



21-24 NOVEMBRE 2023
AREZZO FIERE E CONGRESSI

18

IL DIABETE ALLA LUCE DELLE NUOVE LINEE GUIDA ESC - DIABETE 2023
Approccio multidisciplinare diabete e patologie cardiovascolari

La prospettiva del Diabetologo
Giuseppe Penno



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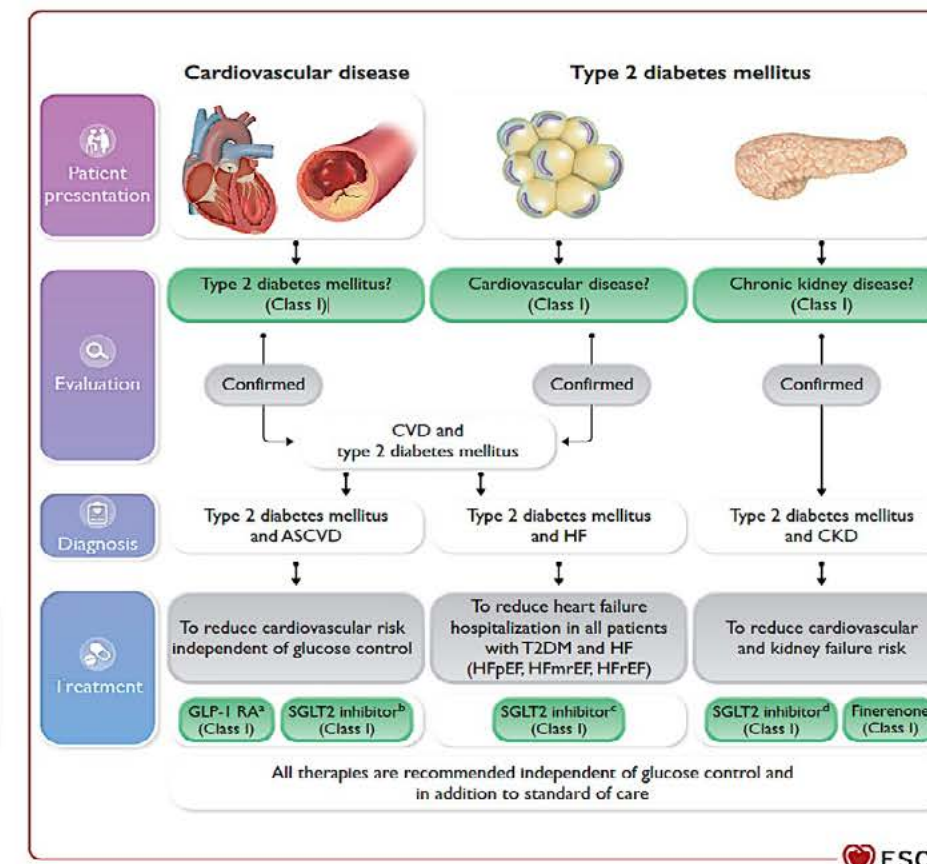
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ESC European Society of Cardiology
 ESC GUIDELINES

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)

Class I Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. **Is recommended or is indicated**



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Marx N, et al. Eur Heart J. 2023 Oct 14; 44: 4043-4140.



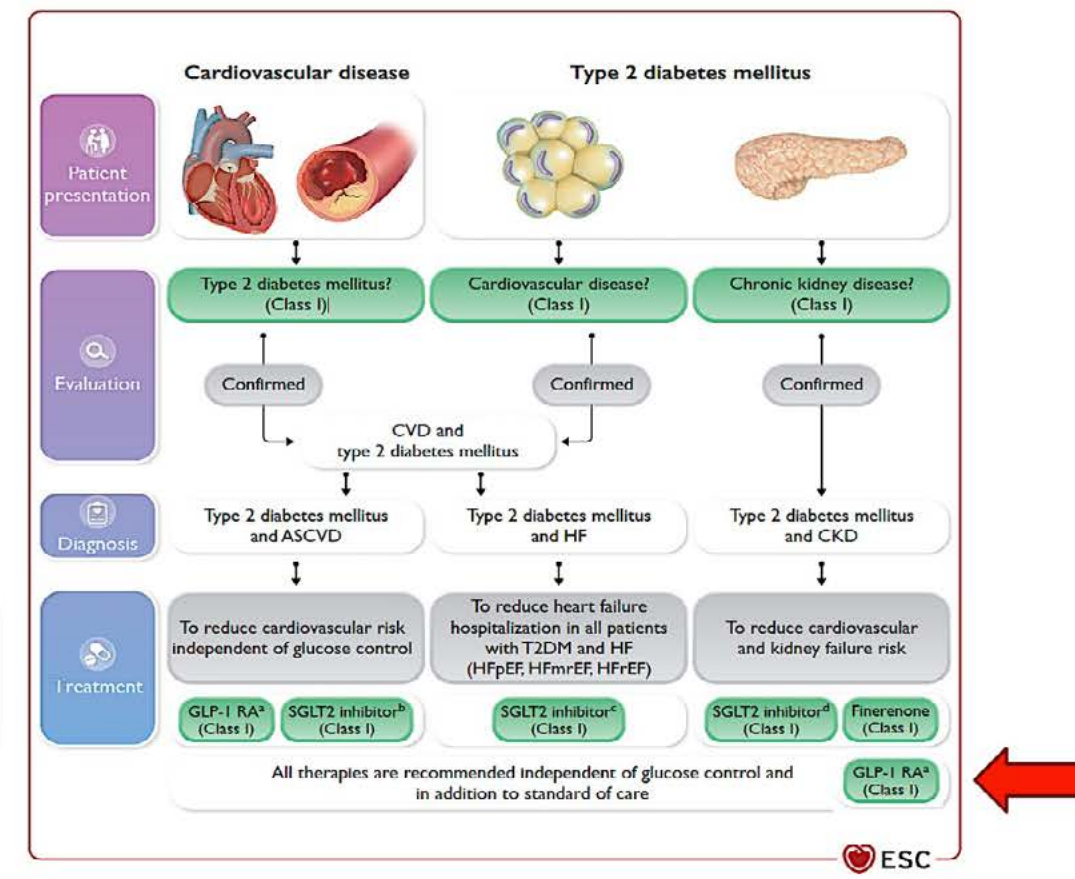
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company announcement

Company will stop the once-weekly injectable semaglutide kidney outcomes trial, FLOW, based on interim analysis

Bagsværd, Denmark, 10 October 2023 – Company today announced the decision to stop the kidney outcomes trial FLOW (Effect of semaglutide versus placebo on the progression of renal impairment in people with type 2 diabetes and chronic kidney disease).

The decision to stop the trial is based on a recommendation from the independent Data Monitoring Committee (DMC) concluding that the results from an interim analysis met certain pre-specified criteria for stopping the trial early for **efficacy**.

Composite primary endpoint consisting of the following five components:

- onset of persistent $\geq 50\%$ reduction in eGFR according to the CKD-EPI equation compared with baseline
- onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m²
- initiation of chronic kidney replacement therapy (dialysis or kidney transplantation)
- death from kidney disease
- death from cardiovascular disease

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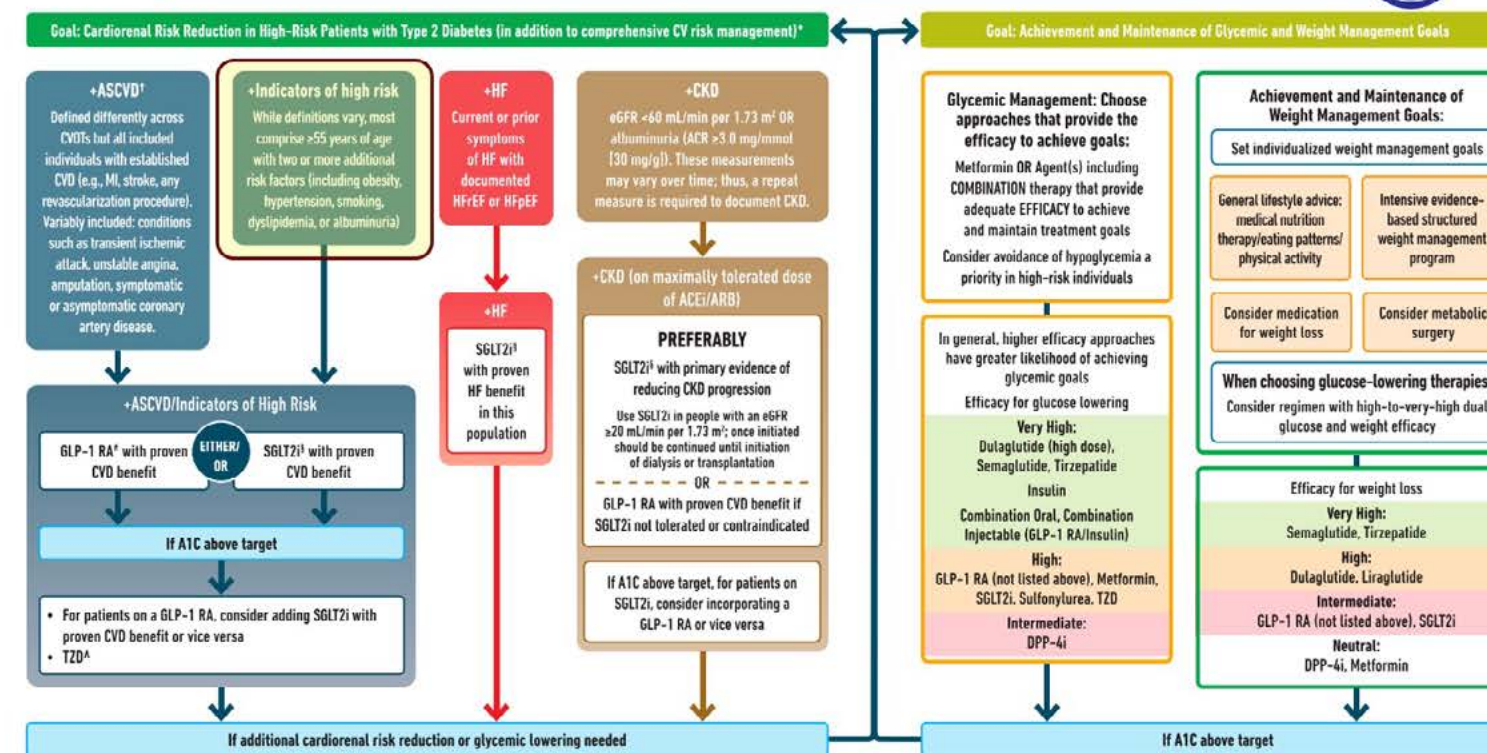
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Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)



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ADA, Diabetes Care 2023; 46(Suppl. 1): S140–S157

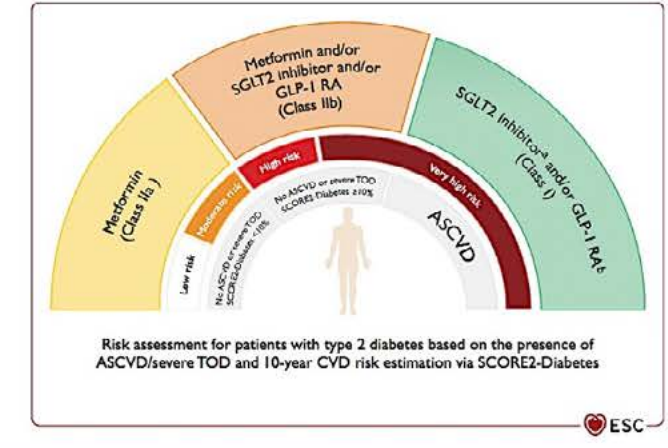
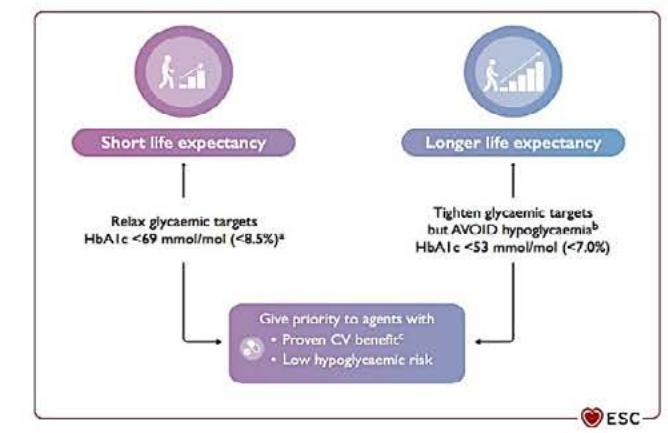
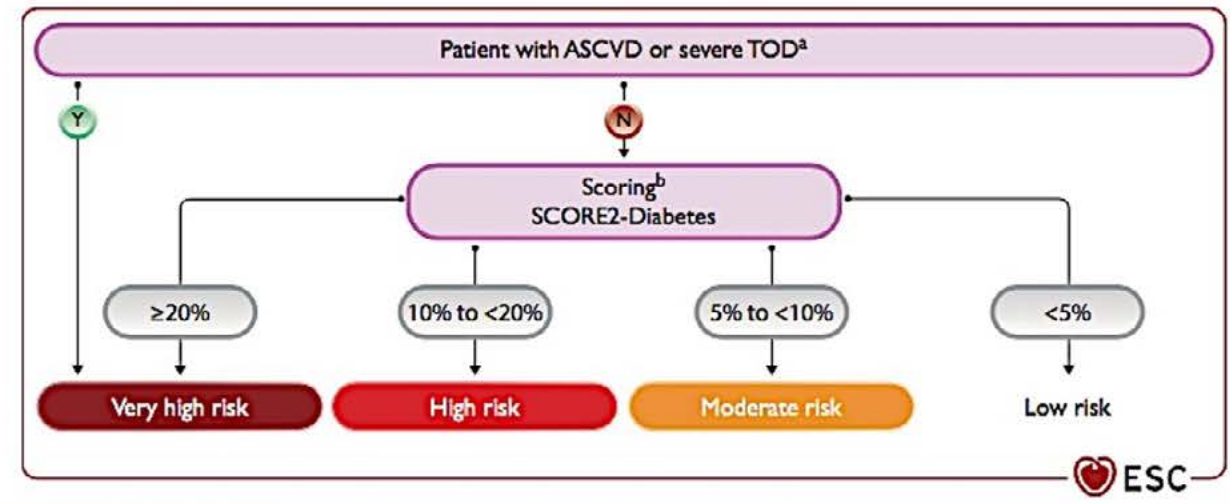


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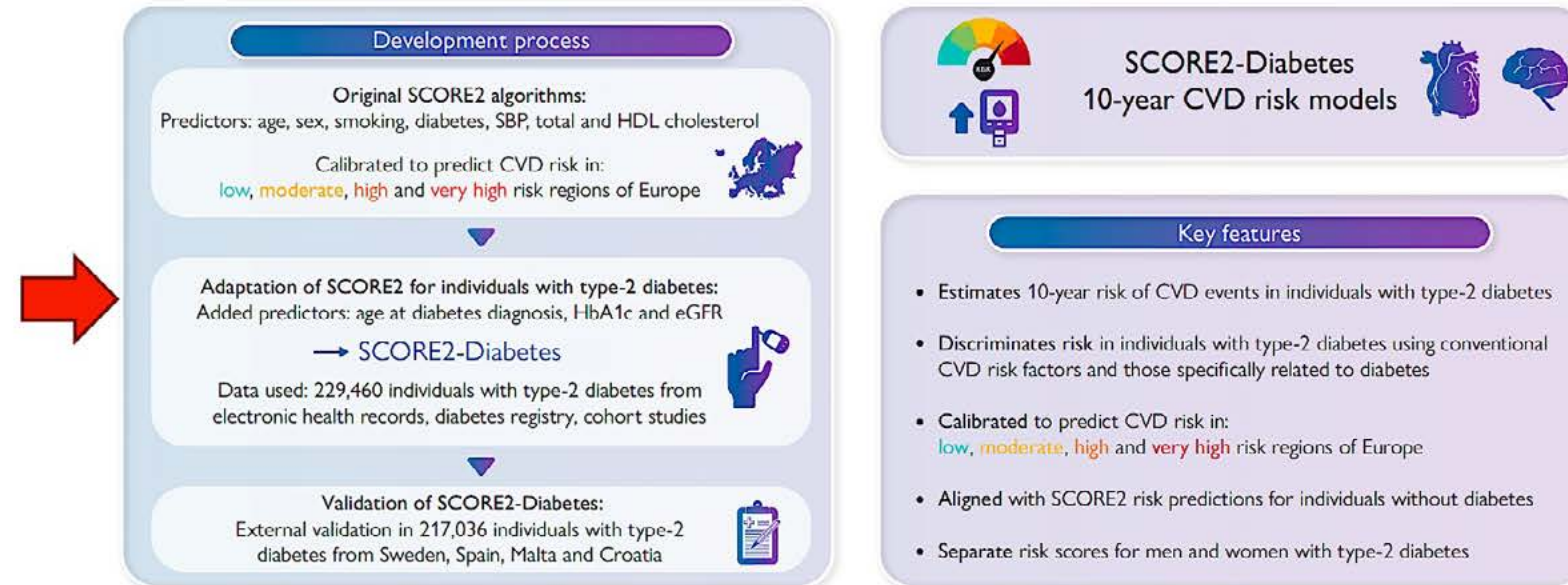


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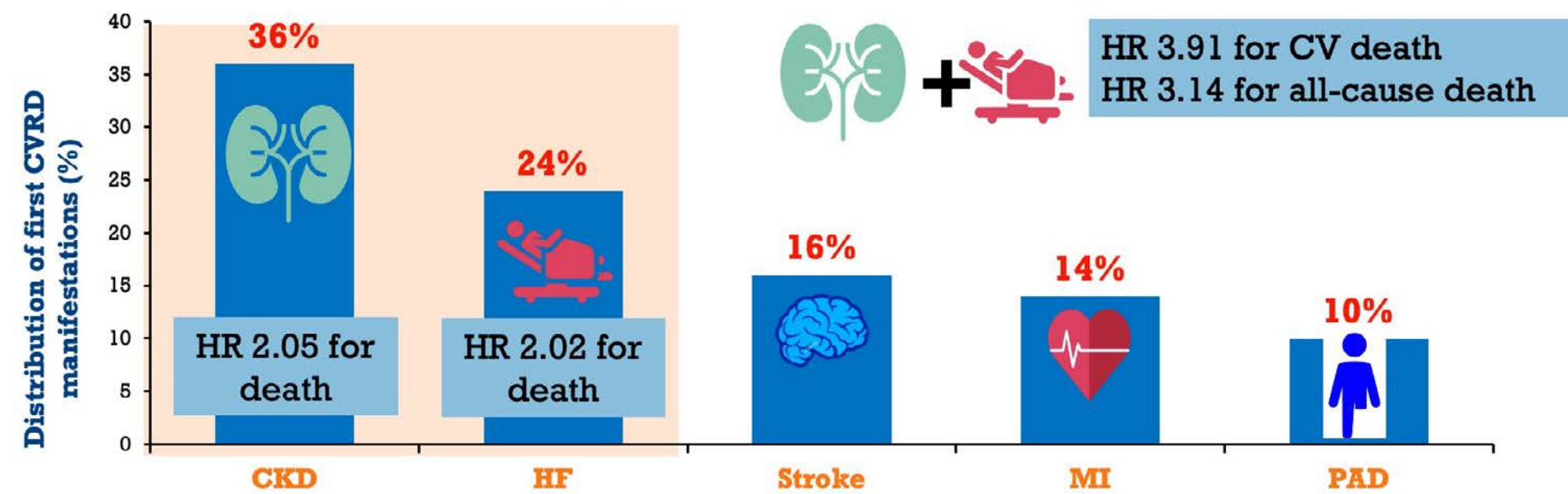
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SCORE2-Diabetes: 10-year cardiovascular risk estimation in type 2 diabetes in Europe

SCORE2-Diabetes Working Group and the ESC Cardiovascular Risk Collaboration^{††}



Development of first CVRD manifestation in patients with T2D (18%) in a large multinational cohort study (N=772,336)* Follow-up: 4.5 years



*All patients had no record of CV or kidney disease at study entry and were followed-up for a mean duration of 4.5 years, during which 137,081 patients developed a first cardiovascular or renal disease (CVRD) manifestation. CKD, chronic kidney disease; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease;

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Birkeland KI et al. *Diabetes Obes Metab* 2020;22:1607



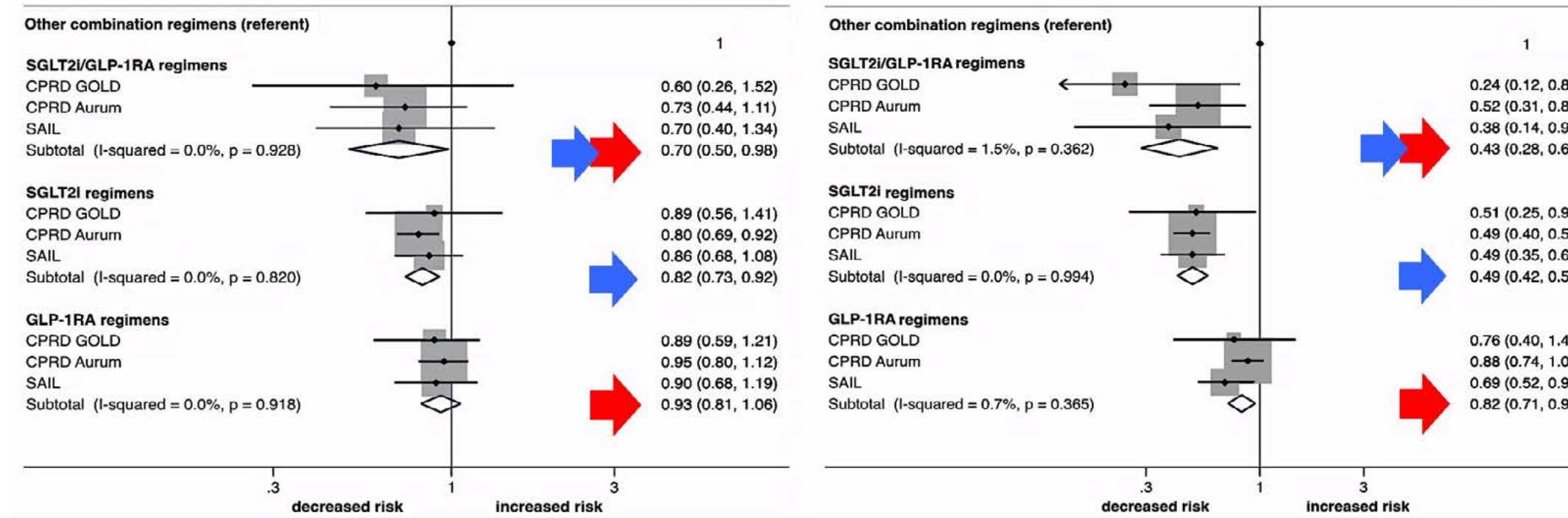
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Primary Prevention of Cardiovascular and Heart Failure Events With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Their Combination in Type 2 Diabetes

Among 336,334 people with T2D and without CVD, 18,531 (5.5%) experienced a **MACCE**. OR (95% CI)

In a cohort of 411,206 with T2D and without HF, 17,451 (4.2%) experienced an **HF event**. OR (95% CI)



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Wright AK et al. Diabetes Care. 2022; 45: 909-918.



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Comparative effectiveness of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas on risk of major adverse cardiovascular events

The final cohort consisted of 283,998 new users of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, or sulfonylureas

	SGLT2 inhibitors (n=46 516)	GLP-1 receptor agonists (n=26 038)	DPP-4 inhibitors (n=55 310)	Sulfonylureas (n=156 134)
Sociodemographic characteristics				
Age, years	64.22 (10.57)	64.25 (10.75)	64.35 (10.80)	64.22 (10.86)
Laboratory and vital signs measurements				
eGFR, mL/min/1.73 m ²	78.23 (20.16)	77.67 (20.65)	77.73 (20.71)	77.83 (20.87)
HbA _{1c} %	8.67 (1.83)	8.61 (1.86)	8.64 (1.82)	8.58 (1.86)
Comorbidities				
Albuminuria	13 071 (28.1%)	7 494 (28.8%)	15 736 (28.5%)	43 312 (27.7%)
Cardiovascular disease	4 531 (9.7%)	2 500 (9.6%)	5 409 (9.8%)	15 848 (10.2%)

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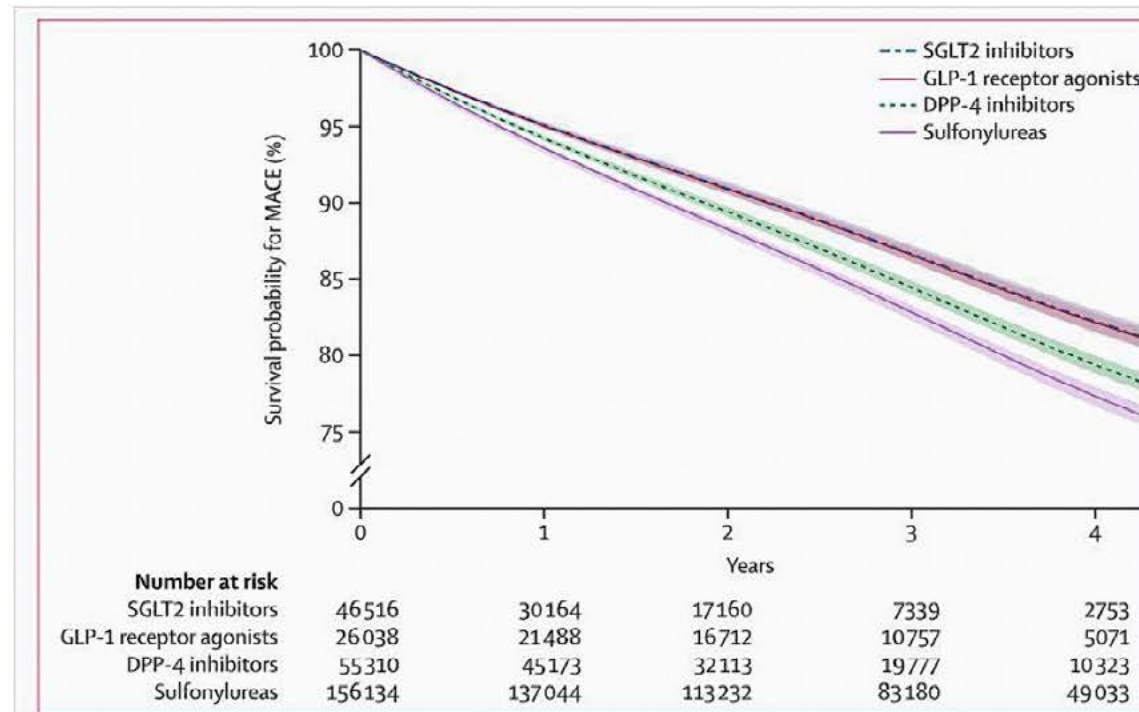
Xie Y et al. Lancet Diabetes Endocrinol. 2023; 11: 644-656.



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Comparative effectiveness of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas on risk of MACE: composite of stroke, myocardial infarction and all-cause mortality

The final cohort consisted of 283,998 new users of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, or sulfonylureas



INTENTION-TO-TREAT

SGLT2i	GLP-1RA	DPP4i	
0.77	0.78	0.90	SU
0.86	0.86		DPP4i
0.99			GLP-1RA

PER-PROTOCOL

SGLT2i	GLP-1RA	DPP4i	
0.77	0.77	0.88	SU
0.88	0.88		DPP4i
1.01			GLP-1RA

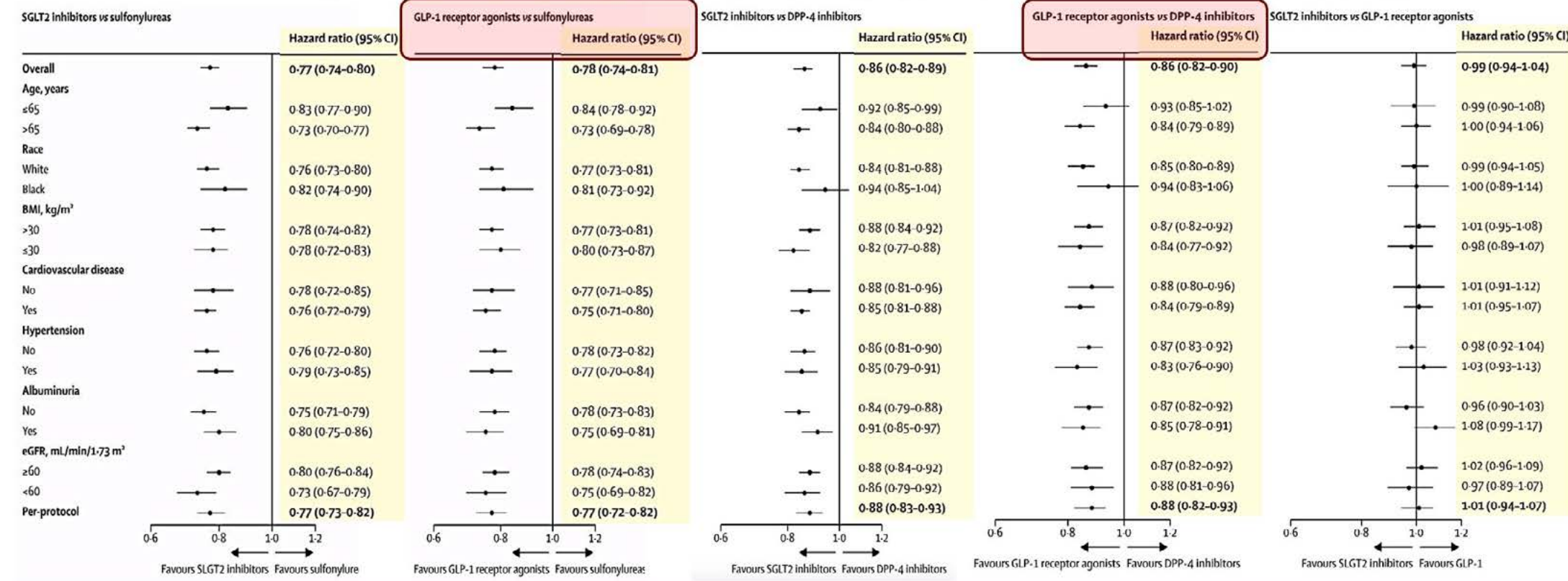
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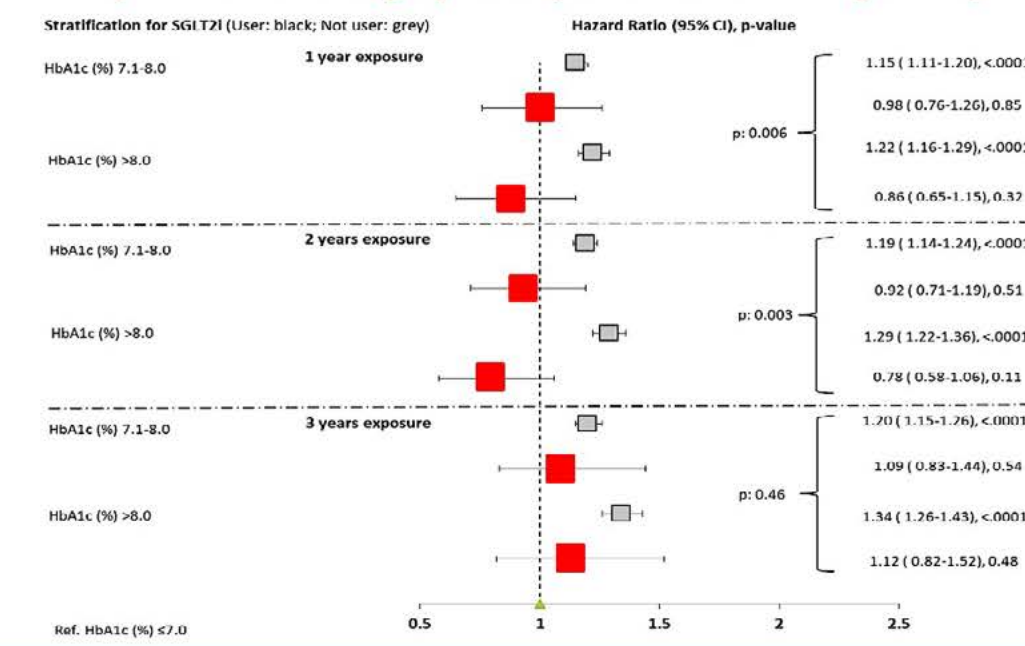
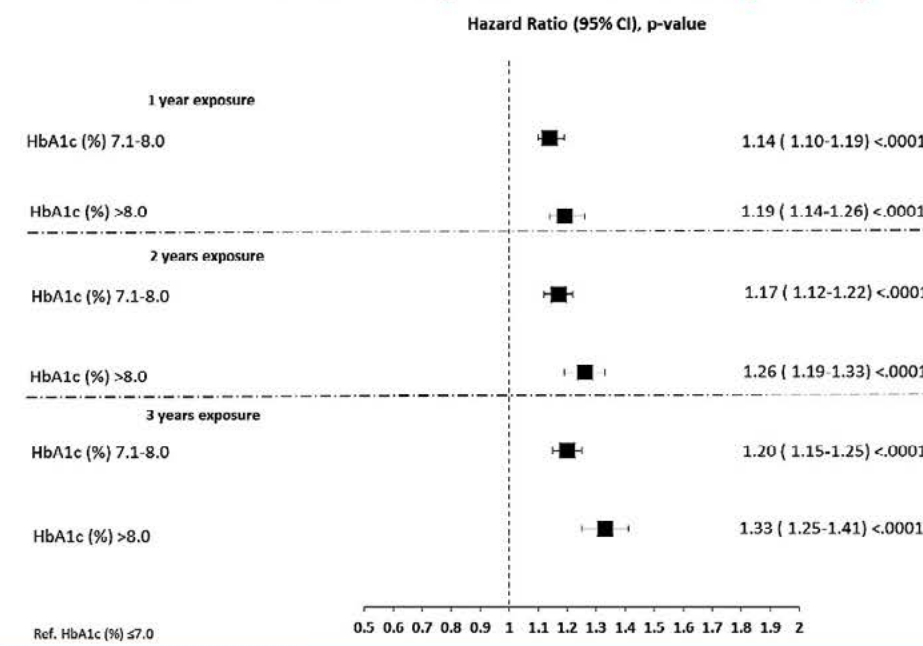


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The legacy effect of hyperglycemia and early use of SGLT-2 inhibitors: a cohort study with newly-diagnosed people with type 2 diabetes
AMD Annals; 251,339 subjects with newly-diagnosed T2D and without CVD at baseline

Poor, early glycemic control and the subsequent risk of cardiovascular diseases (*HbA1c ≤ 7% is the reference*)

SGLT-2i, introduced in the first two years, attenuate the phenomenon of legacy effect (*HbA1c ≤ 7% is the reference*)



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Ceriello A et al. Lancet Regional Health - Europe. 2023; 31: 100666

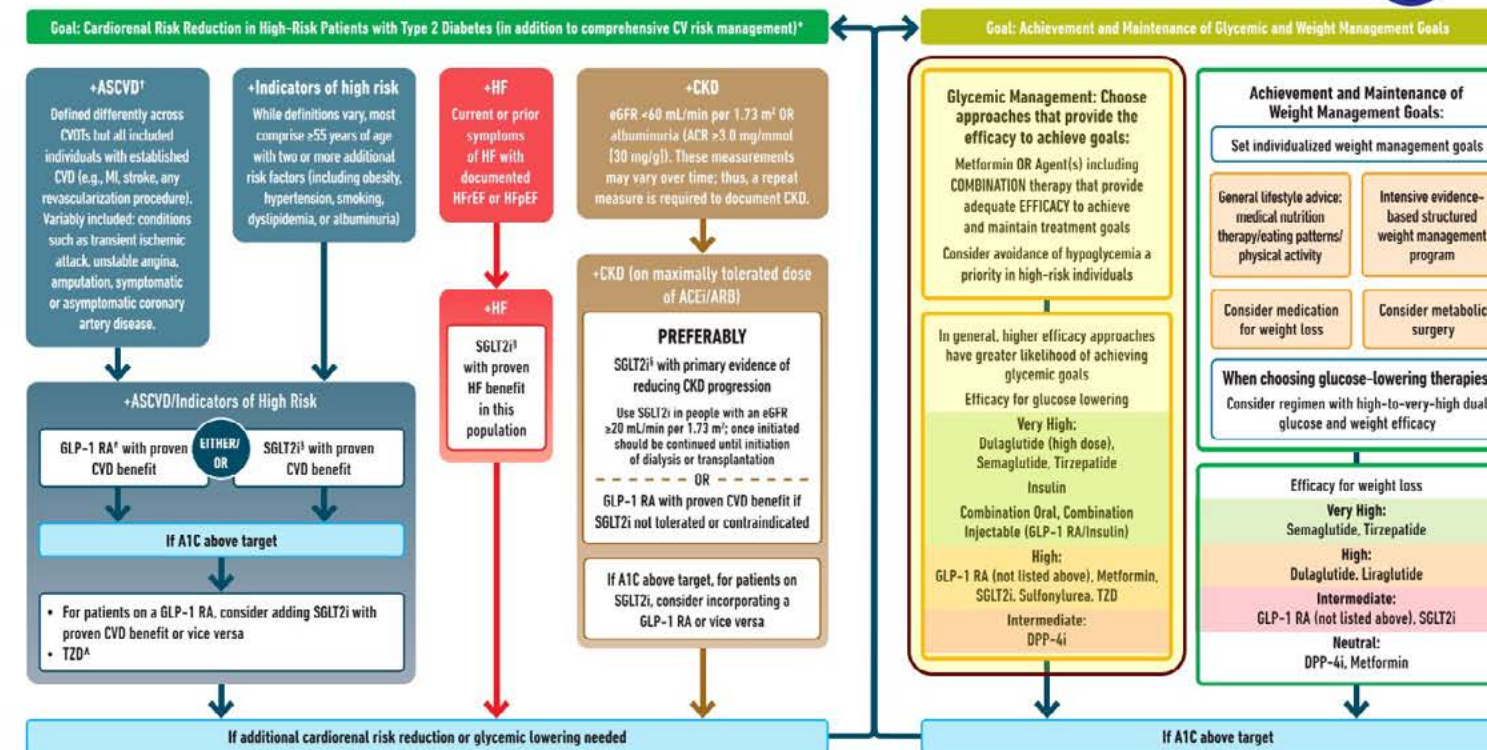
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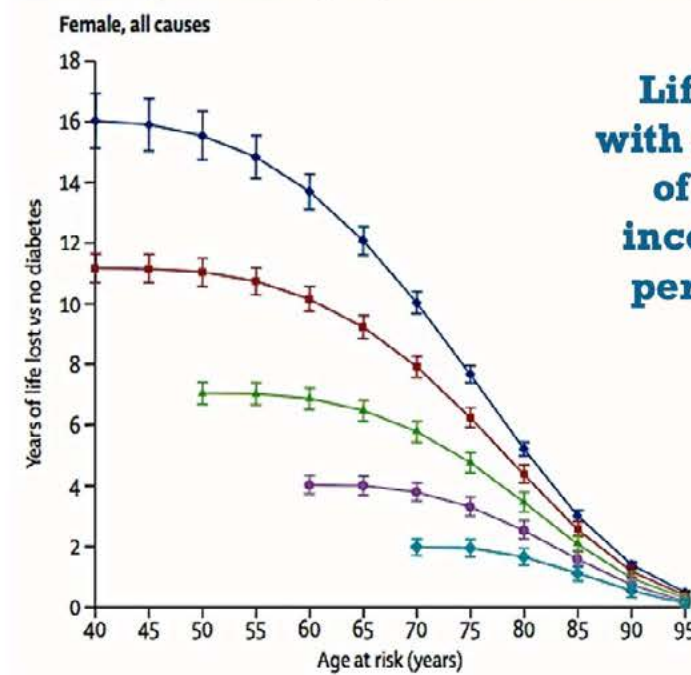
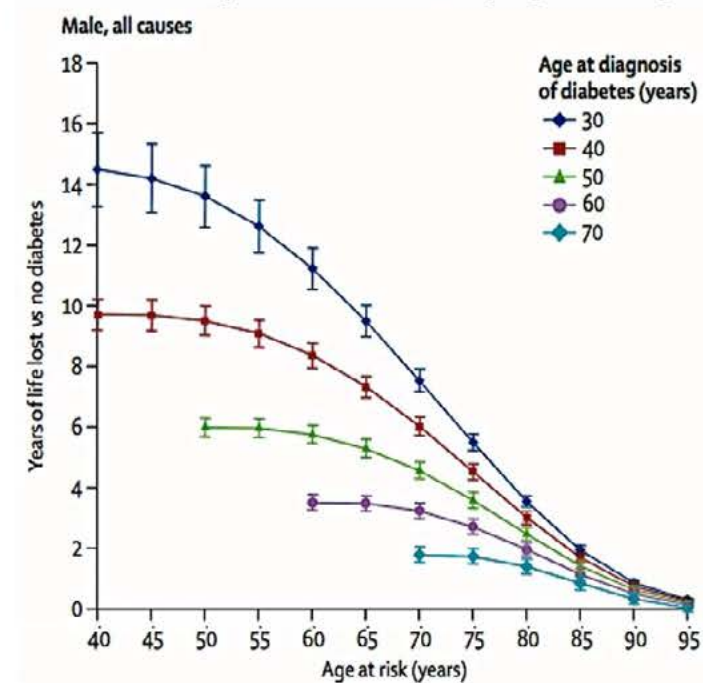


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Age- and sex-adjusted HRs for all-cause mortality according to age at diagnosis of diabetes using data from 1515718 participants, in whom deaths were recorded during 23.1 million person-years of follow-up.

Estimated years of life lost by age at diagnosis of T2DM compared with people without diabetes



Life expectancy associated with different ages at diagnosis of type 2 diabetes in high-income countries: 23 million person-years of observation

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Emerging Risk Factors Collaboration, Lancet Diabetes Endocrinol, Published online September 11, 2023

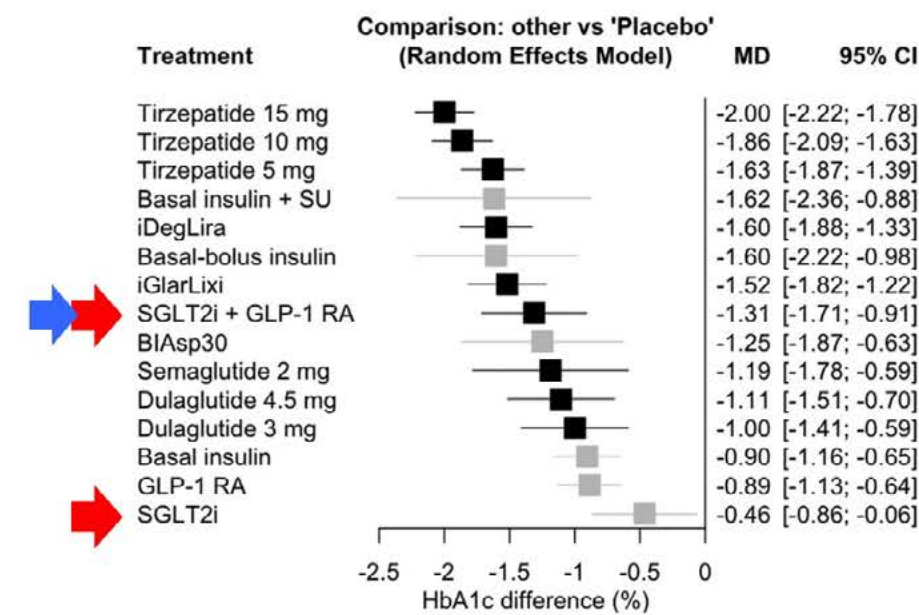
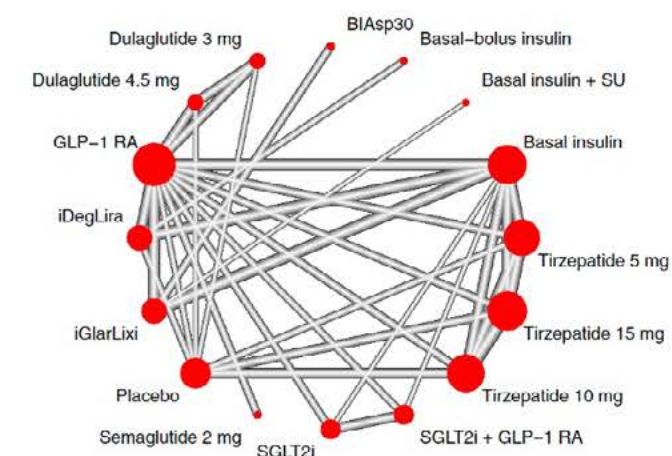


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Glucometabolic outcomes of GLP-1 receptor agonist-based therapies in patients with type 2 diabetes: a systematic review and network meta-analysis

Network meta-analysis results for change from baseline in a. **HbA1c**, b. fasting plasma glucose (FPG), and c. post-prandial glucose (PPG) compared with placebo.

New GLP-1RA-based treatments are highlighted in black, other treatments in grey.



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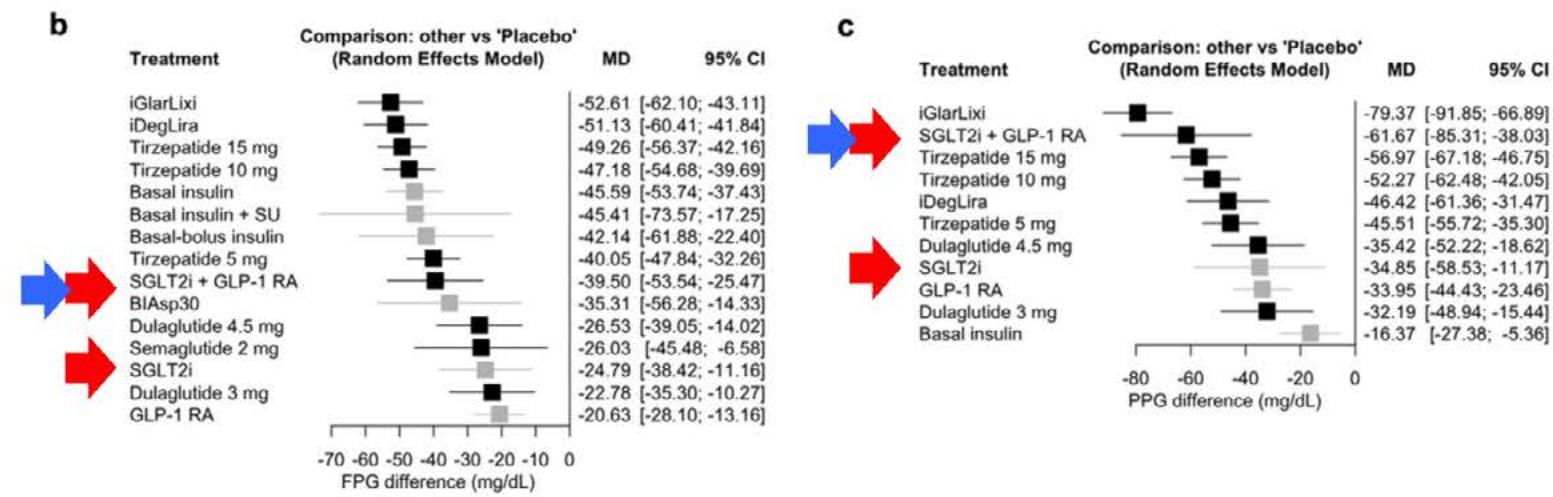
Caruso I et al., EClinicalMedicine 2023;64:102181



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Glucometabolic outcomes of GLP-1 receptor agonist-based therapies in patients with type 2 diabetes: a systematic review and network meta-analysis

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Caruso I et al., EClinicalMedicine 2023;64:102181



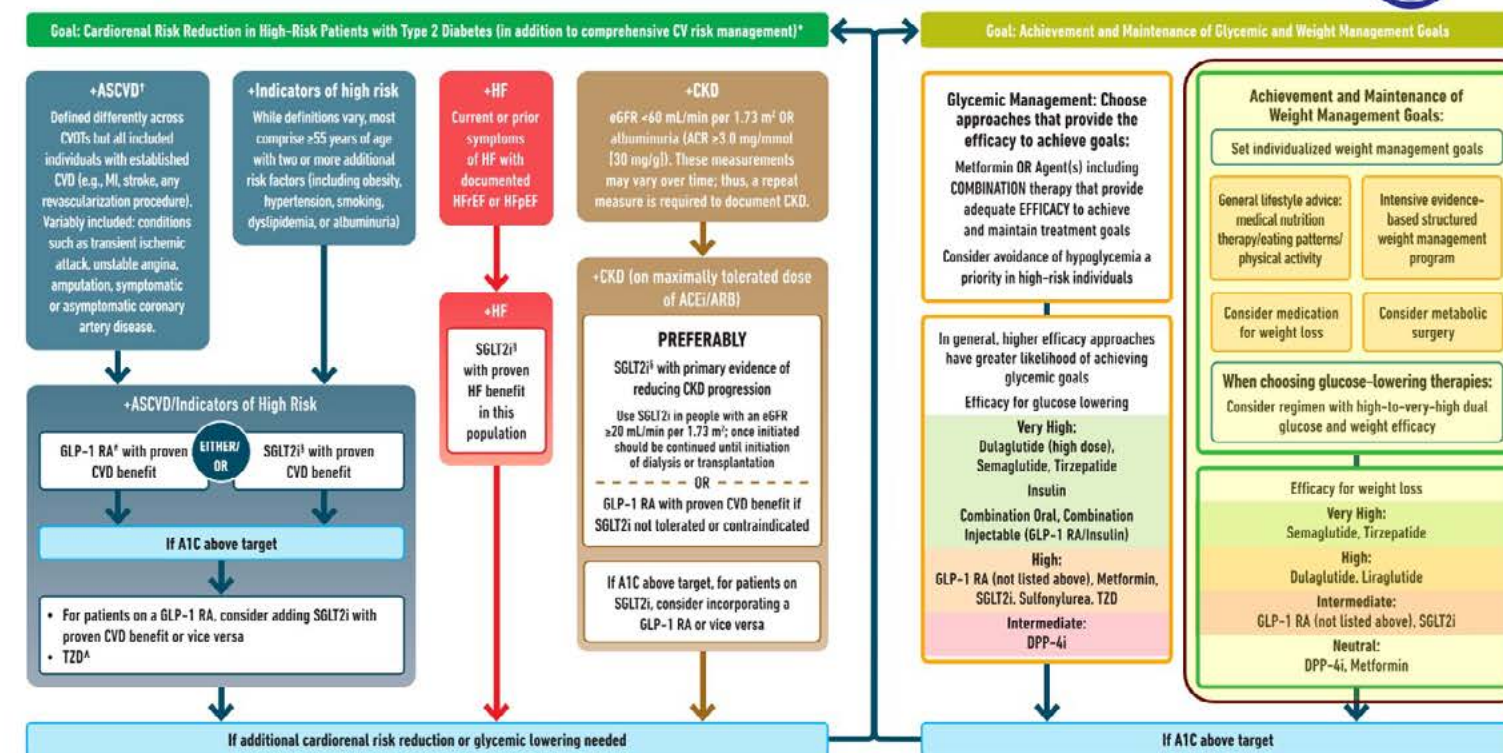
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ADA, Diabetes Care 2023; 46(Suppl. 1): S140–S157

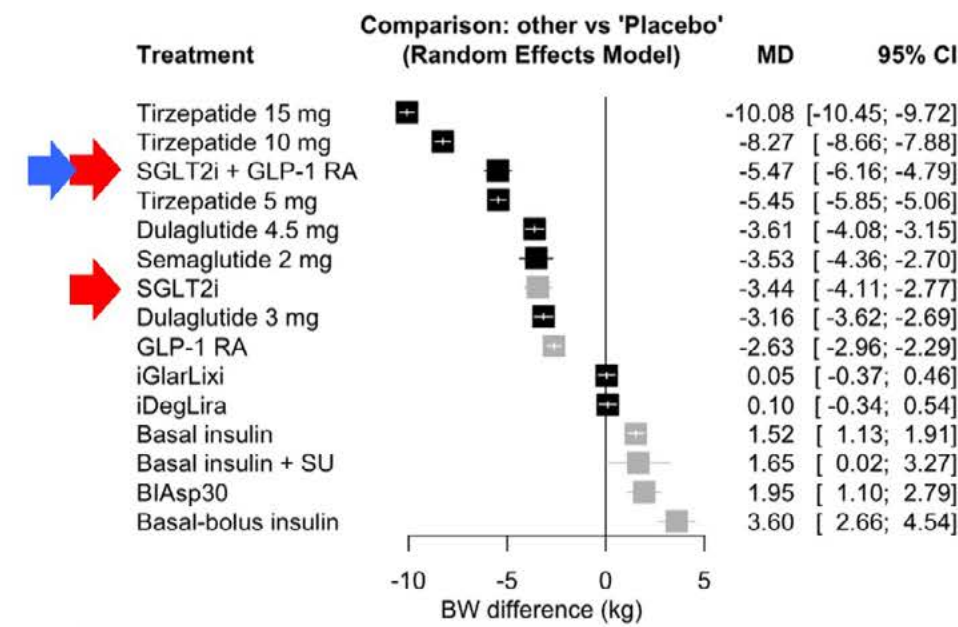


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Glucometabolic outcomes of GLP-1 receptor agonist-based therapies in patients with type 2 diabetes: a systematic review and network meta-analysis

Network meta-analysis results for change from baseline in **bodyweight (BW)** compared with placebo.



New GLP-1RA-based treatments are highlighted in black, other treatments in grey.

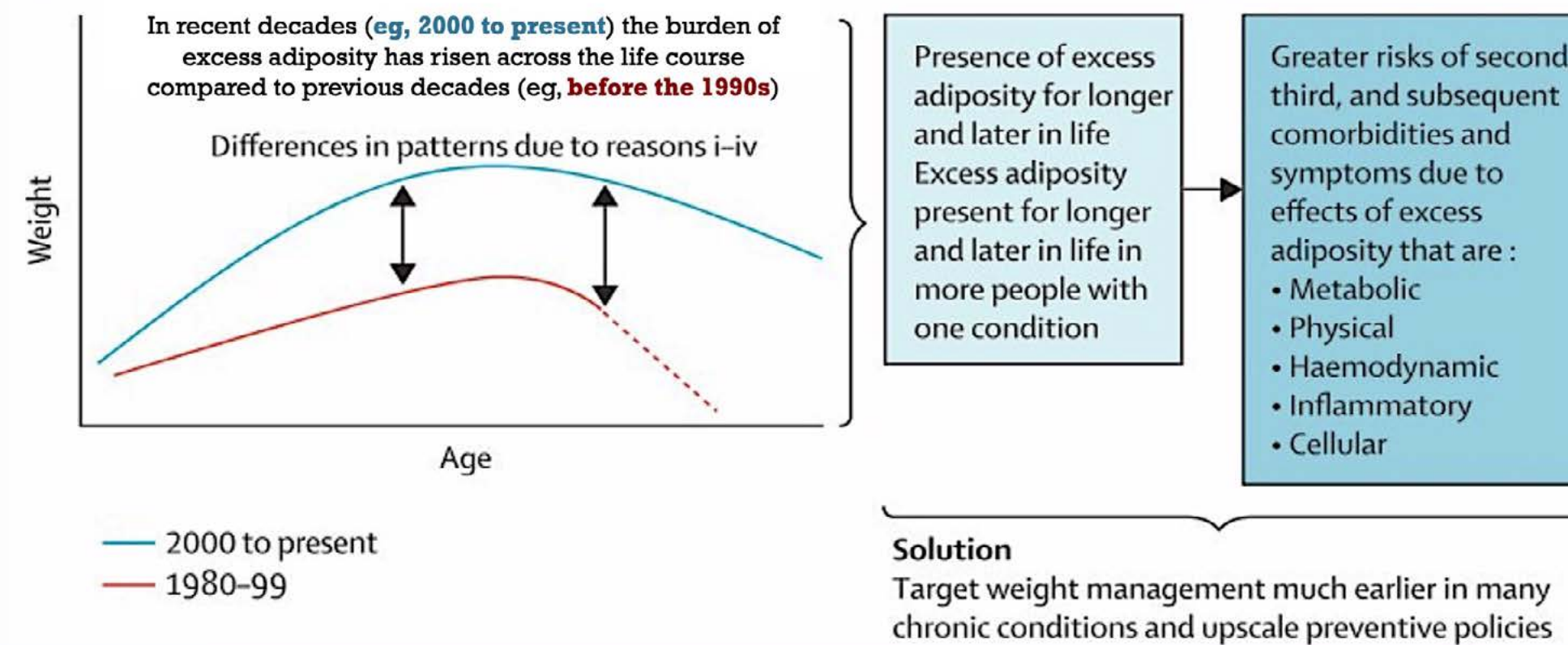
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Caruso I et al., EClinicalMedicine 2023;64:102181



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Treating chronic diseases without tackling excess adiposity promotes multimorbidity



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Sattar N, et al. Lancet Diabetes Endocrinol 11: 58-62, 2023



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Treating chronic diseases without tackling excess adiposity promotes multimorbidity

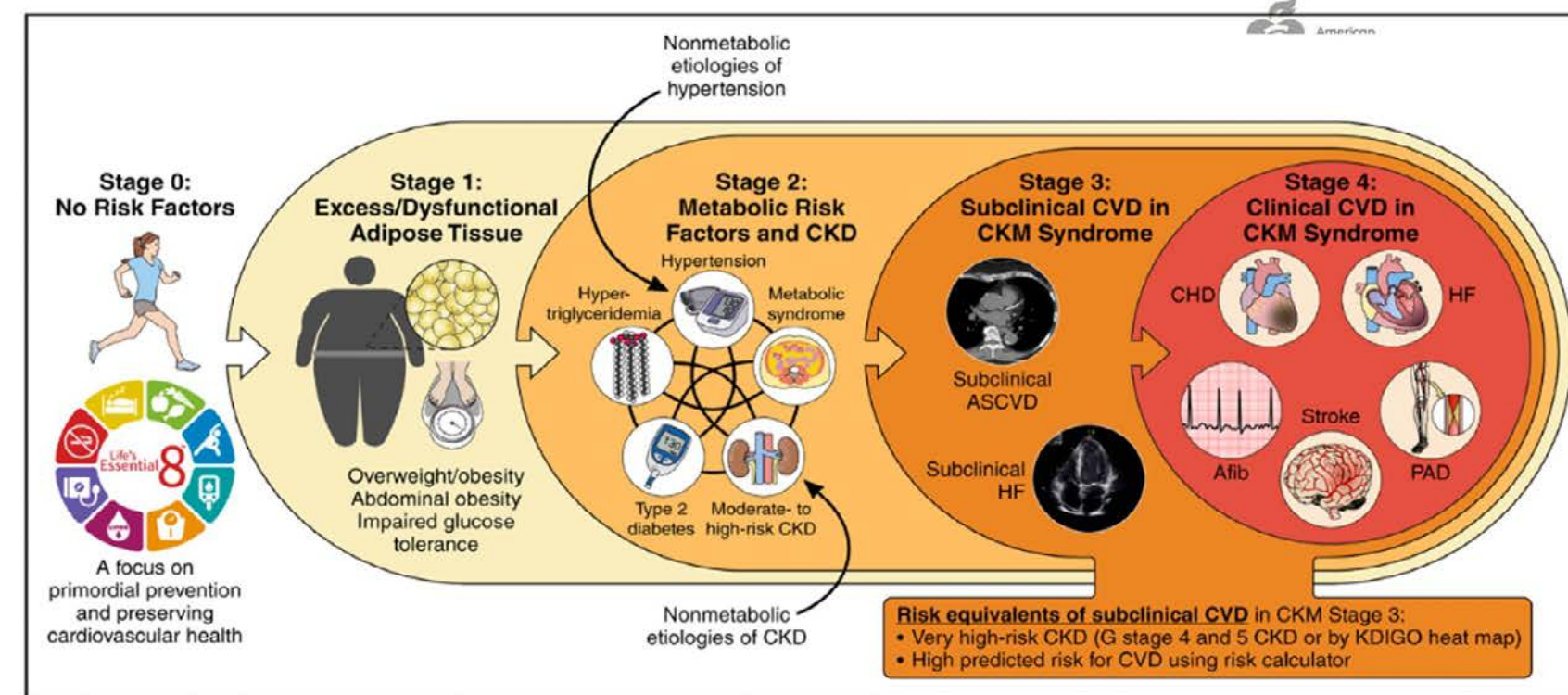
REASONS FOR DIFFERENT AGE TO WEIGHT PATTERN IN SUBSEQUENT DECADES:

- Obesity has increased in general (change in food and activity environments)
- Faster increase in average weight at younger age
- Overall reduction in smoking with other factors (such as obesity) becoming larger contributors to disease development
- The development of better care for many chronic disease (such as many cancers, autoimmune disease, and heart failure) allows longer living
- Mortality for CV and other conditions has reduced, due to better primary and secondary prevention, leading to people living longer with chronic conditions

=

GREATER LIFETIME EXPOSURE TO EXCESS ADIPOSITY AND CONSEQUENT RISE IN DEVELOPMENT OF OTHER CONDITIONS LINKED TO EXCESS ADIPOSITY

Cardiovascular-kidney-metabolic (CKM) health reflects the interplay among metabolic risk factors, chronic kidney disease, and the cardiovascular system and has profound impacts on morbidity and mortality



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Ndumele CE et al., Circulation, 14 novembre 2023



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Cardiovascular-kidney-metabolic (CKM) health reflects the interplay among metabolic risk factors, chronic kidney disease, and the cardiovascular system and has profound impacts on morbidity and mortality

Stage 0 CKM: normal weight, normal glucose, normal blood pressure, normal lipids, normal kidney function, and no evidence of subclinical or clinical CVD

Stage 1 CKM: excess adipose tissue, dysfunctional adipose tissue, or both. Excess adiposity is identified by either weight or abdominal obesity, and dysfunctional adipose tissue is reflected by impaired glucose tolerance and hyperglycemia

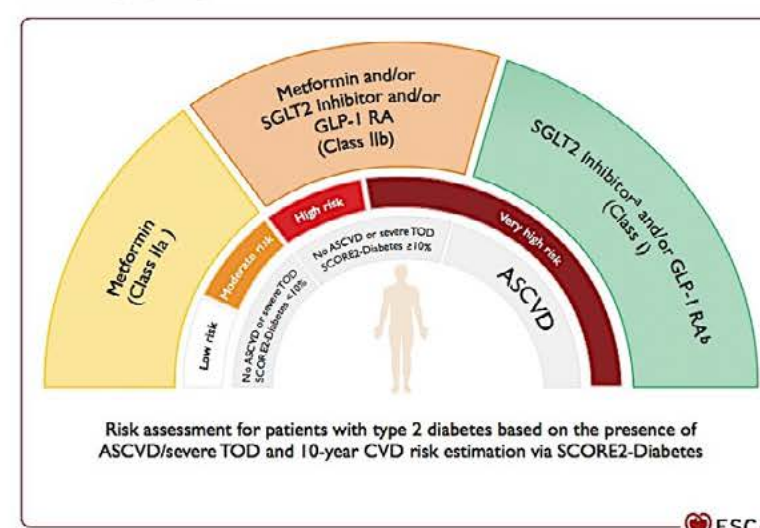
Stage 2 CKM: metabolic risk factors (hypertriglyceridemia, hypertension, metabolic syndrome, or type 2 diabetes), moderate- to high-risk chronic kidney disease (CKD), or both

Stage 3 CKM: subclinical CVD with overlapping CKM risk factors (excess/dysfunctional adipose tissue, metabolic risk factors, or CKD) or those with the risk equivalents of very high-risk CKD or high predicted risk using the forthcoming CKM risk calculator

Stage 4 CKM: individuals with clinical CVD (coronary heart disease, HF, stroke, peripheral artery disease, or atrial fibrillation) overlapping with CKM risk factors

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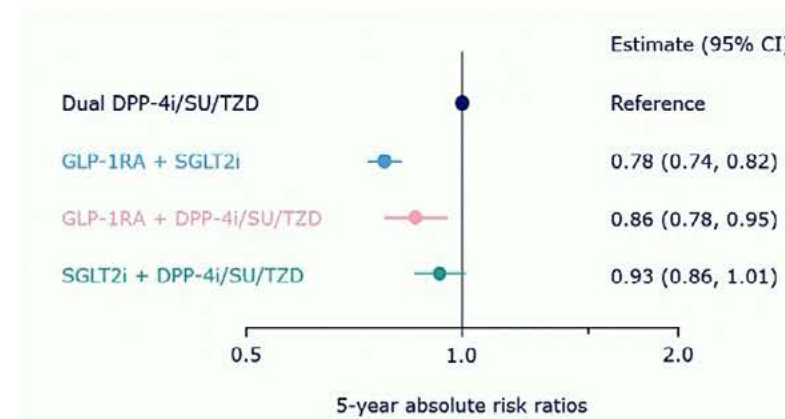
- **GLP-1RA and SGLT2i alone** are recommended as first-line treatment in specific population, including people with established or high risk of CVD, HF, or CKD.
- For patients with T2D at very high cardiovascular risk (including those with established atherosclerotic cardiovascular disease), the **dual therapy with a GLP-1RA and an SGLT2i** to reduce cardiovascular risk independent of glucose control is among the ESC recommendations.

GLP-1 RA + SGLT2i combination vs other combinations

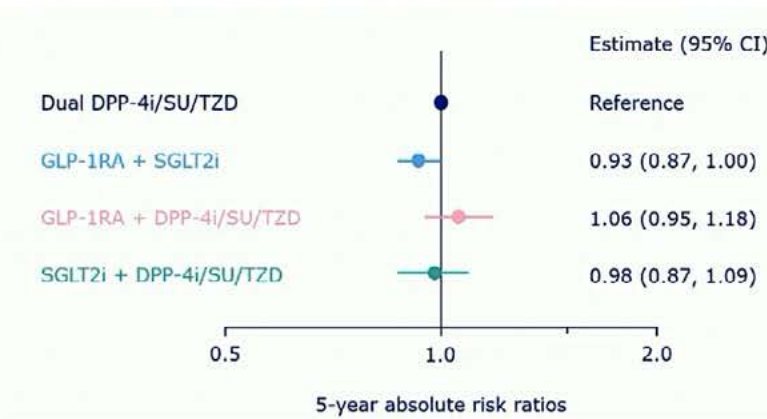
- 87,201 people with T₂DM from Danish registries
- GLP-1 RA + SGLT2i combination resulted in greater 5-year risk **reduction of all-cause mortality, heart failure, end-stage kidney disease, and >50% eGFR decline** compared to other (GLP-1 RA or SGLT2i) combinations

■ Dual DPP-4i/SU/TZD N=29,150
 ■ GLP-1RA + SGLT2i N=14,831
 ■ GLP-1RA + DPP-4i/SU/TZD N=20,417
 ■ SGLT2i + DPP-4i/SU/TZD N=22,803

All-cause mortality



Heart Failure Hospitalization



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Presented at EASD 59^o Annual Meeting (Hamburg 2023)



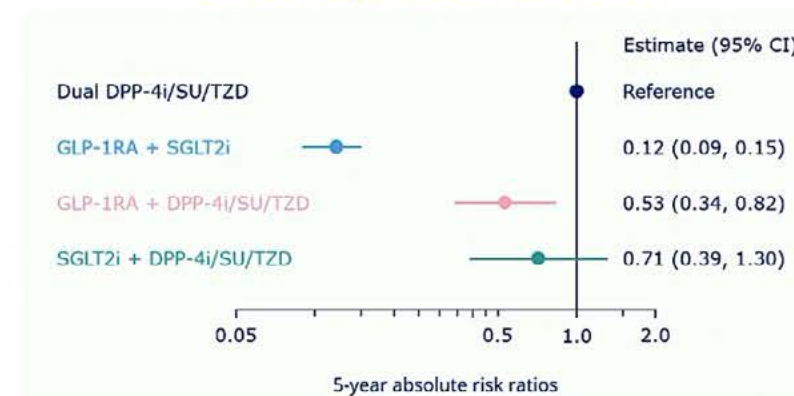
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GLP-1 RA + SGLT2i combination vs other combinations

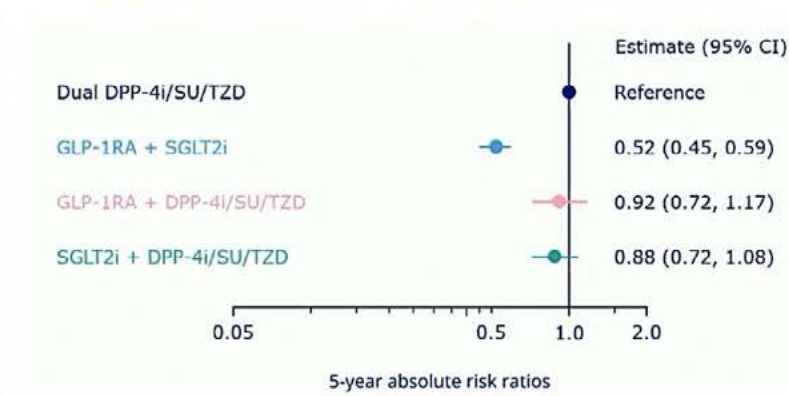
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 GLP-1RA + SGLT2i N=14,831
 GLP-1RA + DPP-4i/SU/TZD N=20,417
 SGLT2i + DPP-4i/SU/TZD N=22,803

End-stage renal disease



eGFR decrease >50% from baseline



THUS

SGLT2i & GLP-1 RA combination therapy could be used in patients with



BUT

Caution is warranted in older frail individuals

Cost (particularly) of GLP-1 RA would need to fall by >> to be cost-effective

ESC
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 of Cardiology

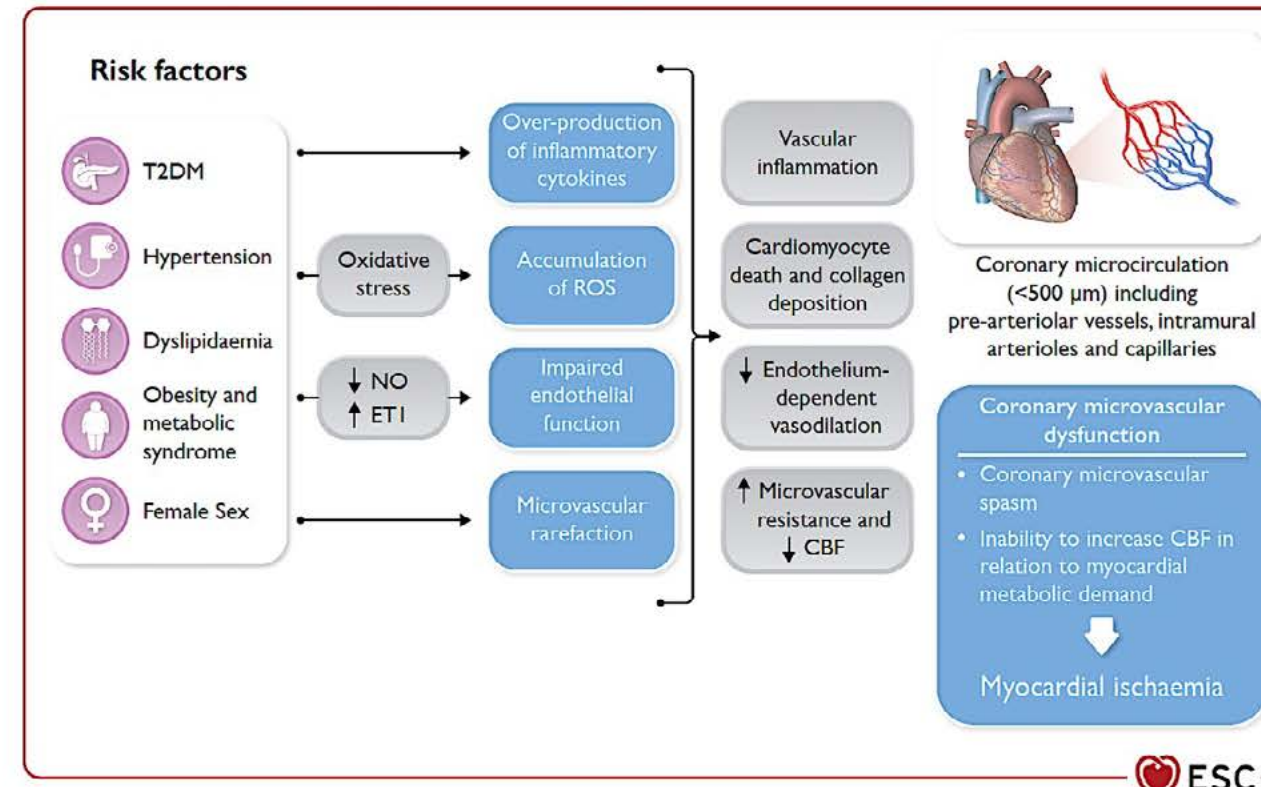
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Supplementary data

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A correlation with albuminuria has also been reported

Pathophysiology of coronary microvascular dysfunction



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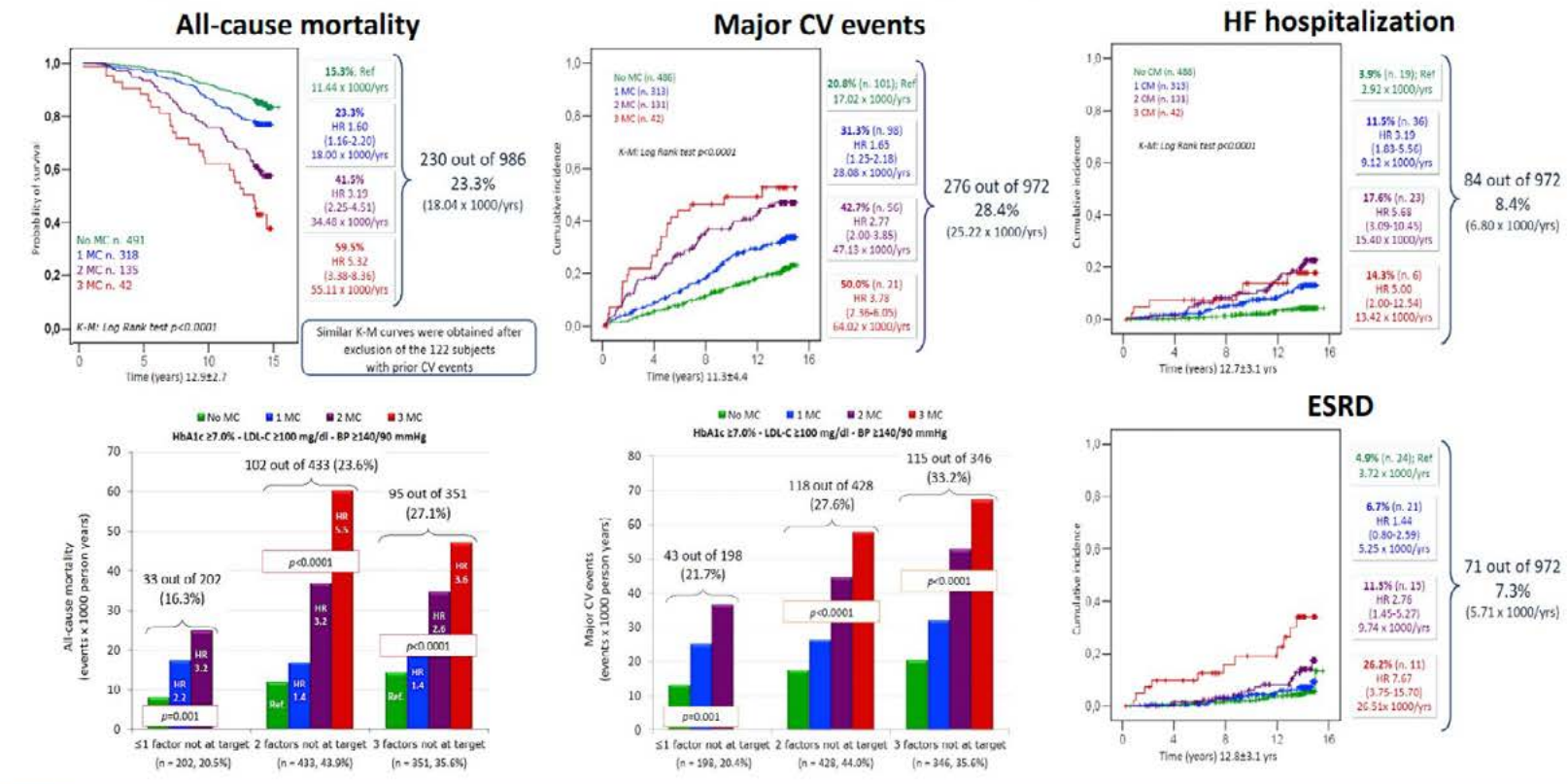
Marx N, et al. Eur Heart J. 2023 Oct 14; 44: 4043-4140.



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Microvascular complications as predictors of all-cause mortality, major vascular outcomes and ESRD in T2DM

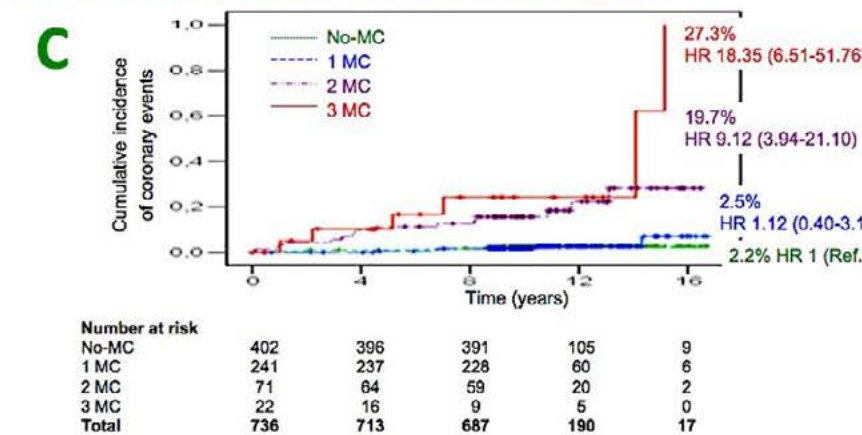
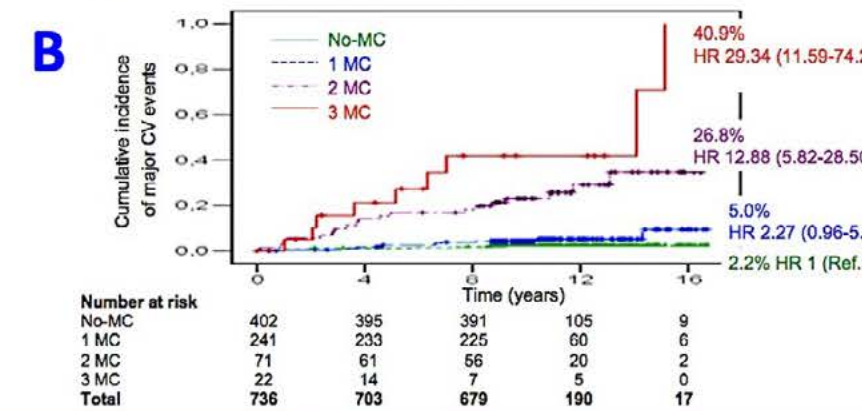
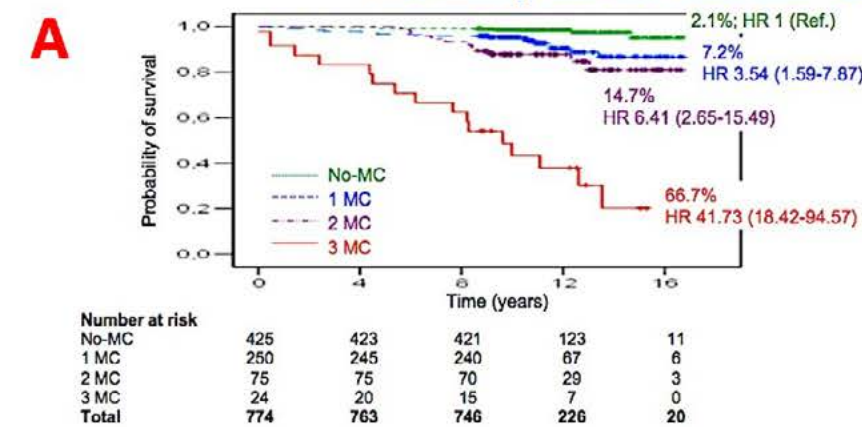


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Garofolo M. et al., **Unpublished data**

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Mortality, cardiovascular outcomes and "microvascular burden" in T1DM



	Outcomes in 3 MC	"Fully" adjusted HR	95% CI	p
A	All-cause mortality	7.02	2.44-20.20	<0.0001
B	Major Vascular Events	9.31	3.18-27.25	<0.0001
C	Coronary events	5.26	1.55-17.85	0.008

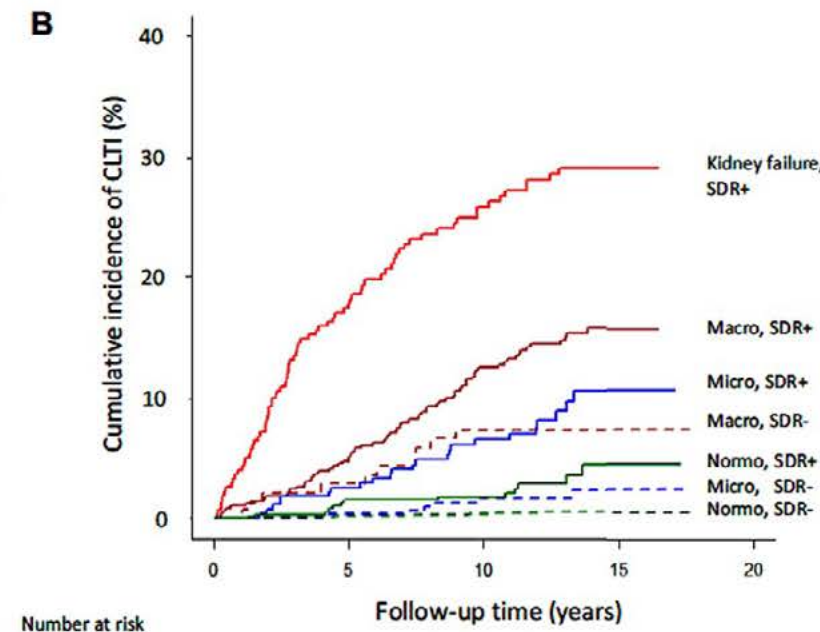
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Garofolo M. et al., *Cardiovasc Diabetol* 18: 159, 2019



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The impact of diabetic nephropathy and severe diabetic retinopathy on chronic limb threatening ischemia risk in individuals with T1DM: a nationwide, population study



Number at risk	0	5	10	15	20
Kidney failure, SDR+	289	166	91	14	
Macro, SDR+	473	410	312	23	
Macro, SDR-	135	120	97	4	
Micro, SDR+	265	234	195	3	
Micro, SDR-	297	291	243	1	
Normo, SDR+	378	356	296	6	
Normo, SDR-	2496	2442	1921	23	

	HR
Kidney failure, SDR+	37.9
Macro, SDR+	15.6
Micro, SDR+	11.9
Macro, SDR-	8.7
Normo, SDR+	4.8
Micro, SDR-	3.2
Normo, SDR-	1



unite for diabetes



Grazie per l'attenzione

Delitti in materia di violazione del diritto d'autore (Art. 25-novies, D.Lgs. n. 231/2001) [articolo aggiunto dalla L. n. 99/2009]

- Messa a disposizione del pubblico, in un sistema di reti telematiche, mediante connessioni di qualsiasi genere, di un'opera dell'ingegno protetta, o di parte di essa (art. 171, legge n.633/1941 comma 1 lett. a) bis)
- Reati di cui al punto precedente commessi su opere altrui non destinate alla pubblicazione qualora ne risulti offeso l'onore o la reputazione (art. 171, legge n.633/1941 comma 3)
- Abusiva duplicazione, per trarne profitto, di programmi per elaboratore; importazione, distribuzione, vendita o detenzione a scopo commerciale o imprenditoriale o concessione in locazione di programmi contenuti in supporti non contrassegnati dalla SIAE; predisposizione di mezzi per rimuovere o eludere i dispositivi di protezione di programmi per elaboratori (art. 171-bis legge n.633/1941 comma 1)
- Riproduzione, trasferimento su altro supporto, distribuzione, comunicazione, presentazione o dimostrazione in pubblico, del contenuto di una banca dati; estrazione o reimpiego della banca dati; distribuzione, vendita o concessione in locazione di banche di dati (art. 171-bis legge n.633/1941 comma 2)
- Abusiva duplicazione, riproduzione, trasmissione o diffusione in pubblico con qualsiasi procedimento, in tutto o in parte, di opere dell'ingegno destinate al circuito televisivo, cinematografico, della vendita o del noleggio di dischi, nastri o supporti analoghi o ogni altro supporto contenente fonogrammi o videogrammi di opere musicali, cinematografiche o audiovisive assimilate o sequenze di immagini in movimento; opere letterarie, drammatiche, scientifiche o didattiche, musicali o drammatico musicali, multimediali, anche se inserite in opere collettive o composite o banche dati; riproduzione, duplicazione, trasmissione o diffusione abusiva, vendita o commercio, cessione a qualsiasi titolo o importazione abusiva di oltre cinquanta copie o esemplari di opere tutelate dal diritto d'autore e da diritti connessi; immissione in un sistema di reti telematiche, mediante connessioni di qualsiasi genere, di un'opera dell'ingegno protetta dal diritto d'autore, o parte di essa (art. 171-ter legge n.633/1941)
- Mancata comunicazione alla SIAE dei dati di identificazione dei supporti non soggetti al contrassegno o falsa dichiarazione (art. 171-septies legge n.633/1941)
- Fraudolenta produzione, vendita, importazione, promozione, installazione, modifica, utilizzo per uso pubblico e privato di apparati o parti di apparati atti alla decodificazione di trasmissioni audiovisive ad accesso condizionato effettuate via etere, via satellite, via cavo, in forma sia analogica sia digitale (art. 171-octies legge n.633/1941).

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