Università di Roma «Sapienza»
Dipartimento Cuore e Grossi Vasi «A. Reale»
Prof. Francesco Barillà

XXIX
CONGRESSO
NAZIONALE
ANCE

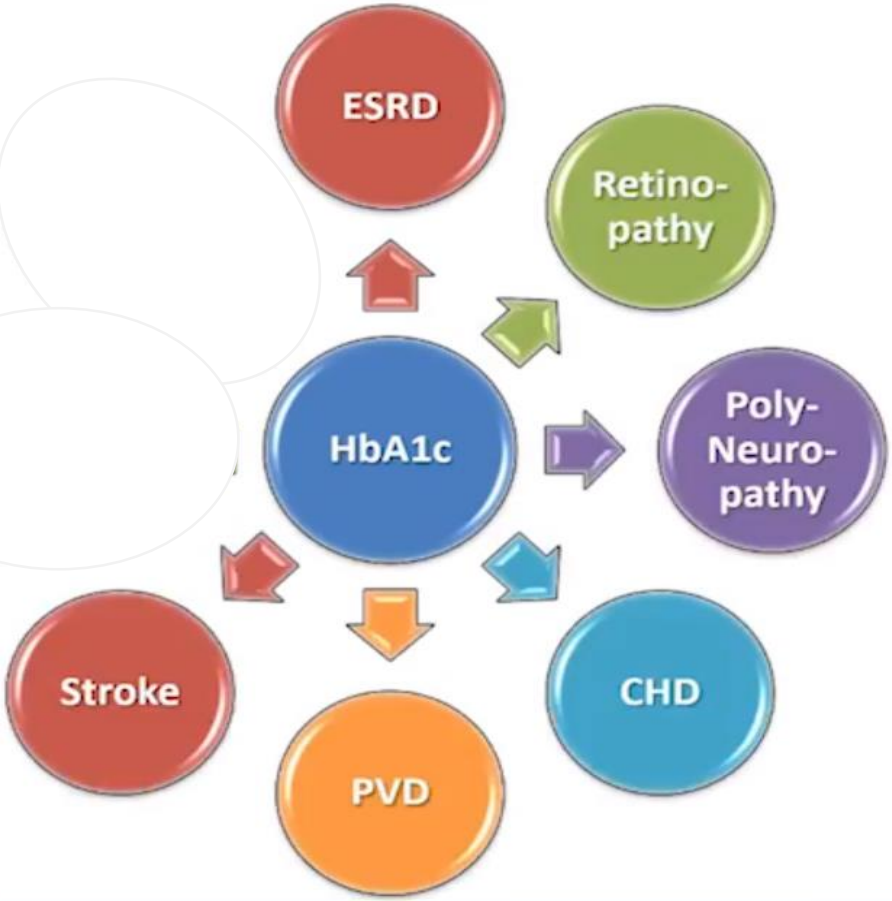
ANCE
Cardiologia Italiana del Territorio

10 - 13 Ottobre 2019
Centro Congressi
Hilton Sorrento Palace
Sorrento (NA)

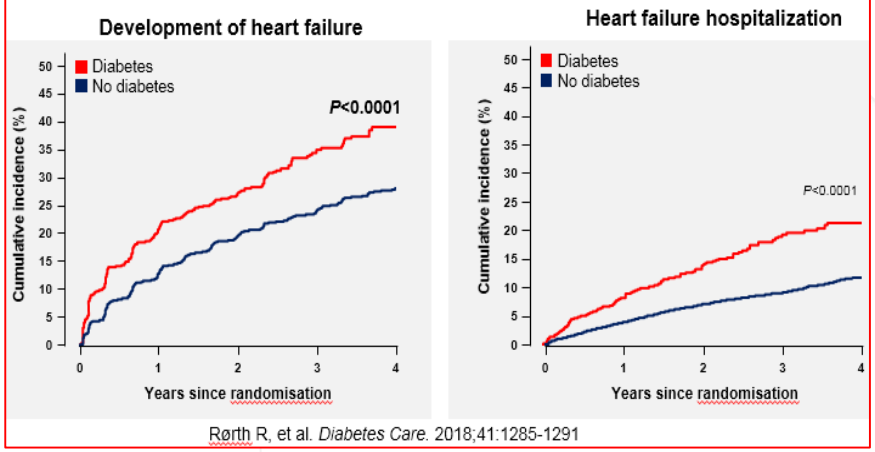
Effetti Cardiovascolari dei Nuovi Farmaci Antidiabetici

Type 2 diabetes and CV outcomes…
We need more than glucose management?

Typ 2 Diabetes



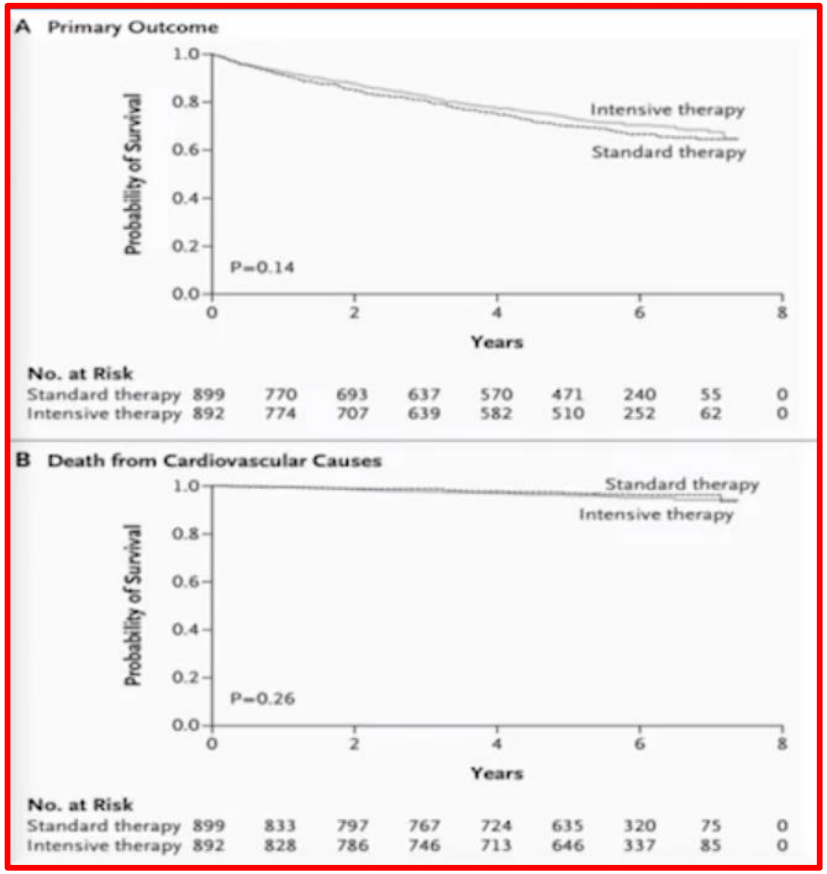
T2D increases the risk of developing HF symptoms and HF hospitalisations



Rørth R, et al. *Diabetes Care*. 2018;41:1285-1291

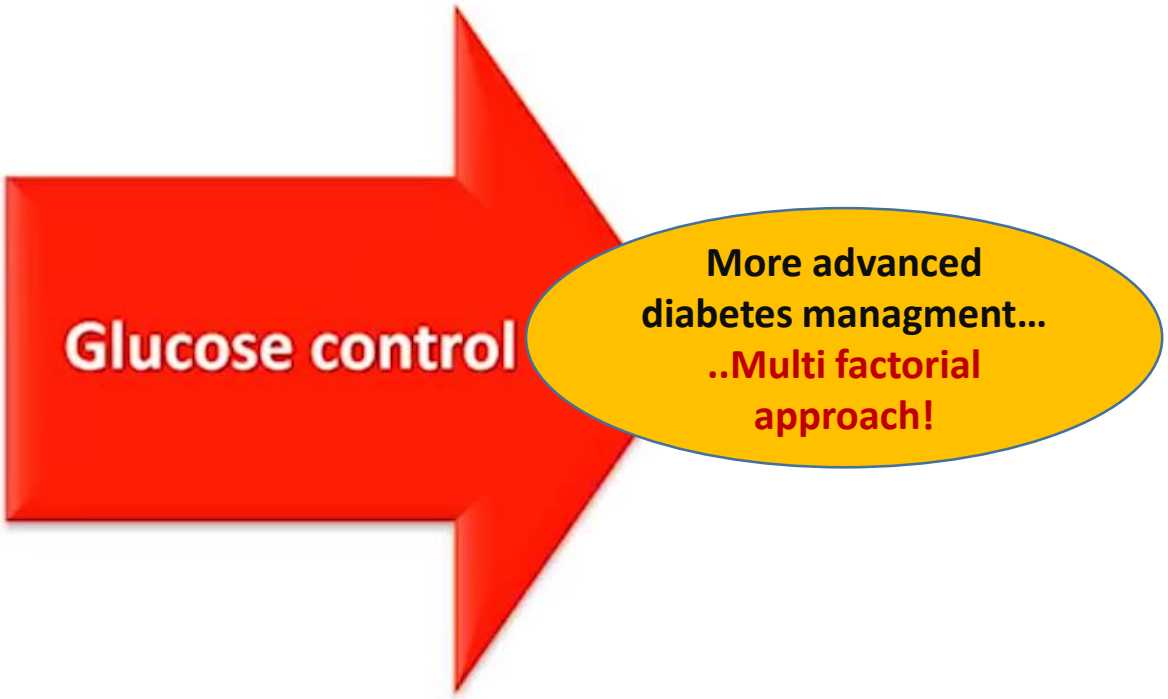
Is reducing HbA_{1c} really successful?

- UKPDS 7 vs 7.9
- ADVANCE 6.3 vs 7
- VADT 6.9 vs 8.4
- ACCORD 6.4 vs 7.5

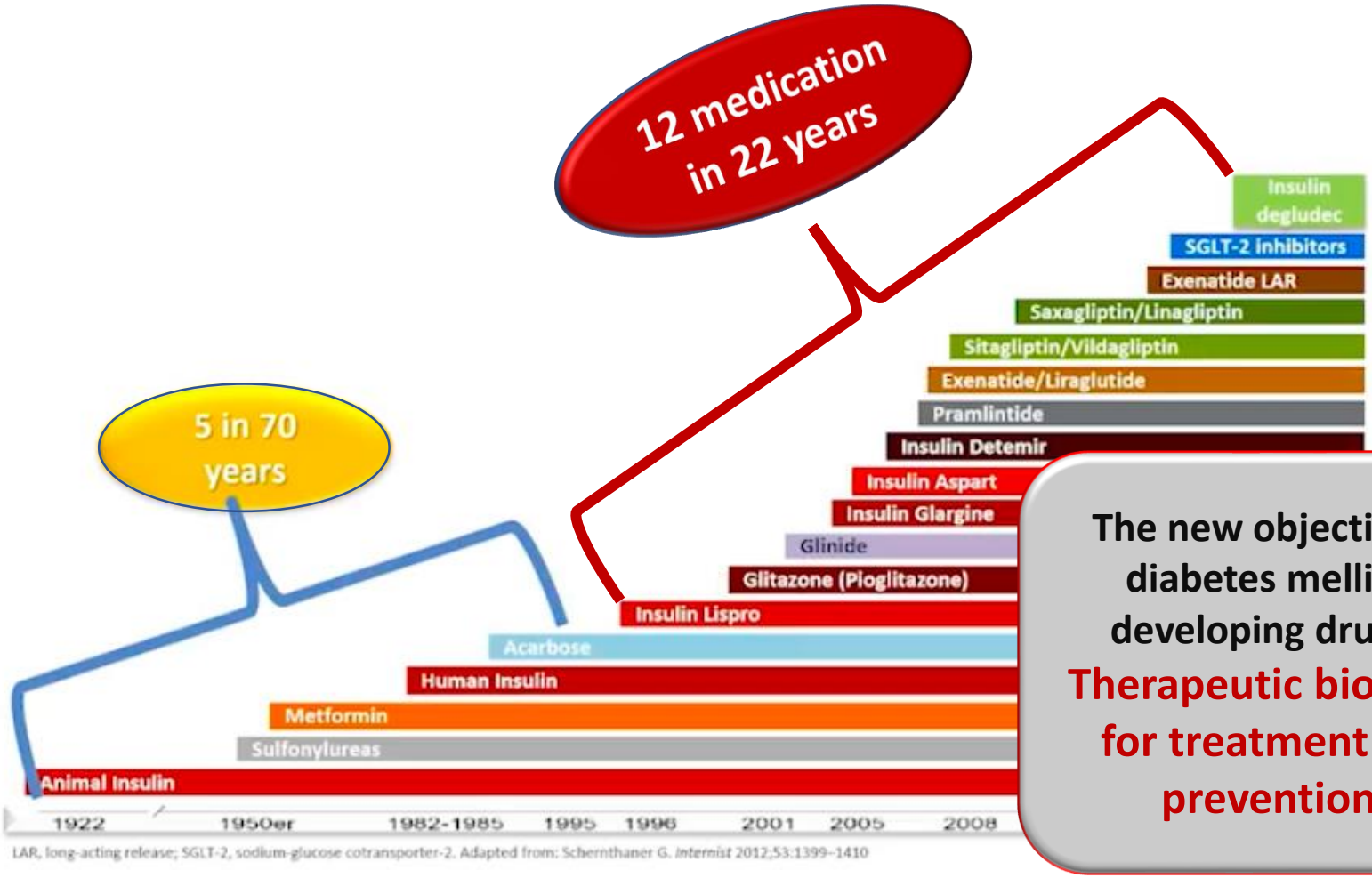


And no reduction in MACE and mortality

Aim of Diabetes management



Anti-hyperglycaemic medication in the last 92 years



LAR, long-acting release; SGLT-2, sodium-glucose cotransporter-2. Adapted from: Schernthaner G. *Internist* 2012;53:1399–1410

The new objective of diabetes mellitus developing drugs…
Therapeutic biologics for treatment and prevention!

After years of frustrations...

EMPA-REG OUTCOME®

DECLARE

NVAS Program

LEADER

Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

SUSTAIN

SEMAGLUTIDE UNABATED SUSTAINABILITY IN TREATMENT OF TYPE 2 DIABETES

HARMONY

These new studies allowed to achieve the goal…

Pasma Glucose Control, CV Prevention and Organ Protection!

New anti-diabetic drugs

1) **GLP-1 agonists** (***Glucagon-Like Peptide-1 Receptor Agonist***)
2) **SGLP-2 inhibitors** (***Sodium-glucose co-trasporter-2 inhibitors***)
3) **DPP-4 inhibitors** (***Dipeptidyl Peptidase-4 Inhibitors***)

Cardiovascular Actions and Clinical Outcomes With Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors

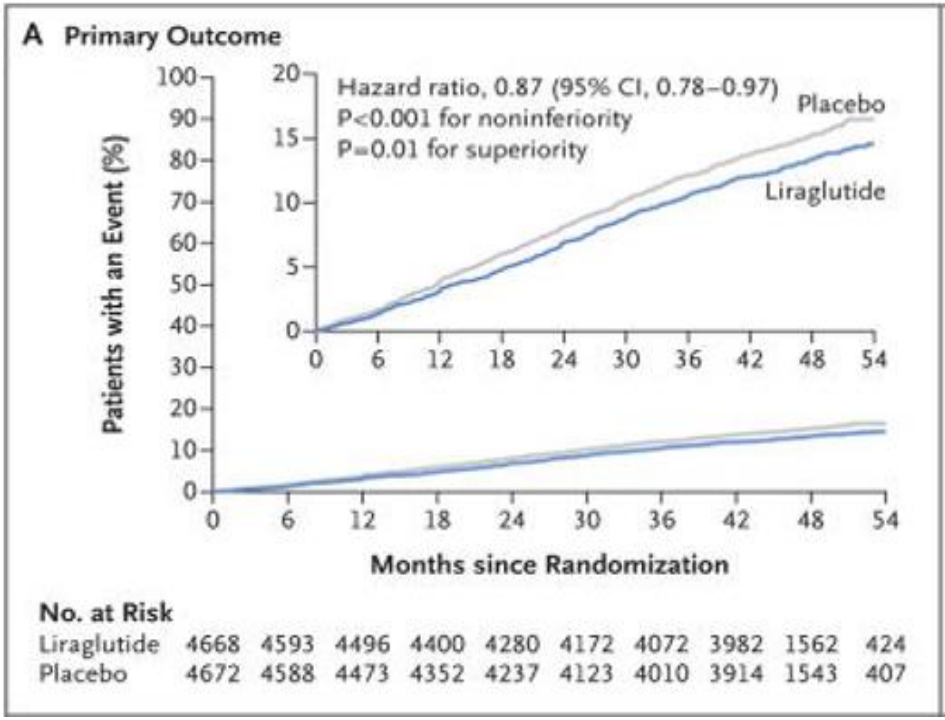
ABSTRACT: Potentiation of glucagon-like peptide-1 (GLP-1) action through selective GLP-1 receptor (GLP-1R) agonism or by prevention of enzymatic degradation by inhibition of dipeptidyl peptidase-4 (DPP-4) promotes glycemic reduction for the treatment of type 2 diabetes mellitus by glucose-dependent control of insulin and glucagon secretion. GLP-1R agonists also decelerate gastric emptying, reduce body weight by reduction of food intake and lower circulating lipoproteins, inflammation,

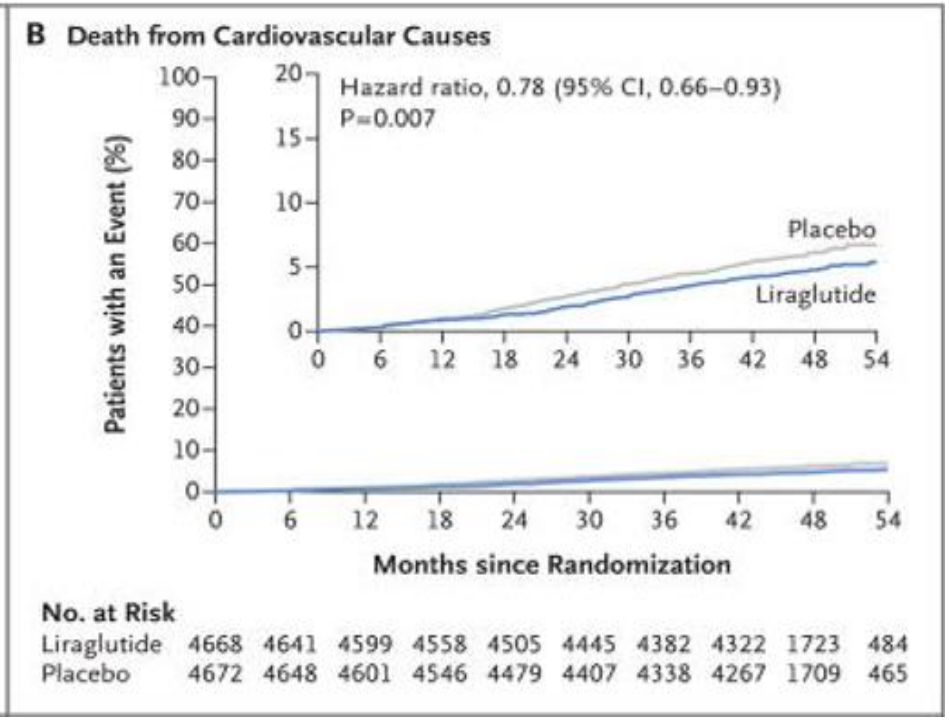
Michael A. Nauck, MD
Juris J. Meier, MD
Matthew A. Cavender, MD, MPH
Mirna Abd El Aziz, MD
Daniel J. Drucker, MD

MACE in GLP1-RA

LEADER
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

CV death, non-fatal myocardial infarction, or non-fatal stroke





SEMAGLUTIDE nel paziente con diabete tipo II

- **La semaglutide appartiene alla famiglia degli analoghi del GLP-1 disponibile oltre che per via sottocutanea (1), anche per via orale.**
- L'obiettivo dello studio **PIONEER 6**, pubblicato *su N Engl J Med* (2), è stato quello di valutare gli effetti cardiovascolari della semaglutide orale una volta al giorno in uno studio randomizzato, controllato in doppio cieco versus placebo.
- **Sono stati coinvolti pazienti con diabete tipo 2 ad alto rischio cardiovascolare:**

  -età ≥50 anni con malattia cardiovascolare o renale oppure,

  -età ≥60 anni con soli fattori di rischio cardiovascolare.
- **L'outcome primario, composito, comprendeva la comparsa di un primo evento cardiovascolare maggiore (infarto miocardico non fatale, ictus non fatale o morte per cause cardiovascolari).**
- Un totale di **3183 pazienti** è stato assegnato in modo casuale a ricevere semaglutide orale o placebo. L'età media dei pazienti era di 66 anni e il tempo mediano nella sperimentazione è stato di 15,9 mesi. **L'84,7%** dei soggetti aveva eventi cardiovascolari preesistenti o insufficienza renale.
- I principali eventi avversi cardiovascolari si sono verificati in **61 paziente su 1591 (3,8%)** nel gruppo in semaglutide orale e in **76 su 1592 (4,8%)** nel gruppo placebo (HR 0,9, IC 95% 0,57-1,11; p <0,001 per la non inferiorità).

ORIGINAL ARTICLE

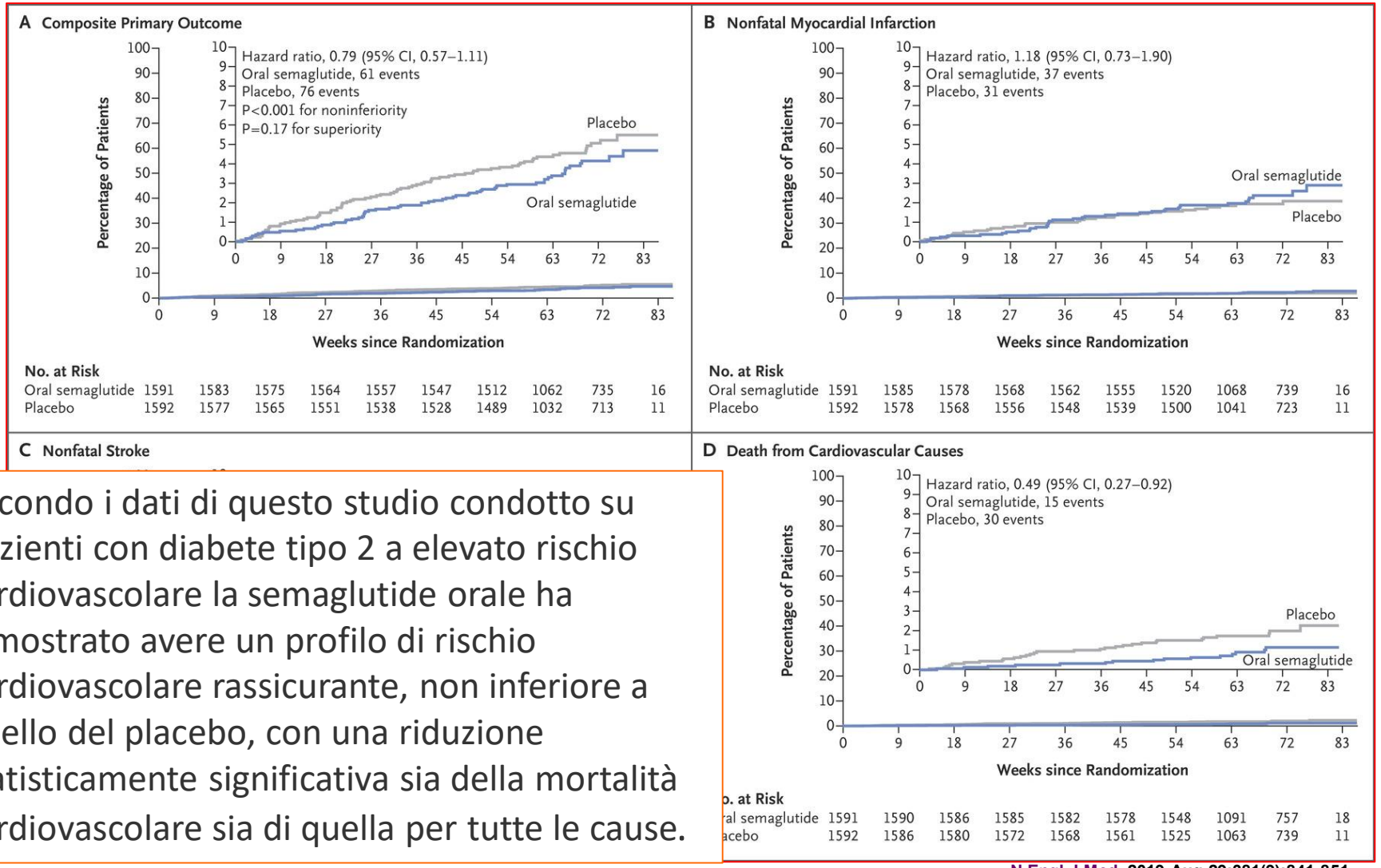
Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Mansoor Husain, M.D., Andreas L. Birkenfeld, M.D., Morten Donsmark, Ph.D., Kathleen Dungan, M.D., M.P.H., Freddy G. Eliaschewitz, M.D., Denise R. Franco, M.D., Ole K. Jeppesen, M.Sc., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Ofri Mosenzon, M.D., Sue D. Pedersen, M.D., Cees J. Tack, M.D., Mette Thomsen, M.D., D.M.Sc., Tina Vilsbøll, M.D., D.M.Sc., Mark L. Warren, M.D., and Stephen C. Bain, M.D., for the PIONEER 6 Investigators*

Il primo analogo del GLP-1 disponibile per os

Primary outcome:

first MACE (composite of death from CV causes, nonfatal MI, or nonfatal stroke)



Secondo i dati di questo studio condotto su pazienti con diabete tipo 2 a elevato rischio cardiovascolare la semaglutide orale ha dimostrato avere un profilo di rischio cardiovascolare rassicurante, non inferiore a quello del placebo, con una riduzione statisticamente significativa sia della mortalità cardiovascolare sia di quella per tutte le cause.

N Engl J Med. 2019 Aug 29;381(9):841-851

ORIGINAL ARTICLE

Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Mansoor Husain, M.D., Andreas L. Birkenfeld, M.D., Morten Donsmark, Ph.D., Kathleen Dungan, M.D., M.P.H., Freddy G. Eliaschewitz, M.D., Denise R. Franco, M.D., Ole K. Jeppesen, M.Sc., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Ofri Mosenzon, M.D., Sue D. Pedersen, M.D., Cees J. Tack, M.D., Mette Thomsen, M.D., D.M.Sc., Tina Vilsbøll, M.D., D.M.Sc., Mark L. Warren, M.D., and Stephen C. Bain, M.D., for the PIONEER 6 Investigators*

Adverse Events (during the Treatment Period unless Specified)

Event	Oral Semaglutide (N=1591)	Placebo (N=1592)
	number of patients (percent)	
Adverse event leading to permanent discontinuation of oral semaglutide or placebo	184 (11.6)	104 (6.5)
According to system organ class†		
Gastrointestinal disorders	108 (6.8)	26 (1.6)
Metabolism and nutrition disorders	19 (1.2)	7 (0.4)
Nervous system disorders	17 (1.1)	13 (0.8)
Serious adverse event	301 (18.9)	358 (22.5)
Leading to permanent discontinuation of oral semaglutide or placebo	41 (2.6)	48 (3.0)
Adverse events of special interest		
Acute kidney injury‡	32 (2.0)	37 (2.3)
Acute pancreatitis‡	1 (0.1)	3 (0.2)
Retinopathy or related complications§¶	113 (7.1)	101 (6.3)
Severe hypoglycemia§	23 (1.4)	13 (0.8)
Malignant neoplasms‡¶‖	41 (2.6)	48 (3.0)

* Adverse events were summarized descriptively for both the treatment period (from the date of the first dose to the date of the last dose plus 38 days or the final follow-up visit [whichever occurred first]) and the in-trial observation period (from randomization to the final follow-up visit). Further adverse events of special interest are shown in Table S9 in the Supplementary Appendix.

† Shown are events with an incidence of at least 1% in either trial group.

‡ These events were confirmed by the event-adjudication committee.

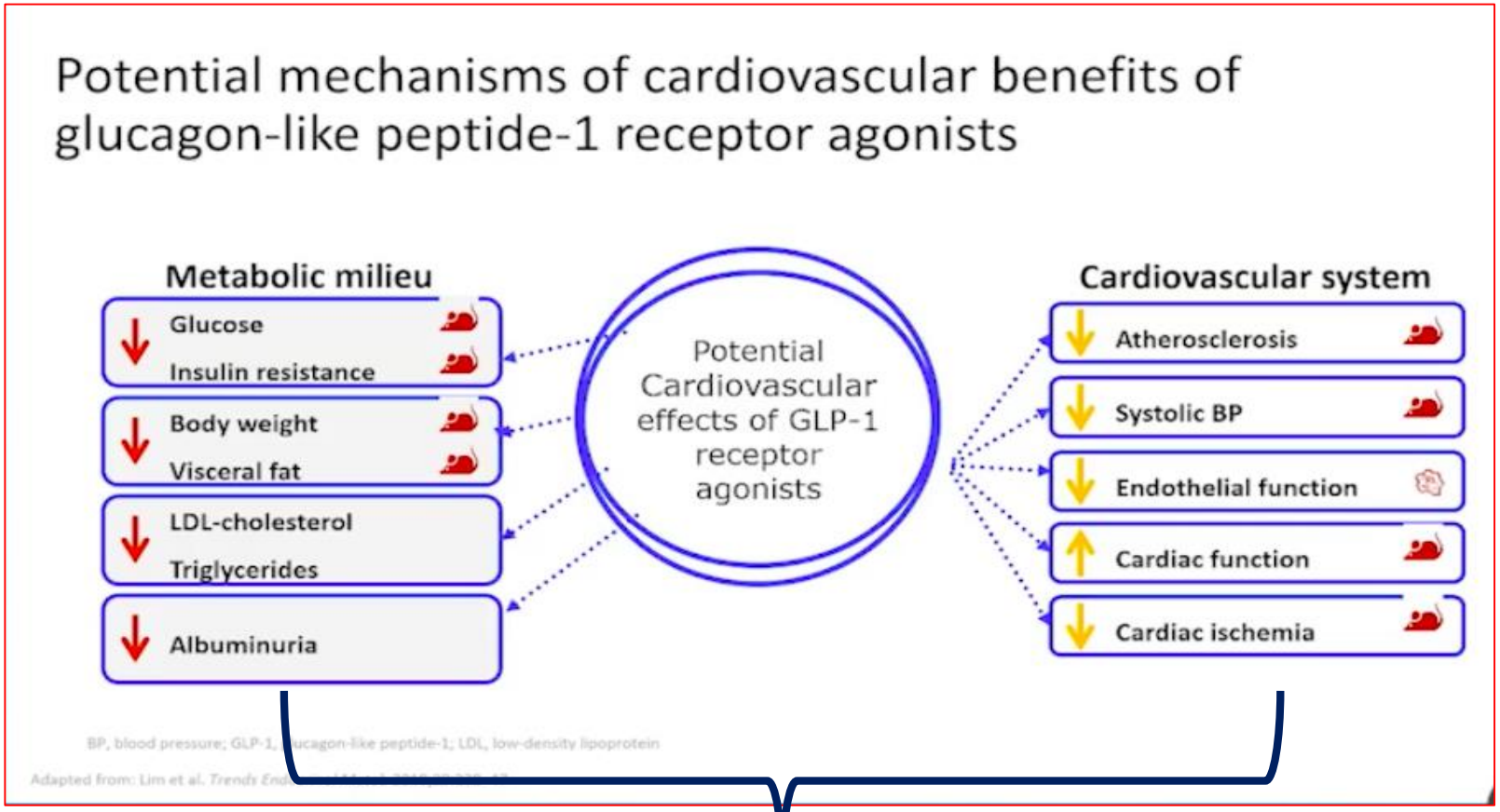
§ These events were identified through a search of terms in the *Medical Dictionary for Regulatory Activities*, version 20.1.

¶ Data are for the in-trial observation period.

‖ Malignant thyroid neoplasms were excluded. Such neoplasms occurred in two patients receiving oral semaglutide: one patient had medullary thyroid cancer and one had a recurrence of a previous thyroid cancer.

N Engl J Med. 2019 Aug 29;381(9):841-851

How do GLP1 receptor agonists improve outcome?



- Inflammation
- Atherosclerosis progression

The sodium-glucose cotransporter 2 (SGLT2) inhibitors…….

…..a new class of glucose-lowering therapies that have been shown to reduce risks of heart failure (HF) events in patients with type 2 diabetes mellitus (T2DM)

Congress News

ESC Congress Paris 2019
Together with World Congress of Cardiology

Day 3

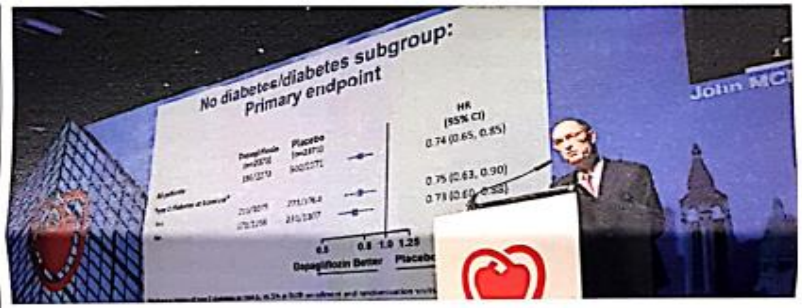
Top picks

Dapagliflozin reduces cardiovascular events in HFrEF, not just diabetes

"Yesterday, we presented once-in-a-lifetime findings that sodium-glucose co-transporter-2 (SGLT2) inhibitors are truly a treatment for heart failure (HF) and not just diabetes," says Professor John McMurray (University of Glasgow, Glasgow, UK), speaking about his Hot Line presentation on the DAPA-HF trial.

"HF is a very common complication of type 2 diabetes, occurring more frequently than stroke and as frequently as myocardial infarction," explains Prof. McMurray. "Trials have shown that, in addition to effectively treating diabetes, SGLT2 inhibitors also reduce the risk of patients developing HF. And the benefits are seen fairly rapidly, within weeks of starting treatment. It follows naturally that the next question would be, 'Can these drugs be used to treat patients with established HF, including those without diabetes?' And this is what we wanted to look at in DAPA-HF."

The trial randomised 4,744 patients with HF with reduced ejection fraction (HFrEF) (left ventricular ejection fraction ≤40%) from 20



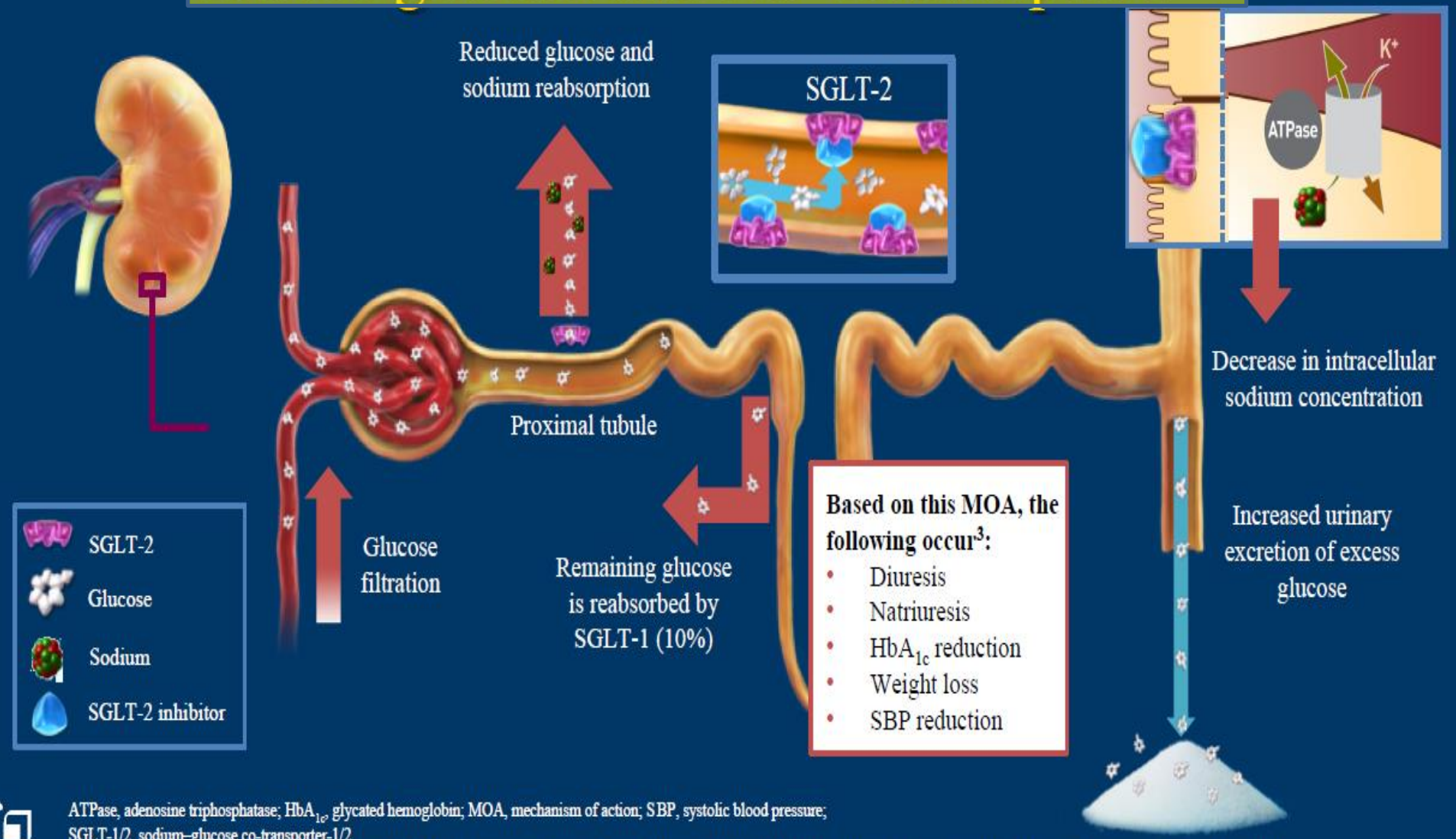
"Dapagliflozin also reduced the risk of death from any cause by 17% (p=0.022) and it is quite unusual to see such a benefit in clinical trials," comments Prof. McMurray.

The safety profile of dapagliflozin was good. There were no notable imbalances in frequencies between the treatment arms, including for serious adverse events or adverse events of interest. Adverse events related to volume

patients' well-being. "Patients with HF report worse QoL than individuals with any other chronic condition. In DAPA-HF, compared with placebo, treatment with dapagliflozin led to more patients having a clinically important improvement in health-related QoL (15% more likely to improve; p<0.001) and fewer patients having an important deterioration in their health-related QoL (16% less likely to deteriorate; p<0.001)."

Summing up the trial results, Prof. McMurray

SGLT-2 inhibitors block SGLT-2 and reduce glucose and Na^+ reabsorption[1–3]



ATPase, adenosine triphosphatase; HbA_{1c}, glycated hemoglobin; MOA, mechanism of action; SBP, systolic blood pressure; SGLT-1/2, sodium–glucose co-transporter-1/2

1. Marsenic O. *Am J Kidney Dis* 2009;53:875–85; 2. FORXIGA. Summary of Product Characteristics 2019. Available at: https://www.medicines.org.uk/emc/product/2865/smpc (accessed May 2019); 3. Mudaliar S et al. *Diabetes Care* 2016;39:1115–22

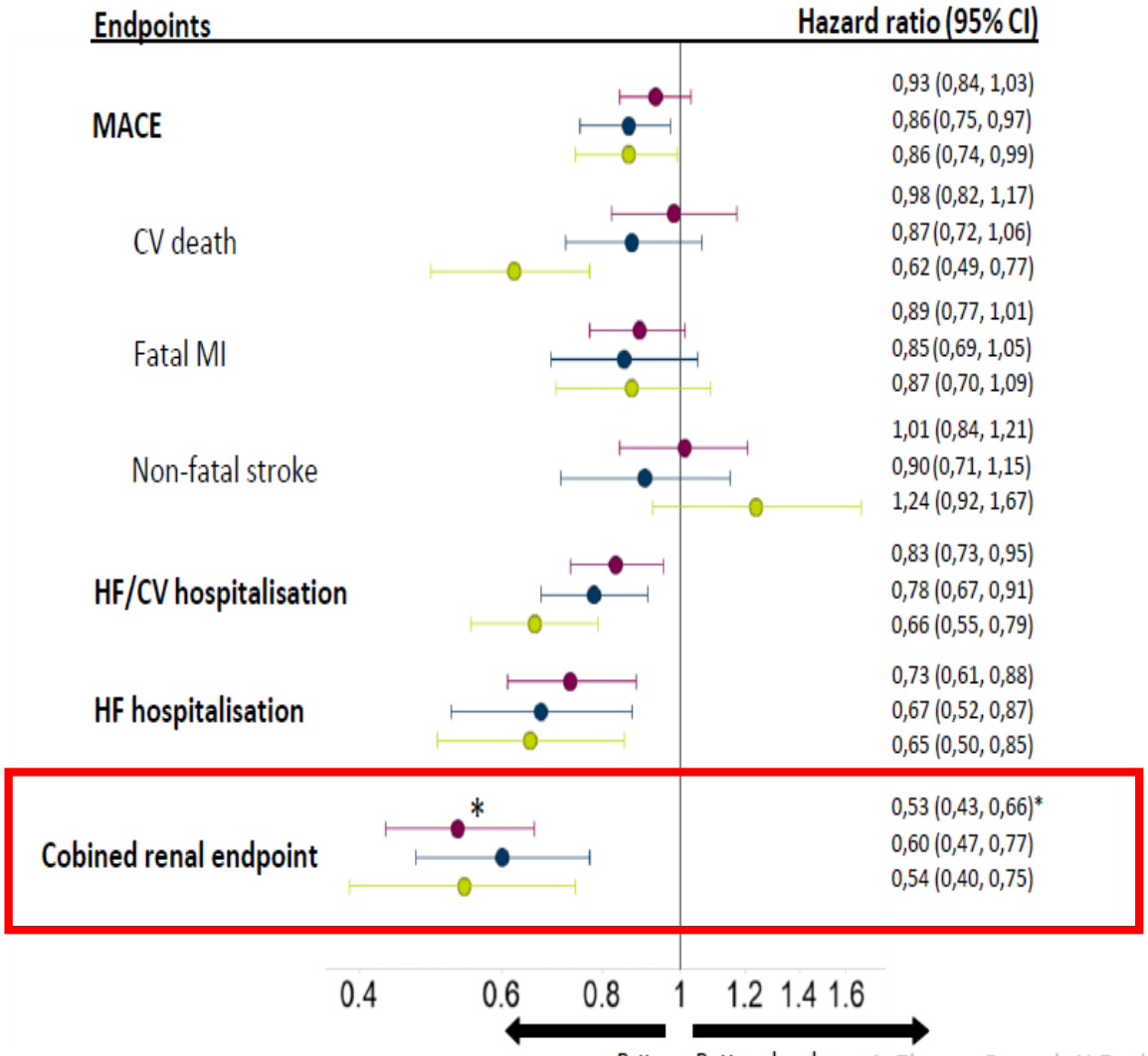
SGLT2is Demonstrated CV Benefits in T2D Patients Across CVOTs, CREDENCE, and Real-World Evidence

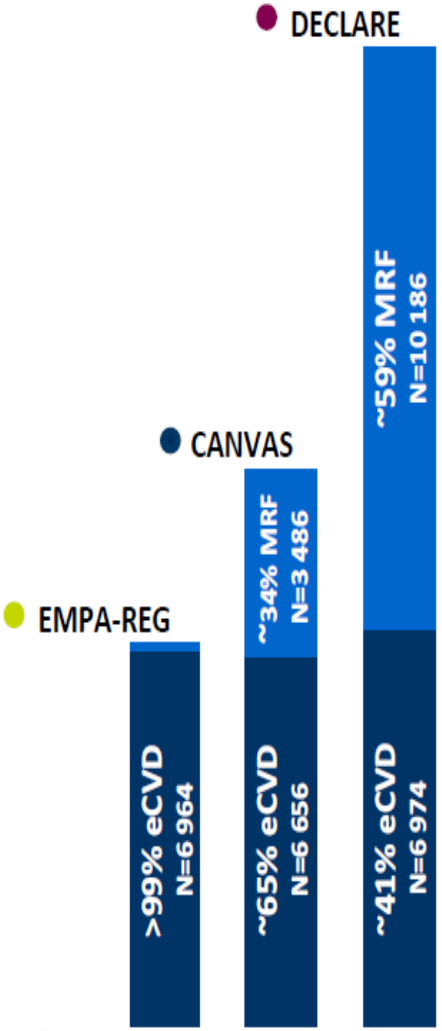
	EMPA-REG[1,2] (n=7020)	CANVAS Program[3-5] (n=10,142)	DECLARE[6] (n=17,160)	CREDENCE[7] (n=4402)	CVD-REAL[8,9] (n>700,000)
Trial population	✓ T2D ✓ Established CVD x Multiple risk factors for CVD, without established CVD ✓ Renal function: eGFR ≥30 mL/min/1.73m^2	✓ T2D ✓ Established CVD ✓ Multiple risk factors for CVD, without established CVD ✓ Renal function: eGFR >30 mL/min/1.73m^2	✓ T2D ✓ Established CVD ✓ Multiple risk factors for CVD, without established CVD ✓ Renal function: CrCl ≥60 mL/min	✓ T2D ✓ Renal function: eGFR ≥30 and <90 mL/min/1.73m^2 and UACR >300 and ≤5000 mg/g	✓ T2D
Patient cohorts	Empagliflozin 10 mg or Empagliflozin 25 mg or Placebo	Canagliflozin 100 mg or Canagliflozin 300 mg or Placebo	Dapagliflozin 10 mg or Placebo	Canagliflozin 100 mg or Placebo	Empagliflozin / Canagliflozin / Dapagliflozin or Other glucose-lowering drug
Primary endpoint(s)	• MACE	CANVAS (n=4330) • MACE CANVAS-R (n=5812) • Progression of albuminuria	• Composite of CV death or hospitalization for heart failure • MACE	• Composite of ESRD, doubling of SCr, renal death, or CV death	• hHF
Select secondary endpoints	• 4-point MACE (CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina) • hHF • New onset albuminuria	• Progression of albuminuria • Change in UACR • Change in eGFR • Change in HbA1c • Composite of CV death and hHF • CV death	Time to first event of renal composite (confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73 m^2 and/or ESRD and/or renal or CV death)	• Composite of CV death and hHF • Composite of CV death, non-fatal MI, non-fatal stroke • hHF • CV death • Composite of CV death, non-fatal MI, non-fatal stroke, hHF, hospitalized unstable angina	• All-cause mortality

CrCl=creatinine clearance; CVD=cardiovascular disease; CVOT=Cardiovascular Outcome Trial; eGFR=estimated glomerular filtration rate; ESRD=end-stage renal disease; HbA1c=glycated hemoglobin; hHF=hospitalization for heart failure; MACE=major adverse cardiac; MI=myocardial infarction; SCr=serum creatinine; UACR=urine albumin to creatinine ratio.

1. ClinicalTrials.gov. EMPA-REG OUTCOME. NCT01131676. https://clinicaltrials.gov/ct2/show/NCT01131676. Accessed May 3, 2019. 2. Zinman B, et al. N Engl J Med. 2015;373:2117-2128. 3. Neal B, et al. Am Heart J. 2013;166:217-233.e11. 4. Neal B, et al. N Engl J Med. 2017;377:644-657. 5. Clinicaltrials.gov. CANVAS. NCT01032629. https://clinicaltrials.gov/ct2/show/NCT01032629. Accessed May 3, 2019. 6. ClinicalTrials.gov. DECLARE. NCT01730534. https://clinicaltrials.gov/ct2/show/NCT01730534. Accessed May 3, 2019. 7. ClinicalTrials.gov. CREDENCE. NCT02065791. https://clinicaltrials.gov/ct2/show/NCT02065791. Accessed June 24, 2019. 8. Kosiborod M, et al. Circulation. 2017;136:249-259. 9. Kosiborod M, et al. J Am Coll Cardiol. 2018;71(23):2628-2639.

SGLT-2 inhibitors decrease CV event rates, particularly HHF, and protects kidneys in patients with T2D



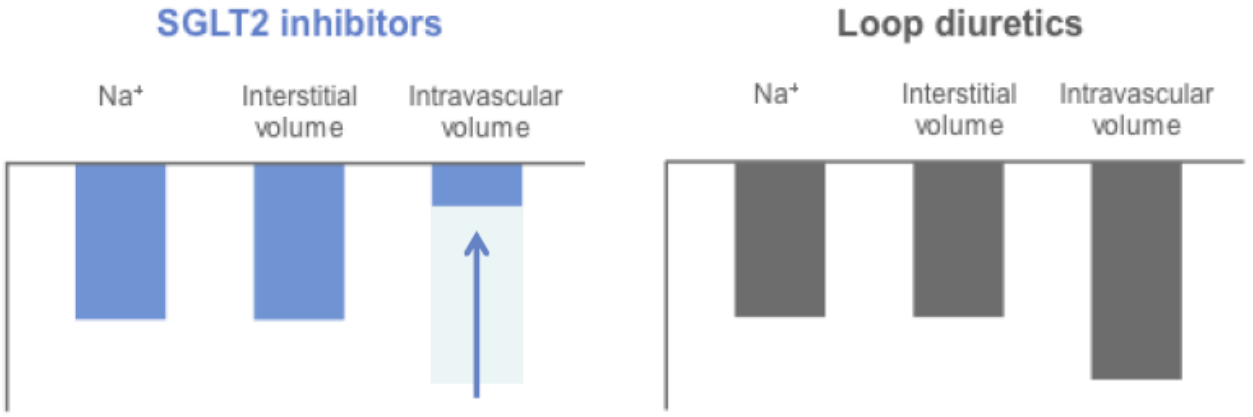


1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 2. Neal B, et al. *N Engl J Med* 2017;377:644–657 3. Wiviott SD et al. Online ahead of print. *N Engl J Med.* 2018.

Plasma glucose remains unchanged with chronic empagliflozin treatment in patients without diabetes

SGLT2 inhibitors may **selectively reduce** interstitial volume with minimal change in blood volume[1]…

…whereas loop diuretics may cause a reduction in both interstitial and intravascular volumes[1]



Larger reductions in interstitial fluid volume may more effectively:[1,2]

- Relieve signs and symptoms of **interstitial congestion**
- Provide some relief of elevated **cardiac filling pressures**
- Prevent harmful effects of **excessive blood volume depletion**, including neurohormonal activation

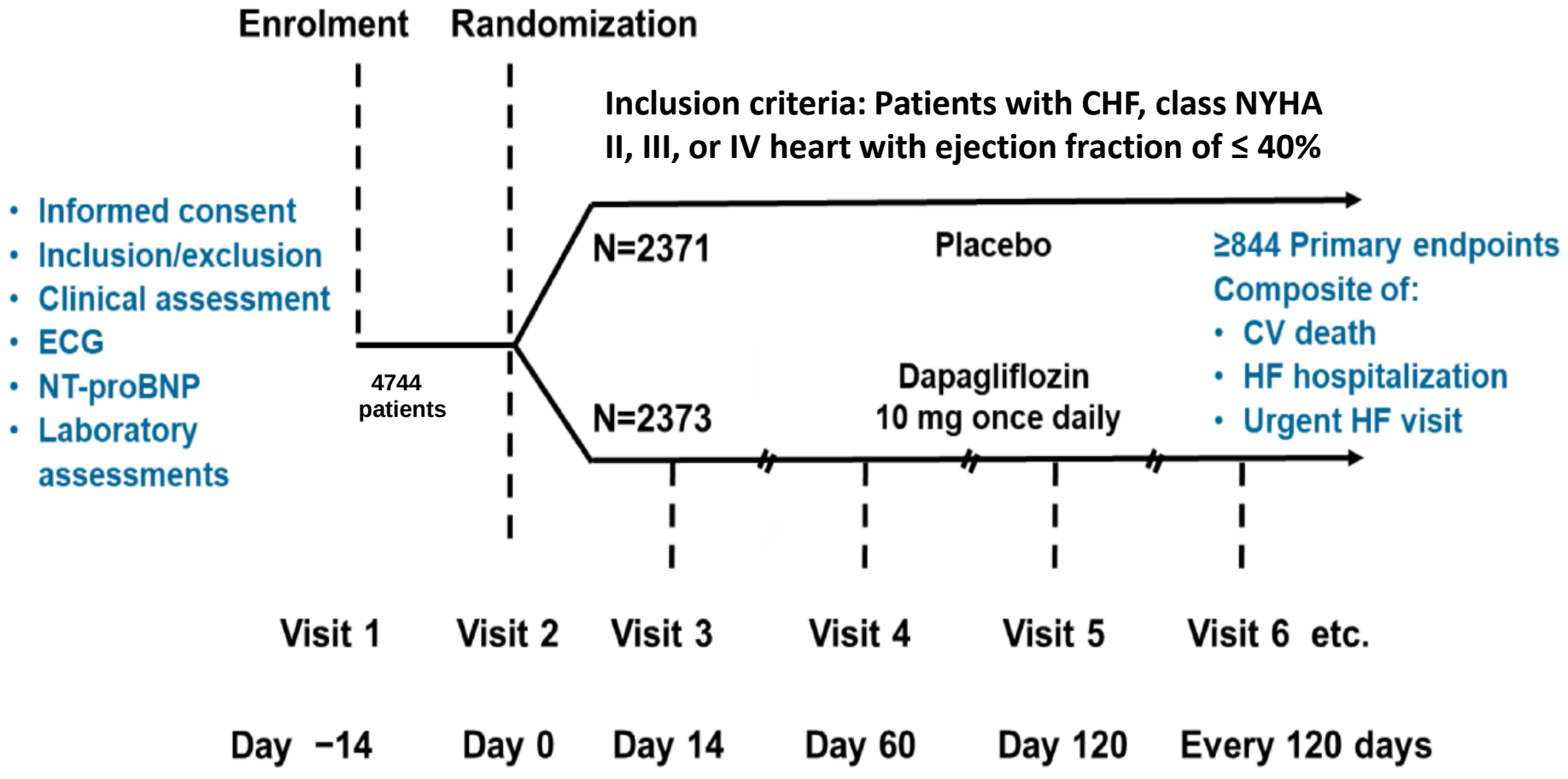
1. Verma S & McMurray J. *Diabetologia* 2018:61;2108; 2. Hallow KM *et al. Diabetes Obes Metab* 2018:20;479

But the most important question is:

- can they be used to treat non-diabetic patients?

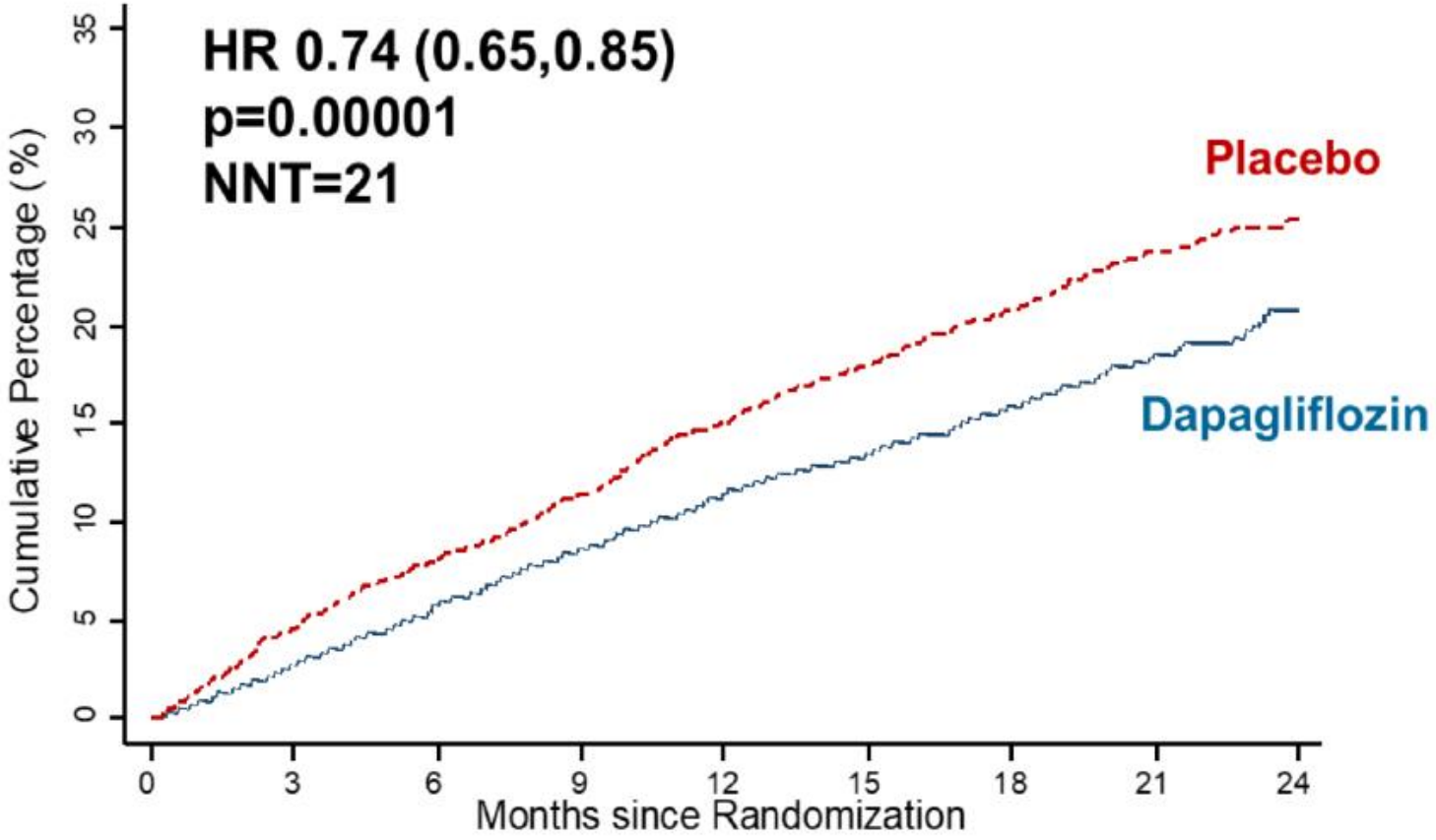
DAPA-HF Design

Phase 3, placebo-controlled trial



Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit



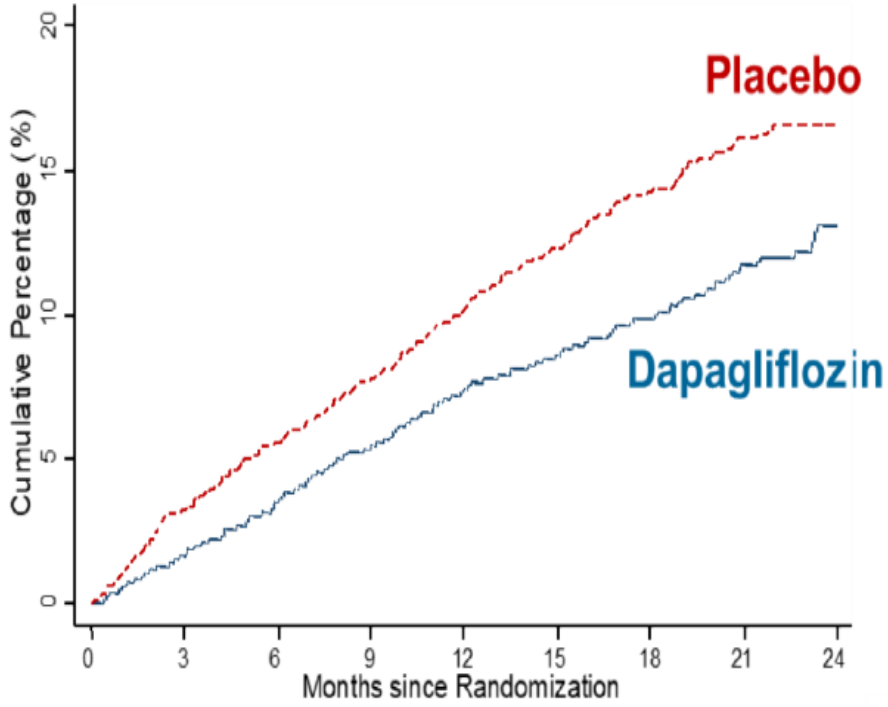
Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

Components of primary outcome

Worsening HF event

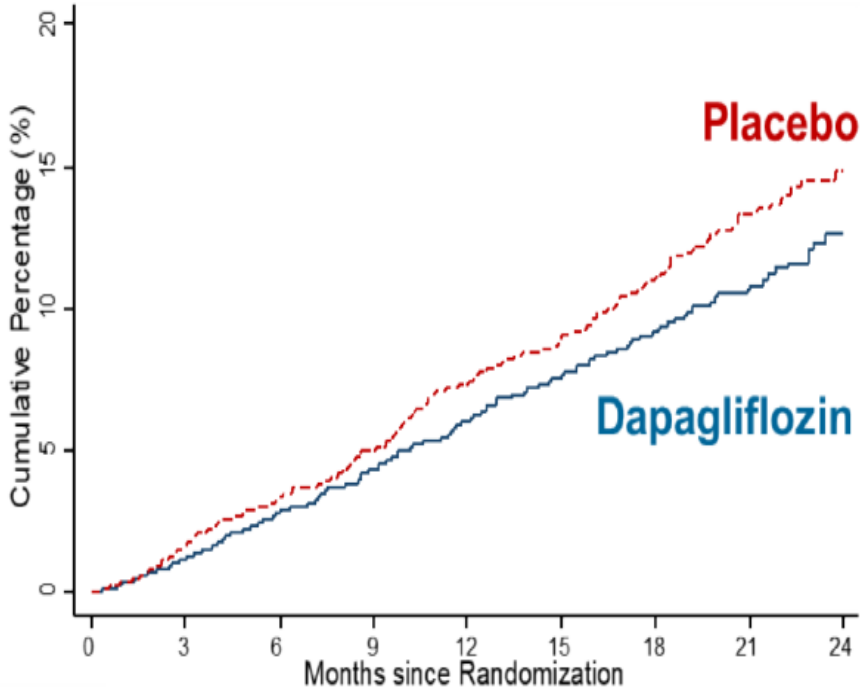
HR 0.70 (0.59, 0.83); p=0.00003



Number at Risk									
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

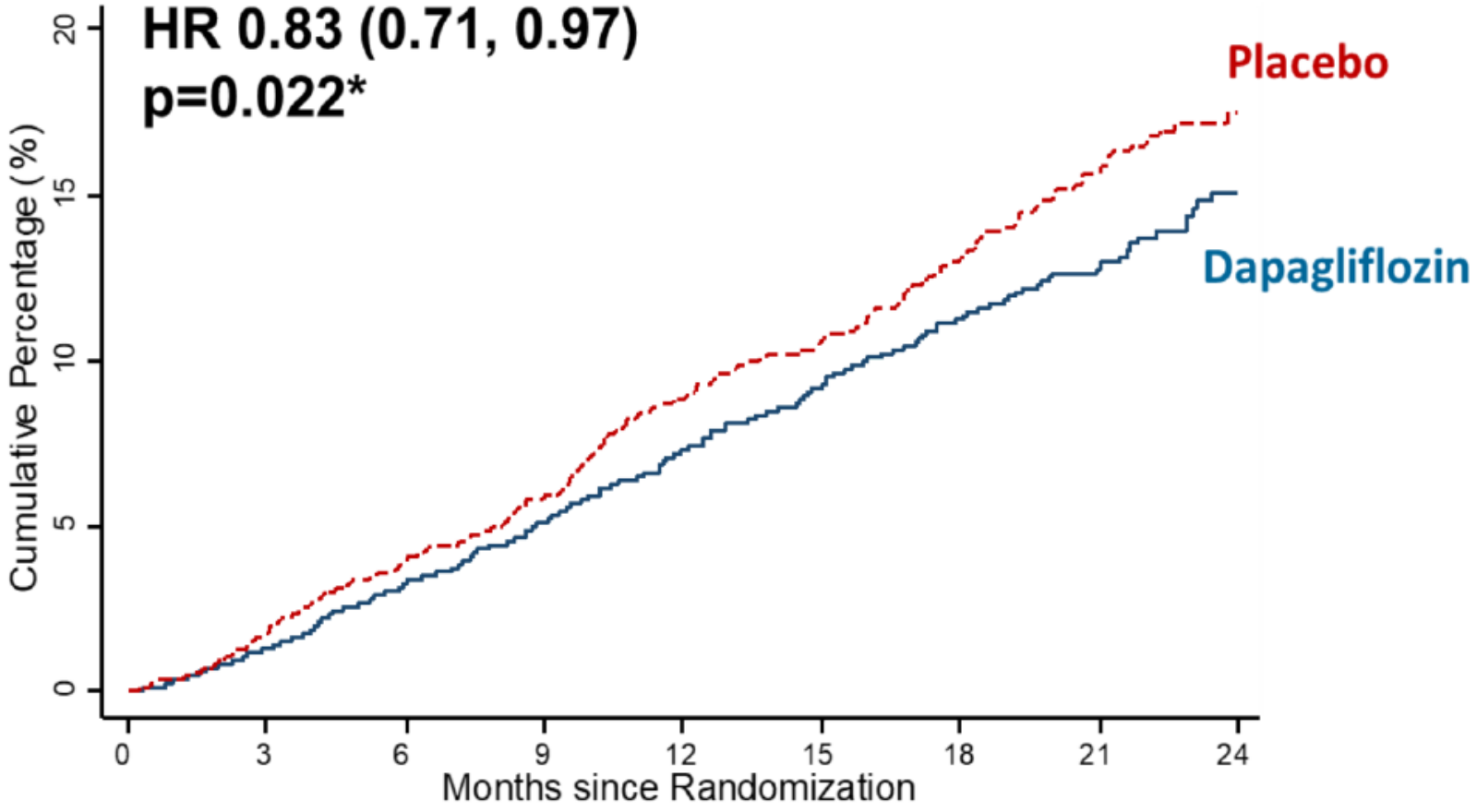
Cardiovascular death

HR 0.82 (0.69, 0.98); p=0.029



	2373	2339	2293	2248	2127	1664	1242	671	232
	2371	2330	2279	2230	2091	1636	1219	664	234

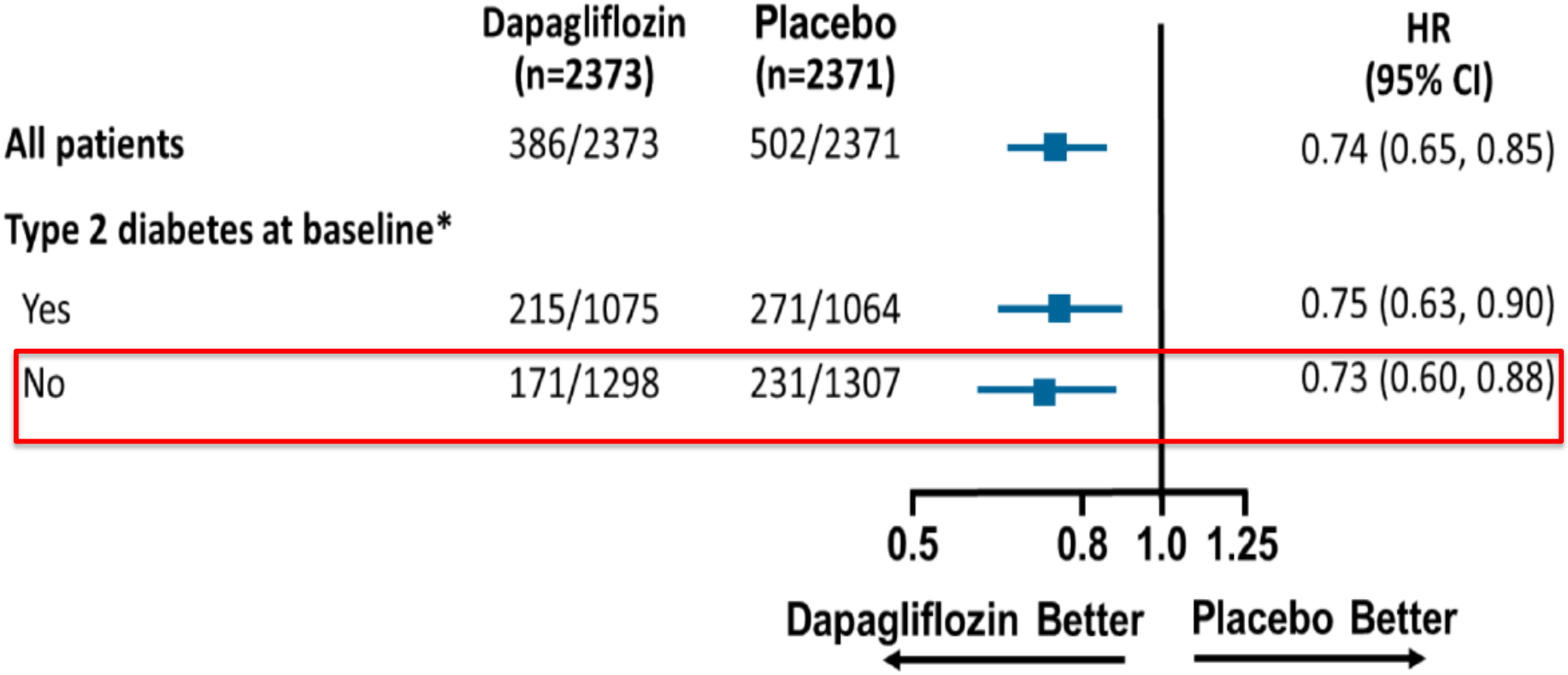
All-cause death



Number at Risk									
Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233
Placebo	2371	2330	2279	2231	2092	1638	1221	665	235

*Nominal p value

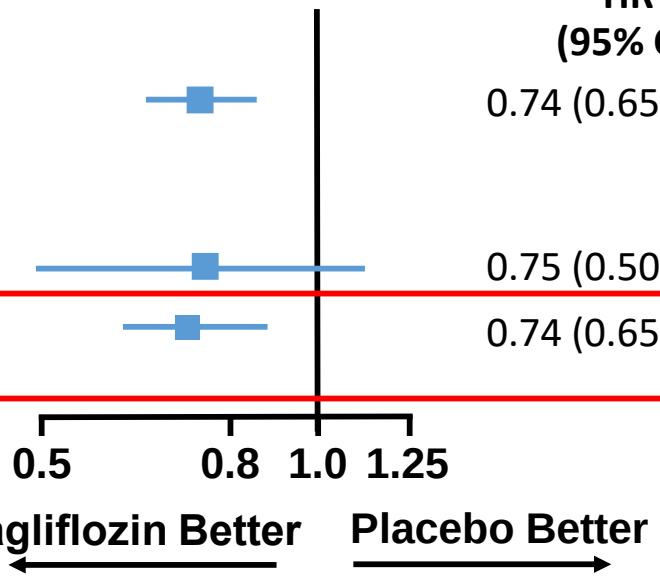
No diabetes/diabetes subgroup: Primary endpoint



*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

Primary Endpoint:
ARNI/No ARNI *Post-hoc* Subgroup Analysis

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Angiotensin Receptor Neprilysin Inhibitor (ARNI)			
Yes	41/250	56/258	0.75 (0.50, 1.13)
No	345/2123	446/2113	0.74 (0.65, 0.86)



CI = confidence interval; HR = hazard ratio

McMurray JJV et al. *N Engl J Med*. 2019. https://doi.org/10.1056/NEJMoa1911303. Accessed September 19, 2019..

Safety/adverse events

Patients exposed to at least one dose of study drug	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
Adverse events (AE) of interest (%)			
Volume depletion[+]	7.5	6.8	0.40
Renal AE[‡]	6.5	7.2	0.36
Fracture	2.1	2.1	1.00
Amputation	0.5	0.5	1.00
Major hypoglycaemia	0.2	0.2	-
Diabetic ketoacidosis	0.1	0.0	-
AE leading to treatment discontinuation (%)	4.7	4.9	0.79
Any serious adverse event (incl. death) (%)	38	42	<0.01

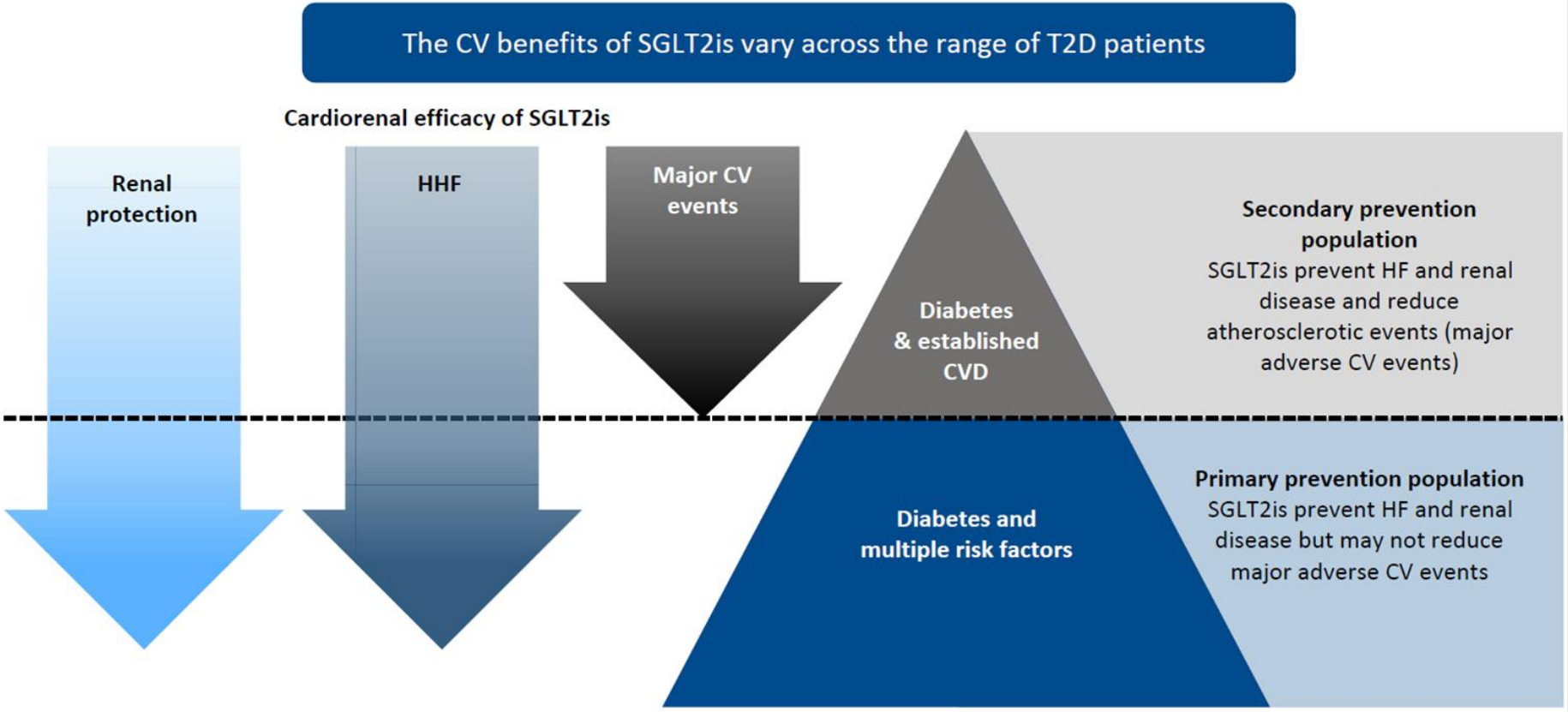
[+] Volume depletion serious AEs in 29 dapagliflozin patients (1.2%) and 40 placebo patients (1.7%), p=0.23

[‡] Renal serious AEs in 38 dapagliflozin patients (1.6%) and 65 placebo patients (2.7%), p=0.009

Quali condizioni sconsigliano l'uso di questi farmaci?

- **Gli SGLT-2 inibitori** possono essere prescritti a pazienti adulti con diabete mellito di tipo 2, per migliorare il controllo glicemico sia da soli (monoterapia), nei casi di intolleranza alla metformina, quando dieta e esercizio fisico da soli non forniscono un controllo adeguato della glicemia, sia in associazione con altri medicinali ipoglicemizzanti inclusa l'insulina, quando questi insieme a dieta e esercizio fisico, non sono sufficienti a controllare il diabete.
- **Gli SGLT-2 inibitori non sono raccomandati in pazienti con insufficienza renale da moderata a grave**. Nei pazienti già in terapia e con filtrato glomerulare di 45-60 ml/min la dose del farmaco va aggiustata e mantenuta a 10mg una volta al giorno (Empaglifozin).
- **Gli SGLT-2 inibitori vanno usati con cautela in pazienti trattati con diuretici** o con patologie che possano provocare disidratazione, come patologie gastrointestinali ed altre malattie acute.
- Deve inoltre essere usato con cautela nei pazienti con malattie CV note, in terapia anti-ipertensiva e/o con una storia di ipotensione, in pazienti anziani di età >75 anni e in terapia con diuretici poichè può provocare calo della pressione sanguigna.
- **Gli SGLT-2 non devono essere usati in pazienti con diabete mellito di tipo 1 o nella chetoacidosi diabetica.**

Benefits of SGLT2 inhibitors in different patient populations[1]



CV, cardiovascular; CVD, cardiovascular disease; HHF, hospitalization for heart failure; HF, heart failure; I, inhibitor; SGLT2i, sodium–glucose co-transporter 2; T2D, type 2 diabetes. 1. Verma S *et al. Lancet* 2019; 393: 3–5.

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«Take home message»

These new studies on GLP-1 agonists and SGLT-2 inhibitors allowed to introduce a new PARADIGM in the treatment of diabetic patients

- **Treat the patient not his sugar!**

and

- **Reduce CV risk not only the HBA1C!**

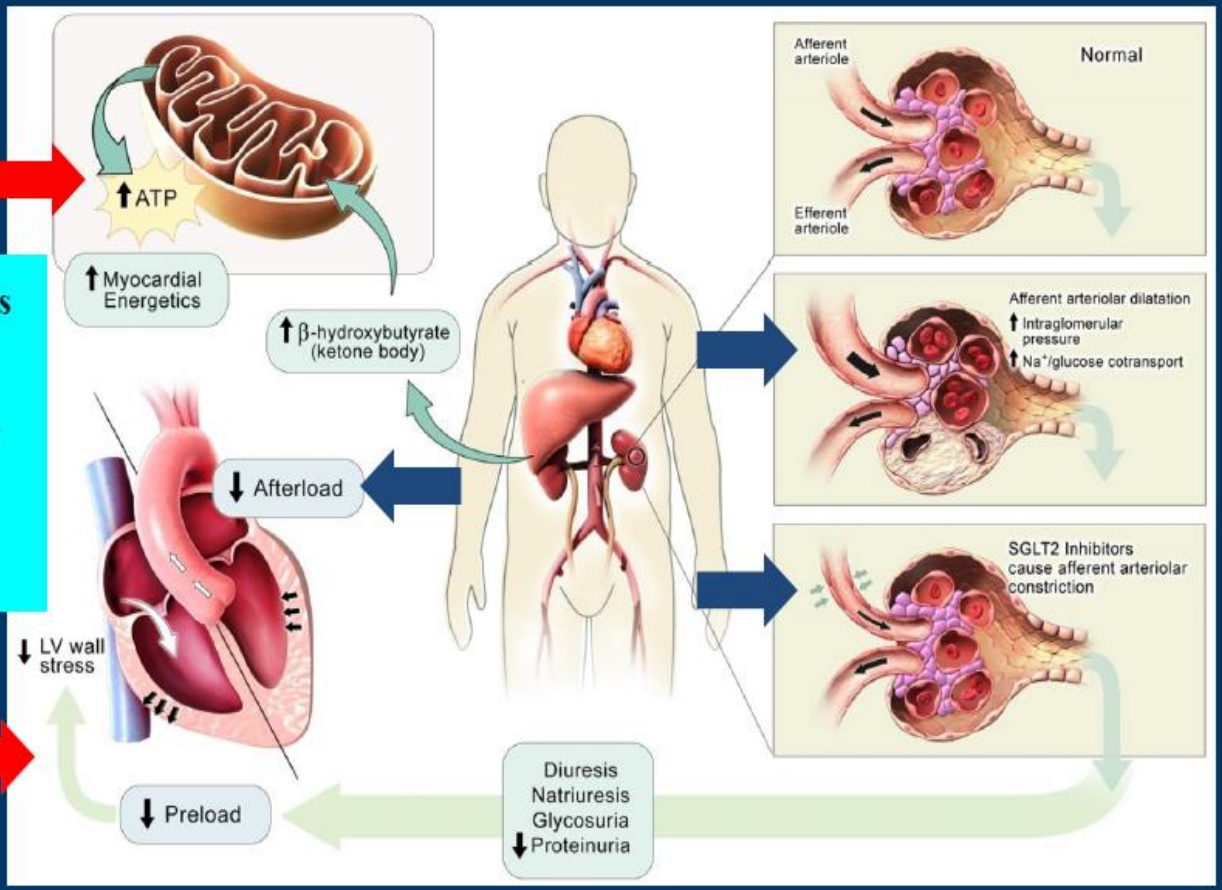
GLUCO-CENTRIC point of view

- **No evidence for a better outcome**

OUTCOME-ORIENTED point of view

- **Improve CV outcome**
- **Improve renal protection**
- **Reduced mortality**

SGLT2 Inhibition and Cardiorenal Protection



Potential mechanisms

- Improve ventricular loading conditions
  - Diuresis
  - Natriuresis
  - Afterload reduction
- Myocardial energetics and metabolomics
- Direct effects on myocardium
- TGF and reduction in IGH

Verma S, McMurray JJV, Cherney D *JAMA Cardiol* 2017;2:939

Quali dosaggi?

- La dose iniziale giornaliera raccomandata di empaglifozin è di 10 mg, da assumere per via orale una volta al giorno.
- Nei pazienti con filtrato glomerulare >60ml/min che necessitano di un maggiore compenso glicemico è possibile aumentare la dose a 25 mg una volta al giorno. Se empagliflozin è usato con una sulfanilurea o con l'insulina andrebbe considerata la riduzione della dose di questi per ridurre ridurre il rischio di ipoglicemia.
- L'empagliflozin può essere assunto una volta al giorno indipendentemente dai pasti in ogni momento della giornata. Le compresse vanno deglutite intere.
- E'utile misurare la glicemia, sia 2 ore dopo i pasti principali, sia al risveglio
- **Interagisce negativamente con altri farmaci?**
  L'empagliflozin può aumentare l'effetto dei diuretici. Non sono state segnalate interazioni importanti con altri farmaci

EFFETTI INDESIDERATI

- **Ipoglicemie?**

- Da solo l'empagliflozin non provoca ipoglicemie. L'ipoglicemia si può verificare se se empagliflozin è somministrato insieme a sulfaniluree o insulina, che sono responsabili della ipoglicemia
- **Non sono stati osservati effetti collaterali gravi.**
- L'aumentata concentrazione di glucosio nelle urine per effetto dell'empagliflozin, può aumentare il rischio di infezione delle basse vie urinarie e genitali, in particolare nel sesso femminile. Nella maggior parte dei casi le infezioni sono state da lievi a moderate, e sono regredite dopo specifica ed appropriata terapia antibiotica.
- Il numero complessivo degli eventi avversi nelle persone trattate con empagliflozin è stato basso negli studi clinici fino ad ora effettuati.
- Gli effetti indesiderati descritti, oltre a quelli già citati, sono stati prurito generalizzato e minzione aumentata.
- Per i pazienti che assumono empagliflozin, in caso di patologie e condizioni intercorrenti che possano portare a perdita di liquidi, sono raccomandati il controllo della pressione sanguigna e degli esami di laboratorio e la temporanea interruzione del trattamento finché la perdita di liquidi non viene corretta.