ANTITHROMBOTIC THERAPHY AND OTHER INTERVENTIONS

TRIALS

NUMBER OF PARTICIPANTS	NUMBER OF WOMEN	PERCENTAGE OF WOMEN	MEAN AGE	MEAN FOLLOW-UP (YEARS)	TRIALS WITH ANALYSIS BY GENDER N, (%)
24,874	7,181	28.9%	65.3	3.4	2/3 (66.7%)

TRIAL	YEAR	POPULATION	AGE	N° OF SUBJECTS	FOLLOW UP	TREATMENT	DESCRIPTION OF END-POINT	PRIMARY END-POINT	PRIMARY END-POINT HR	NOTES
		(Country)	**mean ± sd, range**	**TOTAL (WOMEN n,%)**	**DURATION**			**TOTAL (WOMEN n,%) (MEN n,%)**	**(CI) P (WOMEN (MEN)**	
NORVIT (Bønaa et al [37])	APRIL 2006	Norwegian trial in patients who had had an acute myocardial infarction within seven days before randomzation	Placebo: 62.6±11.4 B6: 62.5±11.7 Folic Acid, B12: 63.2±11.6 Folic Acid, B12, B6: 63.6±11.9	3749 **(WOMEN: 978, 26.1%)** (Men: 2771)	mean 36 months (median, 40 months).	PLACEBO OR VITAMIN B6 (40 mg) OR FOLIC ACID (0.8 mg), Vitamin B12 (0.4 mg), Vitamin B6 (40 mg) OR FOLIC ACID (0.8 mg), Vitamin B12 (0.4 mg)	New nonfatal and fatal myocardial infarction, nonfatal and fatal stroke, and sudden death attributed to CHD	TOTAL: 716 (PLACEBO: 172 B6: 175 FOLIC ACID and B12: 168 FOLIC ACID, B12, and B6: 201)	FOLIC ACID and B12 vs. No Folic Acid and B12: Rate Ratio = 1.14 [95% CI : 0.98–1.32] P = 0.09 FOLIC ACID, B12, and B6 vs. PLACEBO Rate Ratio = 1.22 [95% CI : 1.00–1.50] P = 0.05	Treatment with B vitamins was not associated with a significant benefit in any subgroup **Results by gender not reported**

ANTITHROMBOTIC THERAPY AND OTHER INTERVENTIONS

TRIAL	YEAR	POPULATION	AGE	N° OF SUBJECTS	FOLLOW UP	TREATMENT	DESCRIPTION OF END-POINT	PRIMARY END-POINT	PRIMARY END-POINT HR	NOTES
CHARISMA (Bhatt et al [141])	APRIL 2006	International trial with significant European component in patients either with clinically evident cardiovascular disease or multiple risk factors	PLACEBO PLUS ASPIRIN 64.0 (range: 45.0 - 93.0) vs. CLOPIDOGREL PLUS ASPIRIN 64.0 (range: 39.0 - 95.0)	TOTAL: 15603 **(WOMEN: 4644, 29.8%)** (MEN: 10959)	Median of 28 months	PLACEBO PLUS LOW-DOSE ASPIRIN vs. CLOPIDOGREL (75 mg per day) PLUS LOW-DOSE ASPIRIN (75 to 162 mg per day)	Myocardial infarction, stroke, or death from cardiovascular causes	TOTAL: 1107 PLACEBO PLUS ASPIRIN: 573 (7.3 %) vs. CLOPIDOGREL PLUS ASPIRIN: 534 (6.8 %)	RR = 0.93 [95% CI : 0.83 -1. 0] P = 0.22 Severe bleeding (primary safety end point) PLACEBO PLUS ASPIRIN 104 (1.3) vs. CLOPIDOGREL PLUS ASPIRIN 130 (1.7) RR = 1.25 [95% CI : 0.97–1.61] P = 0. 09)	**No significant gender difference in the outcome**
HOPE - 2 (Lonn et al [38])	APRIL 2006	International trial with significant European component in patients who had vascular disease or diabetes	>55 PLACEBO: 68.9 ± 6.8 vs. ACTIVE : 68.8 ± 7.1	TOTAL: 5522 **(WOMEN: 1559, 28.2%)** (MEN: 3963)	Average of five years	PLACEBO vs. combination of 2.5 mg of folic acid, 50 mg of vitamin B6, and 1 mg of vitamin B12 or with daily (ACTIVE THERAPY)	Death from cardiovascular causes, myocardial infarction, or stroke.	547 (19.8%) PLACEBO 519 (18.8 %) ACTIVE THERAPY Incidence of Primary Outcome in Placebo Group: **WOMEN: 21.0 %** MEN: 19.3 %	RR=0.95 [95% CI : 0.84 to 1.07] P = 0.41 **$P_{INTERACTION} = 0.57$**	**No significant gender difference in the outcome**

META-ANALYSIS

TRIAL	YEAR	POPULATION	AGE	N° OF SUBJECTS	FOLLOW UP	TREATMENT	DESCRIPTION OF END-POINT	PRIMARY END-POINT	PRIMARY END-POINT HR	NOTES
		(Country)	mean ± sd, range	TOTAL (WOMEN n,%)	DURATION			TOTAL (WOMEN n,%) (MEN n,%)	(CI) P (WOMEN (MEN)	

TRIAL	YEAR	POPULATION	AGE	N° OF SUBJECTS	FOLLOW UP	TREATMENT	DESCRIPTION OF END-POINT	PRIMARY END-POINT	PRIMARY END-POINT HR	NOTES
ASA and gender (Berger et al [90])	JAN 2006	Meta-analysis of 6 trials in participants without cardiovascular disease. (3 trials included only men, 1 included only women, and 2 included both sexes)	**WOMEN: 61 YEARS** MEN (NOT AVAILABLE FOR 27210): 61 YEARS	TOTAL: 95456 **(WOMEN: 51342, 53.8%)** (MEN: 44114)	Weighted mean of 6.4 years	CONTROL or PLACEBO vs. ASPIRIN	Cardiovascular events [nonfatal MI, nonfatal stroke, and cardiovascular mortality]	Cardiovascular events: **(WOMEN: 1285 CONTROL: 682/25694 (2.7%) ASPIRIN: 603/25648 (2.4%)** (MEN: 2047 CONTROL: 1022/21192 (4.8%) ASPIRIN 1025/22922 (4.5%)) *Myocardial Infarction:* **(WOMEN: 469 CONTROL: 234/25694 (0.9%) ASPIRIN: 235/25648 (0.9%))** (MEN: 1023 CONTROL: 585/21192 (2.8%) ASPIRIN: 438/22922 (1.9%) *Strokes:* **(WOMEN: 625 CONTROL: 344/25694 (1.3%) ASPIRIN: 281/25648 (1.1%)** (MEN: 597 CONTROL: 266/21192 (1.3%) ASPIRIN: 331/22922 (1.4%))	Cardiovascular events: **OR_{WOMEN} = 0.88 [95% CI : 0.79 - 0.99] P=0.03** OR_{MEN} = 0.86 [95% CI : 0.78-0.94] P=0.01 *Myocardial Infarction:* **OR_{WOMEN} = 1.01 [95% CI : 0.84 -1.21] P=0.95** OR_{MEN} = 0.68 [95% CI : 0.54 -0.86] P=0.001 *Strokes:* **OR_{WOMEN} = 0.83 [95% CI : 0.70-0.97] P=0.02** OR_{MEN} = 1.13 [95% CI : 0.96 -1.33] P = 0.14	**Significant reduction of MI with aspirin in men but not in women. Significant reduction of stroke with aspirin in women but not in men** **Aspirin increased the risk of bleeding in women (OR=1.68; [95% CI: 1.13-2.52], P=0.01) and in men (OR=1.72; [95% CI:1.35-2.20], P<0.001).** **No aspirin effect was observed among women or men on cardiovascular and all-cause mortality**

ANTITHROMBOTIC THERAPY AND OTHER INTERVENTIONS

TRIAL	YEAR	POPULATION	AGE	N° OF SUBJECTS	FOLLOW UP	TREATMENT	DESCRIPTION OF END-POINT	PRIMARY END-POINT	PRIMARY END-POINT HR	NOTES
ASA in PAD (Berger et al [89])	MAY 2009	Meta-analysis of eighteen trials involving patients with peripheral artery disease [7 trials tested aspirin monotherapy vs placebo or control, 7 trials examined combined aspirin and dipyridamole vs placebo or control, 4 trials had multiple arms (aspirin monotherapy, aspirinplusdipyridamole, and placebo)]	NOT REPORTED	5269 (WOMEN: 0% up to 56%)	from 10 days to 6.7 years	CONTROL vs. ASPIRIN (alone or with dipyridamole)	cardiovascular events (nonfatal myocardial infarction[MI], nonfatal stroke, and cardiovascular death)	CONTROL 269/2446 (11.0%) vs. ASPIRIN (alone or with dipyridamole) 251/2823 (8.9%)	RR= 0.88 [95% CI : 0.76-1.04]	The primary safety outcome was the occurrence of major bleeding Aspirin therapy was associated with a significant reduction in the secondary end point of nonfatal stroke. **Results by gender not reported**

TRIAL	YEAR	POPULATION	AGE	N° OF SUBJECTS	FOLLOW UP	TREATMENT	DESCRIPTION OF END-POINT	PRIMARY END-POINT	PRIMARY END-POINT HR	NOTES
Aspirin in the primary and secondary prevention (Antithrombotic Trialists' (ATT) Collaboration (Balgent et al [88])	MAY 2009	Meta-analyses of six primary prevention trials and 16 secondary prevention trials in patients with low average /high risk of serious vascular events	Primary prevention trials: NOT REPORTED (Eligible age range at entry 19 – 94) Secondary prevention trials: NOT REPORTED	6 primary prevention trials TOTAL: 95000 16 secondary prevention trials TOTAL: 17000	Primary prevention trials : 5.8 years (range: 3.7 to 10.0 years) Secondary prevention trials NOT REPORTED	CONTROL vs. Long-Term ASPIRIN	*Serious vascular event* [defined as myocardial infarction, stroke, or death from a vascular cause (including sudden death, pulmonary embolism, haemorrhage, and, for secondary prevention trials only, death from an unknown cause]; *major coronary event* (myocardial infarction, coronary death, or sudden death); *any stroke* (haemorrhagic or probably ischaemic [ie, definitely ischaemic or of unknown type]); *death from any cause; and major extracranial bleed* (mainly gastrointestinal and usually defined as a bleed requiring transfusion or resulting in death). In the primary prevention trials, myocardial infarctions and strokes were classified as fatal or nonfatal in accordance with	Primary Prevention Trials EVENTS (% per year) *Serious vascular event* **WOMEN:** **Control: 690 (0.32)** **Aspirin: 608 (0.28)** MEN: Control: 1193 (1.08) Aspirin: 1063 (0.95) TOTAL: Control: 1883(0.57) Aspirin: 1671 (0.51) *Major coronary event* **WOMEN:** **Control: 314 (0.14)** **Aspirin: 299 (0.14)** MEN Control: 801 (0.72) Aspirin: 635(0.57) TOTAL: Control: 1115(0.34) Aspirin: 934 (0.28) *Ischaemic stroke* **WOMEN** **Control:229(0.11)** **Aspirin:176 (0.09)** MEN Control: l38(0.15) Aspirin: 141(0.15) TOTAL: Control: 367(0.12) Aspirin:317 (0.11)	*Serious vascular event* **RR_{WOMEN} =0.88 [95% CI : 0.76–1.01]** RR_{MEN}=0.88 [95% CI : 0.79–0.98] RR_{TOTAL}= 0.88 [99% CI : 0.82–0.94] p=0.00001 *Major coronary event* **RR_{WOMEN} =0.95 [95% CI : 0.77–1.17]** RR_{MEN}=0.77 [95% CI : 0.67–0.89] RR_{TOTAL}=0.82 [99% CI : 0.75 -0.90] P=0.00002 *Ischaemic stroke* **RR_{WOMEN} =0.77 [95% CI : 0.59–0.99]** RR_{MEN}=1.01 [95% CI : 0.74–1.39] RR_{TOTAL}= 0.86 [99% CI : 0.74–1.00] p=0.05	**Primary prevention: significant reduction of major coronary events with aspirin in men but not in women. Significant reduction of ischemic stroke with aspirin in women but not in men.** Aspirin allocation increased major gastrointestinal and extracranial bleeds

TRIAL	YEAR	POPULATION	AGE	N° OF SUBJECTS	FOLLOW UP	TREATMENT	DESCRIPTION OF END-POINT	PRIMARY END-POINT	PRIMARY END-POINT HR	NOTES
Aspirin in the primary and secondary prevention							each trial's definitions. In the secondary prevention trials, as previously, 2 these outcomes were regarded as non-fatal only if the patient was alive at the end of the trial or died of a non-vascular cause.	Secondary Prevention Trials EVENTS (% per year) *Serious vascular event:* **WOMEN:** **Control: 314 (7.14)** **Aspirin: 250 (5.88)** MEN: Control: 1487 (8.45) Aspirin: 1255 (6.88) TOTAL: Control: 1801(8.19) Aspirin: 1505 (6.69) *Major coronary event* **WOMEN:** **Control: 157 (3.36)** **Aspirin: 115 (2.59)** MEN Control: 1057 (5.79) Aspirin: 880 (4.70) TOTAL: Control: 1214(5.30) Aspirin: 995 (4.30) *Ischaemic stroke* **WOMEN** **Control: 53 (1.17)** **Aspirin: 45 (1.04)** MEN Control: 123 (0.67) Aspirin: 95 (0.51) TOTAL: Control: 176 (0.77) Aspirin: 140 (0.61)	Secondary Prevention Trials *Serious vascular event:* **RR_{WOMEN} = 0.81** **[95% CI : 0.64 -1.02]** RR_{MEN} = 0.81 [95% CI : 0.73–0.90] RR_{TOTAL} = 0.81 [99% CI : 0.75 - 0.87] p<0.00001 *Major coronary event* **RR_{WOMEN} = 0.73** **[95% CI : 0.51–1.03]** RR_{MEN} = 0.81 [95% CI : 0.72 - 0.92] RR_{TOTAL} = 0.80 [99% CI : 0.73 -0.88] P<0.00001 *Ischaemic stroke* **RR_{WOMEN} = 0.91** **[95% CI : 0.52 - 1.57]** RR_{MEN} = 0.73 [95% CI : 0.50 - 1.06] RR_{TOTAL} = 0.78 [99% CI : 0.61 - 0.99] p=0.04	**No significant gender differences with aspirin in secondary prevention**