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Gender differences in cardiovascular disease risk factors, treatments and complications in patients with type 2 diabetes: the RIACE Italian multicentre study

G. Penno[1], A. Solini[2], E. Bonora[3], C. Fondelli[4], E. Orsi[5], G. Zerbini[6], R. Trevisan[7], M. Vedovato[8], G. Gruden[9], L. Laviola[10], A. Nicolucci[11] & G. Pugliese[12], for the Renal Insufficiency And Cardiovascular Events (RIACE) study, group*

From the [1]Department of Endocrinology and Metabolism; [2]Department of Internal Medicine University of Pisa, Pisa; [3]Division of Endocrinology and Metabolic Diseases University of Verona, Verona; [4]Diabetes Unit University of Siena, Siena; [5]Endocrinology and Diabetes Unit Fondazione IRCCS 'Cà Granda – Ospedale Maggiore Policlinico'; [6]Complications of Diabetes Unit, Division of Metabolic and Cardiovascular Sciences San Raffaele Scientific Institute, Milan; [7]Diabetes Unit Hospital of Bergamo, Bergamo; [8]Department of Clinical and Experimental Medicine University of Padua, Padua; [9]Department of Internal Medicine University of Turin, Turin; [10]Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, Department of Emergency and Organ Transplantation University of Bari, Bari; [11]Department of Clinical Pharmacology and Epidemiology Consorzio Mario Negri Sud, S. Maria Imbaro; and [12]Department of Clinical and Molecular Medicine 'La Sapienza' University, Rome Italy

Abstract. Penno G, Solini A, Bonora E, Fondelli C, Orsi E, Zerbini G, Trevisan R, Vedovato M, Gruden G, Laviola L, Nicolucci A, Pugliese G (University of Pisa, Pisa, Italy; University of Verona, Verona, Italy; University of Siena, Siena, Italy; Fondazione IRCCS 'Cà Granda – Ospedale Maggiore Policlinico', Milan, Italy; San Raffaele Scientific Institute, Milan, Italy; Hospital of Bergamo, Bergamo, Italy; University of Padua, Padua, Italy; University of Turin, Turin, Italy; University of Bari, Bari, Italy; Consorzio Mario Negri Sud, S. Maria Imbaro, Italy; La Sapienza' University, Rome, Italy). Gender differences in cardiovascular disease risk factors, treatments and complications in patients with type 2 diabetes: the RIACE Italian multicentre study. *J Intern Med* 2013; 274: 176–191.

Objectives. Poorer control of risk factors for cardiovascular disease (CVD) has been reported in diabetic women, as compared with diabetic men. It has been proposed that this finding is due to gender disparities in treatment intensity. We investigated this hypothesis in a large contemporary cohort of subjects with type 2 diabetes.

Design. Observational, cross-sectional study.

Subjects and setting. Consecutive patients with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study (n = 15 773), attending 19 hospital-based diabetes clinics in 2007–2008.

Main outcome measures. Traditional CVD risk factors, macro- and microvascular complications and current glucose-, lipid- and blood pressure (BP)-lowering treatments were assessed.

Results. Although CVD was more prevalent in men, women showed a less favourable CVD risk profile and worse performance in achieving treatment targets for haemoglobin A_{1c}, LDL, HDL and non-HDL cholesterol, systolic blood pressure (BP) and in particular obesity [body mass index (BMI) and waist circumference], but not for triglycerides and diastolic BP. However, women were more frequently receiving pharmacological treatment for hypertension and to a lesser extent hyperglycaemia and dyslipidaemia than men, and female gender remained an independent predictor of unmet therapeutic targets after adjustment for confounders such as treatments, BMI, duration of diabetes and, except for the systolic BP goal, age.

Conclusions. In women with type 2 diabetes from the RIACE cohort, a more adverse CVD risk profile and a higher likelihood of failing treatment targets, compared with men, were not associated with treatment differences. This suggests that factors other than gender disparities in treatment intensity are responsible.

Keywords: cardiovascular disease risk factors, complications, gender, treatment disparities, type 2 diabetes.

*A complete list of the RIACE investigators can be found in the Appendix.Clinical Trial Registration: http://clinicaltrials.gov/ct2/show/NCT00715481; NCT00715481.

Introduction

Type 2 diabetes is one of the fastest growing disorders worldwide, with the largest increase in incidence in developing countries [1]. This is expected to result in an increasing burden from long-term macro- and microvascular complications – which represent the main cause of morbidity and mortality in diabetic patients – with huge socio-economic costs [2].

However, in the last two decades, the results of several trials have shown that tighter control of cardiovascular disease (CVD) risk factors [3, 4], especially multifactorial intervention [5], is effective in preventing or slowing the onset and progression of complications. Furthermore, several new drugs have become available recently, including various classes of glucose-lowering agents [6]. As a result, control of CVD risk factors has been improving over the past two decades, as seen in the general population [7] and in subjects with type 2 diabetes [8] from the National Health and Nutrition Examination Survey (NHANES). However, current treatment goals are far from being achieved in all patients, as observed in the European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE) II trial [9]. In addition, despite a general trend towards improvement for most CVD risk factors, the magnitude was insufficient to overcome the excess CVD burden in diabetic versus nondiabetic individuals [10].

It has been shown that several factors influence CVD risk in diabetic subjects, including ethnicity [11] and gender. Comparison of the NHANES I, II and III data suggested that all-cause mortality decreased from 1971 to 2000 in men but not in women with diabetes [12]. Conversely, a recent analysis of data from the Framingham Heart Study revealed reductions between 1950 and 2005 in all-cause and CVD mortality amongst women and men with and without diabetes mellitus [13]. Likewise, data from the National Health Interview Surveys showed that all-cause and CVD mortality decreased by 40% and 23%, respectively, amongst diabetic adults between 1997 and 2006, with no differences between men and women [14]. Of interest, similarly conflicting data were reported for type 1 diabetes [15]. In a meta-analysis conducted by the Emerging Risk Factors Collaboration, hazard ratios for coronary heart disease (CHD) and ischaemic stroke in subjects with versus without diabetes, adjusted for baseline covariates, were found to be higher in women than in men [16]. This greater excess risk has been explained by a more adverse CVD risk profile amongst women with diabetes, combined with possible disparities in treatment that favour men [17]. However, whilst diabetic women have consistently shown poorer control of CVD risk factors and a higher likelihood of failing treatment targets than diabetic men, it is unclear whether this is attributable to gender disparities in awareness and treatment for CVD, due to cultural, behavioural, psychosocial and/or socio-economic differences between the two sexes [15].

To investigate this hypothesis, we evaluated gender differences in CVD risk factors, treatments and macro- and microvascular complications in a large contemporary cohort of subjects with type 2 diabetes.

Materials and methods

Study cohort

Data collected at the baseline visit for the Renal Insufficiency and Cardiovascular Events (RIACE) Italian multicentre study were used in the present analysis. The RIACE is an observational, prospective cohort study of the impact of estimated glomerular filtration rate (eGFR) on CVD morbidity and mortality in type 2 diabetes [18–21]. The RIACE cohort consisted of 15 773 consecutive Caucasian patients with type 2 diabetes (defined according to the American Diabetes Association criteria), attending 19 hospital-based diabetes clinics of the National Health Service throughout Italy in 2007–2008. Exclusion criteria were dialysis or renal transplantation. The study protocol was approved by the local ethics committees. A prespecified secondary end-point of this study was the possible effect of gender differences on all outcomes, both in cross-sectional and longitudinal analyses.

CVD risk factors

All patients underwent a structured interview to collect the following information: age, smoking status, known diabetes duration, current glucose-, lipid- and blood pressure (BP)-lowering treatments and antiplatelet and anticoagulant therapy, with indication of the class of drug. Weight and height were measured and body mass index (BMI) was calculated. BP was measured with a sphygmomanometer after resting for 5 min. Waist circumference was measured in 4618 subjects (2644 men and

1974 women). Data from this subgroup were used to derive sex-specific linear regression equations to predict waist circumference in the remaining 11 155 individuals from log-transformed BMI value: for men, waist circumference = BMI · 2.199 + 39.929 ($r = 0.848$, $r^2 = 0.718$, $P < 0.0001$); for women, waist circumference = BMI · 1.911 + 45.859 ($r = 0.816$, $r^2 = 0.666$, $P < 0.0001$). Linear regression was adopted after excluding an independent significant role of other variables, such as log-transformed weight, log-transformed height and age, by stepwise multiple regression analysis or substitution. Haemoglobin (Hb) A_{1c} was measured by high-performance liquid chromatography using Diabetes Control and Complications Trial-aligned methods. Triglycerides, total and HDL cholesterol were determined by standard analytical methods. LDL cholesterol was calculated using the Friedwald formula, and non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol.

Complications and comorbidities

Prevalent CVD was assessed from medical history by recording previous documented major acute CVD events, which were adjudicated based on hospital discharge records or specialist visits by an *ad hoc* committee in each centre [18].

The presence of diabetic retinopathy (DR) was assessed by an expert ophthalmologist by dilated fundoscopy and classified as absent, mild, moderate or severe nonproliferative DR (NPDR), proliferative DR (PDR) or maculopathy, according to the Global Diabetic Retinopathy Project Group, as previously reported [19]. Patients were classified based on fundus appearance or the retinal condition that had eventually required prior photocoagulation or surgical treatment. Based on the worst eye, patients with mild or moderate NPDR were classified as having nonadvanced DR, whereas those with severe NPDR, PDR, maculopathy or blindness were included in the advanced retinopathy group.

The presence of chronic kidney disease (CKD) was assessed by albuminuria and serum creatinine. As previously reported in detail [20, 21], albumin excretion rate (AER) was determined from 24-h urine collections or calculated from the albumin/creatinine ratio in the first morning urine sample, in the absence of interfering clinical conditions. Albuminuria was measured in between one and three fresh urine samples for each patient by immunonephelometry or immunoturbidimetry and, in the case of multiple measurements, the geometric mean was used for analysis. In all subjects with multiple measurements (4062 with at least two and 2310 with three values), the concordance rate between the first value and the geometric mean was >90% [21]. Patients were then assigned to one of the following categories of albuminuria (mg per 24 h): normoalbuminuria (AER < 30), microalbuminuria (AER 30–299) or macroalbuminuria (AER $\geq$ 300). In addition, normoalbuminuric subjects were further classified as having normal (AER < 10) or low albuminuria (AER < 10–29). Serum (and urine) creatinine was measured by the modified Jaffe method. Between one and three measurements were obtained for each patient, and eGFR was calculated using the four-variable Modification of Diet in Renal Disease (MDRD) Study equation or the CKD Epidemiology Collaboration equation, using the mean serum creatinine value in case of multiple measures, as reported previously [20, 21]. Patients were then assigned to one of the following five categories of eGFR (mL min^{-1} per 1.73 m^2): 1 ($\geq$ 90), 2 (60–89), 3 (30–59), 4 (15–29) and 5 (<15). Finally, subjects were classified as having no CKD or CKD stages 1–5, based on the presence or absence of micro- or macroalbuminuria and the value of eGFR, according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative, as previously reported [20]. Data from patients assigned to CKD stages or GFR classes 4 and 5 were pooled. Patients with CKD were further classified as having one of the following CKD phenotypes: albuminuria alone (stages 1/2 CKD), reduced eGFR alone (stage $\geq$3 CKD without albuminuria) or both (stage $\geq$3 CKD with albuminuria) [20].

Statistical analysis

Data are expressed as median (interquartile range) for continuous variables, and number of cases and percentages for categorical variables. Patients were stratified by gender, and the following statistical tests were applied for comparing data for men and women: the Student's *t*-test for parametric or the corresponding Mann–Whitney *U*-test for nonparametric continuous variables and the chi-squared test for categorical variables.

Logistic regression analyses with stepwise variable selection were performed to assess whether gender is an independent predictor of achievement of treatment targets, including HbA_{1c}, systolic BP and LDL and non-HDL cholesterol. Non-HDL cholesterol levels, which reflect all apolipoprotein

B100-containing atherogenic particles, are often increased in diabetic subjects and are significantly associated with increased risk of death from CVD [22]. Age, disease duration, BMI and specific treatments were introduced as covariates. Results of these analyses were expressed as odd ratios with 95% confidence intervals.

All P values were two-sided, and a $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of subjects from the RIACE cohort, as a whole and stratified by gender, are shown in Table 1. Median age and diabetes duration were 67 and 11 years, respectively, and the male/female ratio was 57/43. Women were older, were more frequently nonsmokers and had higher levels of HbA_{1c}, BMI, triglycerides, total, LDL and non-HDL cholesterol and systolic BP and lower levels of albuminuria, serum creatinine and eGFR (especially when eGFR was calculated using the MDRD Study formula). HDL cholesterol levels were higher in women, in line with the higher values in the general population, whereas waist circumference was also higher despite lower reference values than in men.

Table 2 shows the number of subjects on-target for the major CVD risk factors. The best controlled variable was diastolic BP, followed by systolic BP

Table 1 *Characteristics of subjects from the RIACE cohort: as a whole and stratified by gender*

Variables	Total	Men	Women	P*
n (%)	15773 (100)	8960 (56.8)	6813 (43.2)	
Age (years)	67 (59–73)	66 (59–72)	68 (60–75)	<0.0001
Smoking, n (%)				
No	8928 (56.6)	3861 (43.1)	5067 (74.4)	<0.0001
Former	4434 (28.1)	3400 (37.9)	1034 (15.2)	<0.0001
Current	2411 (15.3)	1699 (19.0)	712 (10.5)	<0.0001
Diabetes duration (years)	11 (5–20)	10 (5-20)	11 (5-20)	<0.0001
HbA_{1c} (%)	7.30 (6.51–8.28)	7.22 (6.49–8.18)	7.38 (6.60–8.40)	<0.0001
BMI (kg m^{-2})	28.28 (25.40–31.64)	27.78 (25.28–30.81)	29.05 (25.65–33.02)	<0.0001
Waist circumference (cm)[a]	101.2 (95.0–108.6)	101.0 (95.2–108.0)	101.4 (94.4–109.5)	0.032
Triglycerides (mmol L^{-1})	1.33 (0.97–1.89)	1.32 (0.94–1.89)	1.37 (1.01–1.89)	<0.0001
Total cholesterol (mmol L^{-1})	4.71 (4.12–5.39)	4.58 (3.96–5.23)	4.92 (4.30–5.57)	<0.0001
HDL cholesterol (mmol L^{-1})	1.24 (1.04–1.48)	1.17 (0.98–1.40)	1.35 (1.14–1.58)	<0.0001
LDL cholesterol, mmol L^{-1}[b]	2.74 (2.21–3.30)	2.67 (2.15-3.22)	2.84 (2.30–3.41)	<0.0001
Non-HDL cholesterol, mmol L^{-1}[c]	3.42 (2.83–4.07)	3.34 (2.77–3.99)	3.52 (2.93–4.15)	<0.0001
Systolic BP, mmHg	140 (125–150)	136 (125–150)	140 (130–150)	<0.0001
Diastolic BP, mmHg	80 (70–85)	80 (70–85)	80 (70–85)	0.937
Albuminuria, mg per 24 h	13.59 (6.77–33.28)	16.00 (7.62–43.47)	11.16 (5.88–23.47)	<0.0001
Serum creatinine, μmol L^{-1}	79.6 (68.1–93.7)	85.9 (74.9–97.2)	70.7 (61.9–82.2)	<0.0001
$eGFR^{MDRD}$, mL min^{-1} per 1.73 m^2	78.15 (64.76–92.78)	85.70 (75.1–97.2)	75.26 (61.02–90.12)	<0.0001
$eGFR^{CKD\text{-}EPI}$, mL min^{-1} per 1.73 m^2	84.23 (67.41–95.46)	84.83 (69.48–95.76)	83.26 (64.45–95.10)	<0.0001

Values are median (interquartile range) for continuous variables and n (%) for categorical variables. HbA_{1c}, haemoglobin A_{1c}; BMI, body mass index; BP, blood pressure; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration. [a]Waist circumference was measured in 4618 subjects (2644 men and 1974 women) and was predicted in the remaining individuals as discussed in the Methods. [b]LDL cholesterol was calculated in 15501 subjects (8777 men and 6724 women). [c]non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol. *P values for comparison between male and female subjects using Student's t-test for parametric or the Mann–Whitney U-test for nonparametric (triglycerides, albuminuria, serum creatinine and eGFR) continuous variables and the chi-squared test for categorical variables.

and lipids, particularly triglycerides and HDL cholesterol. The 7.0% target of HbA_{1c} was achieved by two-fifths of subjects, whereas the 6.5% target was met by only a quarter of the cohort. The worst performances were for adiposity, that is, BMI and waist circumference. Significant gender differences were detected, with women performing worse than men for all the above-mentioned targets, except for diastolic BP and triglycerides. In particular, obesity and increased waist circumference were considerably more prevalent amongst women. Of note, the results did not change when subjects who were or were not receiving pharmacological treatment were considered separately, except for HbA_{1c} goals in untreated individuals which were achieved to the same extent by men and women (data not shown).

Treatments for CVD risk factors are shown in Tables 3–6. The percentage of subjects who were not on pharmacological treatment was lower for hyperglycaemia (13.5%) than for hypertension (29.3%) and highest for dyslipidaemia (53.8%). The majority (60.1%) of patients were not treated with antiplatelet drugs, and only a few (4.3%) were receiving anticoagulant therapy. The most used glucose-lowering agent was metformin, followed by sulfonylureas and insulin. Most patients were on monotherapy for hyperglycaemia, mainly with metformin, followed by insulin, with only a few subjects treated with more than two drugs (5.9%); the most used combination was metformin plus sulfonylureas. Statins were used by the vast majority of subjects on lipid-lowering treatment, predominantly as monotherapy, whereas fibrates were used rarely. Only a few individuals were taking two or more lipid-lowering drugs. Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II-receptor blockers (ARBs) were the most used antihypertensive drugs and were also the most common monotherapies. One or two antihypertensive agents were used by about half of the cohort, with one-fifth receiving three or more drugs. ACE-Is and ARBs were often combined with one or two additional drugs, but rarely with each other. Aspirin was the most used antiplatelet agent and warfarin the most used anticoagulant. Women more frequently received pharmacological treatment for hyperglycaemia, dyslipidaemia and particularly hypertension, but antiplatelet and anticoagulant therapies were less common, compared with men. Moreover, women were more frequently on metformin, glitazones, glinides and insulin (both basal and prandial) and used less ACE-Is and more ARBs than men. Finally, combination therapies for hyperglycaemia, mainly with metformin plus insulin, and hypertension but not for dyslipidaemia were more common amongst women than amongst men.

Prevalence rates of macro- and microvascular complications in the RIACE cohort have been reported previously [18–20]. Table 7 shows the percentage prevalence by gender of each complication. The prevalence of major acute CVD events in the RIACE cohort was higher in men than in women. Gender differences were more marked for coronary (twofold) and peripheral (twofold for amputation and lower limb revascularization, but only a 25% increase for ulcer/gangrene) events, than for cerebrovascular events (about 20% and 35% increase for stroke and carotid revascularization, respectively). Whereas the prevalence of DR did not differ significantly between the sexes, rates of increased albuminuria (micro- and macroalbuminuria) and of reduced eGFR (i.e. <60 mL min^{-1} per 1.73 m^2) were higher in men and women, respectively. As a result, the albuminuric CKD phenotypes were more common in men, whereas the nonalbuminuric form was more frequently found in women, as previously reported [20].

Logistic regression analyses with stepwise variable selection are shown in Table 8. Independently of diabetes duration, female gender was associated with a significantly lower probability of reaching the HbA_{1c}, LDL and non-HDL cholesterol and systolic BP targets. This association remained after adjusting for specific treatments as well as for BMI, which was inversely associated with achievement of all targets, except LDL cholesterol (but including non-HDL cholesterol). It is interesting that whilst statin treatment increased the probability of meeting lipid targets (LDL and non-HDL cholesterol), antihypertensive and glucose-lowering therapies were inversely associated with meeting BP and HbA_{1c} targets, respectively; in the case of antihyperglycaemic treatment, the association was strongest for insulin either combined with oral hypoglycaemic agents or alone. These relationships between treatments and achievement of therapeutic goals did not change when men and women were analysed separately. Finally, association between gender and achievement of therapeutic goals, except for systolic BP, remained when age was included in the model (data not shown).

Table 2 *Subjects from the RIACE cohort on-target for cardiovascular disease risk factors: as a whole and stratified by gender*

Variables, *n* (%)	Total	Men	Women	*P**
	15773 (100)	8960 (56.8)	6813 (43.2)	
HbA_{1c}				
<6.5% (<47.5 nmol $mmol^{-1}$)	3817 (24.2)	2337 (26.1)	1480 (21.7)	<0.0001
<7.0% (<53.1 nmol $mmol^{-1}$)	6453 (40.9)	3868 (43.2)	2585 (37.9)	<0.0001
BMI				
<25 kg m^{-2}	3449 (21.9)	2018 (22.5)	1431 (21.0)	0.022
<30 kg m^{-2}	10070 (63.8)	6192 (69.1)	3878 (56.9)	<0.0001
Waist circumference[a]				
<94 cm (men)/<80 cm (women)	1858 (11.8)	1781 (19.9)	77 (1.1)	<0.0001
<102 cm (men)/<88 cm (women)	5310 (33.7)	4759 (53.1)	551 (8.1)	<0.0001
Triglycerides				
<1.70 mmol L^{-1}	10695 (67.8)	6106 (68.2)	4589 (67.4)	0.292
Total cholesterol				
<4.53 mmol L^{-1}	6507 (41.3)	4246 (47.4)	2261 (33.2)	<0.0001
HDL cholesterol				
>1.04 mmol L^{-1} (men)/>1.30 mmol L^{-1} (women)	10139 (64.3)	6284 (70.1)	3855 (56.6)	<0.0001
LDL cholesterol[b]				
<1.81 mmol L^{-1}	1798 (11.4)	1156 (12.9)	642 (9.4)	<0.0001
<2.59 mmol L^{-1}	6603 (41.9)	4030 (45.0)	2573 (37.8)	<0.0001
Non-HDL cholesterol[c]				
<3.37 mmol L^{-1}	7471 (47.4)	4531 (50.6)	2940 (43.2)	<0.0001
Systolic BP				
<130 mmHg	6854 (43.5)	4052 (45.2)	2802 (41.1)	<0.0001
<140 mmHg	10502 (66.6)	6104 (68.1)	4398 (64.6)	<0.0001
Diastolic BP				
<80 mmHg	11537 (73.1)	6350 (70.9)	5007 (73.5)	0.390
<90 mmHg	14861 (94.2)	8466 (94.5)	6394 (93.9)	0.09

HbA_{1c}, haemoglobin A_{1c}; BMI, body mass index; BP, blood pressure. [a]Waist circumference was measured in 4618 subjects (2644 men and 1974 women) and was predicted in the remaining individuals as discussed in the Methods). [b]LDL cholesterol was calculated in 15501 subjects (8777 men and 6724 women). [c]Non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol. **P* values for comparison between male and female subjects using the chi-squared test.

Discussion

The most intriguing finding of this study in the RIACE cohort of subjects with type 2 diabetes is that despite the fact that treatment intensity was not lower in women compared with men, control of CVD risk factors was worse and the percentage of subjects on-target was lower amongst women. That control of CVD risk factors was poorer in diabetic women is consistent with previous surveys from Italy and elsewhere. In fact, the Multifactorial Intervention in type 2 Diabetes in Italy (MIND-IT) study, a cross-sectional survey that enrolled subjects without previous CVD events [23] and, at least in part, the Diabetes and Informatics (DAI) study [24] showed a worse CVD risk profile in women than in men. Likewise, diabetic women were shown to be less frequently on-target: (i) for BP and LDL and HDL cholesterol, but not for HbA_{1c}, triglycerides and non-HDL cholesterol in the NHANES [25]; (ii) for systolic BP and LDL cholesterol (only in subjects with CVD) in the Translating Research Into Action for Diabetes Study [26]; (iii) for systolic BP and total cholesterol, but not for HbA_{1c} and smoking in the Diabetes Audit and Research in Tayside Scotland register

Table 3 *Treatments for cardiovascular disease risk factors in subjects from the RIACE cohort: as a whole and stratified by gender*

Variables, *n* (%)	Total	Men	Women	*P**
	15773 (100)	8960 (56.8)	6813 (43.2)	
Glucose lowering				
Lifestyle alone	2126 (13.5)	1283 (14.3)	843 (12.4)	<0.0001
Metformin	8703 (55.2)	4808 (53.7)	3895 (57.2)	<0.0001
Glitazones	560 (3.6)	341 (3.8)	219 (3.2)	0.047
Sulfonylureas	5278 (33.5)	2966 (33.1)	2312 (33.9)	0.272
Glinides	1534 (9.7)	934 (10.4)	600 (8.8)	<0.0001
Acarbose	171 (1.1)	92 (1.0)	79 (1.2)	0.425
Insulin	3966 (25.1)	2179 (24.3)	1787 (26.2)	0.006
Lipid lowering				
Lifestyle alone	8487 (53.8)	4861 (54.3)	3626 (53.2)	0.199
Statins	6697 (42.5)	3735 (41.7)	2962 (43.5)	0.024
Resins	14 (0.1)	10 (0.1)	4 (0.1)	0.269
Ezetimibe	164 (1.0)	87 (1.0)	77 (1.1)	0.329
Fibrates	396 (2.5)	228 (2.6)	168 (2.5)	0.754
Omega-3 fatty acids	768 (4.9)	525 (5.9)	243 (3.6)	<0.0001
Nicotinic acid	1 (0.0)	1 (0.0)	0 (0.0)	0.383
Orlistat	4 (0.0)	2 (0.0)	2 (0.0)	0.783
BP lowering				
Lifestyle alone	4623 (29.3)	2820 (31.5)	1803 (26.5)	<0.0001
ACE-Is	6122 (38.8)	3585 (40.0)	2537 (37.2)	<0.0001
ARBs	3595 (22.8)	1837 (20.5)	1758 (25.8)	<0.0001
Anti-aldosterone drugs	578 (3.7)	274 (3.1)	304 (4.5)	<0.0001
Thiazide diuretics	3026 (19.2)	1447 (16.1)	1579 (23.2)	<0.0001
Loop diuretics	1744 (11.1)	898 (10.0)	846 (12.4)	<0.0001
DHP-CCBs	2832 (18.0)	1561 (17.4)	1271 (18.7)	0.046
Non-DHP-CCBs	795 (5.0)	445 (5.0)	350 (5.1)	0.627
α-blockers	947 (6.0)	578 (6.5)	369 (5.4)	0.007
ß-blockers	2740 (17.4)	1464 (16.4)	1246 (18.3)	0.008
Others	73 (0.5)	44 (0.5)	29 (0.4)	0.549
Antiplatelet agents				
None	9476 (60.1)	5155 (57.5)	4321 (63.4)	<0.0001
Aspirin	5185 (32.9)	3088 (34.5)	2097 (30.8)	<0.0001
Ticlopidine	780 (5.0)	479 (5.4)	301 (4.4)	0.008
Clopidogrel	60 (0.4)	39 (0.4)	21 (0.3)	0.199
Aspirin/ticlopidine	134 (0.9)	100 (1.1)	34 (0.5)	<0.0001
Aspirin/clopidogrel	137 (0.9)	99 (1.1)	38 (0.6)	<0.0001
Anticoagulants				
None	15100 (95.7)	8549 (95.4)	6551 (96.2)	0.022
Warfarin	579 (3.7)	361 (4.0)	218 (3.2)	0.006
Heparin	38 (0.2)	18 (0.2)	20 (0.3)	0.240
LMWH	56 (0.4)	32 (0.4)	24 (0.4)	0.959

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II-receptor blocker; DHP-CCB, dihydropyridine calcium channel blocker; LMWH, low molecular weight heparin; BP, blood pressure. **P* values for comparison between male and female subjects using the chi-squared test.

Table 4 *Number of drugs, most frequent monotherapies and most frequent drug combinations for glucose-lowering treatment in subjects from the RIACE cohort: as a whole and stratified by gender*

Variables, *n* (%)	Total	Men	Women	*P**
	15773 (100)	8960 (56.8)	6813 (43.2)	
Glucose lowering				<0.0001
Lifestyle alone	2126 (13.48)	1283 (14.32)	843 (12.37)	<0.0001
Monotherapies	8036 (50.95)	4564 (50.94)	3472 (50.96)	0.976
Combinations	5611 (35.57)	3113 (34.74)	2498 (36.67)	0.012
2 drugs	4673 (29.63)	2597 (28.98)	2076 (30.47)	0.043
3 drugs	922 (5.85)	502 (5.60)	420 (6.17)	0.136
4 drugs	16 (0.10)	14 (0.16)	2 (0.03)	0.020
Most frequent monotherapies[a]				
a. Metformin	3405 (42.37)	1874 (41.06)	1531 (44.09)	0.006
b. Insulin	2447 (30.45)	1390 (30.46)	1057 (30.44)	0.991
c. Sulfonylureas	1392 (17.32)	808 (17.70)	584 (16.82)	0.300
a+b+c	7244 (90.14)	4072 (89.22)	3172 (91.36)	0.001
Most frequent combinations[b]				
a. Metformin + sulfonylureas	2943 (52.45)	1645 (52.84)	1298 (51.96)	0.511
b. Metformin + insulin	631 (11.25)	306 (9.83)	325 (13.01)	0.0001
c. Metformin + glinides	566 (10.09)	343 (11.02)	223 (8.93)	0.010
d. Metformin + sulfonylureas + insulin	525 (9.36)	277 (8.90)	248 (9.93)	0.188
a+b+c+d	4665 (83.14)	2571 (82.59)	2094 (83.83)	0.218

[a]Percentage distributions calculated amongst all monotherapies. [b]Percentage distributions calculated amongst all combinations. **P* values for comparison between male and female subjects using the chi-squared test, or two-sided Fisher's exact test for the four-drug combination.

Table 5 *Number of drugs, most frequent monotherapies and most frequent drug combinations for lipid-lowering treatment in subjects from the RIACE cohort: as a whole and stratified by gender*

Variables, *n* (%)	Total	Men	Women	*P**
	15773 (100)	8960 (56.8)	6813 (43.2)	
Lipid-lowering				<0.0001
Lifestyle alone	8487 (53.8)	4861 (54.3)	3626 (53.2)	0.199
Monotherapies	6558 (41.6)	3631 (40.5)	2927 (43.0)	0.002
≥2 drugs	728 (4.6)	468 (5.2)	260 (3.8)	<0.0001
Most frequent monotherapies[a]				
a. Statins	6009 (91.6)	3291 (90.6)	2718 (92.9)	0.001
b. Fibrates	314 (4.8)	182 (5.0)	132 (4.5)	0.343
c. Omega-3 fatty acids	215 (3.3)	145 (4.0)	70 (2.4)	<0.0001
a+b+c	6538 (99.7)	3618 (99.6)	2920 (99.8)	0.385
Most frequent combinations[b]				
a. Statins + omega-3 fatty acids	490 (67.3)	339 (72.4)	151 (58.1)	<0.0001
b. Statins + ezetimibe	129 (17.7)	64 (13.7)	65 (25.0)	<0.0001
c. Statins + fibrates	35 (4.8)	17 (3.6)	18 (6.9)	0.047
a+b+c	654 (89.8)	420 (89.7)	234 (90.0)	0.913

[a]Percentage distributions calculated amongst all monotherapies. [b]Percentage distributions calculated amongst all combinations. **P* values for comparison between male and female subjects using the chi-squared test.

Table 6 *Number of drugs, most frequent monotherapies and most frequent drug combinations for blood pressure-lowering treatment in subjects from the RIACE cohort: as a whole and stratified by gender*

Variables, *n* (%)	Total	Men	Women	*P**
	15773 (100)	8960 (56.8)	6813 (43.2)	
BP lowering				<0.0001
Lifestyle alone	4624 (29.3)	2821 (31.5)	1803 (26.5)	<0.0001
Monotherapies	4203 (26.7)	2435 (27.2)	1768 (26.0)	0.085
Combinations	6946 (44.0)	3704 (41.3)	3242 (47.6)	<0.0001
2 drugs	3780 (24.0)	2036 (22.7)	1744 (25.6)	<0.0001
3 drugs	2229 (14.1)	1161 (13.0)	1068 (15.7)	<0.0001
≥4 drugs	937 (5.9)	507 (5.7)	430 (6.3)	0.086
More frequent monotherapies[a]				
a. ACE inhibitors	2049 (48.8)	1283 (52.7)	766 (43.3)	<0.0001
b. ARBs	860 (20.5)	464 (19.1)	396 (22.4)	0.008
c. ß-blockers	432 (10.3)	230 (9.4)	202 (11.4)	0.037
d. DHP-CCBs	384 (9.1)	205 (8.4)	179 (10.1)	0.058
a+b+c+d	3725 (88.6)	2182 (89.6)	1543 (87.3)	0.019
Distribution of patients on[b]				
ACE-Is				<0.0001
a. monotherapy	2049 (33.5)	1283 (35.8)	766 (30.2)	<0.0001
b. +1 other drug	2163 (35.3)	1243 (34.7)	920 (36.3)	0.200
c. +2 other drugs	1308 (21.4)	723 (20.2)	585 (23.1)	0.007
d. +≥3 other drugs	602 (9.8)	336 (9.4)	266 (10.5)	0.150
a−b+c+d	6122 (100)	3585 (100)	2537 (100)	
ARBs				0.077
a. monotherapy	860 (23.9)	464 (25.3)	396 (22.5)	
b. +1 other drug	1252 (34.8)	621 (33.8)	631 (35.9)	
c. +2 other drugs	971 (27.0)	477 (26.0)	494 (28.1)	
d. +≥3 other drugs	512 (14.2)	275 (15.0)	237 (13.5)	
a+b+c+d	3595 (100)	1837 (100)	1758 (100)	
ACE-Is and/or ARBs				<0.0001
a. monotherapy	2909 (31.7)	1747 (34.2)	1162 (28.6)	<0.0001
b. +1 other drug	3277 (35.8)	1777 (34.8)	1500 (36.9)	0.038
c. +2 other drugs	2070 (22.6)	1083 (21.2)	987 (24.3)	<0.0001
d. +≥3 other drugs	909 (9.9)	495 (9.7)	414 (10.2)	0.438
a+b+c+d	9165 (100)	5102 (100)	4063 (100)	
ß-blockers				0.219
a. monotherapy	432 (15.8)	230 (15.4)	202 (16.2)	
b. +1 other drug	845 (30.8)	485 (32.5)	360 (28.9)	
c. +2 other drugs	842 (30.7)	454 (30.4)	388 (31.1)	
d. +≥3 other drugs	621 (22.7)	325 (21.6)	296 (23.8)	
a+b+c+d	2740 (100)	1494 (100)	1246 (100)	

Table 6 (*Continued*)

Variables, *n* (%)	Total	Men	Women	*P**
DHP-CCBs				0.188
a. monotherapy	384 (13.6)	205 (13.1)	179 (14.1)	
b. +1 other drug	913 (32.2)	528 (33.8)	385 (30.3)	
c. +2 other drugs	955 (33.7)	507 (32.5)	448 (35.3)	
d. +≥3 other drugs	580 (20.5)	321 (20.6)	259 (20.4)	
a+b+c+d	2832 (100)	1561 (100)	1271 (100)	
Thiazide diuretics				0.068
a. monotherapy	58 (1.9)	21 (1.5)	37 (2.3)	
b. +1 other drug	1187 (39.2)	547 (37.8)	640 (40.5)	
c. +2 other drugs	1206 (39.9)	586 (40.5)	620 (39.3)	
d. +≥3 other drugs	575 (19.00)	293 (20.3)	282 (17.9)	
a+b+c+d	3026 (100)	1447 (100)	1579 (100)	
Loop diuretics				0.219
a. monotherapy	121 (6.9)	56 (6.2)	65 (7.7)	
b. +1 other drug	532 (30.5)	268 (29.8)	264 (31.2)	
c. +2 other drugs	643 (36.9)	326 (36.3)	317 (37.5)	
d. +≥3 other drugs	448 (25.7)	248 (27.6)	200 (23.6)	
a+b+c+d	1,744 (100)	898 (100)	846 (100)	
Specific treatments/combinations[c]				
ACE-I and/or ARB	9165 (58.1)	5102 (56.9)	4063 (59.6)	0.001
ACE-I + ARB	552 (3.5)	320 (3.6)	232 (3.4)	0.574
ACE-I + thiazide or loop diuretic	818 (5.2)	397 (4.4)	421 (6.2)	<0.0001
As above + any other drug	1494 (9.5)	809 (9.0)	685 (10.1)	0.029
ARB + thiazide or loop diuretic	614 (3.9)	280 (3.1)	334 (4.9)	<0.0001
As above + any other drug	1220 (7.7)	608 (6.8)	612 (9.0)	<0.0001
ACE-I or ARB + DHP-CCB	698 (4.4)	398 (4.4)	300 (4.4)	0.907
As above + any other drug	1438 (9.1)	778 (8.7)	660 (9.7)	0.030
ACE-I or ARB + ß-blocker	591 (3.8)	360 (4.0)	231 (3.4)	0.040
As above + any other drug	1333 (8.5)	719 (8.0)	614 (9.0)	0.027

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II-receptor blocker; DHP-CCB, dihydropyridine calcium channel blocker. [a]Percentage distributions calculated amongst all monotherapies. [b]Percentage distributions calculated amongst all users of that category of blood pressure-lowering agent. [c]Percentage calculated amongst all patients included in the study. **P* values for comparison between male and female subjects using the chi-squared test.

[27]; (iv) for LDL cholesterol and, only in those with CVD, for systolic BP and HbA_{1c} in the large DUTY registry [28]; (v) and for total and LDL cholesterol and, in those with established CHD, for systolic BP in a study of five academic internal medicine practices from 2000 to 2003 [29].

However, in the present study, women performed worse than men despite not being treated less intensively; indeed, women were more likely to be on medication to reduce CVD risk factors, in keeping with their worse CVD risk profile. This is consistent with previous reports from Italian cohorts, the MIND-IT [23] and DAI studies [24] and a survey from north-western Italy [30], showing that women were more likely than men to take insulin, alone or in combination with oral hypoglycaemic agents [23, 24, 30], to be on antihypertensive drugs [23] and to be receiving lipid-lowering treatment [24]. By contrast, results from other countries have shown that treatment intensity in women was equal to [26, 28, 31] or even lower than [25, 29, 32] that in men despite poorer control of CVD risk factors, probably reflecting differences in

Table 7 *Prevalence of complications in subjects from the RIACE cohort: as a whole and stratified by gender*

Complications, *n* (%)	Total	Men	Women	*P**
	15773 (100)	8960 (56.8)	6813 (43.2)	
Major acute CVD events				
Any	3654 (23.2)	2470 (27.6)	1184 (17.4)	<0.0001
Acute myocardial infarction	1758 (11.2)	1281 (14.3)	477 (7.0)	<0.0001
Coronary revascularization	1584 (10.0)	1167 (13.0)	417 (6.1)	<0.0001
Endoluminal	651 (4.1)	500 (5.6)	151 (2.2)	<0.0001
Surgical	816 (5.2)	579 (6.5)	237 (3.5)	<0.0001
Both	117 (0.7)	88 (1.0)	29 (0.4)	<0.0001
Stroke	515 (3.3)	317 (3.5)	198 (2.9)	0.027
Carotid revascularization	867 (5.5)	557 (6.2)	310 (4.6)	<0.0001
Endoluminal	187 (1.2)	125 (1.4)	62 (0.9)	0.005
Surgical	671 (4.3)	428 (4.8)	243 (3.6)	<0.0001
Both	9 (0.1)	4 (0.1)	5 (0.1)	0.454
Ulcer/gangrene	532 (3.4)	332 (3.7)	200 (2.9)	0.008
Amputation	153 (1.0)	112 (1.3)	41 (0.6)	<0.0001
Minor	129 (0.8)	93 (1.0)	36 (0.5)	0.001
Major	24 (0.2)	19 (0.2)	5 (0.1)	0.027
Lower limb revascularization	456 (2.9)	341 (3.8)	115 (1.7)	<0.0001
Endoluminal	192 (1.2)	143 (1.6)	49 (0.7)	<0.0001
Surgical	245 (1.6)	183 (2.0)	62 (0.9)	<0.0001
Both	19 (0.1)	15 (0.2)	4 (0.1)	0.051
Surgery for aortic aneurysm	58 (0.4)	50 (0.6)	8 (0.1)	<0.0001
Retinopathy, stage				0.341
No	12276 (77.8)	6959 (77.7)	5317 (78.0)	
Nonadvanced	1957 (12.4)	1131 (12.6)	826 (12.1)	
Advanced	1540 (9.8)	870 (9.7)	670 (9.8)	
Preproliferative	660 (4.2)	385 (4.3)	275 (4.0)	
Proliferative	658 (4.2)	373 (4.2)	285 (4.2)	
Maculopathy	205 (1.3)	102 (1.1)	103 (1.5)	
Blindness	17 (0.1)	10 (0.1)	7 (0.1)	
Nephropathy				
Albuminuria				<0.0001
Normal (<10 mg per 24 h)	6023 (38.2)	2993 (33.4)	3030 (44.5)	<0.0001
Low (10–29 mg per 24 h)	5515 (35.0)	3109 (34.7)	2406 (35.3)	0.421
Micro (30–299 mg per 24 h)	3497 (22.2)	2340 (26.1)	1157 (17.0)	<0.0001
Macro (≥300 mg per 24 h)	738 (4.7)	518 (5.8)	220 (3.2)	<0.0001
eGFR				<0.0001
1 (≥90 mL min^{-1} per 1.73 m^2)	4662 (29.6)	2954 (33.0)	1708 (25.1)	<0.0001
2 (60–89 mL min^{-1} per 1.73 m^2)	8152 (51.7)	4657 (52.0)	3495 (51.3)	0.400
3 (30–59 mL min^{-1} per 1.73 m^2)	2701 (17.1)	1226 (13.7)	1475 (21.7)	<0.0001
4 (15–29 mL min^{-1} per 1.73 m^2)	229 (1.5)	106 (1.2)	123 (1.8)	0.001
5 (<15 mL min^{-1} per 1.73 m^2)	29 (0.2)	17 (0.2)	12 (0.2)	0.843

Table 7 (*Continued*)

Complications, *n* (%)	Total	Men	Women	*P**
CKD, stage				<0.0001
0	9865 (62.5)	5526 (61.7)	4339 (63.7)	0.01
1	1052 (6.7)	764 (8.5)	288 (4.2)	<0.0001
2	1897 (12.0)	1321 (14.8)	576 (8.5)	<0.0001
3	2701 (17.1)	1226 (13.7)	1475 (21.7)	<0.0001
4	229 (1.5)	106 (1.2)	123 (1.8)	0.001
5	29 (0.2)	17 (0.2)	12 (0.2)	0.843
CKD, phenotype				<0.0001
No	9865 (62.5)	5526 (61.7)	4339 (63.7)	0.10
Stages 1/2	2949 (18.7)	2085 (23.3)	864 (12.7)	<0.0001
Stages 3–5 (nonalbuminuric)	1673 (10.6)	576 (6.4)	1097 (16.1)	<0.0001
Stages 3–5 (albuminuric)	1286 (8.2)	773 (8.6)	513 (7.5)	0.013

**P* values for comparison between male and female subjects using the chi-squared test or the two-sided Fisher's exact test for lower limb revascularization (both endoluminal and surgical).

the national health systems and access to care. It is interesting that women with type 1 diabetes from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications had a lower frequency than men of use of medication to decrease CVD risk [33]. Finally, in the present study, female gender correlated significantly with failure to achieve targets even after inclusion of specific treatments as covariates in the regression models. Of note, whilst statin treatment was positively associated with probability of achieving lipid targets, an inverse correlation was found between antihypertensive and antihyperglycaemic (especially insulin) therapies and achievement of systolic BP and HbA_{1c} goals, respectively. These opposite associations might be explained by differences in rates of usage and possibly efficacy of treatments. Less than 50% of subjects were on lipid-lowering therapy (only 42.5% on statins), and therefore, a high percentage of patients was not on-target for lipids, which might account for the association between statin treatment and the likelihood of attaining these goals. By contrast, ~70% and 85% of patients were on antihypertensive and antihyperglycaemic treatments, respectively; nevertheless, <50% of participants were on-target for systolic BP and HbA_{1c}, thus suggesting that the inverse correlation between these treatments and achievement of targets was due to an indication effect (i.e. the higher the risk factor the more frequent the treatment) and the difficulty of controlling systolic BP and HbA_{1c} in some patients by the use of current drugs, even in combination.

Despite a higher level of CVD risk factors in women than in men, CVD was ~60% more prevalent in the latter; however, this is a much lower difference than in nondiabetic individuals, in keeping with the observation that the relative risk of CVD is higher in women than in men [16]. Also, in the present cohort, prevalence of acute myocardial infarction was twofold higher in men than in women, whereas stroke frequency was only slightly higher in men. Comparison with data from the general population in Italy [34] or the USA [35] indicates that the male/female ratio is much lower in diabetic subjects for acute myocardial infarction (2.0 vs. 3.3 in the Italian general population), whereas it is similar for stroke.

Taken together, our findings seem to contradict the current view that the worse performance of female patients is attributable primarily to gender disparities in the access to diabetes care and/or to poor awareness of patients or perception of physicians of CVD risk in women, which may vary amongst different countries/settings. However, the finding that, amongst untreated individuals, women were less frequently on-target for lipids and BP levels suggests that the higher treatment rate observed in women compared with men was not sufficient to bridge the gender gap in CVD burden. These results and the lack of evidence for reduced drug efficacy in women compared with men [36] suggest the involvement of other gender-dependent factors. In the present study, (central) obesity was significantly more prevalent in women than in men, with

Table 8 *Independent correlation of achievement of therapeutic targets for HbA_{1c} (< 7.0% or 53.1 nmol $mmol^{-1}$), LDL cholesterol (< 2.59 mmol L^{-1}), non-HDL cholesterol (< 3.37 mmol L^{-1}) and systolic BP (< 130 mmHg)*

	OR	95% CI	*P*
HbA_{1c}			
Female gender	0.871	0.812–0.933	<0.0001
Diabetes duration	0.959	0.955–0.962	<0.0001
BMI	0.972	0.966–0.979	<0.0001
OHA therapy	0.362	0.326–0.402	<0.0001
Combined therapy	0.125	0.106–0.148	<0.0001
Insulin therapy	0.193	0.168–0.221	<0.0001
LDL cholesterol			
Female gender	0.709	0.663–0.758	<0.0001
Diabetes duration	1.008	1.005–1.012	<0.0001
BMI	1.001	0.995–1.008	0.707
Statin treatment	2.266	2.123–2.419	<0.0001
Non-HDL cholesterol			
Female gender	0.750	0.703–0.801	<0.0001
Diabetes duration	1.011	1.008–1.014	<0.0001
BMI	0.976	0.970–0.982	<0.0001
Statin treatment	1.764	1.655–1.880	<0.0001
Systolic BP			
Female gender	0.888	0.825–0.955	<0.0001
Diabetes duration	0.983	0.979–0.987	<0.0001
BMI	0.972	0.964–0.979	<0.0001
Antihypertensive treatment	0.653	0.604–0.705	<0.0001

Logistic regression analysis with stepwise variable selection. OR, odds ratio; CI, confidence interval; BMI, body mass index; BP, blood pressure; OHA, oral hypoglycaemic agent.

huge sex differences particularly in waist circumference. Similar large gender differences have also been reported recently amongst diabetic patients enrolled in the EUROASPIRE II trial [9]. Although CVD risk factors have been declining considerably irrespective of BMI, levels are still higher in obese subjects than in lean individuals [10], and obesity increases the risk of CVD [37] and type 2 diabetes [38] to a greater extent in women than in men. However, although BMI was associated with a lower likelihood of attaining all targets, except LDL cholesterol, female gender remained an independent predictor of failure to achieve treatment targets after adjustment for BMI. This is consistent with data from the DUTY registry [28] and the MIND-IT study [23], showing that HbA_{1c}, LDL cholesterol and BP were less frequently on-target in women than in men independent of BMI and age.

Other mechanisms potentially implicated in the worse performance of diabetic women in reducing CVD risk include hormonal factors, as women with type 2 diabetes showed an impaired ability to convert androgen to oestrogen, which is likely to be due to a reduction in ovarian aromatase activity [39]. This relative hypo-oestrogenism (or hyperandrogenism) might adversely affect the development of CVD in women due to the gender-dimorphic effects of sex hormones. In fact, elevated androgen levels were found to protect against diabetes in men, whilst conferring a higher risk in women [40], and hormone-replacement therapy in women with type 2 diabetes was associated with a reduction in visceral adiposity and improvement in glucose and lipid metabolism [41]. An alternative, although not mutually exclusive, explanation may be a lower compliance to lifestyle and pharmacological interventions in women than in men, and possibly other unidentified cultural or socio-economic factors. It has been shown that women are more sedentary than men and that this may contribute to the higher prevalence of obesity; these differences are already apparent during childhood and adolescence [36]. Moreover, a more pronounced inability of hungry female subjects to control their desire for food as compared to male subjects was shown in a brain imaging study, suggesting that women may be less compliant to dietary prescriptions [42]. Unfortunately, in this respect, the list of possible covariates in our study is incomplete. Data regarding social background, degree of education, physical exercise, diet, alcohol consumption and smoking history, which may all contribute to explaining the gender gap in control of CVD risk factors, were not available. Lack of information on medication dispensing, dosage and adherence further limits speculation on the role of treatment differences, although women are generally more compliant than men with regard to taking medication [15, 43, 44]. The fact that the male/female ratio in the present cohort (57:43) is higher than that of diabetic subjects from the general population in Italy [45, 46], but similar to that reported from a coeval survey in the secondary care setting [47], suggests a selection bias for referral to specialists. However, this gender disparity in the referral to secondary care providers seems to be due to social and cultural but not economical factors, as access to healthcare services in Italy is

free. Finally, the inverse relationship between antihypertensive/antihyperglycaemic treatments and achievement of the corresponding targets suggests an indication bias, and the cross-sectional design did not allow any cause–effect or temporal relationships between the levels of HbA_{1c}, lipids and BP and their treatment to be drawn.

The strengths of this study include the analysis of a contemporary data set, the large size of the cohort and the completeness of data, which were collected from each patient's medical record, thus excluding the confounding effects of self-reporting of prescriptions.

In conclusion, the findings of the RIACE study confirm that a significant proportion of patients with type 2 diabetes do not achieve the recommended HbA_{1c}, lipid and BP targets for CVD prevention, and that CVD risk profile is worse in women than in men. However, in contrast to the findings of previous studies, this gender difference could not be attributed primarily to disparities in treatment, as drug usage was equally or even more intensive in women than in men from this cohort, and female gender remained an independent predictor of failure to achieve therapeutic targets after adjustment for confounders such as diabetes duration, age, BMI and treatments. Whilst treatment behaviours observed in the RIACE cohort might be specific to a particular country/setting, the finding that women are less frequently on-target than men even when treated more intensively is generally valid and supports the need for large prospective studies of the impact of gender as the primary outcome as well as of the pathophysiological mechanisms involved [36]. Finally, these data indicate that there is still considerable potential to improve standards of preventive care amongst subjects with type 2 diabetes in order to reduce CVD risk and death, especially in women.

Conflict of interest statement

None of the authors has any conflicts of interest to declare.

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References

1 Yang W, Lu J, Weng J *et al.* Prevalence of diabetes among men and women in China. *N Engl J Med* 2010; **362:** 1090–101.
2 Hex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabet Med* 2012; **29:** 855–62.
3 Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M *et al.* Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. *BMJ* 2011; **343:** d4169.
4 Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and bayesian random-effects meta-analyses of randomized trials. *Circulation* 2011; **123:** 2799–810.
5 Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; **358:** 580–91.
6 Ismail-Beigi F. Clinical practice. Glycemic management of type 2 diabetes mellitus. *N Engl J Med* 2012; **366:** 1319–27.
7 Gregg EW, Cheng YJ, Cadwell BL *et al.* Secular trends in cardiovascular disease risk factors according to body mass index in US adults. *JAMA* 2005; **293:** 1868–74.
8 Hoerger TJ, Zhang P, Segel JE, Gregg EW, Narayan KM, Hicks KA. Improvements in risk factor control among persons with diabetes in the United States: evidence and implications for remaining life expectancy. *Diabetes Res Clin Pract* 2009; **86:** 225–32.
9 Pyörälä K, Lehto S, De Bacquer D *et al.* Risk factor management in diabetic and non-diabetic patients with coronary heart disease. Findings from the EUROASPIRE I AND II surveys. *Diabetologia* 2004; **47:** 1257–65.
10 Preis SR, Pencina MJ, Hwang SJ *et al.* Trends in cardiovascular disease risk factors in individuals with and without diabetes mellitus in the Framingham Heart Study. *Circulation* 2009; **120:** 212–20.
11 Davis TM. Ethnic diversity in type 2 diabetes. *Diabet Med* 2008; **25(Suppl 2):** 52–6.
12 Gregg EW, Gu Q, Cheng YJ, Narayan KM, Cowie CC. Mortality trends in men and women with diabetes, 1971 to 2000. *Ann Intern Med* 2007; **147:** 149–55.
13 Preis SR, Hwang SJ, Coady S *et al.* Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. *Circulation* 2009; **119:** 1728–35.
14 Gregg EW, Cheng YJ, Saydah S *et al.* Trends in death rates among U.S. adults with and without diabetes between 1997 and 2006: findings from the National Health Interview Survey. *Diabetes Care* 2012; **35:** 1252–7.

15 Maric C. Risk factors for cardiovascular disease in women with diabetes. *Gend Med* 2010; **7:** 551–6.
16 Emerging Risk Factors Collaboration, Sarwar N, Gao P *et al.* Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; **375:** 2215–22.
17 Huxley R, Barzi F, Woodward M. Excess risk of fatal heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ* 2006; **332:** 73–8.
18 Solini A, Penno G, Bonora E *et al.* Diverging association of reduced glomerular filtration rate and albuminuria with coronary and noncoronary events in patients with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study. *Diabetes Care* 2012; **35:** 143–9.
19 Penno G, Solini A, Zoppini G *et al.* Rate and determinants of association between advanced retinopathy and chronic kidney disease in patients with type 2 diabetes. The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study. *Diabetes Care* 2012; **35:** 2317–23.
20 Penno G, Solini A, Bonora E *et al.* Clinical significance of nonalbuminuric renal impairment in type 2 diabetes. *J Hypertens* 2011; **29:** 1802–9.
21 Pugliese G, Solini A, Fondelli C *et al.* Reproducibility of albuminuria in type 2 diabetic subjects. Findings from the Renal Insufficiency And Cardiovascular Events (RIACE) Study. *Nephrol Dial Transplant* 2011; **26:** 3950–4.
22 Li C, Ford ES, Tsai J, Zhao G, Balluz LS, Gidding SS. Serum non-high-density lipoprotein cholesterol concentration and risk of death from cardiovascular diseases among U.S. adults with diagnosed diabetes: the Third National Health and Nutrition Examination Survey linked mortality study. *Cardiovasc Diabetol* 2011; **10:** 46.
23 Franzini L, Ardigò D, Cavalot F *et al.* Women show worse control of type 2 diabetes and cardiovascular disease risk factors than men: Results from the MIND.IT Study Group of the Italian Society of Diabetology. *Nutr Metab Cardiovasc Dis* 2013; **23:** 235–41.
24 Avogaro A, Giorda C, Maggini M *et al.* Incidence of coronary heart disease in type 2 diabetic men and women: impact of microvascular complications, treatment, and geographic location. *Diabetes Care* 2007; **30:** 1241–7.
25 Ford ES. Trends in the risk for coronary heart disease among adults with diagnosed diabetes in the U.S.: findings from the National Health and Nutrition Examination Survey, 1999–2008. *Diabetes Care* 2011; **34:** 1337–43.
26 Ferrara A, Mangione CM, Kim C *et al.* Sex disparities in control and treatment of modifiable cardiovascular disease risk factors among patients with diabetes: Translating Research Into Action for Diabetes (TRIAD) Study. *Diabetes Care* 2008; **31:** 69–74.
27 Guthrie B, Emslie-Smith A, Morris AD. Which people with Type 2 diabetes achieve good control of intermediate outcomes? Population database study in a UK region. *Diabet Med* 2009; **26:** 1269–76.
28 Gouni-Berthold I, Berthold HK, Mantzoros CS, Böhm M, Krone W. Sex disparities in the treatment and control of cardiovascular risk factors in type 2 diabetes. *Diabetes Care* 2008; **31:** 1389–91.
29 Wexler DJ, Grant RW, Meigs JB, Nathan DM, Cagliero E. Sex disparities in treatment of cardiac risk factors in patients with type 2 diabetes. *Diabetes Care* 2005; **28:** 514–20.
30 Cavalot F, Petrelli A, Traversa M *et al.* Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. *J Clin Endocrinol Metab* 2006; **91:** 813–9.
31 McFarlane SI, Castro J, Kaur J *et al.* Control of blood pressure and other cardiovascular risk factors at different practice settings: outcomes of care provided to diabetic women compared to men. *J Clin Hypertens (Greenwich)* 2005; **7:** 73–80.
32 Kautzky-Willer A, Kamyar MR, Gerhat D *et al.* Sex-specific differences in metabolic control, cardiovascular risk, and interventions in patients with type 2 diabetes mellitus. *Gend Med* 2010; **7:** 571–83.
33 Larkin ME, Backlund JY, Cleary P *et al.* Disparity in management of diabetes and coronary heart disease risk factors by sex in DCCT/EDIC. *Diabet Med* 2010; **27:** 451–8.
34 Palmieri L, Donfrancesco C. Heart. Prevalence trend of cardiovascular diseases in the Italian adult population. *Epidemiol Prev* 2011; **35:** 94–5.
35 Lloyd-Jones D, Adams RJ, Brown TM *et al.* Executive summary: heart disease and stroke statistics–2010 update: a report from the American Heart Association. *Circulation* 2010; **121:** 948–54.
36 Kautzky-Willer A, Handisurya A. Metabolic disease and associated complications: sex and gender matter. *Eur J Clin Invest* 2009; **39:** 631–48.
37 Regitz-Zagrosek V, Lehmkuhl E, Mahmoodzadeh S. Gender aspects of the role of the metabolic syndrome as a risk factor for cardiovascular disease. *Gend Med* 2007; **4(Suppl B):** S162–77.
38 Bray GA. Medical consequences of obesity. *J Clin Endocrinol Metab* 2004; **89:** 2583–9.
39 Stamataki KE, Spina J, Rangou DB, Chlouverakis CS, Piaditis GP. Ovarian function in women with non-insulin dependent diabetes mellitus. *Clin Endocrinol (Oxf)* 1996; **45:** 615–21.
40 Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2006; **295:** 1288–99.
41 Samaras K, Hayward CS, Sullivan D, Kelly RP, Campbell LV. Effects of postmenopausal hormone replacement therapy on central abdominal fat, glycemic control, lipid metabolism, and vascular factors in type 2 diabetes: a prospective study. *Diabetes Care* 1999; **22:** 1401–7.
42 Wang GJ, Volkow ND, Telang F *et al.* Evidence of gender differences in the ability to inhibit brain activation elicited by food stimulation. *Proc Natl Acad Sci USA* 2009; **106:** 1249–54.
43 Khan NA, Yun L, Humphries K, Kapral M. Antihypertensive drug use and adherence after stroke: are there sex differences? *Stroke* 2010; **41:** 1445–9.
44 Wong MC, Lau RK, Jiang JY, Griffiths SM. Discontinuation of angiotensin-converting enzyme inhibitors: a cohort study. *J Clin Pharm Ther* 2012; **37:** 335–41.
45 ISTAT, Annuario statistico italiano 2011, http://www3.istat.it/dati/catalogo/20111216_00/contenuti.html.
46 Osservatorio ARNO Diabete, Rapporto 2011, http://www.cureprimarie-ulss21.it/page.asp?id=2499&title=pubblicato-il-rapporto-dellosservatorio-arno-sul-diabete.
47 Annali AMD 2009, http://www.infodiabetes.it/files/2009_annali_AMD_ita.pdf.

Correspondence: Giuseppe Pugliese, MD, PhD, Department of Clinical and Molecular Medicine, 'La Sapienza' University of Rome, Via di Grottarossa, 1035-1039 - 00189 Rome, Italy. (fax: +39-0633775001; e-mail: giuseppe.pugliese@uniroma1.it).

Appendix : The RIACE study group

The RIACE steering committee

Giuseppe Pugliese (Coordinator), Giuseppe Penno (Secretariat), Anna Solini, Enzo Bonora, Emanuela Orsi, Roberto Trevisan, Luigi Laviola and Antonio Nicolucci.

The Diabetic Nephropathy Study Group, Italian Society of Diabetology

Giuseppe Pugliese, Salvatore De Cosmo, Gabriella Gruden, Susanna Morano, Giuseppe Penno, Francesco Pugliese, Giampaolo Zerbini, Luigi Laviola, Anna Solini and Roberto Trevisan.

Participating diabetes centres

1 Azienda Ospedaliera Sant'Andrea, Roma (Coordinating Center): Giuseppe Pugliese, Paola Simonelli, Laura Salvi, Giulia Mazzitelli, Alessandra Bazuro and Aurora Frasheri
2 Ospedale Le Molinette, Torino: Paolo Cavallo-Perin, Gabriella Gruden and Bartolomeo Lorenzati
3 Ospedale San Luigi Gonzaga, Orbassano: Mariella Trovati, Giovanni Anfossi†, Franco Cavalot and Massimo Chirio
4 Ospedale San Raffaele, Milan: Giampaolo Zerbini and Valentina Martina
5 IRCCS 'Cà Granda – Ospedale Maggiore Policlinico', Milan: Emanuela Orsi, Laura Montefusco and Dario Zimbalatti
6 Ospedale San Paolo, Milan: Antonio Pontiroli, Annamaria Veronelli and Barbara Zecchini
7 Ospedale San Giuseppe, Milan: Maura Arosio and Alessia Dolci
8 Ospedali Riuniti, Bergamo: Roberto Trevisan and Anna Corsi
9 Ospedale Maggiore, Verona: Enzo Bonora and Giacomo Zoppini
10 Policlinico Universitario, Padova: Angelo Avogaro, Monica Vedovato and Elisa Pagnin
11 Ospedale Cisanello, Azienda Ospedaliero-Universitaria Pisana, Pisa: Giuseppe Penno, Laura Pucci, Daniela Lucchesi, Eleonora Russo and Monia Garofolo
12 Ospedale Santa Chiara, Azienda Ospedaliero-Universitaria Pisana, Pisa: Anna Solini
13 Ospedale Le Scotte, Siena: Francesco Dotta, Cecilia Fondelli and Laura Nigi
14 Policlinico Umberto I, Roma: Susanna Morano and Alessandra Gatti
15 Ospedale S. Maria Goretti, Latina: Raffaella Buzzetti
16 Ospedali Riuniti, Foggia: Mauro Cignarelli, Olga Lamacchia and Sabina Pinnelli
17 Policlinico Universitario, Bari: Francesco Giorgino, Luigi Laviola and Sebastio Perrini
18 Policlinico Mater Domini, Catanzaro: Giorgio Sesti and Francesco Andreozzi
19 Policlinico Monserrato, Cagliari: Marco Giorgio Baroni and Giuseppina Frau

†Dr Anfossi is deceased.

