STROKE

TRIALS

NUMBER OF PARTICIPANTS	NUMBER OF WOMEN	PERCENTAGE OF WOMEN	MEAN AGE	MEAN FOLLOW-UP (YEARS)	TRIALS WITH ANALYSIS BY GENDER N, (%)
28,790	10,618	36.9%	69.0	1.26	5/10 (50%)

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)**	
ESPRIT (Halkes et al[194])	MAY 2006	European and Australasian trial in patients with a transient ischaemic attack or a minor ischaemic stroke of presumed arterial origin.	63 ± 11	TOTAL: 2739 **(WOMEN: 950, 34.7%)** (MEN: 1789)	Mean of 3.5 years (SD 2.0).	ASPIRIN (30–325 mg daily) with DIPYRIDAMOLE (200 mg twice daily) vs. ASPIRIN ALONE (30–325 mg daily)	Death from all vascular causes or non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication	ASPIRIN WITH DIPYRIDAMOLE 173 (13%) vs. ASPIRIN ALONE 216 (16%)	INTENTION TO TREAT: HR =0.80 [95% CI : 0.66 - 0.98] absolute risk reduction =1.0% per year [95% CI : 0.1 - 1.8] ON TREATMENT: HR = 0.82 [95% CI : 0.66 -1.02]	Patients on aspirin and dipyridamole discontinued trial medication more often than those on aspirin alone (470 vs. 184), mainly because of headache. **Subgroup analyses (sex) for the primary outcome event: $P_{INTERACTION}$ > 0.18.**

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ESPRIT (Halkes et al[195])	FEB 2007	European and Australasian trial in patients within 6 months after a transient ischaemic attack (including transient monocular blindness) or minor ischaemic stroke (grade ≤ 3 on the modifi ed Rankin scale) of presumed arterial origin	62 ± 10 ANTICOAGULANTS 61 ± 9 ASPIRIN	Total: 1068 **(WOMEN 338, 32%)** (MEN 730)	Mean of 4.6 years	ANTICOAGULANTS (target INR range 2.0–3.0) vs. ASPIRIN (30–325 mg daily).	Death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication, whichever occurred first	TOTAL: ANTICOAGULANTS 99 (19%) vs. ASPIRIN 98 (18%)	HR = 1.02 [95% CI : 0.77–1.35] Ischaemic events HR = 0.73 [95% CI : 0.52–1.01] Major Bleeding Complications HR = 2.56 [95% CI : 1.48–4.43]	**Results by gender not reported although subgroup analyses according to randomization scheme, age, sex, history of ischaemic heart disease, type of cerebral ischaemia, and country were planned, but were not undertaken in view of the low number of outcome events.**

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Gender analysis of PROACT-2 (Hill et al [196])	SEPT 2006	Patients with angiographically proven middle cerebral artery occlusion	WOMEN: 70 (IQR: 59–76) MEN: 66 (IQR: 54–75)	TOTAL: 180 **(WOMEN: 74, 41%)** (MEN: 106)		Intra-arterial prourokinase or heparin control	Modified Rankin Scale(mRS) score of 0 to 2 (independent functional outcome) at 90 days compared with a score of 3 to 6 (dependence or death)	mRS 0–2, 90 days: *Recanalization at 2 hours*	mRS 0–2, 90 days CONTROL: **WOMEN: proportion = 0.17 [95% CI : 0.05–0.39]** MEN: proportion = 0.31 [95% CI : 0.16–0.48] ProUK **WOMEN: proportion =0.37 [95% CI : 0.24–0.52]** MEN: proportion = 0.41 [95% CI : 0.30–0.54] **Interaction P=0.021** *Recanalization at 2 hours:* CONTROL: **WOMEN: proportion = 0.23 [95% CI : 0.08–0.45]** MEN: proportion =0.21 [95% CI : 0.09–0.39] ProUK **WOMEN: proportion = 0.61 [95% CI : 0.46–0.75]** MEN: proportion = 0.66 [95% CI : 0.53–0.77] **Interaction NS**	**Women with middle cerebral artery ischemic stroke benefit more from intra-arterial therapy than men, mainly beacause therapy nullifies the worse outcome of untreated women.**

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EPITHET (Davis et al [197])	APRIL 2008	Multinational trial (phase II) done in 15 centres in Australia, New Zealand, Belgium, and the UK in patients with acute ischaemic stroke who were imaged with serial echoplanar MRI	PLACEBO 70.9 ± 13.4 vs. ALTEPLASE 72.2 ± 12.8 *Patients with mismatch:* PLACEBO 72.2 ± 13.1 vs. ALTEPLASE 71.3 ± 14.2	TOTAL: 101 **(WOMEN: 44, 43.6%)** (MEN: 57) *Patients with mismatch:* TOTAL: 80 **(WOMEN: 42, 52.5%)** (MEN: 38)	90 days	PLACEBO vs. ALTEPLASE 3–6 h after onset of ischaemic stroke	Infarct growth between baseline DWI and the day 90 T2 lesion in mismatch patients	TOTAL: ASA–ERDP 916 (9.0%) CLOPIDOGREL 898 (8.8%) *Patients with mismatch*: Primary analytical method: geometric mean PLACEBO 1.78 ALTEPLASE 1.24 Secondary analytical methods: Median relative growth PLACEBO 1.79 (1.09 to 3.15) ALTEPLASE 1.18 (0.49 to 2.42) Median absolute growth (mL): PLACEBO 28.7 (1.01 to 64.2) ALTEPLASE 4.1 (–5.29 to 57.11) Mean difference in cube root volumes (cm): PLACEBO 0.75 (1.06) ALTEPLASE 0.50 (1.59)	HR_{TOTAL}= 1.01 [95% CI : 0.92 - 1.11] *Patients with mismatch:* Primary analytical method: geometric mean RATIO=0.69 [95% CI : 0.38 - 1.28] P=0.239 Secondary analytical methods: Median relative growth: RATIO=0. 66 [95% CI : 0..36 - 0..92] P = 0.054 Median absolute growth (mL): Difference =-24.6 [95% CI : – 40.6 - 3.2] P = 0.126 Mean difference in cube root volumes (cm): Difference = - 0.25 [95% CI : – 0.84 - 0.35] P = 0.415	Reperfusion was more common with alteplase than with placebo and was associated with less infarct growth (p=0.001), better neurological outcome (p<0.0001), and better functional outcome (p=0.010) than was no reperfusion. **Results by gender not reported.**

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PRoFESS (Sacco et al [198])	SEPT 2008	International trial with significant European component in patients who recently had an ischemic stroke	66.1 ± 8.6 ASA–ERDP vs. 66.2±8.5 CLOPIDOGREL	TOTAL: 20332 **(WOMEN: 7310, 36%)** (MEN: 13022)	Mean of 2.5 years (range: 1.5 - 4.4)	Either Aspirin (25 mg) plus extended-release dipyridamole (200 mg) twice daily (ASA–ERDP) or CLOPIDOGREL (75 mg daily)	First recurrence of stroke	TOTAL: ASA–ERDP 916 (9.0%) vs. CLOPIDOGREL 898 (8.8%) **WOMEN: ASA–ERDP: 311 vs. CLOPIDOGREL: 291** MEN: ASA–ERDP: 605 vs. CLOPIDOGREL: 607	HR_{TOTAL}=1.01 [95% CI : 0.92–1.11] **$P_{INTERACTION}$ > 0.05**	Non-inferiority of aspirin+dipiridamol vs clopidogrel was not demonstrated. **No significant gender difference in the outcome.**
PRoFESS (Yusuf et al [199])	SEPT 2008	International trial with significant European component in patients who recently had an ischemic stroke	66.1 ± 8.6 TELMISARTAN 66.2 ± 8.6 PLACEBO	TOTAL: 20332 **(WOMEN: 7310, 36%)** (MEN: 13022)	Mean of 30 months (range: 18 - 52)	PLACEBO vs. TELMISARTAN (80 mg daily)	First recurrence of stroke	TOTAL: PLACEBO 934 (9.2%) vs. TELMISARTAN 880 (8.7%)	HR_{TOTAL}=0.95; [95% CI : 0.86 - 1.04] P = 0.23	No significant effect on the outcome. **Results by gender not reported.**

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PRoFESS (Diener et al [200])	OCT 2008	International trial with significant European component in patients who had had an ischaemic stroke	66.1 ± 8.6 ASA+ER-DP: 66.2 ± 8.5 Clopidogrel; 66.1 ± 8.6 Telmisartan: 66.2 ± 8.6 Placebo: ≥55 years	TOTAL: 20332 **(WOMEN: 7310, 36%)** (MEN: 13022)	Median of 2·4 years	ASPIRIN (ASA) (25 mg) and extended-release dipyridamole (ER-DP) (200 mg) twice a day vs. CLOPIDOGREL (75 mg once a day). TELMISARTAN (80 mg once a day) vs. PLACEBO once per day	Disability after a recurrent stroke (assessed at 3 months with the modified Rankin scale mRS and Barthel index and cognitive function (assessed with the mini-mental state examination MMSE score) at 4 weeks after randomisation and at the penultimate visit	Barthel index ASA+ER-DP 472 (57%), CLOPIDOGREL 446 (54%). TELMISARTAN 450 (56%) PLACEBO 468 (56%). Distribution of patients with MMSE score ≤24 points over time Month 1 ASA+ER-DP 1663 (18%) CLOPIDOGREL 1667(18%) TELMISARTAN 1666 (18%) PLACEBO 1664 (18%) *Penultimate Visit* ASA+ER-DP 1165 (15%) CLOPIDOGREL 1175 (15%) TELMISARTAN 1178 (15.2%) PLACEBO 1162 (15%)	Relative risk=1.06 [95% CI: 0.97–1.15] P=0.21 Relative risk=1.02 [95% CI: 0.93–1.11] P=0.72 Distribution of patients with MMSE score ≤24 points over time Month 1 Relative risk = 1.01 [95% CI: 0.95–1.07] Relative risk = 1.00 [95% CI: 0.94–1.07] *Penultimate Visit* Relative risk= 1.02 [95% CI: 0.94–1.10) Relative risk =1.01 [95% CI: 0.94–1.09]	No significant effect on the outcome. **Results by gender not reported.**

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ECASS III (Hacke et al [201])	SEPT 2008	European trial in patients with acute ischemic stroke (after exclusion of brain hemorrhage or major infarction)	PLACEBO 65.6 ± 11.0 vs. INTRAVENOUS ALTEPLASE 64.9 ± 12.2	TOTAL: 821 **(WOMEN: 326, 39.7%)** (MEN: 495)	3-month	PLACEBO vs. INTRAVENOUS ALTEPLASE (0.9 mg per kilogram of body weight) administered between 3 and 4.5 hours after the onset of a stroke.	Disability at 90 days, (dichotomized as a FAVORABLE OUTCOME (a score of 0 or 1 on the modified Rankin scale, which has a range of 0 to 6, with 0 indicating no symptoms at all and 6 indicating death) or an UNFAVORABLE OUTCOME (a score of 2 to 6 on the modified Rankin scale))	FAVORABLE OUTCOME: PLACEBO 182 (45.2%) vs. ALTEPLASE 219 (52.4%)	OR= 1.34; [95% CI: 1.02 - 1.76] RR = 1.16 [95% CI : 1.01 - 1.34] P = 0.04	**Results by gender not reported**

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EVA-3S (Mas et al [202])	OCT 2008	Multicentre, randomised, open, assessor-blinded, non-inferiority trial done at 30 centres in France in patients who had carotid stenosis of at least 60% that had recently become symptomatic.	70.2 ± 10.7 ENDARTERECTOMY vs. 69.1 ± 10.3 STENTING	TOTAL: 527 **(WOMEN: 130, 24.7%)** (MEN: 397)	median of : 42 months (IQR 30–48 months) STENTING vs. 43 months (IQR 31–48 months) ENDARTERECTOMY	CAROTID STENTING vs. CAROTID ENDARTERECTOMY	Rate of any periprocedural stroke or death (i.e., within 30 days after the procedure)	TOTAL STENTING 25/ 265 (9.4%) vs. ENDARTERECTOMY 10 / 262 (3.8%)	HR =1.97 [95% CI: 1.06–3.67] P=0.03 **Analysis by gender:** **$P_{INTERACTION}$ = 0.03**	The safety committee recommended that enrolment in the trial stop for reasons of safety and futility **The excess risk associated with stenting was greater in men than in women.**

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SPACE (Eckstein et al [203])	OCT 2008	Multinational European trial trial in patients with symptomatic, severe (≥70%) carotid artery stenosis	68.1 ± 8.2 CAS vs. 68.7 ± 8.7 CEA	TOTAL: 1214 **(WOMEN: 338, 28%)** (MEN: 876)	2 years	Carotid artery angioplasty with stenting (CAS) vs. carotid artery endarterectomy (CEA)	The first occurrence of ipsilateral stroke (either ischaemic stroke or intracerebral haemorrhage, with symptoms that lasted for more than 24 h) or death of any cause between randomisation and 30 days after treatment	Between randomisation and day 30 CAS: 42 (6.9%) vs. CEA: 38 (6.5%) 2-year endpoints: Ipsilateral ischaemic strokes within 2 years, including any periprocedural strokes or deaths CAS : 56 (9.5%) vs. CEA : 50 (8.8%) **WOMEN** **CAS:** **14/171 (8.3%)** **CAE** **11/167 (6.7%)** MEN: CAS: 42/436 (9.9%) CAE: 39/422 (9.6%)	Relative risk= 1.07 [95% CI: 0.70–1.63] 2-year endpoints: HR_{TOTAL} = 1.10 [95% CI: 0.75–1.61] **HR_{WOMEN} = 1.30 [95% CI: 0.59–2.85]** HR_{MEN} = 1.07 [95% CI: 0.42–2.74] **$P_{INTERACTION}$ = 0.68**	**No significant difference between treatments in both gender**

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CHHIPS (Potter et al [204])	JAN 2009	DOUBLE-blind pilot trial. in patients recruited at six centres in the UK who had cerebral infarction or cerebral haemorrhage and were hypertensive (systolic blood pressure [SBP] >160 mm Hg	74 ± 11	TOTAL: 172 **(WOMEN: 77, 44,8%)** (MEN: 95)	14 days	Oral labetalol, lisinopril, or placebo(if non-dysphagic), or intravenous labetalol, sublingual lisinopril, or placebo(if patients had dysphagia within 36 h of symptom onset) The doses were titrated up if target blood pressure was not reached.	Death or dependency at 2 weeks	TOTAL: 69 (61%) ACTIVE vs. 35 (59%) PLACEBO 90-day post-randomisation period mortality: 11/113 (10%) ACTIVE vs. 12 / 59 (20%) PLACEBO	RR = 1.03 [95% CI: 0.80–1.33] P=0.82 90-day post-randomisation period mortality: HR=0.40, 95% [95% CI: 0.2-1.0] P=0.05	No significant effect of treatment on the outcome. **Results by gender not reported.**
DIAS-2 (Hacke et al [205])	FEB 2009	International trial with significant European component in patients with acute ischaemic stroke and tissue at risk seen on either MRI or CT imaging	Overall median age of 71.0–73.5 years	TOTAL: 186 **(WOMEN: 93, 50%)** (MEN 93)	90 days	PLACEBO or DESMOTEPLASE (90 μg/kg) or DESMOTEPLASE (125 μg/kg) within 3–9 h after the onset of symptoms of stroke	Clinical response rates at day 90, defined as a composite of improvement in National Institutes of Health stroke scale (NIHSS) score of 8 points or more or an NIHSS score of 1 point or less, a modified Rankin scale score of 0–2 points, and a Barthel index of 75–100	TOTAL: PLACEBO: 29 (46%) DESMOTEPLASE (90 μg/kg): 27 (47%) DESMOTEPLASE (125 μg/kg): 24 (36%)	$P_{GLOBAL\ TEST}$ = 0.47	No benefit of treatment on the outcome. **A somewhat worse outcome in women than in men is indicated in any treatment group, although a specific analysis by gender is not reported.**

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CLOTS (Dennis et al [206])	JUNE 2009	Outcome-blinded, randomised controlled trial in patients, enrolled from 64 centres in the UK, Italy, and Australia, who were admitted to hospital within 1 week of an acute stroke and who were immobile	76 (IQR: 68–83)	TOTAL: 2518 **(WOMEN: 1276, 50.7%)** (MEN 1242)	30 days	ROUTINE CARE plus THIGH-LENGTH GCS or ROUTINE CARE plus AVOIDANCE OF GCS	Occurrence of symptomatic or asymptomatic DVT in the popliteal or femoral veins	THIGH-LENGTH GCS 126 (10.0%) vs. AVOID GCS 133 (10.5%)	Reduction in Risk = 0.5% [95% CI: –1.9% to 2.9%]	**Results by gender not reported.**

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)**	
Carotid artery stenting (CAS) vs. carotid endarterectomy (CEA) (Gurm et al [207])	JAN 2008	Meta-analysis of five trials CEA in patients with symptomatic carotid artery disease.	66.4 to 73	TOTAL: 2122 **WOMEN 32%**	30 days	Carotid artery stenting (CAS) vs. carotid endarterectomy (CEA)	Mortality, stroke, disabling stroke, and death		Using random - effect models: 30- day mortality: $RR_{SUMMARY}$ = 0.57 [95% CI: 0.22-1.47] P = 0.25 Stroke: $RR_{SUMMARY}$ = 1.64, [95% CI: 0.67-4.00] P = 0.34 Disabling stroke: $RR_{SUMMARY}$ = 1.67 [95% CI: 0.50-5.62] P = 0.50 Death and stroke: $RR_{SUMMARY}$ = 1.54 [95% CI: 0.81-2.92] P = 0.19 Death and disabling stroke $RR_{SUMMARY}$ = 1.19 [95% CI: 0.57-2.51] P = 0.64	**Results by gender not reported.**