ATRIAL FIBRILLATION

TRIALS

NUMBER OF PARTICIPANTS	NUMBER OF WOMEN	PERCENTAGE OF WOMEN	MEAN AGE	MEAN FOLLOW-UP (YEARS)	TRIALS WITH ANALYSIS BY GENDER N, (%)
22,511	9,192	40.8%	72.1	2.5	3/7 (42.8%)

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)**	
ACTIVE W (Connolly et al [181])	JUNE 2006	Patients with atrial fibrillation plus one or more risk factor for stroke (International with significant European component)	70.2 ± 9.5 (Oral anticoagulation therapy); 70.2 ± 9.4 (clopidogrel plus aspirin); age≥ 55	TOTAL: 6706 (**WOMEN: 2276, 34%)** (MEN: 4430)	Median 1.28 years	Oral anticoagulation therapy (vitamin K antagonist - international normalised ratio (INR) between 2.0 and 3.0) versus Clopidogrel 75 mg, once daily in addition to aspirin (75–100 mg per day recommended)	Composite of stroke, non-CNS systemic embolus, myocardial infarction, or vascular death	165, Annual risk: 3.93% (oral anticoagulation Therapy) 234 Annual risk: 5.60% (clopidogrel plus aspirin) *Oral anticoagulation therapy at entry* 3.72% (oral anticoagulation Therapy) 5.50% (oral anticoagulation Therapy)	RR = 1.44 [95% CI: 1.18–1.76] P=0.0003 RR = 1.50 [95% CI: 1.19–1.89] P=0.0005 $P_{INTERACTION}$= 0.43 (oral anticoagulation therapy at study entry)	The study was stopped early because of clear evidence of superiority of oral anticoagulation therapy **Results by gender not reported**

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Analysis by age of NASPEAF (Pérez-Gòmez et al [180])	APR 2007	The high risk group (non-valvular AF and prior embolism or mitral stenosis with or without prior embolism); the intermediate risk group (non-valvular AF patients with risk factors, but no prior embolism) (International with significant European component)	*No prior embolism:* Anticoagulant <75: 64.7± 6.9, ≥75: 77.8 ± 2.4; Combined <75: 64.8± 7.7, ≥75: 78.3 ± 2.8; *Prior embolism* Anticoagulant <75: 64.7 ± 7.3, ≥75: 78.6 ± 3.0; Combined <75: 65.3± 7.4, ≥75: 79.6 ± 3.5;	TOTAL: 967 **(WOMEN: 548, 56.6%)** (MEN: 419)	4 years (controlled every 6 months)	High risk group: anti-vitamin K anticoagulant therapy (target INR of 2.0–3.0) versus combined therapy (600 mg of the antiplatelet agent triflusal and a moderate anticoagulation intensity for an INR range from 1.4 to 2.4) (the mean INR was 2.17). *Intermediate risk group:* anticoagulant therapy alone INR range of 2.0–3.0 or combined therapy INR range of 1.25–2.0, although the resultant mean value was 1.97	Fatal and non-fatal ischaemic or haemorrhagic stroke/transient ischaemic attack, systemic embolism and myocardial infarction, sudden death and death from bleeding	Events (rate): patients<75 50 (2.8%) patients≥75 30 (6.0%)	Event-rate HR = 2.31 [95% CI: 1.37–3.90] P< 0.003 *Severe bleeding* HR = 1.75 [95% CI: 0.90-3.40] P=0.110 (anticoagulant Therapy) HR = 0.33 [95% CI: 0.13–0.83] P = 0.012 (Combined therapy)	**Results by gender not reported** (Patients randomized to antiplatelet therapy alone were not included in this analysis).

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Corticosteroid (Halonen et al [182])	APRIL 2007	Patients without prior AF or flutter and scheduled to undergo first on-pump coronary artery bypass graft (CABG) surgery, aortic valve replacement, or combined CABG surgery and aortic valve replacement. (3 University Hospitals in Finland only)	64.4 ± 8.4 (Hydrocortisone) 66.1± 9.5 (Placebo) 30≤age≤85	TOTAL: 241 **(WOMEN : 56 (23.2%)**) (MEN: 185)	84 hours after cardiac surgery.	100-mg Hydrocortisone versus matching placebo: the first dose in the evening of the operative day, then 1 dose every 8 hours during the next 3 days. In addition, all patients received oral metoprolol (50-150 mg/d) titrated to heart rate	Occurrence of AF during the first 84 hours after cardiac surgery	(Hydrocortisone group) 36/120 (30%) (Placebo group) 58/121 (48%)	$HR_{Adjusted}$ = 0.54 [95% CI: 0.35 -0.83] P = 0.004	**Results by gender not reported After adjustment for sex and other factors, corticosteroid treatment remained a significant independent predictor of absence of postoperative AF.**

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BAFTA (Mant et al [183])	AUG 2007	Patients with atrial fi brillation from general practices (England and Wales)	81·5 ±4·2 age≥ 75 years	TOTAL: 973 **(WOMEN: 442, 45.4%)** (MEN: 531)	Mean of 2.7±1.2 years.	Warfarin (target international normalised ratio 2–3) versus aspirin (75 mg per day).	Fatal or disabling stroke (ischaemic or haemorrhagic), intracranial haemorrhage, or clinically signifi cant arterial embolism	Total 24, Risk per year 1.8% warfarin 48, Risk per year 3.8% aspirin (Stroke 21 warfarin 44 aspirin) MEN 10/267, Risk per year 1.4% warfarin 27/264, Risk per year 3.9% aspirin **WOMEN** **14/221, Risk per year 2.3% warfarin** **21/221, Risk per year 3.5% aspirin**	RR = 0.48 [95% CI: 0.28–0.80] P=0.0027 MEN RR = 0.35 [95% CI: 0.15–0.75] **WOMEN** **RR = 0.65 [95% CI: 0.30–1.33]** **$P_{INTERACTION}$ = 0.23**	Oral anticoagulant more effective than aspirin in elderly people **In women the benefit of warfarin is somewhat lower but the interaction is not significant**

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ATHENA (Hohnloser et al [184])	FEB 2009	Patients with atrial fibrillation who had additional risk factors for death (International with significant European component)	TOTAL: 71.6±9.0 71.6±8.9 (Dronedarone) 71.7±9.0 (Placebo)	TOTAL: 4628 **(WOMEN : 2169, 46.9%)** (MEN: 2459)	Mean 21±5 months	Dronedarone, 400 mg twice a day versus placebo	First hospitalization due to cardiovascular events or death	734 (31.9%) (dronedarone group) 917 (39.4%) (placebo group) **WOMEN 801/2169** MEN 850/2459	HR = 0.76 [95% CI: 0.69 - 0.84] (dronedarone) P<0.001 **WOMEN HR = 0.77 [95% CI: 0.67 - 0.89]** MEN HR = 0.74 [95% CI: 0.64 - 0.85] **$P_{INTERACTION}$ = 0.65**	**Significant effect on the outcome in both men and women**

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GISSI-AF (Disertori et al [186])	APRIL 2009	Patients in sinus rhythm but either two or more documented episodes of atrial fibrillation in the previous 6 months or successful cardioversion for atrial fibrillation in the previous 2 weeks, underlying cardiovascular disease, diabetes, or left atrial enlargement. (International with significant European component)	67.5±9.5 (Valsartan) 68.2±8.9 (Placebo) age≥40	TOTAL: 1442 (**WOMEN: 544, 37.7%)** (MEN: 898)	12 Months	Valsartan versus placebo (Valsartan was initiated at a dose of 80 mg daily for 2 weeks and was then increased to 160 mg daily for another 2 weeks. At the 4-week visit, the dose was increased to 320 mg daily, and this regimen was continued until the end of the follow-up period at week 52)	Time to a first recurrence of atrial fibrillation (AF), patients who had more than one recurrence of atrial fibrillation at 1 year	AF recurrence: 371(51.4%) (valsartan group) 375 (52.1%) (placebo group) pt with more than one episode of AF: 194 (26.9%) (valsartan group) 201 (27.9%) (placebo group)	$HR_{Adjusted}$ = 0.97 [96% CI: 0.83-1.14] P=0.73 $OR_{Adjusted}$ =0.89 [99% CI: 0.64-1.23] P = 0.34	**Results by gender not reported**

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ACTIVE A (Connolly et al [185])	MAY 2009	Patients with atrial fibrillation, an increased risk of stroke and for whom vitamin K–antagonist therapy was unsuitable (International with significant European component: 30.5% Western Europe and Israel, 32.7% Eastern Europe)	70.9±10.2 (Clopidogrel plus aspirin) 71.1±10.2 (Aspirin) age≥ 55	TOTAL: 7554 (**WOMEN: 3157, 42%)** (MEN: 4397)	Mean Follow-up 3.6 years	Clopidogrel (75 mg) once daily plus aspirin versus aspirin alone	Stroke or myocardial infarction or non–central nervous system systemic embolism or death from vascular causes	832 (6.8% per year) (clopidogrel group), 924 (7.6% per year) (aspirin alone) **WOMEN** **7.38 (clopidogrel group)** **8.13 (aspirin alone)** MEN 6.32 (clopidogrel group) 7.23 (aspirin alone) *Major bleeding:* 251 (2.0% per year) (clopidogrel group) 162 (1.3% per year) (aspirin alone)	RR = 0.89 [95% CI: 0.81 - 0.98] P = 0.01 (clopidogrel group) **$P_{INTERACTION}$ = 0.71** *Major bleeding* RR = 1.57 [95% CI: 1.29 - 1.92] P<0.001	**Significant benefit with the drug association on the primary outcome in both men and women, but significant increase in major bleedings**

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)	

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Oral anticoagulation meta-analysis of 14 randomized trials (Heneghan et al [187])	FEB 2006	Patients on anticoagulant therapy irrespective of the indication for treatment (European trials 11, Canada 1, USA 2)	Mean age: 42 to 75	TOTAL: 3049	2 months to 24 months.	Self-monitoring versus selfmanagement (self-monitoring and self-adjusted therapy) of anticoagulation versus control and dosage by personal physician, anticoagulation management clinics, or managed services	Major haemorrhage, Thromboembolic events, death, tests in range, minor haemorrhage, frequency of testing, feasibility of self-monitoring	*Major haemorrhage:* Total 34/1349 (self-monitoring+ self-adjusted therapy) Total 55/1471 (control) (9/744 self-monitoring and self-adjusted therapy 12/855 control) *Thromboembolic events:* Total 32/1424(self-monitoring+ self-adjusted therapy) Total 71/1546 (control) (5/744 self-monitoring and self-adjusted therapy, 26/855 control) *All-cause mortality:* Total 29/1201(self-monitoring+ self-adjusted therapy) Total 47/1201 (control) (7/678 self-monitoring and self-adjusted therapy, 21/696 control	*Major haemorrhage* OR =0.65 [95% CI 0.42–0.99] OR = 0.93 [95% CI: 0.42–2.05] *Thromboembolic events:* OR = 0.45 [(95% CI: 0.30–0.68] OR = 0.27 [95% CI: 0.12–0.59] *All-cause mortality:* OR =0.61 [95% CI: 0.38–0.98] OR =0.37 [95% CI: 0.16–0.85]	**Percentage of women enrolled not reported.** **Results by gender not reported.**

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Antithrombotic Therapy to Prevent Stroke Meta-analysis of 29 trials (Hart et al [179])	JUNE 2007	Patients with nonvalvular atrial fibrillation (Europe 16 trials, North America 7 Japan 2, China 1)	mean age 71 years	TOTAL: 28044 **(WOMEN : 9815, 35%)** (MEN: 18229)	Mean follow-up 1.5 years	Adjusted-dose warfarin vs Placebo/control (6 trials, 2900 participants) Antiplatelet agents vs Control (8 trials, 4876 participants) Adjusted-Dose Warfarin vs Antiplatelet (12 trials, 12963 participants).	All stroke (ischemic and hemorrhagic), ischemic stroke, intracranial hemorrhage, all-cause mortality, and major extracranial hemorrhage.	53/1450 Adjusted-Dose Warfarin 133/1450 Placebo or Control 245/2602 Antiplatelet 296/2594 Placebo or No Treatment 205/6558 Adjusted-Dose Warfarin 341/6575 Antiplatelet	Relative Risk Reduction =64% [95% CI: 49% - 74%] RR Reduction = 22% [95% CI: 6% - 35%] RR Reduction, 39% [95% CI: 22% - 52%]	**Results by gender not reported**

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Statin use and development of atrial fibrillation A meta-analysis of 6 randomized clinical trials and 10 observational studies (Liu T et al [188])	MAY 2008	Patients with various type of cardiovascular disease		TOTAL: 7041 Patients included in trials: 3546 Patients included in observational studies: 3495	Trials: 6.3 days - 6 months Observational studies: 1 week – 6.5 years	Statins versus control	Recurrent and new onset AF	Trials: Treatment 179 Control 226 Observational studies: Treatment 351 Control 672	Relative Risk=0.76 [95% CI: 0.55–1.05] P=0.09 RR = 0.77 [95% CI: 0.70–0.85]	**Percentage of women enrolled not reported** **Results by gender not reported**