Gender differences in T2DM therapy

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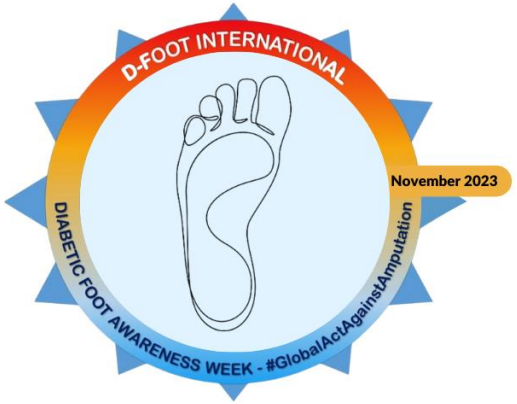
Disclosure:Explicit declaration of transparency of funding sources and relationships with subjects with commercial interests

Dr Roberto Anichini

No Conflict of interest for this presentation

ANGELINI, ABBOTT, ASTRAZENECA, BOEHRINGER INGELHEIM, BAYER, MOLTENI
JOHNSON&JOHNSON, LILLY, MSD, NOVO NORDISK, SANOFI, TAKEDA,



D-FOOT international

world diabetes day

Prevalenza ed Incidenza

DIABETES: A GLOBAL EMERGENCY

14 NOVEMBRE GIORNATA MONDIALE SUL DIABETE

Highlights

In 2021, IDF estimates show that:

1 in 10

Adults (20-79 years) has diabetes
537 million people

1 in 18

Adults (20-79 years) has impaired fasting glucose
319 million people

3 in 4

People with diabetes live in low and middle-income countries

1 in 2

Adults is undiagnosed
240 million people

1 in 6

Live births (21 million) affected by hyperglycaemia in pregnancy, 80% have mothers with GDM

11.5%

Of global health expenditure spent on diabetes (USD 966 billion)

1 in 9

Adults (20-79 years) has impaired glucose tolerance
541 million people

1.2 million

Children and adolescents below 20 years have type 1 diabetes

6.7 million

Deaths attributed to diabetes

Highlights

In 2021, IDF estimates show that:

1.67 million

More adults with impaired glucose tolerance

US$206 billion

More USD spent on diabetes

700,000

More pregnancies affected by hyperglycaemia

7.8 million

More adults with diabetes undiagnosed

149,500

More children and adolescents with type 1 diabetes

2.5 million

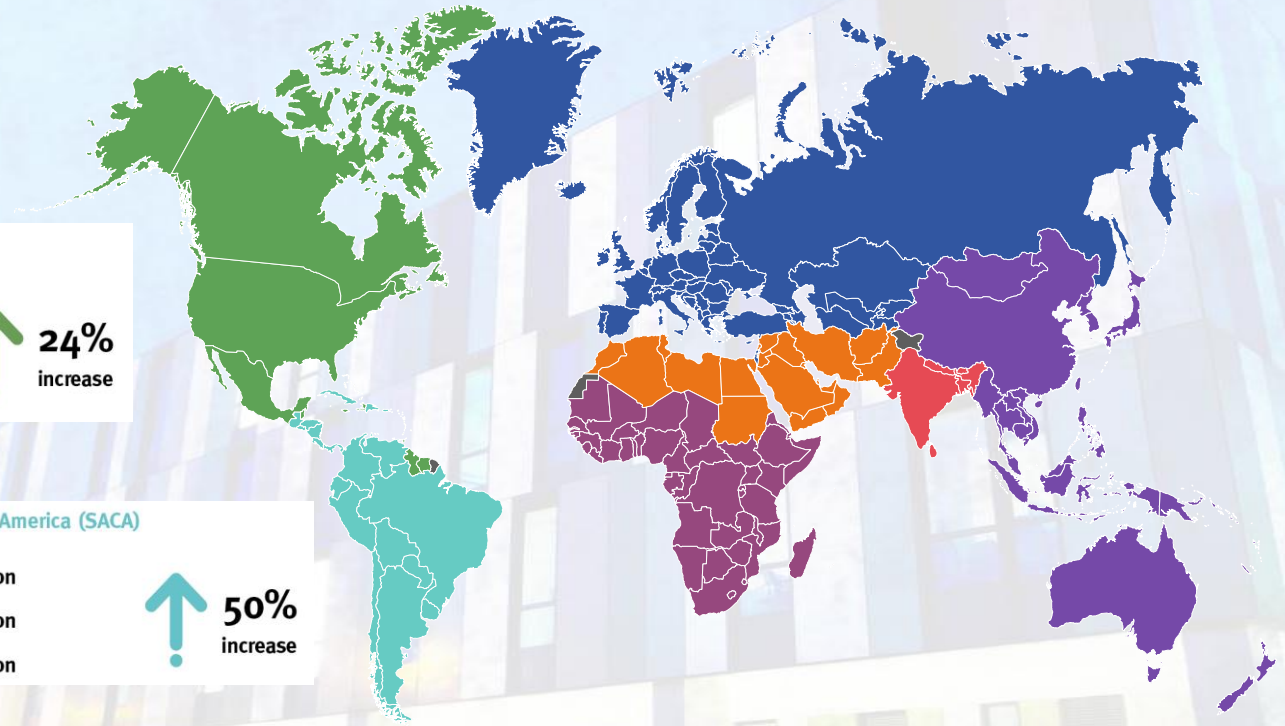
More deaths caused by diabetes

73.6 million

More adults with diabetes

Number of people with diabetes

Aged 20–79 years globally and by IDF region



North America & Caribbean (NAC)

2045	63 million
2030	57 million
2021	51 million

24% increase

South & Central America (SACA)

2045	49 million
2030	40 million
2021	32 million

50% increase

Africa (AFR)

2045	55 million
2030	33 million
2021	24 million

12 % increase

Middle East & North Africa (MENA)

2045	136 million
2030	95 million
2021	73 million

87% increase

Europe (EUR)

2045	69 million
2030	67 million
2021	61 million

13% increase

South-East Asia (SEA)

2045	152 million
2030	113 million
2021	90 million

68% increase

Western Pacific (WP)

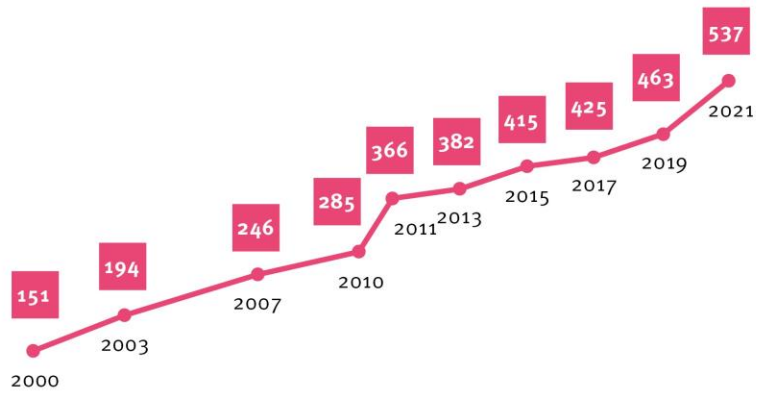
2045	260 million
2030	238 million
2021	206 million

27% increase

Estimates and projections

Global number of adults (20–79 years) in millions

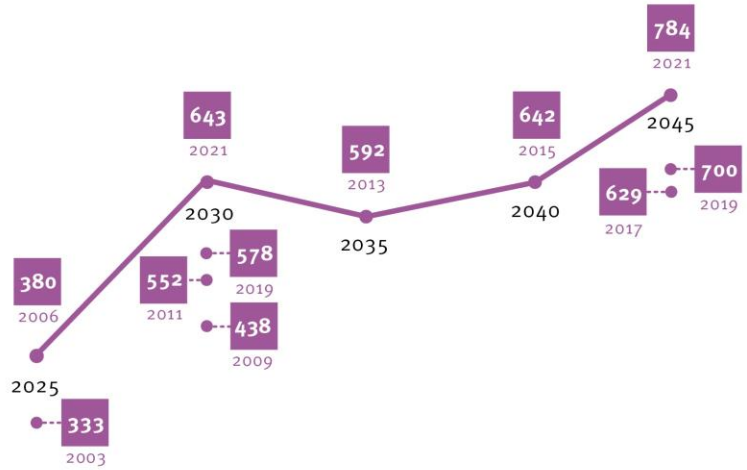
Estimates of the global prevalence of diabetes in the 20–79 year age group (millions)



Key

151 Number of people with diabetes in millions

Projections of the global prevalence of diabetes in the 20–79 year age group (millions)



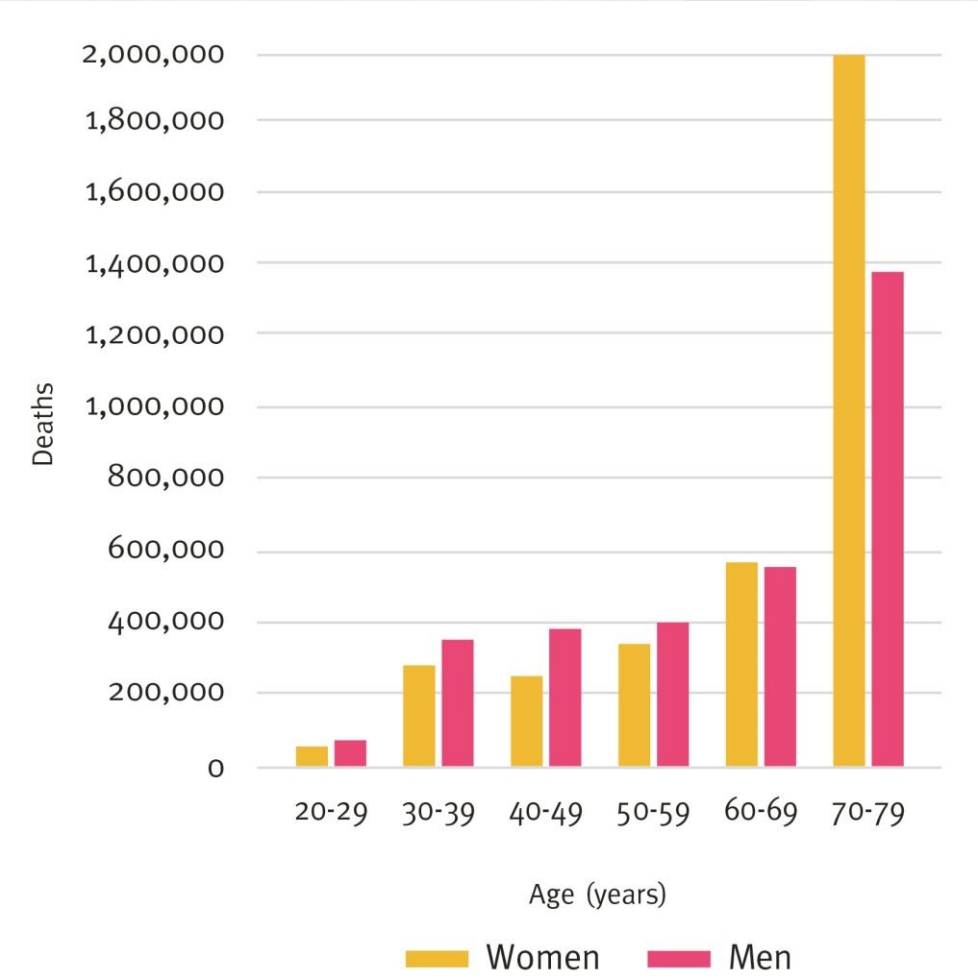
Key

333 Projection in millions

2003 Year projection made

Number of deaths by sex and age

Aged 20–79 years, 2021



Le sfide nel trattamento del diabete tipo 2

- Il diabete tipo 2 è una patologia progressiva caratterizzata da:
  - Declino della funzionalità delle beta-cellule
  - Deterioramento del controllo glicemico
  - Complicanze microvascolari
  - Aumento del rischio di malattia cardiovascolare

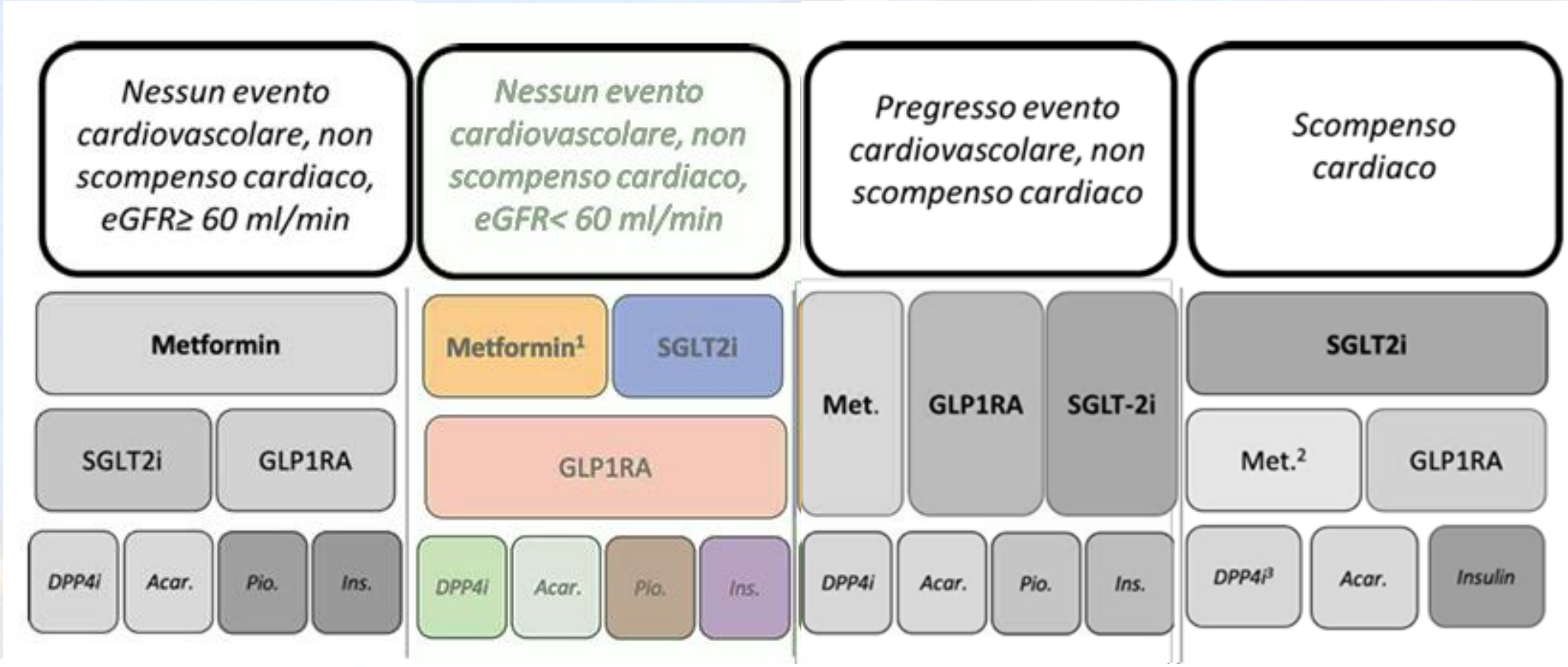
Obbiettivi Terapeutici

1. Raggiungere i targets terapeutici (stabilità)
2. Ridurre la morbilità e la mortalità CV
3. Ridurre incidenza complicanze microangiopatiche

Modificare aspetti caratteristici DMT2:

- Preservare la funzione pancreatica nel tempo
- Ridurre Insulinoresistenza o gli altri fattori responsabili iperglicemia
- Basso rischio ipoglicemie
- Controllo del peso
- Safe del prodotto CV

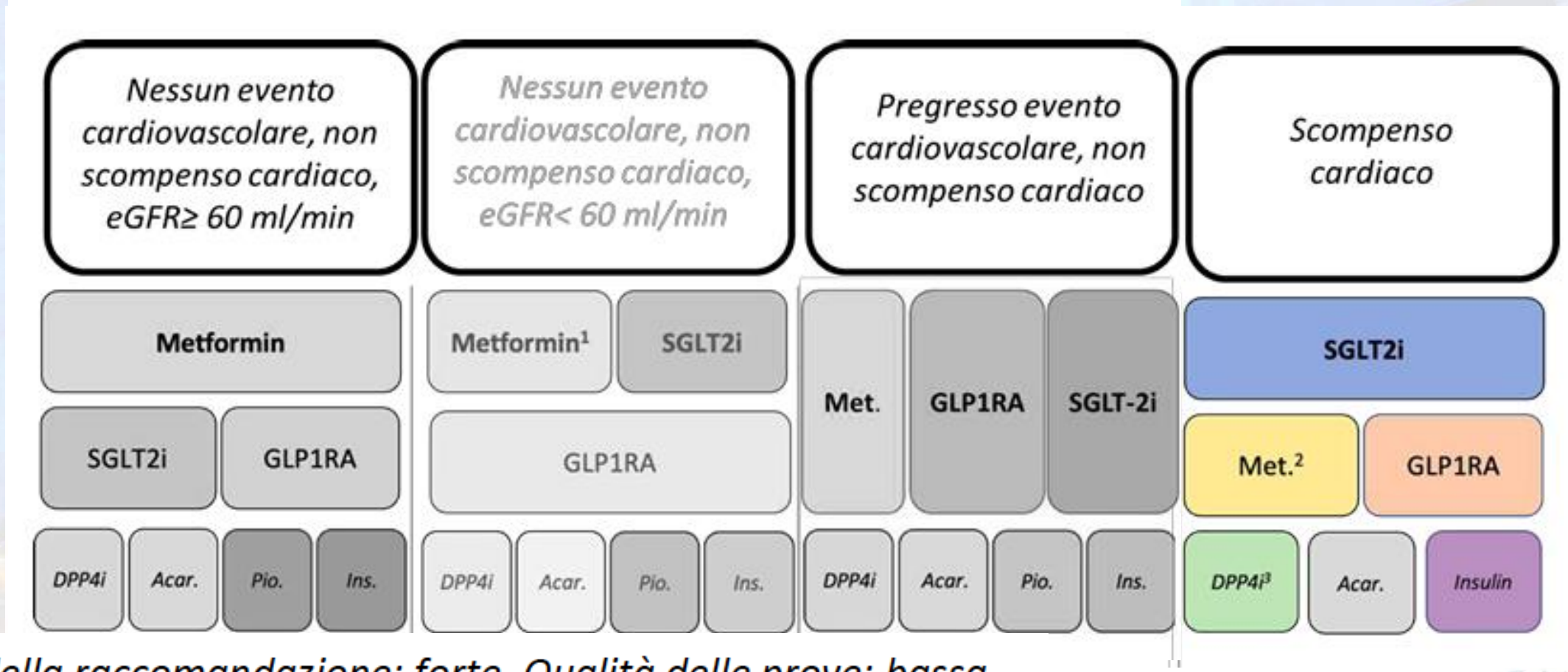
Recommended pharmacological management in patients with T2DM and CKD



Forza della raccomandazione: debole. Qualità delle prove: molto bassa.

Linea Guida SID-AMD - La terapia del diabete mellito di tipo 2. ISS 2023

Recommended pharmacological management in patients with T2DM and HF

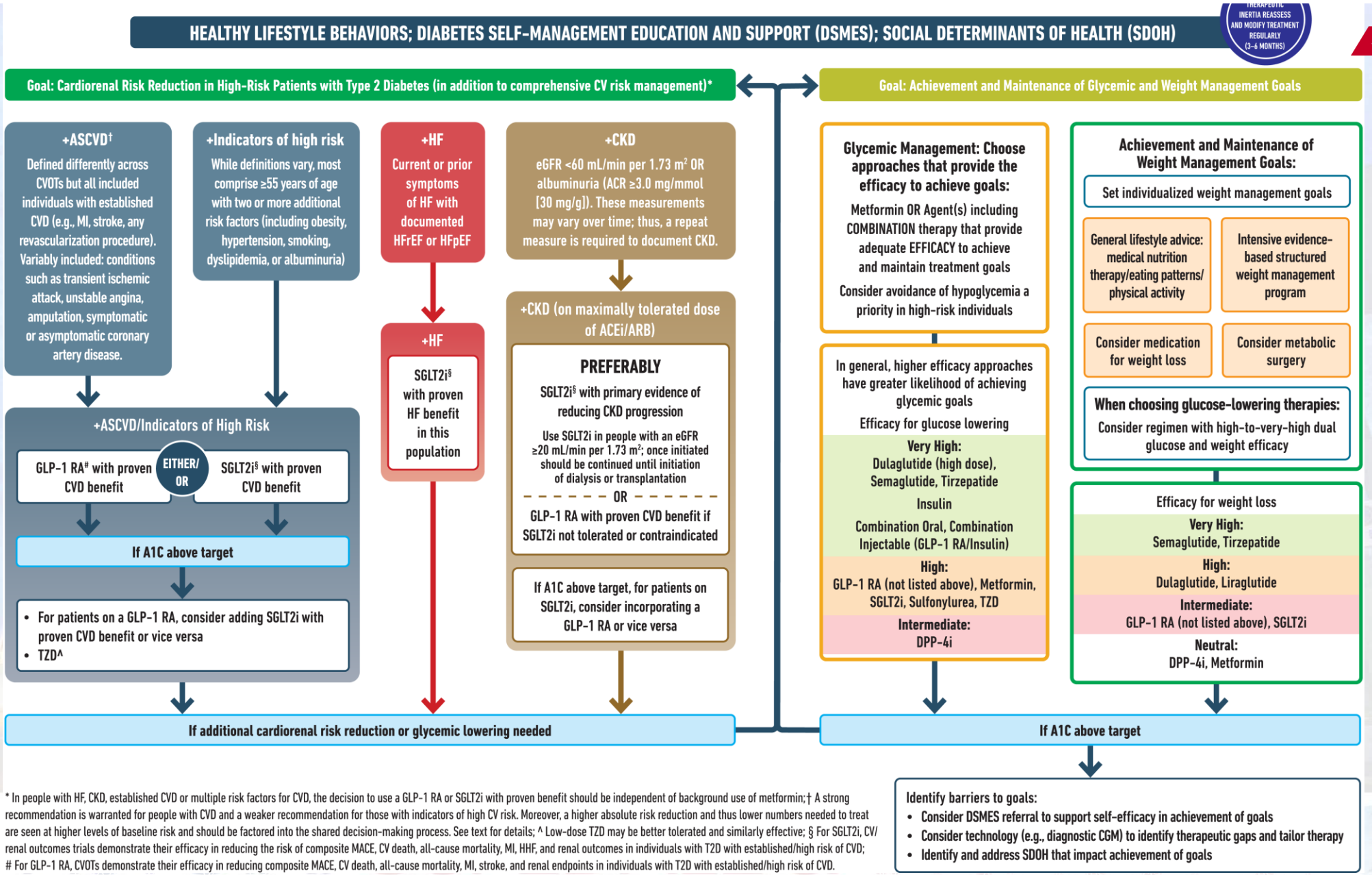


Forza della raccomandazione: forte. Qualità delle prove: bassa.

2: No Met if NYHA III-IV
3: no Saxa

Linea Guida SID-AMD - La terapia del diabete mellito di tipo 2. ISS 2023

Glucose-lowering medication in the management of T2DM

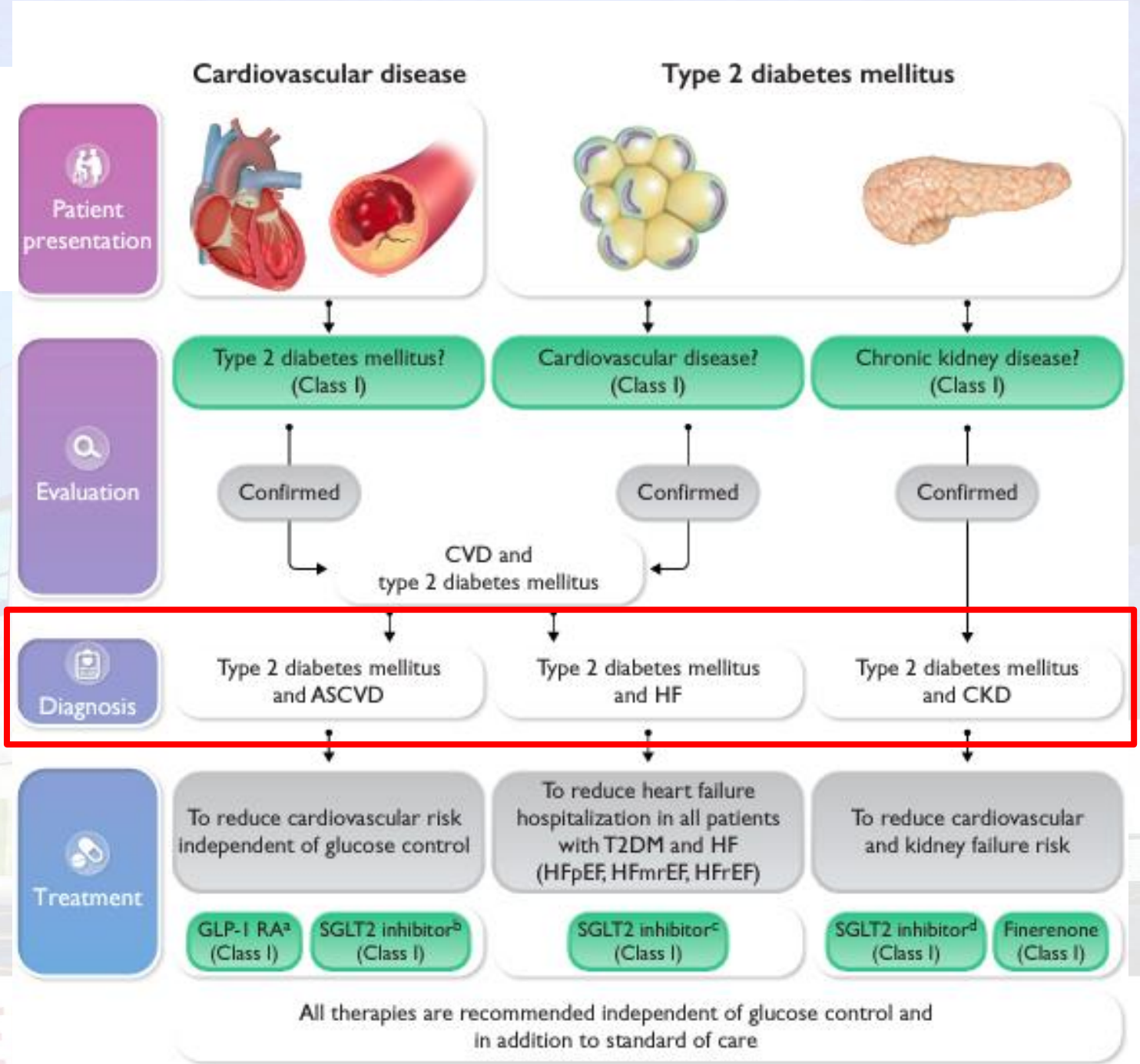


* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Diabetes Care. 2022;46(Supplement_1):S140-S157. doi:10.2337/dc23-S009

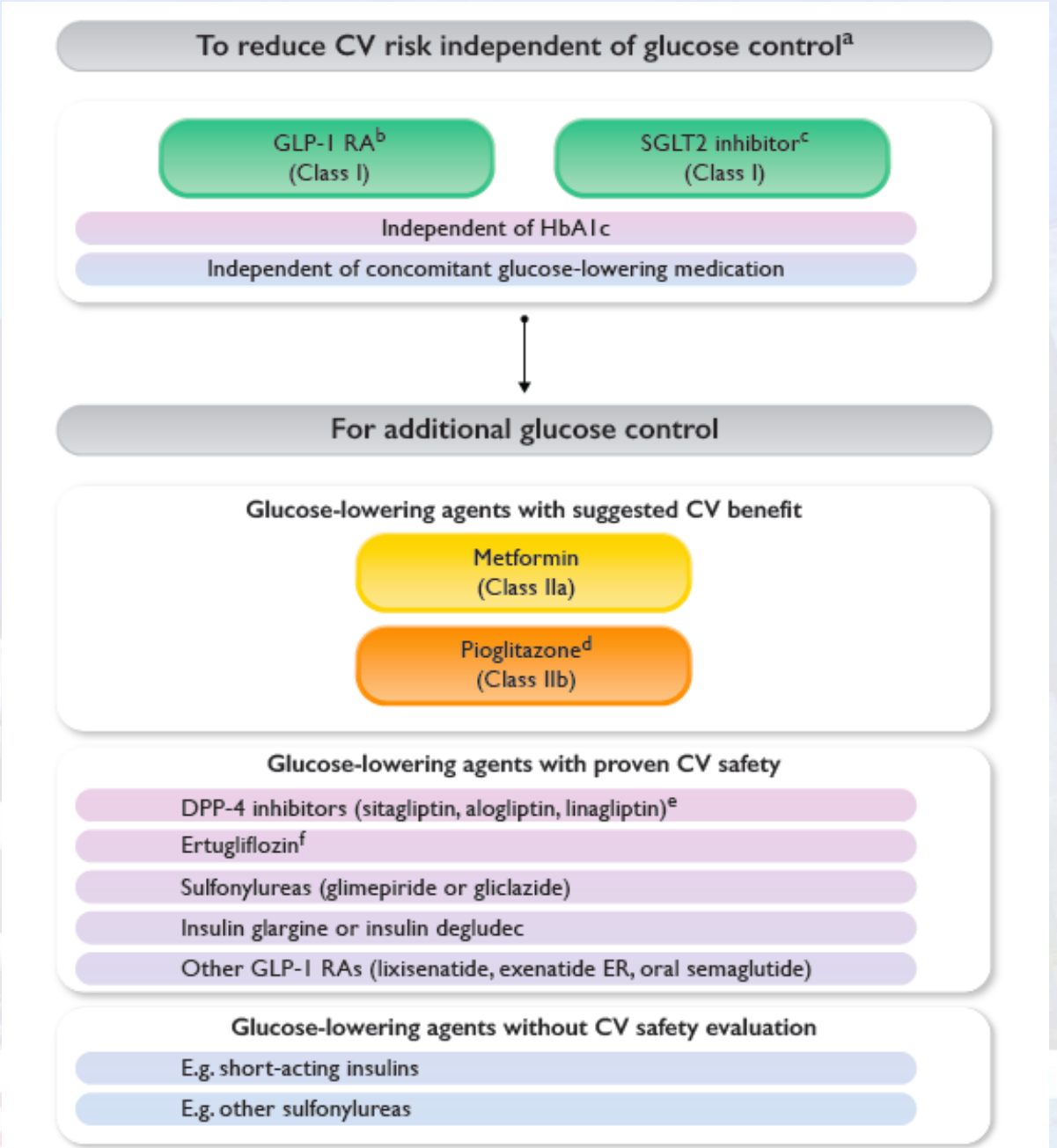
2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

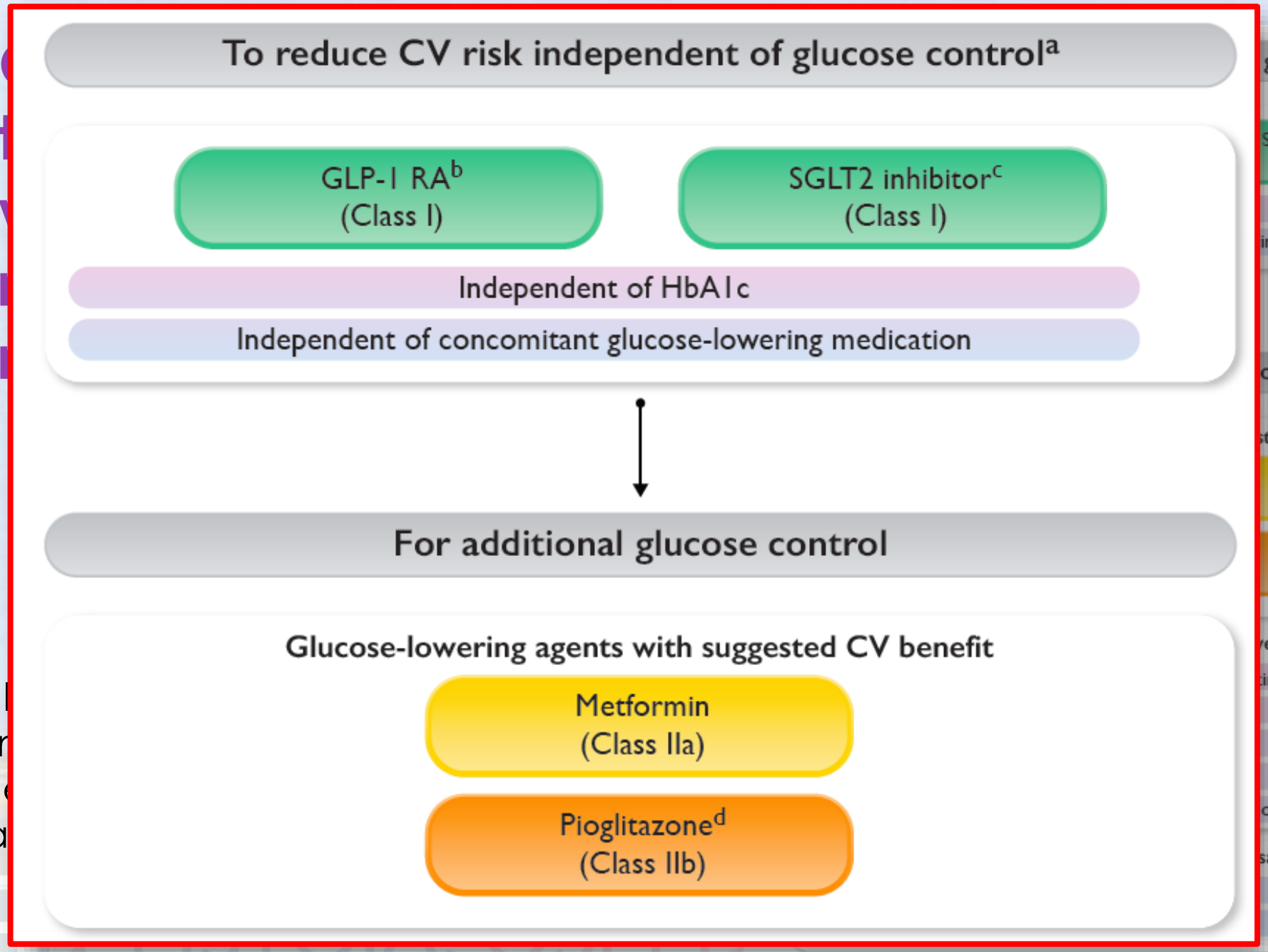


European Heart Journal, 25 Aug 2023

Glucose-lowering treatment for patients with T2DM and ASCVD to reduce cardiovascular risk



European Heart Journal, 25 Aug 2023



b: liraglutide, dulaglutide, semaglutide sc, efpeglenatide
c: *empagliflozin*, *canagliflozin*, dapagliflozin, sotagliflozin

European Heart Journal, 25 Aug 2023

world diabetes day

Diabete Oggi e Genere

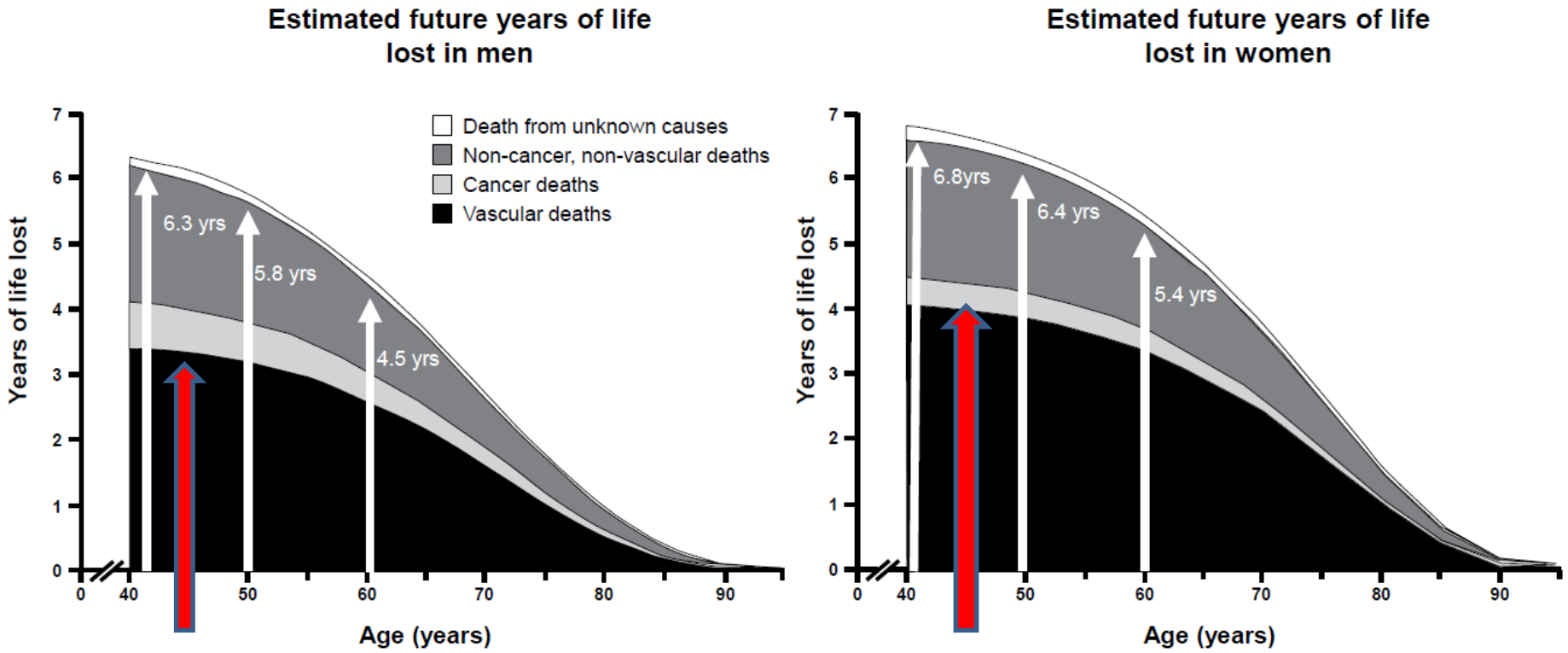
14 NOVEMBER WORLD DIABETES DAY 2023

Kautzky-Willer A et al, *Sex differences in typer 2 diabetes*, Diabetologia (2023)

Medicina di Genere in Diabetologia

- Quali differenze di genere nel diabete in Italia ?
- Differenze di qualità dell'assistenza o differenze biologiche ?
- Resistenza ai farmaci o discontinuità e mancata aderenza alle terapie ?
- Quali scelte - terapeutiche e non solo - da fare subito ?

T2DM is associated with premature death from CV and non-CV causes



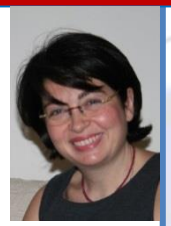
Arrows indicate the number of years of life lost incurred at specific ages by men or women with diabetes but without a history of vascular disease
CV, cardiovascular
Emerging Risk Factors Collaboration. *N Engl J Med* 2011;364:829–841

Anni di vita persi in DT2 in base al genere

Pari Opportunità …. di rischio CV:

Le donne Diabetiche sono colpite da Infarto tanto come gli uomini:

- hanno perso la protezione ormonale dall'infarto in età fertile



Editorial

Type 2 Diabetes and Cardiovascular Risk in Women

Giuseppina T. Russo,[1] Giovannella Baggio,[2] Maria Chiara Rossi,[3] and Alexandra Kautzky-Willer[4]

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Received 18 January 2015; Accepted 18 January 2015

Cardiovascular diseases (CVD) are the leading cause of death, also in diabetic women. Since 1998, when Haffner et al. [1] stated that subjects with type 2 diabetes mellitus (T2DM) had a CVD risk "equivalent" to previous myocardial infarction, a large number of studies have shown that this relative risk for CVD due to diabetes is greater in women than in men [2].

CVD in diabetic subjects is not entirely related to chronic hyperglycaemia and a number of other factors such as dyslipidemia, hypertension, hormonal, genetic, and environmental factors, as well as low-grade systemic inflammation and endothelial damage, lifestyle behaviours, adherence to therapies, and/or psychosocial factors may contribute to the worst outcomes observed in diabetic women. Notably, it is increasingly recognized that many of these factors show gender differences in their prevalence and/or association with CVD events, and this aspect should be specifically targeted when aiming at primary or secondary CVD prevention in diabetic subjects.

In this special issue, we looked at CVD in women than in males for mortality for all causes, for CVD, and for myocardial infarction and renal causes. In the other study, G. Luo et al. showed in a retrospective analysis that fasting plasma glucose was an independent predictor of in-hospital mortality for nondiabetic female patients.

Gender-specific prevalence and management of major and emerging CVD risk factors in different populations were also the main topic of several papers of this special issue.

The paper by S. Chen et al., with a very interesting experimental protocol, clarified the relationships of albuminuria, a well-recognized CVD risk factor, with circulating levels of angiopoietin-1 (Ang-1), Ang-2, and vascular endothelial growth factor (VEGF) in serum and urine.

Potential gender differences in the distribution and control of major CVD risk factors were investigated in another three very large high-risk populations. Thus, in the eControl Study, a study on 286,791 patients with T2DM in Catalonia, Spain, J. Franch-Nadal et al. found that cardiometabolic control was worse in subjects with prior CVD; but control

Registri N-Hanes:

- **Riduzione della CHD nella pop generale**
- **Non nel DM**
- **Aumento nelle Donne con DM**

Intern J Endocrinology ,2015

Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies

Rachel Huxley, Federica Barzi, Mark Woodward

BMJ, 21 December 2006)

Abstract

Objective To estimate the relative risk for fatal coronary heart disease associated with diabetes in men and women.
Design Meta-analysis of prospective cohort studies.
Data sources Studies published between 1966 and March 2005, identified through Embase and Medline, using a combined text word and MESH heading search strategy, in addition to studies from the Asia Pacific Cohort Studies Collaboration.
Review methods Studies were eligible if they had reported estimates of the relative risk for fatal coronary heart disease comparing men and women with and without diabetes. Studies were excluded if the estimates were not adjusted at least for age.
Results 37 studies of type 2 diabetes and fatal coronary heart disease among a total of 447 064 patients were identified. The rate of fatal coronary heart disease was higher in patients with diabetes than in those without (5.4 *v* 1.6%). The overall summary relative risk for fatal coronary heart disease in patients with diabetes compared with no diabetes was signif
3.50,
After
age, t
reduced but still highly significant. The pooled ratio of the relative risks (women: men) from the 29 studies with multiple adjusted estimates was 1.46 (1.14 to 1.88).
Conclusions The relative risk for fatal coronary heart disease associated with diabetes is 50% higher in women than it is in men. This greater excess coronary risk may be explained by more adverse cardiovascular risk profiles among women with diabetes, combined with possible disparities in treatment that favour men.

RR F vs M nei 29 studi corretti per fattori confondenti = **1,49**

Le Donne Diabetiche hanno il 50% in più di rischio di Eventi CV fatali rispetto ai Maschi.

Cause :

- **Peggiore profilo di rischio CV**
- **Sottotrattamento con Statine, ASA, Antiipertensivi , B Bloccanti**

Donne con DM2 hanno un rischio aumentato di eventi CV e di mortalità del 50% rispetto ai maschi

Recent studies found that men with diabetes or established cardiovascular disease are more likely to receive aspirin, statins, or antihypertensive drugs than are women. For example, one study
r cardiovascular
45% of men with
e reported from the United Kingdom prospective diabetes study,[39] where women with diabetes were significantly less likely to use aspirin compared with men. In two recent studies from the United States, women with diabetes were also less likely to be treated with aspirin and lipid lowering agents or to achieve recommended levels of blood pressure or low density lipoprotein cholesterol than were men.[40 41] Therefore more

Le donne con T2DM hanno anche un aumentato rischio di Stroke

Diabetologia (2006) 49:2859–2865
DOI 10.1007/s00125-006-0493-z

ARTICLE

Risk of stroke in people with type 2 diabetes in the UK: a study using the General Practice Research Database

H. E. Mulnier · H. E. Seaman · V. S. Raleigh · S. S. Soedamah-Muthu · H. M. Colhoun · R. A. Lawrenson · C. S. De Vries

Table 4 Hazard ratios (95% CI) for stroke in diabetes compared with no diabetes stratified by sex and attained age-group

	All	Men	Women
Diabetes/no diabetes (*n*)	41,799/ 202,733	22,178/ 107,285	19,621/ 95,448
Age (years)			
35–54	5.64 (3.91–8.13)	4.66 (2.96–7.33)	8.18 (4.31–15.51)
55–64	3.81 (3.23–4.49)	3.31 (2.69–4.07)	4.89 (3.71–6.45)
65–74	2.54 (2.31–2.79)	2.35 (2.07–2.65)	2.83 (2.45–3.28)
75–84	1.90 (1.75–2.06)	1.69 (1.49–1.90)	2.10 (1.89–2.34)
≥85	1.69 (1.49–1.92)	1.60 (1.28–1.99)	1.74 (1.49–2.03)
All ages	2.19 (2.09–2.32)	2.08 (1.94–2.24)	2.32 (2.16–2.49)

Age-adjusted HR for stroke in DM2 subjects vs non diabetic subjects was:
- 2.08 (95%CI:1.94-2.24) in men
- 2.32 (95%CI: 2.16-2.49) in women.

The increase in risk attributable to diabetes was highest
- in young women (HR 8.18; 95%CI 4.31-15.51) and decreased with age.

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Reggio Emilia
IRCCS Istituto in tecnologie avanzate e modelli assistenziali in oncologia

MACE

Research Article

Sex Differences in the Effect of Type 2 Diabetes on Major Cardiovascular Diseases: Results from a Population-Based Study in Italy

International Journal of Endocrinology
Volume 2017, Article ID 6039356, 9 pages

Paola Ballotari,[1,2] Francesco Venturelli,[3] Marina Greci,[4] Paolo Giorgi Rossi,[1,2] and Valeria Manicardi[5]

	UOMINI			DONNE		
EVENTO:	**SENZA DM2**	**CON DM2**	**IRR (95%CI)**	**SENZA DM2**	**CON DM2**	**IRR (95%CI)**
ICTUS	37.28	74.70	**1.86 (1.68-2.06)**	30.10	61.73	**1.81 (1.60-2.04)**
INFARTO	39.04	78.02	**1.78 (1.60-1.98)**	16.13	47.58	**2.58 (2.22-2.99)**
SCOMPENSO	**21.47**	**63.71**	**2.78 (2.48-3.12)**	**17.10**	**48.83**	**2.59 (2.27-2.97)**

I Diabetici hanno un rischio aumentato (quasi doppio per ICTUS E INFARTO, quasi triplo per SCOMPENSO), ma le DONNE con DT2 hanno un RISCHIO di IMA >> Maschi

Diabete
Differenze di genere nel Rischio CV e Renale

Current Diabetes Reports (2018) 18: 33
https://doi.org/10.1007/s11892-018-1005-5

DIABETES EPIDEMIOLOGY (E SELVIN AND K FOTI, SECTION EDITORS)

Sex Differences in the Burden and Complications of Diabetes

Sanne A. E. Peters[1] · Mark Woodward[1,2,3]

Published online: 18 April 2018

Abstract

Purpose of the Review To review the latest evidence on sex differences in the b
the potential explanations for the sex differences described.

Recent Findings Diabetes is a strong risk factor for vascular disease, with comp
diseases conferred by diabetes are considerably greater in women than men.
relative risk of vascular disease from diabetes are unknown. Sex differences
management, and treatment of diabetes and its complications could contribute to
complications. However, since the excess risk of vascular disease is not seen
biological factors may be more likely to be involved. In addition to other cardio
composition and fat distribution may be particularly important in explainin
complications of diabetes.

Summary There is strong evidence to suggest that diabetes is a stronger risk
Although several mechanisms may be involved, further research is needed to
anisms underpinning sex differences in the association between diabetes an
patients, health care professionals, and policy makers to ensure that women
and will help to reduce the burden in both sexes.

Keywords Diabetes · Cardiovascular disease · Men · Women · Sex differences

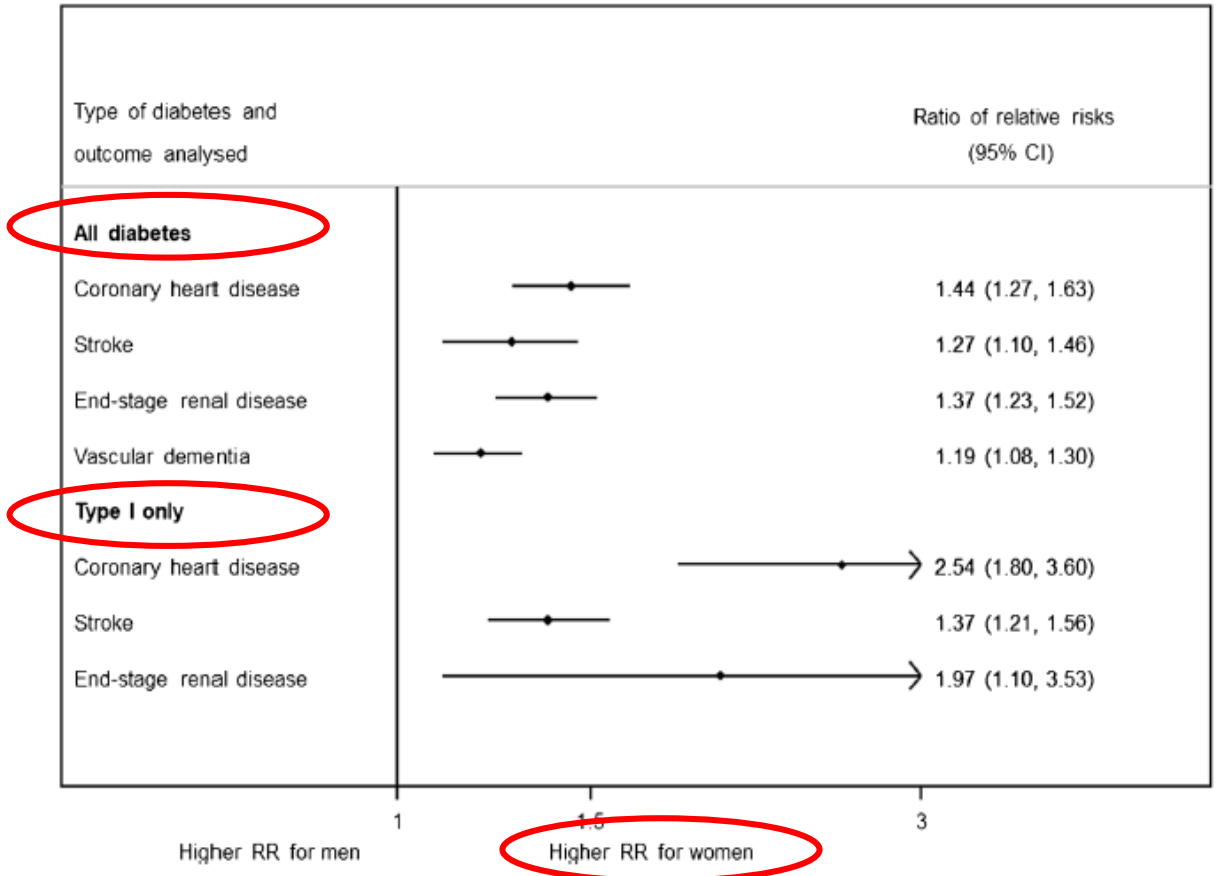


Fig. 2 Results from prior meta-analyses of sex differences in the effects of diabetes on vascular outcomes, summarised through the ratios of women-to-men adjusted relative risks (and 95% confidence intervals) pooled across cohort studies

Diabetologia (2019) 62:1761–1772
https://doi.org/10.1007/s00125-019-4939-5

REVIEW

Sex differences in the burden of type 2 diabetes and cardiovascular risk across the life course

Amy G. Huebschmann[1,2] · Rachel R. Huxley[3,4] · Wendy M. Kohrt[1,5,6] · Philip Zeitler[7] · Judith G. Regensteiner[1,2,8] · Jane E. B. Reusch[1,6,9]

Received: 20 April 2019 / Accepted: 29 May 2019 / Published online: 27 August 2019

In terms of relative risk for CVD, large meta-analyses of observational data have shown that women with type 2 diabetes have 25–50% greater excess risk of an incident cardiovascular event compared with similarly affected men [1, 15, 72, 73]. For example, recent data from the UK Biobank showed that, in the presence of type 2 diabetes, the excess risk of a cardiovascular event was approximately 50% higher in women (HR 1.96 [95% CI 1.60, 2.41]) than in men (HR 1.33 [95% CI 1.18, 1.51]) [74].

La Medicina di Genere in Diabetologia nasce in AMD nel 2010 :

il patrimonio degli ANNALI in ottica di genere

Esistono differenze genere - specifiche

- nella **Qualità della Cura erogata ?**
- nel **profilo di rischio CV ?**
- nella **appropriatezza ed intensità di cura ?**

Strumento indispensabile : **Cartella Informatizzata SDC**

Differenze di Genere nel Diabete : dal 2011 al 2019

2011 → **2016** → **2019** **In press**

DT2

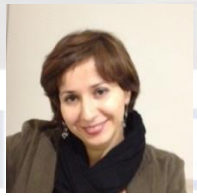
Sex Disparities in the Quality of Diabetes Care: Biological and Cultural Factors May Play a Different Role for Different Outcomes

A cross-sectional observational study from the AMD Annals initiative

MARIA CHIARA ROSSI, MSCPHARMCHEM[1]
MARIA ROSARIA CRISTOFARO, MD[2]
SANDRO GENTILE, MD[3]
GIUSEPPE LUCISANO, MSCSTAT[1]
VALERIA MANICARDI, MD[4]
MARIA FRANCA MULAS, MD[5]
ANGELA NAPOLI, MD[6]
ANTONIO NICOLUCCI, MD[1]
FABIO PELLEGRINI, MSCSTAT[1]
CONCETTA SURACI, MD[7]
CARLO GIORDA, MD[8]
ON BEHALF OF THE AMD ANNALS STUDY GROUP*

Gender medicine integrates aspects of biology, sociology, ethnicity, and culture responsible for different responses to care in women and men (1). Gender medicine applied to the field of diabetes care is particularly relevant because women with diabetes, regardless

OBJECTIVE—To investigate the quality of type 2 diabetes care according to sex.



- ✓236 centri
- ✓188,125 donne
- ✓227,169 uomini

Differenze di genere nel DT2 (2011)

- **COMPENSO METABOLICO (HbA1c)**
- **PROFILO LIPIDICO (LDL-C)**
- **OBESITA' (BMI)**

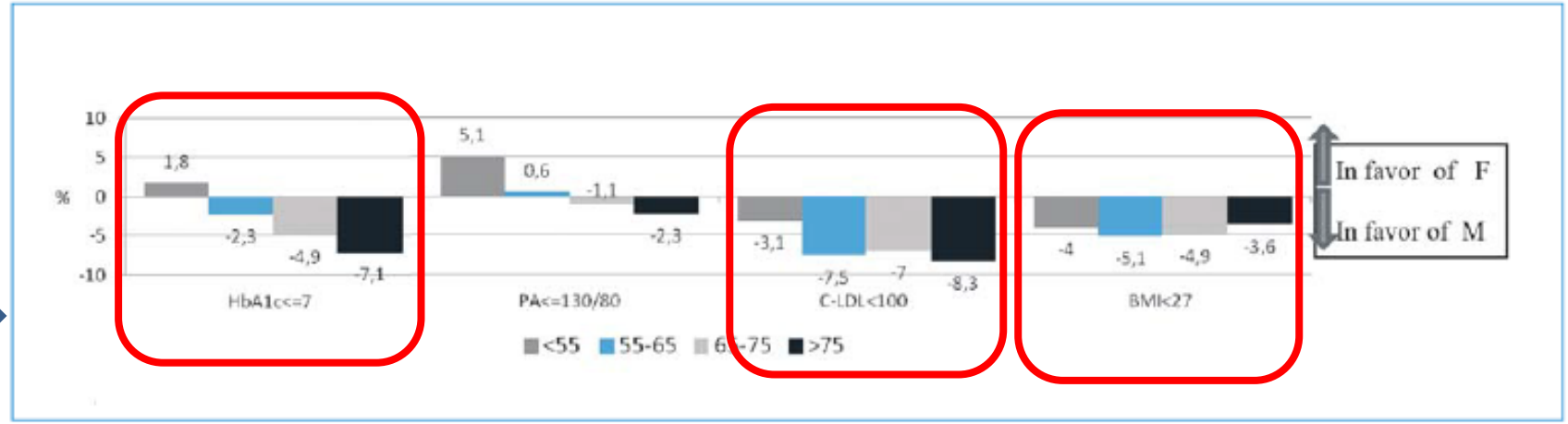


Figure 1. Favorable outcomes in diabetic men and women and age (*AMD Annals*). The intermediate outcomes (target of HbA1c, PA, C-LDL, BMI) are systematically in favor of men, independently of age.

Trend delle differenze di genere nel DT2

Indicatori di esito intermedio favorevole nel DT2

DT2 a target	2011 F/M (%)	Diff %	2019 F/M (%)	Diff %
HbA1c ≤7.0% F/M	41,7/45,5	- 3,8	50,3/53,3	- 3.0
C-LDL <100 mg/dl F/M	38,4/44,6	- 6,2	60,3/68,5	+ 8.2
PA <140/90 mmHg F/M	41,9/43,8	-1,9	54,5/ 53,4	+ 1.2

Miglioramento continuo della Qualità di cura, ma invariate le differenze di genere

Il Miglioramento continuo: Diabete Tipo 2

Indicatori di esito intermedio sfavorevole nel DT2

Indicatore	2011 F/M (%)	Diff %	2019 F/M (%)	Diff %
HbA1c >8.0%	**29,1/26,9**	**+ 2,2**	**19,5/17,9**	**+1,4**
C-LDL ≥130 mg/dl	**28,9/23,6**	**+ 5,3**	**14,2/9,7**	**+ 4,5**
PA ≥140/90 mmHg	58,1/56,2	+1,9	45,5/46,6	- 1,1
BMI ≥ 30 Kg/m^2	**46,8/37,2**	**+ 10,6**	**43,8/36,3**	**+ 7,5**
Fumatori	**//**		**12,5/20,3**	**- 7,8**

OBESITA'

Circulation 2016

AHA Scientific Statement

Acute Myocardial Infarction in Women

A Scientific Statement From the American Heart Association

Abstract—Cardiovascular disease is the leading cause of mortality in American women. Since 1984, the annual cardiovascular disease mortality rate has remained greater for women than men; however, over the last decade, there have been marked reductions in cardiovascular disease mortality in women. The dramatic decline in mortality rates for women is attributed partly to an increase in awareness, a greater focus on women and cardiovascular disease risk, and the increased application of evidence-based treatments for established coronary heart disease. This is the first scientific statement from the American Heart Association on acute myocardial infarction in women. Sex-specific differences exist in the presentation, pathophysiological mechanisms, and outcomes in patients with acute myocardial infarction. This statement provides a comprehensive review of the current evidence of the clinical presentation, pathophysiology, treatment, and outcomes of women with acute myocardial infarction. (*Circulation*. 2016;133:00-00. DOI: 10.1161/CIR.0000000000000351.)

BMI=>30 : F 45,8%

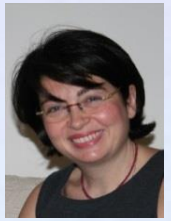
Obesity and Type 2 DM

compared with lean women.[169] Obesity is a major risk factor for AMI in women and increases their risk almost 3-fold.[170] The risk of AMI associated with the metabolic syndrome is higher in younger women than any of the other groups, increasing their odds of AMI almost 5-fold.[171] DM, related to obesity and the metabolic syndrome, is associated with a higher relative risk of coronary events in women compared with men, in part as a result of a higher rate of coexisting risk factors in women with DM[170] and better survival (relative to men) of women without DM.[172] DM is an especially powerful risk factor in young women, increasing their risk of CHD, including ACS, by 4- to 5-fold.[173] For both men and women with DM, mortality after STEMI or UA/NSTEMI is significantly increased compared with their nondiabetic counterparts at 30 days and 1 year.[174]

OBESITA':
Maggior fattore di rischio di Infarto nella donna(x3)

S.Metabolica e DM : x 4 - 5 Nelle donne giovani

Profilo LIPIDICO



Il mancato raggiungimento dei target di LDL-C è sempre a sfavore delle Donne con DT2 :

- Sia trattate che non trattate con Statine
- le differenze aumentano con età e durata del DM.

Le Donne con DT2 più anziane sono a maggior rischio di CHD.

Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2015, Article ID 957105, 8 pages
http://dx.doi.org/10.1155/2015/957105

Hindawi

Research Article

Age- and Gender-Related Differences in LDL-Cholesterol Management in Outpatients with Type 2 Diabetes Mellitus

Giuseppina Russo,[1] Basilio Pintaudi,[2] Carlo Giorda,[3] Giuseppe Lucisano,[2] Antonio Nicolucci,[2] Maria Rosaria Cristofaro,[4] Concetta Suraci,[5] Maria Franca Mulas,[6] Angela Napoli,[7] Maria Chiara Rossi,[2] and Valeria Manicardi[8]

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[2]*Department of Clinical Pharmacology and Epidemiology, Fondazione Mario Negri Sud, Via Nazionale, 66030 S. Maria Imbaro, Italy*
[3]*Diabetes and Metabolism Unit, ASL TO5, 10023 Chieri, Italy*
[4]*Diabetes and Endocrinology Unit, Cardarelli Hospital, 86100 Campobasso, Italy*
[5]*Diabetes and Metabolism Unit, Sandro Pertini Hospital, 00157 Rome, Italy*

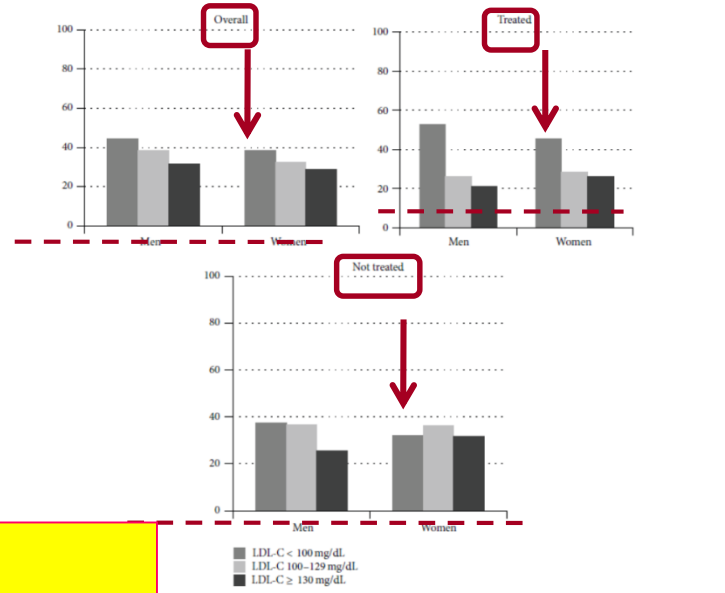
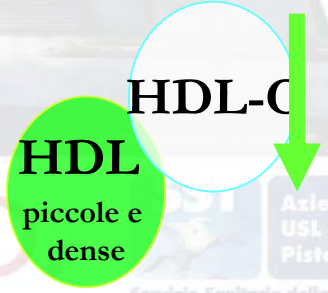
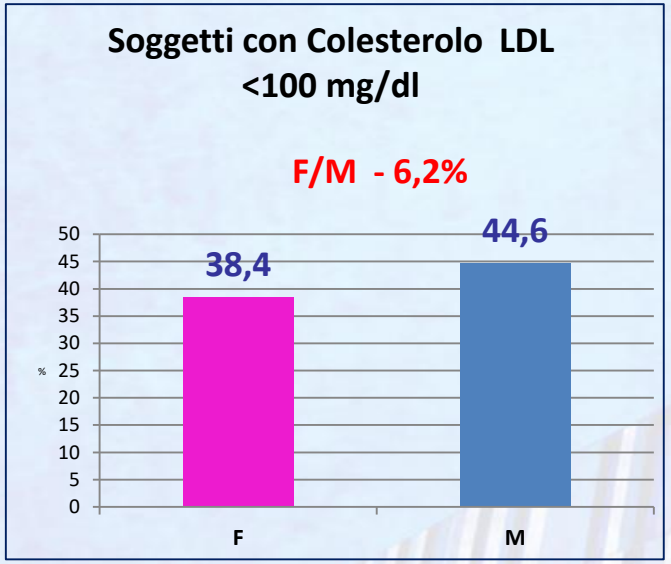


FIGURE 1: LDL-C classes according to gender and lipid-lowering treatment.

Donne DM2 senza CHD hanno lo stesso profilo sottopopolazioni HDL degli uomini con pregresso IMA: HDL meno ateroprotettiva *(Atherosclerosis, 2010:204)*



Trend dell'LDL-Colesterolo nel DT2 in base al genere

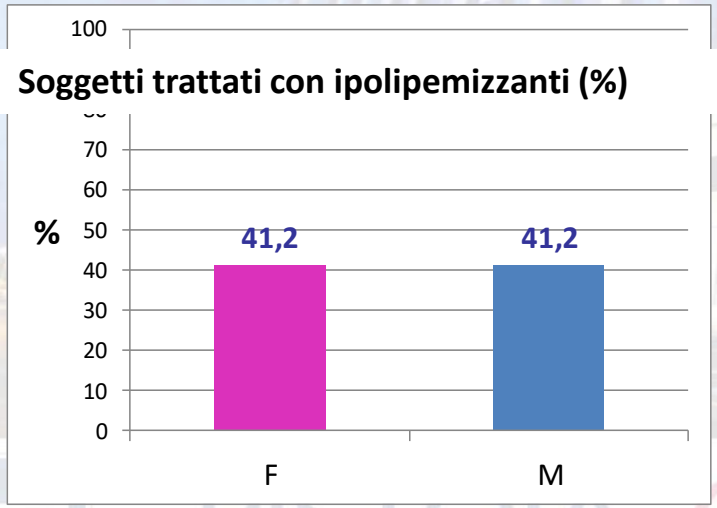


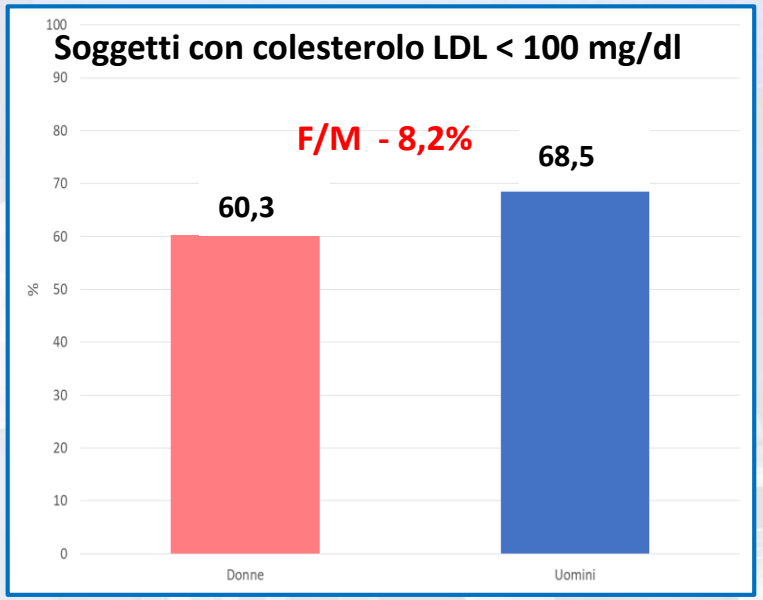
2011

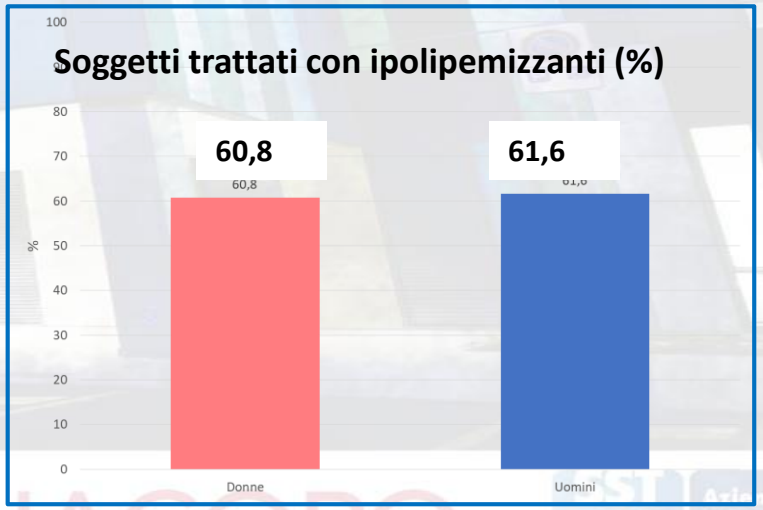
2019

I dati degli Annali 2011 → 2019

I Target sono migliorati sia nei M che nelle F ,
ma le differenze a sfavore delle donne sono rimaste,
a parità di trattamento con Ipolipemizzanti







I nuovi Target di LDL-C

LDL-COL in base al genere nel DT2 (a.2019)

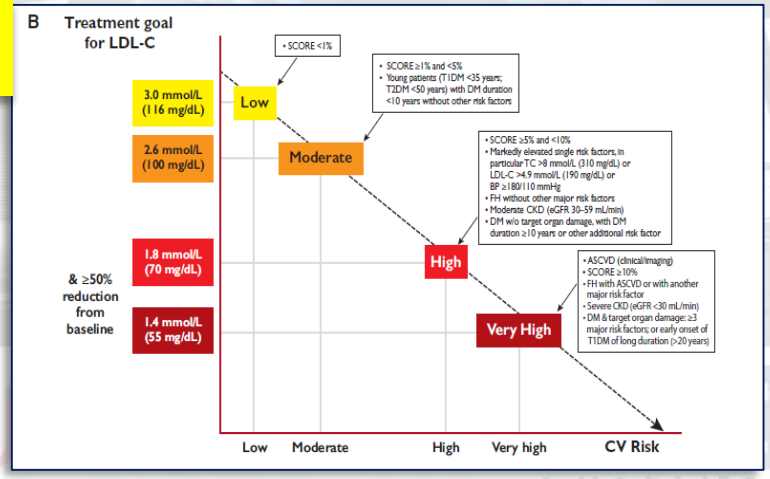
Andamento per 5 classi del colesterolo LDL (%)

CLASSI LDL (mg/dl)	Donne	Uomini
<70,0	22,4	31,3
70,0-99,9	37,9	37,2
100,0-129,9	25,5	21,8
130,0-159,9	10,3	7,5
≥160	3,9	2,2

Perché ?

- Le donne hanno più effetti collaterali da statine
- Non conosciamo i dosaggi
- Non conosciamo l'aderenza e la persistenza

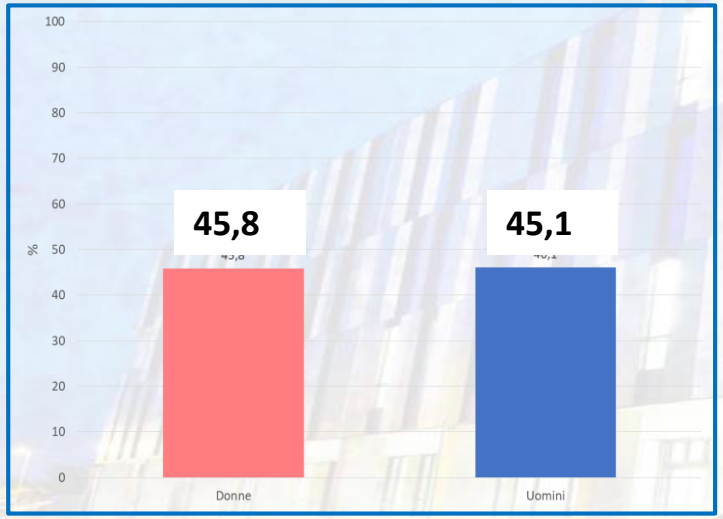
ESC-2021



Trend nel trattamento Ipolipemizzante nel DT2

Soggetti non trattati con ipolipemizzanti nonostante valori di colesterolo LDL ≥ 130 mg/dl (%)

2011	F	M
No terapia	52,6	51,3



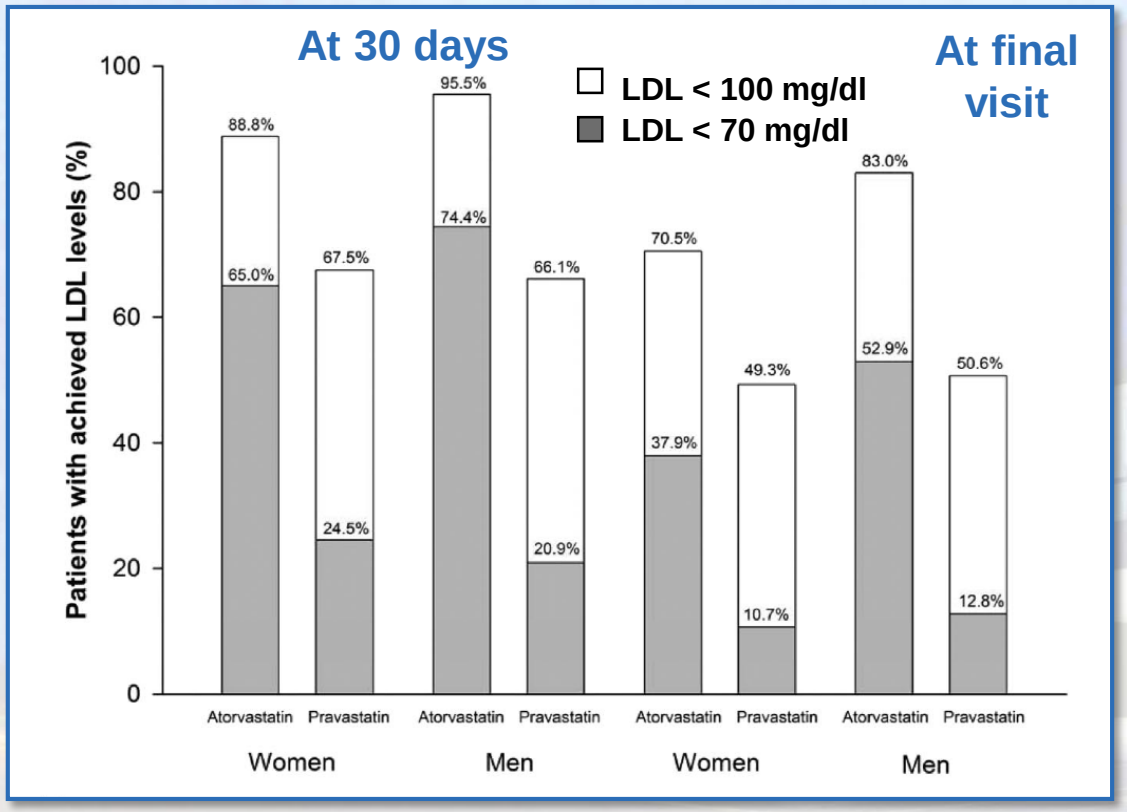
Soggetti con colesterolo LDL ≥130 mg/dl nonostante il trattamento con ipolipemizzanti (%)

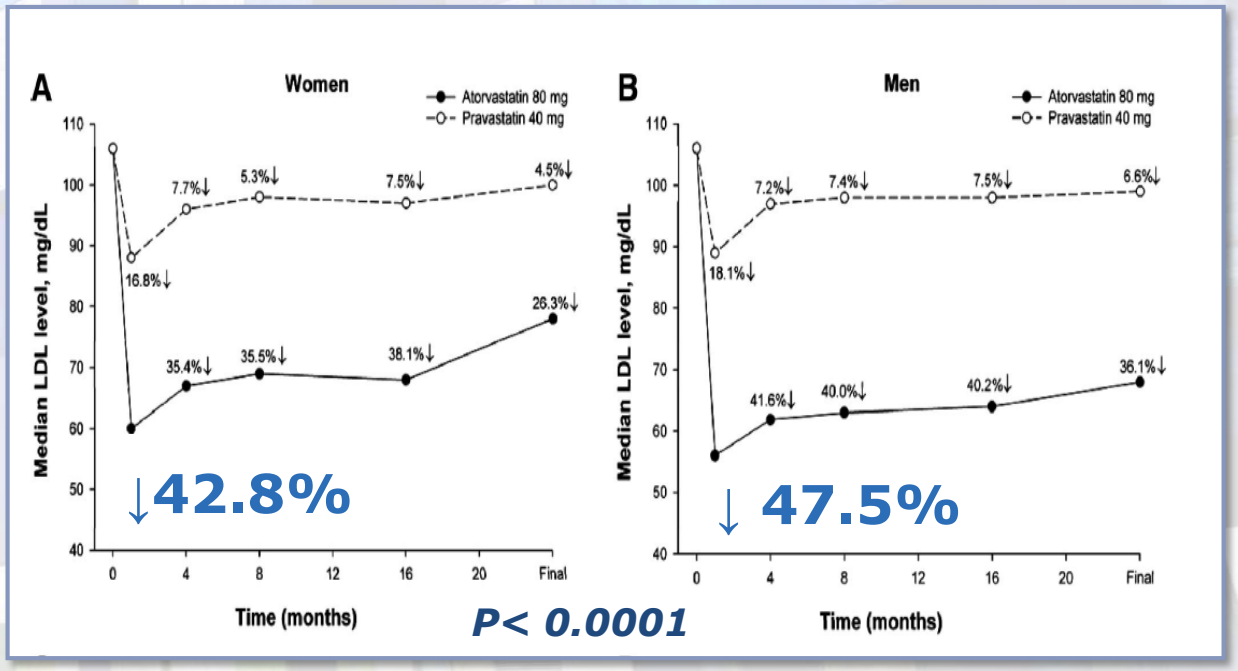
2011	F	M
LDL > 130	25,9	21.1

I dati degli Annali 2019

Resistenza o Discontinuità ?

Differenza tra uomini e donne
Nel raggiungimento dei target di LDL-C
e nella risposta al trattamento con statine





Truong QA Circ Cardiovasc Qual Outcomes. 2011;4:328-336

Il genere influenza le scelte Terapeutiche ?

European Heart Journal (2011) **32**, 1337–1344
doi:10.1093/eurheartj/ehr027

CLINICAL RESEARCH

Factors influencing underutilization of evidence-based therapies in women†

Raffaele Bugiardini[1]*, Andrew T. Yan[2], Raymond T. Yan[2], David Fitchett[2], Anatoly Langer[2], Olivia Manfrini[1], and Shaun G. Goodman[2], on behalf of the Canadian Acute Coronary Syndrome Registry I and II Investigators*

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Received 18 October 2010; revised 8 January 2011; accepted 25 January 2011; online publish-ahead-of-print 7 March 2011

See page 1313 for the editorial comment on this article (doi:10.1093/eurheartj/ehr083)

Aims Previous studies have reported differences in the use of cardiovascular medications for acute coronary syndromes (ACSs) according to the sex of the patient. We analysed which clinical factors are associated with underutilization of evidence-based therapies in women.

Methods and results From the Canadian Registry of ACS I and II, 6558 patients (4471 men and 2087 women) with a final diagnosis of ACS were selected for the current analysis. Covariates were chosen using the approach described by Blackstone. The final selected model included 23 patient clinical variables. Women were less likely than men to receive beta-blockers (75.76 vs. 79.24%; $P < 0.01$), lipid-modifying agents (56.37 vs. 65.44%; $P < 0.0001$), and angiotensin-converting enzyme (ACE)-inhibitors (55.52 vs. 59.99%; $P < 0.01$). Female sex and clinical decision not to investigate with cardiac catheterization were the strongest independent predictors for not receiving lipid-modifying agents and ACE-inhibitors. Age, Killip class 2, and Killip class 3/4 were significant independent predictors of underutilization of beta-blocker use. Women were older (69 ± 12 vs. 64 ± 12; $P < 0.01$) with a higher prevalence of Killip class ≥ 2 (19.95 vs. 15.54%; $P < 0.068$), and they were less likely to be referred for cardiac catheterization (41.9 vs. 49.6%; $P < 0.001$).

Conclusions The current findings demonstrate that underutilization of evidence-based therapies in women with ACS compared with men is associated with multiple factors related to the patient (age), the consequences of the disease (congestive heart failure), and the physician's assessment of patient risk (decision to catheterize). Female gender remains associated with underutilization of lipid-modifying agents and ACE-inhibitors despite adjustment for these confounders.

Keywords Women • Evidence-based therapies

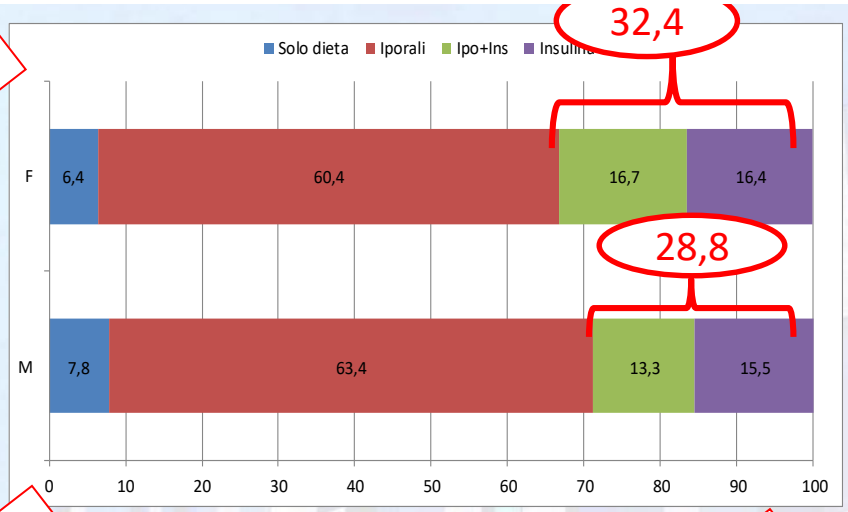
Il genere femminile Resta un predittore indipendente di sotto Utilizzo di Statine e ACE-I

Sottotrattamento delle donne con Diabete vs uomini

WHO : Women are not little men

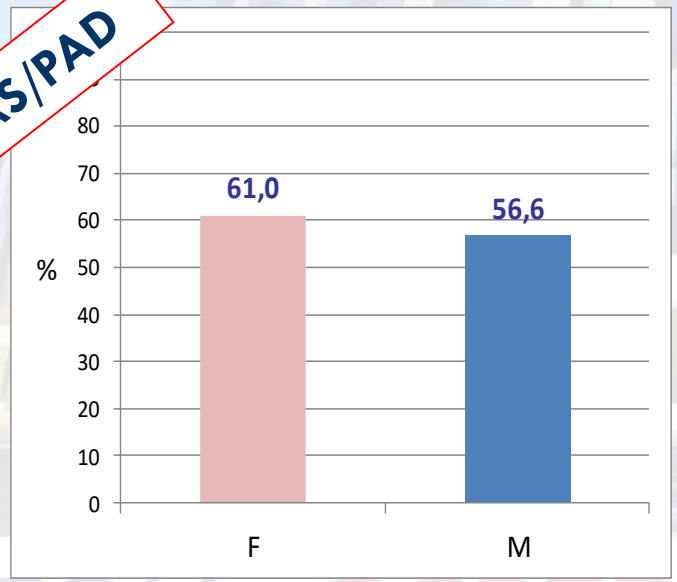
DT2 – Trattamento del diabete in base al genere (2011): Appropriatezza e Intensità

Compenso metabolico



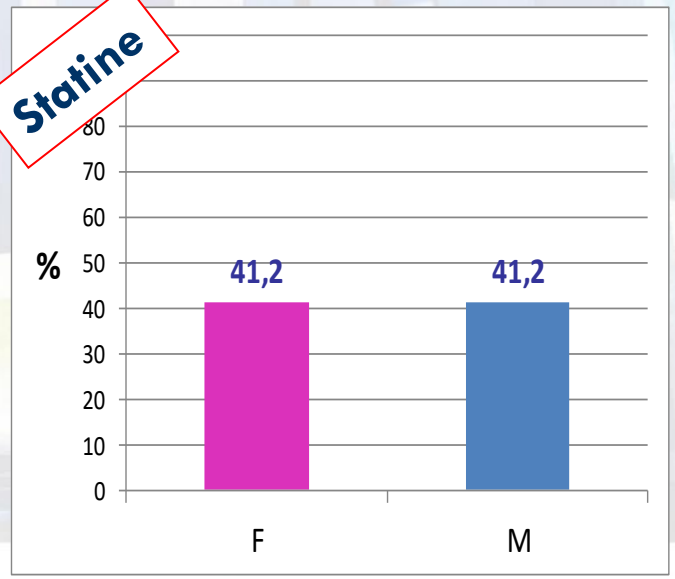
Le donne con DT2 sono trattate più intensamente :
con Insulina e Insulina + Ipo-Orali

PAS/PAD



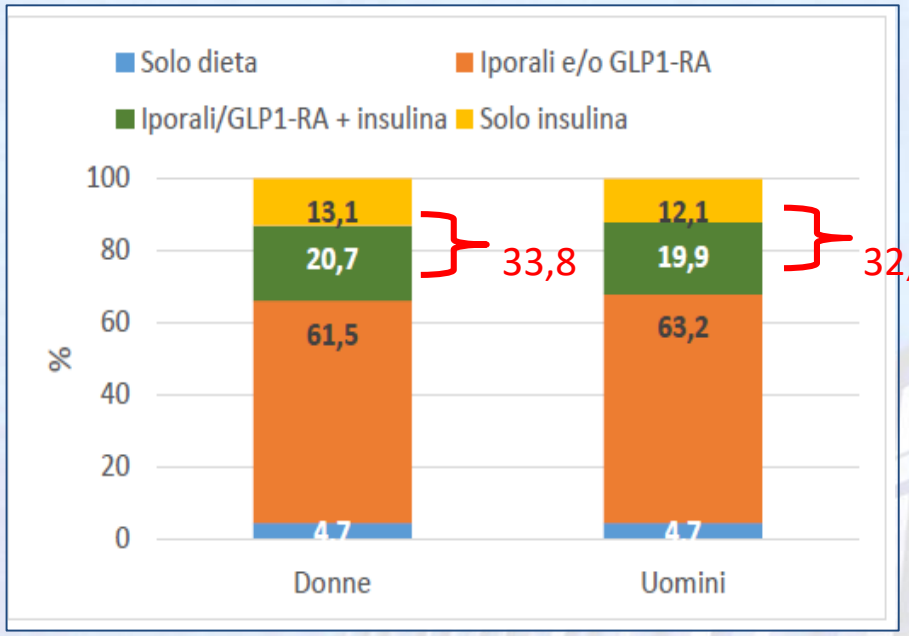
Le donne sono più trattate con farmaci antiipertensivi e con più di 2 farmaci.

Statine



Stessa % di M e F trattati con statine

DT2 – Trattamento del diabete in base al genere (2019): Appropriatezza e Intensità



Controllo metabolico

Nuovi Farmaci	F	M
GLP1-RA	10,7	11,1
SGLT2i	9,8	13,8

PAS/PAD

Anti ipertensivi	F	M
% trattati	71,3	67,5
ACEi/sart %	81,7	84

Stessa % di M e F trattati con antiipertensivi

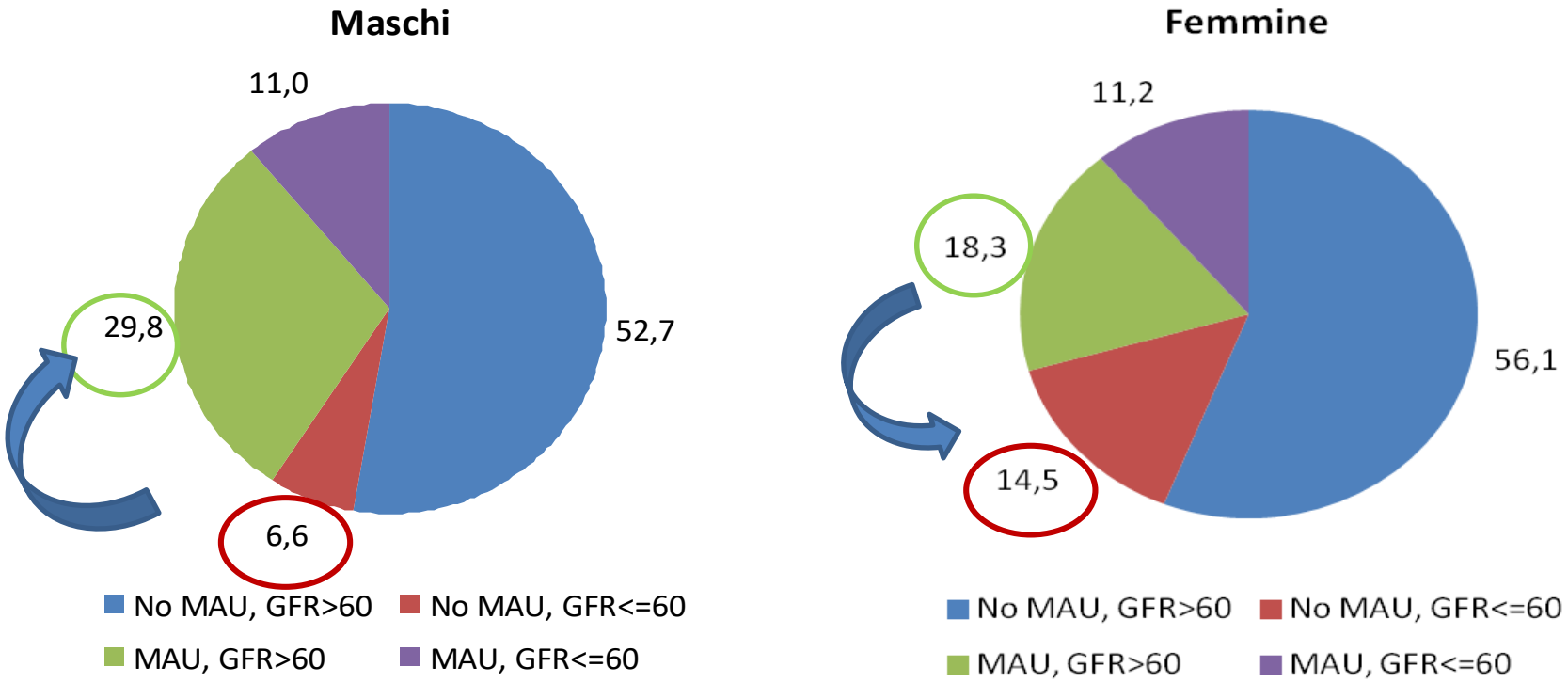
Ipolipemizzanti

Ipo lipemizzanti	F	M
% trattati	60,8	61,6
Ezetimibe	5,1	4,5

Stessa % di M e F trattati con statine

Differenze di genere e funzione renale : a. 2011

RENE



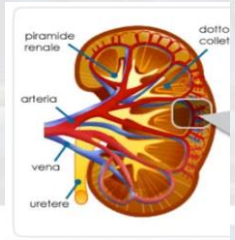
presenza di MAU

riduzione del GFR (%)

Nephrol Dial Transplant (2014) 29: 657–662
doi: 10.1093/ndt/gft506
Advance Access publication 6 January 2014

Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes

Salvatore De Cosmo[1], Maria Chiara Rossi[2], Fabio Pellegrini[2], Giuseppe Lucisano[2], Simonetta Bacci[1], Sandro Gentile[3], Antonio Ceriello[4], Giuseppina Russo[5], Antonio Nicolucci[2], Carlo Giorda[6], Francesca Viazzi[7], Roberto Pontremoli[7] and the AMD-Annals Study Group



Funzione Renale : differenze di genere (a.2019)

Fig.5 – Andamento per 4 classi del filtrato glomerulare (%).

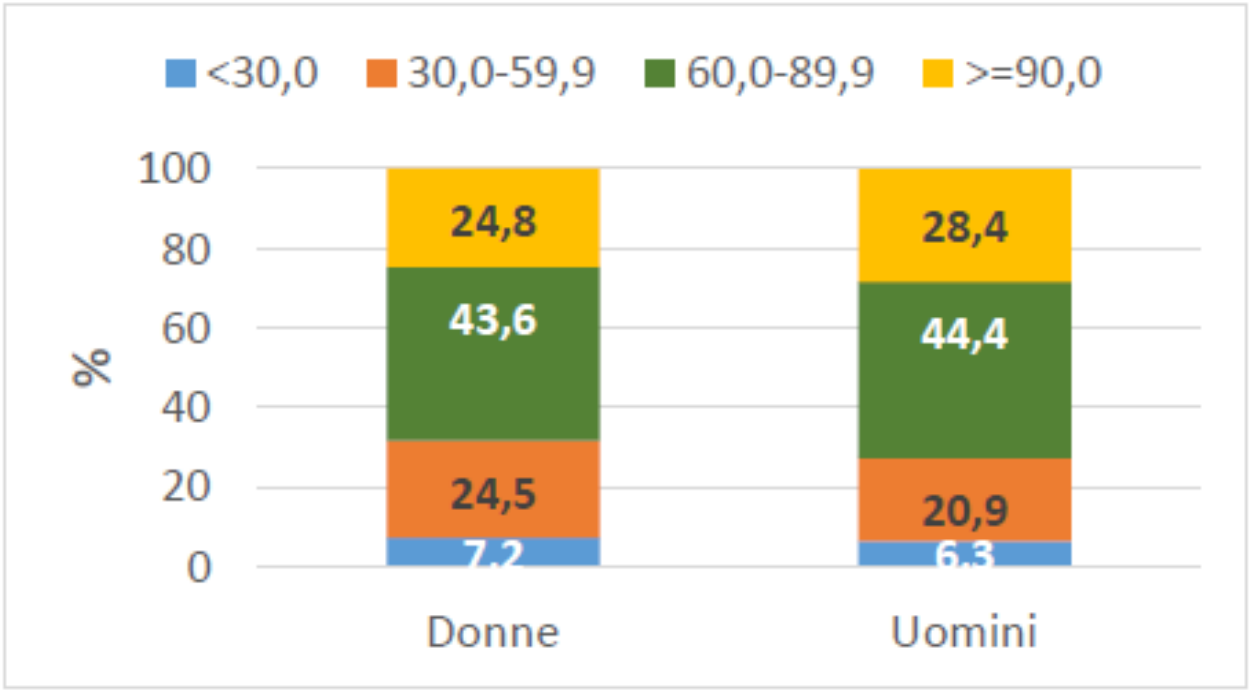
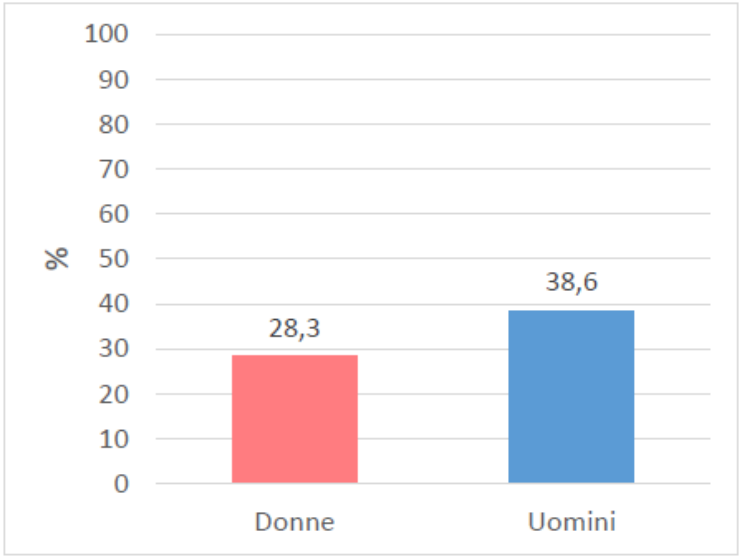


Fig.6 - Soggetti con micro/macroalbuminuria (%).



eGFR < 60 ml/m: 3 1,7 27,2 MAU 28,3 38,6

ANNALI 2011

Ital J Gender-Specific Med 2016; 2(2): 60-68

Gender differences in type 2 diabetes (Italy)

Valeria Manicardi[1], Maria Chiara Rossi[2], Elisabetta L Romeo[3], Annalisa Giandalia[3], Mariella Calabrese[4], Elena Cimino[5], Daniela Antenucci[6], Paola Bollati[7], Patrizia Li Volsi[8], Ada Maffettone[9], Guglielmina Speroni[10], Concetta Suraci[11], Elisabetta Torlone[12], Giuseppina Russo[3] (on behalf of Gruppo Donna AMD)

1. Department of Internal Medicine, Hospital of Montecchio, AUSL of Reggio Emilia, Italy; 2. CORESEARCH - Center for Outcomes
tal Medicine, University of Messina, Messina, Italy;
ly; 6. Endocrinology, Lanciano (Chieti), Italy;
Diabetology Department, AAS5, Pordenone, Italy;
ne and Diabetology, Hospital of Codogno (ASST
EM, Perugia, Italy.

Key messages

- Gender-differences have been reported in diabetic patients: in Italy they are less pronounced than in other countries, but it exists despite equal access to specialist care.
- The likelihood to reach metabolic targets (HbA1c, LDL-C, BMI, PA) is systematically unfavorable in diabetic women as compared with men.
- Diabetic women have a worse lipid profile than men, and have a 2-fold higher CHD risk compared
- Pathophysiological factors are involved in the greater difficulty to reach LDL-C targets in diabetic women, despite the same drug treatment in Italy.

enze di genere nell'utilizzo di questi farmaci.
ologici, e non solo, non ancora del tutto cono-
ono queste differenze e vanno esplorati.
e: genere, diabete di tipo 2, rischio cardiova-

Nel DT2 in Italia ci sono differenze a sfavore delle donne (meno evidenti che in altri paesi), ma le donne non sono sottotrattate

Studi Italiani di intervento confermano i dati degli ANNALI di Genere

Original Article | Journal of INTERNAL MEDICINE

doi: 10.1111/joim.12073

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. Lavalle[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 'Ca 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, Lavalle L, Nicolucci A, Pugliese G (University of Pisa, Pisa, Italy; University of Verona, Verona, Italy; University of Siena, Siena, Italy; Fondazione IRCCS 'Ca' 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.

Studio RIACE

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.

Donne con DT2:

- Peggiore profilo di rischio CV
- Più frequente fallimento nel raggiungimento dei target per i FdR CV
- Nessuna differenza di trattamento

RISPOSTA alle STATINE , all' ASA.....

Statin Therapy for Secondary Prevention: Is There a Gender Difference? Test for Interaction in Meta-Analysis Revisited

Gutierrez et al,[1] in an analysis of 11 trials with 43,193 patients, concluded that statin therapy has no benefit on stroke and all-cause mortality in women. The investigators found statistically significant 21% and 18% reductions in mortality and stroke with statins for men but only 19% and 8% reductions in women, which did not reach statistical signifi-

Statine e ASA in prev 2aria
Meno efficaci nelle donne

1 – donne meno rappresentate

2 – la terapia con Statine non ha effetti benefici sullo Stroke e su tutte le cause di morte nelle Donne Diabetiche in Prev 2aria.

Pharmacological Research 119 (2017) 195–207

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Sex-gender-related therapeutic approaches for cardiovascular complications associated with diabetes

Ilaria Campesi[a,*], Flavia Franconi[a,b], Giuseppe Seghieri[c], Marco Meloni[d]

[a] Department of Biomedical Sciences, University of Sassari, Sassari, Italy
[b] Dipartimento Politiche della Persona, Regione Basilicata, Italy
[c] Centro Studi Salute di Genere, AUSL 3, Pistoia, Italy
[d] BHF Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, UK

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Available online 9 February 2017

Keywords:
Diabetes mellitus
Sex-gender differences
Risk factors
Cardiovascular complications
Therapeutic approaches

ABSTRACT

Diabetes is a chronic disease associated with micro- and macrovascular complications and is a well-established risk factor for cardiovascular disease. Cardiovascular complications associated with diabetes are among the most important causes of death in diabetic patients. Interestingly, several sex-gender differences have been reported to significantly impact in the pathophysiology of diabetes. In particular, sex-gender differences have been reported to affect diabetes epidemiology, risk factors, as well as cardiovascular complications associated with diabetes. This suggests that different therapeutic approaches are needed for managing diabetes-associated cardiovascular complications in men and women. In this review, we will discuss about the sex-gender differences that are known to impact on diabetes, mainly focusing on the cardiovascular complications associated with the disease. We will then discuss the therapeutic approaches for managing diabetes-associated cardiovascular complications and how differences in sex-gender can influence the existing therapeutic approaches.

Diversa risposta ai farmaci ; necessità di nuovi studi e di nuovi farmaci

These novel biomarkers can be considered as promising biomarkers for early detection of diabetes in women, and might be used as basis for developing sex-gender specific treatments for diabetes-associated cardiovascular (or also other) complications.

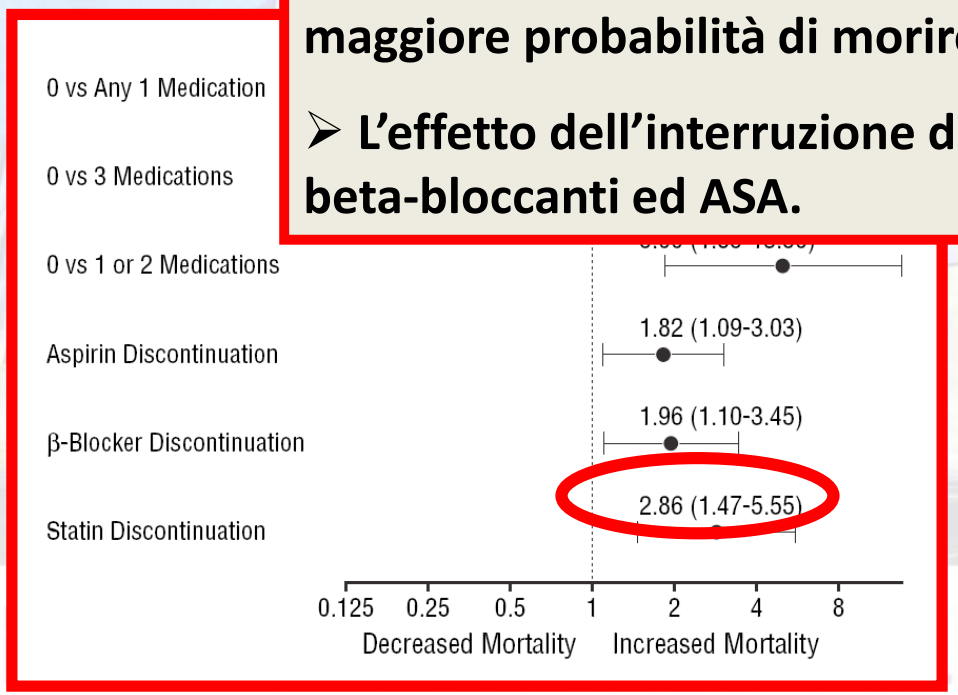
Discontinuità Terapeutica ed eventi CV

ORIGINAL INVESTIGATION

Impact of Medication Therapy Discontinuation on Mortality After Myocardial Infarction

P. Michael Ho, MD, PhD; John A. Spertus, MD, MPH; Frederick A. Masoudi, MD, MSPH; Kimberly L. Reid, MS; Eric D. Peterson, MD, MPH; David J. Magid, MD, MPH; Har

Arch Intern Med. 2006;166:1842-1847

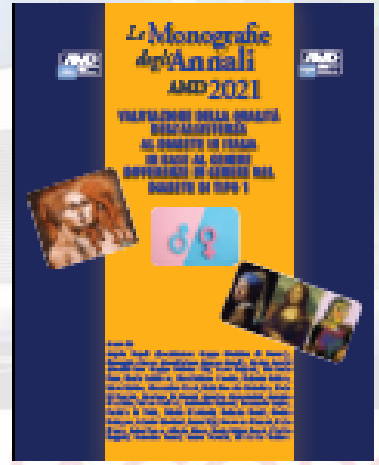


- **I pazienti che interrompono le statine dopo un IMA hanno una maggiore probabilità di morire (circa 3 volte).**
- **L'effetto dell'interruzione delle statine è maggiore rispetto a beta-bloccanti ed ASA.**

RESISTENZA o Discontinuità terapeutica ?

Differenze di Genere nel Diabete : dal 2011 al 2019

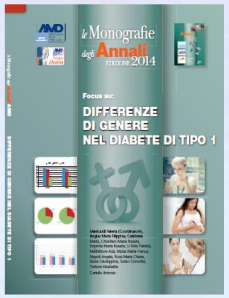
2011 → 2016 → 2019



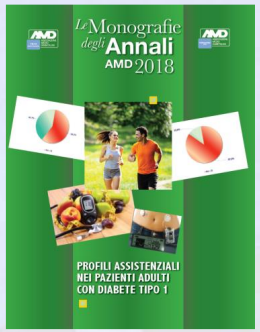
Trend differenze di genere nel DT 1 : 2011 - 2019

Indicatori di esito intermedio favorevole nel DT1

Indicatore	2011 F/M (%)	Diff %	2019 F/M (%)	Diff %
HbA1c ≤7.0%	20,4/25,6	-5,2	25,6/31,7	- 6,1
C-LDL <100 mg/dl	41,5/41,4	0,1	53,7/54,3	0,6
PA < 140/90 mmHg	69,5/61,5	+ 8.0	73,9/67,7	+ 6,2
eGFR < 60 ml/m	9,6/7,8	+ 1,8	12,2/10,3	+ 1,9
MAU	24,7/30,1	- 6,6	17,2/21,3	- 3,9



Qualità di cura per genere e per schema di trattamento nel DT1: 2011 vs 2016



2011	HbA1c	F	M	Diff %
MDI	<= 7 %	19,3	24,7	- 5,4
CSII	<= 7%	25,1	31,2	- 6,1

2016	HbA1c	F	M	Diff %
MDI	<= 7%	24,2	30,3	-6,1
CSII	<= 7%	30,9	35,5	-4,6

P < 0.001

Score Q medio - 2011

	Uomini	Donne	p
MDI	24.9±8.5	24.7±8.5	0.26
CSII	25.8±8.3	26.2±8.4	0.03

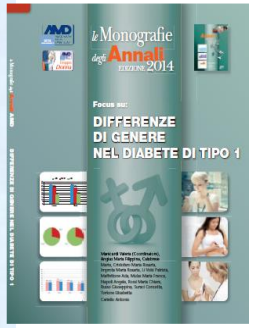
Score Q medio - 2016

	Uomini	Donne	p
MDI	26.7±84	26.7±8.6	0.66
CSII	28.0±8.1	28.5±8.3	0.04

Lo Score Q medio migliora in modo significativo nelle Donne trattate con CSII rispetto a quelle trattate con MDI

E nel DT1 ?

PLOS ONE | DOI:10.1371/journal.pone.0162960 October 3, 2016



DT1

RESEARCH ARTICLE

Gender-Disparities in Adults with Type 1 Diabetes: More Than a Quality of Care Issue. A Cross-Sectional Observational Study from the AMD Annals Initiative

Valeria Manicardi[1☯], Giuseppina Russo[2☯], Angela Napoli[3☯], Elisabetta Torlone[4☯], Patrizia Li Volsi[5☯], Carlo Bruno Giorda[6☯], Nicoletta Musacchio[7☯], Antonio Nicolucci[8☯], Concetta Suraci[9☯], Giuseppe Lucisano[8☯], Maria Chiara Rossi[8☯*], AMD Annals Study Group[¶]

Favorable outcome indicators	M (%)	F (%)	p-value
HbA1c ≤7.0% (≤53 mmol/mol)	25.6	20.4	<0.0001
LDL-C <100 mg/dl	41.4	41.5	0.91
BP ≤130/80 mmHg	61.5	69.5	<0.0001
Unfavorable outcome indicators			
HbA1c >8.0% (>64 mmol/mol)	41.6	47.3	<0.0001
LDL-C ≥130 mg/dl	22.1	20.7	0.02
BP ≥140/90 mmHg	31.5	25.2	<0.0001
BMI ≥30 Kg/m2	8.7	9.8	0.002
GFR ≤60 ml/min	7.8	9.6	<0.0001
MAU	30.1	24.7	<0.0001

Rischio di morte nel DT1 : Metanalisi

E nel DT1 ?

Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis

Lancet Diabetes Endocrinol 2015; 3: 198–206

Rachel R Huxley, Sanne A E Peters, Gita D Mishra, Mark Woodward

	Studies	Individuals	Events	Ratio of SMR (95% CI)	p value	I^2	I^2 p value
Coronary heart disease[10,12,27,31,39,40,44]	7	59 383	1427	2·54 (1·80–3·60)	<0·0001	67·86%	0·33
Stroke[12,16,26,39]	4	45 677	371	1·37 (1·03–1·81)	0·0308	0·00%	0·01
Cardiovascular disease[10,12,17,21,28,33,39,40,42]	9	75 983	2166	1·86 (1·62–2·15)	<0·0001	2·39%	0·42
Renal disease[10,21,28]	3	30 332	142	1·44 (1·02–2·05)	0·0404	0·00%	0·60
Cancer[illegible]	4	31 018	119	1·23 (0·79–1·98)	0·32	0·00%	0·99
Accident and suicide[10,21,28,33,44]	6	36 320	260	1·34 (0·97–1·84)	0·073	0·00%	0·77

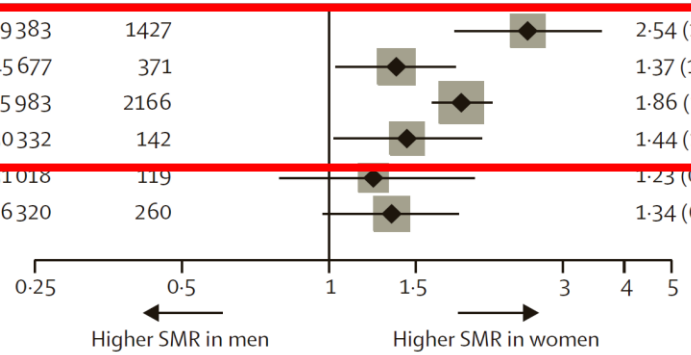


Figure 4: **Pooled women-to-men ratios of SMRs for incident coronary heart disease and stroke, and for mortality from cardiovascular disease, renal disease, cancer, and accident and suicide**

Two studies[12,17] reported the sex-specific age-adjusted hazard ratio (and variance) for coronary heart disease, stroke, and cardiovascular disease events in patients with type 1 diabetes compared with individuals who were free from previous cardiovascular disease; therefore the ratios of the hazard ratios (women:men) were obtained and included in the summary estimate. SMR=standardised mortality ratio.

Mortalità per tutte le cause nelle Donne con DT1 : + 40%

Nutrition, Metabolism & Cardiovascular Diseases (2022) 32, 2297–2309

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

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

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,*]

Ruolo di sesso/genere

RASSEGNA

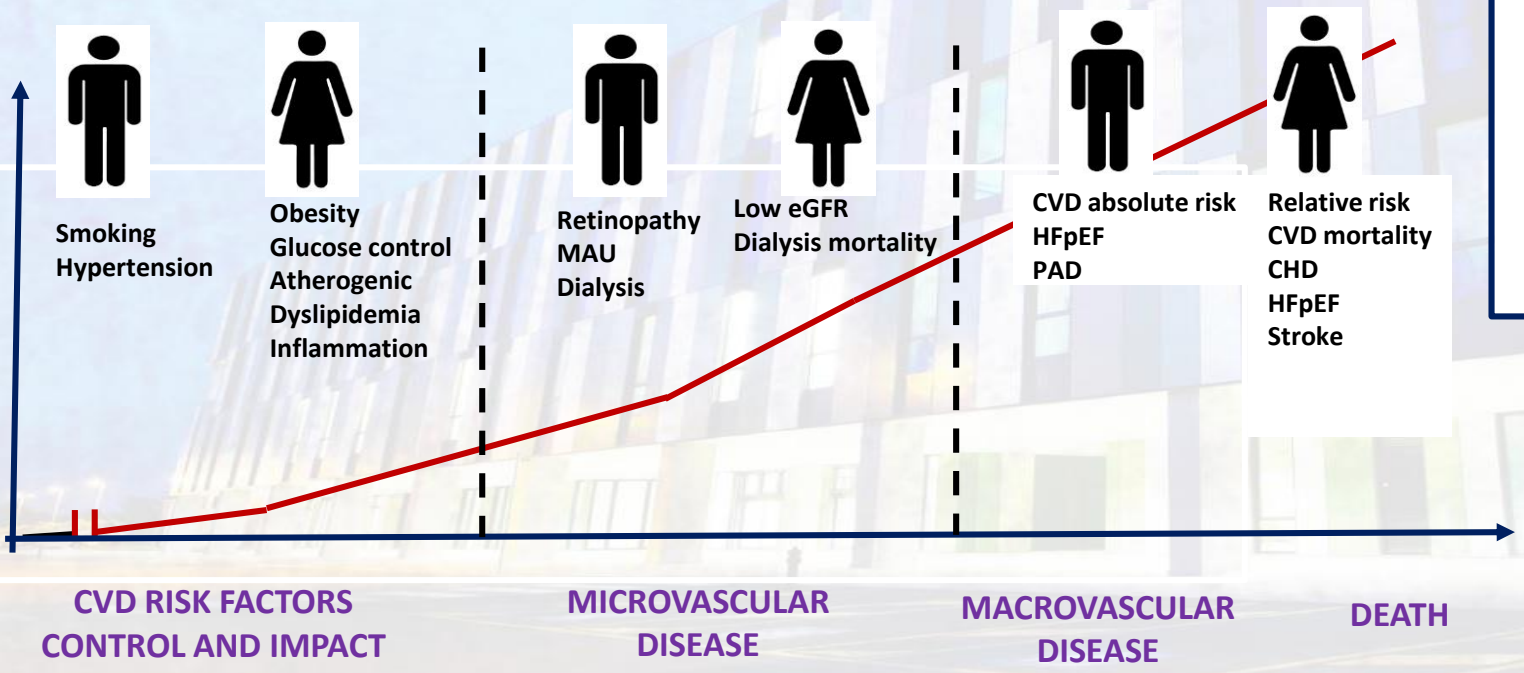
Differenze di genere nel diabete mellito di tipo 1 e di tipo 2: i dati italiani

Giuseppina T. Russo[1], Valeria Manicardi[2], Maria Chiara Rossi[3], Emanuela Orsi[4], Anna Solini[5]

[1]Dipartimento di Medicina Clinica e Sperimentale, Università di Messina; [2]Coordinatore Gruppo ANNALI AMD, Reggio Emilia; [3]CORESEARCH – Center for Outcomes Research and Clinical Epidemiology, Pescara; [4]Fondazione IRCCS Cà Grande Ospedale Maggiore Policlinico di Milano; [5]Dipartimento di Patologia Chirurgica, Medica, Molecolare e di Area Critica, Università di Pisa

DOI: https://doi.org/10.30682/ildia2103a

Sex/Gender differences in diabetes complications and risk factors



Diversi FdR nell'uomo e nella donna con Diabete nella storia di malattia condizionano l'insorgenza di complicanze e la mortalità

I Risultati degli ANNALI di Genere :

Nel DT2 non ci sono diversità di trattamento ,

ma esiti peggiori sui FdR CV

Quindi quali differenze ?

- Differenze biologiche /genetiche ?
- Diversa risposta ai farmaci ? (resistenza alle statine, ASA)
- Diversa aderenza alle terapie ?

Il peggiore profilo di rischio CV nelle donne con DT2 può spiegare la loro maggiore mortalità rispetto agli uomini in Italia ?

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

Nutrition, Metabolism & Cardiovascular Diseases (2022) 32, 2297–2309

world diabetes day

E i nuovi Farmaci???

14 NOVEMBER WORLD DIABETES DAY 2023

Roberto Anichini[1]
Sabrina Cosimi[2]
Alberto Di Carlo[3]
Paola Orsini[4]
Alessandra De Bellis[1]
Giuseppe Seghieri[1]
Flavia Franconi[5]
Fabio Baccetti[6]

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy
Dovepress
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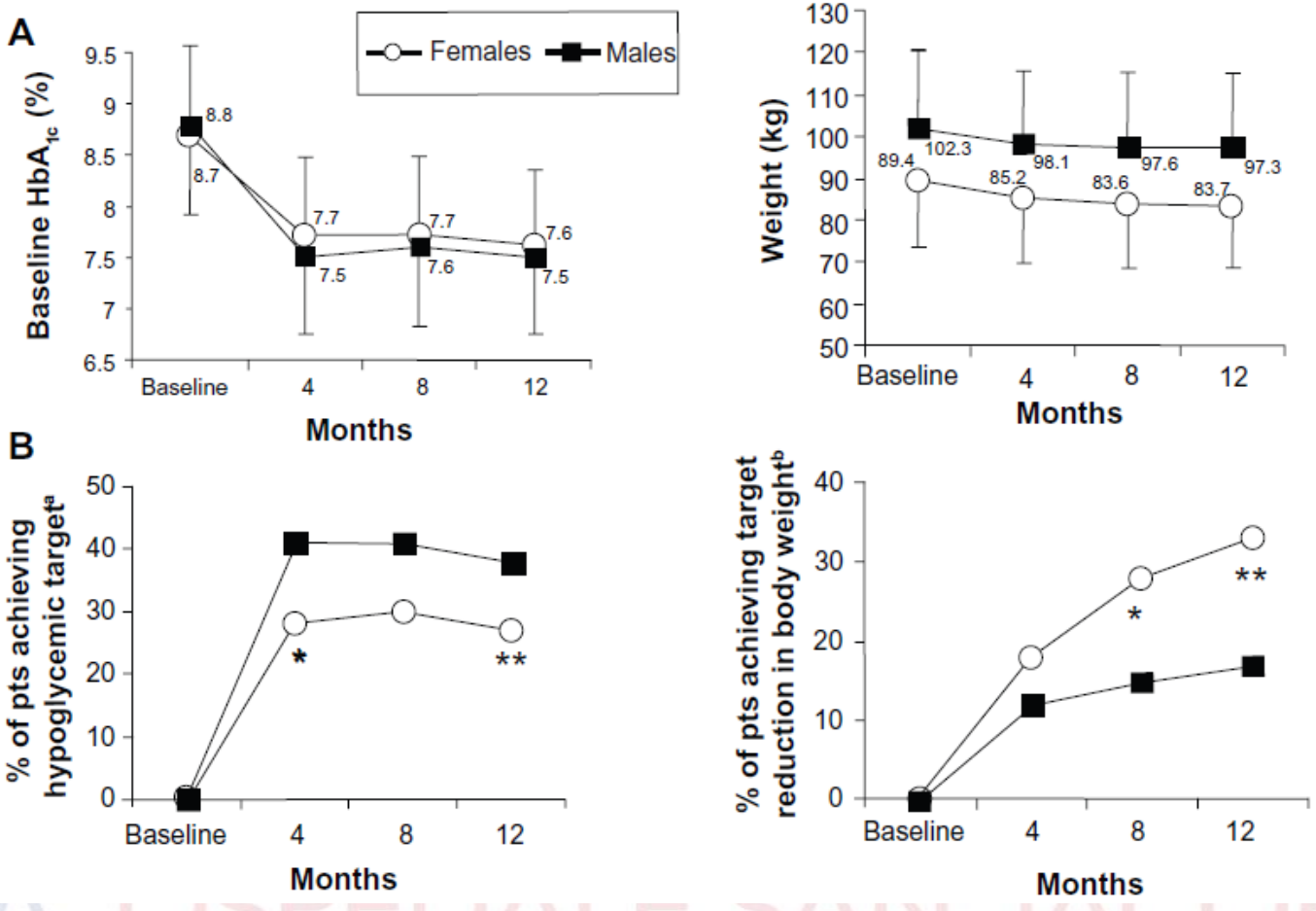
ORIGINAL RESEARCH

Gender difference in response predictors after 1-year exenatide therapy twice daily in type 2 diabetic patients: a real world experience

This article was published in the following Dove Press journal:
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy
5 April 2013
Number of times this article has been viewed



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Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy
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5 April 2013
Number of times this article has been viewed

Table 4 Side effects and reasons for drop-outs at 1 year

	Males (n)	Females (n)
Failure of therapy	11	13
Transfer to other therapy	6	8
Nausea	60	63
Vomiting	13	14
Diarrhea	16	18
Lack of compliance	1	2
Other	1	5

Abbreviation: n, number.

Received: 23 May 2017 | Revised: 9 August 2017 | Accepted: 10 August 2017
DOI: 10.1111/dom.13086

WILEY

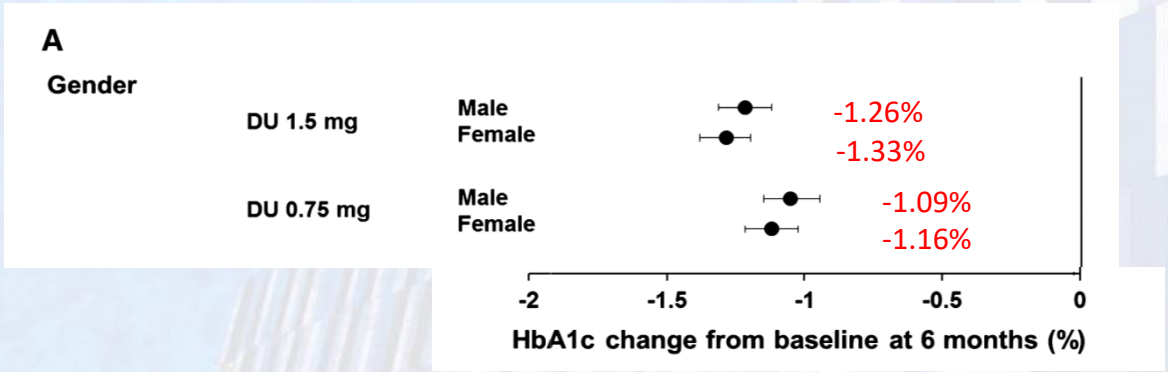
ORIGINAL ARTICLE

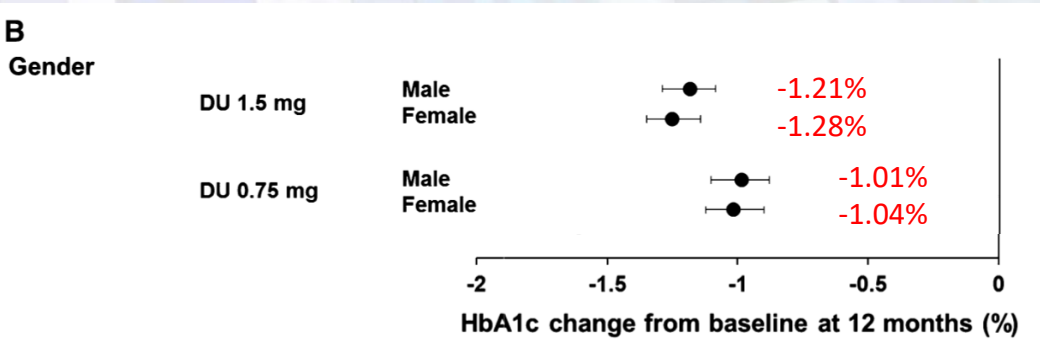
Effect of once-weekly dulaglutide on glycated haemoglobin (HbA1c) and fasting blood glucose in patient subpopulations by gender, duration of diabetes and baseline HbA1c

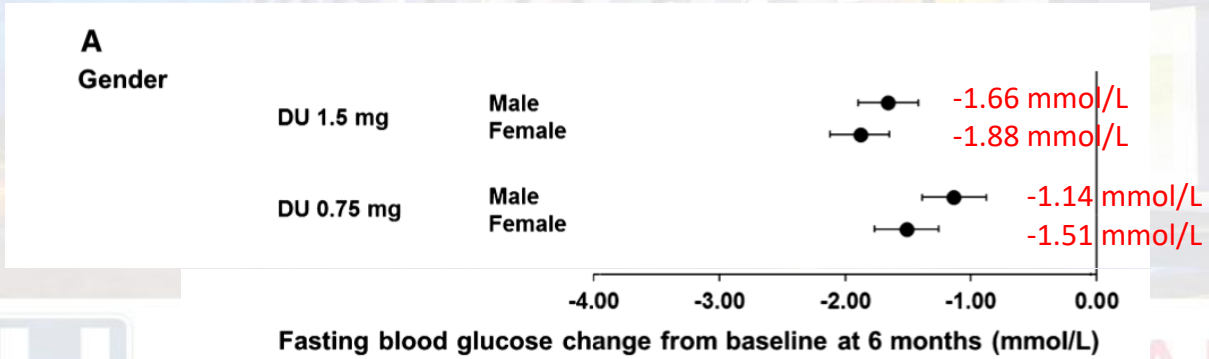
Baptist Gallwitz MD[1] | Samuel Dagogo-Jack MD[2] | Vivian Thieu PhD[3] | Luis-Emilio Garcia-Perez MD, PhD[3] | Imre Pavo MD[4] | Maria Yu MS[5] | Kenneth E. Robertson PharmD[3] | Nan Zhang PhD[3] | Francesco Giorgino MD[6]

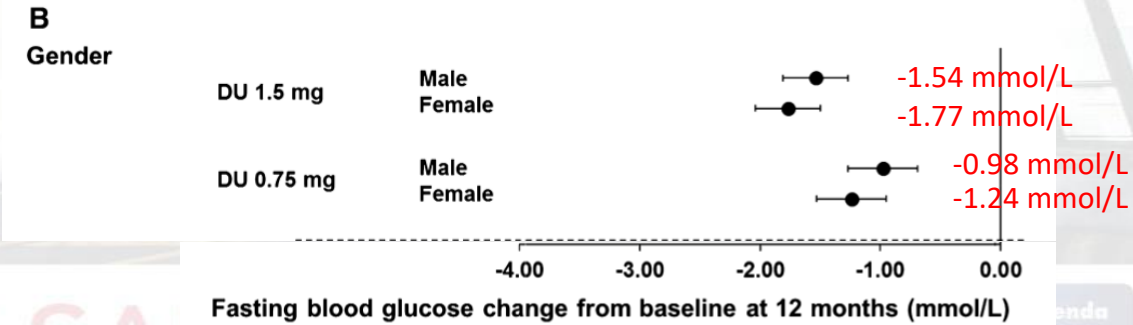
Post-hoc analysis of 7 fase III studies (AWARD-1 to -6 and -8)

Similar reduction in HbA1c and FBG









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Women had a greater weight loss with both dulaglutide 0.75 mg and 1.5 mg.

	Gender	
Weight (kg)	Men	Women
AWARD-3		
DU 1.5 mg	−1.77 (−2.44, −1.11)	−2.71 (−3.31, −2.11)
DU 0.75 mg	−0.91 (−1.56, −0.26)	−1.75 (−2.35, −1.16)
Metformin	−1.90 (−2.56, −1.24)	−2.53 (−3.12, −1.93)
AWARD-8		
DU 1.5 mg	−0.24 (−0.91, 0.43)	−0.75 (−1.35, −0.16)
Placebo	0.54 (−0.58, 1.65)	−0.39 (−1.39, 0.61)
AWARD-5		
DU 1.5 mg	−2.56 (−3.07, −2.06)	−3.77 (−4.26, −3.27)
DU 0.75 mg	−1.97 (−2.51, −1.44)	−3.20 (−3.69, −2.71)
Sitagliptin	−1.15 (−1.65, −0.65)	−1.78 (−2.26, −1.29)
Placebo	−1.31 (−1.95, −0.67)	−1.67 (−2.32, −1.01)
AWARD-6		
DU 1.5 mg	−2.35 (−2.95, −1.74)	−3.28 (−3.84, −2.72)
Liraglutide	−2.91 (−3.49, −2.32)	−4.21 (−4.78, −3.64)
AWARD-1		
DU 1.5 mg	−0.92 (−1.62, −0.22)	−1.87 (−2.66, −1.08)
DU 0.75 mg	0.15 (−0.53, 0.84)	0.25 (−0.57, 1.06)
Exenatide twice daily	−1.23 (−1.94, −0.52)	−0.89 (−1.67, −0.11)
Placebo	0.95 (0.05, 1.85)	1.64 (0.57, 2.71)
AWARD-2		
DU 1.5 mg	−1.39 (−1.91, −0.87)	−2.23 (−2.77, −1.69)
DU 0.75 mg	−1.14 (−1.67, −0.61)	−1.71 (−2.24, −1.18)
Insulin glargine	1.30 (0.77, 1.84)	0.81 (0.26, 1.35)
AWARD-4		
DU 1.5 mg	−0.33 (−0.98, 0.33)	−1.63 (−2.37, −0.88)
DU 0.75 mg	0.61 (−0.07, 1.28)	−0.33 (−1.04, 0.37)
Insulin glargine	2.34 (1.69, 3.00)	2.20 (1.47, 2.93)

Received: 22 May 2019 | Revised: 12 August 2019 | Accepted: 29 August 2019
DOI: 10.1111/dom.13876

BRIEF REPORT

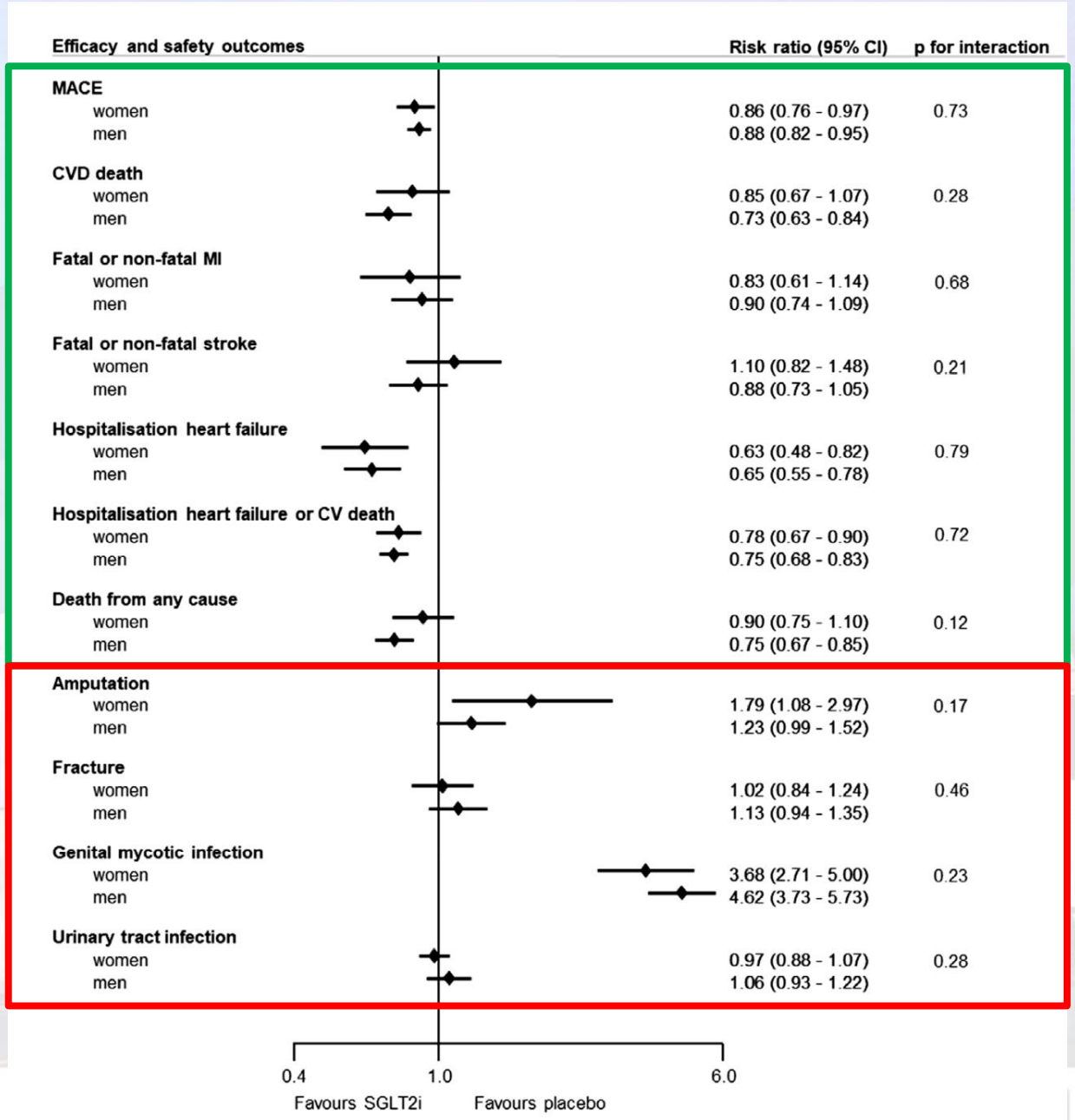
Effects of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes in women versus men

Karin Rådholm PhD[1,2] | Zien Zhou MD[2,3] | Kristin Clemens PhD[4,5,6] | Bruce Neal PhD[2,7,8] | Mark Woodward PhD[2,9,10]

Pooled analysis of outcomes for patients T2DM treated with SGLT2i from:
- CANVAS trial (35.8% women)
- CREDENCE trial (33.9% women)
- EMPA REG OUTCOME trial (28.8% women)
- DECLARE-TIMI 58 trial (37.4% women).

No sex differences for efficacy outcome.

No sex differences for safety outcome.



Diabetes & Metabolic Syndrome: Clinical Research & Reviews
Volume 14, Issue 3, May–June 2020, Pages 181-187

Gender difference in cardiovascular outcomes with SGLT-2 inhibitors and GLP-1 receptor agonist in type 2 diabetes: A systematic review and meta-analysis of cardio-vascular outcome trials

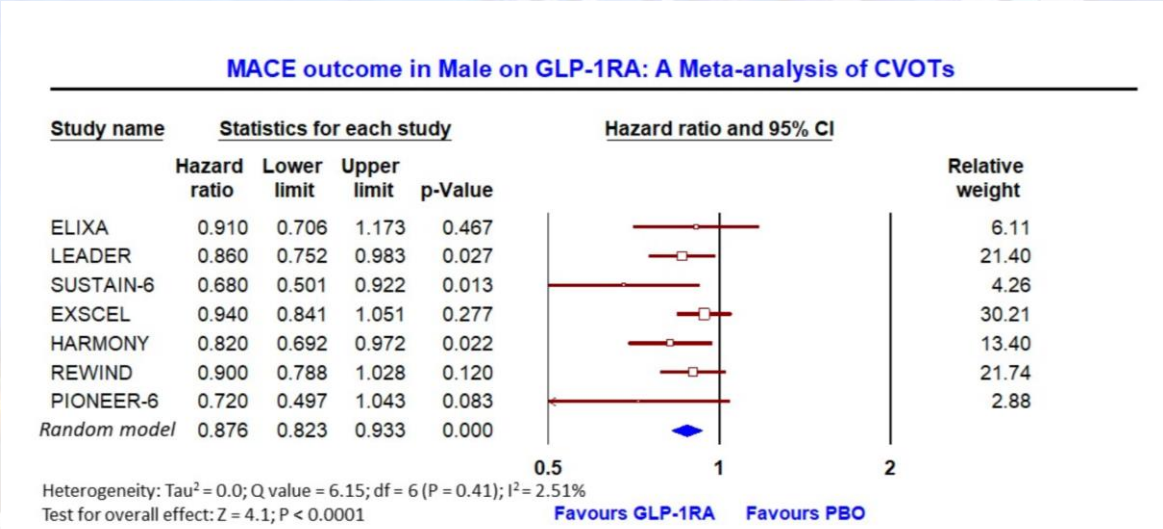
Awadhesh Kumar Singh, Ritu Singh

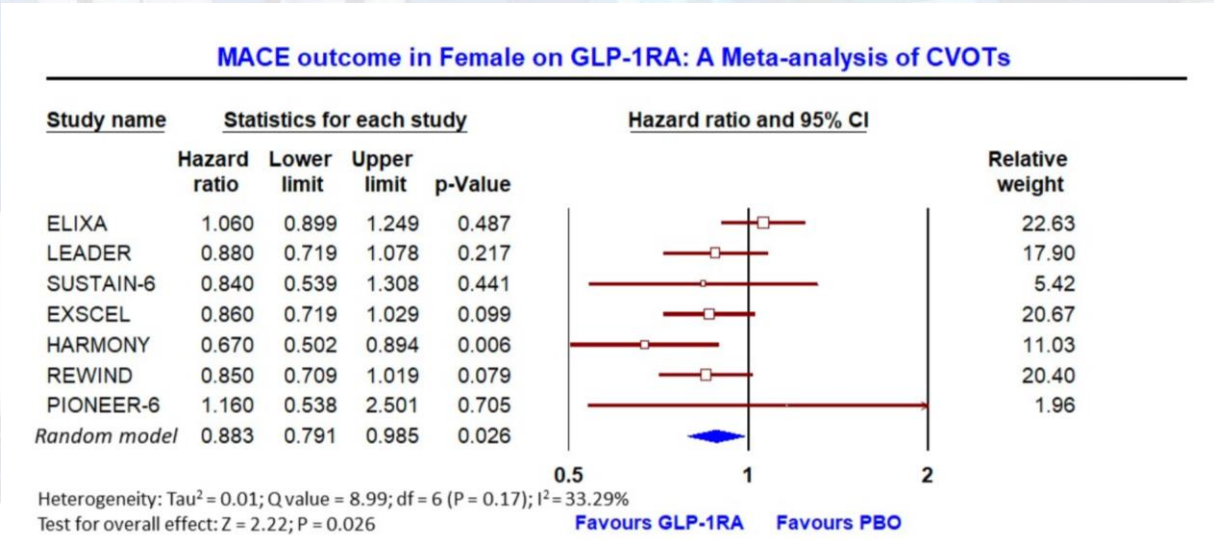
Meta-analysis of seven RCTs conducted with GLP1RAs

56,004 patients: 37% female, 63% male

Significant reduction in MACE in man

Significant reduction in MACE in women





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Gender difference in cardiovascular outcomes with SGLT-2 inhibitors and GLP-1 receptor agonist in type 2 diabetes: A systematic review and meta-analysis of cardio-vascular outcome trials

Awadhesh Kumar Singh, Ritu Singh

Meta-analysis of three RCTs conducted with SGLT2is

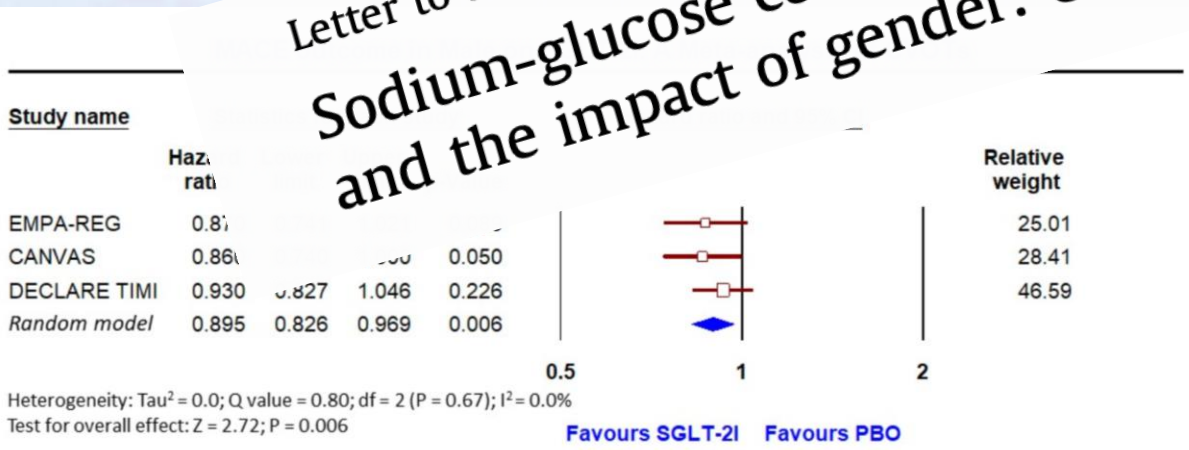
34,222 patients: 35% female, 65% male

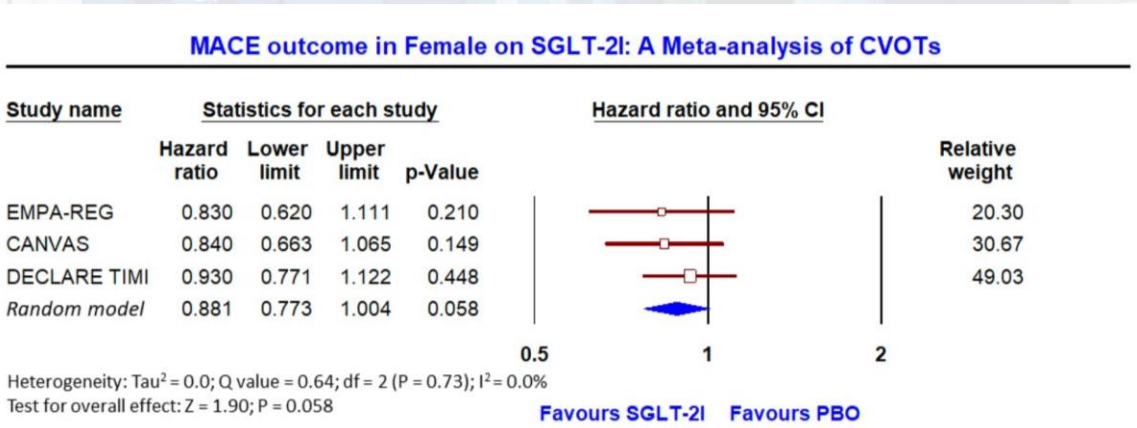
Signifi-

women

Letter to the Editor

Sodium-glucose co-transporter-2 inhibitors, cardiovascular outcomes and the impact of gender: Class effect or statistical play of chance?





American heart journal plus : cardiology research and practice

Author Manuscript HHS Public Access

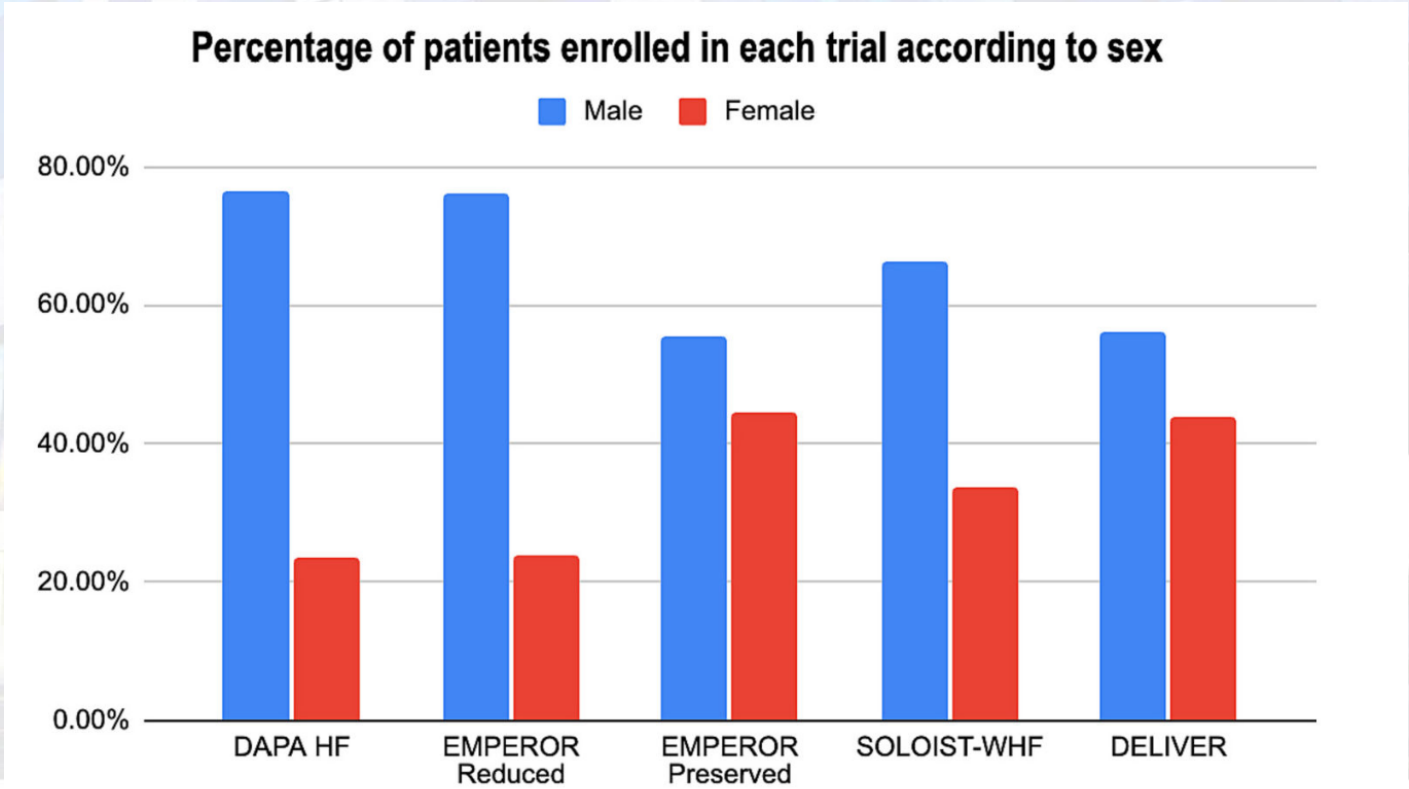
Sex differences in cardiovascular outcomes of SGLT-2 inhibitors in heart failure randomized controlled trials: A systematic review and meta-analysis

Frederick Berro Rivera, Vincent Anthony S. Tang, [...], and

Annabelle Santos Volgman

Meta-analysis of five RCTs conducted with SGLT2is in patients with Heart Failure

21,947 patients: 35.7% female, 64.3% male



American heart journal plus : cardiology research and practice

Author Manuscript HHS Public Access

Sex differences in cardiovascular outcomes of SGLT-2 inhibitors in heart failure randomized controlled trials: A systematic review and meta-analysis

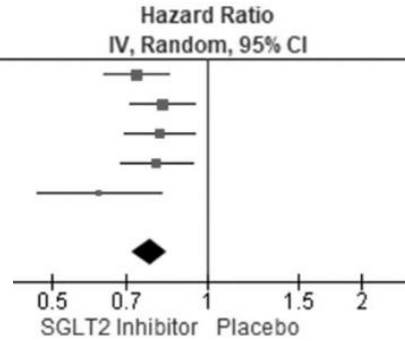
Frederick Berro Rivera, Vincent Anthony S. Tang, [...], and Annabelle Santos Volgman

Meta-analysis of five RCTs conducted with SGLT2is in patients with Heart Failure

21,947 patients: 35.7% female, 64.3% male

Male

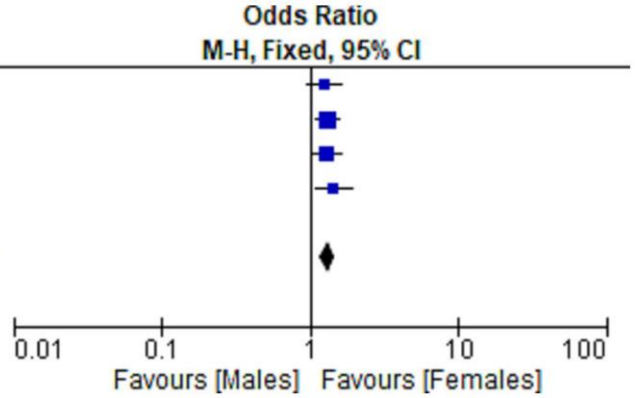
Study or Subgroup	log[Hazard Ratio]	SE	SGLT 2 Inhibitor Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
DAPA HF 2019	-0.3147	0.0752	1809	1826	24.9%	0.73 [0.63, 0.85]
DELIVER 2022	-0.1985	0.0735	1767	1749	26.0%	0.82 [0.71, 0.95]
Emperor Preserved 2021	-0.2107	0.0818	1659	1653	21.2%	0.81 [0.69, 0.95]
Emperor Reduced 2021	-0.2231	0.0829	1426	1411	20.6%	0.80 [0.68, 0.94]
SOLOIST-WHF 2021	-0.478	0.1413	410	400	7.3%	0.62 [0.47, 0.82]



Study or Subgroup	Males Events	Males Total	Females Events	Females Total	Weight	Odds Ratio M-H, Fixed, 95% CI
DAPA HF 2019	307	1809	79	564	19.5%	1.25 [0.96, 1.64]
DELIVER 2022	317	1767	195	1364	35.1%	1.31 [1.08, 1.59]
Emperor Preserved 2021	253	1659	162	1338	29.6%	1.31 [1.06, 1.61]
Emperor Reduced 2021	294	1426	67	437	15.8%	1.43 [1.07, 1.92]
Total (95% CI)		**6661**		**3703**	**100.0%**	**1.32 [1.17, 1.48]**
Total events	1171		503			

Heterogeneity: Chi² = 0.47, df = 3 (P = 0.93); I² = 0%

Test for overall effect: Z = 4.68 (P < 0.00001)



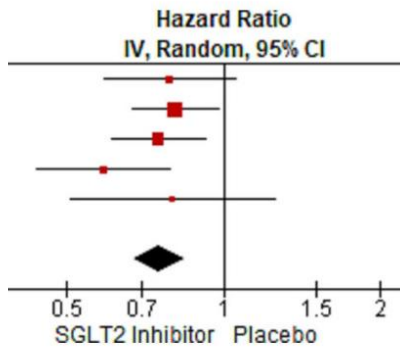


Fig. 6.
Primary composite outcomes in males vs. females receiving SGLT-2is.

P-673

Time Spent in Glucose Control After Initiating Tirzepatide vs Comparators: Exploratory Analysis of Fasting Serum Glucose in SURPASS 1-5 Trials

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Rachel L. Batterham[1,2], Julio Rosenstock[3], W. Timothy Garvey[4], Minzhi Liu[5], Yanyun Chen[2], Brandon K. Bergman[2], Andrea Hemmingway[2], Vivian Thuyanh Thieu[2]

[1]Centre for Obesity Research, University College London, London, UK, [2]Eli Lilly and Company, Indianapolis, USA, [3]Velocity Clinical Research at Medical City, Dallas, USA, [4]UAB Diabetes Research Center, The University of Alabama at Birmingham, Birmingham, USA, [5]Tigermed-BDM Inc., Somerset, USA

OBJECTIVE

- To evaluate continuous time spent with FSG ≤6.94 mmol/L (125 mg/dL) during treatment with tirzepatide vs. comparators in participants with T2D throughout the duration of each of the SURPASS-1 through -5 trials

CONCLUSIONS

- In the SURPASS-1, -2 and -5 trials, tirzepatide resulted in greater continuous time spent with FSG ≤6.94 mmol/L vs. placebo and semaglutide 1 mg in participants with T2D
- In trials with a basal insulin comparator (SURPASS-3 and -4), continuous time spent with FSG ≤6.94 mmol/L with the tirzepatide 10 mg and 15 mg doses was similar to iDeg and greater than with iGlar
- The percentage of the trial spent with FSG ≤6.94 mmol/L was 60-80% for studies of 40 weeks' duration and 38-69% for studies of 52 weeks' duration

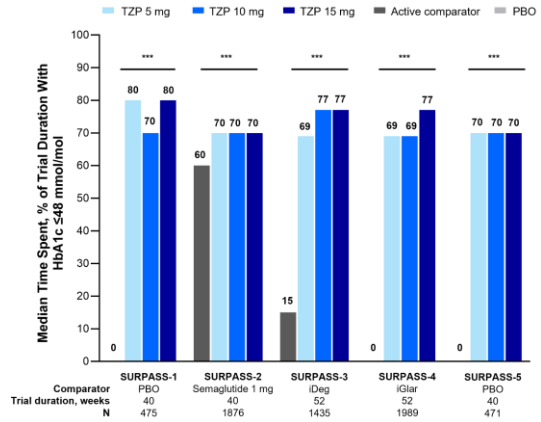
In conclusion, treatment with tirzepatide 5 mg, 10 mg and 15 mg resulted in a longer continuous time in glycaemic control with FSG ≤6.94 mmol/L compared with placebo and semaglutide 1 mg

European Association for the Study of Diabetes 2023; Hamburg, Germany;
2 – 6 October 2023

BACKGROUND

- Tirzepatide is a long-acting glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist. Tirzepatide has a mean half-life of ~5 days, enabling once-weekly dosing. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1
  - Tirzepatide is approved for treatment of people with type 2 diabetes (T2D) and under investigation for chronic weight management
- In the SURPASS-1 through -5 trials, adults with T2D treated with tirzepatide (5 mg, 10 mg or 15 mg) showed improvements in glycaemic control at the primary endpoints of 40 or 52 weeks[1-5]
  - 81-97% of participants achieved glycated haemoglobin (HbA1c) <53 mmol/mol (7.0%) and 66-86% achieved HbA1c ≤48 mmol/mol (6.5%)
  - Fasting serum glucose (FSG) was significantly decreased from baseline
- Participants with T2D reached glycaemic targets of HbA1c <53 mmol/mol (7.0%) and ≤48 mmol/mol (6.5%) 4 weeks faster with tirzepatide compared with semaglutide 1 mg and titrated insulin degludec (iDeg), based on data from SURPASS-2 and -3[6]

Tirzepatide Treatment Led to a Longer Continuous Time With HbA1c ≤48 mmol/mol (6.5%) vs. Comparators[7]

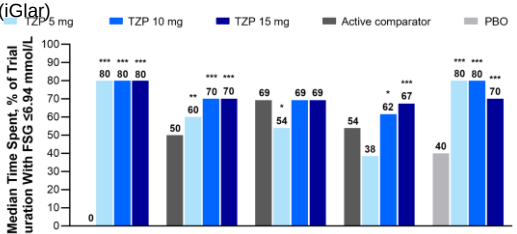


***p<0.001 vs. comparator.
Note: Continuous time spent in control presented as percentage of trial duration for each study.

KEY RESULTS

Duration of Time Spent With FSG ≤6.94 mmol/L (125 mg/dL)

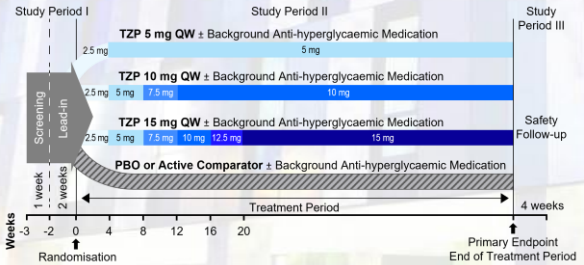
- All tirzepatide doses demonstrated significantly greater median duration of continuous time spent with FSG ≤6.94 mmol/L vs. placebo and semaglutide 1 mg
- Median duration of continuous time spent with FSG ≤6.94 mmol/L with the tirzepatide 10 mg and 15 mg doses was similar to iDeg and significantly greater than with insulin glargine (iGlar)



*p<0.05; **p<0.01; ***p<0.001 vs. comparator.
Notes: Continuous time spent in control presented as percentage of trial duration using median data. The analysis population for the data presented includes all randomised participants who took ≥1 dose of study drug, excluding participants who discontinued study drug due to inadvertent enrolment; data after initiating rescue medications or permanently stopping study drug were set to missing and imputed.

METHODS

Study Design: SURPASS-1 Through -5



Trial	(Sample Size); Randomisation Ratio; Background Glucose-Lowering Therapy	Comparator	Primary Endpoint
SURPASS-1	(N=478); 1:1:1:1; None	PBO QW	Wk 40
SURPASS-2	(N=1878); 1:1:1:1; Add-on to metformin	Semaglutide 1 mg QW	Wk 40
SURPASS-3	(N=1437); 1:1:1:1; Add-on to metformin ± SGLT-2i	Titrated iDeg QD	Wk 52
SURPASS-4	(N=1995); 1:1:1:3; Add-on to 1-3 OAMs (metformin, SGLT-2i and/or SU)	Titrated iGlar QD	Wk 52
SURPASS-5	(N=475); 1:1:1:1; Add-on to titrated iGlar ± metformin	PBO QW	Wk 40

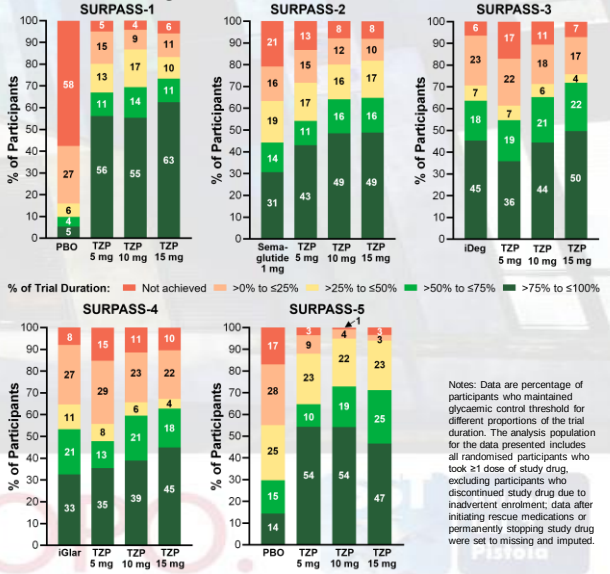
Data Collection and Statistical Analysis

- FSG was collected and analysed via central laboratory at a minimum of every 4 weeks for the first 24 weeks, at the primary endpoint of each study and at 1 additional time point between Week 24 and the primary endpoint for SURPASS-1, -3 and -4
- This post hoc analysis included all randomised participants who took ≥1 dose of study drug, excluding participants who discontinued study drug due to inadvertent enrolment
  - Analyses were done by study
  - Data after initiating rescue medications or permanently stopping study drug were set to missing and imputed from the mixed model for repeated measures
  - The time point achieving target was assessed based on FSG-time curves using all visits and linear interpolation between consecutive visits
  - The longest continuous[a] time spent with FSG ≤6.94 mmol/L (125 mg/dL) was used in the analysis
- Non-parametric analysis (Wilcoxon rank sum test) was used to compare median duration of continuous time spent with FSG ≤6.94 mmol/L

[a]Defined as time spent with FSG ≤6.94 mmol/L (125 mg/dL) across consecutive visits.

RESULTS

Proportion of Participants Maintaining FSG ≤6.94 mmol/L (125 mg/dL) Threshold for Different Intervals During Each Trial



Notes: Data are percentage of participants who maintained glycaemic control threshold for different proportions of the trial duration. The analysis population for the data presented includes all randomised participants who took ≥1 dose of study drug, excluding participants who discontinued study drug due to inadvertent enrolment; data after initiating rescue medications or permanently stopping study drug were set to missing and imputed.

References: 1. Rosenstock J, et al. *Lancet*. 2021;398:143-155. 2. Frías JP, et al. *N Engl J Med*. 2021;385:503-515. 3. Ludvik B, et al. *Lancet*. 2021;398:583-598. 4. Del Prato S, et al. *Lancet*. 2021;398:1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327:534-545. 6. Viljoen A, et al. *Diabetes Ther*. 2023;14:925-936. 7. Rosenstock J, et al. Poster presented at: *ADA 2023*. Poster 751-P.

Abbreviations: *FSG=fasting serum glucose; GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide-1; HbA1c=glycated haemoglobin; iDeg=insulin degludec; iGlar=insulin glargine; mITT=modified intent-to-treat; N=number of randomised participants who took ≥1 dose of study drug (mITT); OAM=oral anti-hyperglycaemic medication; PBO=placebo; QD=once weekly; QW=once weekly; SGLT-2i=sodium-glucose co-transporter-2 inhibitor; SU=sulphonylurea; T2D=type 2 diabetes; TZP=tirzepatide; Wk=Week*

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P-643

HbA1c Reduction With Tirzepatide in People With Type 2 Diabetes: A Mediation Analysis Using Body Weight Loss as a Factor

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[1]Clinical Research, Steno Diabetes Center Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark, [2]Eli Lilly and Company, Indianapolis, USA, [3]Department of Metabolic Diseases, Jagiellonian University Medical College, Kraków, Poland

Background

Background

- Tirzepatide is a long-acting glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist. Tirzepatide has a mean half-life of ~5 days, enabling once-weekly dosing. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1
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4. Del Prato S, et al. *Lancet*. 2021;398:1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327:534-545.

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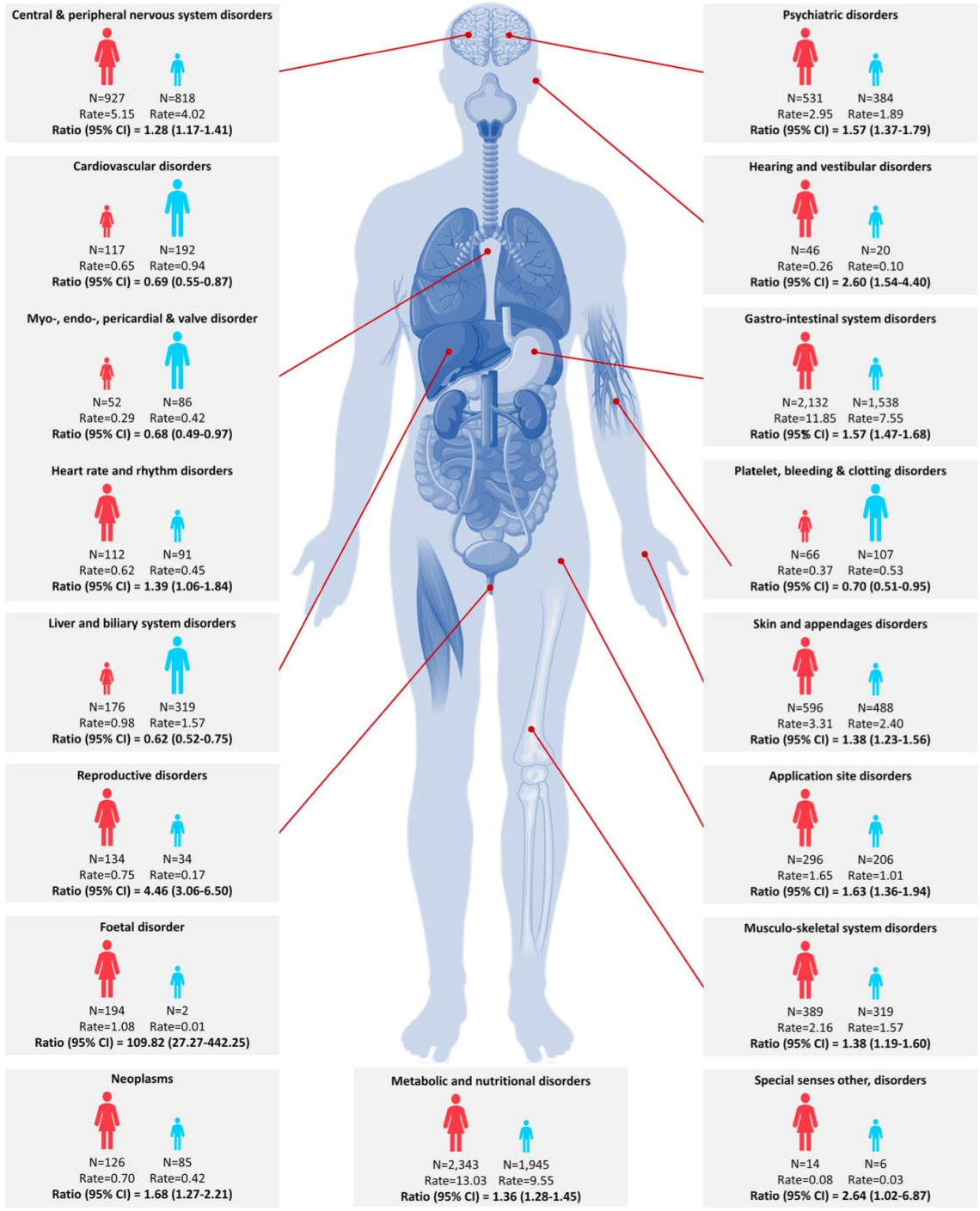
Gender differences in adverse event reports associated with antidiabetic drugs

Kyung-In Joung[1,2], Gyu-Won Jung[1,2], Han-Heui Park[1], Hyesung Lee[1], So-Hee Park[1] & Ju-Young Shin[1]✉

13 out of 17 system organ class level disorders with significant gender differences were reported more often by women than men.



Conclusioni 1– Diabete T2

- Nella popolazione con Diabete T2 anche in Italia ci sono differenze di genere, che definiscono un peggior profilo di rischio CV
- Negli anni tutti gli indicatori di esito intermedio sono migliorati , ma le differenze sono rimaste invariate

Ma non c'è differenza di trattamento tra i generi

- Ci sono differenze biologiche/ormonali da studiare e approfondire
- C'è resistenza ad alcuni farmaci, ma anche verosimilmente minore aderenza e persistenza nella terapia nelle donne con diabete T2
- Occorrono farmaci nuovi e studiati specificamente per genere

Conclusioni 2 – Diabete T1

- Le differenze di genere nel **DT1** riguardano i target del compenso metabolico , che sono più difficili da raggiungere e mantenere nelle donne
- L'uso dei **microinfusori** migliora il compenso metabolico anche se non azzera le differenze
- Ma certamente l'uso più esteso delle tecnologie potrà favorire un miglior controllo e ridurre il rischio CV e renale anche nel DT1
- I **Maschi con DT1 hanno un peggior controllo pressorio**: anche questo dato deve indurci ad una maggior appropriatezza e intensità di cura
- **Sia nel DT1 che nel DT2** le donne hanno **meno microalbuminuria , ma più riduzione del eGFR**, che a sua volta aumenta il rischio CV

Conclusioni 3 – Cosa fare subito ?

- Trattare subito tutti i FdR CV e Renali
- Intensificare le terapie per raggiungere i target
- Verificare l'aderenza e la persistenza alle terapie, motivando i pazienti

- Non abbiamo per ora **farmaci genere specifici,** ma abituiamoci all'uso delle statine ad alta efficacia, degli iPCSK9 e dell'ac Bempedoico

e della associazioni con Ezetimibe, per ottenere e mantenere i target desiderati di LDL-Colesterolo e

- di SGLT2i e GLP1- RA per ottenere il target di HbA1c e ridurre il rischio CV e Renale

Conclusioni 4

Occorre

- Riorientare la ricerca farmacologica e clinica in ottica di genere
- Aumentare la sensibilità e la conoscenza dei medici italiani sulle differenze per migliorare la qualità della cura in base al genere
- Insegnare alle donne a prendersi cura di sé (ruoli sociali)
- Sperimentare nuove strategie di educazione terapeutica e di intervento per colmare il gap