, ST	TIMI+GUSTO/ PLATO defined TIMI bleeding	Low
3	Saito et al[23]	2014	Japan	PRASFIT-ACS[23]	2010	ACS	Prasugrel: 65.4, clopidogrel: 65.1	1363 289 ♀ 1074 ♂	PCI with BMS or DES	210.5 d†	When scheduled for PCI	Prasugrel+ aspirin	Clopidogrel+ aspirin	MACE: CVM, nonfatal MI, and stroke	TIMI	Low
4	Cuisset et al[24]	2017	France	TOPIC, 2017[24]	2014	ACS	Ticagrelor/ prasugrel: 59.6, clopidogrel: 60.6	646 114 ♀ 532 ♂	PCI	359 d	1 mo after PCI	Prasugrel/ ticagrelor+ aspirin	Clopidogrel+ aspirin	MACE: CVM, UR, stroke	BARC	Low
5	Roe et al[25]	2012	United States (multicenter)	TRILOGY ACS[25]	2008	NSTEMI or UA	Prasugrel: 66, clopidogrel: 66	9326 3650 ♀ 5676 ♂	No	17 mo	Within 10 d after index event	Prasugrel+ aspirin	Clopidogrel+ aspirin	MACE: CVM, nonfatal MI, and stroke	TIMI/GUSTO	Low
6	Wiviott et al[3]	2007	France (multicenter)	TRITON-TIMI 38[3]	2004	ACS	Prasugrel: 74, clopidogrel: 74	13 608 3523 ♀ 10 085♂	PCI with DES or BMS	14.5 mo	When scheduled for PCI	Prasugrel+ aspirin	Clopidogrel+ aspirin	MACE: ACM, CVM, MI, ST	TIMI	Low

*Indication: acute coronary syndrome (ACS), non–ST-segment–elevation myocardial infarction (NSTEMI), unstable angina (UA). Revascularization: percutaneous coronary intervention (PCI), drug-eluting stent (DES), bare-metal stent (BMS). Efficacy end points: all-cause mortality (ACM), cardiovascular mortality (CVM), myocardial infarction (MI), stent thrombosis (ST), cerebrovascular accident (CVA), unplanned revascularization (UR), major cardiovascular event (MACE). BARC indicates Bleeding Academic Research Consortium; DISPERSE-2, Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs Clopidogrel in NSTEMI 2; GUSTO, Global Utilization of Streptokinase and TPA for Occluded Arteries; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; PLATO, Platelet Inhibition and Patient Outcomes; PRASFIT-ACS, Prasugrel Compared With Clopidogrel for Japanese Patients With ACS Undergoing PCI; TIMI, thrombolysis in myocardial infarction; TOPIC, Timing of Platelet Inhibition After Acute Coronary Syndrome; TRILOGY ACS, Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes; TRITON-TIMI, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction.

†The median follow-up was not mentioned; therefore, we used the weighed mean follow-up of the intervention and control group.

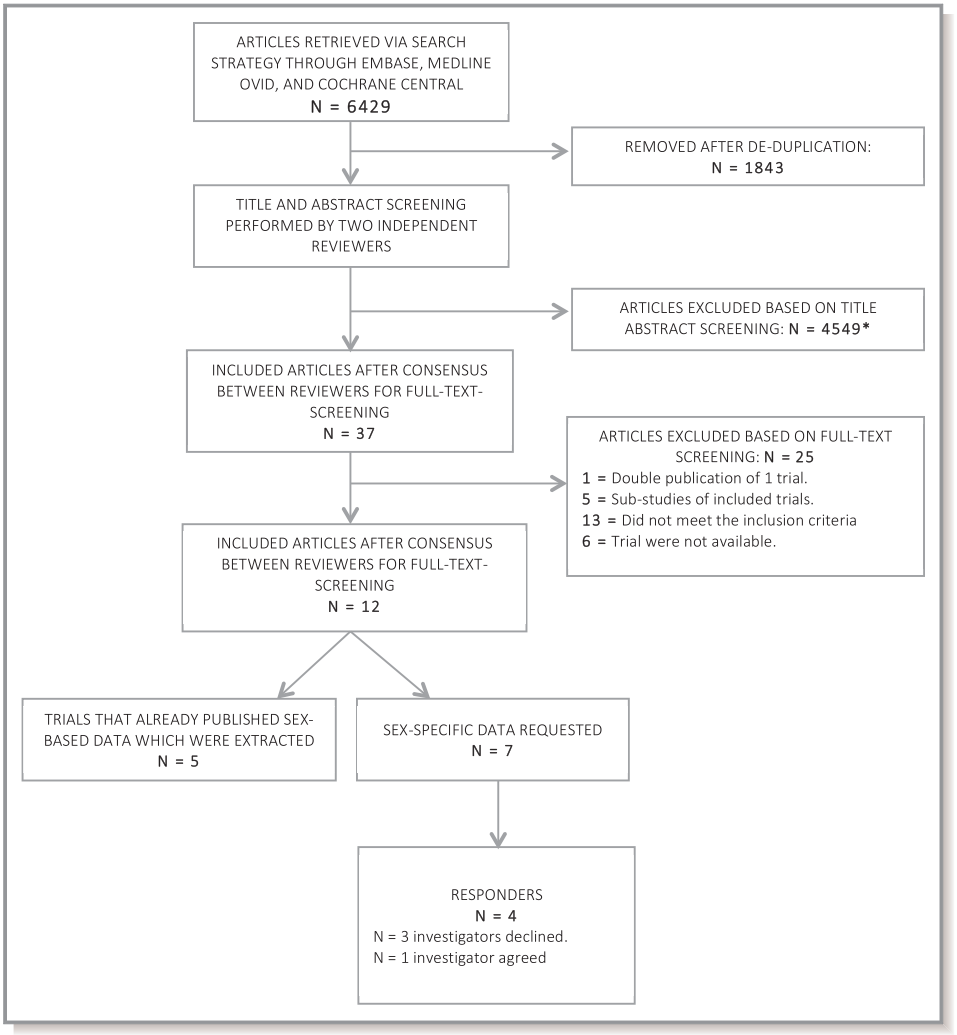

Figure 1. Flowchart describing the screening and selection process. *See Table S3 for the appropriate exclusion reasons for title and abstract screening.

Disagreements during the title/abstract and full-text screening about whether to include a study were resolved by discussion with a third investigator (M.M.S.) to reach consensus.

Of the included trials, the following relevant data were extracted: trial name, first author, journal, publication year, country, the blinding method that was applied, treatment of intervention and control arms, demographic characteristics (indication, duration of follow-up, sample size), age, and sex. Efficacy and safety end points were extracted, if reported, for women and men separately.

If data of the included trials were not available, we requested both efficacy and safety end points per sex by contacting the corresponding author.

The risk of bias in the included trials for the meta-analysis was assessed with the Cochrane Collaboration's tool[13] (Table 1 and Table S3). This tool consists of 6 domains of bias in which different aspects are covered. The risk per aspect was categorized by the reviewers as low, unclear, or high.

Efficacy and Safety End Points

The primary efficacy end point was major cardiovascular event (MACE). For the definition of MACE per included trial, see Table S4. The secondary efficacy end points were all-cause mortality, cardiovascular mortality, MI, stroke, and ST.

The primary safety end point was defined as major bleeding, based on the thrombolysis in MI bleeding criteria 1; Bleeding Academic Research Consortium (BARC) 2, 3, and 5; or Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) bleeding criteria 1.[14–16] The secondary safety end point was defined as minor bleeding, based on the thrombolysis in MI bleeding criteria 2.

Statistical Analyses

Potential sex differences in efficacy and safety of potent $P2Y_{12}$ inhibitors (prasugrel or ticagrelor)+aspirin versus clopidogrel+

Table 2. Efficacy and Safety Analysis of High Potent $P2Y_{12}$ Inhibitor+Aspirin vs Clopidogrel+Aspirin

End Points	RR (95% CI)	Events Intervention	Events Control	*P* Value
MACE				
High potent $P2Y_{12}$ inhibitor+aspirin vs clopidogrel+aspirin	0.87 (0.80–0.94)	2211/21 828	2540/21 754	<0.001
Major bleeding				
High potent $P2Y_{12}$ inhibitor+aspirin vs clopidogrel+aspirin	1.06 (0.97–1.17)	901/22 078	842/21 998	0.184

MACE indicates major cardiovascular event; RR, relative risk.

aspirin were determined by extracting MACE end points and major bleeding for women and men separately from the selected trials. The pooled relative risks (RRs) for efficacy and safety end points and 95% CIs were then estimated per sex with a random effect model computed based on the DerSimonian and Laird method.[17] Under the null hypothesis, the difference in $\ln(RR_{pooled})$ between women and men follows (approximately) a normal distribution. We therefore calculated the statistic *Z* difference in $\ln(RR_{pooled})$/standard error, which we then compared with the standard normal distribution to reveal the level of significance.

The pooled absolute risk reduction was determined as follows. First, for each trial, the absolute risks in treatment and control arms were calculated as the number of patients with an end point event divided by the corresponding sample size. Then, the absolute risk reduction was defined as the difference in absolute risk in the treatment arm minus control. Finally, trial estimates were pooled using the inverse of the variance of the absolute risk reductions as weighing factor. Numbers needed to treat/harm were calculated for the differences in absolute risk, based on the weighed median duration of follow-up of all trials.

Statistical analyses were performed in STATA (version 14, StataCorp LLC) and in R. For the STATA scripts, see Table S5. All tests were 2-sided, with significance defined as a *P* value of <0.05.

Heterogeneity

Heterogeneity between studies was assessed based on the Q-statistic and quantified by I^2 statistic. Moreover, a 95% prediction interval was determined in order to better report heterogeneity between studies.[18–20] Small-study effects were assessed using contoured funnel plots and the Egger test.[21]

Table 3. Sex-Specific Efficacy and Safety Analysis of High Potent $P2Y_{12}$ Inhibitor+Aspirin vs Clopidogrel+Aspirin

Efficacy and Safety Analysis Based on High Potent DAPT vs Clopidogrel+Aspirin							
	Female			Male			
End Points	RR (95% CI)	Events Intervention	Events Control	RR (95% CI)	Events Intervention	Events Control	Sex Interaction
MACE*	0.91 (0.83–1.00)	737/6497	818/6543	0.85 (0.80–0.91)	1474/15 410	1722/15 277	*P*=0.24
All-cause mortality	0.91 (0.79–1.05)	360/6530	396/6574	0.86 (0.77–0.95)	630/15 620	732/15 503	*P*=0.53
Cardiovascular mortality	0.88 (0.76–1.03)	294/6530	333/6574	0.85 (0.76–0.96)	516/15 620	603/15 503	*P*=0.72
MI	0.88 (0.78–1.00)	455/6530	520/6574	0.82 (0.74–0.93)	991/15 620	1201/15 503	*P*=0.41
ST†	0.52 (0.23–1.16)	24/6307	51/6369	0.56 (0.44–0.70)	111/15 416	197/15 286	*P*=0.86
Stroke‡	1.03 (0.78–1.37)	100/6497	98/6551	1.02 (0.82–1.26)	178/15 512	174/15 392	*P*=0.96
Major bleeding	1.18 (0.98–1.41)	237/6509	201/6554	1.03 (0.93–1.14)	664/15 569	641/15 444	*P*=0.20
Minor bleeding	1.13 (0.75–1.71)	207/6509	196/6554	1.20 (0.94–1.52)	357/15 569	293/15 444	*P*=0.80

ACS indicates acute coronary syndrome; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; MI, myocardial infarction; RR, relative risk; NSTEMI, non–ST-segment–elevation myocardial infarction.

*The TOPIC (Timing of Platelet Inhibition After Acute Coronary Syndrome) trial was not included because they did not report a major cardiovascular event (MACE) end point.

†DISPERSE-2 (Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs Clopidogrel in NSTEMI 2) was not included because they did not report a stent thrombosis (ST) end point and the TOPIC ticagrelor and PRASFIT-ACS (Prasugrel Compared With Clopidogrel for Japanese Patients With ACS Undergoing PCI) trials were not included because there were no ST events during follow-up.

‡TOPIC ticagrelor was not included because there were no stroke events during follow-up. Stroke was defined as either ischemic stroke (TOPIC, TRITON-TIMI 38 [Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38], and PRASFIT-ACS) or ischemic/hemorrhagic stroke (DISPERSE-2, TRILOGY ACS [Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes], and PLATO [Platelet Inhibition and Patient Outcomes] trials).

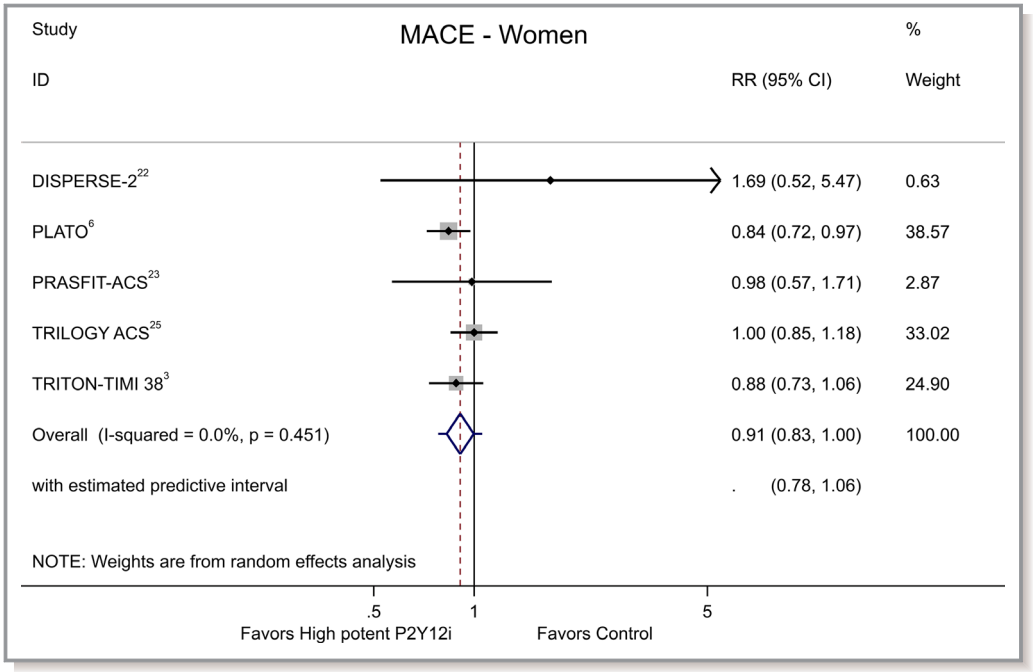

Figure 2. The relative risk (RR) of major cardiovascular events (MACEs) in women treated with a high potent P2Y$_{12}$ inhibitor (prasugrel/ticagrelor) vs clopidogrel. ACS indicates acute coronary syndrome; DISPERSE-2, Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs Clopidogrel in NSTEMI 2; PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes; PRASFIT-ACS, Prasugrel Compared With Clopidogrel for Japanese Patients With ACS Undergoing PCI; TRILOGY ACS, Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes; NSTEMI, non–ST-segment–elevation myocardial infarction; TRITON-TIMI 38, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38.

Results

Characteristics of the RCTs

Twelve trials were found eligible for inclusion in our meta-analysis. Five trials reported their outcomes for women and men separately in the original publications, subanalyses, or in previously published systematic reviews and meta-analyses (Figure 1, Table S6). One of the corresponding authors of the remaining trials who was contacted for their efficacy and safety outcomes stratified by sex provided the required sex-specific data. Three investigators declined to perform the additional analyses requested as a result of low capacity in staff, and 2 authors did not respond to our requests.

Thus, 6 trials with a total of 13 030 (30%) female and 30 960 (70%) male participants were included in our meta-analysis.

Key characteristics of these trials are presented in Table 1.[3,6,22–25] The weighed median follow-up time was 1.06 years. The population of the PLATO (Platelet Inhibition and Patient Outcomes), PRASFIT-ACS (Prasugrel Compared With Clopidogrel for Japanese Patients With ACS Undergoing PCI), TOPIC (Timing of Platelet Inhibition After Acute Coronary Syndrome), and TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38) trials consisted of patients with ACS, whereas the DISPERSE-2 (Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs Clopidogrel in NSTEMI 2) trial exclusively enrolled patients with non–ST-segment elevation ACS, and the TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial included only patients with non–ST-segment–elevation myocardial infarction (NSTEMI) or unstable angina. All trials enrolled patients who underwent revascularization, except for the TRILOGY ACS trial, in which patients were only eligible if they received medical treatment without revascularization after the index event. Prasugrel was used as the high potent P2Y$_{12}$ inhibitor in 3 trials, ticagrelor was used as the high potent P2Y$_{12}$ inhibitor in 2 trials, and prasugrel or ticagrelor was used as the high potent P2Y$_{12}$ inhibitor in 1 trial. In the DISPERSE-2 trial, the 90 mg ticagrelor dosage group was included as the treatment group.

Quality Assessment

Quality assessment is presented in Table S3. All included trials scored low on selection bias, performance bias, detection bias, attrition bias, and reporting bias; therefore,

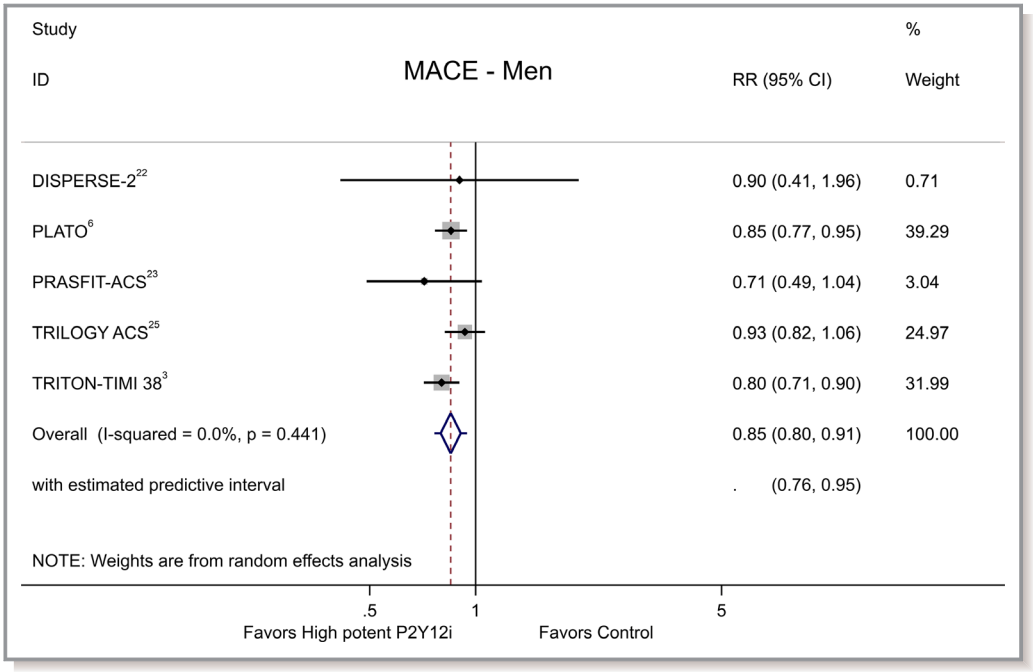

Figure 3. The relative risk (RR) of major cardiovascular events (MACEs) in men treated with a high potent P2Y$_{12}$ inhibitor (prasugrel/ticagrelor) vs clopidogrel. ACS indicates acute coronary syndrome; DISPERSE-2, Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs Clopidogrel in NSTEMI 2; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes; PRASFIT-ACS, Prasugrel Compared With Clopidogrel for Japanese Patients With ACS Undergoing PCI; TRILOGY ACS, Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes; TRITON-TIMI 38, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38.

all have been evaluated as having low risk of bias. The most prevalent potential risk of bias was because studies did not clearly indicate the allocation concealment.

Efficacy Outcomes

High potent P2Y$_{12}$ inhibitor (prasugrel or ticagrelor)+aspirin was associated with an additional reduction in MACE compared with clopidogrel+aspirin (RR, 0.87; 95% CI, 0.80–0.94 [P<0.001]) (Table 2). Women and men had similar relative risk reduction (women: RR, 0.89 [95% CI, 0.80–1.00]; men: RR, 0.84 [95% CI, 0.79–0.91] (P for interaction=0.39) (Table 3 and Figures 2 and 3[3,6,22–25]). The number needed to treat with high potency DAPT versus clopidogrel+aspirin to prevent 1 MACE was 88 for women and 55 for men based on a weighed median duration of treatment of 1.06 years (Table 4).

Our secondary efficacy end points (all-cause mortality, cardiovascular mortality, MI, ST, and stroke) also did not show any significant difference between women and men (Figures S1 through S10). The statistics of all efficacy end points are summarized in Table 3. Regarding the absolute numbers, women compared with men showed less absolute risk reduction in all-cause mortality (0.3% versus 0.6%), cardiovascular mortality (0.3 versus 0.4), MI (0.8% versus 1.3%), and ST (1.15% versus 1.22%) (Table 4). In addition, the absolute risks for the efficacy end points were slightly higher in women than men for high potent P2Y$_{12}$ inhibitors, except for ST and stroke (Table 4).

Safety Outcome

Risk for major bleeding in patients treated with high potent P2Y$_{12}$ inhibitor+aspirin compared with clopidogrel+aspirin was not significantly increased (RR, 1.06; 95% CI, 0.97–1.17 [P=0.2]) (Table 2). Also, no differences between women and men were observed regarding major bleeding in patients randomized to high potent DAPT versus clopidogrel+aspirin (women: RR, 1.18 [95% CI, 0.98–1.41]; men: RR, 1.03 [95% CI, 0.93–1.14]) (P for interaction=0.2) (Table 3 and Figures 4 and 5[3,6,22–25]).

Adding prasugrel or ticagrelor to aspirin instead of clopidogrel was associated with an increased risk of major bleeding of 0.2% in women and 0.04% in men, resulting in a number needed to harm for high potent DAPT treatment of 538 women versus 2489 men based on a weighed median duration of treatment of 1.05 years (Table 4).

Table 4. Pooled Absolute Event Rates and NNT/NNH With High Potent $P2Y_{12}$ Inhibitor+Aspirin vs Clopidogrel+Aspirin

	High Potent $P2Y_{12}$ Inhibitor, %	Control, %	Absolute Risk Difference, %	NNT/NNH
MACE				
Women	11.1	11.9	0.8	131
Men	9.3	11.1	1.8	58
All-cause mortality				
Women	4.8	5.1	0.3	364
Men	3.1	3.7	0.6	191
CVM				
Women	4.0	4.3	0.3	424
Men	2.4	2.8	0.4	232
MI				
Women	6.9	7.7	0.8	114
Men	6.5	7.8	1.3	74
ST				
Women	0.06	1.3	1.2	140
Men	0.6	1	0.4	256
Stroke*				
Women	1.4	0.4	1	96
Men	1	1.1	0.1	5912
Major bleeding				
Women	2.8	2.6	0.2	541
Men	2.6	2.6	0.04	2474
Minor bleeding				
Women	2.6	1.8	0.8	911
Men	2.6	2.9	0.3	268

CVM indicates cardiovascular mortality; MACE, major cardiovascular event; MI, myocardial infarction; NNH, number needed to harm; NNT, number needed to treat; NSTEMI, non–ST-segment–elevation myocardial infarction; ST, stent thrombosis.
*DISPERSE-2 (Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs Clopidogrel in NSTEMI 2), TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes), and PLATO (Platelet Inhibition and Patient Outcomes) trials defined stroke as either ischemic or hemorrhagic.

Minor bleeding also showed no sex differences (Table 3 and Figures S11 and S12). Regarding the absolute numbers, the additional risks for minor bleeding in men using high potent $P2Y_{12}$ inhibitor+aspirin were slightly higher compared with women (0.8% versus 0.3%) (Table 4).

Heterogeneity

Some heterogeneity was found in the efficacy end point of MI in men between studies for MI in men (I^2=29.2%, Q statistic P=0.205) and ST in women (I^2=49.3%, Q statistic P=0.1) with prediction intervals slightly exceeding the CI of the pooled effect. However, the Egger test showed no indication for small-study effects (Figures S13 through S28).

Discussion

Our systematic review and meta-analysis show that the efficacy and safety of high potent DAPT (prasugrel or ticragelor in combination with aspirin) compared with clopidogrel+aspirin in patients with ACS are similar in both men and women. No sex difference was observed in additional reduction of MACE or increase of bleeding risk in patients randomized to high potent DAPT versus clopidogrel+aspirin. However, women randomized to aspirin+clopidogrel had 1.3% higher MACE risk and 1.1% lower risk of major bleeds, so that the differences in absolute treatment effects between women and men were negligibly small. Hence, our study supports similar DAPT management in both sexes.

Sex Differences in Response to Antiplatelet Therapy

It has currently been acknowledged that poor response to clopidogrel can be explained by increased platelet reactivity.[26,27] In vitro studies have shown that women have increased platelet reactivity compared with men; however, the underlying mechanism of this sex difference is not completely understood. It has been suggested that it may be caused by higher levels of estrogen in women, which leads to increased platelet to platelet aggregation,[28,29] increased platelet adhesion to fibrinogen,[30] and platelet interaction with leukocytes.[31]

A subanalysis of the ADAPT-DES (Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents) study (8448 patients [25.6% women who underwent PCI]) compared the risk for ST and bleeding in patients with high platelet reactivity (HPR) versus patients without HPR, stratified by sex. They found that both men and women with HPR had an increased risk of ST, but only a significantly lower risk of bleeding in women with HPR was observed.[32] They also observed that HPR was more prevalent in women than men (51.7% versus 39.6%; P<0.0001), which might explain sex differences in response to treatment with clopidogrel.

However, a sex-specific meta-analysis of 5 trials including 79 613 patients (30% women) compared clopidogrel+aspirin versus aspirin monotherapy in patients with CVD and found that DAPT was slightly less effective in the prevention of CVD in women but there were no significant sex differences in efficacy to prevent MACE or safety depicted as major bleeding.[33] Another meta-analysis focusing on short- versus long-term DAPT treatment in men and women, including 6 randomized trials, concluded that short-term treatment leads to similar rates of MACE as

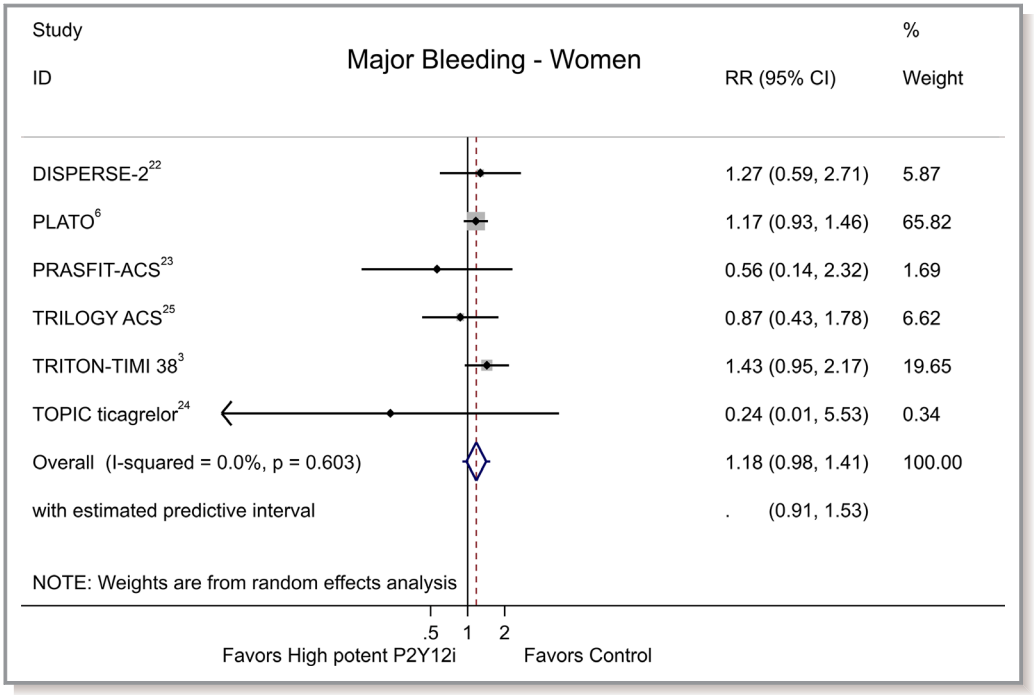

Figure 4. The relative risk (RR) of major bleeding in women treated with a high potent P2Y$_{12}$ inhibitor (prasugrel/ticagrelor) vs clopidogrel. ACS indicates acute coronary syndrome; DISPERSE-2, Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs Clopidogrel in NSTEMI 2; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes; PRASFIT-ACS, Prasugrel Compared With Clopidogrel for Japanese Patients With ACS Undergoing PCI; TRILOGY ACS, Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes; TRITON-TIMI 38, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38.

long-term treatment, but a lower risk of bleeding with no sex differences was observed.

High potent P2Y$_{12}$ inhibitors prasugrel, ticagrelor, and cangrelor have a stronger antiplatelet action and therefore are also effective in patients with HPR. Two sex-specific meta-analyses assessing the efficacy and safety of high-potent DAPT were previously published. Lau et al[34] included 7 trials involving 87 840 patients (24 494 women) with CAD and found no sex differences for MACE or major bleeding. However, in this meta-analysis, 3 trials assessing cangrelor were included and the effect of cangrelor, prasugrel, and ticagrelor was pooled, while we excluded trials assessing cangrelor in our meta-analysis because this drug is intravenously administered and only prescribed in the first 48 hours following PCI.

A less extensive meta-analysis compared with the current study was published by Zaccardi et al,[35] consisting of 3 trials with 24 844 patients (7232 women) testing prasugrel versus clopidogrel or placebo and 1 trial with 18 624 participants (5288 women) treated with ticagrelor versus clopidogrel. No significant differences were found in cardiovascular or bleeding events in the prasugrel or ticagrelor subgroups.[35]

Therefore, our results are in line with these meta-analyses but add to the current literature in that it contains the largest number of studies and patients treated with high potent DAPT according to the recommendations of the current guidelines in patients who are treated >1 year. With this meta-analysis we show that the guidelines statement that no relevant sex differences in efficacy and safety of DAPT exist, can be validated.

Management of Men and Women With ACS

Women have worse cardiovascular outcomes than men after ACS.[36,37] Underlying causes for this are women's higher age at ACS and women having more comorbidities than men, such as diabetes mellitus, hypertension, and renal failure.[36] Moreover, differences in the management of ACS in women have been suggested as a reason for worse clinical outcomes. Multiple registry studies have shown that women with ACS are less likely to be treated according to the guidelines.[8,37–39] The SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry previously showed that women with ST-segment–elevation myocardial infarction (STEMI) are less likely to be given reperfusion therapy.[40]

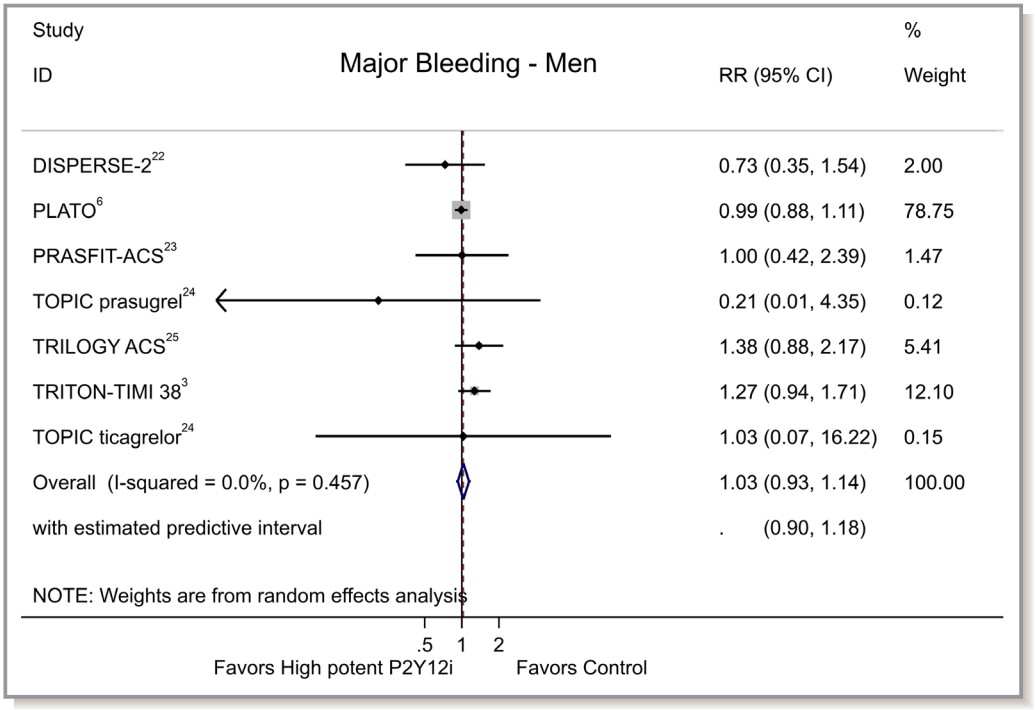

Figure 5. The relative risk (RR) of major bleeding in men treated with a high potent P2Y$_{12}$ inhibitor (prasugrel/ticagrelor) vs clopidogrel. ACS indicates acute coronary syndrome; DISPERSE-2, Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs Clopidogrel in NSTEMI 2; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes; PRASFIT-ACS, Prasugrel Compared With Clopidogrel for Japanese Patients With ACS Undergoing PCI; TRILOGY ACS, Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes; TRITON-TIMI 38, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38.

Moreover, DAPT is more often prescribed in men than women with ACS. When DAPT was prescribed in women, the low-intensity P2Y$_{12}$ inhibitor clopidogrel was more frequently used in women compared with men, while the more effective high potent P2Y$_{12}$ inhibitor prasugrel was preferred in men.[41]

The most likely reason for this undertreatment is the hypothetical concern for higher risk of bleeding in women.[42,43] Regarding milder forms of bleeding, it should be noted that access site hematomas occur more often in women than men (22% versus 5.8%, respectively; $P<0.0001$).[44] However, we showed no evidence for an increased risk of major bleeding in women. Therefore, more research on bleeding avoidance strategies is warranted to reduce access site hematomas, especially in women, but it is unjustified to treat women differently or less aggressively with DAPT in the long term because of risk for major bleeding.

Moreover, in the 2 years following PCI, both physician-recommended disruption (mostly because of bleeding) and nonrecommended disruption of DAPT (because of patient noncompliance) were more common in women than in men (59.1% versus 55.9%, respectively; $P=0.007$).[41,45] The impact of DAPT cessation was similar in women and men, with disruption significantly associated with ischemic and bleeding events in both sexes.[45,46] Therefore, it is important to resume DAPT after cessation to prevent cardiovascular events in the long term in both sexes.

Study Strengths and Limitations

Our meta-analysis included all contemporary studies using guideline-recommended high potency DAPT. Treatment in control groups was homogeneous (clopidogrel+aspirin), and we reported an average follow-up of at least 1 year, thus describing the longer-term effects of high potency DAPT in women and men.

Limitations are that we found inter-trial variations in study design, study population, follow-up duration, percentage of women included, dosage of prasugrel/ticagrelor, and definition of MACE and stroke end points. In addition, it should be noted that our results are based on RCT data, in which the included patients may not fully reflect real-life patients with ACS. In particular, women are less likely to be representative as they develop cardiovascular disease at a later age then men and might thus exceed the upper age limit determined by the RCT.[47] Also, women with cardiovascular disease in general have more comorbidities than men, which can lead to exclusion from an RCT.[48] Last, our study added only

received sex-specific data from 1 extra trial that was not previously presented; however, the sex-specific stroke data of the trials have not been published before in a meta-analysis.[34]

Conclusions

No significant sex differences in efficacy and safety of the high potent $P2Y_{12}$ inhibitors were observed and therefore there is no reason to treat women and men differently. Our meta-analysis can be used to substantiate the essential evidence that sex-specific recommendations regarding the use of high potent DAPT are unjustified. Therefore, this should lead the way to implementation of prescribing guideline-recommended DAPT in both men and women.

Sources of Funding

The project was funded by the Dutch Heart Foundation. There are no relations with industry.

Disclosures

Dr Roeters van Lennep reports grants from the Dutch Heart Foundation and from Amryt during the conduct of the study. Dr Versmissen reports grants from the Dutch Heart Foundation during the conduct of the study. Dr Kavousi reports grants from the Dutch Heart Foundation during the conduct of the study. Professor Boersma reports grants from the Dutch Heart Foundation during the conduct of the study. Dr Visser reports grants from the Dutch Heart Foundation during the conduct of the study. Ms Schreuder reports grants from the Dutch Heart Foundation during the conduct of the study. Professor Roos-Hesselink reports grants from the Dutch Heart Foundation during the conduct of the study. The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL

Table S1. Syntax Electronic Databases

Provided in the table down below are the syntax used for the different electronic databases. All results were imported into EndNote. After de-duplication the screening process was started.

Table 1. Database syntax used for the respective electronic databases accessible via Erasmus MC network.

Embase.com	('dual antiplatelet therapy'/de OR (((dual OR combin*) NEAR/3 (antiplatelet* OR anti-platelet*)) OR dapt):ab,ti OR (('acetylsalicylic acid'/exp OR 'acetylsalicylic acid plus clopidogrel'/de OR (acetylsalicyl* OR acetyl-salicyl* OR aspirin):ab,ti) AND ('purinergic p2y receptor antagonist'/exp OR (cangrelor OR clopidogrel OR elinogrel OR prasugrel OR regrelor OR ticagrelor OR ticlopidine OR ((P2Y*) NEAR/3 (antagonist* OR inhibitor*))):ab,ti))) AND ('coronary artery disease'/exp OR 'ischemic heart disease'/de OR (((myocard* OR coronar*) NEAR/3 (disease* OR infarct* OR syndrom* OR acute* OR ischem* OR ischaem* OR obstruct*)) OR angina OR ((heart OR cardiac*) NEAR/3 (infarct* OR ischem* OR ischaem*))):ab,ti) AND ('adverse drug reaction'/exp OR 'side effect'/exp OR adverse:lnk OR 'bleeding'/exp OR (adverse* OR side-effect* OR bleeding OR hemorrhag* OR haemorrhag* OR (blood NEAR/3 (loss OR effusion))):ab,ti) AND ('Controlled clinical trial'/exp OR 'Crossover procedure'/de OR 'Double-blind procedure'/de OR 'Single-blind procedure'/de OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim
Medline Ovid	(exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ OR (statin* OR simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR lovastatin OR atorvastatin OR fluvastatin OR ((hmg OR hydroxymethylglutaryl) ADJ3 (coa OR coenzyme-A) ADJ3 inhibitor*)).ab,ti.) AND (exp Coronary Artery Disease/ OR exp Myocardial Ischemia/ OR (((myocard* OR coronar*) ADJ3 (disease* OR infarct* OR syndrom* OR acute* OR ischem* OR ischaem* OR obstruct*)) OR angina OR ((heart OR cardiac*) ADJ3 (infarct* OR ischem* OR ischaem*))).ab,ti.) AND (Drug-Related Side Effects and Adverse Reactions/ OR "adverse effects".fs. OR exp Hemorrhage/ OR (adverse* OR side-effect* OR bleeding OR hemorrhag* OR haemorrhag* OR (blood ADJ3 (loss OR effusion))).ab,ti.) AND (Exp Controlled clinical trial/ OR "Double-Blind Method"/ OR "Single-Blind Method"/ OR "Random Allocation"/ OR (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) ADJ blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups).ab,ti.) NOT (Animals/ NOT Humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.
Cochrane CENTRAL	((statin* OR simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR lovastatin OR atorvastatin OR fluvastatin OR ((hmg OR hydroxymethylglutaryl) NEAR/3 (coa OR coenzyme-A) NEAR/3 inhibitor*)):ab,ti) AND ((((myocard* OR coronar*) NEAR/3 (disease* OR infarct* OR syndrom* OR acute* OR ischem* OR ischaem* OR obstruct*)) OR angina OR ((heart OR cardiac*) NEAR/3 (infarct* OR ischem* OR ischaem*))):ab,ti) AND ((adverse* OR side-effect* OR bleeding OR hemorrhag* OR haemorrhag* OR (blood NEAR/3 (loss OR effusion))):ab,ti)

Table S2. Selection criteria used during title-/abstract- and full-text screening.

Selection Criteria
Inclusion Criteria: - Subjects with ACS treated with dual antiplatelet therapy (DAPT), which includes the use of Aspirin and P2Y12-receptor antagonists (prasugrel/ticagrelor) as a form of secondary prevention. **Population:** - At least 18 years of age - Secondary prevention - Patients with acute coronary syndrome (STEMI, NSTEMI, myocardial infarction, or unstable angina pectoris) - Patients were treated for coronary heart disease with revascularization either: percutaneous coronary intervention (PCI) + stent placement **Study Type:** - Double blind, randomized controlled trials, single-blind randomized controlled trials, and open-label studies. - Original article - Published as full text article - Written in English language - > 50 patients per group **Exclusion Criteria:** - All other indications not covering ACS - Primary prevention studies. - Non-human studies (e.g. animal studies)

Table S3. Cochrane Collaboration's Tool

TRIAL	SELECTION BIAS		PERFORMANCE BIAS	DETECTION BIAS	ATTRITION BIAS	REPORTING BIAS	OTHER BIAS
	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT					
DISPERSE -2 [1]	LOW	LOW	LOW	LOW	LOW	LOW	LOW
PLATO[2]	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW
PRASFIT ACS[3]	LOW	UNCLEAR	LOW	LOW	LOW	LOW	HIGH
TOPIC[4]	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW
TRILOGY ACS[5]	LOW	LOW	LOW	LOW	LOW	LOW	LOW
TRITON TIMI 38[6]	LOW	LOW	LOW/UNCLEAR	LOW	LOW	LOW	LOW

Table S4. Overview of primary efficacy endpoints per included trial.

TRIAL	PRIMARY EFFICACY ENDPOINT
DISPERSE – 2[1]	Composite of CVM, MI (fatal and non-fatal) and stroke
PLATO [2]	Composite of CVM, MI and stroke
PRASFIT – ACS[3]	Incidence of MACE at 24 weeks: composite of: CVM, non-fatal MI, nonfatal ischemic stroke
TOPIC[4]	Composite of: CVM, unplanned hospitalization leading to urgent coronary revascularization, stroke, and bleeding episodes as defined by the BARC classification > 2 at 1 year after ACS.
TRILOGY ACS[5]	Composite of: CVM, non-fatal MI, and non-fatal stroke.
TRITON – TIMI 38[6]	Composite of: CVM, non-fatal MI, and non-fatal stroke.

Efficacy endpoints: Cardiovascular mortality (CVM), Myocardial infarction (MI), Major adverse cardiovascular events (MACE)

Table S5. Overview of syntax used in STATATM

To generate an RR in STATA the following code was used:	gen rr=(mi/ni)/(mc/nc)
To generate the log RR:	gen logrr=log(rr)
To generate the standard error of the log RR:	gen selogrr=sqrt(1/mi-1/ni+1/mc-1/nc)
To generate the log lower confidence interval:	gen loglci=logrr-1.96*selogrr
To generate the log upper confidence interval:	gen loguci=logrr+1.96*selogrr
To re-calculate the log	gen lci=exp(loglci)
To perform the meta-analysis the metan command was used. We performed a fixed effects model, seconded by a random effects model. The model was separated by gender and sorted per trial included.	*metan mi nmi mc nmc, rr random rfdist label(namevar=trial) xlabel (0.5,1,5) xtitle() favours (Favors High Potent DAPT # Favors Control) boxsca(30)*
To calculate the funnel plot the data of each trial were pooled into one group and entered into STATA, after which the log RR and standard error of the log RR were calculated. Using the confunnel command, a contour enhanced funnel plot can be plotted. The Egger's test for small study effects was calculated with the metabias command.	confunnel _ES _selogES metabias _ES _selogES, egger

Table S6. Overview of excluded articles based on title- and abstract screening.

ANTICOAGULANT STUDIES	
EXCLUSION BASED ON: ANTIPLATELET THERAPIES OR ANTICOAGULANTS THERAPIES SUCH AS CANGRELOR (N=19), ELINOGREL (N = 6), GLYCOPROTEINS (N= 74), HEPARIN (N = 258), TICLOPIDINE (N=46), AND THROMBOLYTICS.	**N = 739**
CARDIOVASCULAR DISEASE	
EXCLUSION BASED ON: ATRIAL FIBRILLATION STUDIES (N=82), HEART FAILURE (N= 29), HEART VALVE (N=27), PERIPHERAL ARTERIAL DISEASE (N=42), AND CORONARY ARTERY BYPASS GRAFT (N=74)	**N = 254**
CEREBROVASCULAR STUDIES	
EXCLUSION BASED ON: CEREBROVASCULAR STUDIES E.G. STROKE.	**N = 172**
CHILDREN STUDIES	
EXCLUSION BASED ON INCLUSION CRITERIA.	**N = 1**
OTHER MEDICATION	
EXCLUSION BASED ON: CILOSTAZOL (N=50), MONOTHERAPEUTIC STUDIES (N=6), PROTONPUMP INHIBITORS (N=72), STATINS (N=77), TRIPLE THERAPY (N=29).	**N = 234**
STUDY DESIGN	
EXCLUSION BASED ON: NO DAPT STUDIES (N=323), NO RCT (N=1229), PRIMARY PREVENTION (N=7), STUDY DESIGN (N=26), SYSTEMTIC REVIEWS (N=117), TITLE AND ABSTRACT (N=169), DOUBLES (N=6), FOLLOW-UP STUDIES (N=2), NO ABSTRACT (N=10), SUBSTUDIES (N=33)	**N = 1922**
PHARMACOLOGY	**N = 201**

EXCLUSION BASED ON: PHARAMCODYNAMIC OR PHARMACOKINETIC STUDIES (N=131), PLATELET REACTIVITY STUDIES (N=70)	
STENT STUDIES EXCLUSION BASED ON: TYPE OF DAPT OR TRIAL FOCUS ON DAPT.	**N = 1026**

Due to overflow of the flow-chart excluded articles are noted here separately. Each row is described by a main topic, under which the excluded subtopics (n =) are described. The right column provides the total amount of excluded articles per main-topic.

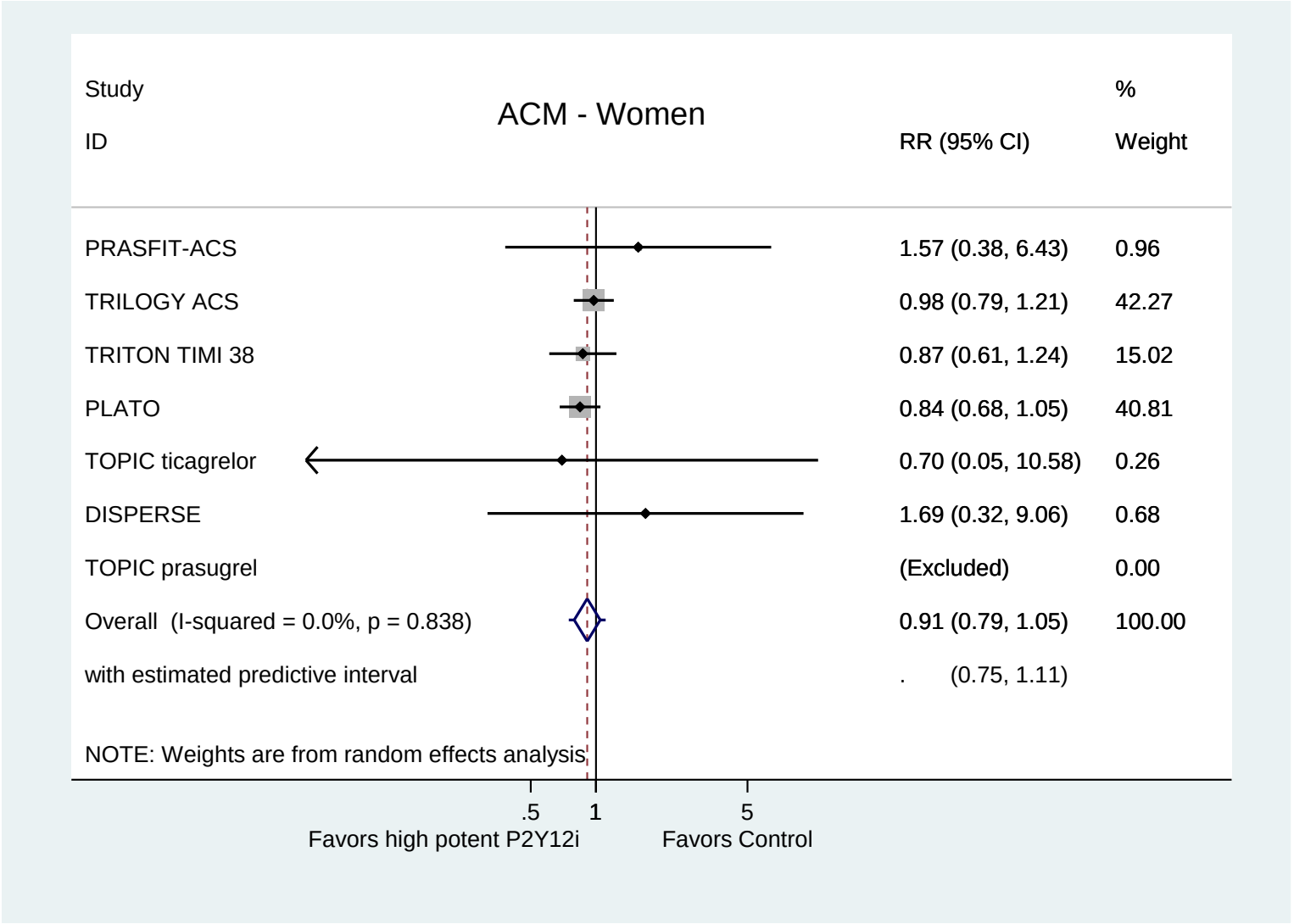


Figure S1. The relative risk of all-cause mortality in women treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel.

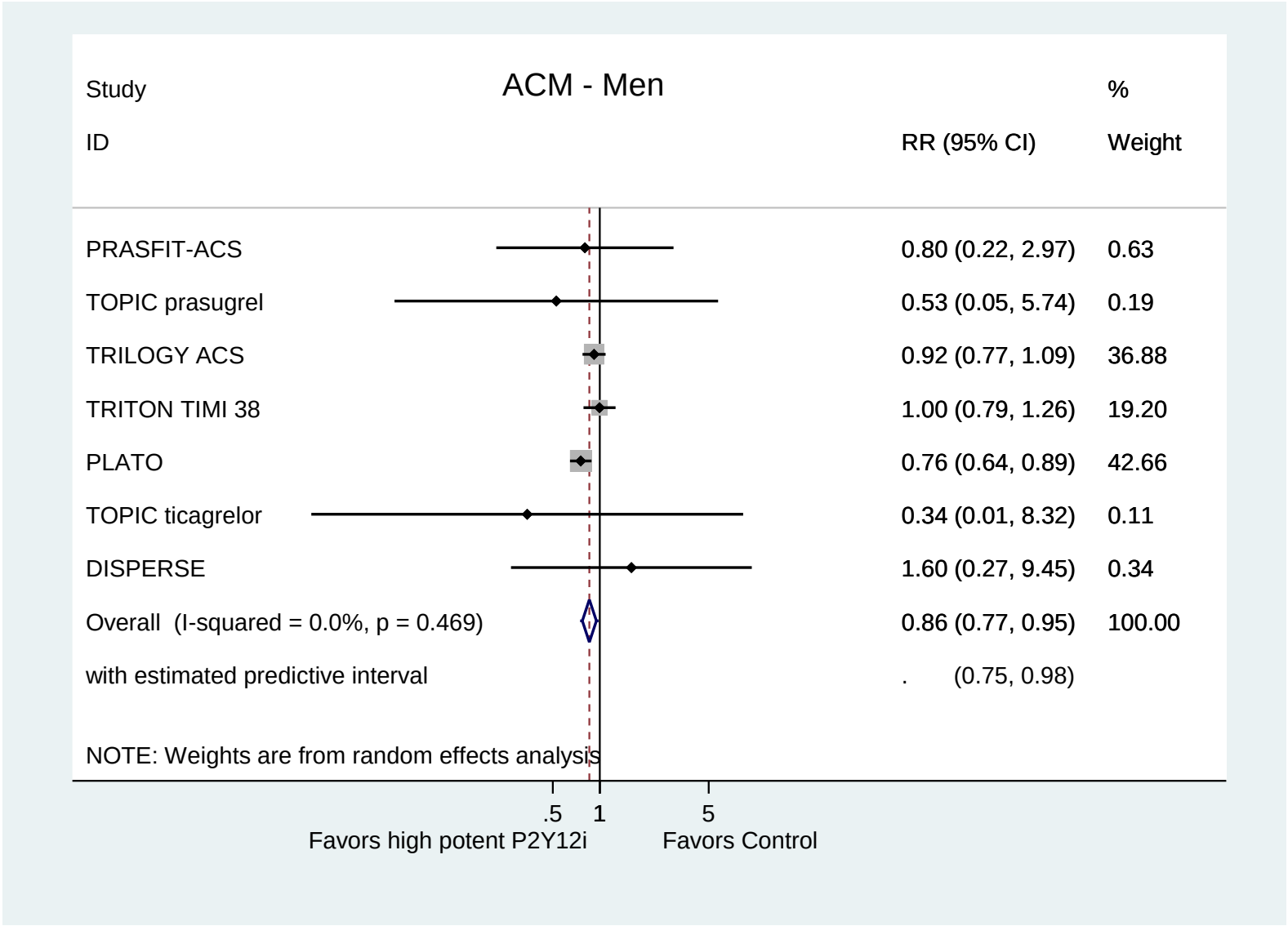


Figure S2. The relative risk of all-cause mortality in men treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

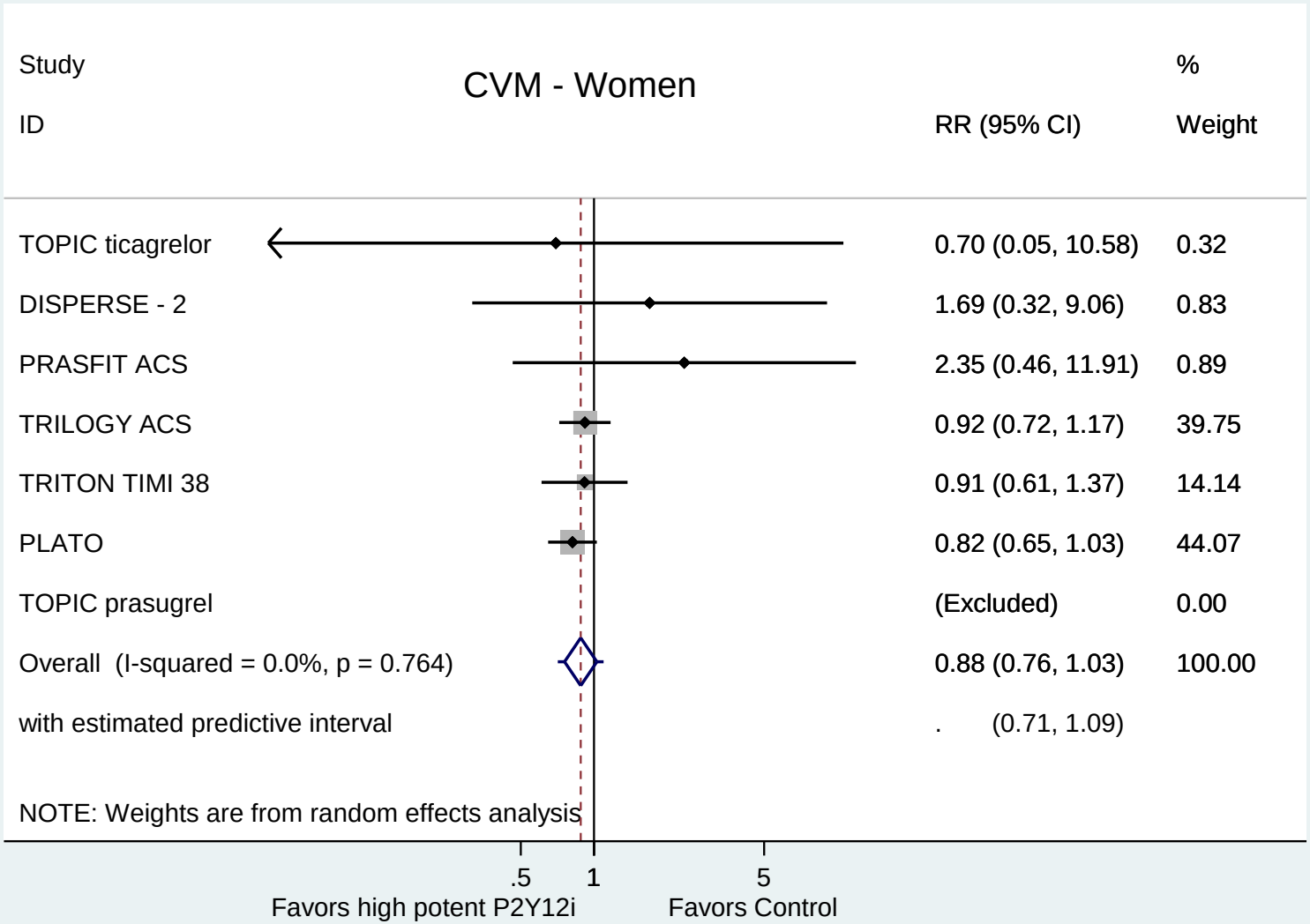


Figure S3. The relative risk of cardiovascular mortality in women treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

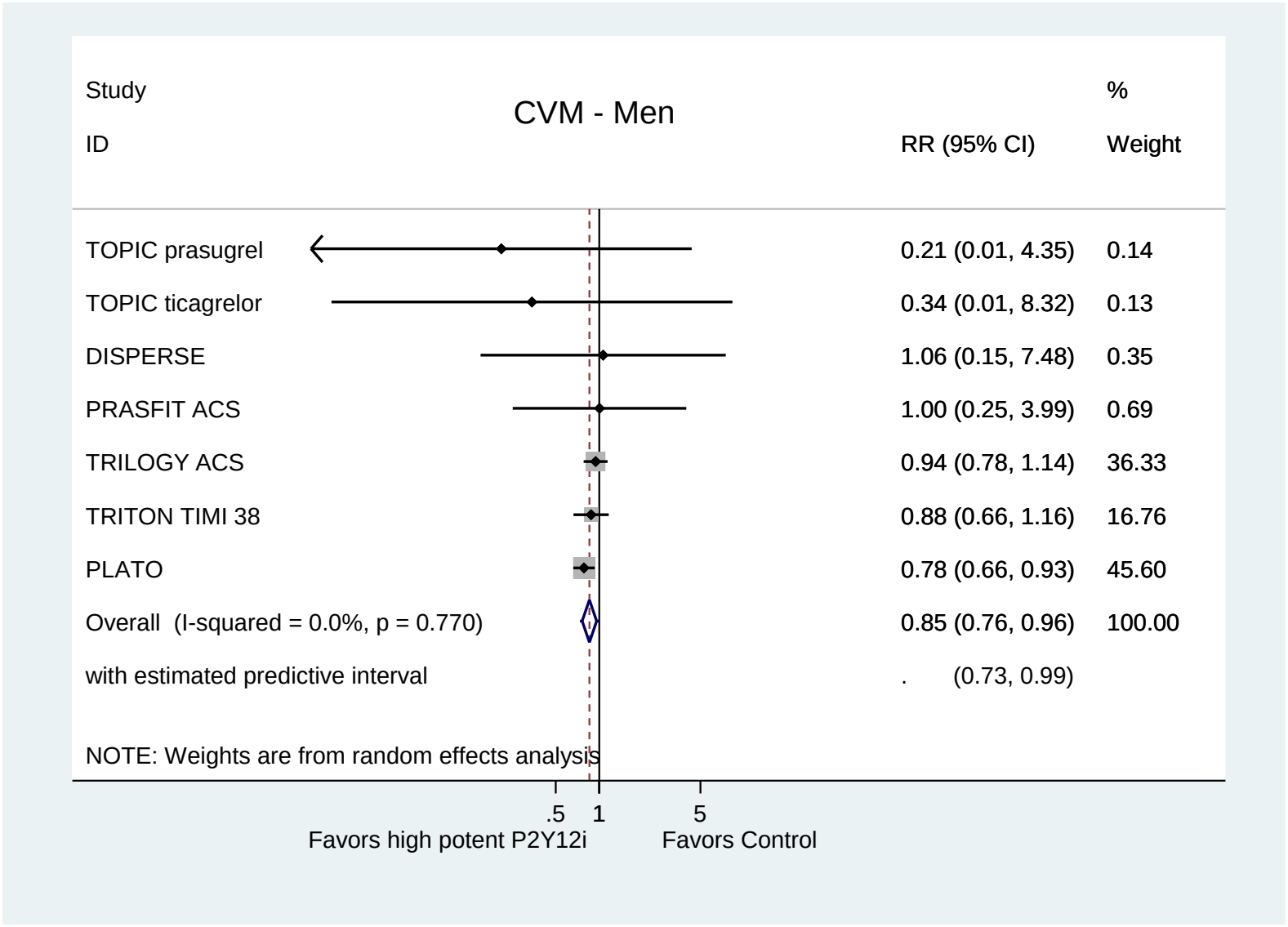


Figure S4. The relative risk of cardiovascular mortality in men treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

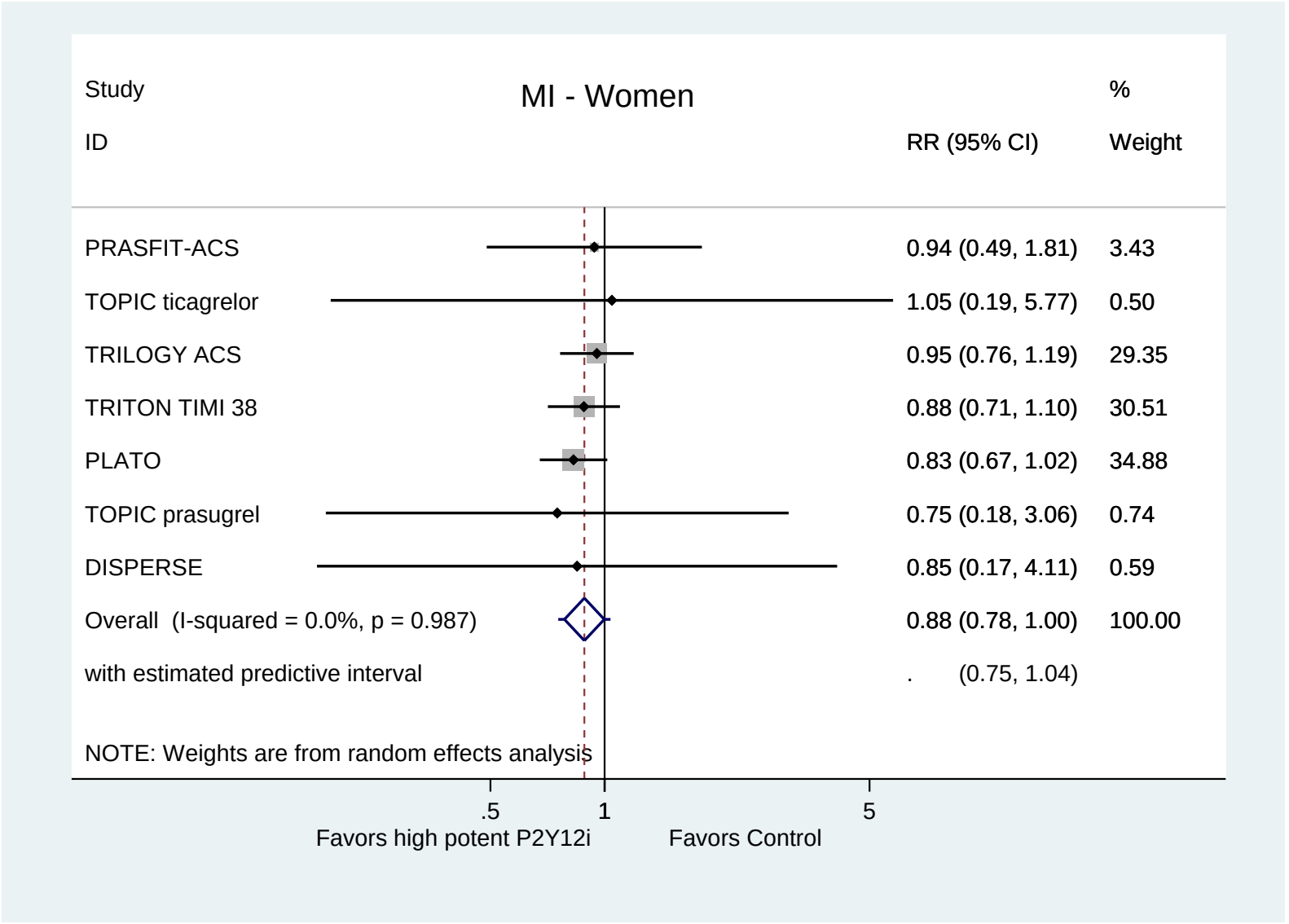


Figure S5. The relative risk of myocardial infarction in women treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

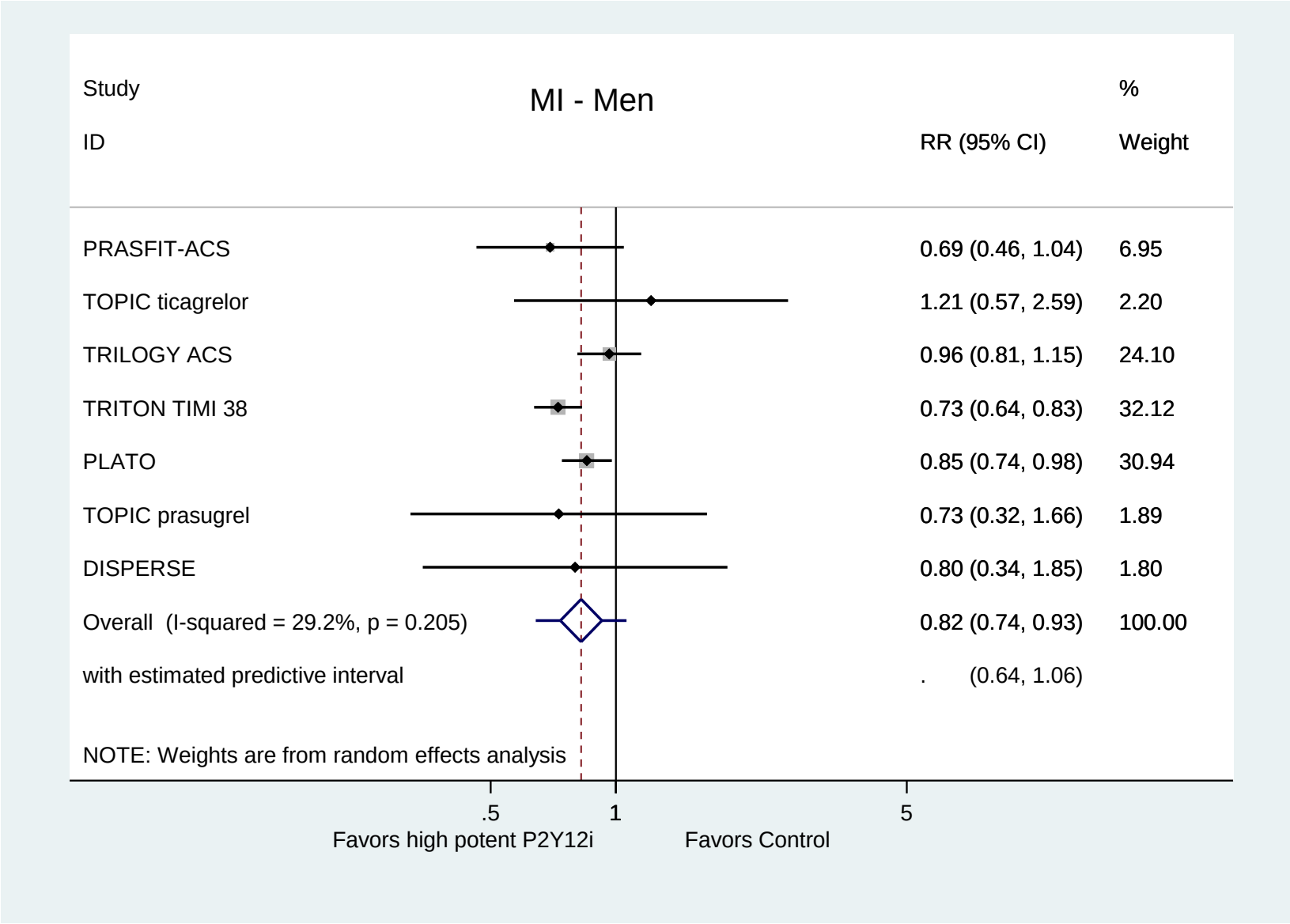


Figure S6. The relative risk of myocardial infarction in men treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

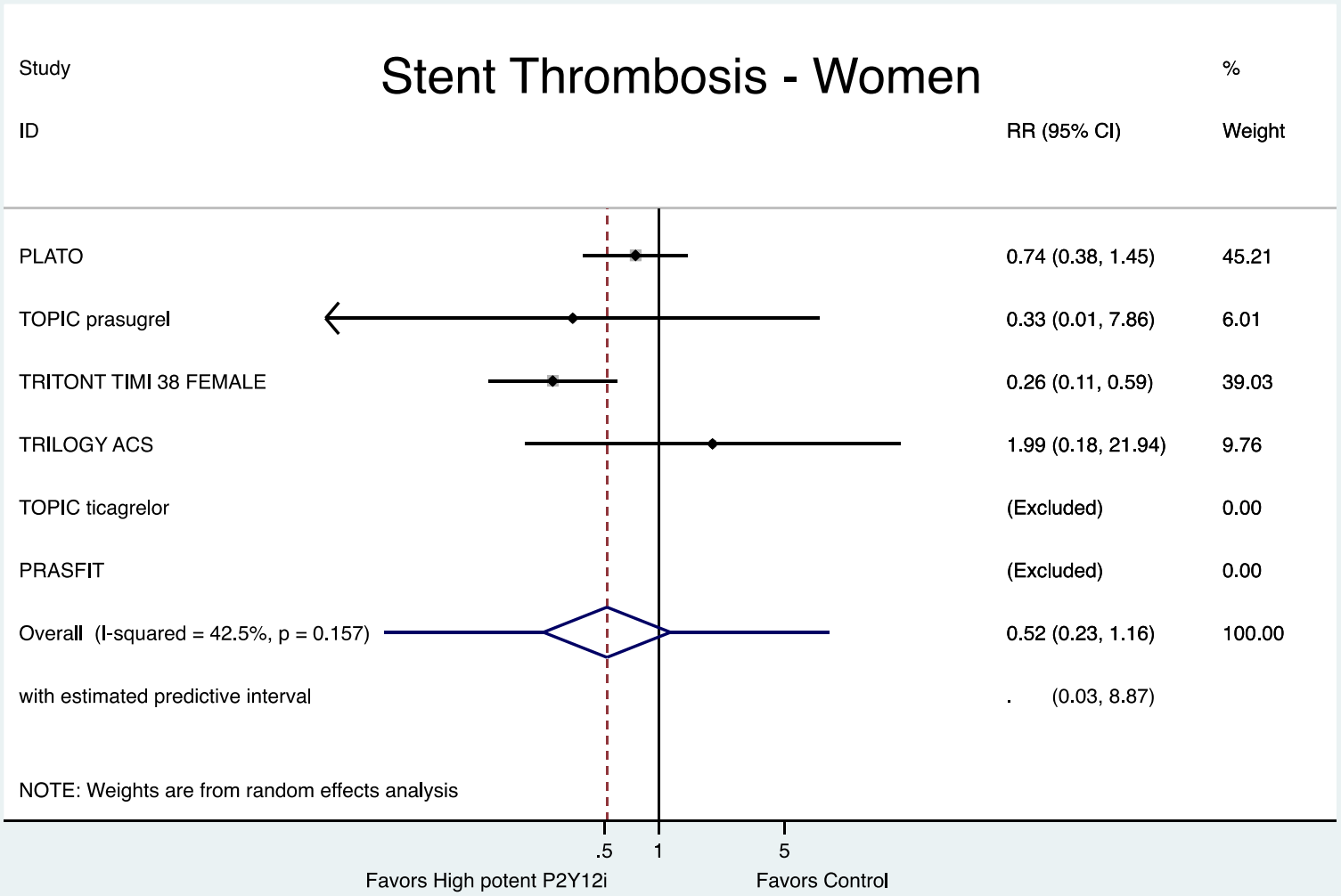


Figure S7. The relative risk of stent thrombosis in women treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

TOPIC ticagrelor and PRASFIT ACS were excluded because there were no events during follow-up. DISPERSE-2 was excluded because there was no stent thrombosis endpoint reported.

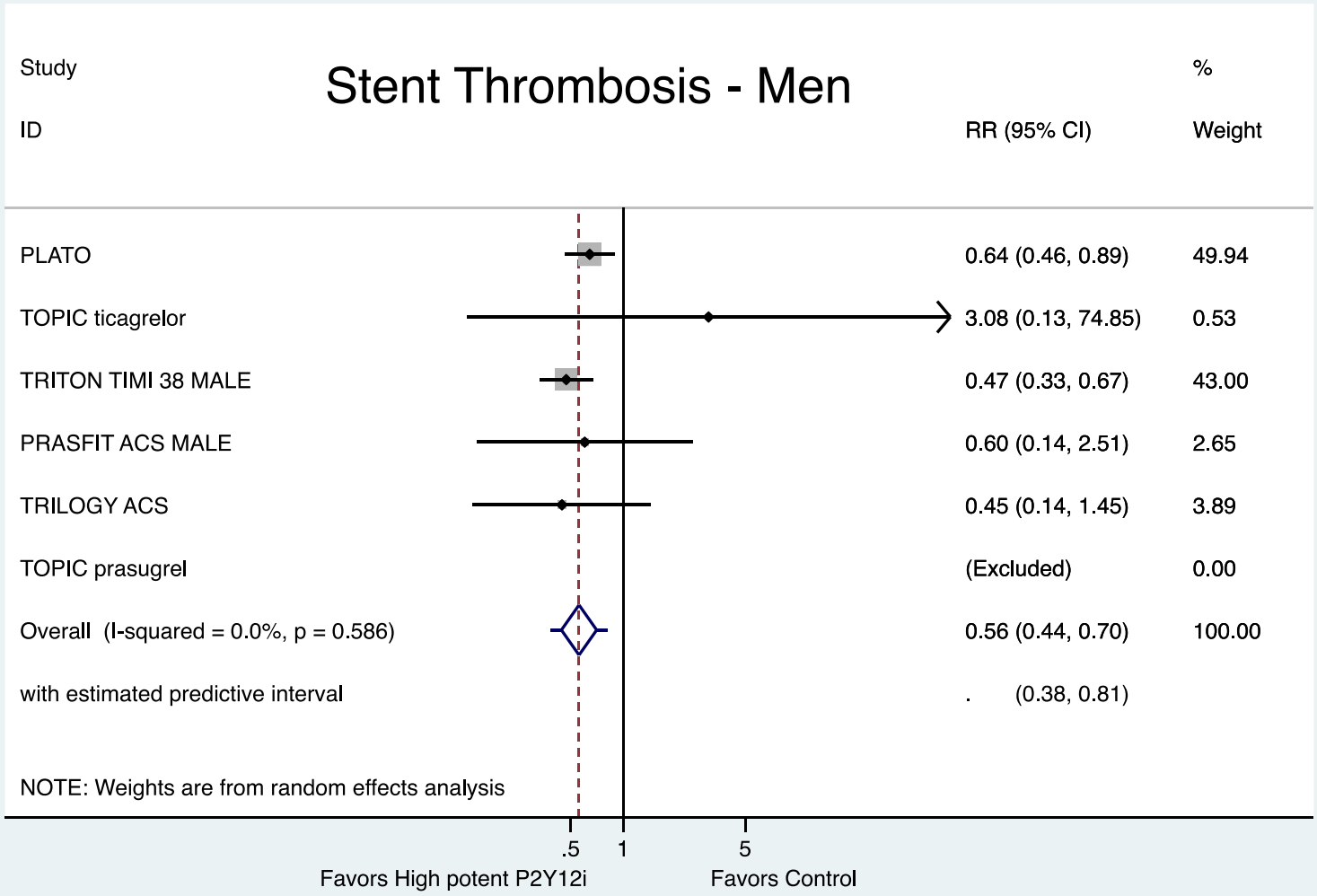


Figure S8. The relative risk of stent thrombosis in men treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

TOPIC prasugrel was excluded because there were no events during follow-up. DISPERSE-2 was excluded because there was no stent thrombosis endpoint reported.

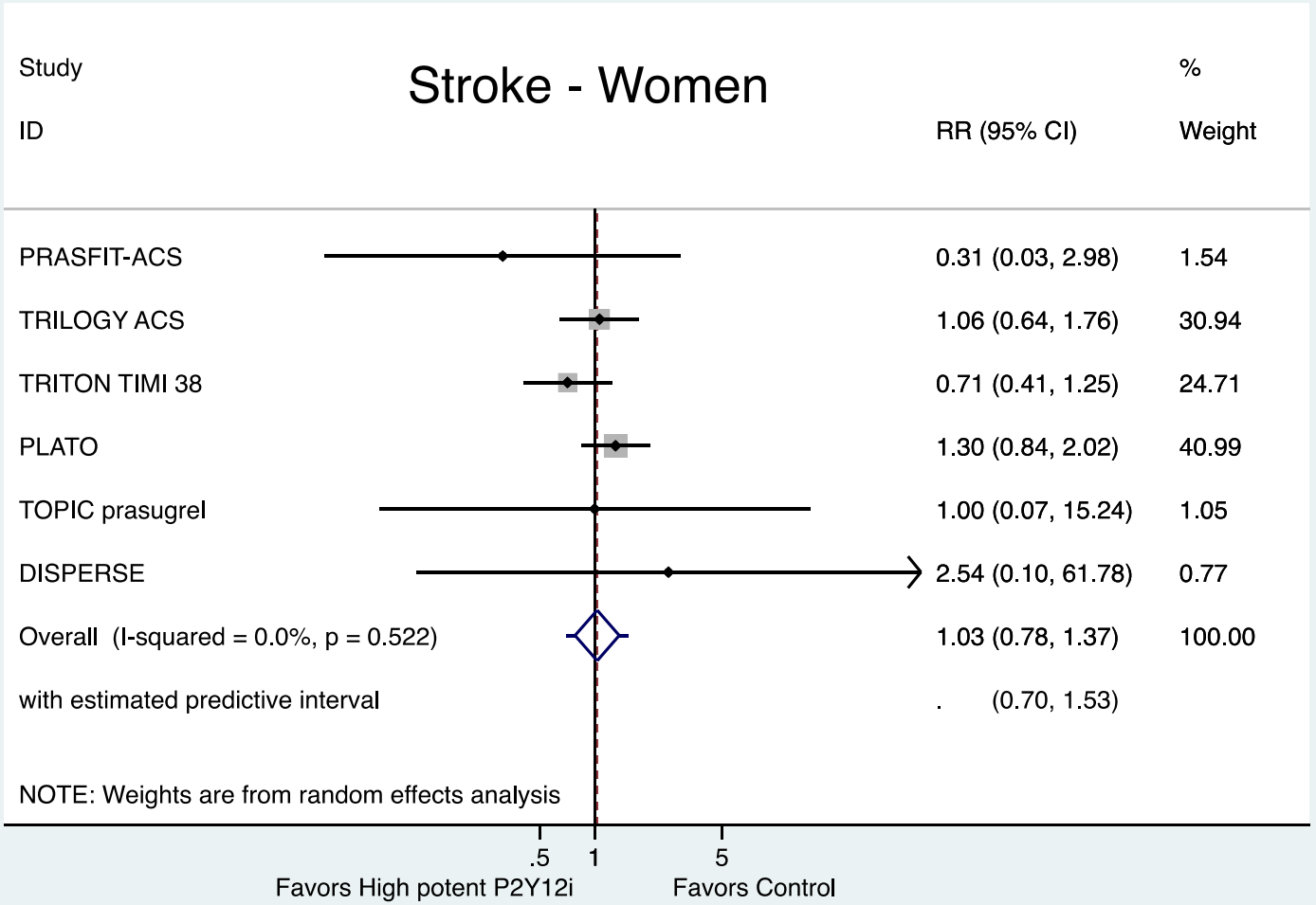


Figure S9. The relative risk of stroke in women treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

TOPIC ticagrelor was excluded because there were no events during follow-up.

DISPERSE-2, TRILOGY ACS and PLATO defined stroke as either ischemic or hemorrhagic.

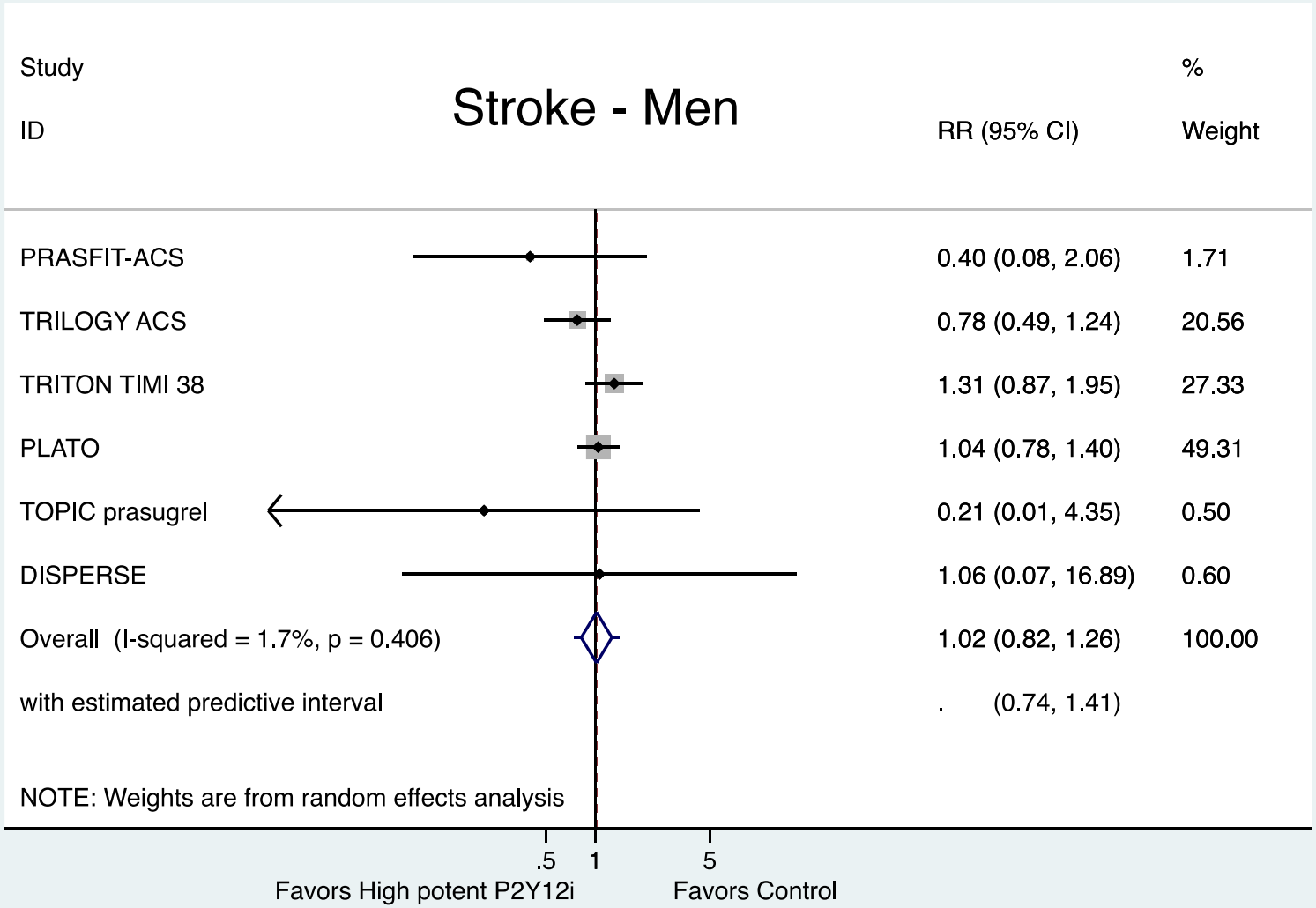


Figure S10. The relative risk of stroke in men treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

TOPIC ticagrelor was excluded because there were no events during follow-up.
DISPERSE-2, TRILOGY ACS and PLATO defined stroke as either ischemic or hemorrhagic.

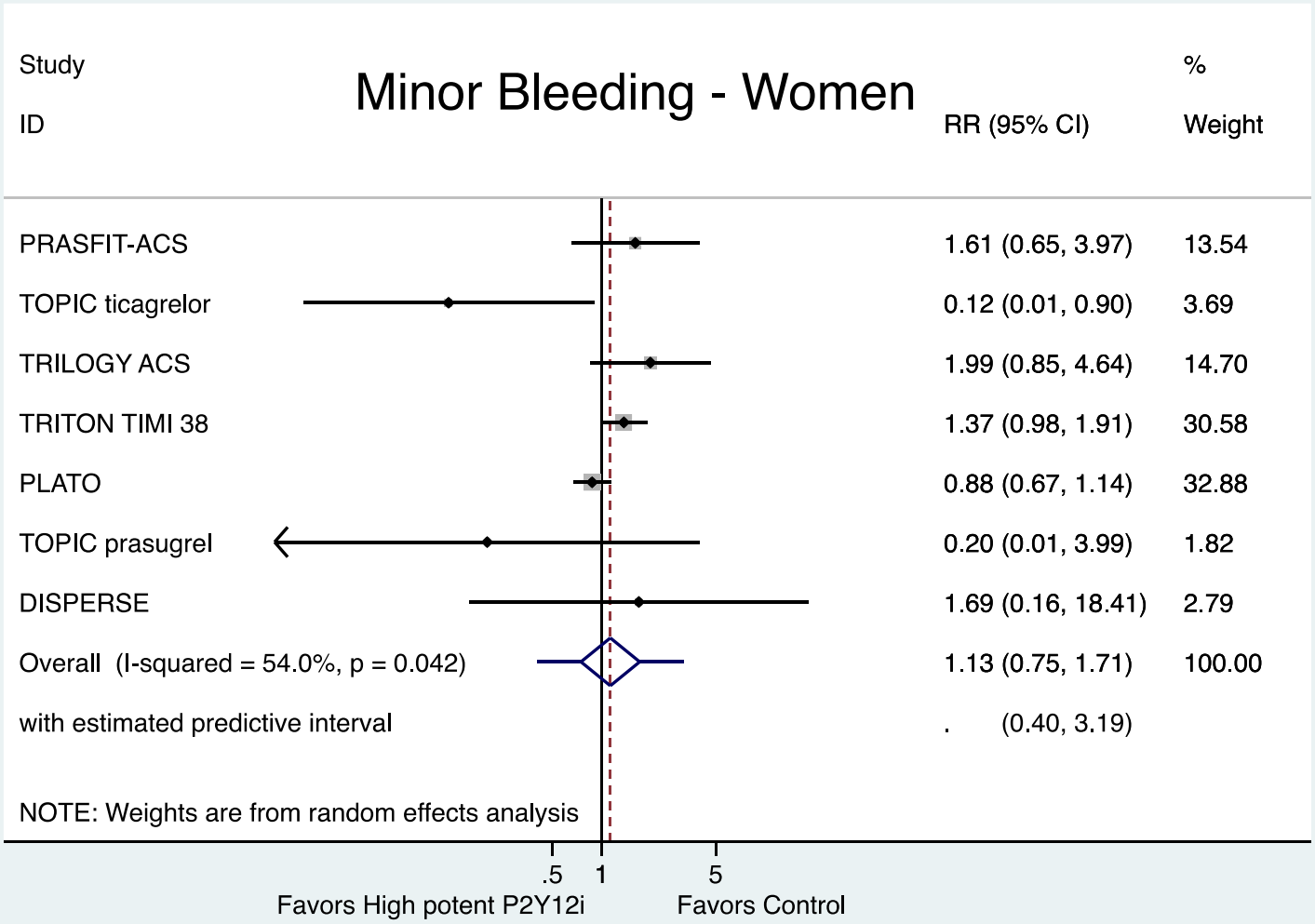


Figure S11. The relative risk of minor bleeding in women treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

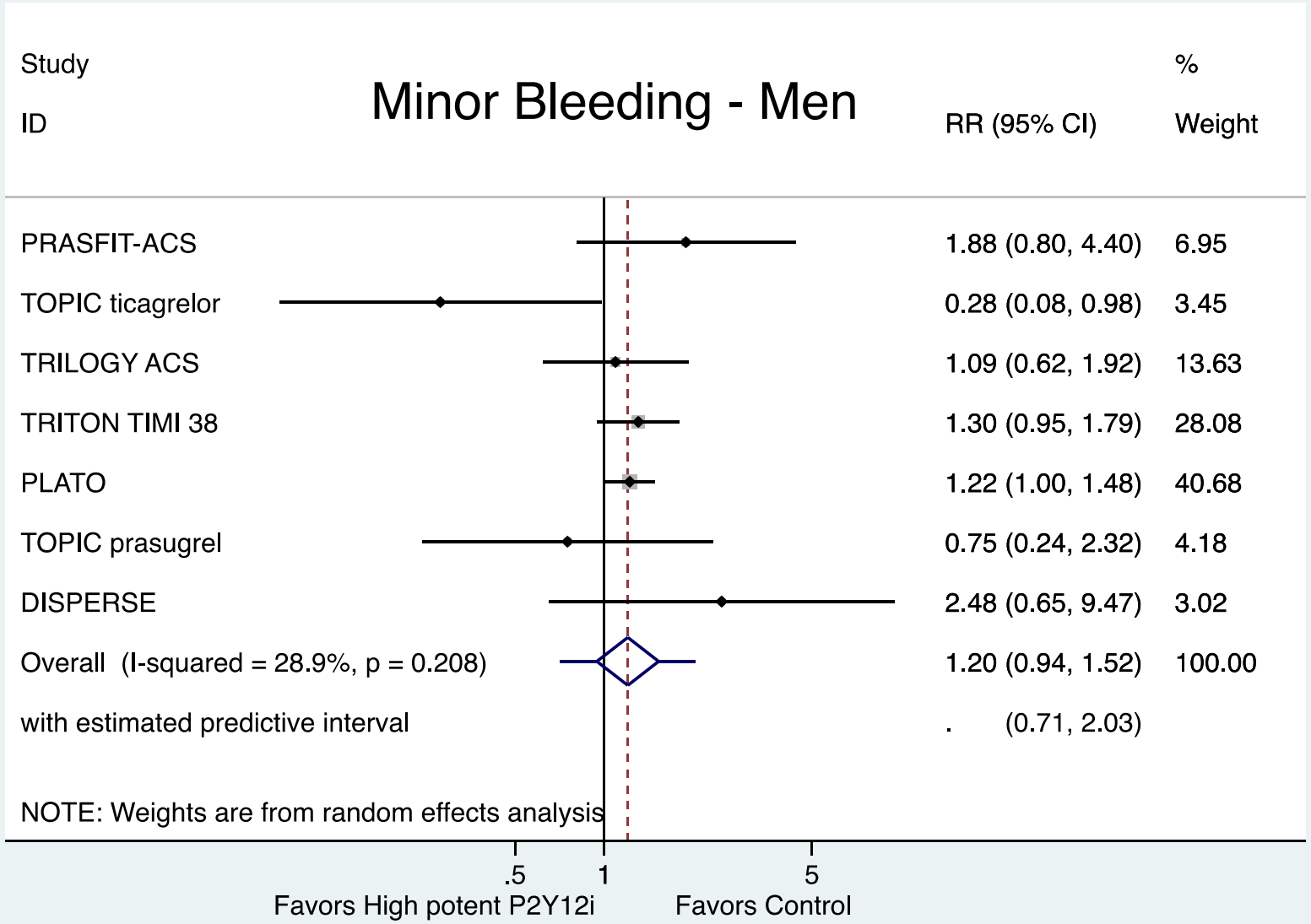
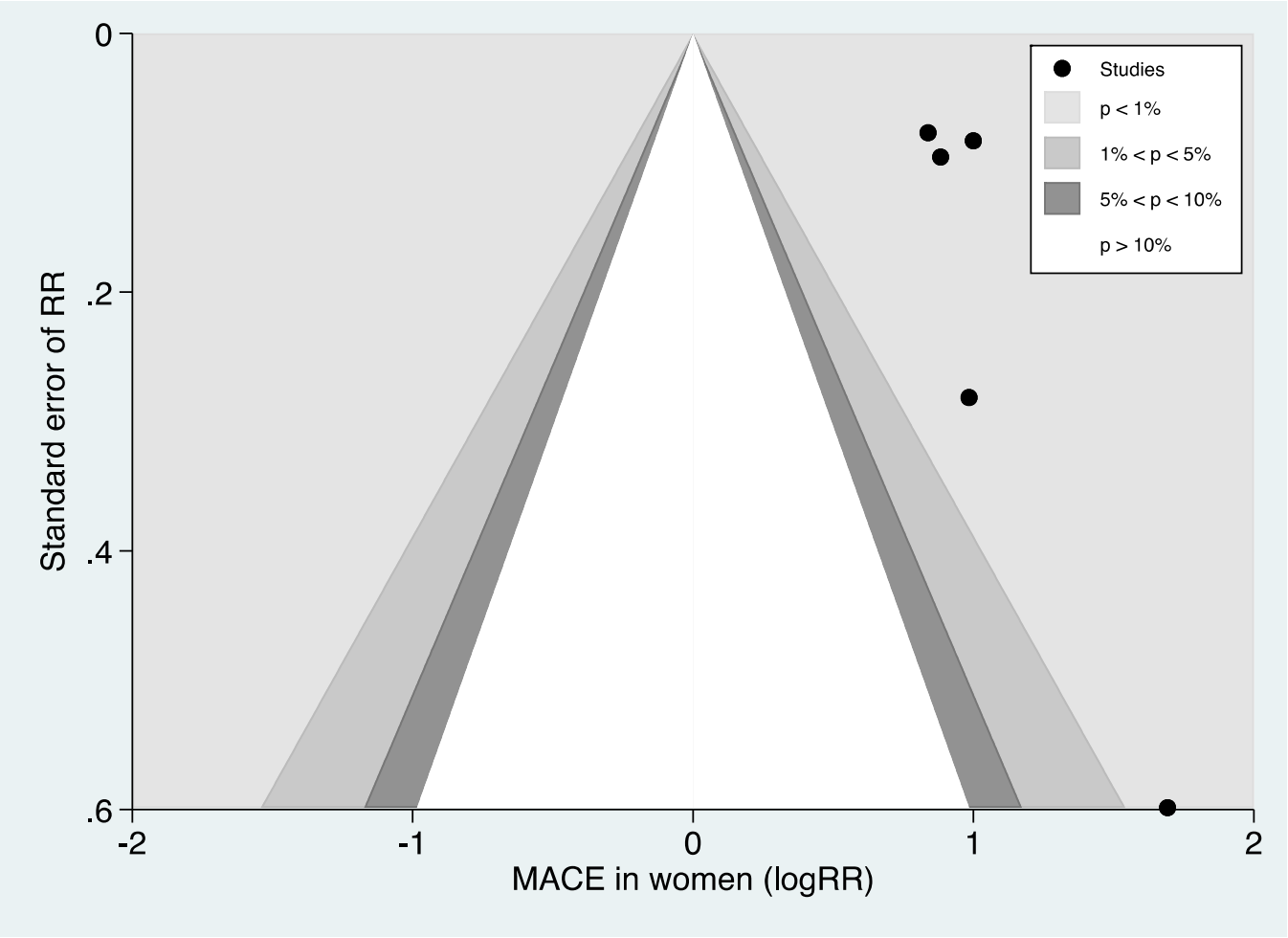
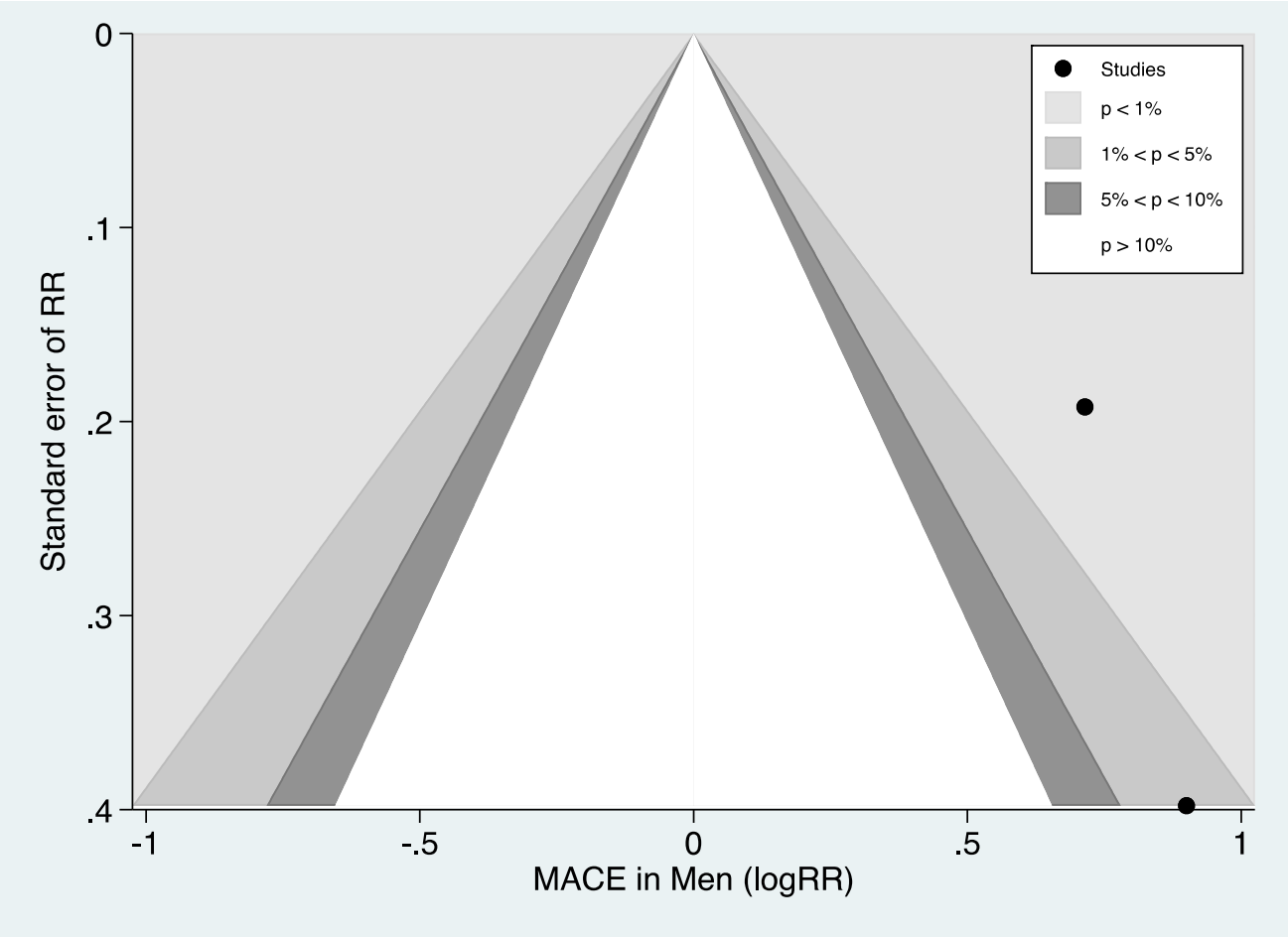


Figure S12. The relative risk of minor bleeding in men treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel



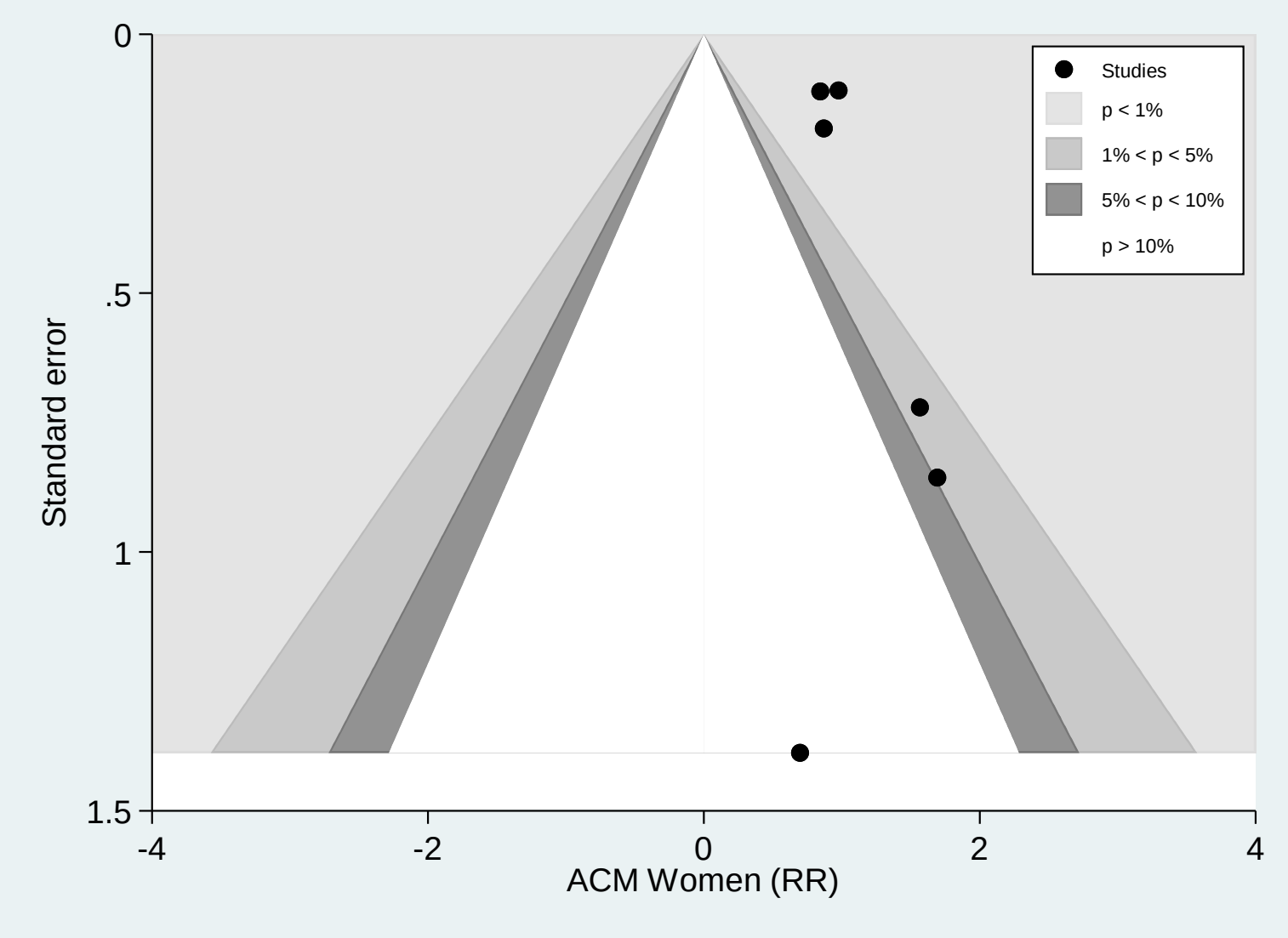
Test of H0: no small-study effects P = 0.270

Figure S13. Contour enhanced funnel plot of MACE in women



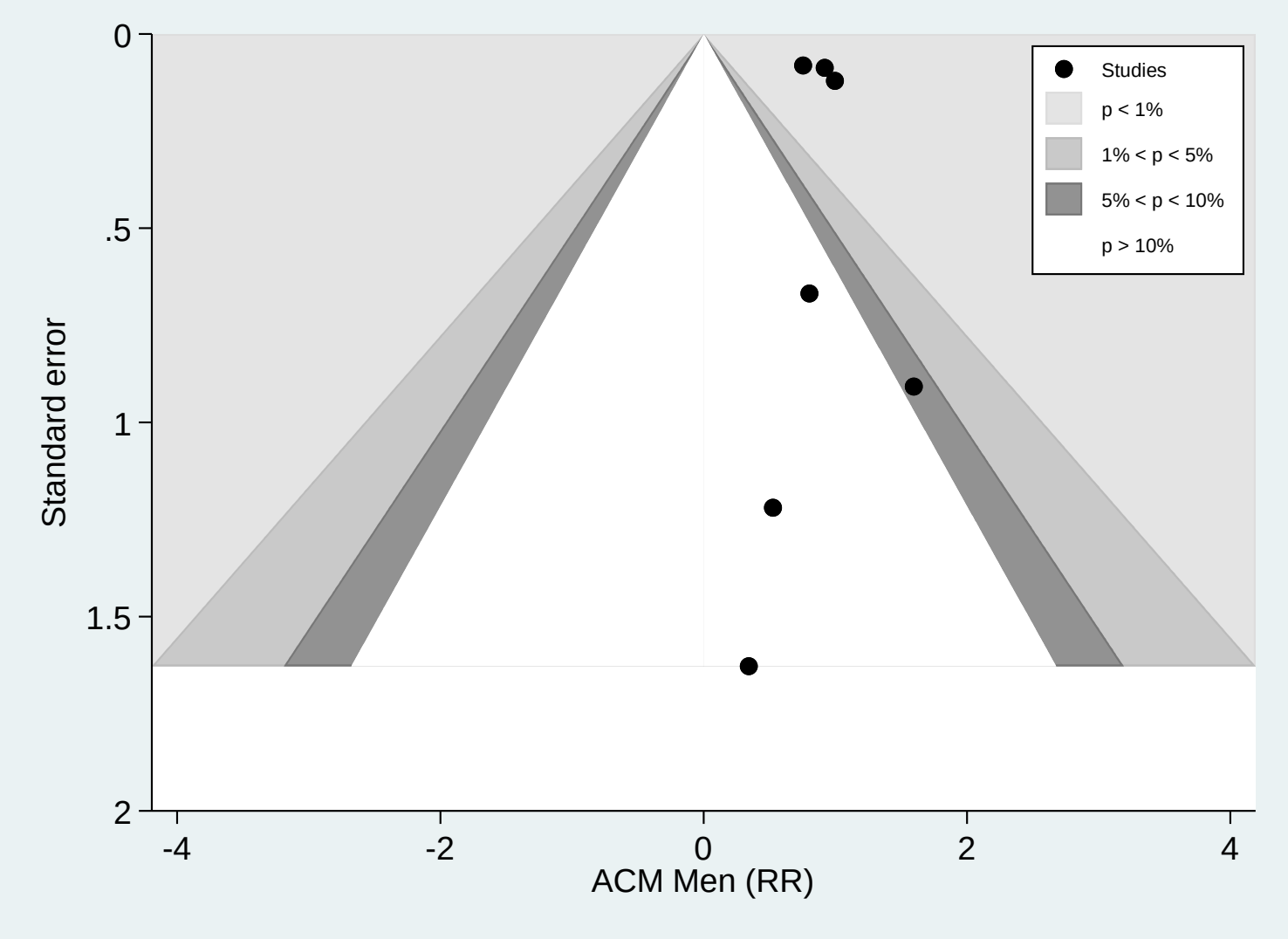
Test of H0: no small-study effects P = 0.826

Figure S14. Contour enhanced funnel plot of MACE in men



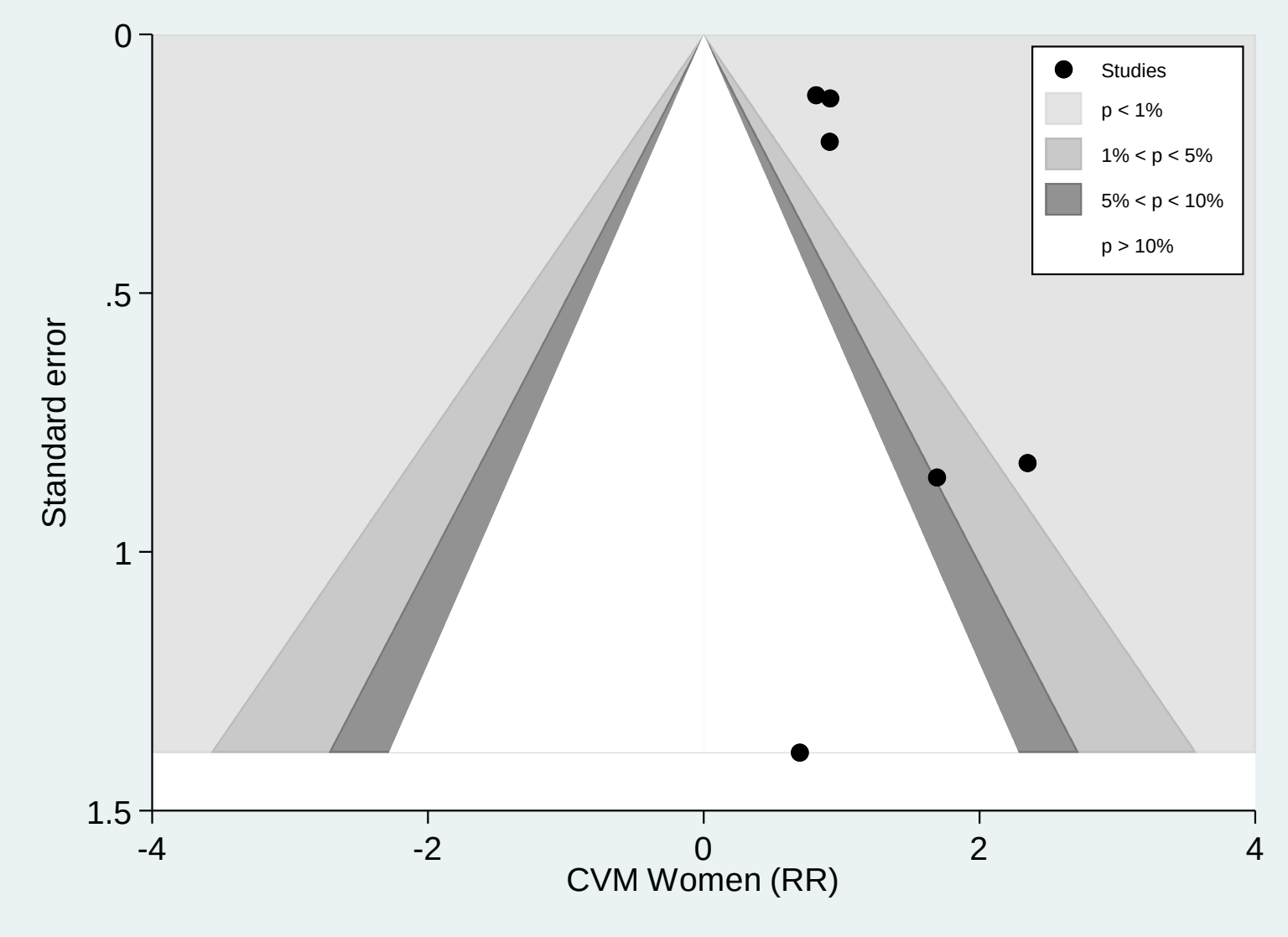
Test of H0: no small-study effects P = 0.271

Figure S15. Contour enhanced funnel plot of ACM in women



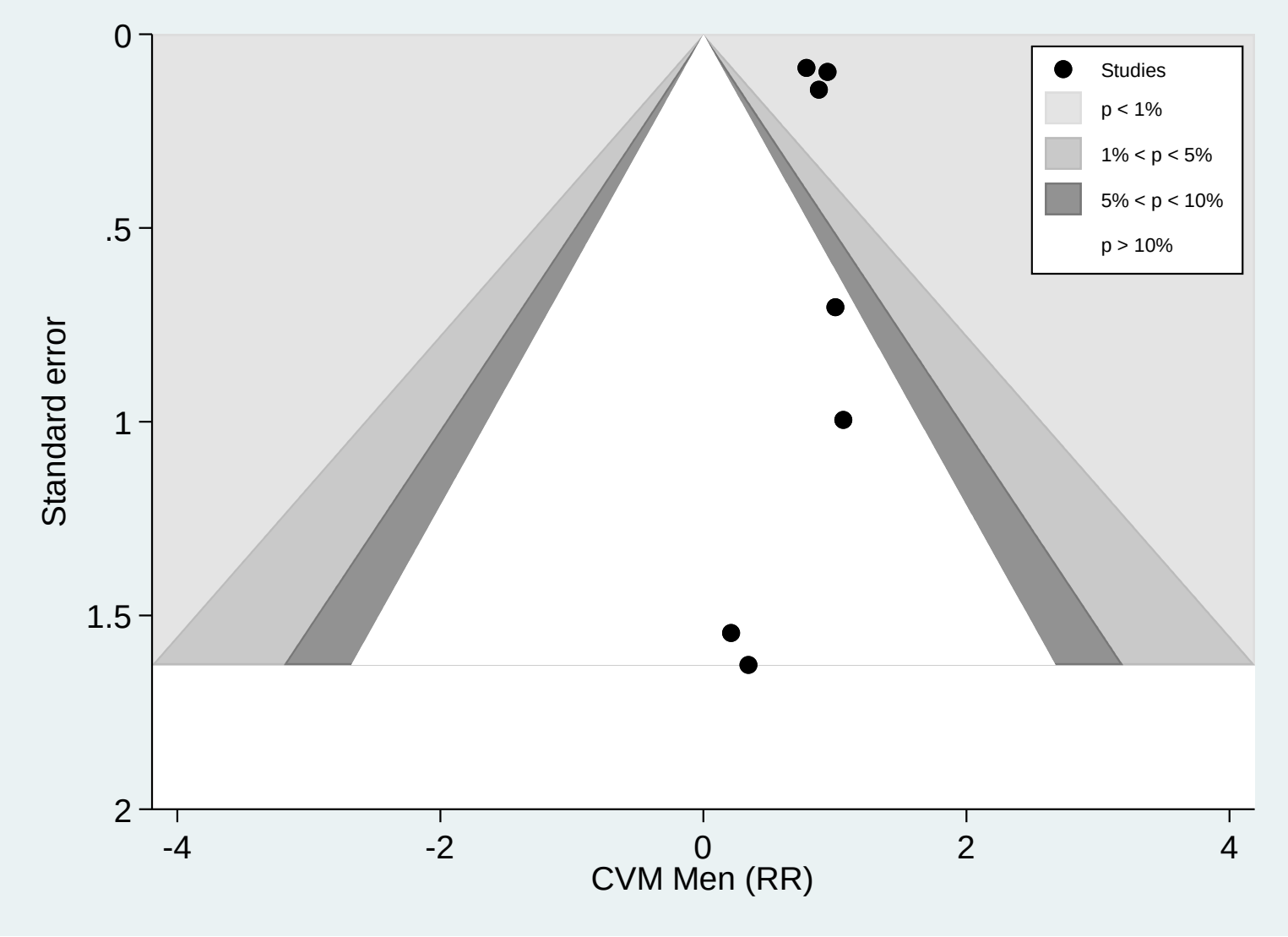
Test of H0: no small-study effects P = 0.779

Figure S16. Contour enhanced funnel plot of ACM in men



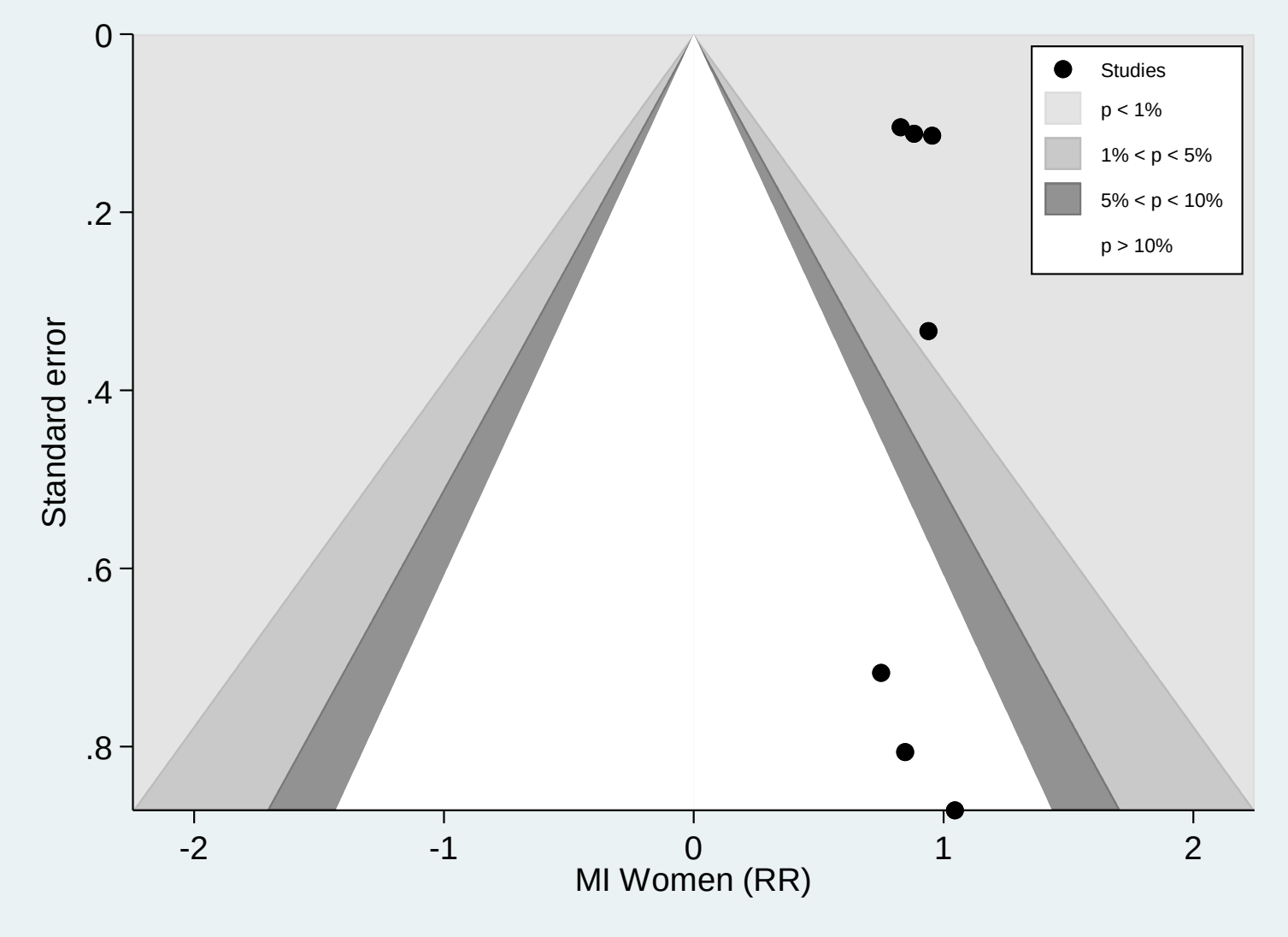
Test of H0: no small-study effects P = 0.125

Figure S17. Contour enhanced funnel plot of CVM in women



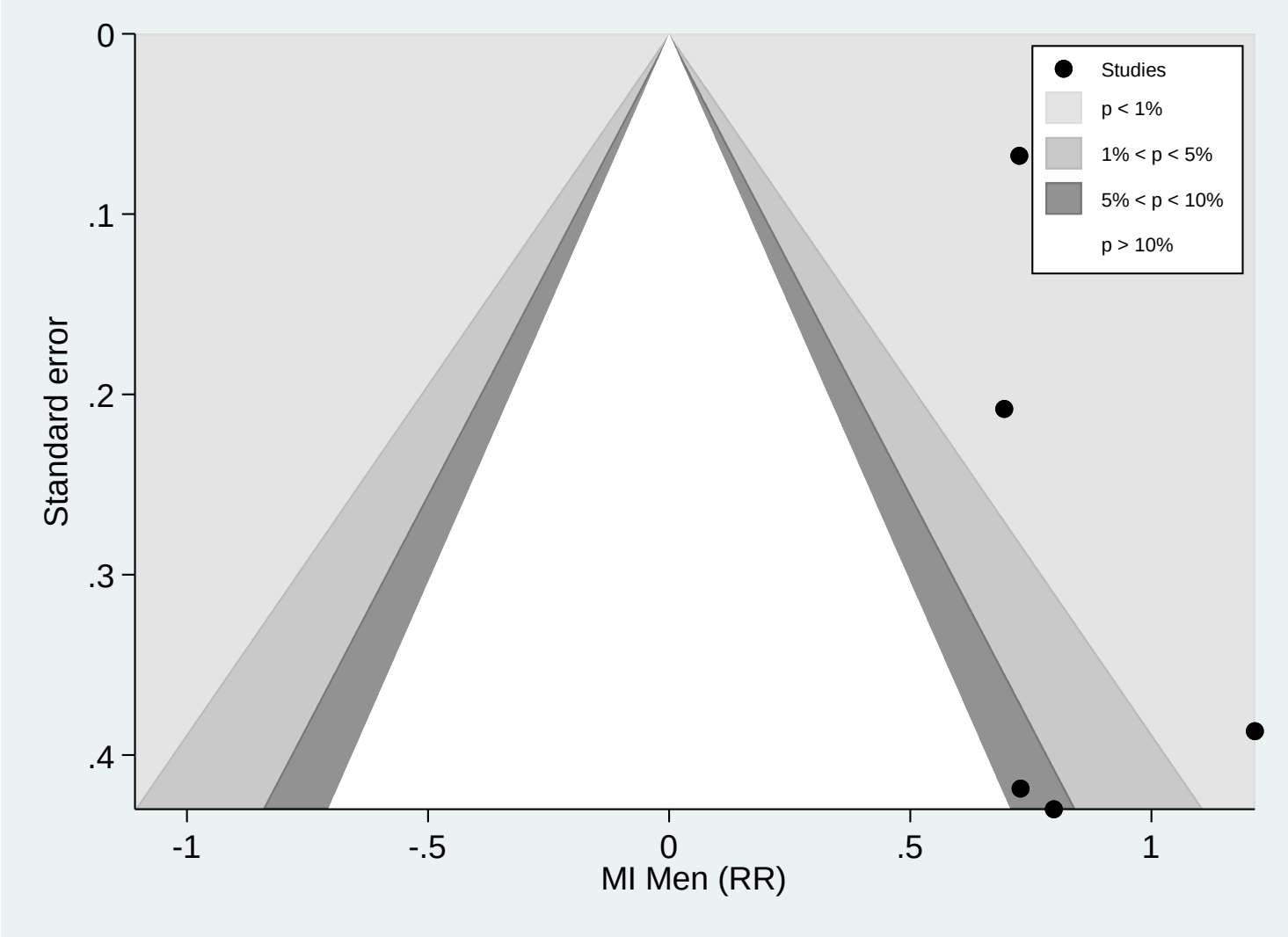
Test of H0: no small-study effects P = 0.878

Figure S18. Contour enhanced funnel plot of CVM in men



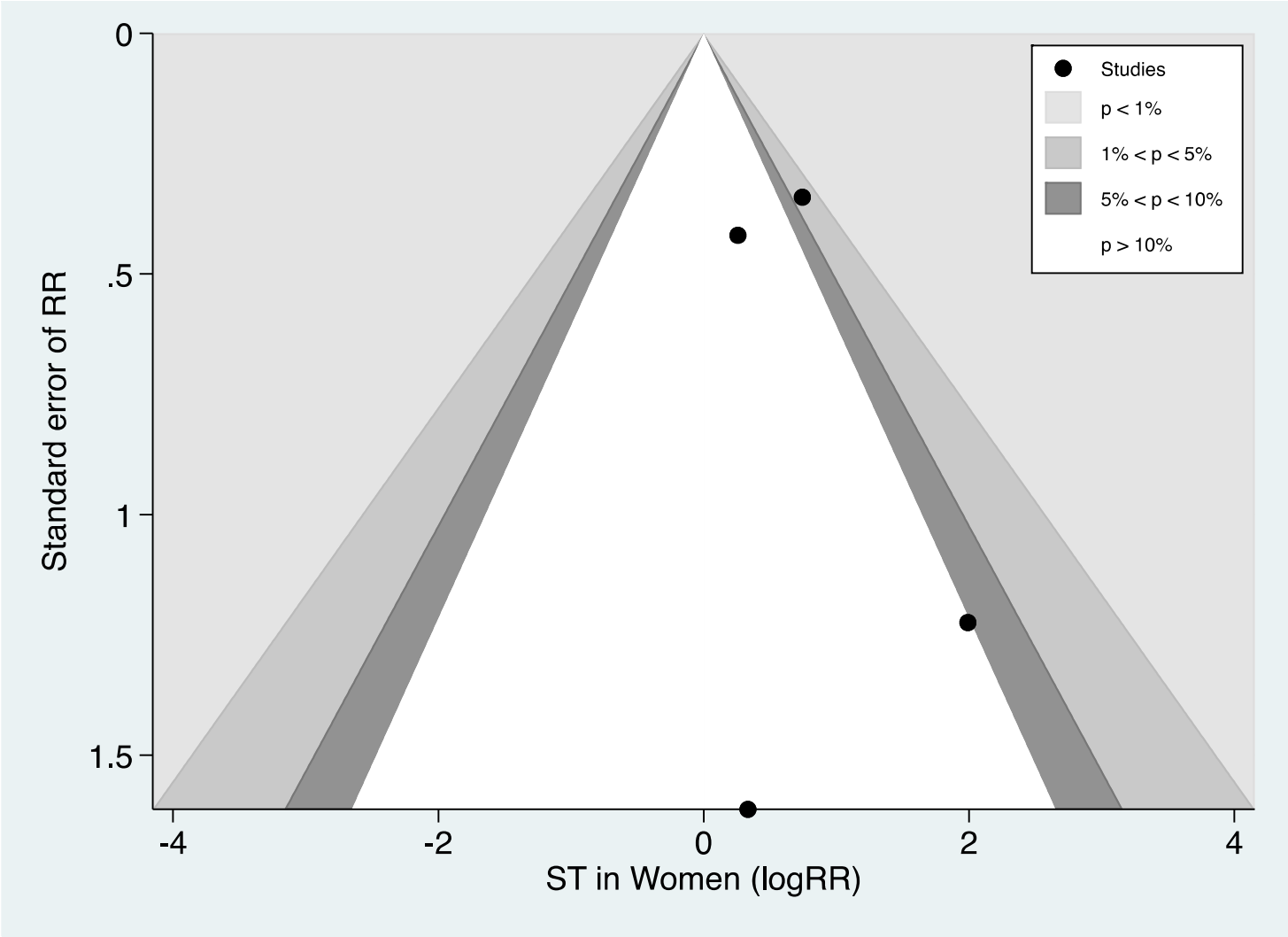
Test of H0: no small-study effects P = 0.864

Figure S19. Contour enhanced funnel plot of MI in women



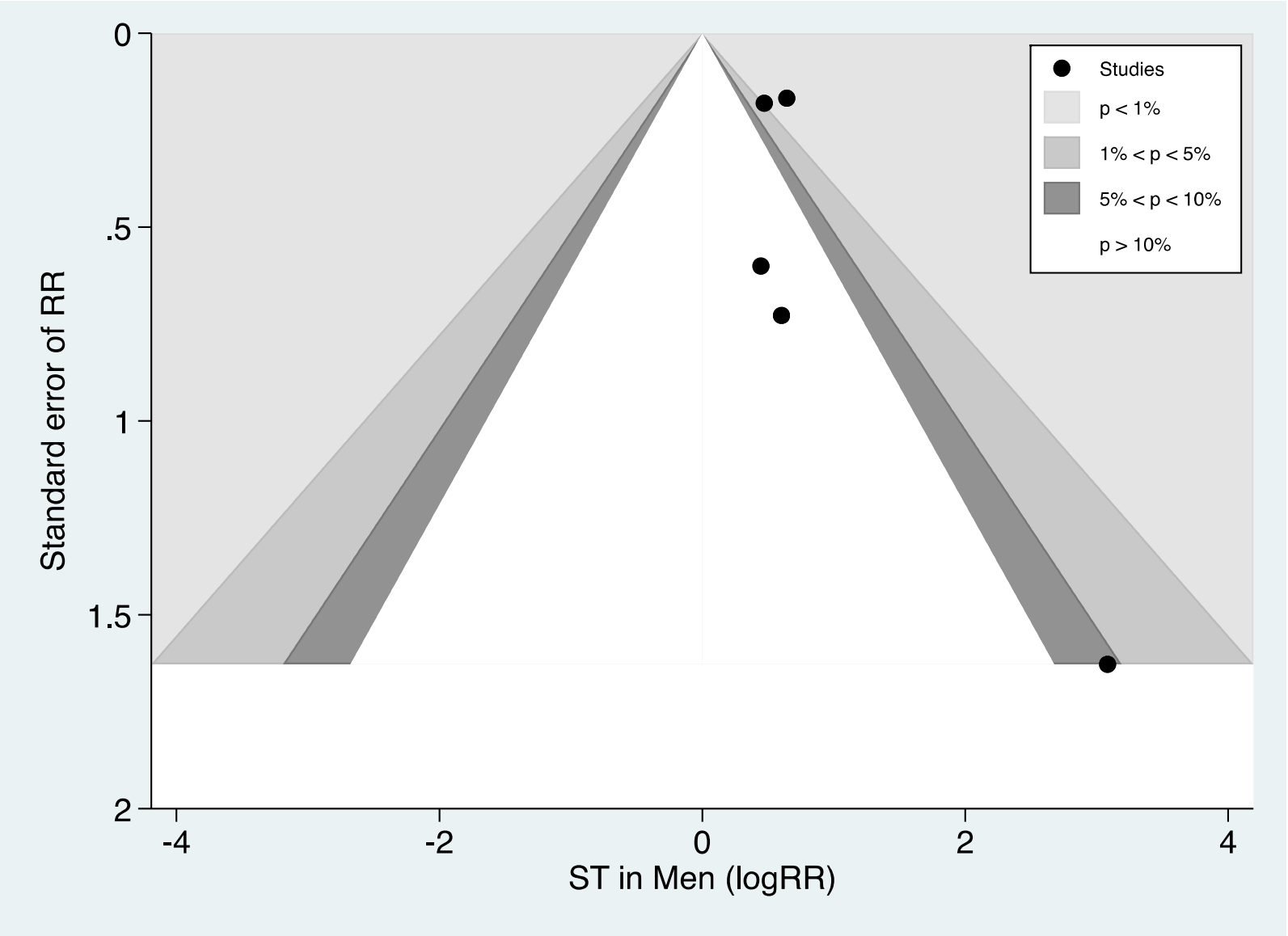
Test of H0: no small-study effects P = 0.747

Figure S20. Contour enhanced funnel plot of MI in men



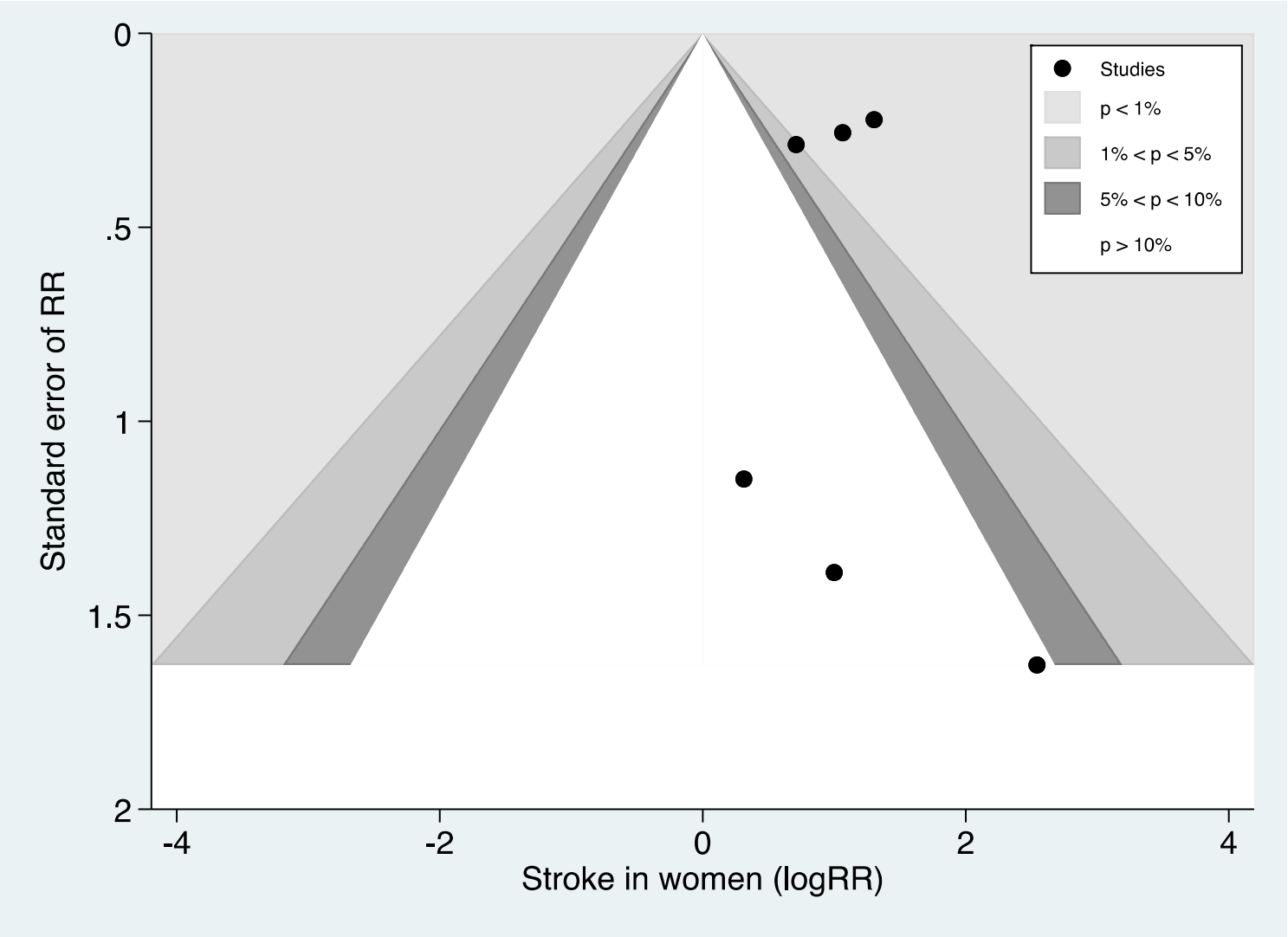
Test of H0: no small-study effects P = 0.648

Figure S21. Contour enhanced funnel plot of ST in women



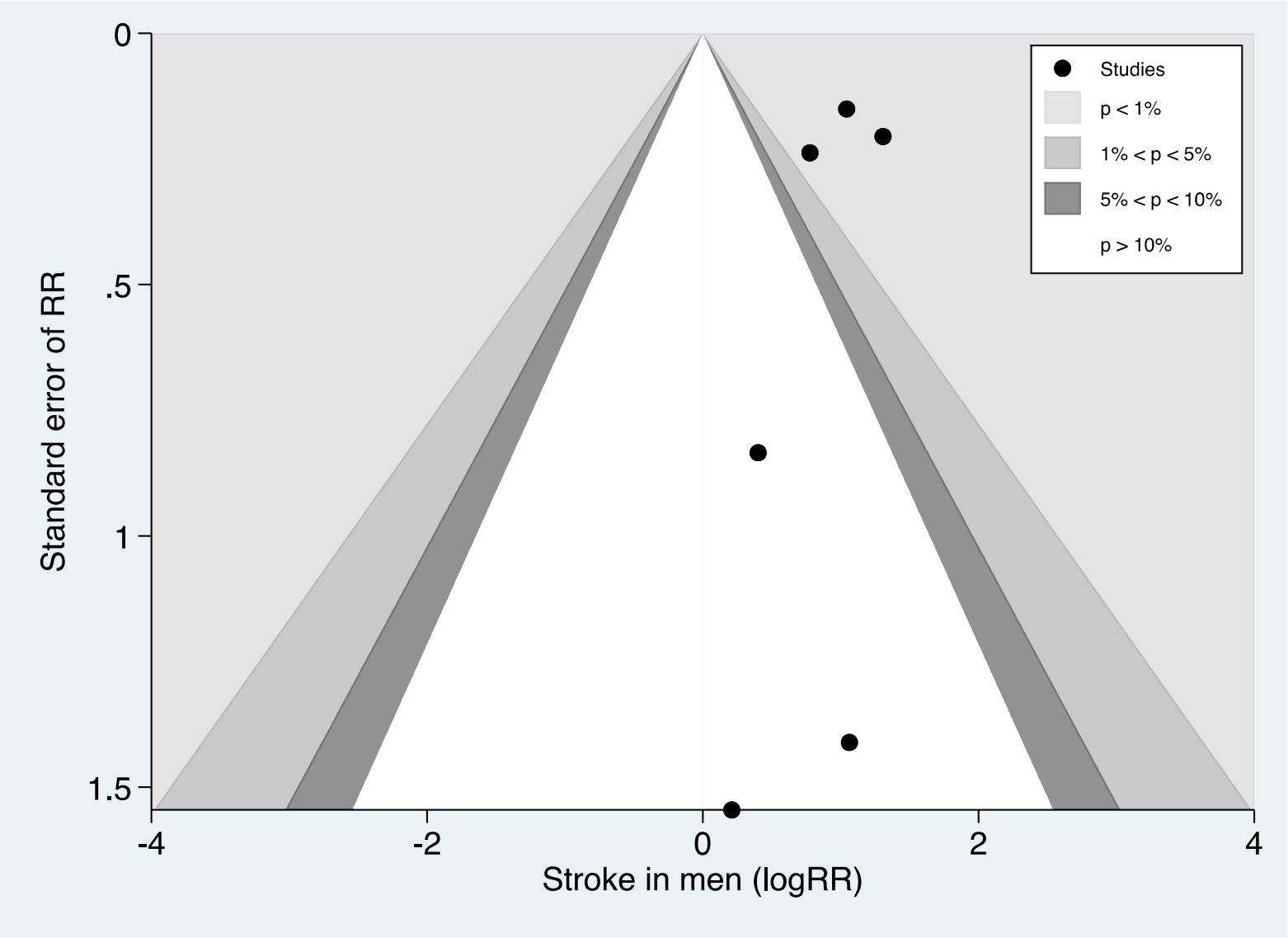
Test of H0: no small-study effects P = 0.352

Figure S22. Contour enhanced funnel plot of ST in men



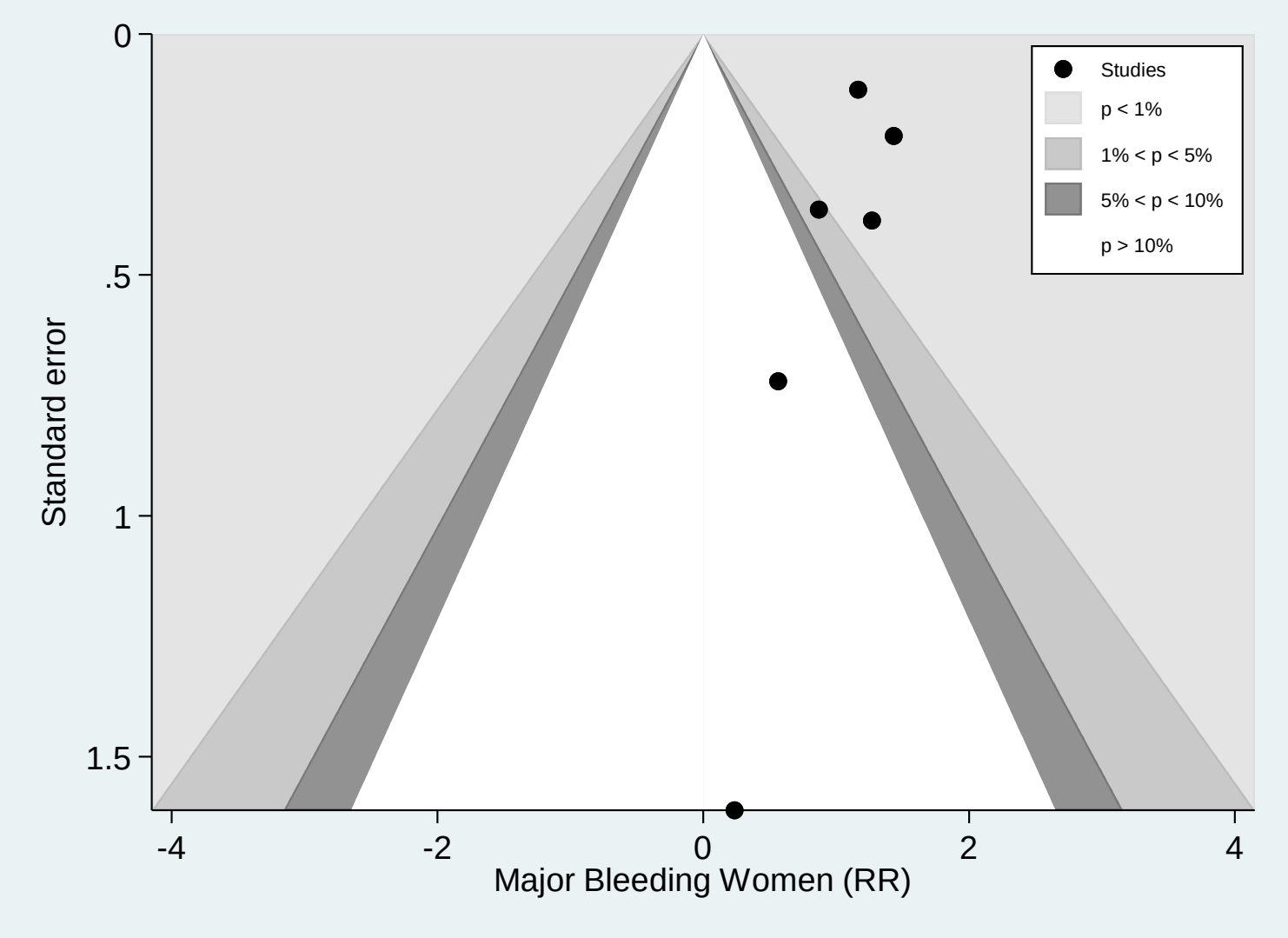
Test of H0: no small-study effects P = 0.952

Figure S23. Contour enhanced funnel plot of stroke in women



Test of H0: no small-study effects P = 0.416

Figure S24. Contour enhanced funnel plot of stroke in women

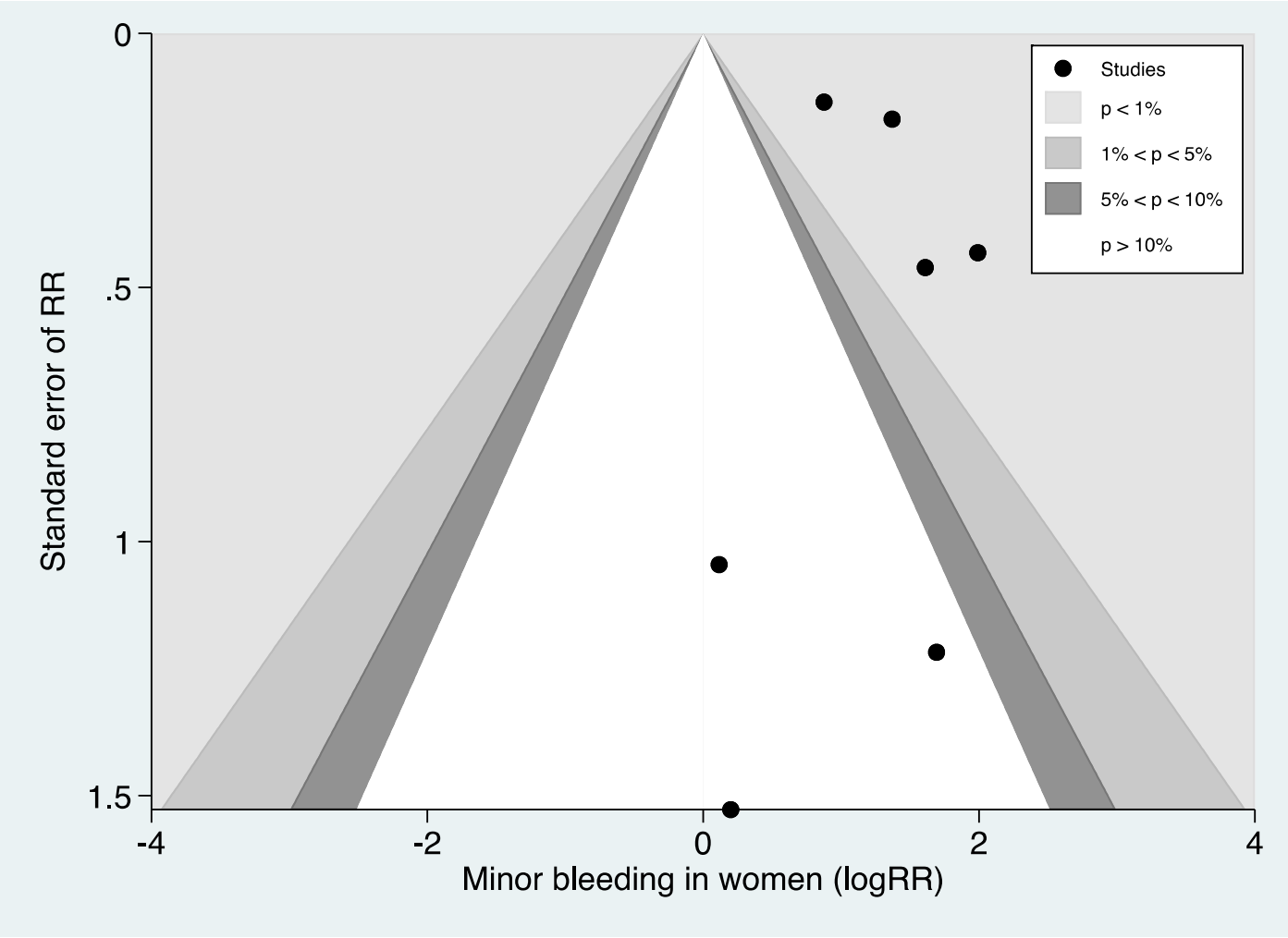


Test of H0: no small-study effects P = 0.366

Figure S25. Contour enhanced funnel plot of major bleeding in women

Test of H0: no small-study effects P = 0.745

Figure S26. Contour enhanced funnel plot of major bleeding in men



Test of H0: no small-study effects P = 0.632

Figure S27. Contour enhanced funnel plot of minor bleeding in women

Test of H0: no small-study effects P = 0.829

Figure S28. Contour enhanced funnel plot of minor bleeding in men

Supplemental References:

1. Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, Storey RF and Investigators D. Safety, Tolerability, and Initial Efficacy of AZD6140, the First Reversible Oral Adenosine Diphosphate Receptor Antagonist, Compared With Clopidogrel, in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome. Primary Results of the DISPERSE-2 Trial. *J Am Coll Cardiol.* 2007;50:1844-1851.
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6. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM, Investigators T-T. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *New Engl J Med.* 2007;357:2001-2015.