Cardiovascular Diabetology

RESEARCH

Open Access

Sex-difference of multifactorial intervention on cardiovascular and mortality risk in DKD: post-hoc analysis of a randomised clinical trial

Roberto Minutolo[1], Vittorio Simeon[2], Luca De Nicola[1], Paolo Chiodini[2], Raffaele Galiero[1], Luca Rinaldi[3], Alfredo Caturano[1], Erica Vetrano[1], Celestino Sardu[1], Raffaele Marfella[1] and Ferdinando Carlo Sasso[1*] on behalf of NID-2 Study Group Investigators

Abstract

Objective Women with type 2 diabetes experience higher cardiovascular and mortality risk than men possibly because of a sub-optimal cardio-protective treatment. We evaluated whether an intensive multifactorial therapy (MT) produces similar protective effect on development of adverse outcomes in women and men.

Research design and methods Nephropathy in Diabetes type 2 study is an open-label cluster randomized trial comparing the effect of Usual Care (UC) or MT of main cardiovascular risk factors (blood pressure < 130/80 mmHg, HbA1c < 7%, LDL < 100 mg/dL, and total cholesterol < 175 mg/dL) on cardiovascular and mortality risk in patients with type 2 diabetes. In this post-hoc analysis, we stratified patients by sex to compare the occurrence of MACEs (primary endpoint) and all-cause death (secondary endpoint) between women (104 MT and 105 UC) and men (103 MT and 83 UC).

Results Achievement of therapeutic goals was similar by sex, with 44% and 47% of women and men in MT achieving at least 3 targets vs. 16% and 20% of women and men in UC. During a median follow-up of 13.0 years, we recorded 262 MACE (48.5% in women) and 189 deaths (53.6% in women). Compared to the UC group, the risk of MACE in the MT group was reduced by 52% in women and by 44% in men ($P = 0.11$). Conversely, the reduction in mortality risk by MT was greater in women (44% versus 12%, $P = 0.019$).

Conclusions MT similarly reduces the risk of MACEs in either sex. This therapeutic approach is associated with a survival advantage in women as compared with men and it may represent an important rationale to motivate physicians in overcoming their therapeutic inertia often encountered in female patients as well as to encourage patients of both sexes at improving their adherence to multidrug therapy.

The list of investigators is reported in the Appendix.

*Correspondence:
Ferdinando Carlo Sasso
ferdinando.sasso@unicampania.it

Full list of author information is available at the end of the article

Introduction

The global age-standardized total prevalence of diabetes was estimated to be 6.1% in 2021 and it is expected to increase by about 60% in 2050 to 9.8%, resulting in 1.3 billion people living with diabetes worldwide [1]. Globally, age-standardized prevalence of diabetes was 14% higher in males than in females (6.5% vs. 5.8%) [1]. The overwhelming majority of people with diabetes (96%) have type 2 diabetes that represents worldwide the leading cause of cardiovascular events, end-stage kidney disease and death [2, 3]. More important, outcomes associated with type 2 diabetes also strongly differ by sex with women having a higher risk of mortality and all cardiovascular complications [4–8]. The renal involvement in type 2 diabetes remarkably worsens cardiovascular prognosis, as demonstrated by studies showing that risks of adverse outcomes are higher among patients with diabetic kidney disease (DKD) throughout the whole spectrum of disease [2, 3].

Sex-difference in the management of cardiovascular risk has been advocated to explain difference in the outcome [9, 10]. Indeed, women are currently less likely than men to receive an extensive cardioprotective treatment including statins, aspirin, beta blockers, sodium–glucose cotransporter 2 inhibitors (SGLT2i) or GLP-1 receptor agonists (GLP-1RA) [9, 11, 12]. Furthermore, some sex-specific difference in drug efficacy have been reported particularly for statin, fenofibrate, RAS inhibitors and urate-lowering therapy [10, 13]. Women in comparison with men, more frequently report side effects under many therapies such as, gastrointestinal effect with metformin and GLP1-RA [14, 15], genital or urinary tract infections with SGLT2i [16], higher rate of severe and nocturnal hypoglycemic episodes with basal insulin therapy [17], cough with ACE-inhibitors [18] and increased liver enzymes and myalgia with statins [19]. Finally, it has been reported a lower adherence to therapy in women than men with type 2 diabetes due not only to the more frequent occurrence of side-effects but also as a result of higher depression rates and differences in education levels and socioeconomic status [10, 12, 20]. These epidemiological and pharmacological differences associated with sex may promote a different management of risk factors in women and men [21].

We recently published a RCT demonstrating improved cardiovascular outcome and survival, of multifactorial goal-oriented strategy as compared with usual care in patients with DKD [22]. The trial setting represents the ideal condition to evaluate sex-difference in the outcome because women and men were prescribed the same intensive multifactorial non-pharmacological and pharmacological treatment aimed at correcting simultaneously the most relevant risk factors (hypertension, dyslipidemia, and hyperglycemia). Therefore, this post-hoc analysis was aimed at disentangling the effect of intensified treatment between women and men on cardiovascular and mortality risk. Secondary endpoint was the achievement rate of therapeutic goals by sex.

Research design and methods

Study design and participants

This is a post-hoc analysis of the Nephropathy In Diabetes type 2 (NID-2) study, an open-label cluster RCT in patients with type 2 diabetes steadily followed in diabetology clinics [22]. Study design, eligibility criteria, randomization, interventions, primary and secondary outcomes for NID-2 trial have been described in detail previously [22, 23]. Briefly, NID-2 study enrolled patients with type 2 diabetes aged ≥ 40 years, with persistent albuminuria ≥ 30 mg/24 h and severe diabetic retinopathy (DR) referred to 14 Italian diabetology clinics from at least one year during the period 10/01/2005-10/01/2008. Patients with previous MI or stroke, severe hepatic or cardiac failure were excluded. Centers were randomly assigned to either multifactorial intensive therapy (MT) or Usual Care (UC). The intervention phase was scheduled for a period of four years, and it was completed in December 2011. Then, patients were followed until May 2019 to achieve the number of events needed for the primary outcome.

The protocol was approved by the ethics committee of University of Campania "Luigi Vanvitelli" (clinicaltrials.gov: NCT00535925) and the study has been carried out in accordance with the Declaration of Helsinki. Informed consent was signed by all participants.

Study arms

The targets recommended in either group by the available guidelines for type 2 diabetes management at the time of study initiation [24–26] were as follows: (a) blood pressure (BP) < 130/80 mmHg, (b) glycated hemoglobin (HbA1c) < 7% (< 53 mmol/mol), (c) fasting serum LDL cholesterol < 100 mg/dL, and (d) fasting total serum cholesterol < 175 mg/dL. In UC group, the subjects received all therapeutic prescriptions considered appropriate by their physician, in the respect of the good clinical practice aimed at controlling blood pressure, glycemic status and dyslipidemia.

In MT group, the patients received non-pharmacological and pharmacological treatment for management of hypertension, metabolic control and dyslipidemia, according to a pre-specified algorithm (Supplementary Appendix 1). Non-pharmacological intervention included recommendation for physical activity and low sodium diet provided to patients in written form. Pharmacological treatment included inhibition of renin–angiotensin system, followed by stepwise addition of other anti-hypertensive drug classes, statins if dietary

counseling was not effective and low-dose aspirin, unless contraindicated or not tolerated.

Patients in both arms were visited at their own diabetes center every six months to evaluate laboratory data, clinical parameters and compliance to pharmacological and non-pharmacological prescriptions. At each visit, investigators assessed the compliance to therapy by carefully reviewing the prescriptions in each patient. We considered a missing rate of pills in the two weeks prior to any visit ≥ 20% as measure of non-adherence to pharmacological prescriptions. For the implementation of lifestyle recommendations (diet and physical activity), we performed periodical monitoring at each visit by a personal diary. At each visit, the occurrence of adverse events as well as outcomes of interest were carefully monitored and recorded in an electronic chart form.

eGFR was estimated using the CKD-EPI equation after reducing creatinine values by 5% because creatinine was not standardized [3].

Outcomes

Primary endpoint was a composite of major fatal and non-fatal cardiovascular events (MACEs), including MI (documented instrumentally and/or enzymatically), stroke, coronary-artery by-pass, revascularization procedures (PTCA) and non-traumatic lower limbs amputation, whichever occurred first. Diagnosis of MACEs was performed in agreement with the international guidelines [27–29] and were assessed by cardiologists blinded to the study arm. Since the planned number of events was not reached during the initial 4-year time frame (interventional phase), incidence of the primary end point was extended throughout the follow-up phase, initially planned to assess the durability of effects of the intensified treatment. During this extension phase, following the end of intervention, all patients enrolled in both arms were treated by their own physicians according to the good clinical practice.

Secondary endpoints were all-cause death at the end of the follow-up phase, and the achievement of targets (BP, HbA1c, total cholesterol and LDL) at the end of intervention period.

Statistical analysis

Descriptive statistics were used to compare baseline characteristics based on treatment and gender. Specifically, categorical data were presented as numbers and percentages, while continuous variables were expressed as either median and interquartile range or mean and standard deviation, depending on their distribution, as assessed by the Shapiro-Wilk test. Student's t-tests, Wilcoxon tests or Chi-square tests were used, where appropriate, to examine gender differences.

Median follow-up time has been calculated by the inverse Kaplan-Meier procedure. The primary and secondary endpoints were analyzed according to the intention-to-treat principle, with event curves for the time-to-first event based on Kaplan-Meier analysis. Time-to-event endpoints were furthermore analyzed using a Cox regression model with frailty effect to correct for the cluster design. In the Cox models, the main independent variables were treatment group and gender, followed by interaction assessment. Proportionality assumption was checked using log–log plot of survival and tested using Schoenfeld residuals.

A Generalized Estimating Equation (GEE) model with cluster as the grouping variable, adjusted for baseline values, was used to assess the gender effect in achieving therapeutic targets. For the GEE model as well, the main independent variables were the treatment group and gender, followed by interaction assessment. Data were analyzed using STATA 16.0 software (StataCorp.2019. College Station, TX: StataCorp LLC).

Results

Sex comparison at baseline

The NID-2 study comprised 52.9% women (209 out of 395 patients). The mean age at recruitment was comparable (67.7 ± 8.8 and 66.4 ± 9.0 years, in women and men, respectively, $P = 0.14$). Overall, eGFR at baseline was significantly lower in women with a higher prevalence of eGFR < 60 mL/min/1.73m^2 (51.7% vs. 34.9% in men). Moreover, albuminuria was lower in women (Table 1). No major sex-difference emerged for glycemic control and dyslipidemia (Table 1). At baseline, blood pressure was less frequently at goal in women (43.5% versus 55.9% in men), mainly due to a poor control of systolic component (Table 1). Among women, patients randomized to UC group had lower albuminuria and a better control of BP, anemia, HbA1c and triglycerides; same differences by assigned group were detected in men (Table 1).

At baseline, the prescription of drugs for hypertension, hyperglycemia, dyslipidemia and aspirin did not differ between women and men (Table 1). Of note, in either sex statins and aspirin were less frequently prescribed in the control group as compared with the multifactorial treatment arm (Table 1).

Achievement of targets at the end of interventional phase

At the end of interventional phase, patients to MT group achieved a better control of most clinical targets (Table 2). In particular, as compared with UC, women assigned to multifactorial intervention were more likely to achieve target for systolic BP, systolic plus diastolic BP, total and LDL-cholesterol while among men, the assignment to MT group allowed a better control of BP and LDL-cholesterol (Table 2). Interestingly, no difference

Table 1 Clinical data, laboratory parameters and therapy at baseline in women and men overall and by group

Factor	Women			Men		
	Overall	***UC***	***MT***	***Overall***	***UC***	***MT***
N	209	105	104	186	83	103
Age, years	67.7 ± 8.8	68.2 ± 9.1	67.3 ± 8.6	66.4 ± 9.0	68.3 ± 8.5[§]	64.9 ± 9.2
SBP, mmHg	135 ± 13	136 ± 12	135 ± 14	133 ± 14	134 ± 13	133 ± 14
DBP, mmHg	79.0 ± 8.0	76.8 ± 7.5[§]	81.3 ± 8.0	78.4 ± 7.3	76.4 ± 7.4[§]	80.2 ± 6.8
SBP target	98 (46.9%)*	48 (45.7%)	50 (48.1%)	109 (58.6%)	47 (56.6%)	62 (60.2%)
DBP target	153 (73.2%)	89 (84.8%)[§]	64 (61.5%)	144 (77.4%)	72 (86.7%)	72 (69.9%)
SBP/DBP target	91 (43.5%)*	45 (42.9%)	46 (44.2%)	104 (55.9%)	45 (54.2%)	59 (57.3%)
GFR (mL/min/1.73m^2)	58 [44–74]*	58 [45–73][#]	58 [44–76][#]	71 [54–85]	70 [52–82]	71 [55–88]
GFR < 60 mL/min/1.73m^2	108 (51.7%)*	56 (53.3%)[#]	52 (50.0%)[#]	65 (34.9%)	32 (38.6%)	33 (32.0%)
Albuminuria, mg/24 h	90 [36–160]*	46 [31–127][§#]	120 [89–200]	120 [47–207]	60 [35–170][§]	140 [75–259]
Hemoglobin, g/dL	12.8 ± 1.3*	13.0 ± 1.3[§#]	12.5 ± 1.3[#]	13.6 ± 1.5	14.0 ± 1.2[§]	13.3 ± 1.6
Glycaemia, mg/dL	156 ± 49	151 ± 49	161 ± 49	152 ± 42	155 ± 49	150 ± 36
HbA1c, %	7.5 ± 1.1	7.4 ± 1.1	7.6 ± 1.0	7.3 ± 1.1	7.2 ± 1.0	7.4 ± 1.1
HbA1c target	82 (39.2%)	54 (51.4%)[§]	28 (26.9%)	84 (45.2%)	46 (55.4%)[§]	38 (36.9%)
Total cholesterol, mg/dL	191 ± 33*	189 ± 34	192 ± 32	182 ± 34	182 ± 34	183 ± 34
Total cholesterol target	63 (30.1%)	33 (31.4%)	30 (28.8%)	68 (36.6%)	34 (41.0%)	34 (33.0%)
LDL, mg/dL	111 ± 27	112 ± 30	110 ± 24	108 ± 31	111 ± 32	106 ± 30
LDL target	71 (34.0%)	38 (36.2%)	33 (31.7%)	71 (38.2%)	35 (42.2%)	36 (35.0%)
Triglycerides, mg/dL	132 [100–164]	113 [95–150][§]	143 [112–182]	138 [91.5–186]	100 [80–170][§]	154 [120–193]
Triglycerides *target*	135 (64.6%)	80 (76.2%)[§]	55 (52.9%)	106 (57.0%)	60 (72.3%)[§]	46 (44.7%)
Number of BP drugs	2 [1–3]	1 [1–3]	2 [1–3]	1 [1–3]	1 [1–3]	2 [1–3]
BP drugs						
1	101 (48.3%)	55 (52.4%)	46 (44.2%)	98 (52.7%)	50 (60.2%)	48 (46.6%)
2	32 (15.3%)	11 (10.5%)	21 (20.2%)	19 (10.2%)	9 (10.8%)	10 (9.7%)
3	39 (18.7%)	21 (20.0%)	18 (17.3%)	37 (19.9%)	11 (13.3%)	26 (25.2%)
4/5	37 (17.7%)	18 (17.1%)	19 (18.3%)	32 (17.2%)	13 (15.7%)	19 (18.5%)
RAS blockers	209 (100%)	105 (100%)	104 (100%)	186 (100%)	83 (100%)	103 (100%)
Diuretics	108 (51.7%)	50 (47.6%)	58 (55.8%)	88 (47.3%)	33 (39.8%)	55 (53.4%)
Calcium Channel Blockers	76 (36.4%)	39 (37.1%)	37 (35.6%)	69 (37.1%)	24 (28.9%)[§]	45 (43.7%)
Beta-blockers	37 (17.7%)	18 (17.1%)	19 (18.3%)	32 (17.2%)	13 (15.7%)	19 (18.4%)
Alpha-blockers	11 (5.3%)	6 (5.7%)	5 (4.8%)	13 (7.0%)	7 (8.4%)	6 (5.8%)
Hypoglycemic therapy						
Diet only	14 (6.7%)	11 (10.5%)	3 (2.9%)	7 (3.8%)	5 (6.0%)	2 (1.9%)
Insulin	57 (27.3%)	27 (25.7%)	30 (28.8%)	53 (28.5%)	23 (27.7%)	30 (29.1%)
Oral drugs	102 (48.8%)	52 (49.5%)	50 (48.1%)	103 (55.4%)	45 (54.2%)	58 (56.3%)
Combined therapy	36 (17.2%)	15 (14.3%)	21 (20.2%)	22 (11.8%)	10 (12.0%)	12 (11.7%)
Statins	132 (63.2%)	42 (40.0%)[§]	90 (86.5%)	112 (60.2%)	30 (36.1%)[§]	82 (79.6%)
Aspirin	102 (48.8%)	40 (38.1%)[§]	62 (59.6%)[#]	95 (51.1%)	31 (37.3%)[§]	64 (62.1%)

Data are N (%), mean ± SD or median [IQR]

UC, usual care arm; MT, multifactorial treatment arm; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; RAS renin-angiotensin system

*$P < 0.05$ vs. men overall; [§]$P < 0.05$ vs. MT arm; [#]$P < 0.05$ vs. men in the corresponding arm

emerged in the achievement of clinical targets between men and women (P for interaction not significant, with 44% and 47% of women and men in MT group achieving at least 3 targets as compared with 16% and 20% of women and men in UC group (Table 2). At the end of intensive treatment period, a more frequent use of statin and aspirin was detected for women and men in MT versus UC group; differences in antihypertensive drugs and hypoglycemic treatment were less marked (Supplementary Table S1). Compliance to pharmacological prescription was excellent in women (93%) and men (94%).

Survival analyses

During follow-up (median 13.0 years, IQR 12.4–13.3), we recorded 262 MACE (48.5% occurring in women) and 189 deaths (53.6% occurring in women). The Kaplan-Meier curves depict the unadjusted comparison of the treatment assignment in women and in men for the two outcomes of interest (Fig. 1). We found that MACE-free

Table 2 Achievement of clinical targets at the end of treatment in women and men in the two study arms

	Women		Men		OR (95% CI) for MT to UC		
	UC	*MT*	*UC*	*MT*	*Women*	*Men*	*P for interaction*
N	94	101	75	98			
Systolic BP target	44 (48%)	72 (77%)	40 (56%)	78 (84%)	4.9 (1.1–21.9)	4.3 (1.6–11.5)	0.47
Diastolic BP target	67 (74%)	76 (82%)	52 (73%)	81 (87%)	2.8 (0.7–10.1)	5.04 (1.2–21.7)	0.09
Systolic and diastolic BP target	40 (44%)	59 (63%)	37 (52%)	73 (78%)	3.9 (1.03–14.9)	4.9 (1.9–12.9)	0.36
HbA1c target	43 (48%)	63 (64%)	31 (43%)	66 (68%)	2.9 (0.9–9.6)	3.2 (0.9–12.1)	0.44
Total cholesterol target	25 (28%)	51 (53%)	22 (31%)	54 (57%)	4.2 (1.3–13.8)	3.7 (0.9–14)	0.48
LDL target	17 (20%)	54 (57%)	15 (23%)	45 (52%)	8.9 (1.9–42.1)	6.5 (2.0-21.1)	0.43
Number of target							
0–2	79 (84%)	57 (56.4%)	60 (80%)	52 (53.1%)			
3–4	15 (16%)	44 (43.6%)	15 (20%)	46 (46.9%)	6.2 (1.5–25.6)	5.03 (0.9–27.4)	0.791

UC, usual care arm; MT, multifactorial treatment arm; BP, blood pressure

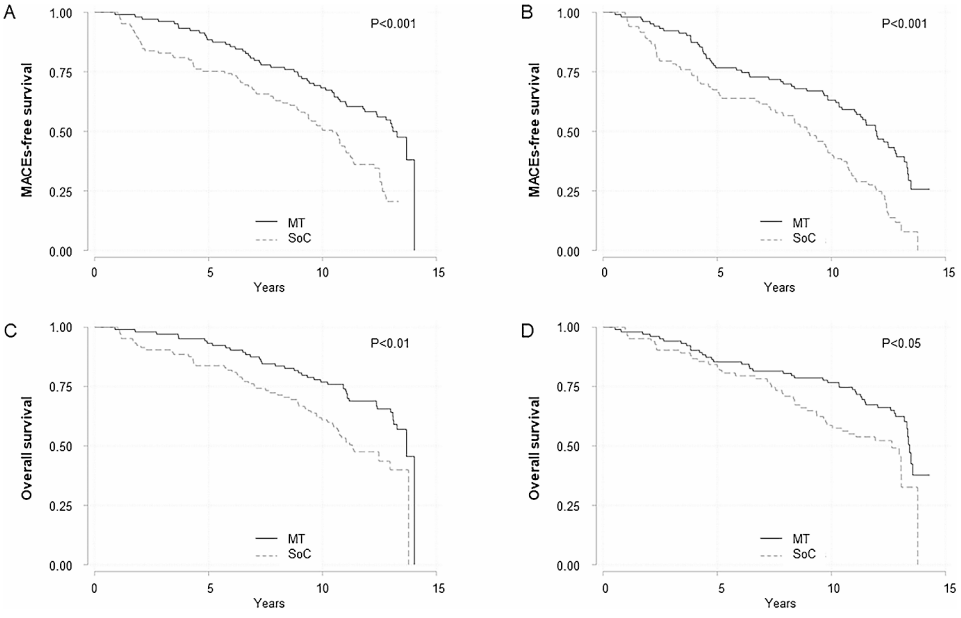

Fig. 1 Kaplan–Meier Estimates of the Composite Endpoint of MACEs during the whole study period (intervention and follow-up) in women (**A**) and men (**B**) and of mortality during the whole study period (intervention and follow-up) in women (**C**) and in men (**D**) receiving Usual Care (UC) or Multifactorial Treatment (MT)

survival was significantly higher in patients receiving multifactorial intervention, independently form sex (Fig. 1A and B). In women, median MACE-free survival was 13.1 years in MT arm and 10.5 years in UC arm while median survival in men was 12.0 years and 8.9 years in MT and UC arms, respectively. A similar difference between treatment groups was detected for overall survival in women and men (Fig. 1C and D).

Compared to the UC group, the risk of MACE in the intensive treatment group was reduced by 52% in women and by 44% in men; the interaction between treatment and gender was not significant in the fully adjusted model (Table 3). Conversely, the difference in mortality risk between women and men according to intensity of treatment was more pronounced. Specifically, patients randomized to multifactorial treatment showed, as compared to UC, a risk of all-cause death reduced by 44% in women and by only 12% in men, with a significant P values for interaction (treatment x gender, $P=0.019$) (Table 3).

Discussion

This secondary analysis of a RCT testifies that no substantial difference emerges when comparing women and men for the achievement of major goals in the treatment of CV risk; similarly, the CV-free survival did not differ between sexes even after adjustment for clinical and laboratory parameters. Conversely, we found a significant sex-interaction for all-cause death indicating a lower mortality risk in women vs. men when multifactorial intensive intervention was implemented.

Table 3 Events recoded during the study and risks of MACE and all-cause death in MT group versus UC group in women and men

Factor	Women		Men		HR (95% CI) for MT versus UC		
	UC	*MT*	*UC*	*MT*	*Women*	*Men*	*P for interaction**
N	105	104	83	103			
MACEs	75 (71.4%)	52 (50.0%)	71 (85.5%)	64 (62.1%)	0.48 (0.33–0.71)	0.56 (0.33–0.97)	0.11
All-cause death	59 (56.2%)	42 (40.4%)	44 (53.0%)	44 (42.7%)	0.56 (0.32–0.96)	0.88 (0.42–1.86)	0.019

UC, usual care arm; MT, multifactorial treatment arm; HR hazard ratio; CI, confidence interval

*Model adjusted for age, SBP, hemoglobin, eGFR, albuminuria, HbA1c, total cholesterol, triglycerides (log-scaled)

In this trial, women and men received similar therapeutic approach aimed at reaching the same BP, lipids and glycemic target. We found that in the long-term (4 years), the intensive goal-oriented therapeutic approach was equally effective in controlling HbA1c (Table 2). In a pooled-analysis of RCTs, a significantly smaller HbA1c reduction emerged in women than in men after starting insulin treatment (−0.2%) with fewer women achieving target HbA1c of <7% (<53 mmol/mol) in comparison with men (27% vs. 33%, respectively) [17]. Similar findings were reported in larger pooled-analysis of 16 RCTs on insulin glargine during a 24-week follow-up; in that study, women were 24% less likely to achieve the goal for HbA1c [30]. However, these findings can be hardly compared with our results because RCTs included in the pooled analyses had short-term follow-up (maximum up to 36 weeks) In this regard, it is important to note that glycemic control with oral hypoglycemic agents may also differ by sex, with metformin and sulfonylureas associated with greater HbA1c decline in men than in women [10]. We cannot test this hypothesis due to the limited sample size even though no significant difference were found at baseline and at the study end in the use of oral drugs (Table 1). The value of intensive metabolic therapy in MT patients is remarkable when considering that by chance those in UC subgroups, independently from sex, started the trial with a better control of HbA1c, and consequently of TG as well, versus MT.

Previous meta-analyses have provided evidence that men and women experience diabetes-related adverse outcomes differently, with women showing an excess risk for stroke, coronary heart disease and all-cause mortality [4–8]. Several factors have been claimed to explain the increased cardiovascular and mortality risk in women including biological factors (higher levels in women of factor VIII and plasminogen activator inhibitor 1, adiponectin, endogenous testosterone, insulin resistance) [31–33], and longer exposure to cardiovascular risk factors in women [34]. The reproductive ageing is an additional aspect that should be considered because the menopausal transition period associates with an increased cardiovascular risk [35]. We did not collect information on menopausal status in our patients; however, the randomization process ensures that hormonal, metabolic and cardiovascular changes reported during the menopausal transition period similarly occurred in MT and UC groups. In addition, despite reproductive ageing is relatively independent form chronological ageing, enrolled women had a mean age (67.7 years) not different from that of two large cohorts of women with type 2 diabetes followed in Italy (68.4 years and 68 years, respectively) [36, 37]. Furthermore, the proportion of women in our study aged > 50 years, the cut-off usually adopted to separate pre- and post-menopausal women [38], was the same in MT and UC groups (96%). These data suggest that menopausal status has a minor impact on our results. On the other hand, the higher risk of adverse cardiovascular outcomes in women with diabetes may be also dependent on sex disparity in the management and treatment of cardiovascular risk factors with a less frequent achievement of therapeutic goals in women [36, 37, 39, 40]. Our data indirectly support this latter hypothesis. Indeed, when treatment of main cardiovascular risk factors was properly intensified, as required by the trial setting, the extent of achieved control did not differ in women and men. This likely conditioned the main result of the absence of difference by sex in the occurrence of cardiovascular events. In addition, the finding that at study entry statin and aspirin use were more frequent in MT than in UC group may suggest a longer exposure of MT patients to these cardioprotective drugs that however was similar in women and men. These two latter findings may contribute to the similar reduced incidence of MACE in women and men enrolled in MT groups.

Multifactorial treatment is effective in reducing all-cause mortality in men and women (Table 3). At variance with cardiovascular outcome, the effect of intensified treatment on all-cause death differed by sex. We found, in fact, that intensive multifactorial treatment significantly reduced the risk of mortality in women but not in men (Table 3). The reason for the global survival advantage in women associated with more aggressive therapeutic approach is not readily apparent. We can postulate that multifactorial treatment may have produced a more evident improvement in mortality risk because more women at baseline had a GFR value below 60 mL/min/1.73m^2 (51.7% vs. 34.9%). In this condition, in fact, the baseline risk in women is higher than in men [41], and, therefore, it is likely that treating aggressively and simultaneously blood pressure, glycaemia and dyslipidemia may have

reduced the association between low GFR and mortality in women more efficaciously [41].

An original aspect of our study is that this study analysis allows assessing the sex difference on cardiovascular and mortality risk in the absence of discrepancy in the management and treatment of risk factors as women and men were similarly treated to achieve the same therapeutic goal. This uniform management between women and men cannot be confirmed by previous meta-analyses where only observational cohort studies were included [4–8]. Indeed, in comparison with men, women enrolled in those early cohorts were likely exposed to the same concerns for a sub-optimal treatment [36, 37, 39, 40] thus explaining why the risk of adverse outcomes was found consistently higher in women [4–8]. As a further difference, it is remarkable that in previous studies women were underrepresented (from 33 to 45%) as compared with our trial (53%).

Our study has several strengths. First, this represent a proper analysis to explore differences in cardiovascular and mortality risks between women and men because by analyzing groups with the same strategy we overcome possible biases due to discrepancies in therapeutic approach. Second, our results show that an intensive multifactorial treatment on MACEs is equally effective in both sexes. Third, randomization by center makes the study closer to real-life clinical practice. In this regard, it is noteworthy that the UC arm showed a more favorable clinical picture at baseline in comparison with the intervention arm. This finding reasonably excludes the possibility of selecting in UC arm those physicians with lower attitude to adhere to clinical guidelines. However, the cluster-randomized design has a number of limitations, related to the lack of blind assignment, lower power and precision in comparison with individually randomized trial and a reduced ability to control for both known and unknown confounder. Main additional limitation is inherent to the observational nature of the study that cannot test any cause-effect relationship. Furthermore, we did not collect clinical and laboratory data during the follow-up occurring after intervention phase but only events of interest (death and cardiovascular events) thus precluding the possibility of identify a prevailing factor definitely associated with risk reduction. However, our original aim was to evaluate efficacy of a global approach rather than effects of single interventions. Finally, we did not consider the efficacy of newer drugs now considered the standard of care for DKD, such as SGLT2i and GLP-1RA that were not immediately available at the time of the study. However, we do not expect that using SGLT2i would have changed our results because the protective effect of these drugs on MACEs occurrence do not differ between women and men [42, 43].

In conclusion, we provided evidence that the implementation of a uniform and multifactorial management is effective in reducing MACEs in both sexes by a similar extent. This therapeutic approach is associated with a survival advantage in women as compared with men and it may represent an important rationale to motivate physicians in overcoming their therapeutic inertia often encountered in female patients (falsely believed at low risk), as well as to encourage patients of both sexes at improving their adherence to multidrug therapy.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02371-3.

Supplementary Material 1

Acknowledgements

NID-2 Study Group Investigators: U. Amelia, C. Acierno, P. Calatola, O. Carbonara, A. Caturano, G. Conte, G. Corigliano, M. Corigliano, R. D'Urso, A. De Matteo, L. De Nicola, N. De Rosa, E. Del Vecchio, G. Di Giovanni, A. Gatti, S. Gentile, L. Gesuè, L. Improta, A. Lampitella Jr, A. Lampitella, A. Lanzilli, N. Lascar, S. Masi, P. Mattei, V. Mastrilli, P. Memoli, R. Minutolo, R. Nasti, A. Pagano, M. Pentangelo, E. Pisa, E. Rossi, F.C. Sasso, S. Sorrentino, R. Torella, R. Troise, P. Trucillo, A. A. Turco, S. Turco, F. Zibella, L. Zirpoli.

Author contributions

RM, LDN and FCS were involved in the conception and study design and interpretation of the results. RG, LR, AC, EV, CS, RMa., were involved in the conduct of the study and interpretation of the results. VS and PC were involved in the conception and the analysis of the results. RM, LDN and FCS wrote the first draft of the manuscript, All authors edited, reviewed, and approved the final version of the manuscript.

Funding

The study was funded by Ministero dell'Università e della Ricerca, PRIN 2007 (ID: 2007PSYLRX_003). Dr. Raffaele Galiero, and Dr. Vittorio Simeon were supported by the Programma VALERE, University of Campania "Luigi Vanvitelli". No funder had an involvement in data collection, analysis, or interpretation; trial design; patient recruitment; or any aspect pertinent to the study.

Data availability

FCS is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The datasets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest

Roberto Minutolo has been member of Advisory Boards for Astellas, and invited speaker at meetings supported by Amgen, Astellas, Vifor Pharma, Bayer, Astrazeneca. Luca De Nicola has received fees for scientific consultation and/or lectures by Astellas, AstraZeneca, Bayer, Novo. Ferdinando Carlo Sasso has been member of Advisory Boards for Boehringer and for Ely-Lilly and has received fees for scientific consultation and/or lectures by Jansen, Roche Diagnostics, Novo Nordisk, Sanofi, MSD, Astrazeneca. Vittorio Simeon, Paolo Chiodini, Raffaele Galiero, Luca Rinaldi, Raffaele Marfella, Celestino Sardu, have no conflict of interest to disclose.

Author details

[1]Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Piazza Luigi Miraglia 2, 80138 Naples, Italy
[2]Medical Statistics Unit, Department of Physical and Mental Health and Preventive Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy

[3]Department of Medicine and Health Sciences "Vincenzo Tiberio", University of Molise, Campobasso, Italy

Received: 8 June 2024 / Accepted: 21 July 2024
Published online: 05 August 2024

References

1. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the global burden of Disease Study 2021. Lancet. 2023;402(10397):203–34.
2. Rawshani A, Rawshani A, Franzén S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2018;379(7):633–44.
3. Minutolo R, Gabbai FB, Provenzano M, et al. Cardiorenal prognosis by residual proteinuria level in diabetic chronic kidney disease: pooled analysis of four cohort studies. Nephrol Dial Transpl. 2018;33(11):1942–9.
4. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ. 2006;332(7533):73–8.
5. Prospective Studies Collaboration, Asia Pacific Cohort Studies Collaboration. Sex-specific relevance of diabetes to occlusive vascular and other mortality: a collaborative meta-analysis of individual data from 980 793 adults from 68 prospective studies. Lancet Diabetes Endocrinol. 2018;6(7):538–46.
6. Xu G, You D, Wong L, et al. Risk of all-cause and CHD mortality in women versus men with type 2 diabetes: a systematic review and meta-analysis. Eur J Endocrinol. 2019;180(4):243–55.
7. Ohkuma T, Komorita Y, Peters SAE, Woodward M. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. Diabetologia. 2019;62:1550–60.
8. Peters SAE, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and metanalysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. Lancet. 2014;383(9933):1973–80.
9. Clemens KK, Woodward M, Neal B, Zinman B. Sex disparities in cardiovascular outcome trials of populations with diabetes: a systematic review and meta-analysis. Diabetes Care. 2020;43(5):1157–63.
10. Kautzky-Willer A, Leutner M, Harreiter J. Sex differences in type 2 diabetes. Diabetologia. 2023;66(6):986–1002.
11. Funck KL, Bjerg L, Isaksen AA, Sandbaek A, Grove EL. Gender disparities in time-to-initiation of cardioprotective glucose-lowering drugs in patients with type 2 diabetes and cardiovascular disease: a Danish nationwide cohort study. Cardiovasc Diabetol. 2022;21(1):279.
12. Harreiter J, Fadl H, Kautzky-Willer A, Simmons D. Do women with diabetes need more intensive action for cardiovascular reduction than men with diabetes? Curr Diab Rep. 2020;20(11):61.
13. Puri R, Nissen SE, Shao M, et al. Sex-related differences of coronary atherosclerosis regression following maximally intensive statin therapy: insights from SATURN. JACC Cardiovasc Imaging. 2014;7(10):1013–22.
14. Walker EA, Molitch M, Kramer MK, et al. Adherence to preventive medications: predictors and outcomes in the diabetes Prevention Program. Diabetes Care. 2006;29(9):1997–2002.
15. Onishi Y, Oura T, Matsui A, Matsuura J, Iwamoto N. Analysis of efficacy and safety of dulaglutide 0.75 mg stratified by sex in patients with type 2 diabetes in 2 randomized, controlled phase 3 studies in Japan. Endocr J. 2017;64(5):553–60.
16. Raparelli V, Elharram M, Moura CS, et al. Sex differences in cardiovascular effectiveness of newer glucose-lowering drugs added to metformin in type 2 diabetes mellitus. J Am Heart Assoc. 2020;9(1):e012940.
17. Kautzky-Willer A, Kosi L, Lin J, Mihaljevic R. Gender based differences in glycaemic control and hypoglycaemia prevalence in patients with type 2 diabetes: results from patient-level pooled data of six randomized controlled trials. Diabetes Obes Metab. 2015;17(6):533–40.
18. Eisenberg E, Di Palo KE, Piña IL. Sex differences in heart failure. Clin Cardiol. 2018;41(2):211–6.
19. Goldstein LB, Amarenco P, Lamonte M, et al. Relative effects of statin therapy on stroke and cardiovascular events in men and women: secondary analysis of the Stroke Prevention by Aggressive reduction in cholesterol levels (SPARCL) study. Stroke. 2008;39(9):2444–8.
20. Manteuffel M, Williams S, Chen W, Verbrugge RR, Pittman DG, Steinkellner A. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. J Womens Health (Larchmt). 2014;23(2):112–9.
21. Kautzky-Willer A, Harreiter J. Sex and gender differences in therapy of type 2 diabetes. Diabetes Res Clin Pract. 2017;131:230–41.
22. Sasso FC, Pafundi PC, Simeon V, et al. Efficacy and durability of multifactorial intervention on mortality and MACEs: a randomized clinical trial in type-2 diabetic kidney disease. Cardiovasc Diabetol. 2021;20(1):145.
23. Sasso FC, Simeon V, Galiero R, et al. The number of risk factors not at target is associated with cardiovascular risk in a type 2 diabetic population with albuminuria in primary cardiovascular prevention. Post-hoc analysis of the NID-2 trial. Cardiovasc Diabetol. 2022;21(1):235.
24. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2005;28(Suppl 1):S4–36. Erratum in: Diabetes Care. 2005;28(4):990.
25. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens. 2003;21(6):1011–53.
26. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. Third joint Task Force of European and other societies on Cardiovascular Disease Prevention in Clinical Practice. European guidelines on cardiovascular disease prevention in clinical practice. Third joint Task Force of European and other societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 2003;24(17):1601–10.
27. Powers WJ, Rabinstein AA, Ackerson T, American Heart Association Stroke Council. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018;49(3):e46–110.
28. Ponikowski P, Voors AA, Anker SD, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129–200.
29. Thygesen K, Alpert JS, Jaffe AS, ESC Scientific Document Group, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019;40(3):237–69.
30. Owens DR, Landgraf W, Frier BM, et al. Commencing insulin glargine 100 U/mL therapy in individuals with type 2 diabetes: determinants of achievement of HbA1c goal less than 7.0. Diabetes Obes Metab. 2019;21(2):321–9.
31. Wannamethee SG, Papacosta O, Lawlor DA, Whincup PH, Lowe GD, Ebrahim S, Sattar N. Do women exhibit greater differences in established and novel risk factors between diabetes and non-diabetes than men? The British Regional Heart Study and British women's Heart Health Study. Diabetologia. 2012;55(1):80–7.
32. 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(11):1288–99.
33. Donahue RP, Rejman K, Rafalson LB, Dmochowski J, Stranges S, Trevisan M. Sex differences in endothelial function markers before conversion to prediabetes: does the clock start ticking earlier among women? The Western New York Study. Diabetes Care. 2007;30(2):354–9.
34. Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. Diabetologia. 2014;57(8):1542–51.
35. Mehta JM, Manson JE. The menopausal transition period and cardiovascular risk. Nat Rev Cardiol. 2024;21(3):203–11.
36. Rossi MC, Cristofaro MR, Gentile S, et al. Sex disparities in the quality of diabetes care: biological and cultural factors may play a different role for different outcomes: a cross-sectional observational study from the AMD annals initiative. Diabetes Care. 2013;36(10):3162–8.
37. Penno G, Solini A, Bonora E, et al. Gender differences in cardiovascular disease risk factors, treatments and complications in patients with type 2 diabetes: the RIACE Italian multicenter study. J Intern Med. 2013;274(2):176–91.
38. Boggia J, Thijs L, Hansen TW, et al. Ambulatory blood pressure monitoring in 9357 subjects from 11 populations highlights missed opportunities for cardiovascular prevention in women. Hypertension. 2011;57:397–405.
39. 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(3):514–20.

40. Gouni-Berthold I, Berthold HK, Mantzoros CS, Bohm M, Krone W. Sex disparities in the treatment and control of cardiovascular risk factors in type 2 diabetes. Diabetes Care. 2008;31(7):1389–91.
41. Nitsch D, Grams M, Sang Y, et al. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. BMJ. 2013;346:f324.
42. Rådholm K, Zhou Z, Clemens K, Neal B, Woodward M. Effects of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes in women versus men. Diabetes Obes Metab. 2020;22(2):263–6.
43. Young KG, McInnes EH, Massey RJ, et al. Treatment effect heterogeneity following type 2 diabetes treatment with GLP1-receptor agonists and SGLT2-inhibitors: a systematic review. Commun Med (Lond). 2023;3(1):131.

Publisher's Note