



DIABETE OGGI

Benefici degli Sodium-glucose co-transporter 2 inhibitors:
glicemia e molto altro



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Dichiaro di aver ricevuto negli ultimi due anni compensi o finanziamenti anche per partecipazioni a congressi dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

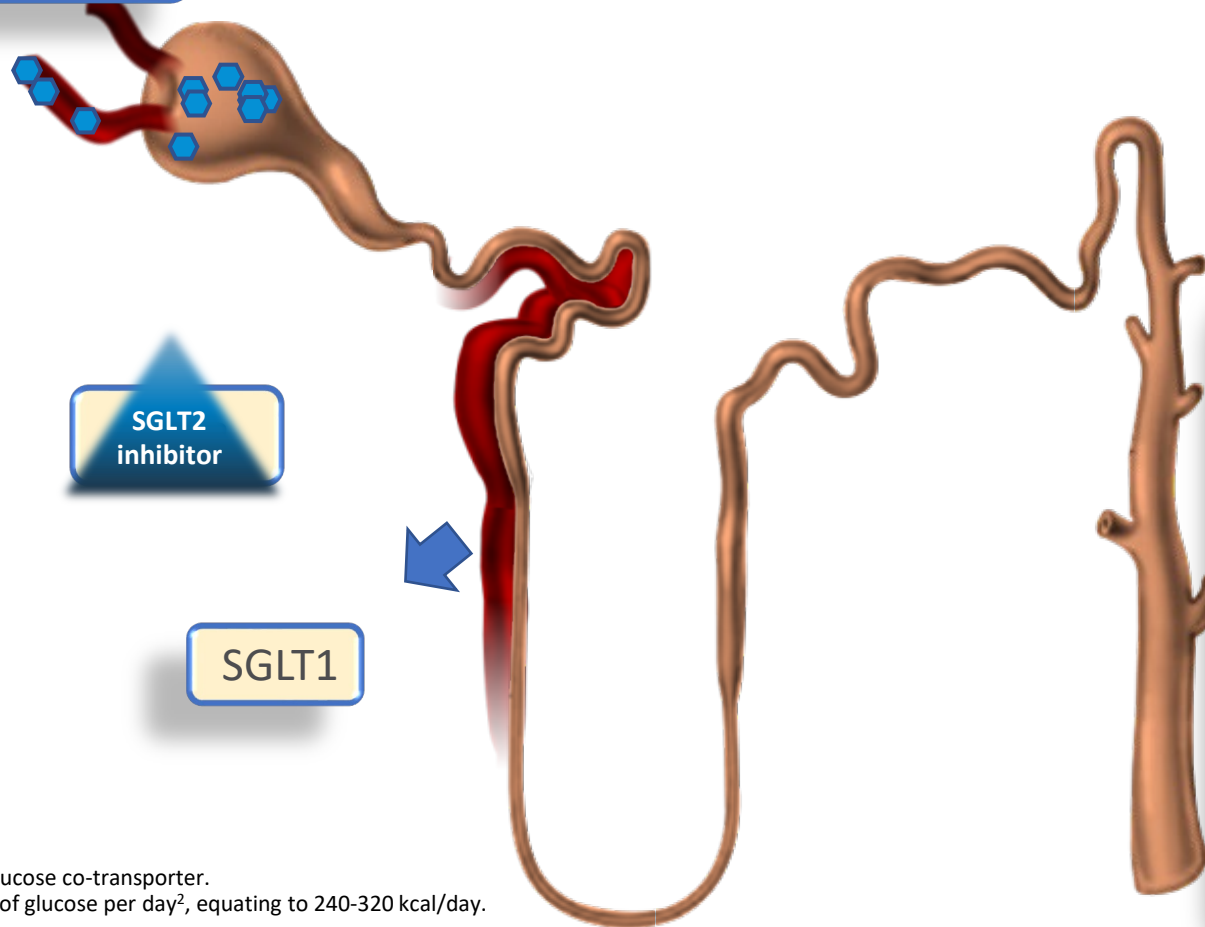
- Sanofi
- ABBOTT
- Movì

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).



Urinary glucose excretion via SGLT2 inhibition¹

Filtered glucose
load > 180 g/day



SGLT2 inhibitors
reduce glucose
re-absorption
in the proximal
tubule, leading to
urinary glucose
excretion* and
osmotic diuresis

SGLT, sodium glucose co-transporter.

* Loss of ~ 78 g of glucose per day², equating to 240-320 kcal/day.

References

1. Bakris GL, et al. *Kidney Int.* 2009;**75**:1272–1277.

Comparing Agents

Medication	Average A1C lowering	Hypoglycemic Agent	Weight Gain/Loss
Metformin	1.5%	No	Loss
Sulfonylureas	1.5%	Yes	Gain
Glinides	1-1.5%	No	Gain
SGLT-2 Inhibitors	1%	No	Loss
TZDs	0.5-1.4%	No	Gain
α -Glucosidase Inhibitor	0.5-0.8%	No	Neutral
DPP-4 Inhibitors	0.5-1%	No	Neutral

An overview of obesity-related complications: The epidemiological evidence linking body weight and other markers of obesity to adverse health outcomes

Disease, condition

Required weight loss (%) for improvement or resolution

Type 2 diabetes

- Prevention

- Remission

Hypertension

MAFLD

Cardiovascular outcomes

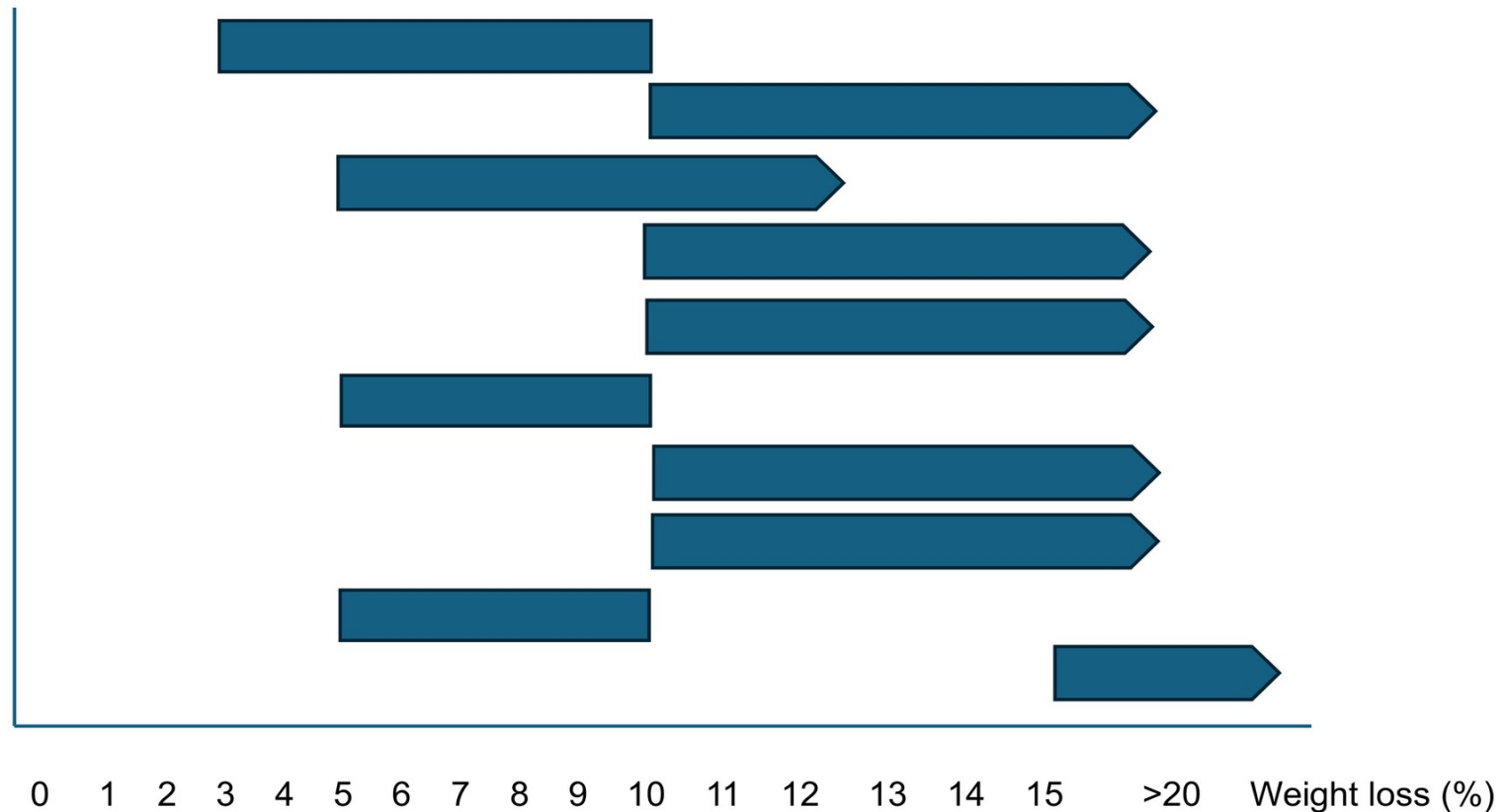
Dyslipidemia

OSAS

Gastroesophageal reflux

Stress incontinence

Breast cancer (women)



SGLT2-i e perdita di Peso Corporeo

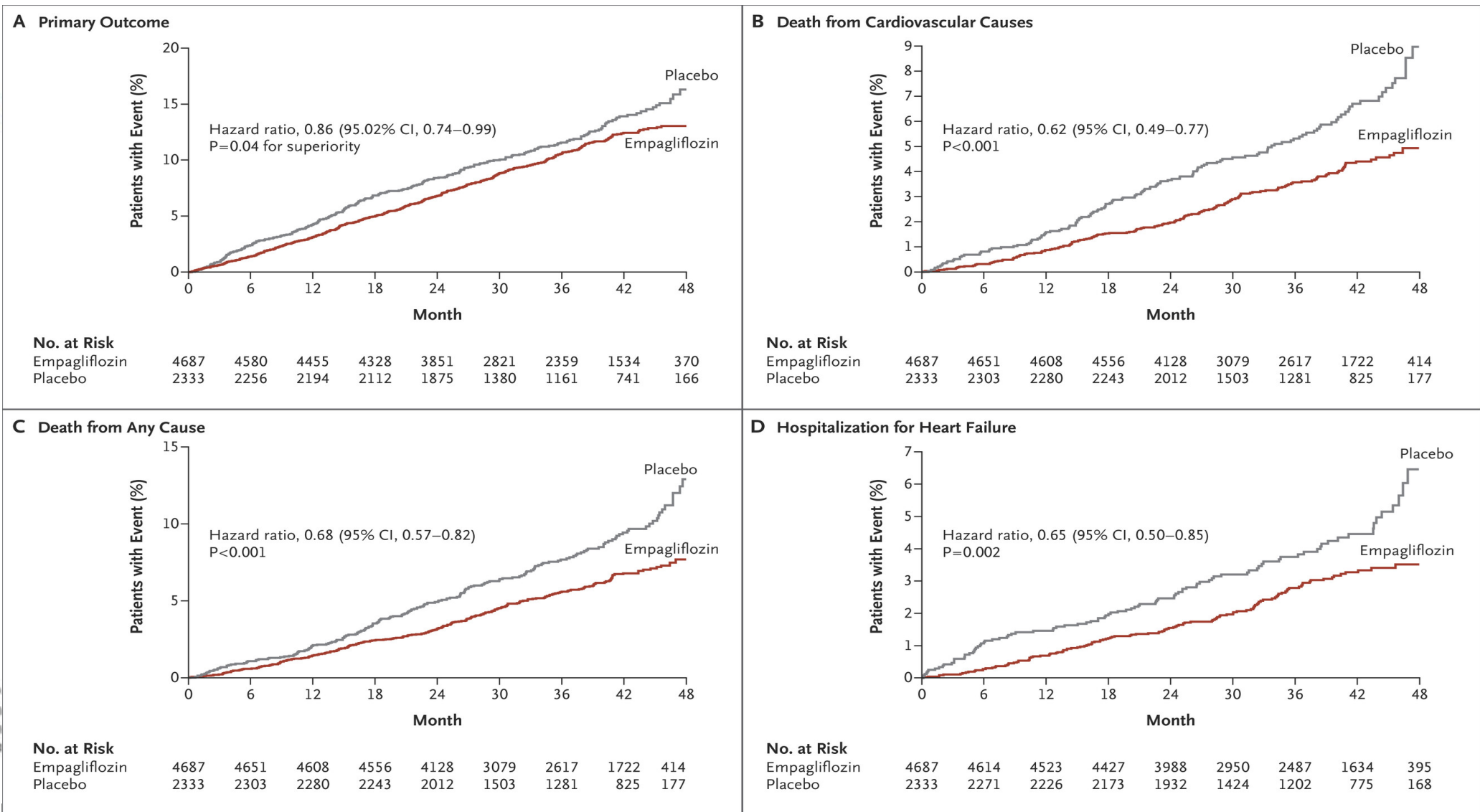
TABLE 1 Weight change achieved in published Phase III trials with available glucagon-like peptide receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter 2 inhibitors (SGLT2i)

Drug	Properties	Route of Administration/Dosing	Weight Change in T2DM Trials: Absolute (kg)
GLP-1 RA			
Dulaglutide	GLP-1 RA peptide fused to IgG4 molecule	sc 0.75-1.5 mg weekly	-0.8 to 2.9 ¹²
Exenatide	39 AA peptide	sc 5-10mcg bd	-1.4 to 4 ¹³⁻¹⁸
Exenatide-QW	Encapsulated in biodegradable polymer microspheres	sc 2 mg weekly	-1.6 to 3.7 ^{12,13,18}
Liraglutide	C-16 fatty acid to lys26, non-covalent bond to albumin	sc 1.2 mg-1.8 mg od	-2 to 5.0 ^{11,14,19-21}
Liraglutide	C-16 fatty acid to lys26, non-covalent bond to albumin	sc titrate in 0.6 mg weekly increments to 3 mg od	-6.0 ¹⁹
Lixisenatide	44 AA derivative of exenatide	sc 10-20mcg od	-1.3 to 3.0 ¹⁵
SGLT2i	SGLT2:SGLT1 relative specificity	↓ Glicemia e Insulina ↑ Glucagone con stimolo alla lipolisi ↑ FAO (ossidazione acidi grassi) ↑ della glicogenolisi e della gluconeogenesi	
Canagliflozin	75 gr/die di		
Dapagliflozin	escrezione di		
Empagliflozin	glucosio ≈ 300 kcal		
Ertugliflozin			

Abbreviations: bd, twice daily; od, once daily; po, oral; sc, subcutaneous. These data are from separately published studies and, therefore, are not intended to indicate comparative efficacy.

Non solo Glicemia....

EMPA-REG OUTCOME: Summary



*Defined due to re

1. Zinman B et al. *N Engl J Med* 2015;373:2117; 2. Wanner C et al. *N Engl J Med* 2016 (submitted)



SGLT2 INHIBITORS: CARDIOVASCULAR OUTCOMES TRIALS

	EMPA-REG OUTCOME 2016	CANVAS Program 2017	DECLARE-TIMI 58 2019	VERTIS CV 2020
DRUG	Empagliflozin 10-25 mg daily	Canagliflozin 100-300 mg daily	Dapagliflozin 10 mg daily	Ertugliflozin 5-15 mg daily
# RANDOMIZED	7020 (active, n=4687; placebo, n=2333)	10,141 (active, n=5764; placebo, n=4347)	17,160 (active, n=8582; placebo, n=8578)	8246 (active, n=5499; placebo, n=2747)
INCLUSION CRITERIA	- Type 2 diabetes; HgA1c 7.0-10% - Established cardiovascular disease - eGFR $\geq$30 mL/min	- Type 2 diabetes; HgA1c 7.0-10.5% - Established cardiovascular disease, or $\geq$2 risk factors - eGFR $>$30 mL/min	- Type 2 diabetes; HgA1c 6.5-12% - Established cardiovascular disease, or multiple risk factors - CrCl $\geq$60 mL/min	- Type 2 diabetes - HgA1c 7.0-10.5% - Established cardiovascular disease
BASELINE CHARACTERISTICS	- Age ~63 years; male ~71% - HgA1c ~8.1% - CAD ~76%; prior MI ~47%	- Age ~63 years; male ~64% - HgA1c ~8.2% - Established ASCVD ~72%	- Age ~64 years; male ~63% - HgA1c ~8.3% - Established ASCVD ~41%	- Age ~64 years; male ~70% - HgA1c ~8.2% - CAD ~76%
DURATION	Median follow-up period of 3.1 years	Median follow-up period of ~3.6 years	Median follow-up period of ~4.2 years	Mean follow-up period of 3.5 years
PRIMARY OUTCOME	Composite of cardiovascular death, non-fatal MI and non-fatal stroke	Composite of cardiovascular death, non-fatal MI and non-fatal stroke	Composite of cardiovascular death, myocardial infarction and stroke	Composite of cardiovascular death, non-fatal MI and non-fatal stroke
RESULTS	Primary Composite Outcome: 490 (10.5%) vs 282 (12.1%) HR 0.86 (95% CI 0.74-0.99) p=0.04; ARR 1.63%; NNT ~62	Primary Composite Outcome: 26.9 vs 31.5 (# pts per 1000 pt-years) HR 0.86 (95% CI 0.75-0.97); p=0.02	Primary Composite Outcome: NSD 756 (8.81%) vs 803 (9.36%); HR 0.93 (95% CI 0.84-1.03); p=0.17	Primary Composite Outcome: NSD 653/5493 (11.9%) vs 327/2745 (11.9%) HR 0.97 (95.6% CI 0.85-1.11)
MORBIDITY OUTCOMES	Non-Fatal MI: NSD Non-Fatal Stroke: NSD Heart Failure Hospitalization: 126 (2.69%) vs 95 (4.07%) HR 0.65 (95% CI 0.50-0.85) p=0.002; ARR 1.38%; NNT ~73	Non-Fatal MI: NSD Non-Fatal Stroke: NSD Heart Failure Hospitalization: 5.5 vs 8.7 (# pts per 1000 pt-years) HR 0.67 (95% CI 0.52-0.87)	Non-Fatal MI: NSD Non-Fatal Stroke: NSD Heart Failure Hospitalization: 212 (2.47%) vs 286 (3.33%) HR 0.73 (95% CI 0.61-0.88) ARR 0.86%; NNT ~116	Non-Fatal MI: NSD Non-Fatal Stroke: NSD Heart Failure Hospitalization: 139 (2.53%) vs 99 (3.60%) HR 0.70 (95% CI 0.54-0.90)
MORTALITY OUTCOMES	Cardiovascular Death: 172 (3.67%) vs 137 (5.87%) HR 0.62 (95% CI 0.49-0.77) p<0.001; ARR 2.20%; NNT ~46	Cardiovascular Death: NSD	Cardiovascular Death: NSD	Cardiovascular Death: NSD

Neal B et al. N Engl J Med ;377:644-657

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)

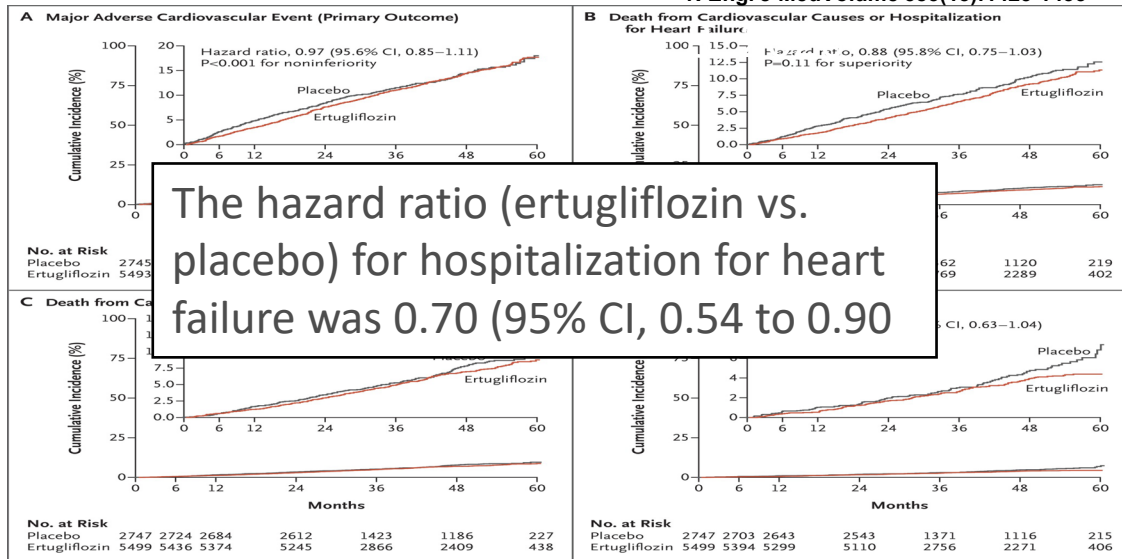
**Major Cardiovascular and Renal Outcomes and Death from Any Cause:
DECLARE TIMI 58.** Wiviott SD et al. N Engl J Med 2019;380:347-357

Wiviott SD et al. N Engl J Med 2019;380:347-357

Outcome	Dapagliflozin (N=8582)		Placebo (N=8578)		Hazard Ratio (95% CI)	P Value
	no. (%)	rate/1000 patient-yr	no. (%)	rate/1000 patient-yr		
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m ² , ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m ² , ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	

Dapagliflozin Better Placebo Better

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes
N Engl J Med Volume 383(15):1425-1435



Effetto favorevole sull'insufficienza cardiaca

ORIGINAL INVESTIGATION

Open Access



Association between sodium glucose co-transporter 2 inhibitors and a reduced risk of heart failure in patients with type 2 diabetes mellitus: a real-world nationwide population-based cohort study

Young-Gun Kim^{1,2}, Seung Jin Han³, Dae Jung Kim³, Kwan-Woo Lee³ and Hae Jin Kim^{3*}

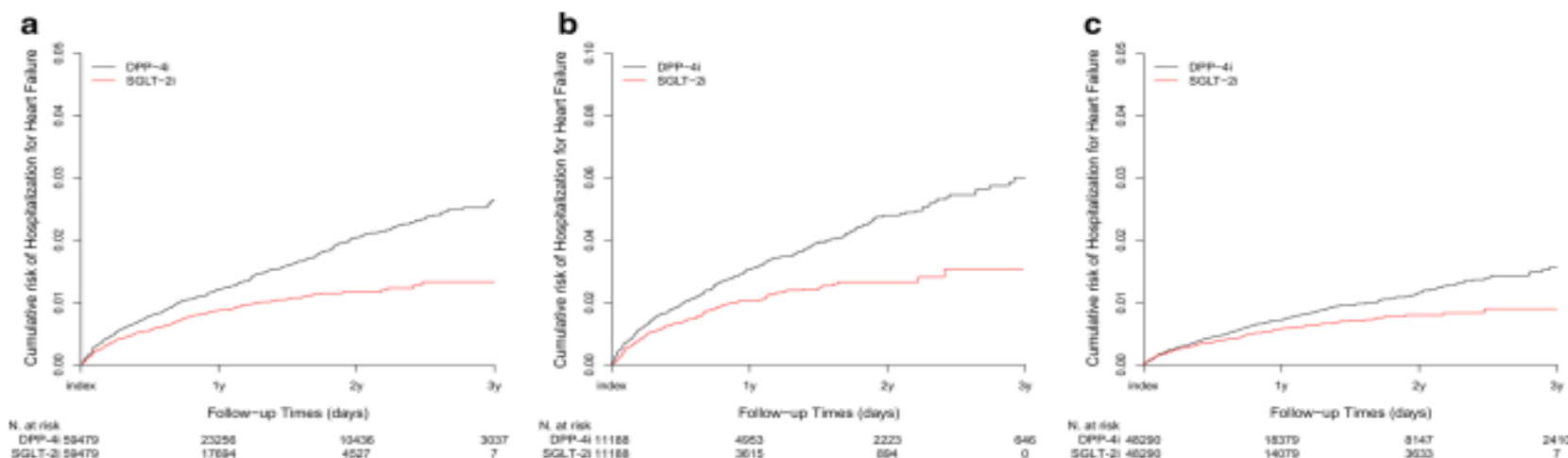


Fig. 2 Kaplan–Meier plots of hospitalization for heart failure in all patients (**a**) and baseline cardiovascular stratifications (**b** with baseline cardiovascular disease, **c** without baseline cardiovascular disease). *DPP-4i* dipeptidyl-peptidase IV inhibitor, *N* number, *SGLT-2i* sodium-glucose co-transporter 2 inhibitor, *y* year(s)

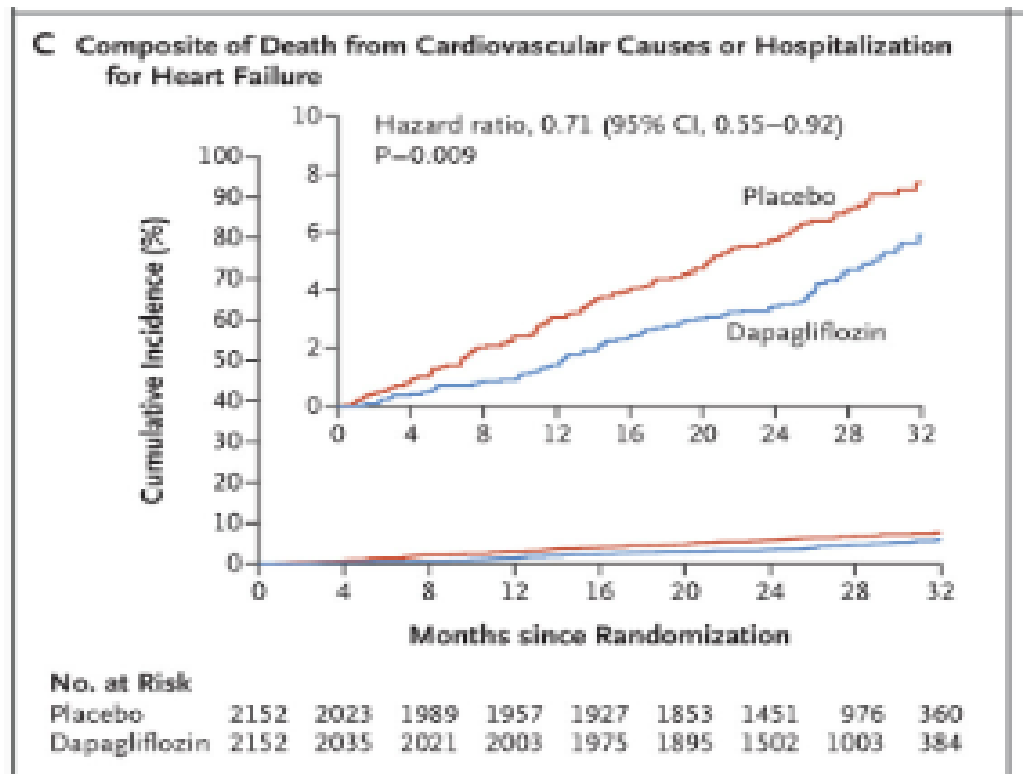
Conclusions

Our results suggest that SGLT-2i reduced hHF compared with DPP-4i. A HF protective effect of SGLT-2i vs. DPP-4i was shown 30 days after initiating the SGLT-2i among patients with established CVD, but this effect appeared later in patients without established CVD.

Benefici su Outcome CV in pazienti con Diabete Mellito e Malattia Renale Cronica

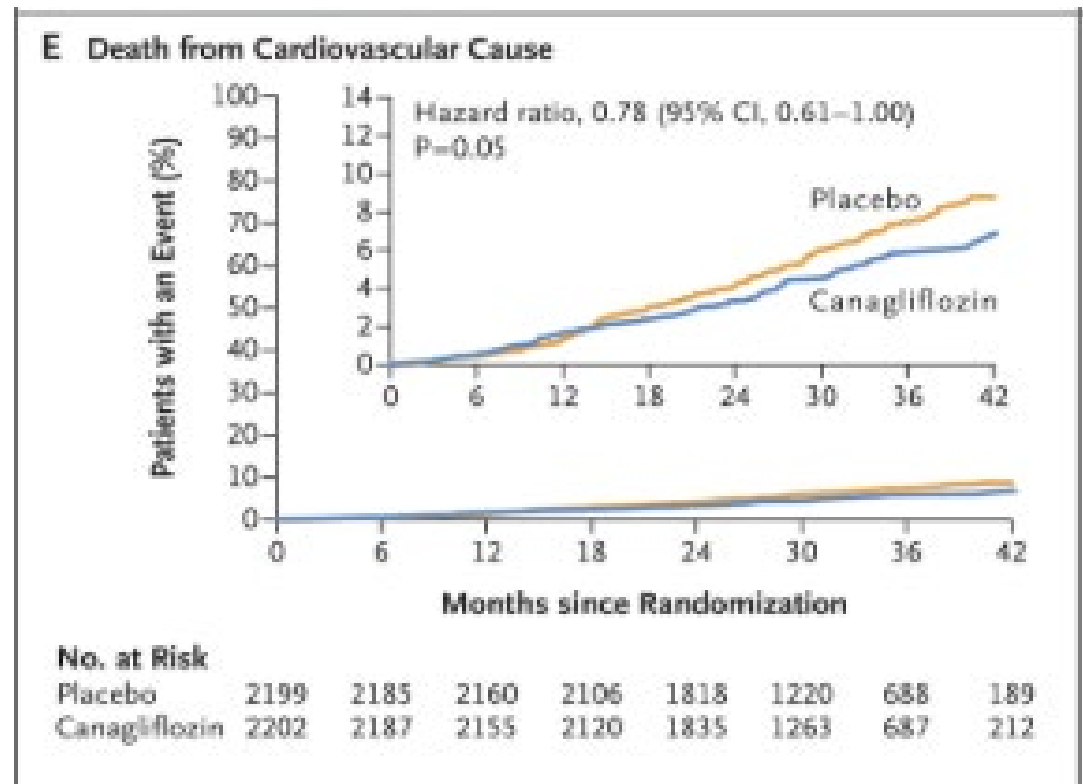
Dapagliflozin in Patients with Chronic Kidney Disease

N ENGL J MED 383;15 NEJM.ORG OCTOBER 8, 2020



Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

N ENGL J MED 380;24 NEJM.ORG JUNE 13, 2019



Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes

A Meta-analysis

Figure 3. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Hospitalization for Heart Failure

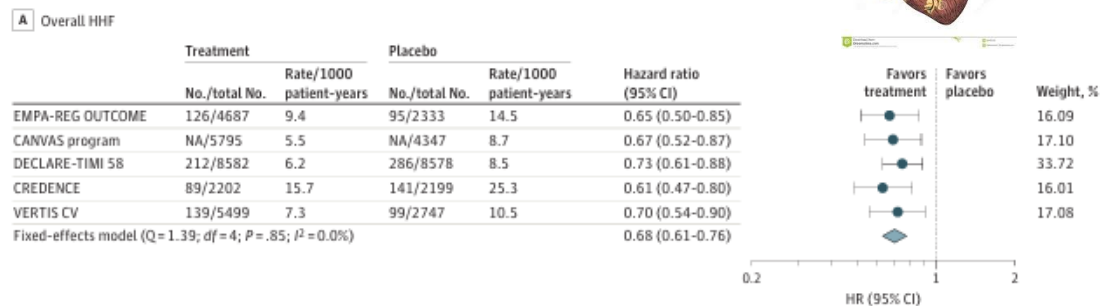
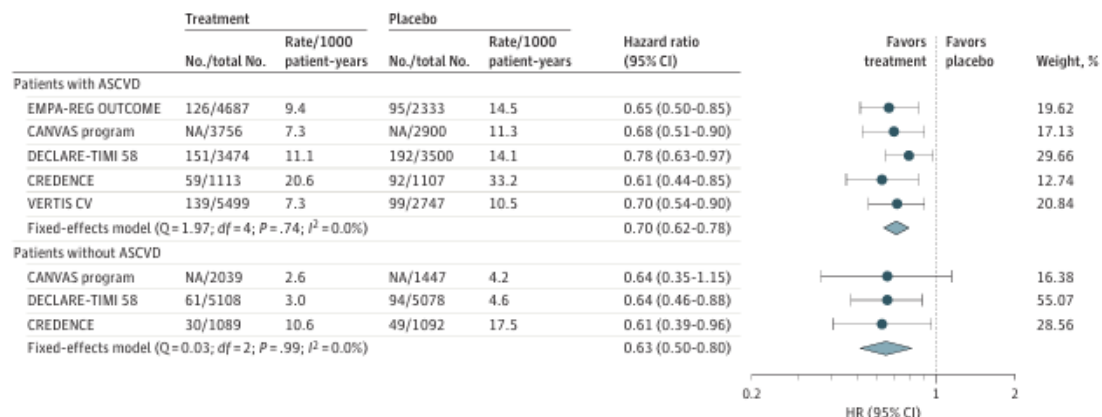
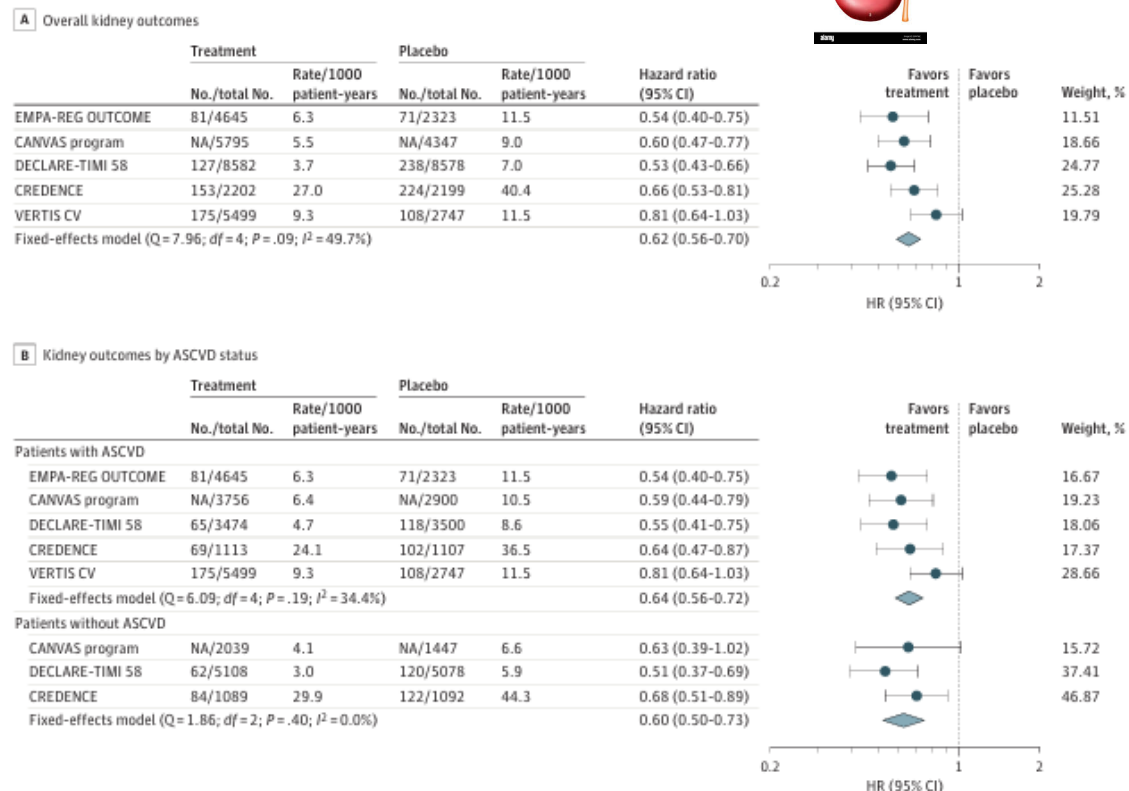
**B** HHF by ASCVD status

Figure 4. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Kidney-Related Outcomes



CONCLUSIONS AND RELEVANCE In this meta-analysis, SGLT2 inhibitors were associated with a reduced risk of major adverse CV events; in addition, results suggest significant heterogeneity in associations with CV death. The largest benefit across the class was for an associated reduction in risk for HHF and kidney outcomes, with benefits for HHF risk being the most consistent observation across the trials.



SGLT2 INHIBITORS: SUMMARY OF HEART FAILURE TRIALS

DAPA-HF
2019



EMPEROR-Reduced
2020



DELIVER
2022



EMPEROR-Preserved
2021



DRUG

Dapagliflozin 10 mg daily

Empagliflozin 10 mg daily

Dapagliflozin 10 mg daily

Empagliflozin 10 mg daily

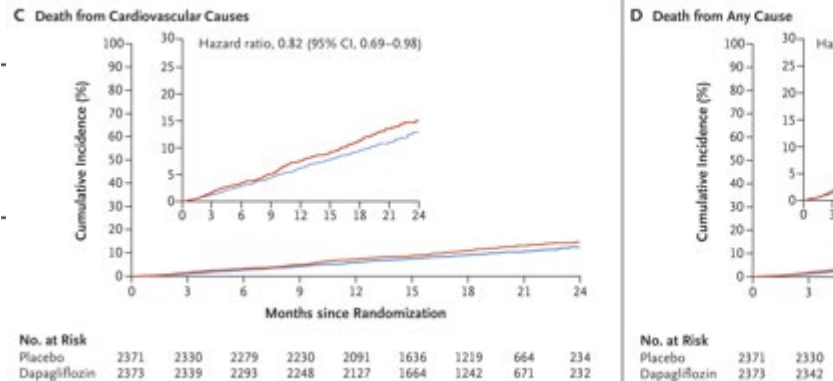
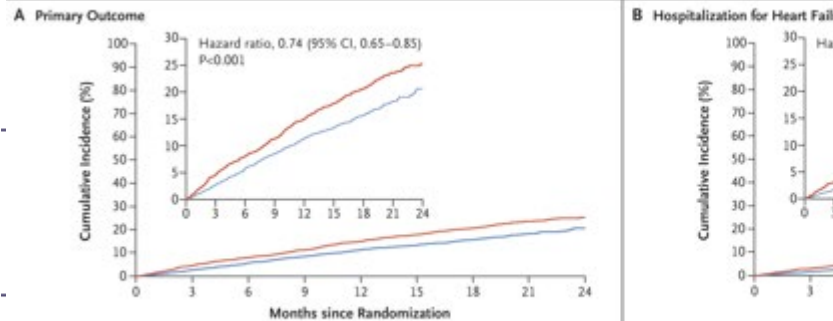
RANDOMIZED

4744 (active, n=2373; placebo, n=2371)

3730 (active, n=1863; placebo, n=1867)

3688 (active, n=1844; placebo, n=1844)

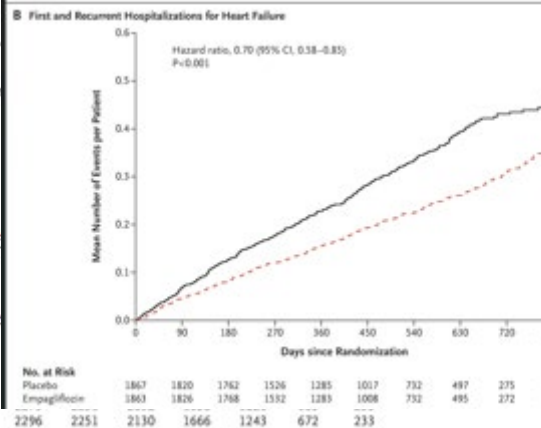
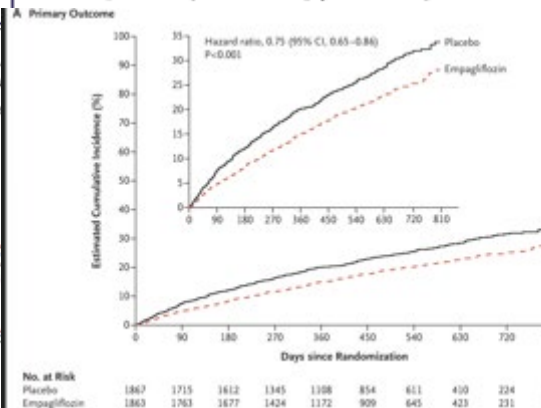
5988 (active, n=2997; placebo, n=2991)



10 (0.42%) vs 23 (0.97%)
HR 0.43 (95% CI 0.20-0.90)
ARR 0.55%; NNT ~183

MORTALITY
OUTCOMES

Cardiovascular Death:
227 (9.57%) vs 273 (11.5%)
HR 0.82 (95% CI 0.69-0.98)
ARR 1.95%; NNT ~52



Cardiovascular Death:
No significant difference

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

Solomon SD et al. DOI: 10.1056/NEJMoa2206284

CLINICAL PROBLEM
Clinical guidelines recommend the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors in patients with chronic heart failure and a reduced ejection fraction (rEF), but the benefits in patients with a higher ejection fraction are less certain.

CLINICAL TRIAL
Design: An international, double-blind, randomized, placebo-controlled trial examined the efficacy and safety of the SGLT2 inhibitor dapagliflozin in patients with stable heart failure and a mildly reduced or preserved ejection fraction.

INTERVENTION
6261 patients 40 years of age or older with a left ventricular ejection fraction of more than 40% were assigned to receive either dapagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of worsening heart failure (as assessed by hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death.

RESULTS
Efficacy: Overall, during a median follow-up of 2.3 years, a primary-outcome event occurred in significantly fewer patients in the dapagliflozin group than in the placebo group. A similar benefit was observed in a subgroup of patients with a left ventricular ejection fraction of less than 60%.

SAFETY
The incidence of serious adverse events was similar in the two groups.

CONCLUSIONS
The SGLT2 inhibitor dapagliflozin, when added to usual therapy, reduced the risk of a composite of worsening heart failure or cardiovascular death in patients with heart failure and a mildly reduced or preserved ejection fraction.

Link: Full Article | NEJM Quick Take | Editorial

Cardiovascular Death:
No significant difference

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Arner SD et al. DOI: 10.1056/NEJMoa2107038

CLINICAL PROBLEM
Treatment options for patients with heart failure and a preserved ejection fraction are limited. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to reduce heart failure progression in patients with a reduced ejection fraction, but whether they improve outcomes in patients with a preserved ejection fraction is unclear.

CLINICAL TRIAL
Design: A multicenter, double-blind, randomized, placebo-controlled trial examined the effects of the SGLT2 inhibitor empagliflozin in patients with heart failure and a preserved ejection fraction.

INTERVENTION
5988 adults with New York Heart Association functional class II-IV chronic heart failure and a left ventricular ejection fraction >40% were randomly assigned to receive empagliflozin (10 mg once daily) or placebo, in addition to their usual treatment. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

RESULTS
Efficacy: During a median follow-up of 26.2 months, a primary composite outcome event occurred significantly less often in the empagliflozin group than in the placebo group, largely owing to a decrease in hospitalizations for heart failure with empagliflozin. The benefit of empagliflozin appeared similar in patients with or without diabetes.

SAFETY
Serious adverse events occurred in 47.9% of patients in the empagliflozin group and in 51.0% of those in the placebo group. Uncomplicated genital and urinary tract infections and hypotension were more common with empagliflozin.

CONCLUSIONS
In patients with heart failure and a preserved ejection fraction, the SGLT2 inhibitor empagliflozin lowered the risk of a composite of cardiovascular death or hospitalization for heart failure, mainly owing to a reduction in hospitalizations for heart failure.

Link: Full Article | NEJM Quick Take | Editorial

Cardiovascular Death:
No significant difference



ESC

European Society
of Cardiology

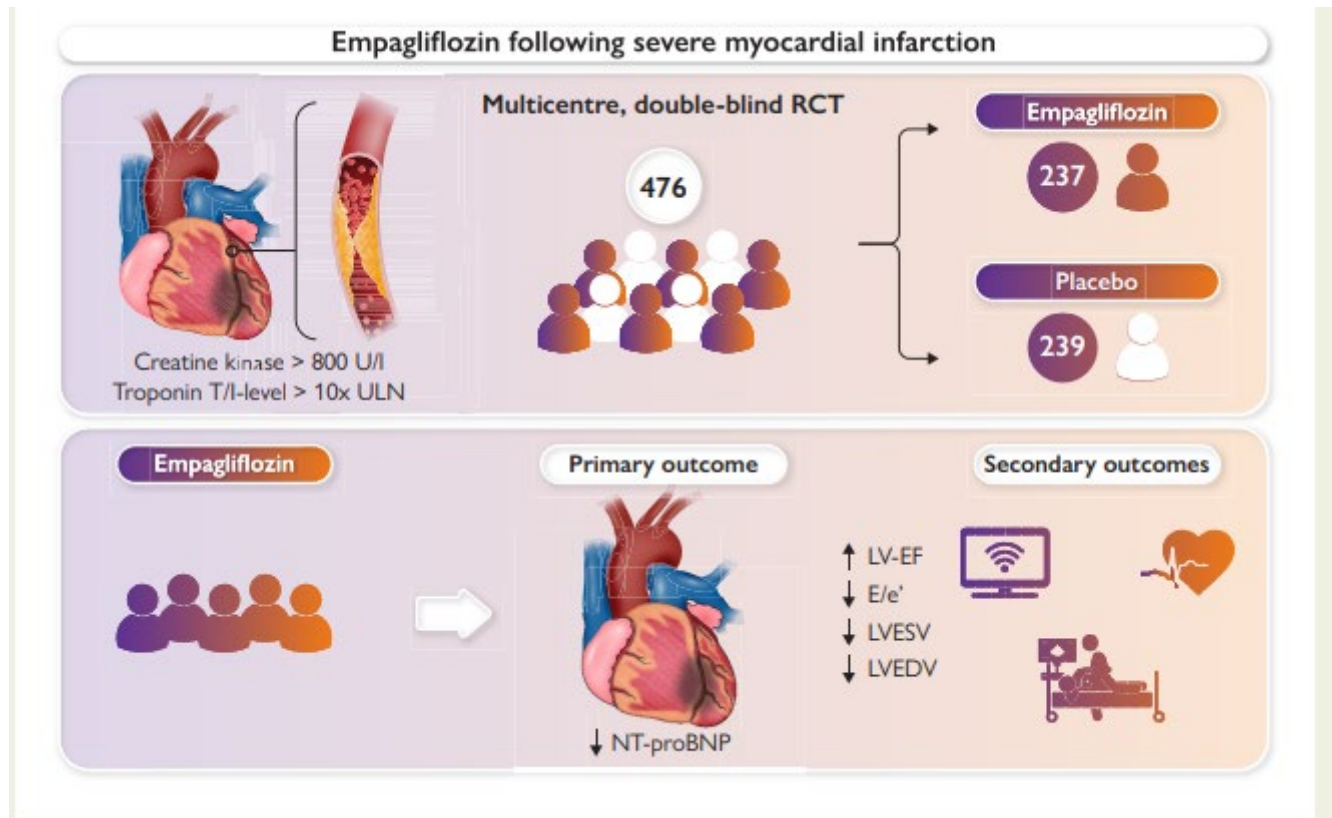
European Heart Journal (2022) 43, 4421–4432
<https://doi.org/10.1093/eurheartj/ehac494>

FASTTRACK CLINICAL RESEARCH

Clinical trials

.....molto altro

Empagliflozin in acute myocardial infarction: the EMMY trial



Conclusion

In patients with a recent myocardial infarction, empagliflozin was associated with a significantly greater NT-proBNP reduction over 26 weeks, accompanied by a significant improvement in echocardiographic functional and structural parameters.

Empagliflozin after Acute Myocardial Infarction

Butler J et al. DOI: 10.1056/NEJMoa2314051

CLINICAL PROBLEM

Treatment with sodium-glucose cotransporter 2 (SGLT2) inhibition improves cardiovascular outcomes in high-risk patients with diabetes, chronic kidney disease, or heart failure. The effects of SGLT2 inhibitors after an acute myocardial infarction are unknown.

CLINICAL TRIAL

Design: In an international, event-driven, double-blind, randomized, placebo-controlled trial, the efficacy and safety of the SGLT2 inhibitor empagliflozin were assessed in patients with acute myocardial infarction and an increased risk of heart failure.

Intervention: 6522 adults who had been hospitalized with an acute myocardial infarction and had either evidence of a newly developed left ventricular ejection fraction of <45% or signs or symptoms of congestion that resulted in treatment during the index hospitalization (or both), plus at least one additional factor associated with an increased risk of heart failure, were assigned to receive empagliflozin at a dose of 10 mg daily or placebo in addition to standard care within 14 days after admission. The primary end point was a composite of hospitalization for heart failure or death from any cause as assessed in a time-to-first-event analysis.

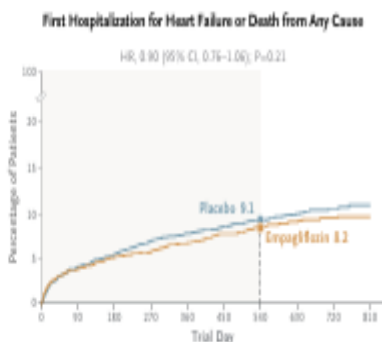
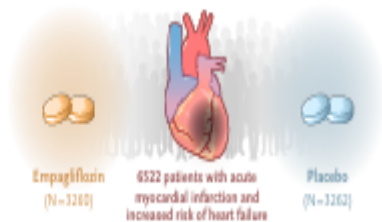
RESULTS

Efficacy: During a median follow-up of 17.9 months, the percentage of patients with a primary end-point event did not differ significantly between the trial groups.

Safety: The incidence of serious adverse events and adverse events that resulted in permanent discontinuation of the trial regimen was similar in the two trial groups.

LIMITATIONS AND REMAINING QUESTIONS

- The end points were not centrally adjudicated but were assessed by site investigators according to prespecified definitions.
- Outpatient heart-failure events were not assessed as clinical end points.
- The representation of women, older adults, and historically underrepresented racial and ethnic groups was suboptimal, and some patients in these groups are at increased risk for heart failure after myocardial infarction.



CONCLUSIONS

Among adults at high risk for heart failure after an acute myocardial infarction, daily treatment with empagliflozin did not result in a significantly lower risk of a first hospitalization for heart failure or death from any cause than placebo.

Early initiation of SGLT2 inhibitors after acute myocardial infarction

Andreas Hammer¹, Samuel Sossalla^{2,3}, and Patrick Sulzgruber^{1,*}

EMPACT-MI

1:1 RCT

DAPA-MI

Inclusion: Newly LVEF ↓/Congestion

Exclusion: History of HF

Acute MI (NSTEMI/STEMI)

Inclusion: LVEF ↓ or Q-wave MI

Exclusion: History of HF/DM

6522 Patients
78% with LVEF <45%

Placebo

10mg o.d.
Empagliflozin**Composite Endpoint:**
First hospitalization for HF / all-cause death

HR 0.90 (95% CI 0.76-1.06, p=0.21)

4017 Patients
67% with LVEF 30–49%

Placebo

10mg o.d.
Dapagliflozin**Composite Endpoint:**
Death, HF-hosp., nonfatal MI, AFIB onset, DM onset, NYHA reduction, weight loss >5%

Win-Ratio: 1.34 (95% CI 1.20-1.50, p<0.001)

2 Years

In conclusion, while SGLT2 inhibitors offer promising cardiometabolic and HF benefits in post-AMI patients, their long-term impact on robust outcomes such as mortality remains unclear. However, the absence of a mortality signal in both DAPA-MI and EMPACT-MI raises questions about their routine post-AMI use of SGLT2 inhibitors, especially considering cost and safety concerns

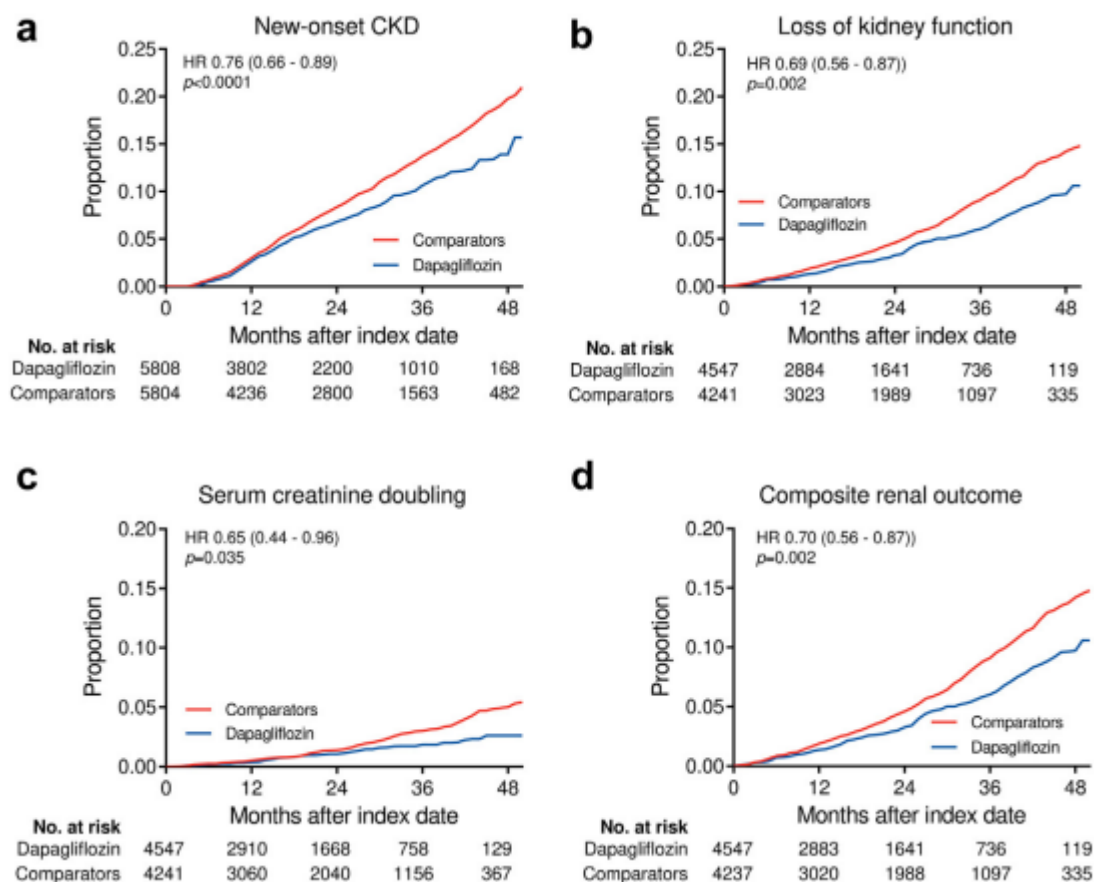
The DAPA-MI trial investigated the effect of dapagliflozin on cardiometabolic outcomes in patients with AMI without a history of diabetes mellitus (DM) or HF

CONCLUSIONS

In patients with acute MI as noted above, after approximately 1 year of treatment with dapagliflozin there were significant benefits with regard to improvement in cardiometabolic outcomes but no impact on the composite of cardiovascular death or hospitalization for heart failure compared with placebo.

Long-term benefits of dapagliflozin on renal outcomes of type 2 diabetes under routine care: a comparative effectiveness study on propensity score matched cohorts at low renal risk

Gian Paolo Fadini,^{a,b,f,*} Enrico Longato,^{c,f} Mario Luca Morieri,^a Stefano Del Prato,^d Angelo Avogaro,^a and Anna Solini^e
DARWIN-Renal Study Investigators



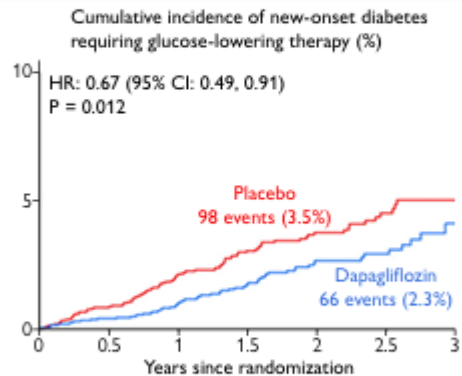
In summary, our study, designed to overcome some issues with prior observational research, supports the strong protective effects of dapagliflozin against the loss of kidney function under routine care, even in patients without baseline CKD. Based on real-world evidence, it is expected that broadening the population of patients with T2D who are receiving SGLT2i will drive a change in the epidemiology of ESKD in the next decades.

Sodium-glucose co-transporter 2 inhibitors and new-onset diabetes in cardiovascular or kidney disease

- Effetto glicosurico
- ↓ del peso corporeo e della adiposità viscerale
- ↑ della sensibilità insulinica e della funzione β cellulare

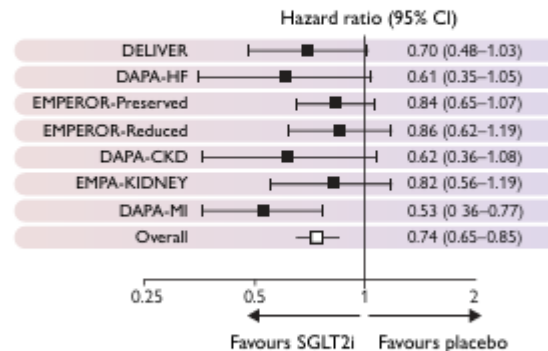
SGLT2i and new-onset diabetes in patients with cardiovascular or kidney disease

Participant-level pooled analysis of DAPA-HF and DELIVER (n = 5623)



33% Reduction in the rate of new-onset diabetes requiring new glucose-lowering therapy with dapagliflozin vs placebo, with consistent findings across the LVEF spectrum and key subgroups

Fixed-effects meta-analysis of 7 cardiovascular and kidney trials (n = 17 855)



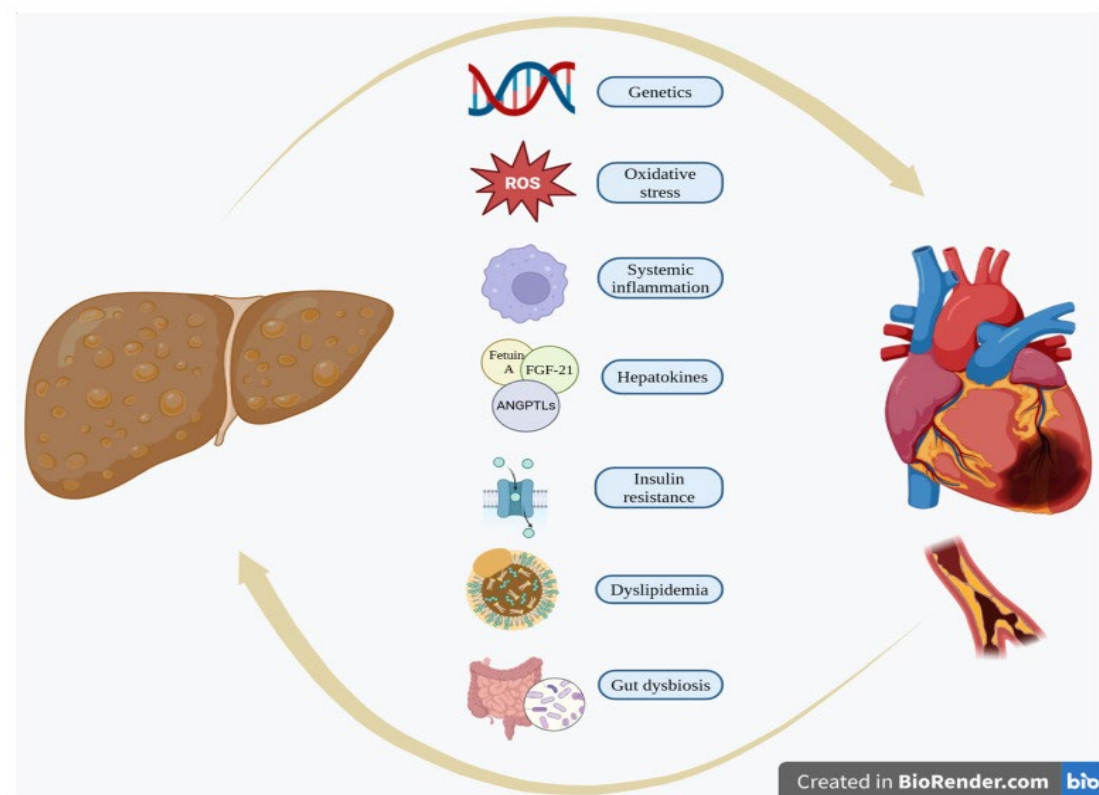
26% Reduction in the rate of new-onset diabetes with SGLT2i vs placebo (test for overall treatment effect: $P < 0.001$), without heterogeneity in treatment effects across trials

Conclusions

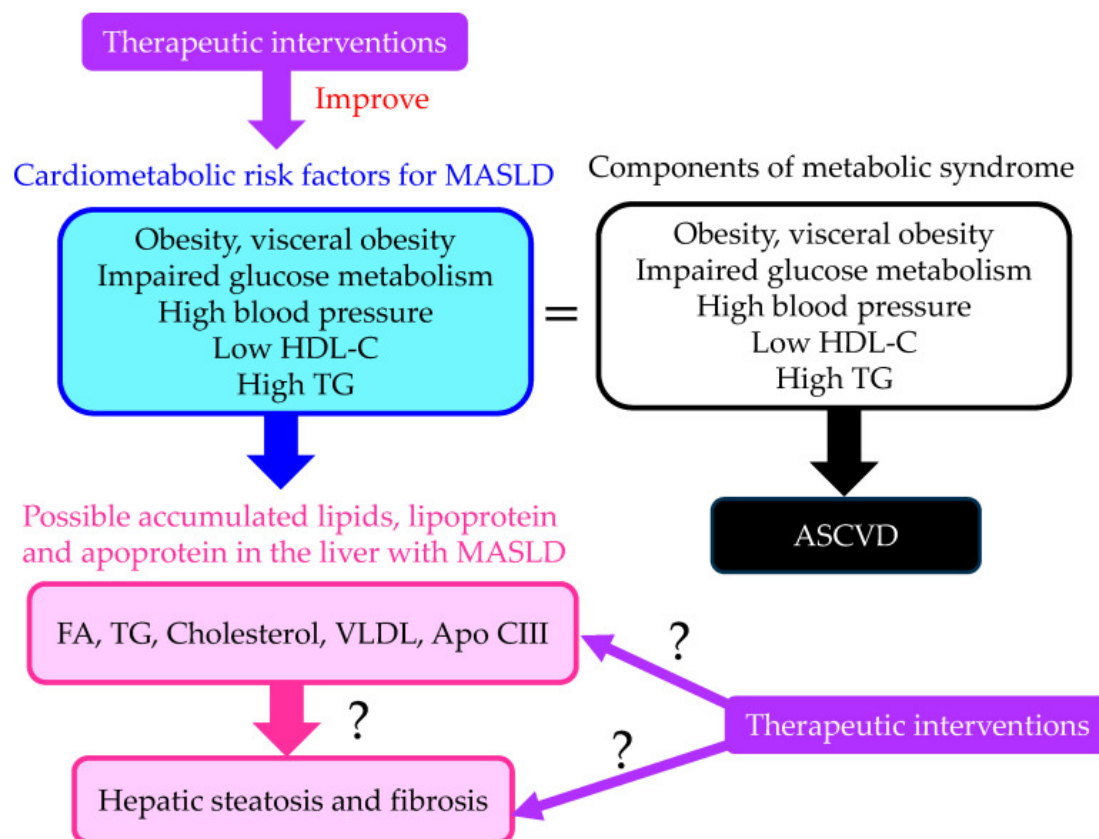
SGLT2i reduced incident diabetes necessitating the initiation of GLT in patients with HF across the LVEF spectrum, without excess risk of major hypoglycaemia. In a comprehensive meta-analysis of seven trials of patients with cardiovascular or kidney diseases, we estimate that SGLT2i reduce risk of new-onset diabetes by 26%. These findings further emphasize the role of SGLT2i as a core component of comprehensive strategies to improve cardiovascular-kidney-metabolic health.

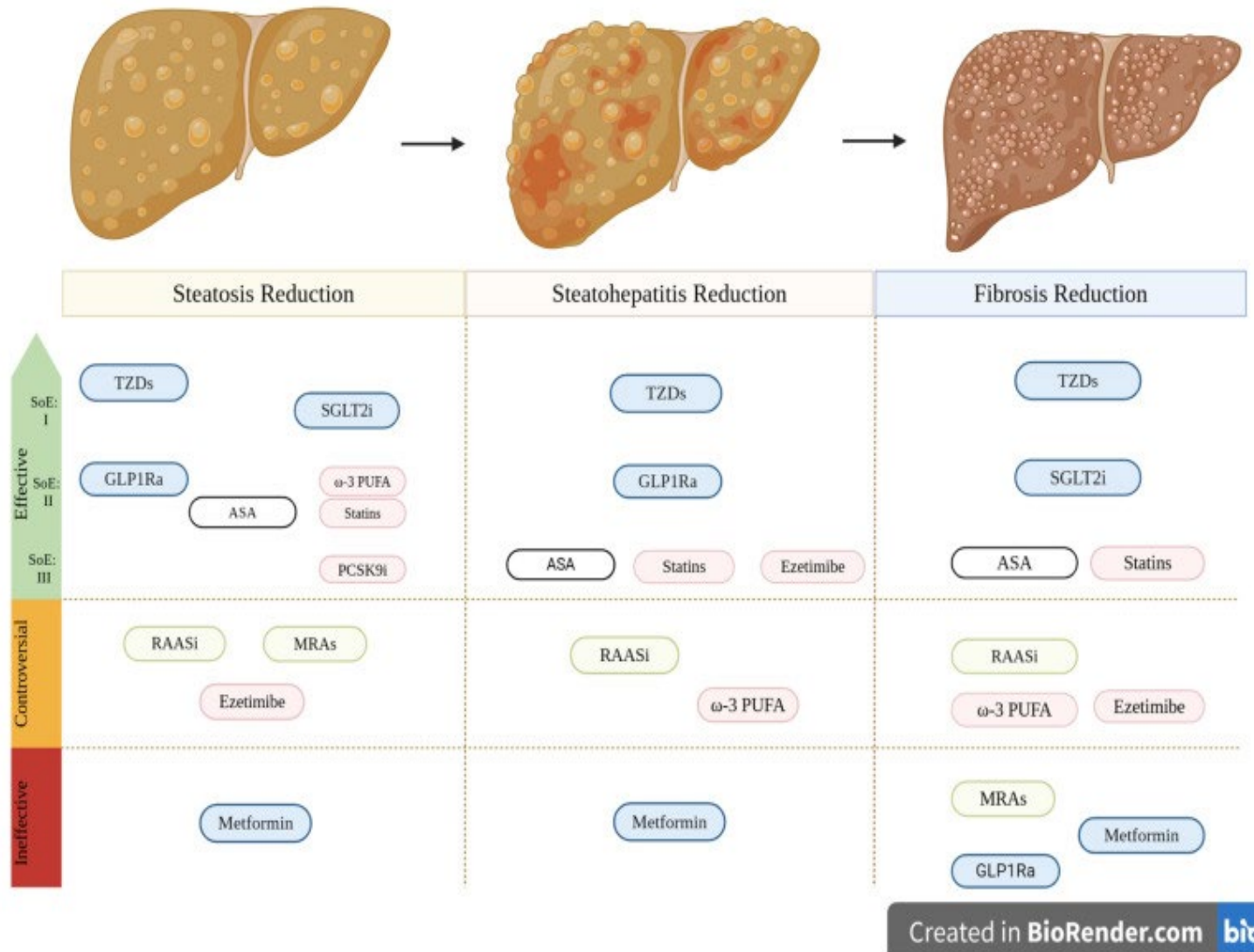
Linking Cardiovascular Disease and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): The Role of Cardiometabolic Drugs in MASLD Treatment

Marios Zisis ¹, Maria Eleni Chondrogianni ^{2,3,†}, Theodoros Androutsakos ^{4,†}, Ilias Rantos ¹, Evangelos Oikonomou ⁵, Antonios Chatzigeorgiou ⁶ and Eva Kassi ^{2,3,*}



.....molto altro





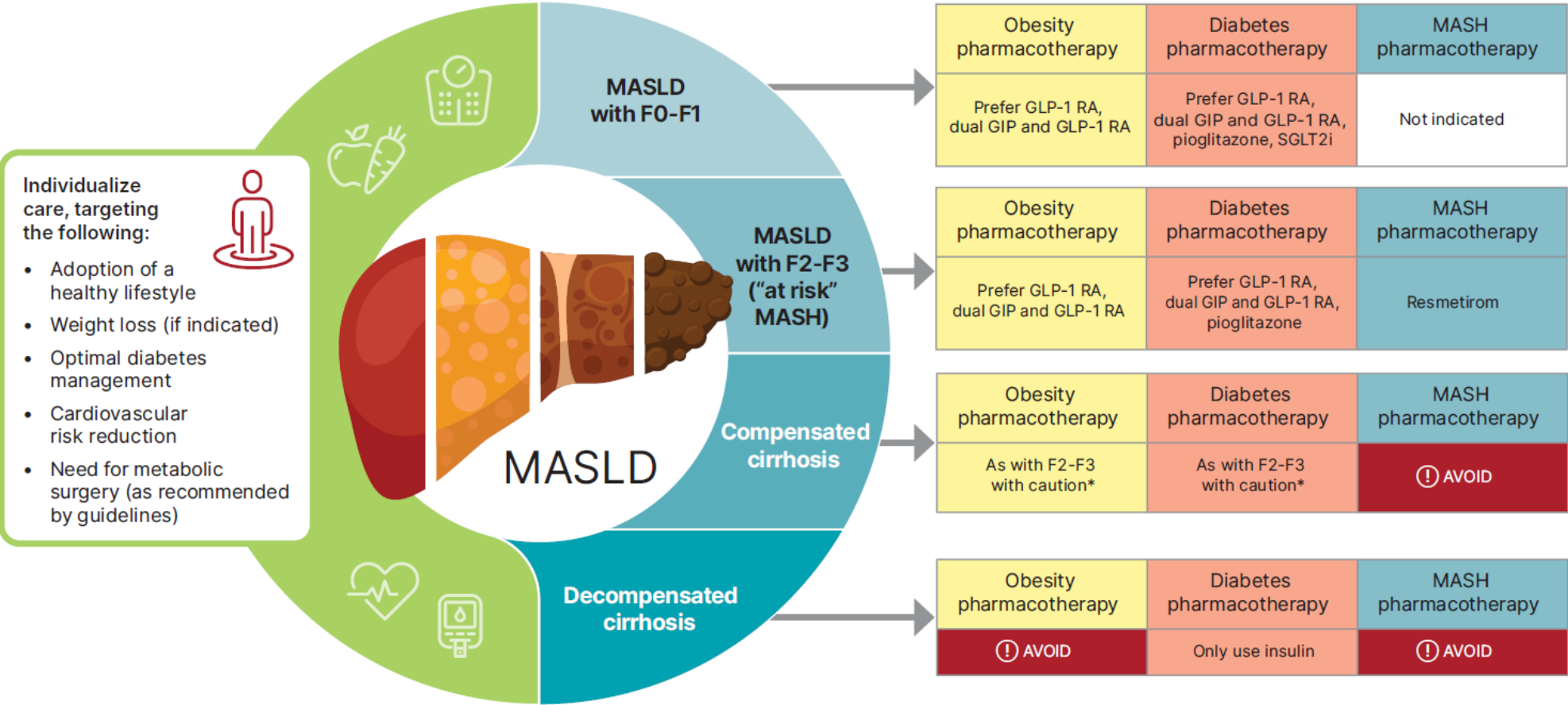
SGLT2i

- ↓ Insulina e ↓ lipogenesi
- α cells ↑ glucagone: β ossidazione FFA con ↓ trigliceridi epatici
- ↓ glucotossicità e ROS e induzione di enzimi antiossidanti

SGLT2i

- ↓ Steatosi epatica
- ↓ livelli di aminotransferasi
- ↓ Peso corporeo

Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) Treatment Algorithm



*Individualized care and close monitoring needed in compensated cirrhosis given limited safety data available.

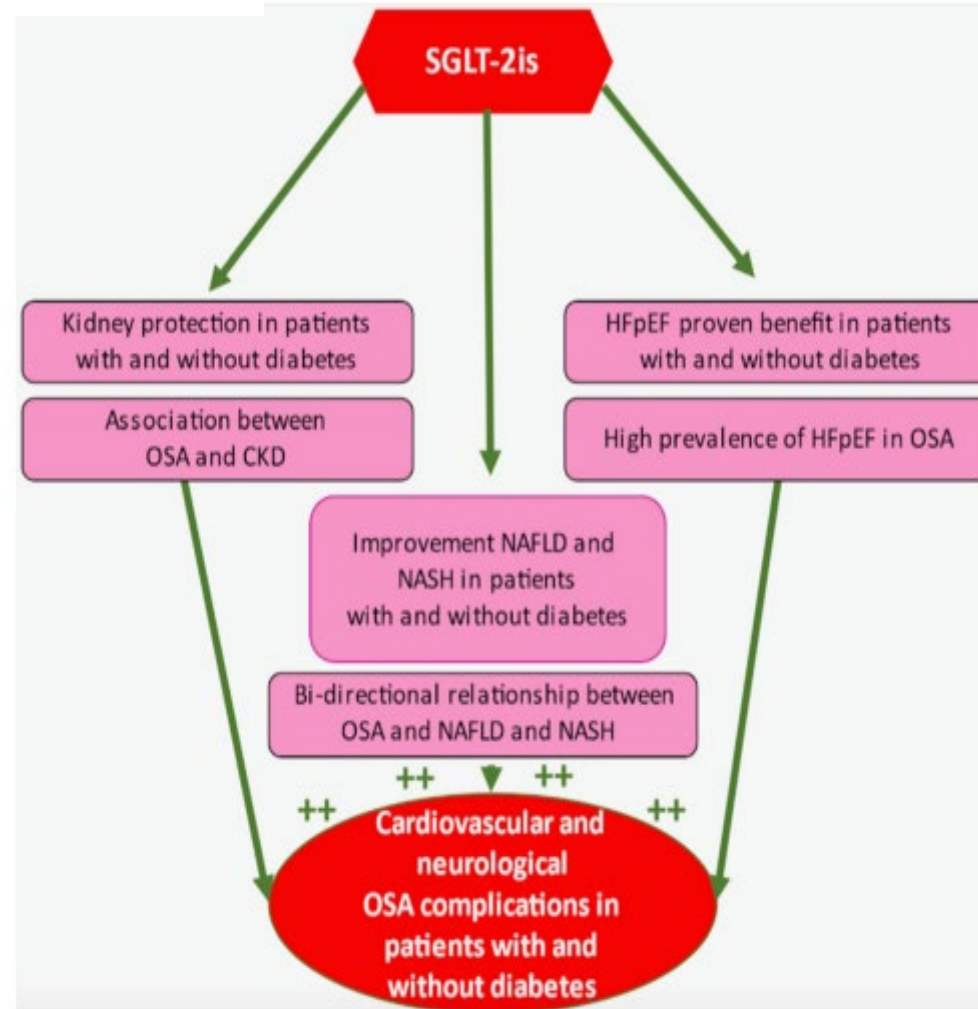
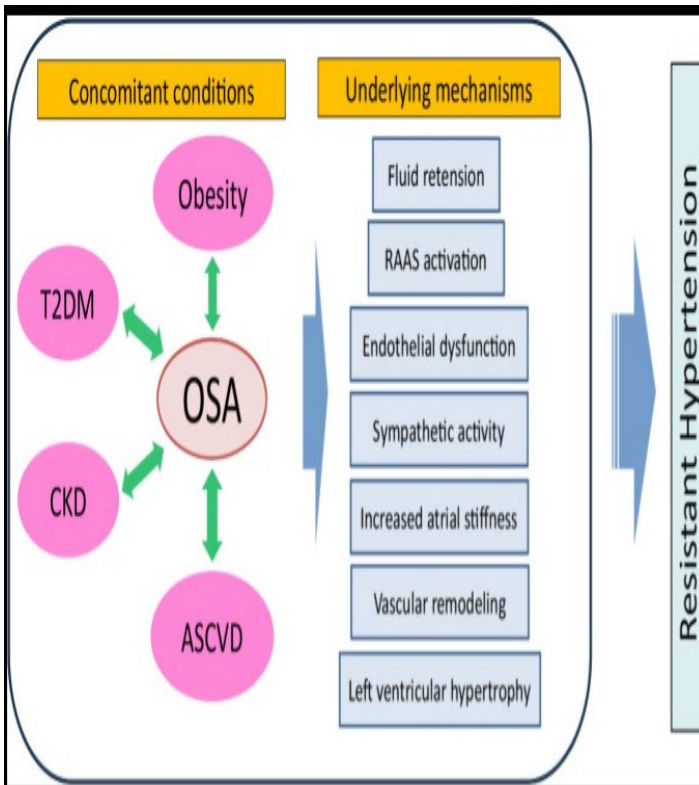
Figure 4.3—Metabolic dysfunction–associated steatotic liver disease (MASLD) treatment algorithm. F0-F1, no to minimal fibrosis; F2-F3, moderate fibrosis; F4, cirrhosis; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MASH, metabolic dysfunction–associated steatohepatitis; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Comprehensive Medical Evaluation and Assessment of Comorbidities:
Standards of Care in Diabetes - 2025. Diabetes Care 2025;48(Suppl. 1):S59-S85

Heart Failure with Preserved Ejection Fraction and Obstructive Sleep Apnea: A Novel Paradigm for Additional Cardiovascular Benefit of SGLT2 Inhibitors in Subjects With or Without Type 2 Diabetes

Vincenzo Maria Monda · Sandro Gentile · Francesca Porcellati · Ersilia Satta · Alessandro Fucili · Marcello Monesi · Felice Strollo

.....molto altro ancora



In conclusion, the putative favorable effect of SGLT2is in patients with OSA is likely due to the ability to reduce cardiovascular events in patients with HFpEF [31] and improve renal function independently of diabetes [37, 38].

Considering the close association between OSA and HFpEF, SGLT2is might also be promising for OSA prevention, treatment, and rehabilitation regardless of coexisting T2DM, as well as for the often-associated NAFLD when T2DM is present.

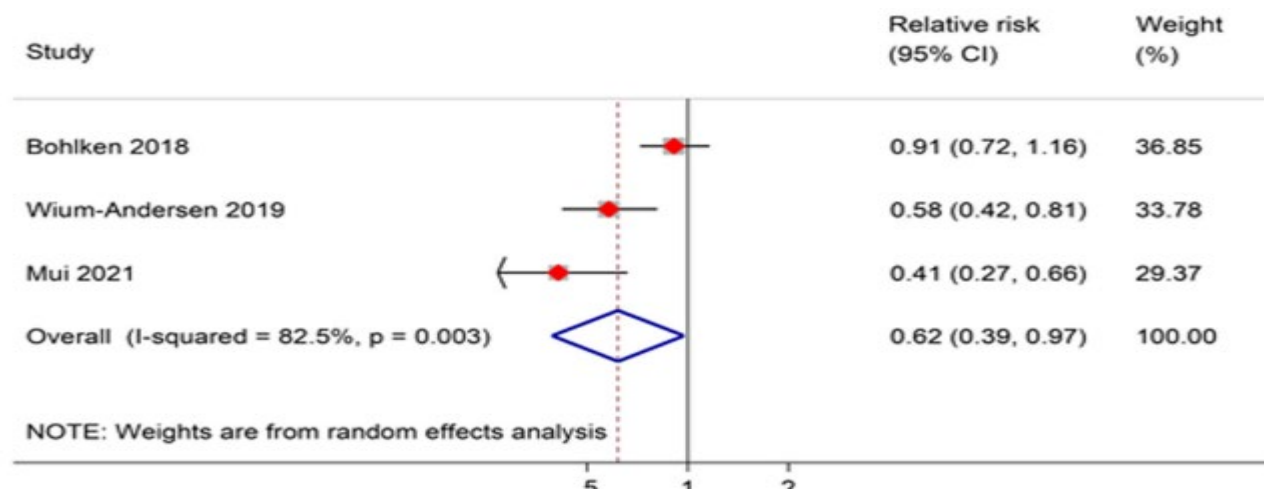
.....molto altro ancora



Newer glucose-lowering drugs and risk of dementia: A systematic review and meta-analysis of observational studies

Huilin Tang MSc, Hui Shao MD, PhD, C. Elizabeth Shaaban PhD, Keming Yang PhD, Joshua Brown PharmD, PhD, Stephen Anton PhD, Yonghui Wu PhD ... See all authors ✓

First published: 23 February 2023 | <https://doi.org/10.1111/jgs.18306> | Citations: 51



Our meta-analysis of the three observational studies showed that SGLT2 inhibitor use was significantly associated with a decreased risk of all-cause dementia, compared to nonSGLT2 inhibitor users (RR, 0.62; 95% CI, 0.39–0.97) (Figure 2). However, a high level of heterogeneity between studies was observed in this meta-analysis

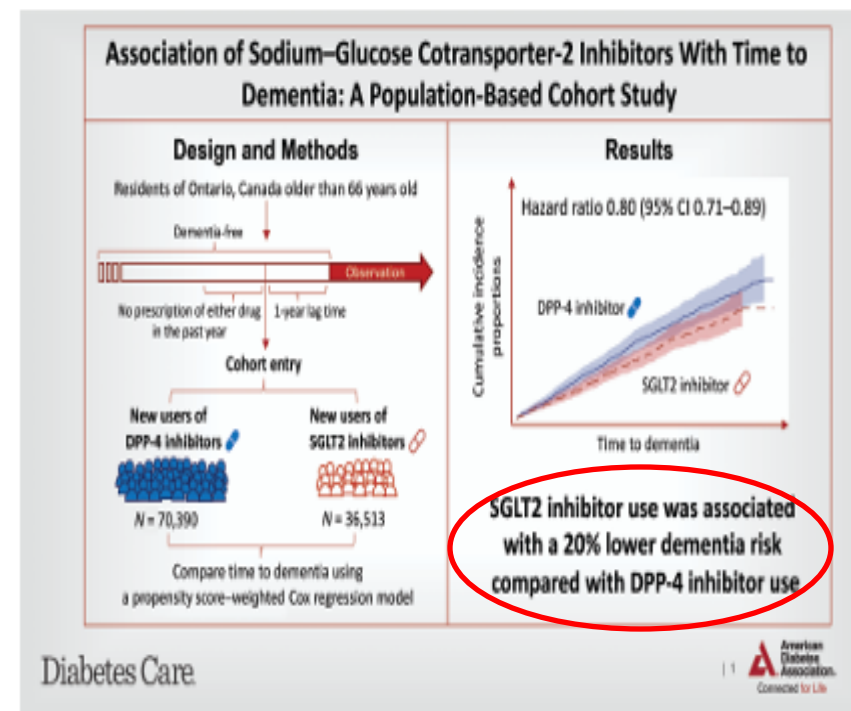
Diabetes Care.



Association of Sodium–Glucose Cotransporter 2 Inhibitors With Time to Dementia: A Population-Based Cohort Study

Che-Yuan Wu, Carina Iskander, Christa Wang, Lisa Y. Xiong, Baiju R. Shah, Jodi D. Edwards, Moira K. Kapral, Nathan Herrmann, Krista L. Lancôt, Mario Masellis, Richard H. Swartz, Hugo Cogo-Moreira, Bradley J. MacIntosh, Jennifer S. Rabin, Sandra E. Black, Refik Saskin, and Walter Swardfager

Diabetes Care 2023;46(2):297–304 | <https://doi.org/10.2337/dc22-1705>

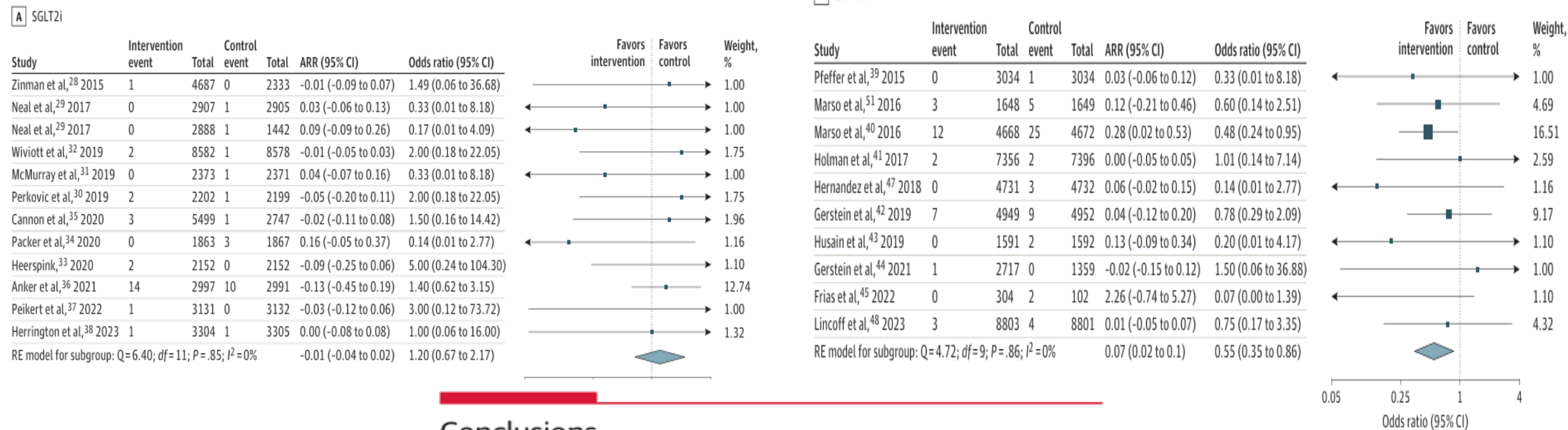


Cardioprotective Glucose-Lowering Agents and Dementia Risk

A Systematic Review and Meta-Analysis

Allie Seminer, MSc; Alfredi Mulihano; Clare O'Brien, MD; Finn Krewer, PhD; Maria Costello, PhD; Conor Judge, PhD; Martin O'Donnell, PhD; Catriona Reddin, MD

Figure 1. Association of Glucose-Lowering Therapy With All-Cause Dementia



SGLT2 Inhibitor Use and Risk of Dementia and Parkinson Disease Among Patients With Type 2 Diabetes

Hae Kyung Kim, MD , Geert Jan Biessels, MD, PhD , Min Heui Yu, MS, Namki Hong, MD, PhD, Yong-ho Lee, MD, PhD, Byung-Wan Lee, MD, PhD, Eun Seok Kang, MD, PhD, Bong-Soo Cha, MD, PhD, Eun Jig Lee, MD, PhD, and Minyoung Lee, MD, PhD  | [AUTHORS INFO & AFFILIATIONS](#)

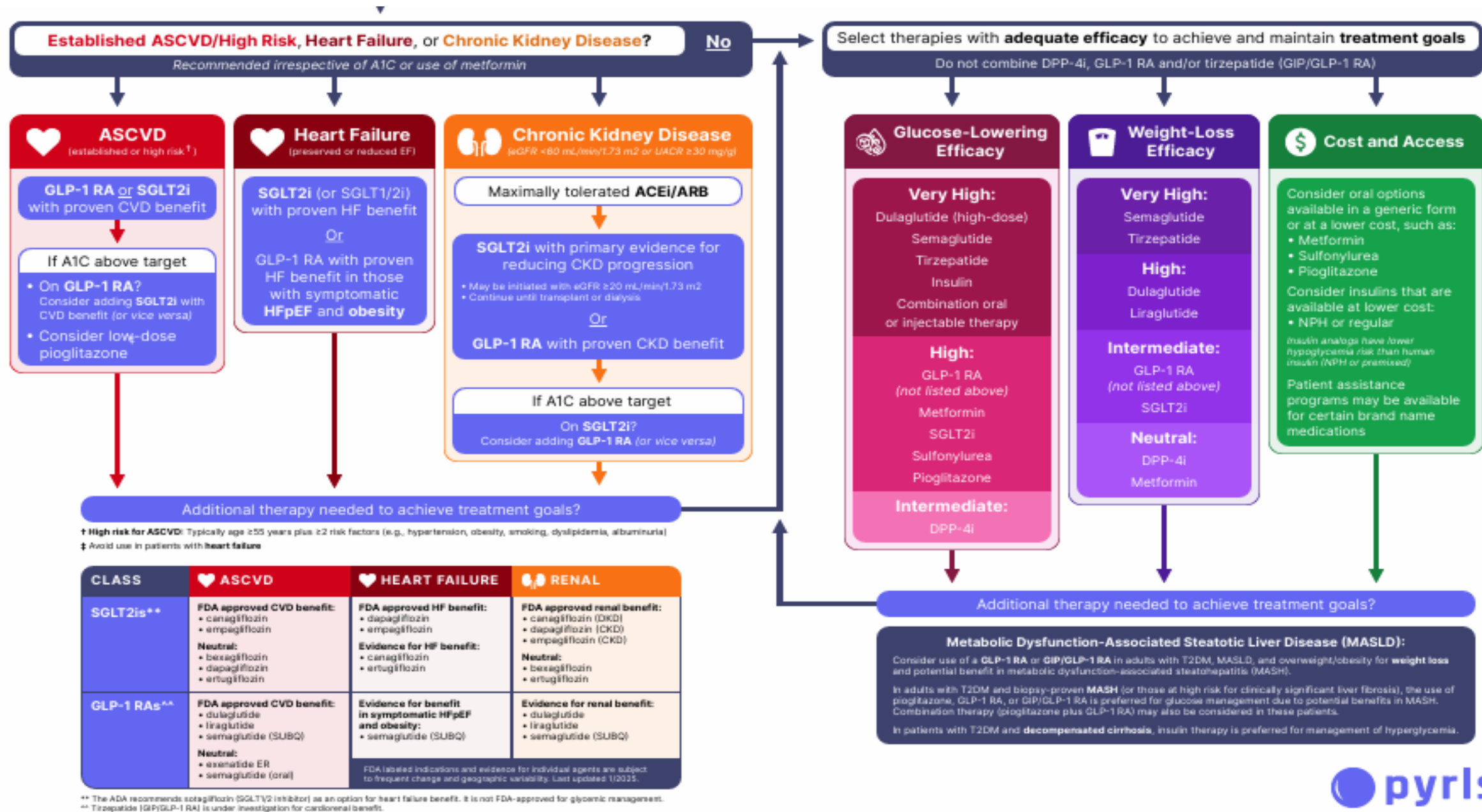
October 22, 2024 issue • 103 (8) • <https://doi.org/10.1212/WNL.0000000000209805>

Results

From the 358,862 participants analyzed (mean [SD] age, 57.8 [9.6] years; 58.0% male), 6,837 incident dementia or PD events occurred. Regarding the individual endpoints, SGLT2i use was associated with reduced risks of AD (adjusted hazard ratio [aHR] 0.81, 95% CI 0.76–0.87), VaD (aHR 0.69, 95% CI 0.60–0.78), and PD (aHR 0.80, 95% CI 0.69–0.91) with a 6-month drug use lag period. In addition, use of SGLT2i was associated with a 21% lower risk of all-cause dementia (aHR 0.79, 95% CI 0.69–0.90) and a 22% lower risk of all-cause dementia and PD than use of other OADs (aHR 0.78, 95% CI 0.73–0.83). The association between the use of SGLT2i and the lowered risk of these neurodegenerative disorders was not affected by sex, Charlson Comorbidity Index, diabetic complications, comorbidities, and medications. Sensitivity analysis further

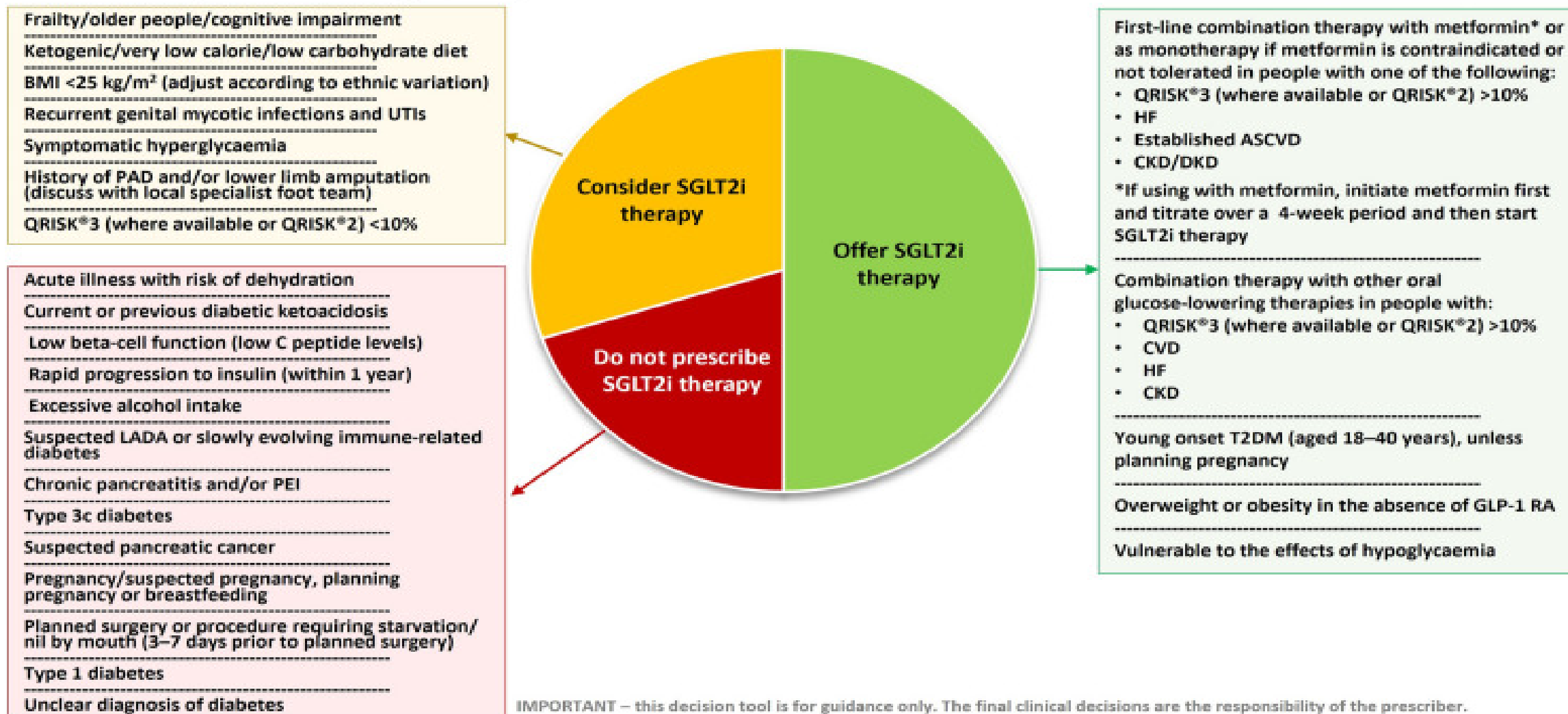
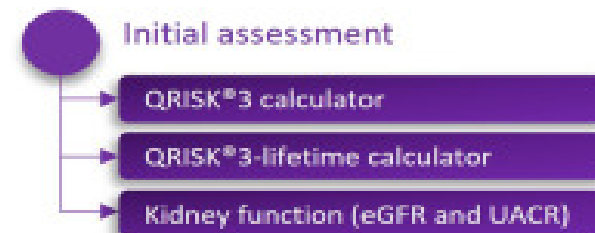
Discussion

In this nationwide population-based study, SGLT2i use significantly reduced the risks of neurodegenerative disorders in patients with type 2 diabetes independent of various factors including comorbidities and bioclinical parameters.



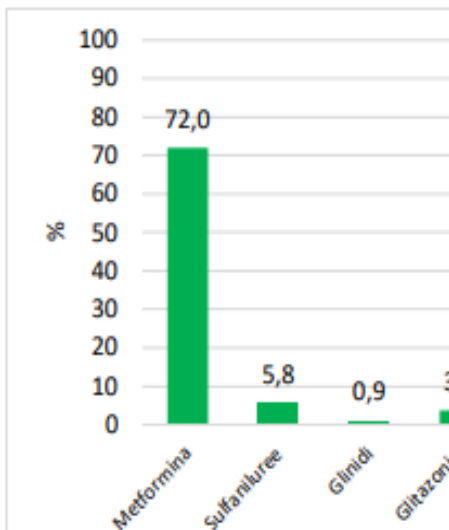
Key practice points:

- Discuss the relative benefits and risks of SGLT2i therapy with the person you are treating.
- Use dual first-line SGLT2i therapy with metformin (unless contraindicated). Initiate 4 weeks after metformin, post-date the SGLT2i prescription and do not wait for HbA1c assessment at 3 months after metformin initiation.
- Emphasise the importance of ongoing hydration and good personal hygiene.
- Give written information/electronic resources to support advice on the management of T2DM medicines during periods of acute or dehydrating illness.
- If symptomatic of hyperglycaemia, start rescue therapy and then reassess initiation of SGLT2i when symptoms resolved.
- For planned surgery or procedures requiring nil by mouth, advise on the importance of pausing SGLT2i treatment 3–7 days prior to surgery or liaise with pre-operative team.
- Please refer to the relevant SmPC before prescribing any SGLT2i therapy.
- Discussion with an expert clinician is advisable for more complex cases.

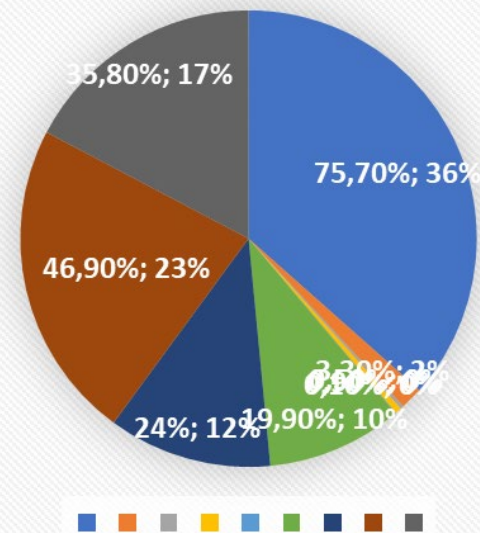




Farmaci per il diabete (%)

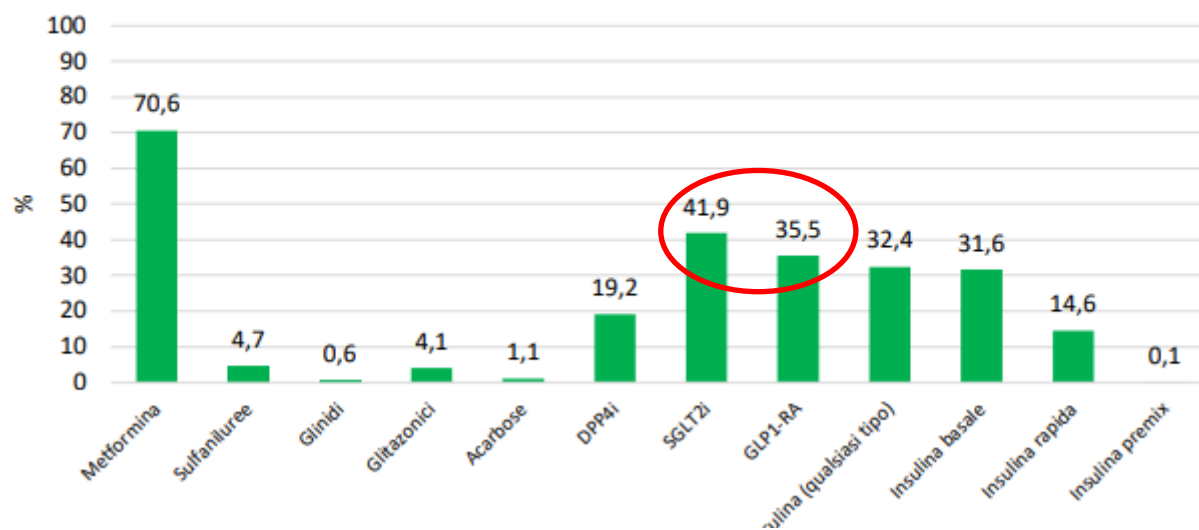


Centro Diabetologico



..... ancora molto altro da fare

Farmaci per il diabete (%)



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