Diabete e cuore: come le differenze di genere influiscono sulle terapie?

Emanuela Orsi

UOS Diabetologia

Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico

Disclusures

La Dottoressa Emanuela Orsi negli ultimi due anni ha percepito compensi per Board Scientifici, relazioni a Convegni e Docenze

- Università degli Studi di Milano
- Eli Lilly
- Novo Nordisk
- Sanofi
- Astra Zeneca

Perché parlare di Diabete, cuore e genere

- Il diabete è un importante fattore di rischio per le malattie cardio-vascolari e renali. Il rischio di andare incontro ad eventi cardiovascolari è più elevato nelle donne che negli uomini

- Si evidenzia una differente risposta genere-specifica agli interventi terapeutici. Le donne sono meno studiate nei trial clinici, meno trattate o trattate con meno attenzione e determinazione, nella pratica clinica e nel raggiungimento degli obiettivi terapeutici.

- In Italia l'attenzione alla cura delle donne diabetiche è pressoché sovrapponibile a quella prestata agli uomini. Ciò nonostante, i benefici che la donna ne trae sono inferiori, con un minor numero di donne che raggiungono i livelli di protezione in termini di controllo della glicemia, della pressione arteriosa, della colesterolemia.

- Il diabete, nella donna, assume poi aspetti e sfumature del tutto peculiari a seconda delle fasi della vita. Può rappresentare un problema sociale nell'età giovanile, un problema ulteriore nell'età fertile, in particolare in occasione di una gravidanza e un problema di gestione nell'età post-menopausale, dove il rischio cardiovascolare aumenta in modo esponenziale.

Agenda

- Differenze di genere nella diagnosi di diabete
- Differenza di genere nei fattori di rischio
- Differenza di genere nelle complicanze
- Differenza di genere e terapia farmacologica

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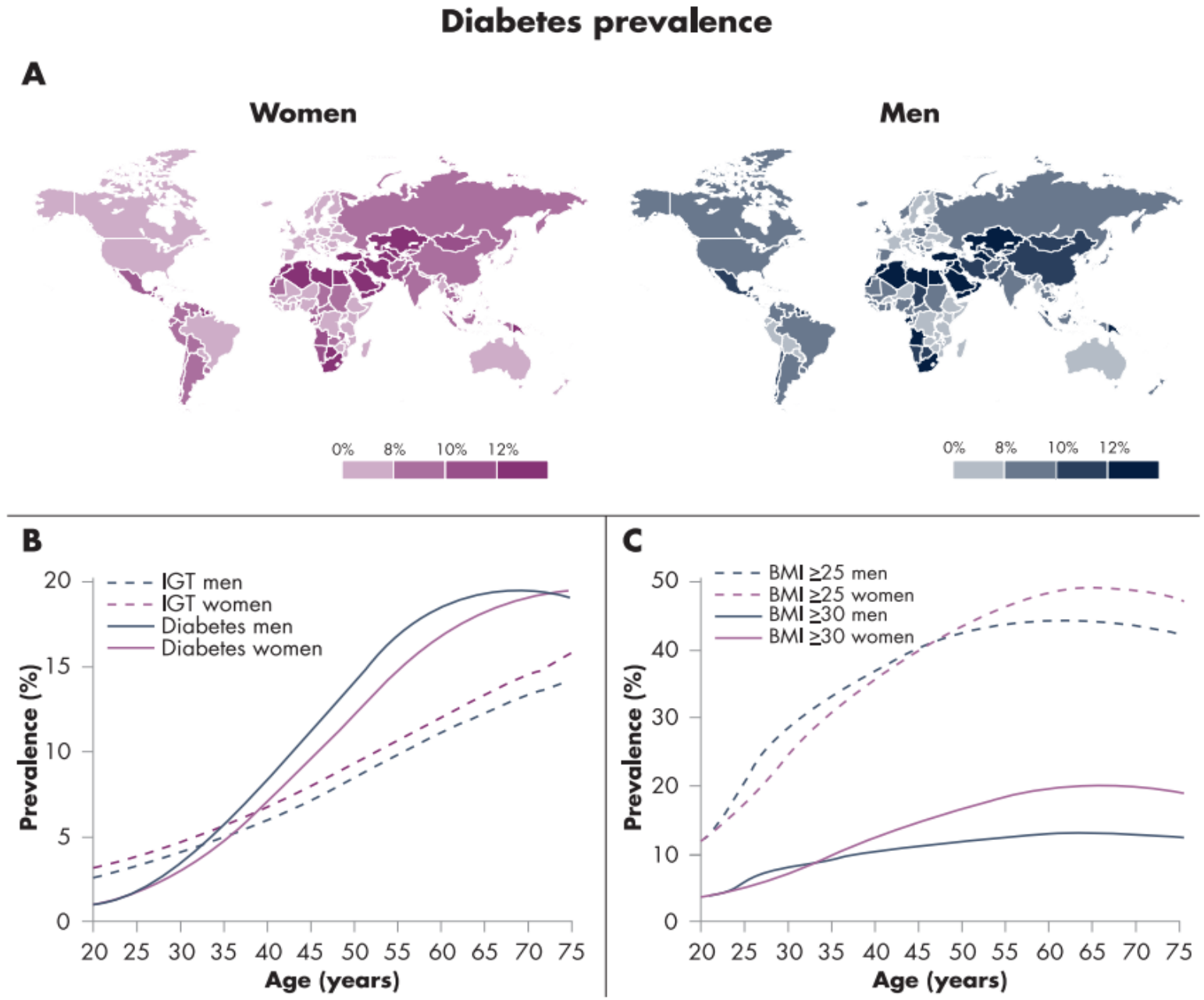

Kautzky-Willer A et al, Endocrine Rev, 2016

Factors contributing to Sex and Gender differences in T2DM

Biological factors

Genetic and epigenetic factors:

- Epigenetic modifiers
- Sex-specific gene expression
- Mitochondrial function
- Sex chromosomes and dimorphic gene expression

Hormonal factors:

- Puberty
- Reproductive age
- Menopause
- Imbalance of androgens in men

Biological Risk Factors:

- Body fat distribution
- Expression of adipokines
- Mass and activity of brown adipose tissue
- Insulin sensitivity
- Energy balance

Non- biological factors

- Socio-economic status
- Lifestyle
- Culture and education
- Behavioral factors
- Environmental factors
- Work activity and family role
- Nutrition and physical activity

Comorbidities

- Obesity
- Depression and anxiety
- Physical limitations
- Cognitive impairment
- Geriatric syndromes

Russo GT et al, Nutr Metab Cardiovasc Dis, 2022

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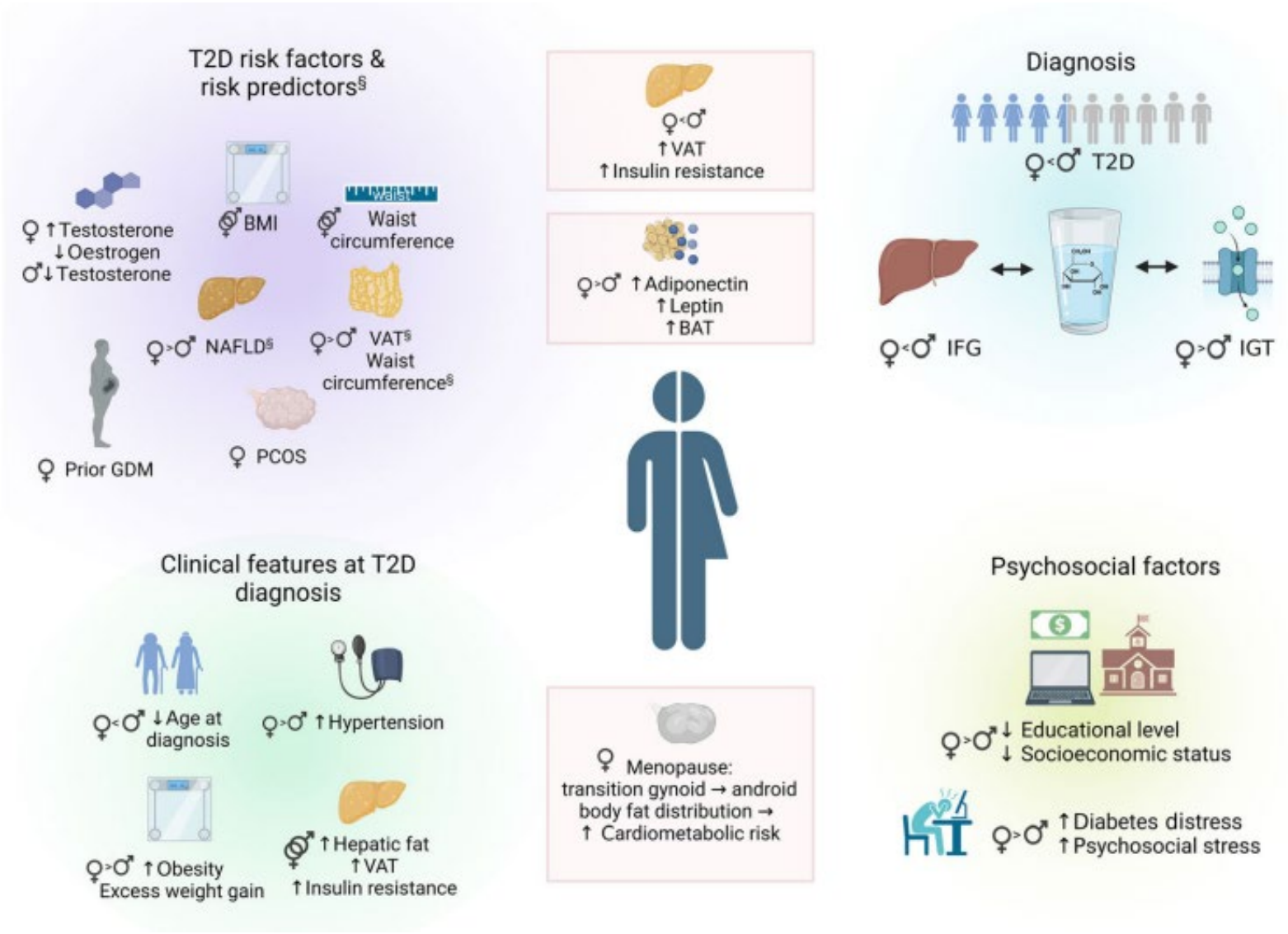
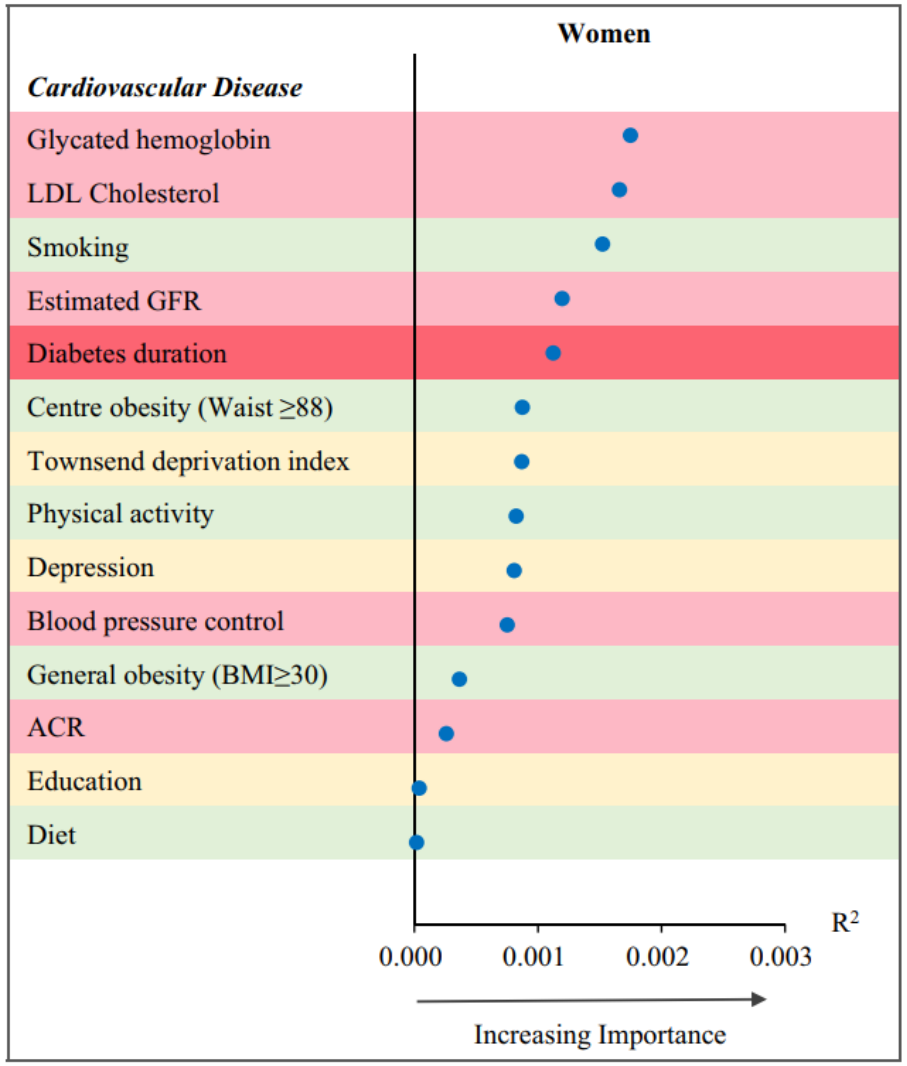
Sex-specific risks and sex and gender differences in risk factors and clinical features of men and women with type 2 diabetes

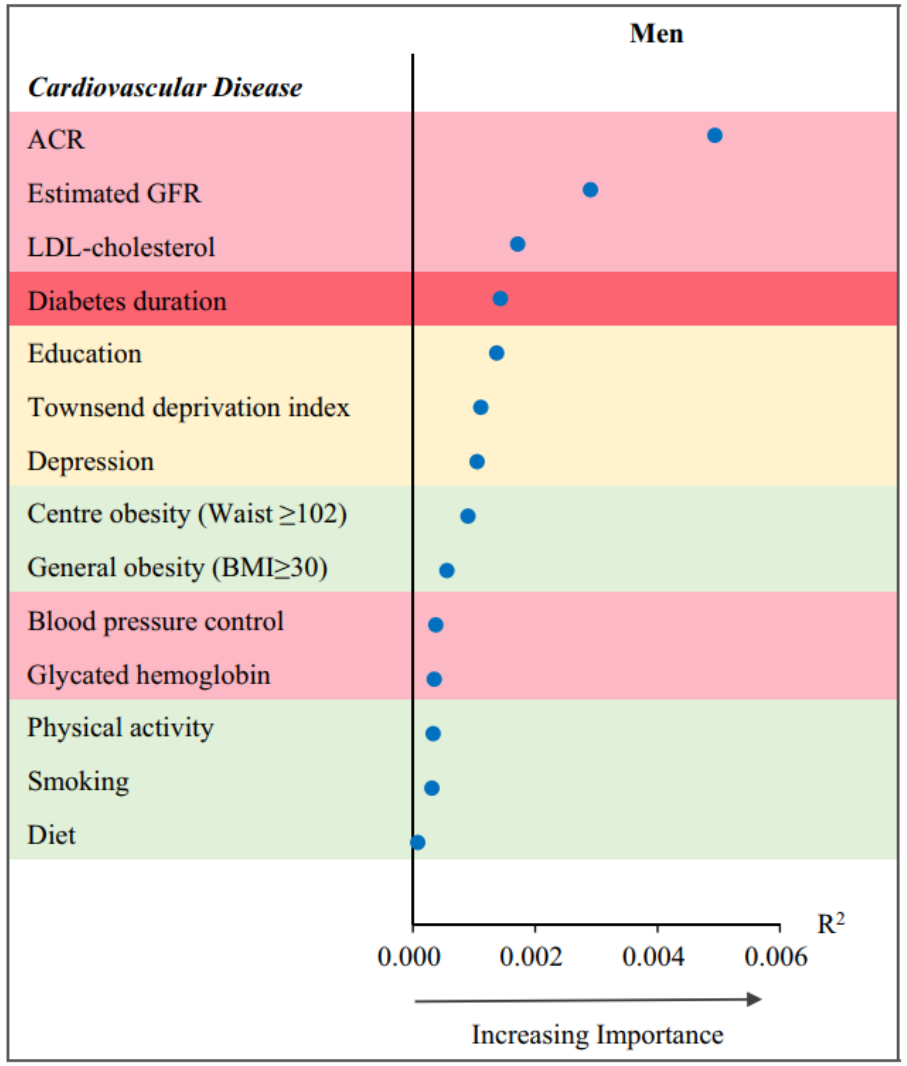


Kautzky-Willer A et al, Diabetologia, 2023

Risk factor control and incident cardiovascular disease in patients with diabetes: Sex-specific relations

17 260 patients UK Biobank





Diabetes Duration
Clinical Biomarkers
Socioeconomic and Psychological Factors
Lifestyle Factors

CONCLUSION

The degree of risk factors control is more strongly associated with a lower risk of CVD in women that in men with diabetes , and a well-managed risk factors has a potential to eliminate the diabetes-related excess risk of CVD

Wang X et al, Diabetes Obes Metab, 2024

Women show worse control of type 2 diabetes and cardiovascular disease risk factors than men

Proportion (%) of men and women out of target for HbA1c and the cardiovascular risk factors

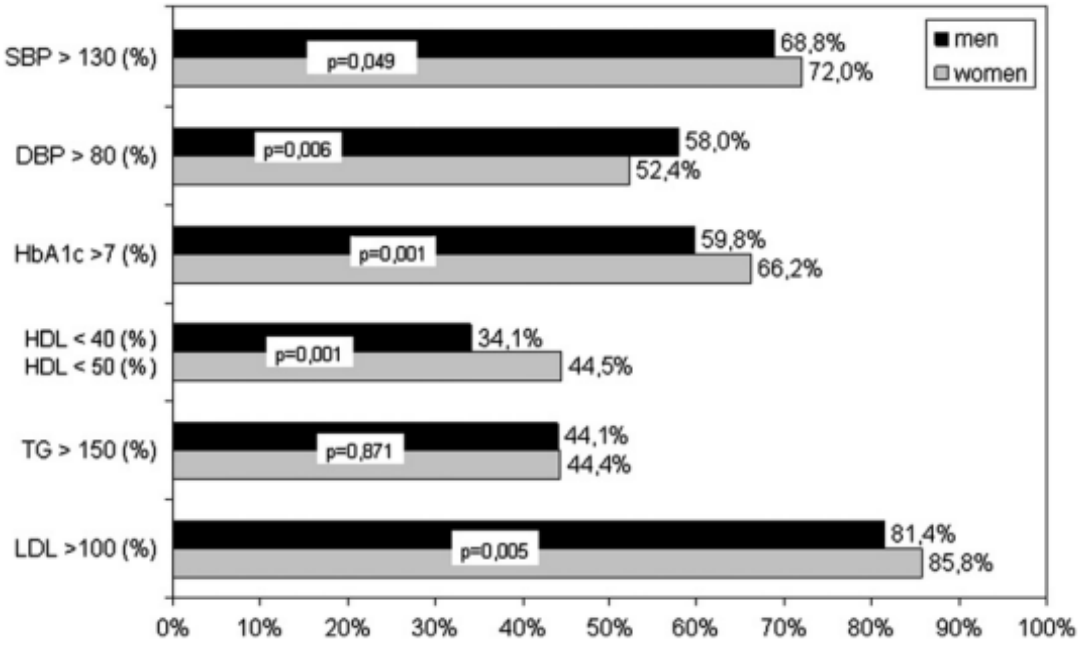


Table 1 Clinical characteristics and major cardiovascular disease risk factors in men and women by abdominal obesity status.

Variables	Without abdominal obesity		*p*	With abdominal obesity		*p*
	Women (n = 159)	Men (n = 696)		Women (n = 963)	Men (n = 543)	
Age (years)	62 ± 5	60 ± 6	**0.008**	61 ± 5	60 ± 5	0.087
Diabetes duration (years)	9 (8)	9 (7)	0.652	9 (7)	8 (7)	0.093
Waist circumference (cm)	80.8 ± 6.0	93.6 ± 6.1	**0.001**	103.5 ± 10.9	110.0 ± 7.1	**0.001**
BMI (Kg/m^2)	24.8 ± 3.9	26.5 ± 2.8	**0.001**	31.7 ± 5.5	31.4 ± 3.8	0.312
Systolic blood pressure (mmHg)	142 ± 18	140 ± 16	0.154	143 ± 17	142 ± 15	0.198
Diastolic blood pressure (mmHg)	84 ± 9	84 ± 9	0.762	84 ± 9	86 ± 9	**0.001**
Heart rate (beat/min)	73 ± 8	71 ± 10	**0.032**	75 ± 11	72 ± 10	**0.001**
Fasting plasma glucose (mg/dL)	159 ± 52	151 ± 43	**0.042**	161 ± 46	157 ± 40	0.141
Glycated haemoglobin (%)	7.6 ± 1.3	7.4 ± 1.3	**0.042**	7.7 ± 1.4	7.6 ± 1.4	**0.025**
HDL cholesterol (mg/dL)	56 ± 14	47 ± 12	**0.001**	52 ± 13	45 ± 10	**0.001**
Triglycerides (mg/dL)	120 (92)	135 (93)	0.152	142 (95)	153 (111)	**0.001**
LDL cholesterol (mg/dL)	140 ± 36	131 ± 34	**0.008**	135 ± 34	129 ± 34	**0.001**
Non-HDL cholesterol (mg/dL)	167 ± 39	161 ± 37	**0.050**	167 ± 37	163 ± 38	**0.039**
Fibrinogen (mg/dL)	330 ± 92	318 ± 73	0.124	345 ± 84	327 ± 80	**0.001**
Current smokers (%)	38 (24.2%)	210 (30.2%)	0.145	157 (16.4%)	133 (24.6%)	**0.001**

Abdominal obesity is defined as waist circumference ≥ 88 cm for women and ≥102 cm for men. Data is given as mean ± SD or median and (inter-quartile range) or as number and (%).
Significant values ($p < 0.05$) are highlighted in bold.

Tot 2361 , 47.5% F

Franzini L et al, Nutr Metab Cardiovasc Dis, 2012
On behalf of the MIND.IT Study Group of the Italian Society of Diabetology

Sex Disparities in the Treatment and Control of Cardiovascular Risk Factors in Type 2 Diabetes: data from DUTY registry

	With CVD (n = 9,521 men and 8,050 women)			Without CVD (n = 12,417 men and 14,905 women)		
	OR	95% CI	*P*	OR	95% CI	*P*
CVD risk factors not in control (unadjusted)						
SBP ≥140 mmHg	1.20	1.12–1.27	<0.0001	1.08	1.03–1.13	0.003
LDL cholesterol ≥130 mg/dl	1.33	1.25–1.42	<0.0001	1.21	1.15–1.28	<0.0001
A1C ≥ 8%	1.04	0.97–1.11	0.32	1.01	0.95–1.07	0.82
CVD risk factors not in control (multiple adjusted)						
SBP ≥140 mmHg	1.19	1.11–1.29	<0.0001	1.0	0.95–1.06	0.99
LDL cholesterol ≥130 mg/dl	1.44	1.33–1.55	<0.0001	1.25	1.18–1.32	<0.0001
A1C ≥8%	1.15	1.06–1.25	0.0009	1.04	0.97–1.1	0.29
Intensity of medication management (unadjusted)						
≥2 antihypertensive agents	1.09	1.02–1.16	0.014	1.19	1.12–1.26	<0.0001
≥1 lipid-lowering drug	0.76	0.72–0.81	<0.0001	0.99	0.93–1.04	0.62
≥2 oral antihyperglycemic agents or insulin	1.11	1.03–1.18	0.003	1.05	0.995–1.11	0.073
Intensity of medication management (multiple adjusted)						
≥2 antihypertensive agents	0.998	0.92–1.08	0.97	1.01	0.95–1.08	0.71
≥1 lipid-lowering drug	0.85	0.79–0.91	<0.0001	0.99	0.93–1.05	0.65
≥2 oral antihyperglycemic agents or insulin	1.04	0.95–1.13	0.40	0.96	0.9–1.03	0.25

*Outcomes analyzed as binary variables (≥140 vs. <140 mmHg for SBP, ≥130 vs. <130 mg/dl for LDL cholesterol, and ≥8.0 vs. <8.0% for A1C) according to the levels considered not in control and therefore requiring more action, as recommended by the American Diabetes Association. More intense medication management was defined as the use of two or more drug classes of antihypertensive agents for hypertension, of one or more lipid-lowering agents for lipid management, and of two or more oral agents or insulin for antihyperglycemic treatment.

CONCLUSIONS Women with diabetes and CVD have poorer control of important modifiable risk factors than men and receive less intensified lipid-lowering treatment.

Gouni-Berthold I et al, Diabetes Care, 2008

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
$eGFR^{CKD-EPI}$, 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

Penno G et al, J Intern Med, 2013

Subjects on target for CVD risk factors in the RIACE Cohort

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

Penno G et al, J Intern Med, 2013

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Available online at www.sciencedirect.com

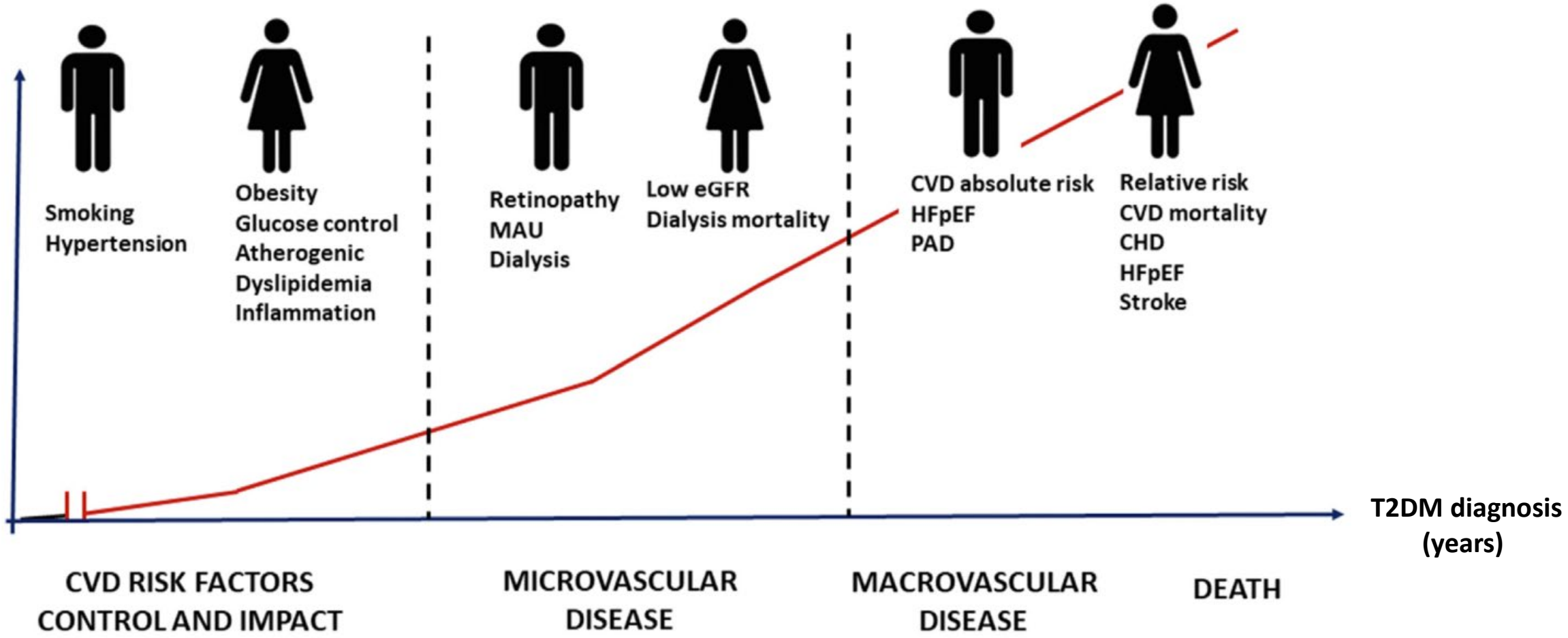
Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd 2022

REVIEW

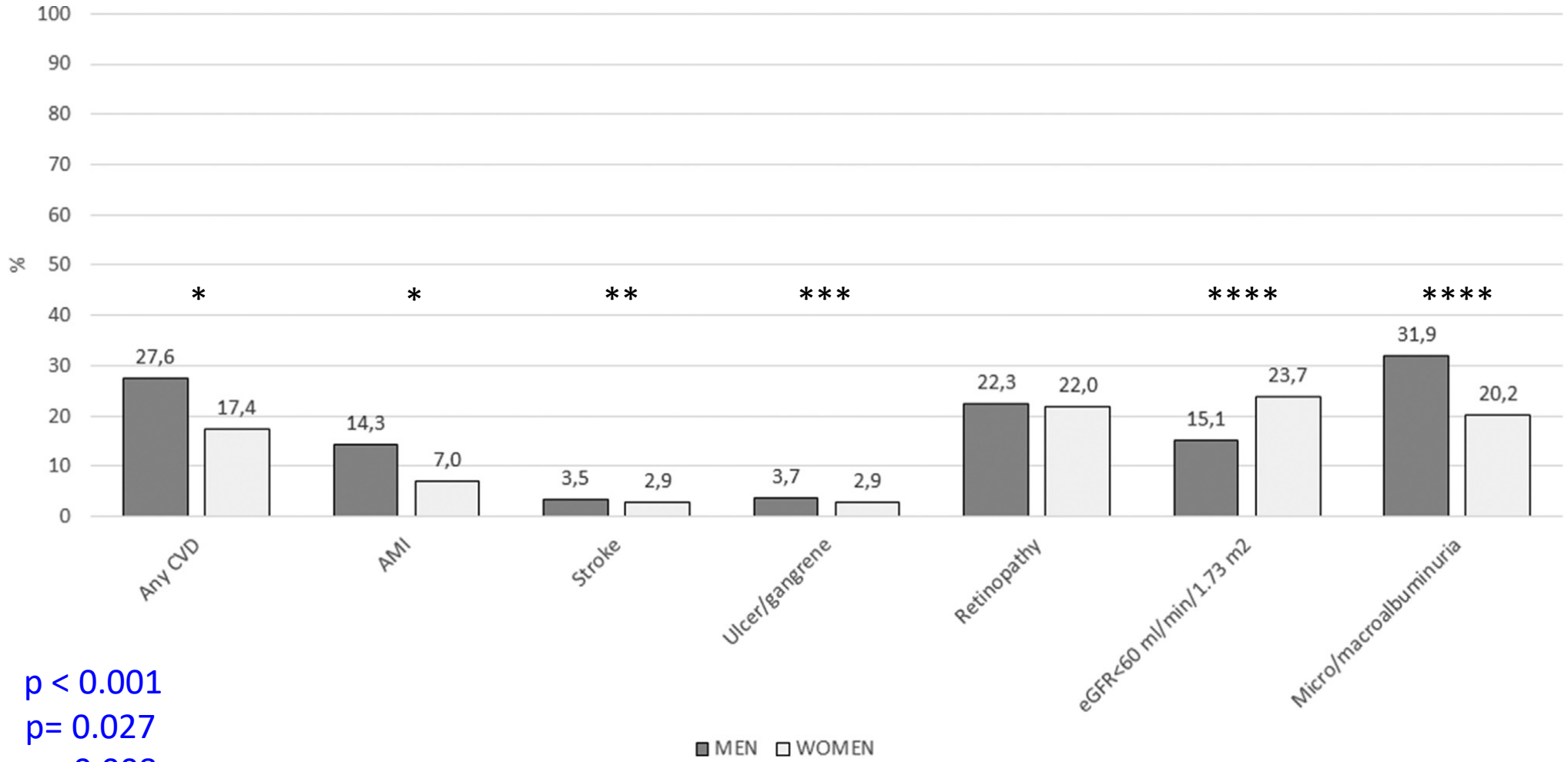
Sex- and gender-differences in chronic long-term complications of type 1 and type 2 diabetes mellitus in Italy

G.T. Russo [a,**], V. Manicardi [b], M.C. Rossi [c], E. Orsi [d], A. Solini [e,*]



Nutr Metab Cardiovasc Dis, 2022

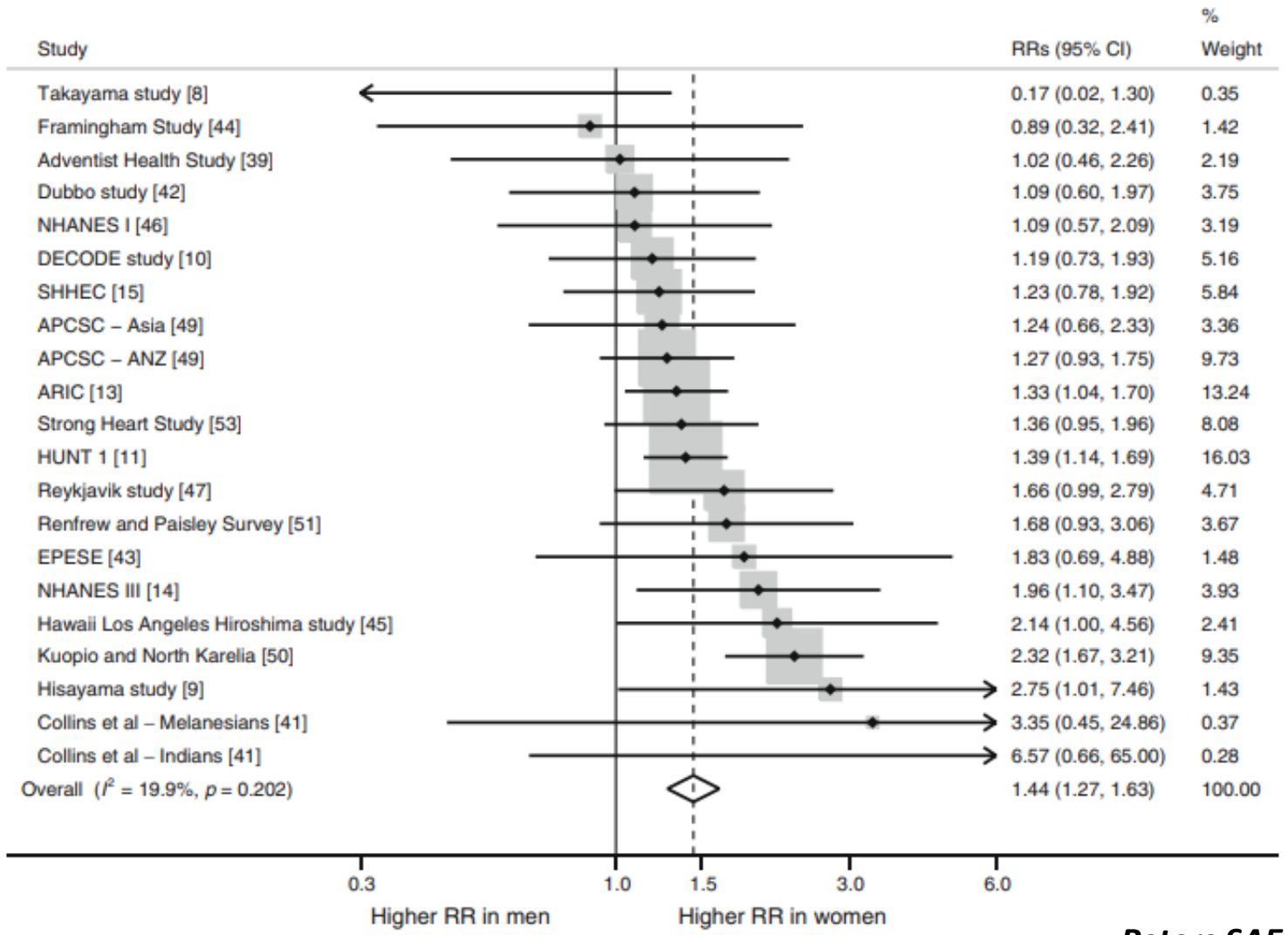
Prevalence of complications in subjects from the RIACE cohort



* p < 0.001
** p= 0.027
*** p= 0.008
**** p < 0.0001

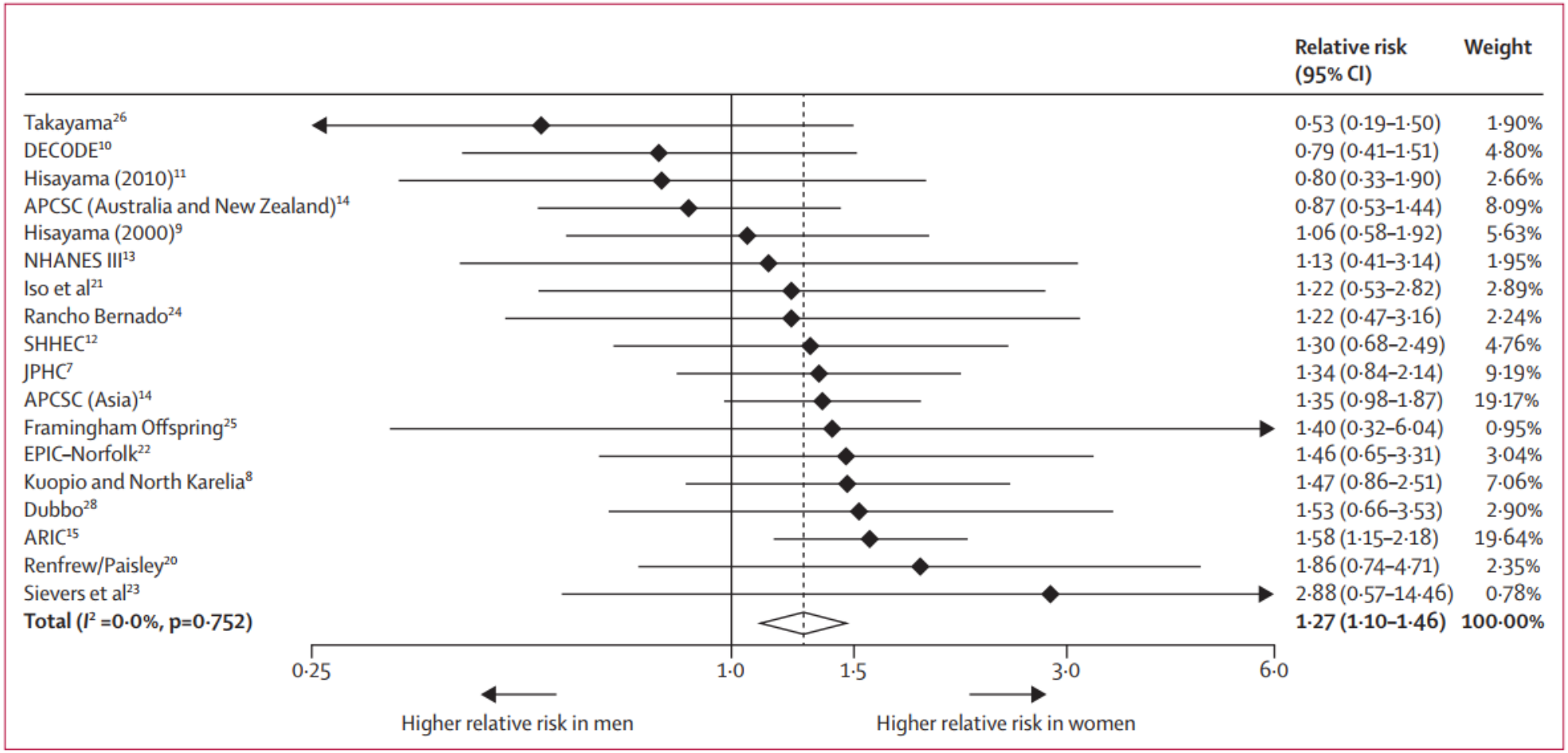
Russo G et al, NMCD, 2022

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



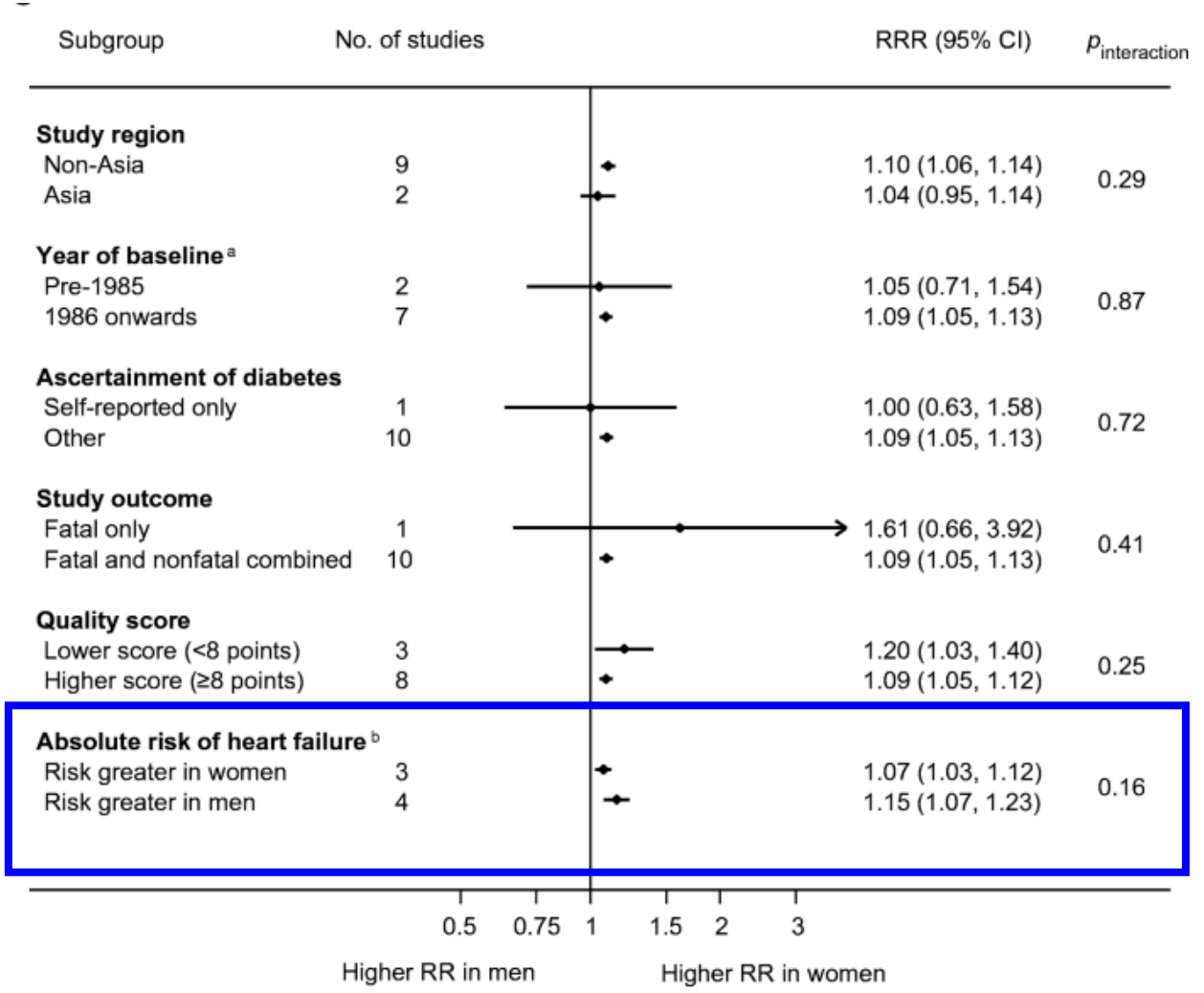
Peters SAE et al, Diabetologia, 2014

Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes



Peters SAE et al,Lancet , 2014

Subgroup analyses of multiple adjusted women to men risk for heart failure



Conclusions/interpretation

The excess risk of heart failure associated with diabetes is significantly greater in women with diabetes than in men with diabetes.

Ohkuma T et al, Diabetologia, 2019

Agenda

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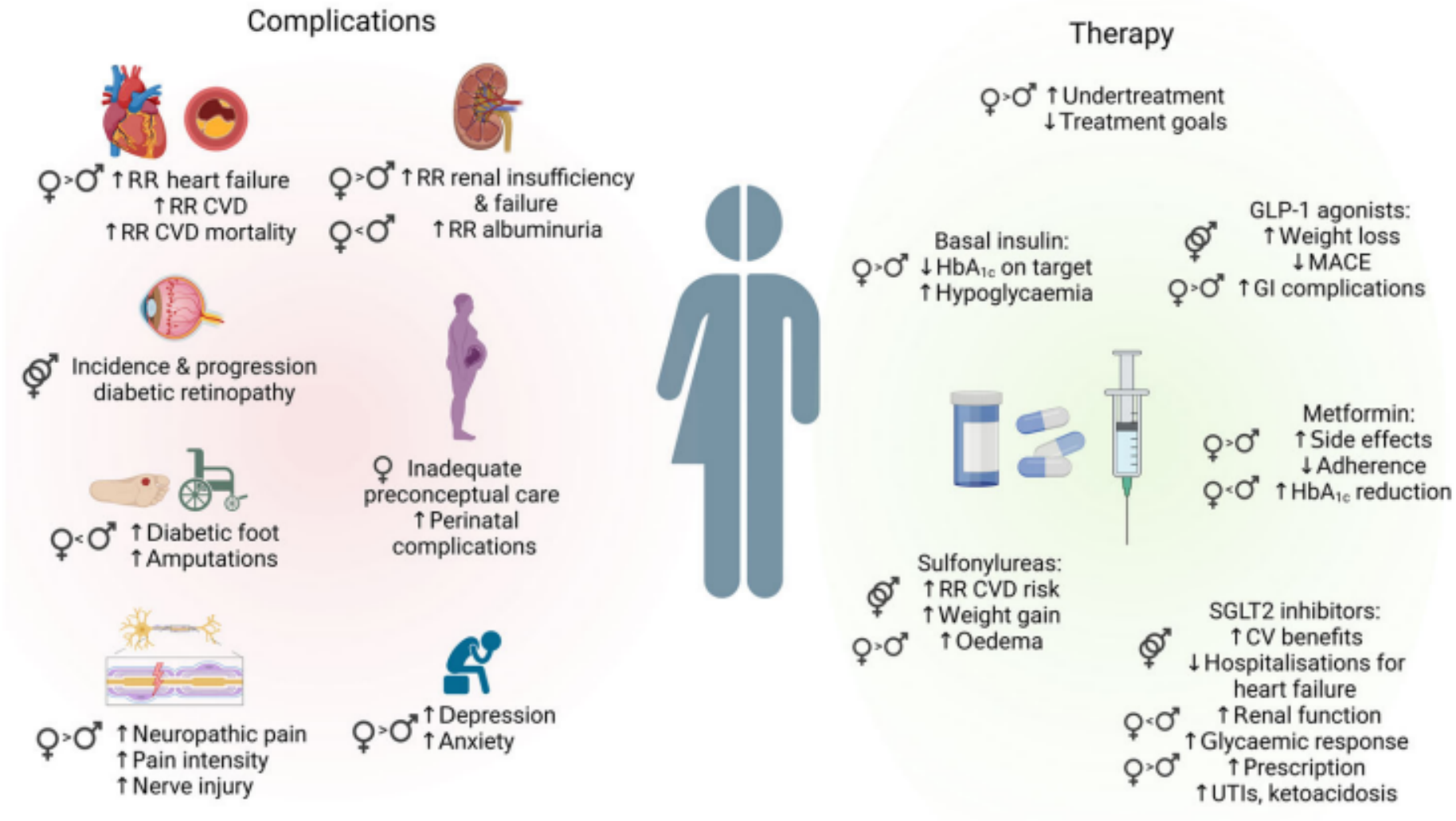
Sex differences in the complications and possible effects of pharmacological therapy and management of patients with type 2 diabetes



Kautzky-Willer A et al, Diabetologia, 2023

Potential sex and gender differences in (adverse) effects of glucose-lowering- and cardiovascular medications in patients with type 2 diabetes

Therapy	Efficacy and adverse effects	Notes
Metformin	Glucose metabolism	Men: greater HbA_{1c} reduction. Women: greater reduction of body weight [98]
	Adherence	Women: less adherent to therapy [96]
	Adverse effects	Women: more likely to suffer side effects (e.g. gastrointestinal symptoms) [96]; increased hospitalisation rate [97]
	Possible fetal programming effects	Mother undergoing metformin therapy: higher rates of infants born SGA and of childhood adiposity, possibly with slightly higher risk in boys [121]; father undergoing metformin therapy: exposure associated with major birth defects, particularly genital birth defects in boys [122]
Sulfonylureas	Glucose metabolism	Male sex and lower BMI: greater HbA_{1c} reduction, similar hypoglycaemia risk [100]
	Outcome	Women and men: higher risk of CHD [101, 102]
Thiazolidinediones	Glucose metabolism	Women with obesity: greater HbA_{1c} reduction compared with sulfonylurea therapy [100]
	Adverse effects	Women: women with obesity have a higher risk of weight gain and oedema risk [100]; higher risk of bone fractures; women with type 2 diabetes have a higher mortality rate under a therapy with rosiglitazone [62]. Men: pioglitazone is related to a moderately increased risk of bladder cancer [123]
SGLT-2I	Glucose metabolism	Men: (trend for) better glycaemic response to treatment [124]
	Outcome	Similar between men and women: cardiovascular benefits, risk of hospitalisation due to heart failure and changes (incident or worsening) in nephropathy [102, 104, 105]. Women: lower prescription rate [103]
	Adverse effects	Women: higher risk of adverse events in general, higher risk of genital infection or urinary tract infections, more urosepsis, fractures and ketoacidosis [102, 108, 109]. Men: higher risk of Fournier gangrene, more acute renal failure, more lower limb amputation, more pancreatitis [102, 125]. Similar between men and women: risk of adverse events in general, amputation and genital infection or urinary tract infections [104]
GLP-1RA	Weight reduction	Women: greater weight reduction [110–113]
	Glucose metabolism	Majority of the trials: similar HbA_{1c} reduction between sexes [110, 112]. Men: better glycaemic control under add-on exenatide therapy (to metformin ± sulfonylurea). Women: combination therapy with exenatide and metformin is more effective [113]. Dulaglutide: similar HbA_{1c} reduction in men and women [112]. General: female sex could be a predictor of better glycaemic response [62, 126]
	Outcome	Similar reduction of MACE in men and women [114, 115]. Women: comparison GLP-1RA vs sulfonylurea: better CV-reducing effect [102]
	Adverse effects	Women: greater risk of gastrointestinal complications (e.g. nausea + diarrhoea) [62, 112, 127]
DPP-IV inhibitors	Glucose metabolism	No sex differences [116]
Insulin	Glucose metabolism	Women: achieve HbA_{1c} targets (<7%) with basal insulin glargine less often [117]
	Adverse effects	Women: higher risk of severe (nocturnal) hypoglycaemic events compared with men with basal insulin therapy with NPH insulin or insulin glargine, especially if without obesity [128]. Men: in a Japanese study in which patients with a mean BMI of <25 kg/m^2 with longstanding type 2 diabetes received a CSII for 7 days and subsequent therapy with premixed insulin, men had a higher risk of hypoglycaemia, although they required lower doses of insulin; similar results have been shown for CSII therapy only [118]
Statins	Cardiovascular outcomes	Similar effects in men and women undergoing statin therapy [129]
	Volume reduction of coronary atheroma	Women: stronger reduction in women undergoing high-dose statin therapy [130]
Evolocumab	Coronary atheroma reduction	Women: more relative (but not total volume) coronary atheroma reduction [131]
Fenofibrate	Lipid-lowering effect and outcome	Women: more total, LDL- and non-HDL-cholesterol reduction compared with men, similar CVD outcomes [132]
ACE inhibitors	Outcome	Women: decreasing efficacy over time, less reduction of mortality rate but greater beneficial effects on nephropathy [133]
	Adverse effects	Women: experience side effects (cough) more often than men [134]
ACE inhibitors and ATII blockers	HFrEF	Comparable in both sexes: mortality and hospitalisation due to HFrEF [134]
Beta blockers	Outcome	Women: optimal survival under lower dosages of beta blockers [5]
Acetylsalicylic acid	Outcome	Women: no reduction of MCI risk, but reduction of ischaemic strokes, increased bleeding risk [135]. Men: MACE reduction exclusively in men [136]
ARNI	HFpEF	Women: decreased risk of cardiovascular death or hospitalisation with HF [137]. Specific subgroup analysis: only in women reduction of the primary endpoint cardiovascular death and hospitalisation due to HF [138]

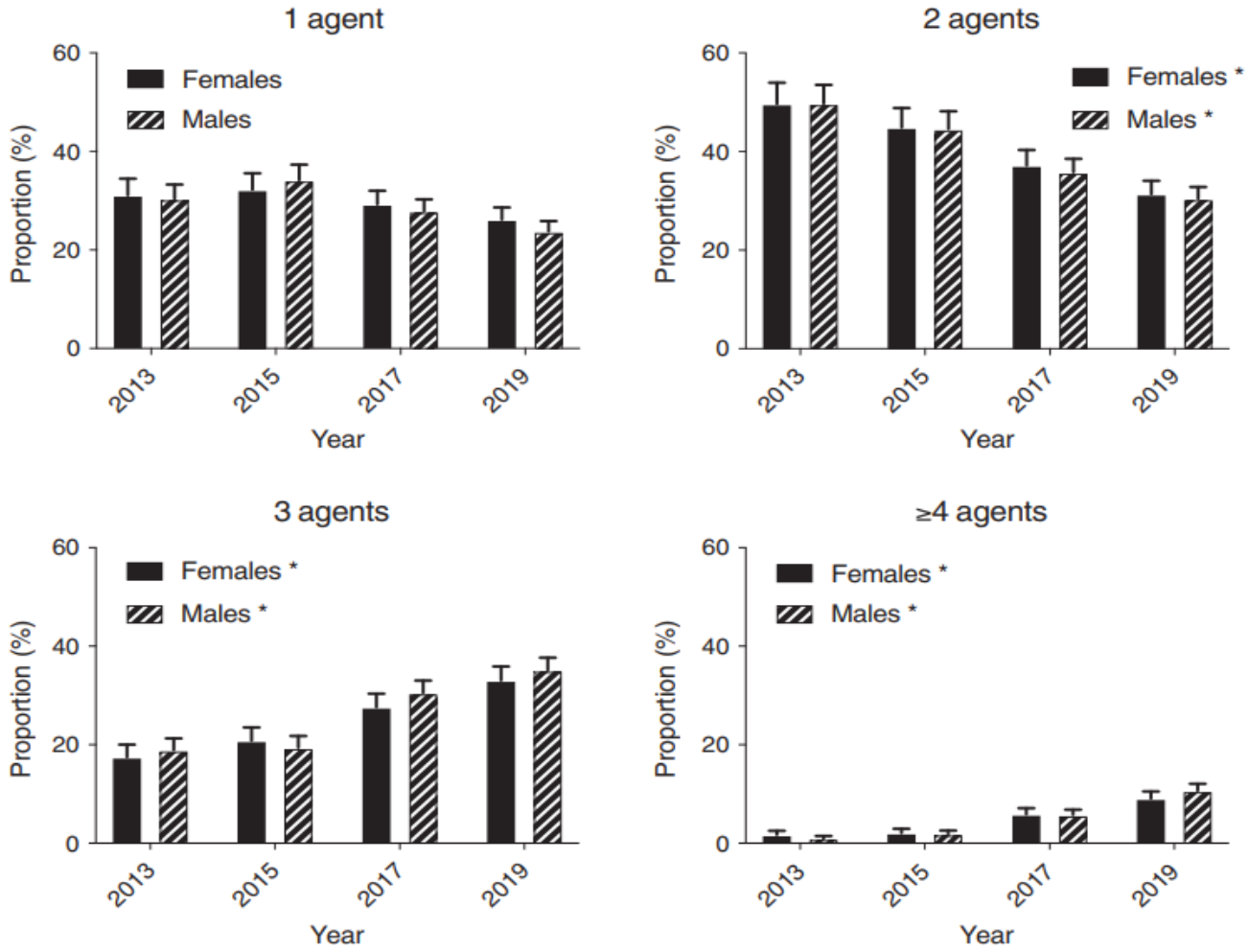
ARNI, angiotensin receptor–neprilysin inhibitor; ATII, angiotensin II; CSII, continuous subcutaneous insulin infusion; CV, cardiovascular; DPP-IV, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist, HF= heart failure; HFrEF, heart failure with reduced ejection fraction; MCI, myocardial infarction; SGA, small for gestational age

Women are currently less likely than men to receive the treatment and cardiovascular disease risk reduction recommended by guidelines.
Moreover, they more frequently report side effects under many cardiometabolic therapies

Kautzky-Willer A et a, Diabetologia, 2023

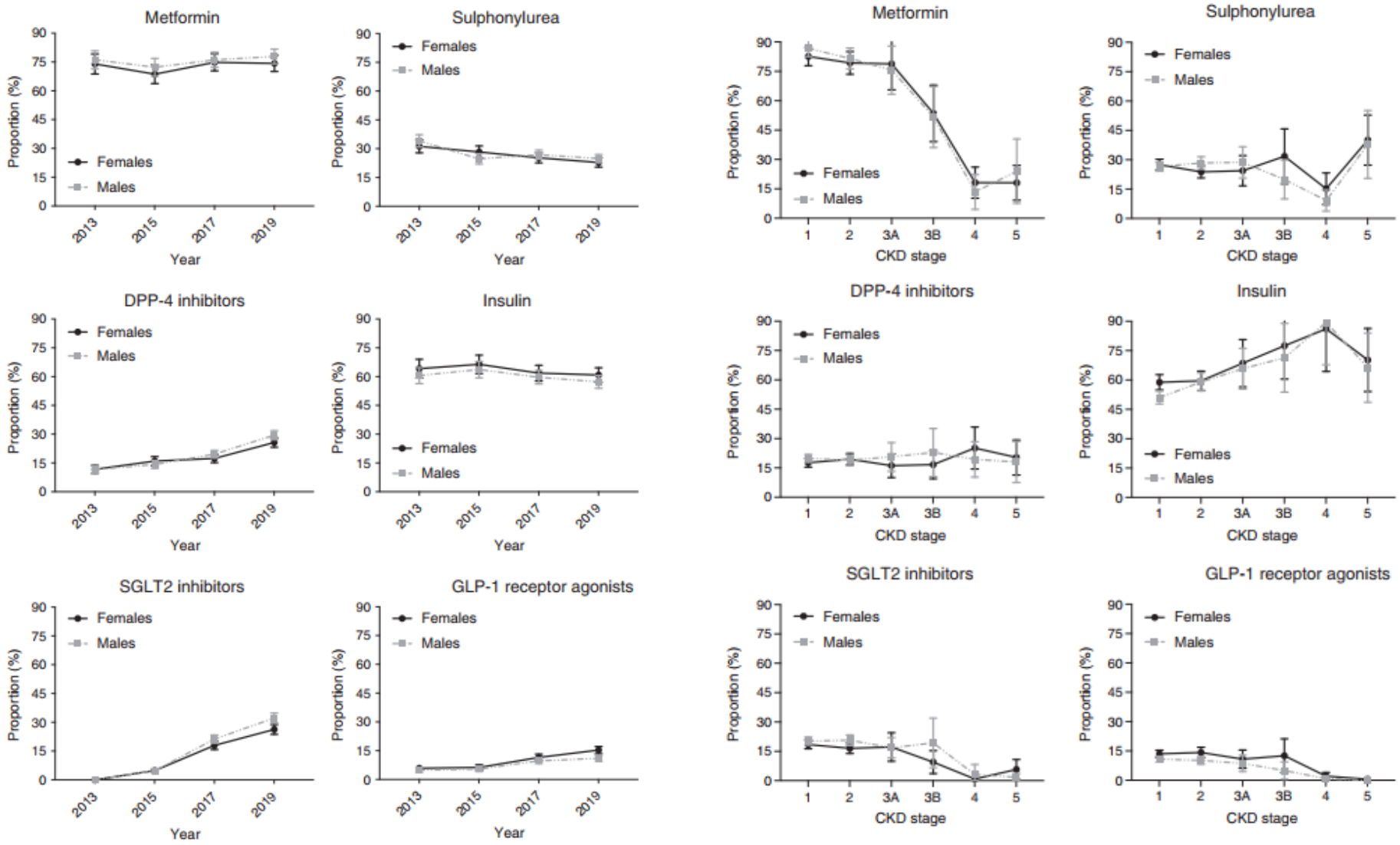
Trends in glycaemic control and drug use in males and females with type 2 diabetes: Results of the Australian National Diabetes Audit from 2013 to 2019

11 930 T2DM 44.9% females



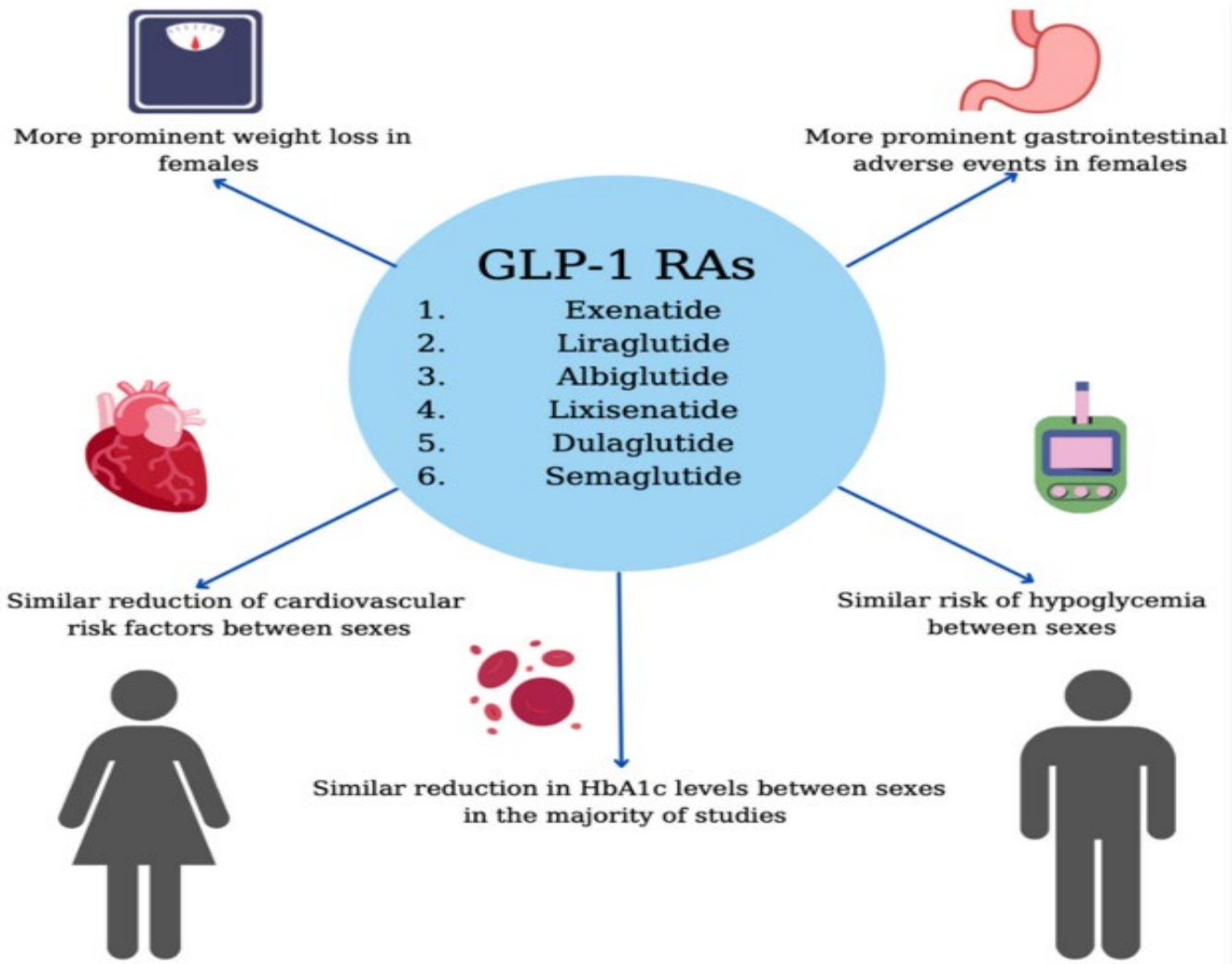
Xiang AS et al, Diabetes Obes Metab, 2021

Trends in glycaemic control and drug use in males and females with type 2 diabetes: Results of the Australian National Diabetes Audit from 2013 to 2019 11 930 T2DM 44.9% females



Xiang AS et al, Diabetes Obes Metab, 2021

Sex differences and treatment with GLP-1 RAs



Rentzeperi E et al, J Pers Med, 2022

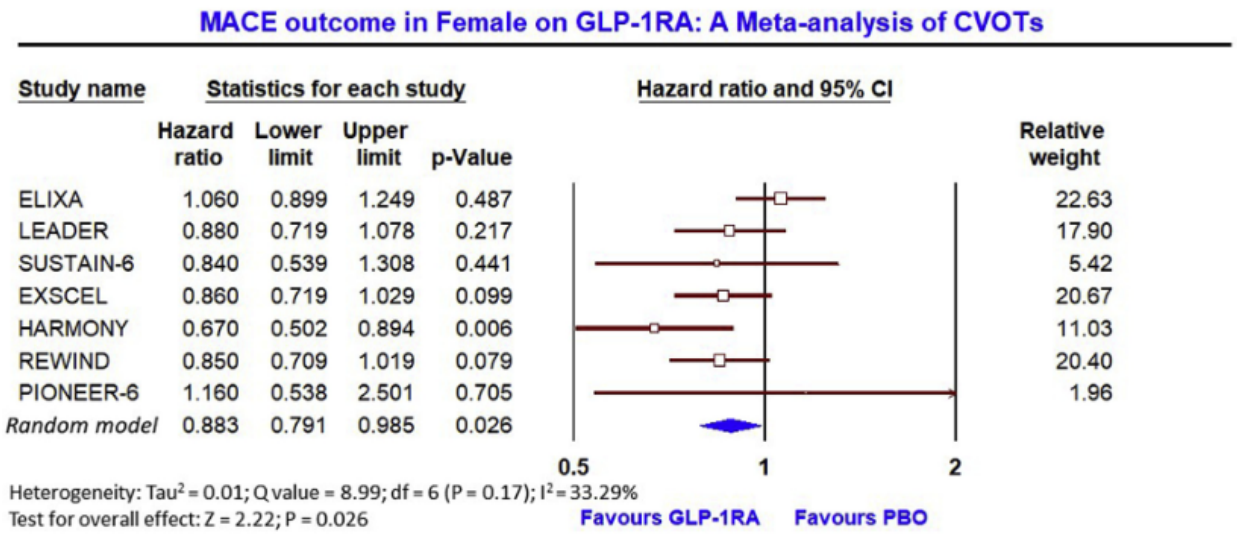
	ELIXA (n=6068)	LEADER (n=9340)	SUSTAIN-6 (n=3297)	EXSCEL (n=14752)	Harmony Outcomes (n=9463)	REWIND (n=9901)	PIONEER 6 (n=3183)	AMPLITUDE-O (n=4076)
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide	Efpeglenatide
Structural basis	Exendin-4	Human GLP-1	Human GLP-1	Exendin-4	Human GLP-1	Human GLP-1	Human GLP-1	Exendin-4
Administration route	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Oral	Subcutaneous
Dose	10 µg/day or 20 µg/day	1·8 mg/day	0·5 mg/week or 1 mg/week	2 mg/week	30 mg/week or 50 mg/week	1·5 mg/week	14 mg/day	4 mg/week or 6 mg/week
Age, years	60 (10)	64 (7)	65 (7)	62 (9)	64 (7)	66 (7)	66 (7)	65 (8)
Sex								
Female	1861 (31%)	3337 (36%)	1295 (39%)	5603 (38%)	2894 (31%)	4589 (46%)	1007 (32%)	1344 (33%)
Male	4207 (69%)	6003 (64%)	2002 (61%)	9149 (62%)	6569 (69%)	5312 (54%)	2176 (68%)	2732 (67%)
BMI, kg/m²	30·1 (5·6)	32·5 (6·3)	32·8 (6·2)	32·7 (6·4)	32·3 (5·9)	32·3 (5·7)	32·3 (6·5)	32·7 (6·2)
White ethnicity	4576 (75%)	7238 (77%)	2736 (83%)	11175 (76%)	6583 (70%)	7498 (76%)	2300 (72%)	3534 (87%)
Diabetes duration, years	9·2 (8·2)	12·8 (8·0)	13·9 (8·1)	13·1 (8·3)	14·2 (8·8)	10·5 (7·2)	14·9 (8·5)	15·4 (8·8)
HbA_{1c}, %	7·7 (1·3)	8·7 (1·6)	8·7 (1·5)	8·1 (1·0)	8·7 (1·5)	7·3 (1·1)	8·2 (1·6)	8·9 (1·5)
Established cardiovascular disease	6068 (100%)	7598 (81%)	2735 (83%)	10782 (73%)	9463 (100%)	3114 (31%)	2695 (85%)	3650 (90%)
History of heart failure	1358 (22%)	1667 (18%)	777 (24%)	2389 (16%)	1922 (20%)	853 (9%)	388 (12%)	737 (18%)
Systolic blood pressure (mm Hg)	129 (17)	136 (18)	136 (17)	135 (17)	135 (17)	137 (17)	136 (18)	135 (16)
eGFR, mL/min per 1·73 m²	78 (21)	80 (NR)	80 (61–92)	77 (61–92)	79 (25)	77 (23)	74 (21)	72 (22)
Glucose-lowering drugs used (%)								
Insulin	2374 (39%)	4169 (45%)	1913 (58%)	6836 (46%)	5597 (59%)	2363 (24%)	1930 (61%)	2560 (63%)
Biguanide	4021 (66%)	7144 (76%)	2414 (73%)	11295 (77%)	6969 (74%)	8037 (81%)	2463 (77%)	2985 (73%)
Sulfonylurea	2004 (33%)	4733 (51%)	1410 (43%)	5401 (37%)	2725 (29%)	4552 (46%)	1027 (32%)	1036 (25%)
Thiazolidinedione	95 (2%)	575 (6%)	76 (2%)	579 (4%)	194 (2%)	168 (2%)	118 (4%)	NR
DPP-4 inhibitor	NR	6 (<1%)	5 (<1%)	2203 (15%)	1437 (15%)	564 (6%)	2 (<1%)	0
SGLT2 inhibitor	NR	NR	5 (<1%)	77 (1%)	575 (6%)	3 (<1%)	305 (10%)	618 (15%)

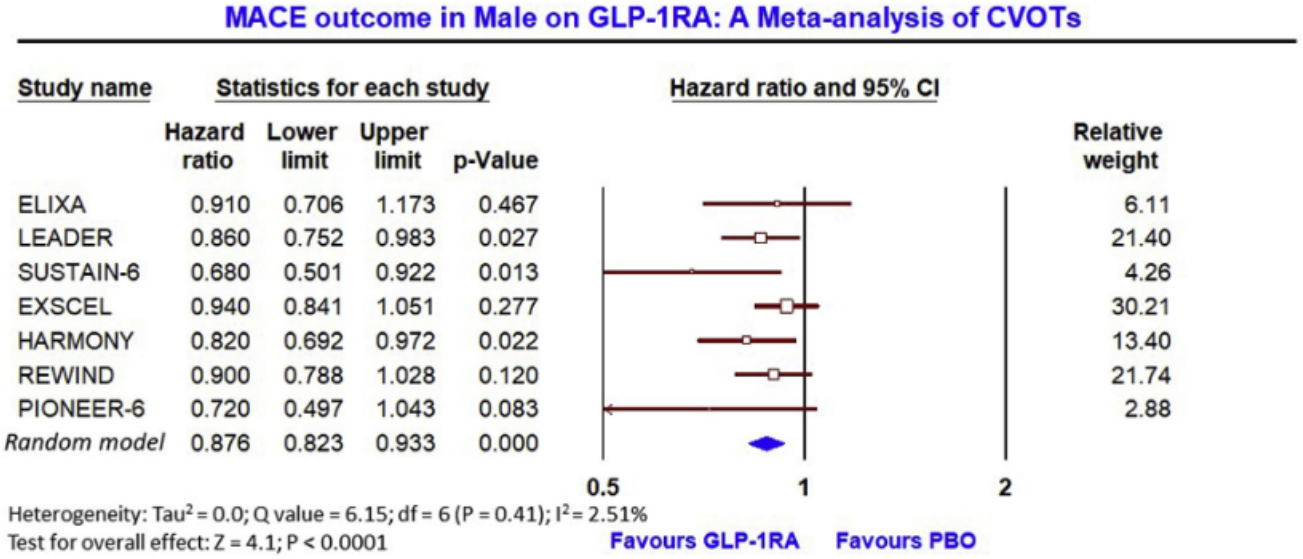
Data are mean (SD), n (%), or median (IQR), unless otherwise specified. eGFR=estimated glomerular filtration rate. NR=not reported.

Table: **Baseline characteristics and use of glucose-lowering agents across trials**

Sattar N et al, Lancet Diabetes Endocrinol, 2021

Gender difference in cardiovascular outcomes with GLP-1 receptor agonist in type 2 diabetes





Singh AK et al, Diabetes Metab Syndr, 2021

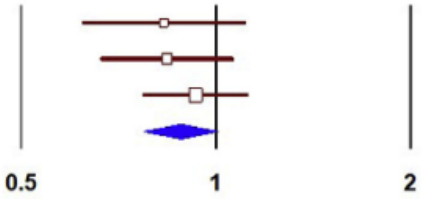
Characteristic	No. (%)[b] EMPA-REG outcome[19] (n = 7020)	CANVAS program[20] (n = 10 142)	DECLARE-TIMI 58[21] (n = 17 160)	CREDENCE[22] (n = 4401)	VERTIS CV[16] (n = 8246)
SGLT2 inhibitor	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin
Duration of follow-up, median, y	3.1	2.4	4.2	2.6	3.0
Patient characteristics					
Men	5016 (71.5)	6509 (64.2)	10 738 (62.6)	2907 (66.1)	5769 (70.0)
Women	2004 (28.5)	3633 (35.8)	6422 (37.4)	1494 (33.9)	2477 (30.0)
Age, mean (SD), y	63.1 (8.6)	63.3 (8.3)	63.9 (6.8)	63.0 (9.2)	64.4 (8.1)
Race/ethnicity					
White	5081 (72.4)	7944 (78.3)	13 653 (79.6)	2931 (66.6)	7240 (87.8)
Asian	1517 (21.6)	1284 (12.7)	2303 (13.4)	877 (19.9)	498 (6.0)
Black or African American	357 (5.1)	336 (3.3)	603 (3.5)	224 (5.1)	235 (2.8)
Other/missing	65 (0.9)	578 (5.7)	601 (3.5)	369 (8.4)	273 (3.3)
Diabetes characteristics					
HbA_{1c}, mean (SD), %	8.1 (0.8)	8.2 (0.9)	8.3 (1.2)	8.3 (1.3)	8.2 (1.0)
Diabetes duration, mean (SD), y	57 > 10[c]	13.5 (7.8)	11.8 (7.8)	15.8 (8.6)	13.0 (8.3)
Cardiovascular characteristics					
Established cardiovascular disease	7020 (100)	6656 (65.6)	6974 (40.6)	2220 (50.4)	8246 (100)
History of heart failure	706 (10.1)	1461 (14.4)	1724 (10.0)	652 (14.8)	1958 (23.7)
Renal characteristics					
Reduced kidney function[d]	1819 (25.9)	2039 (20.1)	1265 (7.4)	2631 (59.8)	1807 (21.9)
Urine ACR≥300 mg/g	769 (11.0)	760 (7.6)	1169 (6.8)	3874 (88.0)	755 (9.2)
Cardiovascular medications					
ACEI or ARB blockade	5666 (80.7)	8116 (80.0)	13 950 (81.3)	4395 (99.9)	6686 (81.1)
β-Blocker	4554 (64.9)	5421 (53.5)	9030 (52.6)	1770 (40.2)	5692 (69.0)
Statin/ezetimibe	5403 (77.0)	7599 (74.9)	12 868 (75.0)	3036 (69.0)	6790 (82.3)
Antihyperglycemic medications					
Insulin	3387 (48.2)	5095 (50.2)	7013 (40.9)	2884 (65.5)	3900 (47.3)
Metformin	5193 (74.0)	7825 (77.2)	14 068 (82.0)	2545 (57.8)	6292 (76.3)
Sulfonylurea	3006 (42.8)	4361 (43.0)	7322 (42.7)	1268 (28.8)	3390 (41.1)
DPP-4 inhibitor	796 (11.3)	1261 (12.4)	2888 (16.8)	751 (17.1)	911 (11.0)
GLP-1 receptor agonist	196 (2.8)	407 (4.0)	750 (4.4)	183 (4.2)	278 (3.4)

McGuire DK et al, JAMA Cardiol, 2021

Gender difference in cardiovascular outcomes with SGLT-2 inhibitors in type 2 diabetes

MACE outcome in Female on SGLT-2I: A Meta-analysis of CVOTs

Study name	Hazard ratio	Lower limit	Upper limit	p-Value	Relative weight
EMPA-REG	0.830	0.620	1.111	0.210	20.30
CANVAS	0.840	0.663	1.065	0.149	30.67
DECLARE TIMI	0.930	0.771	1.122	0.448	49.03
Random model	0.881	0.773	1.004	0.058	

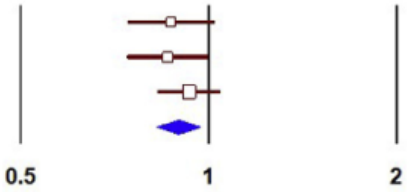


Heterogeneity: $Tau^2 = 0.0$; Q value = 0.64; df = 2 (P = 0.73); $I^2 = 0.0\%$
Test for overall effect: Z = 1.90; P = 0.058

Favours SGLT-2I Favours PBO

MACE outcome in Male on SGLT-2I: A Meta-analysis of CVOTs

Study name	Hazard ratio	Lower limit	Upper limit	p-Value	Relative weight
EMPA-REG	0.870	0.741	1.021	0.089	25.01
CANVAS	0.860	0.740	1.000	0.050	28.41
DECLARE TIMI	0.930	0.827	1.046	0.226	46.59
Random model	0.895	0.826	0.969	0.006	

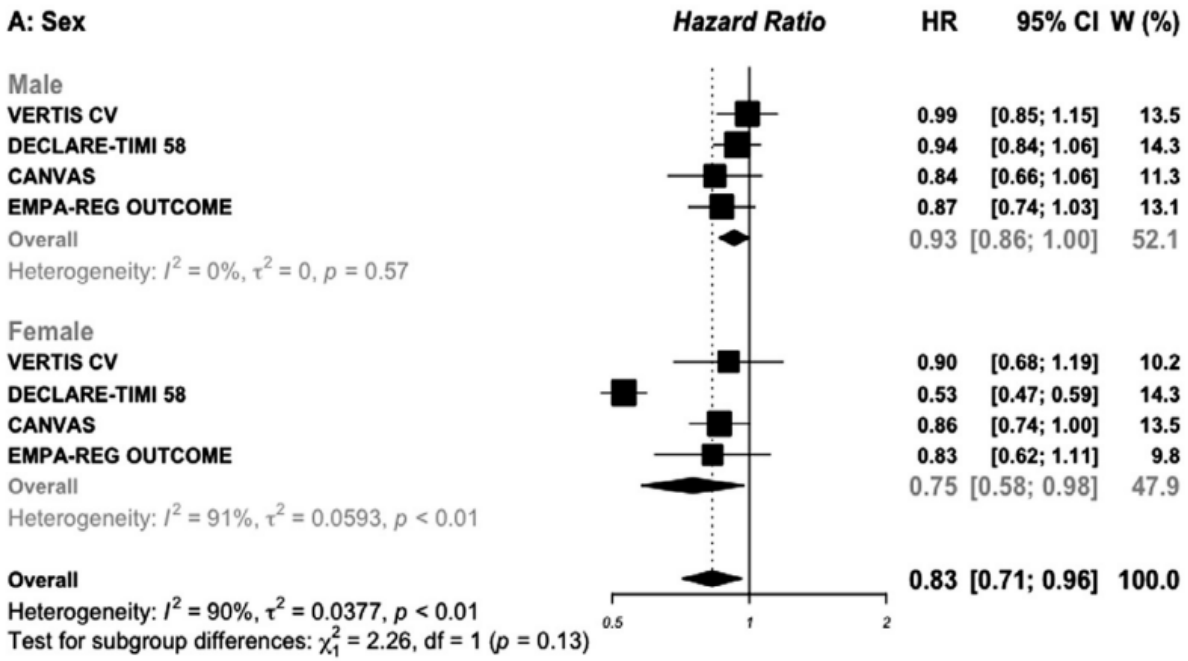


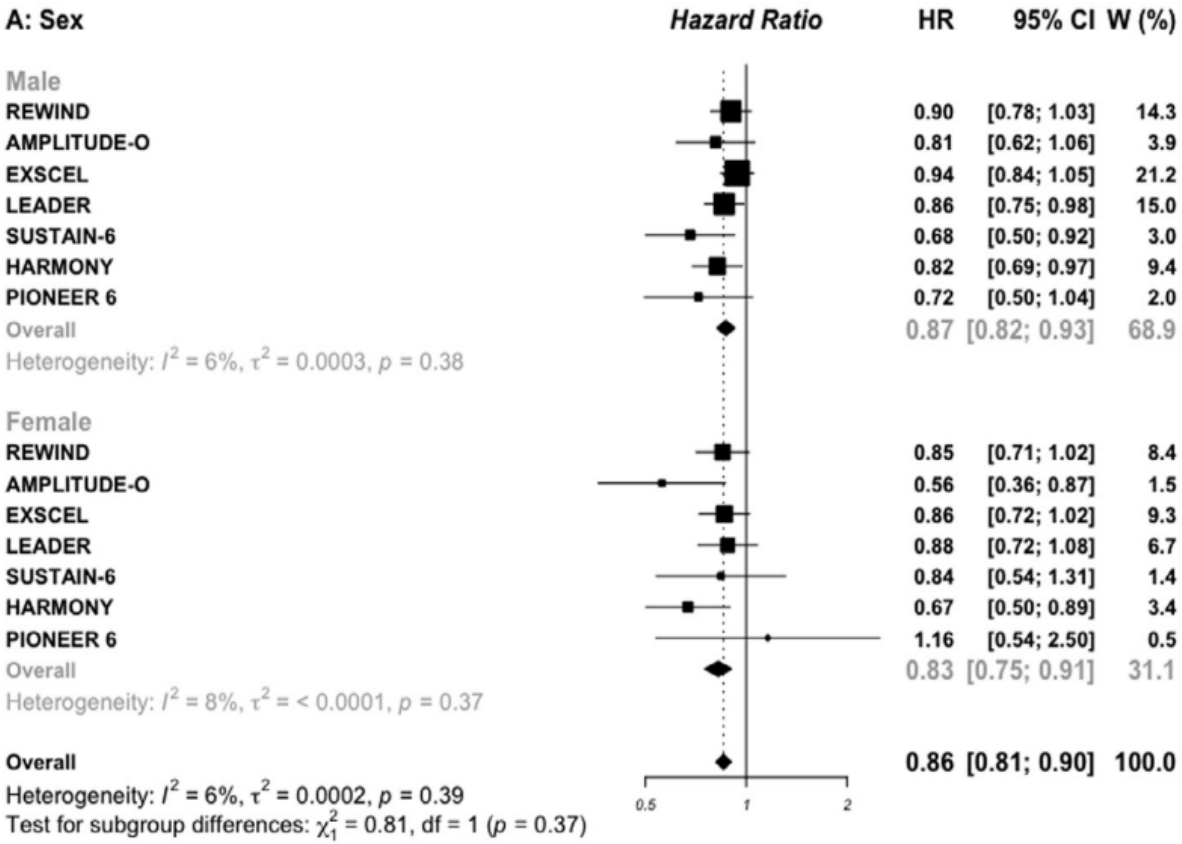
Heterogeneity: $Tau^2 = 0.0$; Q value = 0.80; df = 2 (P = 0.67); $I^2 = 0.0\%$
Test for overall effect: Z = 2.72; P = 0.006

Favours SGLT-2I Favours PBO

Singh AK et al, Diabetes Metab Syndr, 2020

SGLT2 inhibitors and GLP1 RA: Risk for MACE outcome by sex





Discussion

The MACE benefit of SGLT2i and GLP-1 RAs was similar across age, sex, BMI, and other race subgroups.

However, participant contributed data to the female subgroup (34%) than to the men subgroup (66%), meaning that the analysis may not be able to detect subgroup difference

Diallo A et al, Lancet eClinicalMedicine, 2022

Sex Differences in Cardiovascular Effectiveness of Newer Glucose Lowering Drugs Added to Metformin in Type 2 Diabetes Mellitus. The Marketscan-Database: 2011–2017
Major CV events and CV effectiveness to sulfonilurea

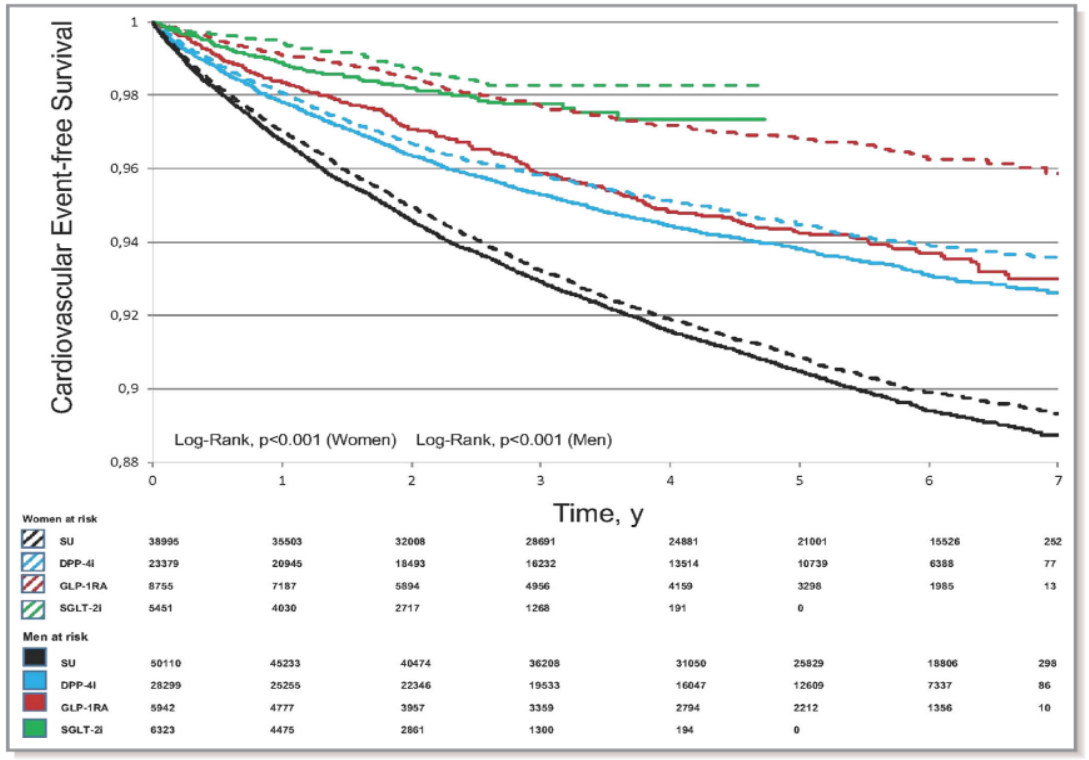


Figure 2. Kaplan–Meier curves for major cardiovascular events in women and men. DPP-4i indicates dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists; SGLT-2i, sodium-glucose-like transport-2 inhibitors; SU, sulfonylureas.

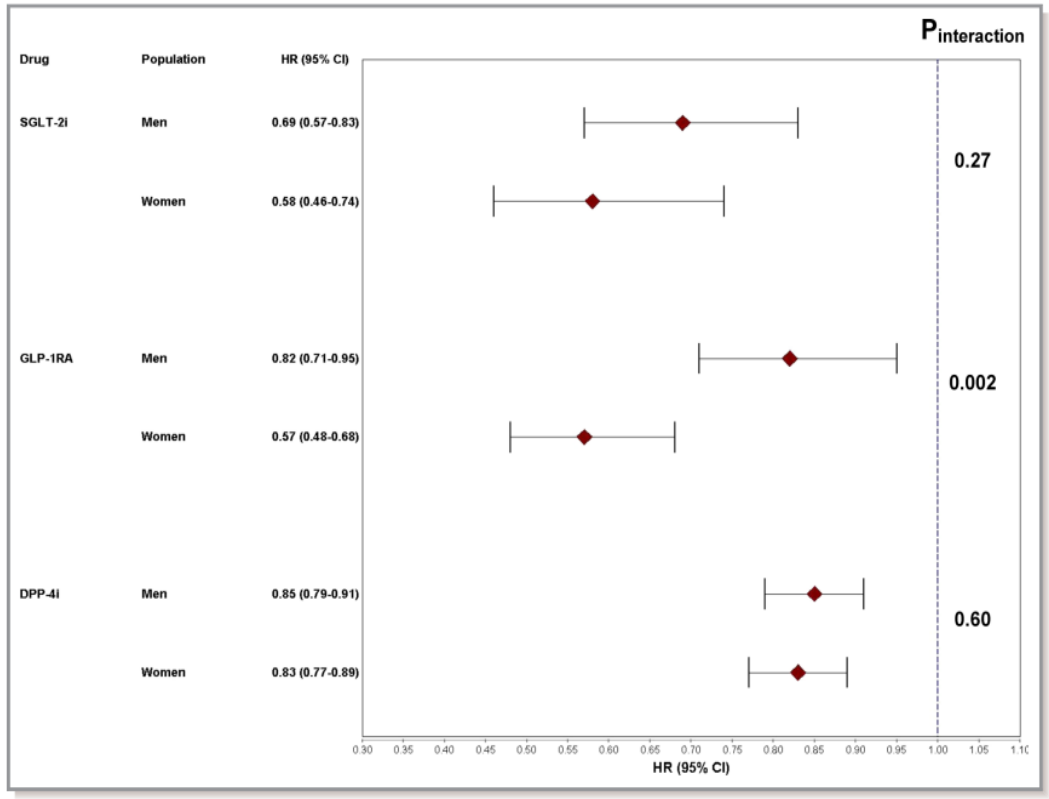


Figure 3. Adjusted hazard ratios (HR) relative to sulfonylureas for cardiovascular effectiveness outcomes in women and men. DPP-4i indicates dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists; SGLT-2i, sodium-glucose like transport-2 inhibitors. The model was adjusted for age, baseline comorbidities, employment status, region, year entry, and sex-by-drug interactions.

Raparelli V et al, J Am Heart Assoc, 2020

Sex Differences in Cardiovascular Effectiveness of Newer Glucose Lowering Drugs Added to Metformin in Type 2 Diabetes Mellitus. The Marketscan-Database: 2011–2017
Safety outcomes

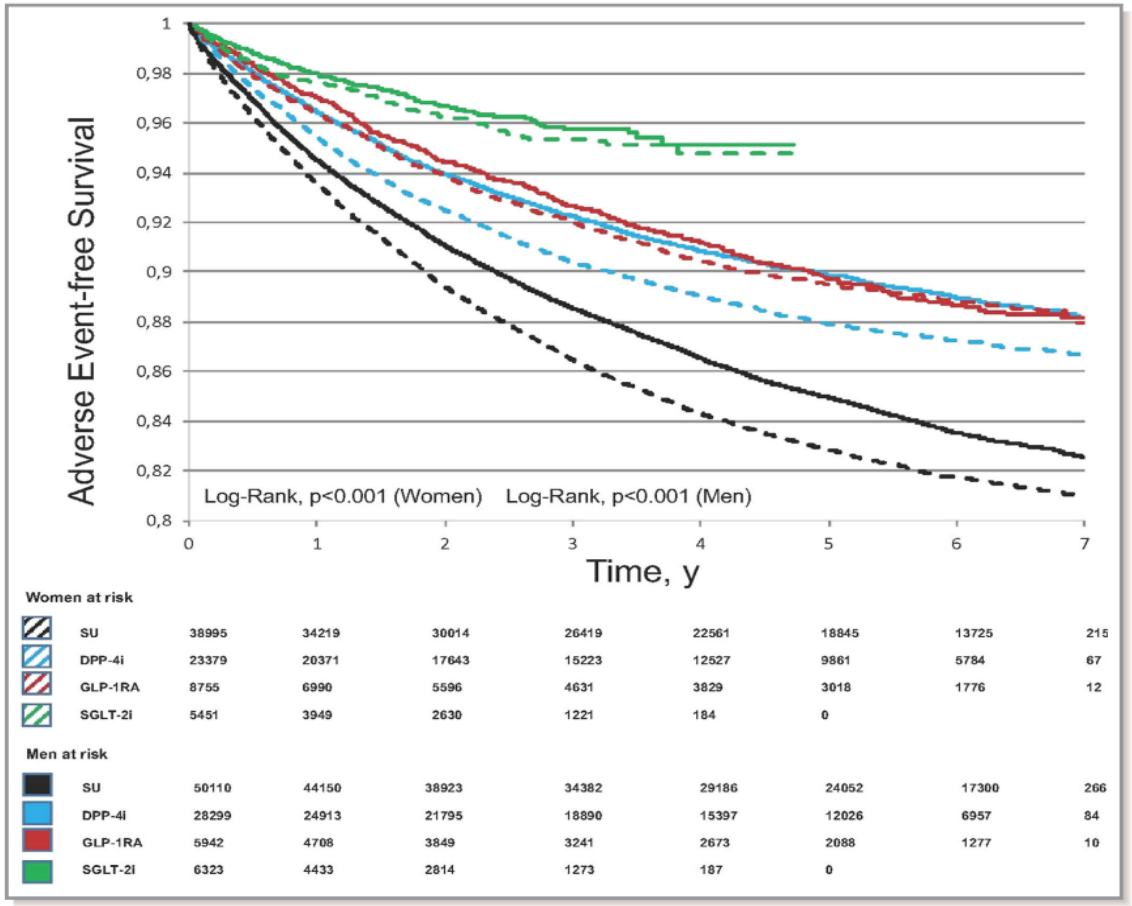


Figure 4. Kaplan–Meier curves for safety outcomes in women and men. DPP-4i indicates dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide 1 agonists; SGLT-2i, sodium-glucose-like transport-2 inhibitors; SU, sulfonylureas.

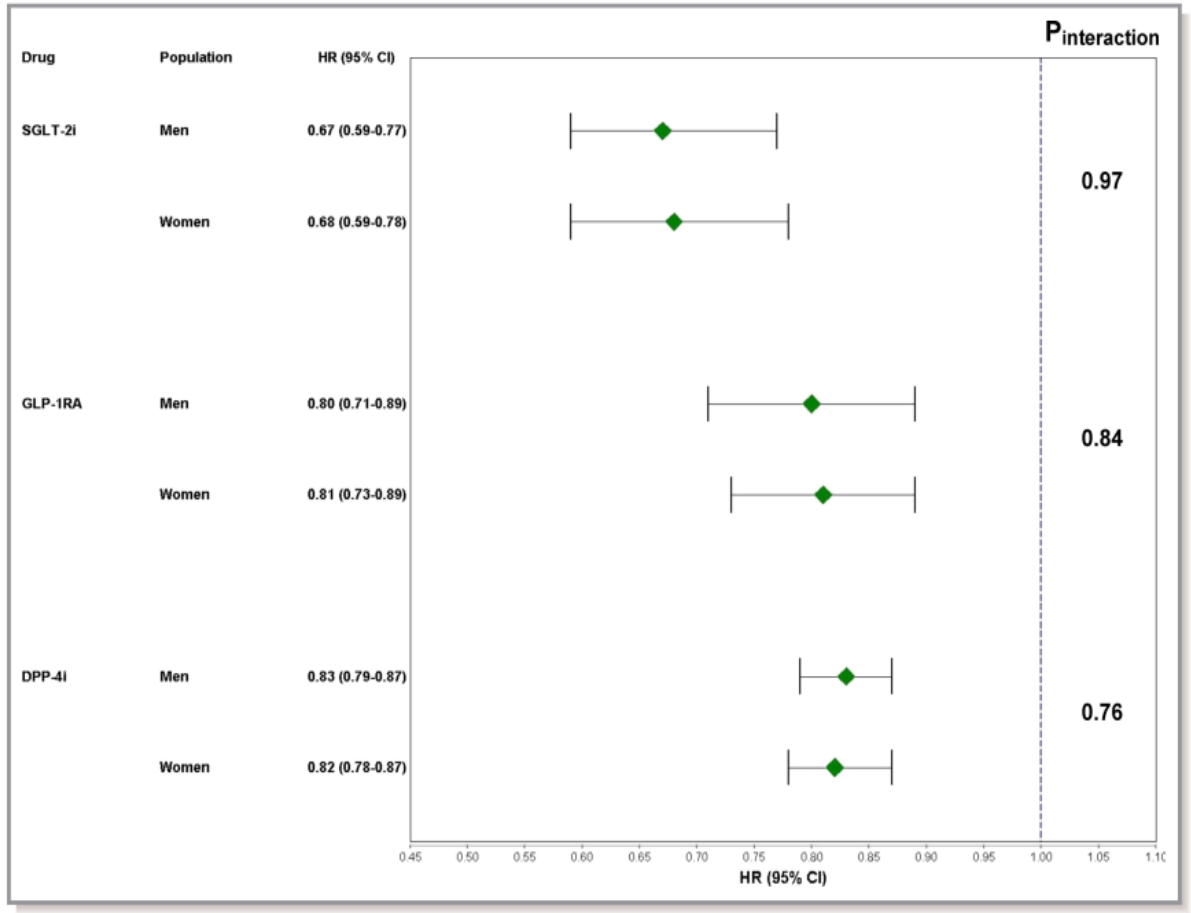
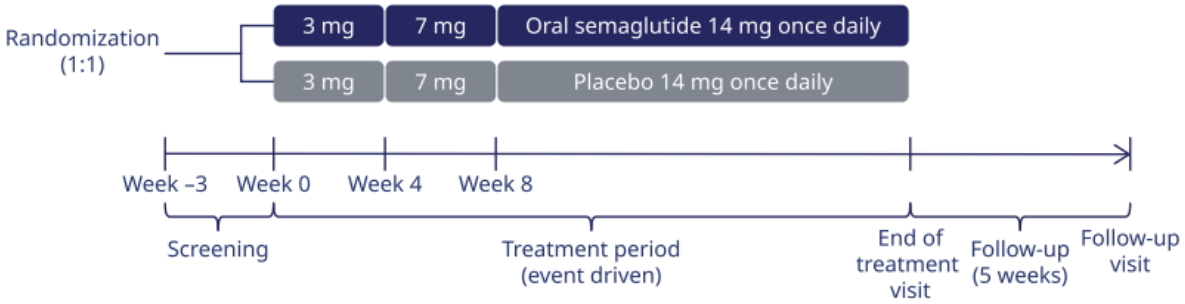


Figure 5. Adjusted HR relative to sulfonylureas for safety outcomes in women and men. DPP-4i indicates dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists; HR, hazard ratios; SGLT-2i, sodium-glucose-like transport-2 inhibitors. The model was adjusted for age, baseline comorbidities, employment status, region, year entry, and sex-by-drug interactions.

Raparelli V et al, J Am Heart Assoc, 2020

Semaglutide cardiOvascular oUtcomes triaL (SOUL) in type 2 diabetes: outcomes



(3.5 – 5 ys)

Outcome title	Timeframe
Primary outcome	
Time to first occurrence of MACE, a composite outcome consisting of:	From randomization (week 0) to end of trial (up to 61 months or more[a])
• CV death	
• Nonfatal MI	
• Nonfatal stroke	

TABLE 2 Patient demographics and baseline characteristics

	Total randomized population (N = 9650)
Age, years	66.1 (7.6)
Male, n (%)	6860 (71.1)

Outcome title	Timeframe
Confirmatory secondary outcomes	
Time to first occurrence of a composite outcome consisting of:	From randomization (week 0) to end of trial (up to 61 months or more[a])
• CV death	
• Kidney-related death	
• Persistent ≥50% reduction in eGFR (CKD-EPI)[b]	
• Persistent eGFR (CKD-EPI) <15 mL/min/1.73 m^2	
• Initiation of chronic kidney replacement therapy (dialysis or kidney transplantation)	
Time to occurrence of CV death	From randomization (week 0) to end of trial (up to 61 months or more[a])
Time to first occurrence of major adverse limb events, a composite outcome consisting of:	From randomization (week 0) to end of trial (up to 61 months or more[a])
• Acute limb ischaemia hospitalization	
• Chronic limb ischaemia hospitalization	

McGuire DK et al, Diabetes Obes Metab, 2023

Tirzepatide: Benefits Beyond Glycemic Control and Weight Reduction

Blood Pressure

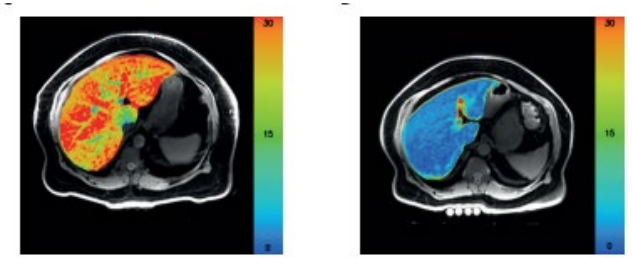
- Mean systolic blood pressure reduced by **6–9 mmHg**
- Mean diastolic blood pressure reduced by **3–4 mmHg**

Triglycerides

- Mean triglycerides reduced by **15–27%**

Liver Fat Content

- Liver fat content reduced by **52%** as measured by MRI



MRI scans LFC (%) at baseline and at week 52

Waist Circumference

- Mean waist circumference reduced by **6.9–9.9 cm**

Frias JP et al, NEJM, 2021
Rosenstock J et al, Lancet, 2021
Ludvik B et al, Lancet, 2021
Gastaldelli A et al, Lancet Diabetes Endocrinol, 2022
Del Prato S et al, Lancet, 2022
Dahl D et al, JAMA, 2022

SURPASS-CVOT in type 2 diabetes

Objective	Outcome
Primary	
Assess efficacy of maximally tolerated tirzepatide dose up to 15 mg QW vs QW dulaglutide 1.5 mg on time to first occurrence of the composite outcome of MACE* when both are added to standard of care in patients with T2D and high CV risk. Primary analysis will be a non-inferiority assessment of tirzepatide to dulaglutide for MACE. After establishing non-inferiority, superiority will be confirmed versus a putative placebo, and evaluated versus dulaglutide.	• Time to first occurrence of any component event of MACE
Key Secondary	
Efficacy	
Assess the superiority of tirzepatide up to 15 mg QW compared with dulaglutide 1.5 mg QW	• Time to death due to any cause • Time to CV death • Time to first occurrence of MI • Time to first occurrence of stroke • Time to first occurrence of the expanded composite CV outcome† • Cumulative number of CV deaths and total (first and recurrent) HF events requiring hospitalization and/or urgent HF visits
Additional Secondary	

Assess the superiority of tirzepatide up to 15 mg QW compared with dulaglutide 1.5 mg QW.	• Proportion of patients with more than 10% weight loss from screening after 36 months
	• Change from baseline in:
	  ○ weight, BMI, and waist circumference
	  ○ HbA1c
	  ○ urinary albumin to creatinine ratio
	  ○ blood lipids: total, HDL-, and LDL cholesterol, and triglycerides
	• Time to first occurrence of:
	  ○ coronary, carotid, or peripheral revascularizations, individually and as composite
	  ○ hospitalization due to unstable angina
	  ○ composite outcome of new or worsening nephropathy
	• Cumulative number of primary composite events of CV death and total (first and recurrent) MI and/or stroke

Table II. Baseline clinical characteristics in SURPASS-CVOT.

	SURPASS-CVOT (*N* = 13,299)
Age, years	64.1 ± 8.8
Sex, female	3849 (28.9)

Nicholls SJ et al, Am Heart J, 2024

Future agenda in sex- and gender-specific diabetes research

Causality association studies
Use of appropriate animal models and translational research
Studies on sex-differences in the pathophysiology, including the complex interplay of genes, epigenetic, hormones and lifestyle
Appropriate methodology for sex- and gender-specific analysis in clinical studies
RCTs proving evidence of sex-specific differences by adequate intervention and study design
Adequate inclusion of women in clinical studies
Addition of gender-related variables in clinical studies
Efficacy and tolerability of drugs in men and women
Intervention studies to overcome hormones default
Inclusion of pre- and post-menopausal women in clinical trials

Russo GT et al, Nutr Metab Cardiovasc Dis, 2022

Grazie per l'attenzione