DIABETES AND METABOLIC SYNDROME

TRIALS

NUMBER OF PARTICIPANTS	NUMBER OF WOMEN	PERCENTAGE OF WOMEN	MEAN AGE	MEAN FOLLOW-UP (YEARS)	TRIALS WITH ANALYSIS BY GENDER N, (%)
48,508	20,091	41.4%	61.1	4.3	4/7 (57.1%)

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)**	
PROactive (Dormandy et al [61])	OCT 2005	International trial in patients from 19 countries in Europe with type 2 diabetes who had evidence of macrovascular disease, recruited from primary-care practices and hospitals	PLACEBO 61.6 ± 7.8 vs. PIOGLITAZONE 61.9 ± 7.6	TOTAL: 5238 **(WOMEN: 1775, 34%)** (MEN: 3463)	34.5 months	MATCHING PLACEBO (in addition to their glucose-lowering drugs and other medications) vs. ORAL PIOGLITAZONE TITRATED (from 15 mg to 45 mg)	All-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle	TOTAL: 1086 PLACEBO: 572 vs. PIOGLITAZONE: 514	HR =0.90 [95% CI: 0.80–1.02] P = 0.095	**Results by gender not reported**

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FIELD (Keech et al [62])	NOV 2005	International trial done in 63 centres in Australia, New Zealand, and Finland in patients with type 2 diabetes mellitus, and not taking statin therapy at study entry	RANGE: 50–75	TOTAL: 9795 **(WOMEN 3657, 37%)** (MEN 6138)	Median of 5 years	MICRONISED FENOFIBRATE (200 mg daily) vs. MATCHING PLACEBO	Coronary events (coronary heart disease death or non-fatal myocardial infarction)	TOTAL: 544 PLACEBO 288 (5.9%) vs. FENOFIBRATE 256 (5.2%)	HR = 0.89 [95%CI: 0.75–1.05] P=0.16	**No effect on the primary endpoint in both men and women.** **Significant effect of FENOFIBRATE treatment on secondary endpoint (total cardiovascular disease (CVD) events (CVD death, myocardial infarction, stroke, coronary, or carotid revascularisation) in women but not in men:** Proportion of events (%) **(WOMEN: PLACEBO 9.5% vs. FENOFIBRATE 7.7%)** **$P_{WOMEN} = 0.04$** (MEN: PLACEBO 16.6% vs. FENOFIBRATE 15.4%) $P_{MEN} = 0.2$

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FIELD analysis (Rajamani et al [63])	MAY 2009	International trial done in 63 centres in Australia, New Zealand, and Finland in patients with type 2 diabetes mellitus, and not taking statin therapy at study entry	RANGE: 50–75	TOTAL: 9795 **(WOMEN: 3657, 37%)** (MEN: 6138)	Median of 5 years	MATCHING PLACEBO vs. MICRONISED FENOFIBRATE (200 mg daily)	Non-traumatic amputation (a prespecified tertiary endpoint of the study) Amputations were classified as minor or major (below or above the ankle, respectively). Amputations were also classified on the basis of whether or not large-vessel disease was present in the limb, to distinguish those related to large-artery atherosclerosis from those predominantly related to microvascular disease	TOTAL:115 **(22 WOMEN,** 93 MEN) (lower-limb amputations due to diabetes, 47 from 2 to 6 amputation) PLACEBO: 70 FENOFIBRATE: 45 *Minor amputations*: PLACEBO: 52 (1.1%) FENOFIBRATE: 28 (0.6%) *Major amputations*: PLACEBO: 26 (0.5%) FENOFIBRATE: 24 (0.5%) *Minor, without large-vessel disease:* TOTAL: 39 (**9 WOMEN,** 30 MEN) PLACEBO: 34 (0.7%) FENOFIBRATE: 18 (0.4%) *Major or minor, with large-vessel disease:* TOTAL: 76 **(13 WOMEN,** 63 MEN) PLACEBO: 42 (0.9%) FENOFIBRATE: 34 (0.7%)	First non-traumatic amputation: HR_{TOTAL} = 0.64 [95%CI: 0.44–0.94] P=0. 02 *Minor amputations:* HR_{TOTAL} = 0.54 [95%CI: 0.34–0.85] P = 0.007 *Major amputations:* HR_{TOTAL}= 0.93 [95%CI: 0.53–1.62] P = 0.79 *Minor, without large-vessel disease:* HR_{TOTAL} = 0.53 [95%CI: 0.30–0.94] P = 0.027 *Major or minor, with large-vessel disease:* HR_{TOTAL} = 0.81 [95%CI: 0.52–1.28] P = 0. 37	**From baseline characteristics patients who had on-study amputations were more likely to be male, taller, or smoke, and had a longer median duration of diabetes than patients from the other two groups.** **Primary outcome in the treatment and in the placebo arms not reported by gender.**

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DREAM (Bosch et al [64])	OCT 2006	International trial with significant European component in patients without cardiovascular disease but with impaired fasting glucose levels (after an 8-hour fast) or impaired glucose tolerance	54.7 ± 10.9	TOTAL: 5269 **(WOMEN 3120, 59%)** (MEN 2149)	Median of 3 years	PLACEBO (AND ROSIGLITAZONE OR PLACEBO) vs. RAMIPRIL (up to 15 mg per day)	Newly diagnosed diabetes or death	TOTAL: 992 PLACEBO 517 (19.5%) vs. RAMIPRIL 475 (18.1%)	HR = 0.91 [95% CI: 0.81 -1.0] P = 0.15	**Results by gender not reported**

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ADVANCE (Patel et al [65])	JUNE 2008	International trial with significant European component in patients with type 2 diabetes	66 ± 6	TOTAL: 11140 (European 5083) **(WOMEN : 4733, 42.5%)** (MEN: 6407)	Median of 5 years	STANDARD GLUCOSE CONTROL vs. INTENSIVE GLUCOSE CONTROL (defined as the use of gliclazide (modified release) plus other drugs as required to achieve a glycated hemoglobin value of 6.5% or less)	Major macrovascular or microvascular events	TOTAL: 2125 STANDARD CONTROL: 1116 (20.0%) vs. INTENSIVE CONTROL: 1009 (18.1%) **(WOMEN: STANDARD GLUCOSE 411 (17.4%) vs. INTENSIVE GLUCOSE 374 (15.7%))** (MEN : STANDARD GLUCOSE 705 (21.9%) vs. INTENSIVE GLUCOSE 635 (19.9%))	HR = 0.90 [95% CI: 0.82 - 0.98] P = 0.01 **RR REDUCTION WOMEN = 10% [95% CI: -3 – 22%]** RR REDUCTION MEN = 10% [95% CI: 0 – 19%] $P_{HETEROGENEITY} \geq 0.10$	**No significant gender difference in the negative outcome**

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ACCORD (Gerstein et al [66])	JUNE 2008	International trial with significant European component in patients with a median glycated hemoglobin level of 8.1%	62.2 ± 6.8	TOTAL: 10251 **(WOMEN 3952, 38.5%)** (MEN 6299)	Mean of 3.5 years	STANDARD THERAPY (targeting a level from 7.0 to 7.9%) vs. INTENSIVE THERAPY (targeting a glycated hemoglobin level below 6.0%)	First occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes	TOTAL: 723 STANDARD-THERAPY 371 vs. INTENSIVE-THERAPY 352 **(WOMEN: 212 (5.4%))** (MEN: 511 (8.1%))	HR = 0.90; [95%CI: 0.78–1.04] P_{TOTAL} = 0.16 $P_{INTERACTION}$ =0.74	**No significant gender difference in the outcome**

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BARI 2D (Frye et al [67])	JUNE 2009	International trial done in 49 clinical sites in the United States, Canada, Brazil, Mexico, the Czech Republic, and Austria patients with both type 2 diabetes mellitus and stable ischemic heart disease. All patients had to be candidates for elective percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)	62.4 ± 8.9	TOTAL: 2368 **(WOMEN: 701, 29.6%)** (MEN: 1667)	Average of 5.3 years (range: 3 - 6 years)	Either prompt CORONARY REVASCULARIZATION or MEDICAL THERAPY vs. EITHER INSULIN SENSITIZATION THERAPY or INSULIN PROVISION THERAPY to achieve a target glycated hemoglobin level of less than 7.0%.	Death from any cause	The 5-year rate of survival: 88.3% REVASCULARIZATION vs. MEDICALTHERAPY The 5-year rate of survival: 88.2% INSULINSENSITIZATION vs. 87.9% INSULINPROVISION	DIFFERENCE= 0.5% [95%CI: -2.0 - 3.1] P = 0.97 DIFFERENCE = 0.3% [95%CI: -2.2 - 2.9] P = 0.89 Among the four mutually exclusive groups: $P_{INTERACTION}$ >0.05 Treatment differences: P>0.05 for all four group comparisons by the logrank test	In 2005, the follow-up period was extended by 1.5 years to increase the average follow-up to 5.3 years because recruitment of patients took longer than planned and the original target of 2800 patients was not met. **Results by gender not reported**

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RECORD (Home et al [68])	JUNE 2009	Open-label trial done in 364 centres in 25 countries in Europe and Australasia in patients with type 2 diabetes on metformin or sulfonylurea monotherapy with mean haemoglobin A1c (HbA1c) of 7.9%	Background metformin: ROSIGLITAZONE 57.0 ± 8.0 SULFONYLUREA 57.2 ± 8.1 Background sulfonylurea ROSIGLITAZONE 59.8± 8.3 METFORMIN 59.7 ± 8.2	TOTAL: 4447 **(WOMEN: 2153, 48.4%)** (MEN: 2294)	Mean of 5.5 years	Addition of ROSIGLITAZONE or METFORMIN (if already on sulfonylurea) or of ROSIGLITAZONE or SULFONYLUREA (if already on metformin)	Cardiovascular hospitalisation or cardiovascular death (with a hazard ratio non-inferiority margin of 1.20)	TOTAL: 644 ROSIGLITAZONE: 321 vs. ACTIVE CONTROL: 323 **(WOMEN: ROSIGLITAZONE: 129/1078 (12%) vs. ACTIVE CONTROL: 124/1075 (11. 5%))** (MEN: ROSIGLITAZONE : 192/1142 (16.8%) vs. ACTIVE CONTROL: 199/1152 (17.2%))	HR_{TOTAL}= 0. 99 [95%CI: 0.85 -1.16] P=0. 93 **HR_{WOMEN} =1.02 [95%CI: 0. 80 -1. 31]** HR_{MEN} =0.98 [95%CI: 0.80 - 1.20] $P_{INTERACTION}$ = 0.79	**No significant gender difference in the primary outcome.** Addition of rosiglitazone to glucose-lowering therapy is confirmed to increase the risk of heart failure (RR= 2.10, [95%CI: 1.35-3.27], P=0.001) and of fractures (RR= 1.57, [95%CI: 1.26-1.97], P<0.0001) **Significant increased risk of fractures in women and not in men** **RR_{WOMEN} =1.82, [95%CI: 1.37–2.41]** ***vs.*** RR_{MEN} = 1.23,[95%CI: 0.85–1.77]; $p_{INTERACTION}$ = 0.10) **Upper and distal lower limb fracture rates were increased mainly in women assigned to rosiglitazone (RR = 1.75 upper limb and RR= 2.93 distal lower limb)**

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)**	
Long-term use of thiazolidinediones and fractures in type 2 diabetes (Loke et al [74])	JAN. 2009	Meta-analysis of 10 randomized controlled parallel-design trials of any THIAZOLIDINEDIONE (rosiglitazone, pioglitazone or troglitazone). The participants had impaired glucose tolerance or type 2 diabetes mellitus		TOTAL: 13715 (overall) 5 trials: **(WOMEN: 4400)** (MEN: 7001)	At least 1 year (1 - 4 years)	PLACEBO vs. oral therapy with an active comparator as the control arm (the treatment groups differed only in the use of thiazolidinediones)	Fractures	OVERALL: CONTROL 186/7593 (2.5%) vs. THIAZOLIDINEDIONE 185/6122 (3%) **(WOMEN: CONTROL 76/2497 (3%) vs. THIAZOLIDINEDIONE 111/1903 (5.8%))** (MEN: CONTROL 95/3937 (2.4%) vs. THIAZOLIDINEDIONE 64/3064 (2%))	Overall: $OR_{OVERALL}$=1.45 [95%CI: 1.18-1.79] P < 0.001 **OR_{WOMEN} = 2.23 [95%CI: 1.65-3.01] P < 0.001** OR_{MEN} = 1.00 [95%CI: 0.73-1.39] P = 0.98 **χ^2= 12.01 $P_{INTERACTION}$ < 0.001**	**Significant increase in fractures in women and not in men** **Data on fractures were available by sex in 5 trials**

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Glycemic Control (Ray et al [76])	MAY 2009	Meta-analysis of 5 prospective randomised controlled trials (UKPDS, PROactive, ADVANCE, VADT, ACCORD)	62 ± 7	TOTAL: 33040 **(WOMEN: 12423, 28%)** (MEN: 20617)	Overall : 4.95 years	STANDARD TREATMENT vs. INTENSIVE GLUCOSE - LOWERING REGIMEN	Non-fatal myocardial infarction, coronary heart disease, fatal and non-fatal stroke, deaths from any cause	Non-fatal myocardial infarction: TOTAL:1497 STANDARD: 754 vs. INTENSIVE: 743 Coronary heart disease: TOTAL: 2318 STANDARD: 1136 vs. INTENSIVE: 1182 Fatal and non-fatal stroke: TOTAL:1127 STANDARD: 539 vs. INTENSIVE : 588 Deaths from any cause: TOTAL: 2892 STANDARD: 1319 vs. INTENSIVE: 1573	Non-fatal myocardial infarction: OR = 0.83 [95%CI: 0.75–0.93] Coronary heart disease: OR = 0.85 [95%CI: 0.77 - 0.93] Fatal and non-fatal stroke: OR = 0.93 [95%CI: 0.81 - 1.06] Deaths from any cause: OR = 1.02 [95%CI: 0.87 - 1.19]	**Results by gender not reported** The effect estimate was not heterogeneous between studies for either of these outcomes: non-fatal myocardial infarction and coronary heart disease. Intensive treatment did not significantly affect stroke or all-cause mortality. The effect estimate was not heterogeneous for stroke but heterogeneity was high for all-cause mortality.