

2023

SID
Società Italiana
di Diabetologia

AMD
Associazione
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ASSISI (PG)
15/17
GIUGNO 2023
Grand Hotel Assisi

**Congresso
Nazionale
PIEDE DIABETICO
GDS SID-AMD**

La **S**indrome
del **piede diabetico**:
competenze
in azione
con uno sguardo
al futuro



SGLT2-I e GLP1-RAs nella sindrome da piede diabetico: «unmet needs» nel continuum cardio-metabolico?

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Disclosures

Il sottoscritto Dr. Giuseppe Murdolo dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da parte di Aziende Farmaceutiche e/o Diagnostiche:

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.).

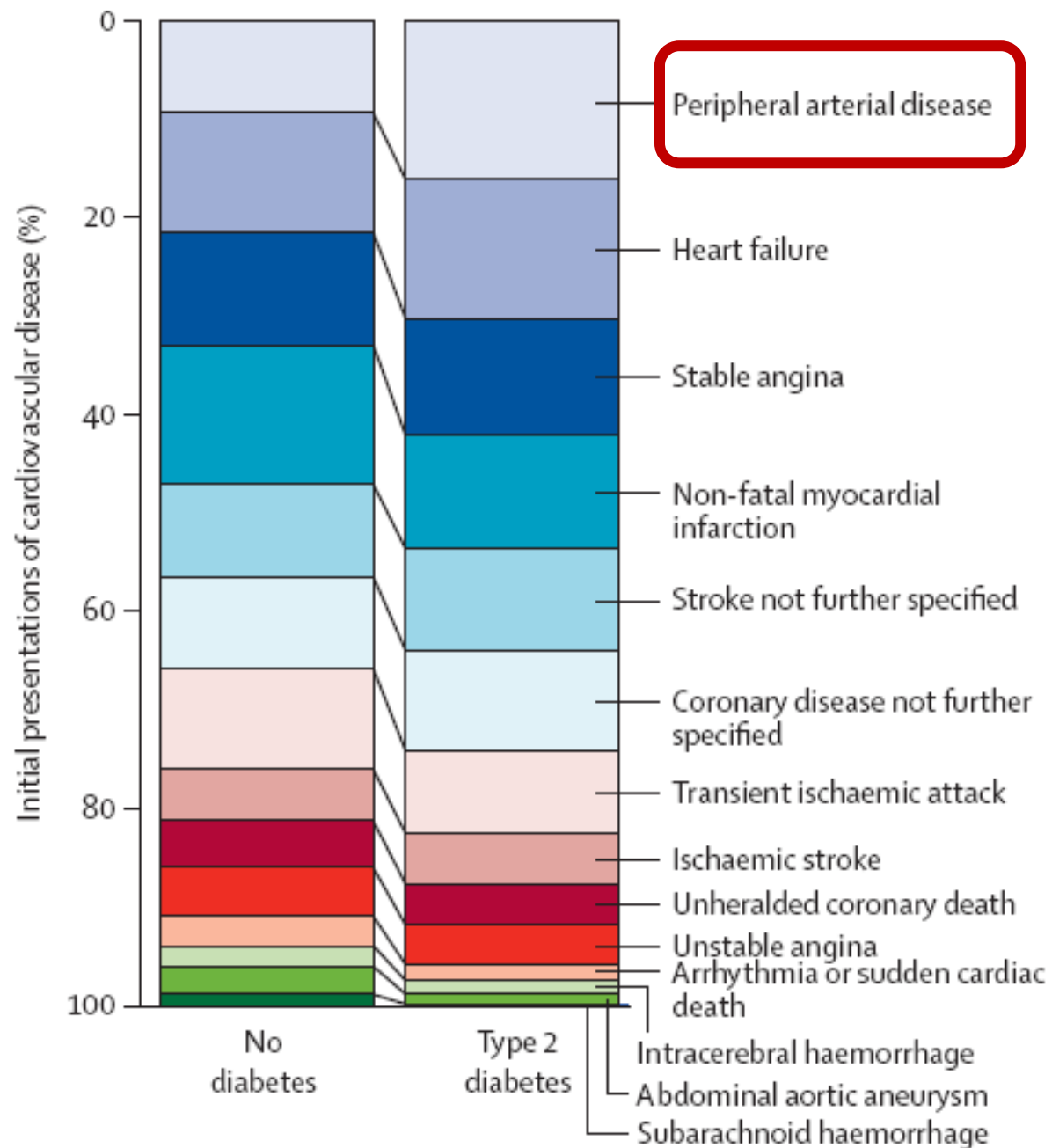
AGENDA

- 📊 S. piede diabetico «vascolare» e continuum cardio-renale:
 - 📊 *“La messe è tanta ... ma gli operai sono pochi”;*
 - 📊 *Arteriopatia Periferica (PAD) manifestazione d’esordio ed amplificatore del rischio cardio-renale;*
- 📊 SLGT2-Is e/o GLP1-RAs nella protezione cardio-renale e nella prevenzione degli eventi avversi maggiori arti inferiori (MALE):
 - 📊 *Risultati dei CVOTs;*
 - 📊 *Unmet needs: SGLT2-I in settings “acuti” o “sub-acuti”?*
 - 📊 *Real-world evidence*

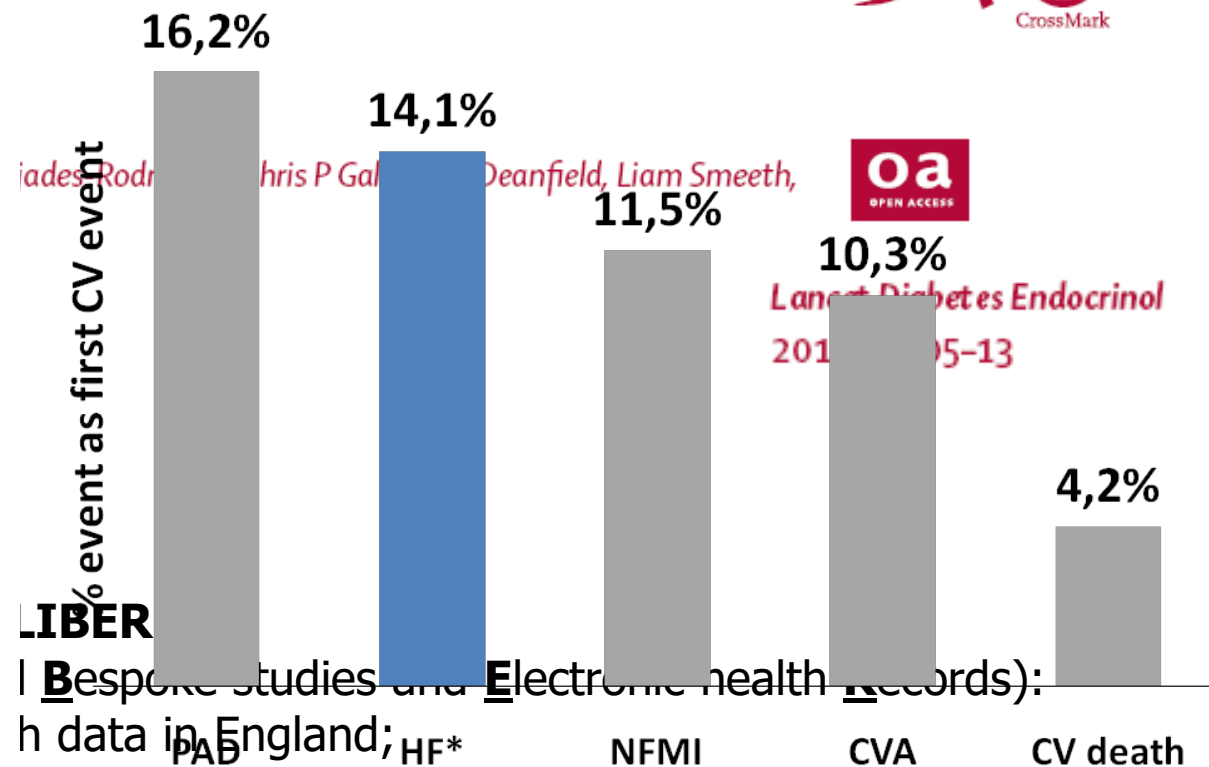
- 
- A satellite map of Italy and the surrounding Mediterranean Sea, serving as a background for the text.
- 60 M di abitanti
 - 3,5 M di persone diabetiche (6,5%)
 - 300.000 *pts con sindrome da piede diabetico*
 - 7.000 *amputazioni*
 - 3.382 *sec PNE 2021*
 - 0.07/1000/anno

Quality of Diabetes Care Indicators





Cardiovascular diseases:



LIBRA

Libra (Bespoke studies and Electronic health records):

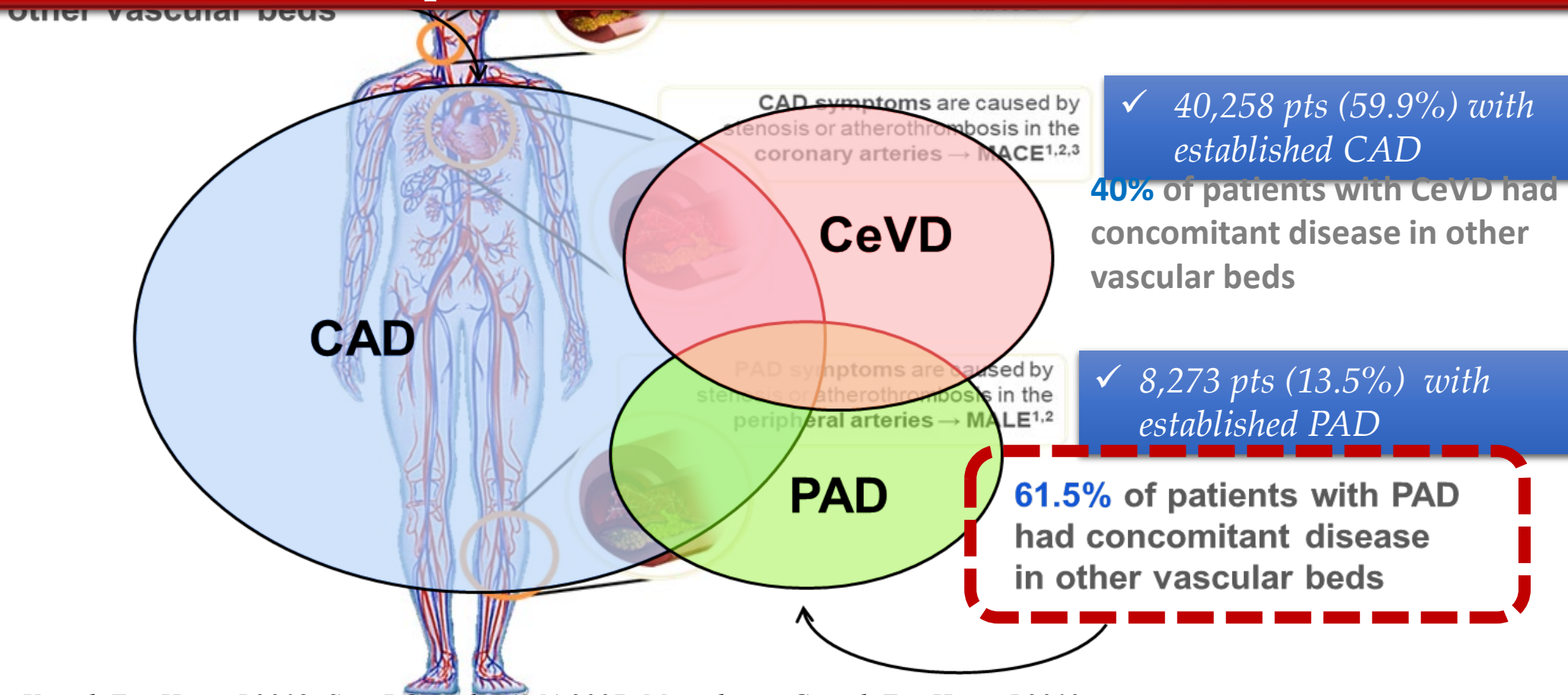
h data in England;

*Heart failure post MI was not included in this definition of HF

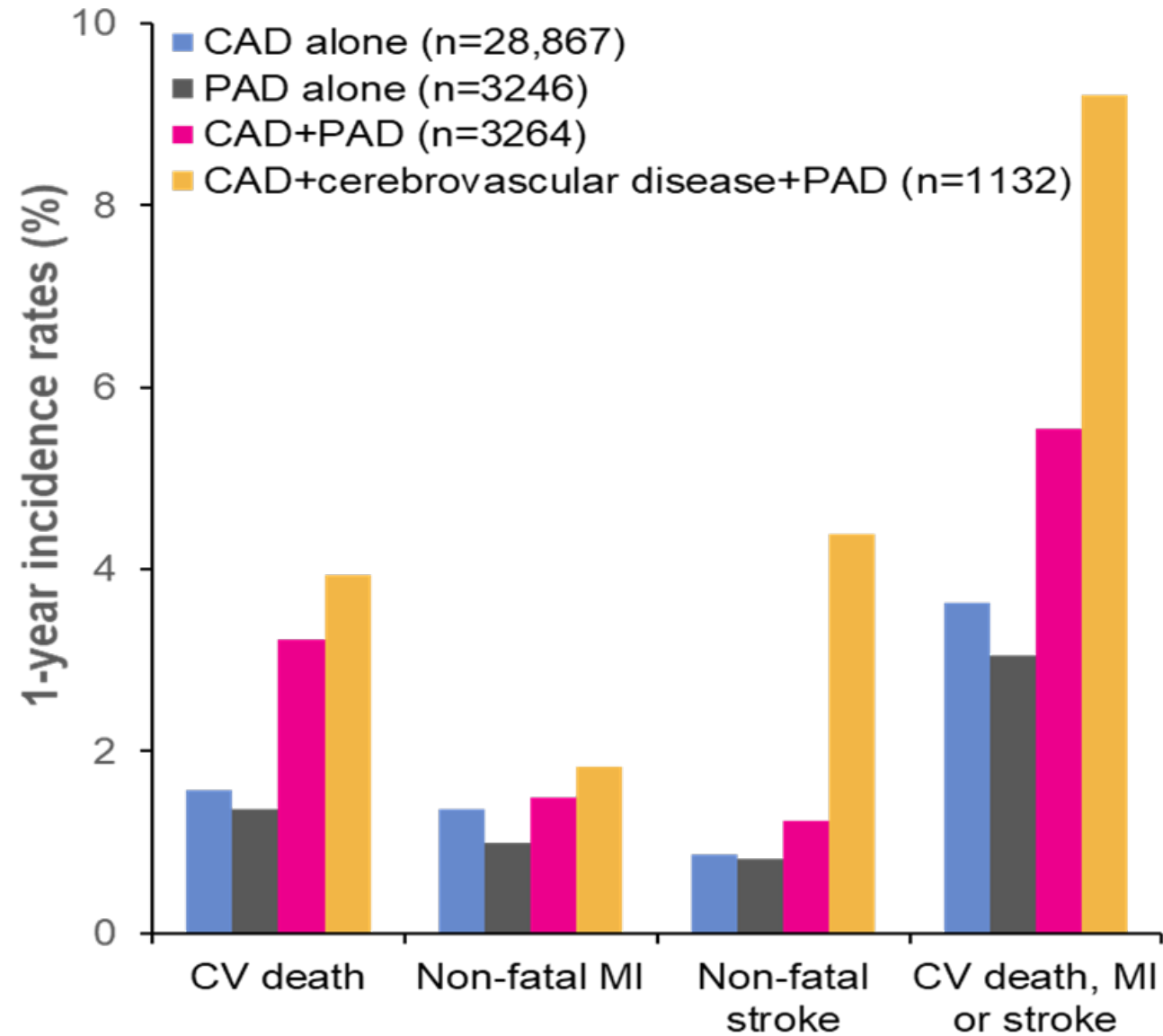
921,260 individuals;
113,638 CV events
Follow-up 5.5 yrs)

Atherothrombosis Is a Polyvascular Disease: substantial overlap between PAD, CAD and CeVD

REACH (Reduction of Atherothrombosis for Continued Health)
68,236 pts from 44 countries (40% with Diabetes)

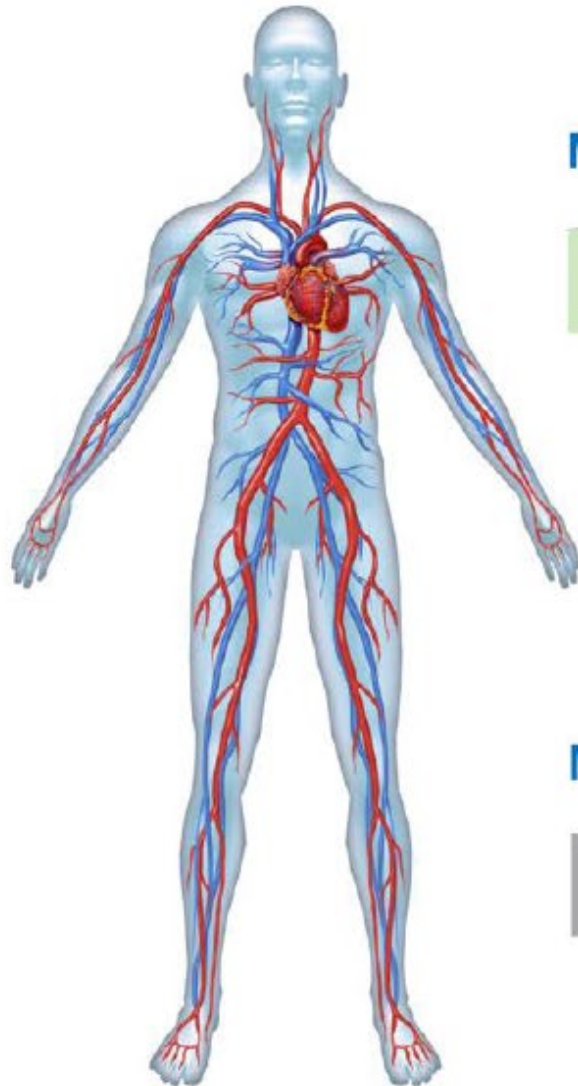


1-YEAR OUTCOMES IN PATIENTS WITH ATHEROSCLEROTIC DISEASE²

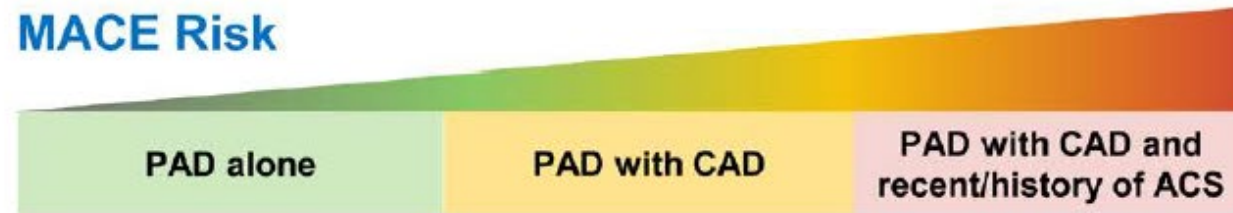


Spectrums of ischemic risk in PAD:

T2D underlies a «malignant» athero-thrombo-embolic phenotype

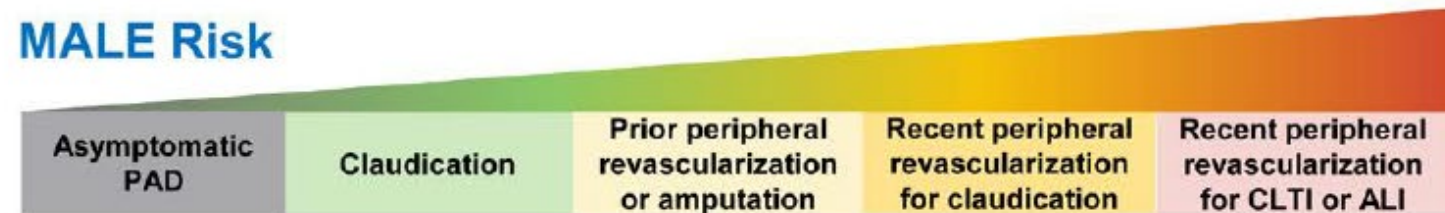


MACE Risk



PAD is associated with significant morbidity and mortality from both **cardiovascular** and **limb-related events**

MALE Risk



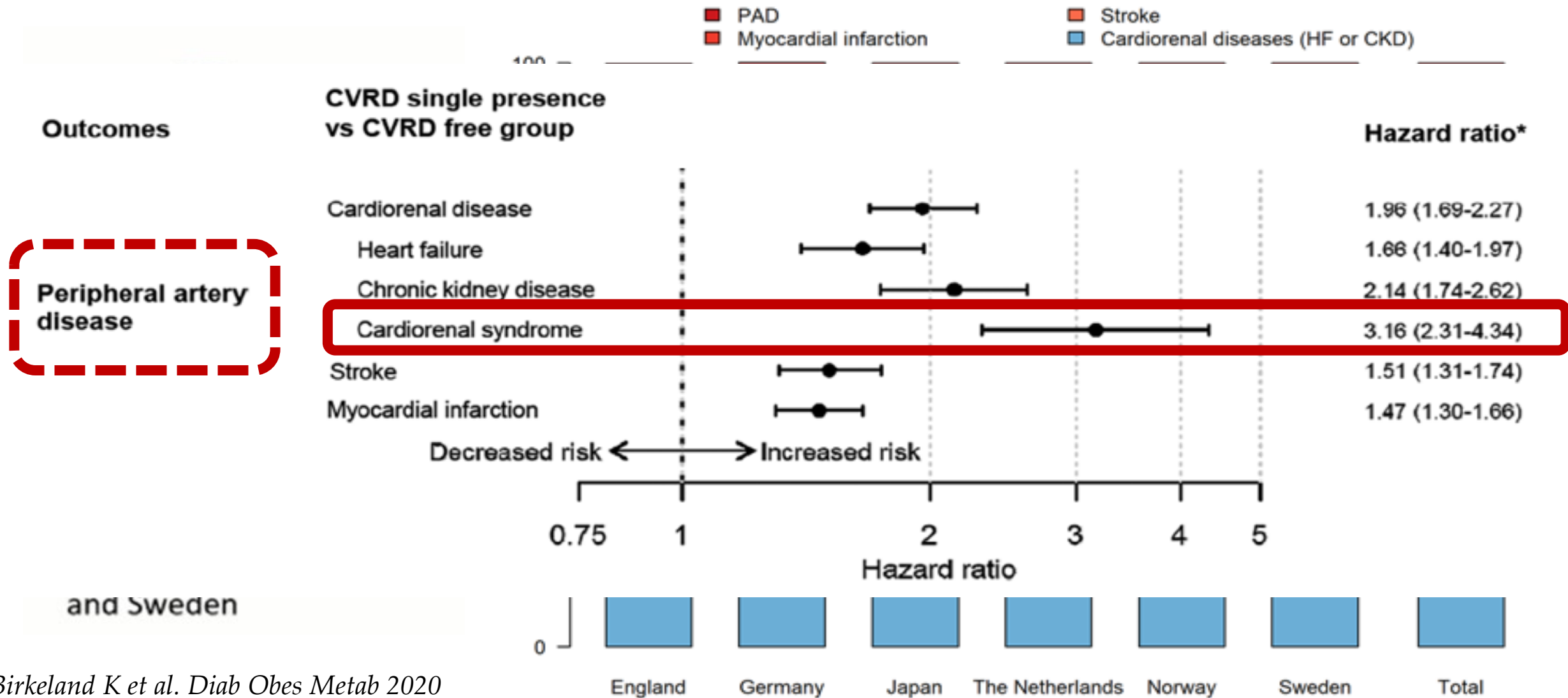
La Sindrome Cardiorenale:

complicanza frequente e potenzialmente fatale del T2D



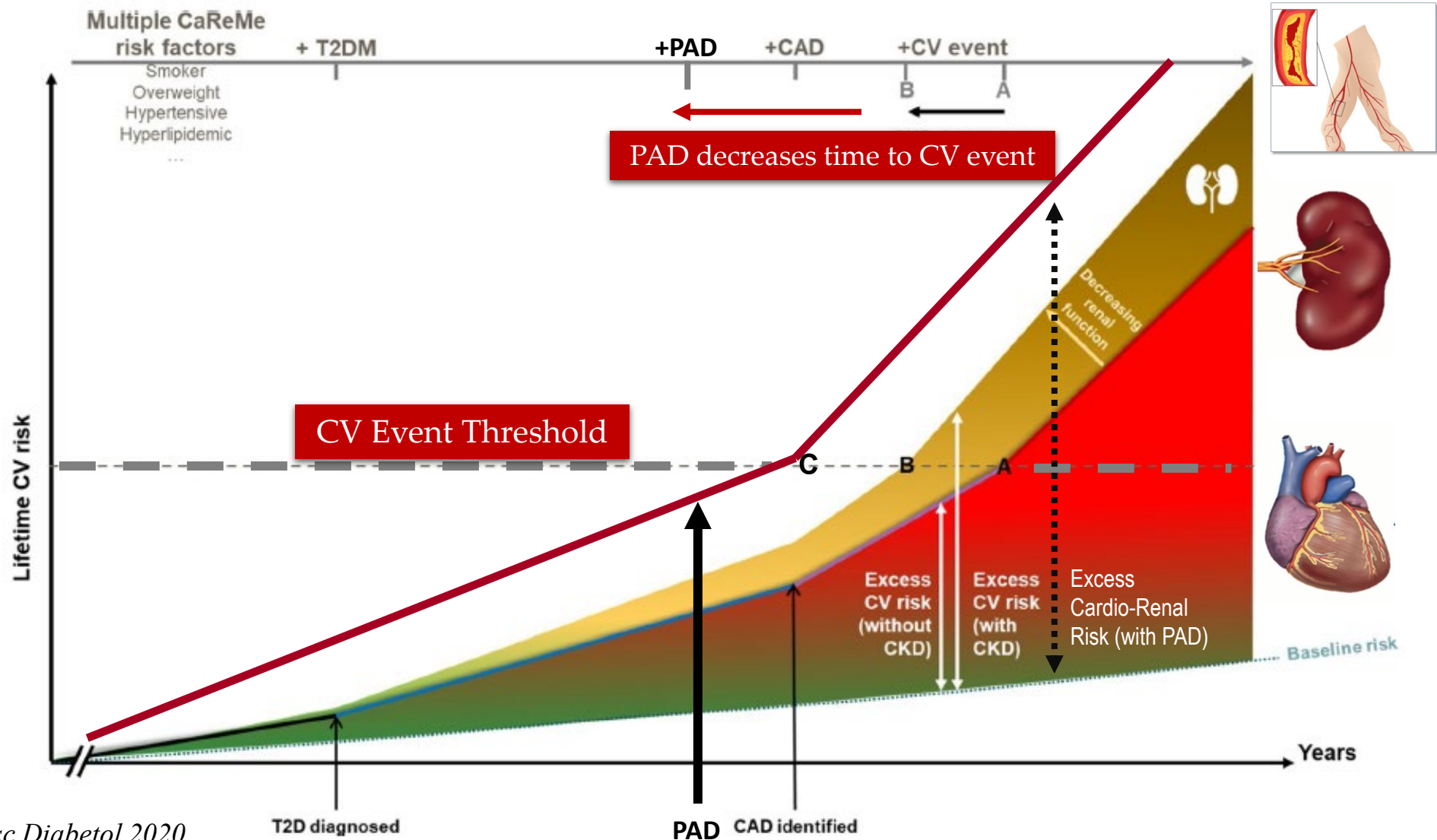
*Birkeland K, et al. Diabetes Obes Metab. 2020; Alciac RZ, et al. Clin J Am Soc Nephrol. 2017;
Rangaswami J, et al. Circulation. 2019; Ponikowski P, et al. Eur J Heart Fail. 2016; Webster AC, et al. Lancet 2017;*

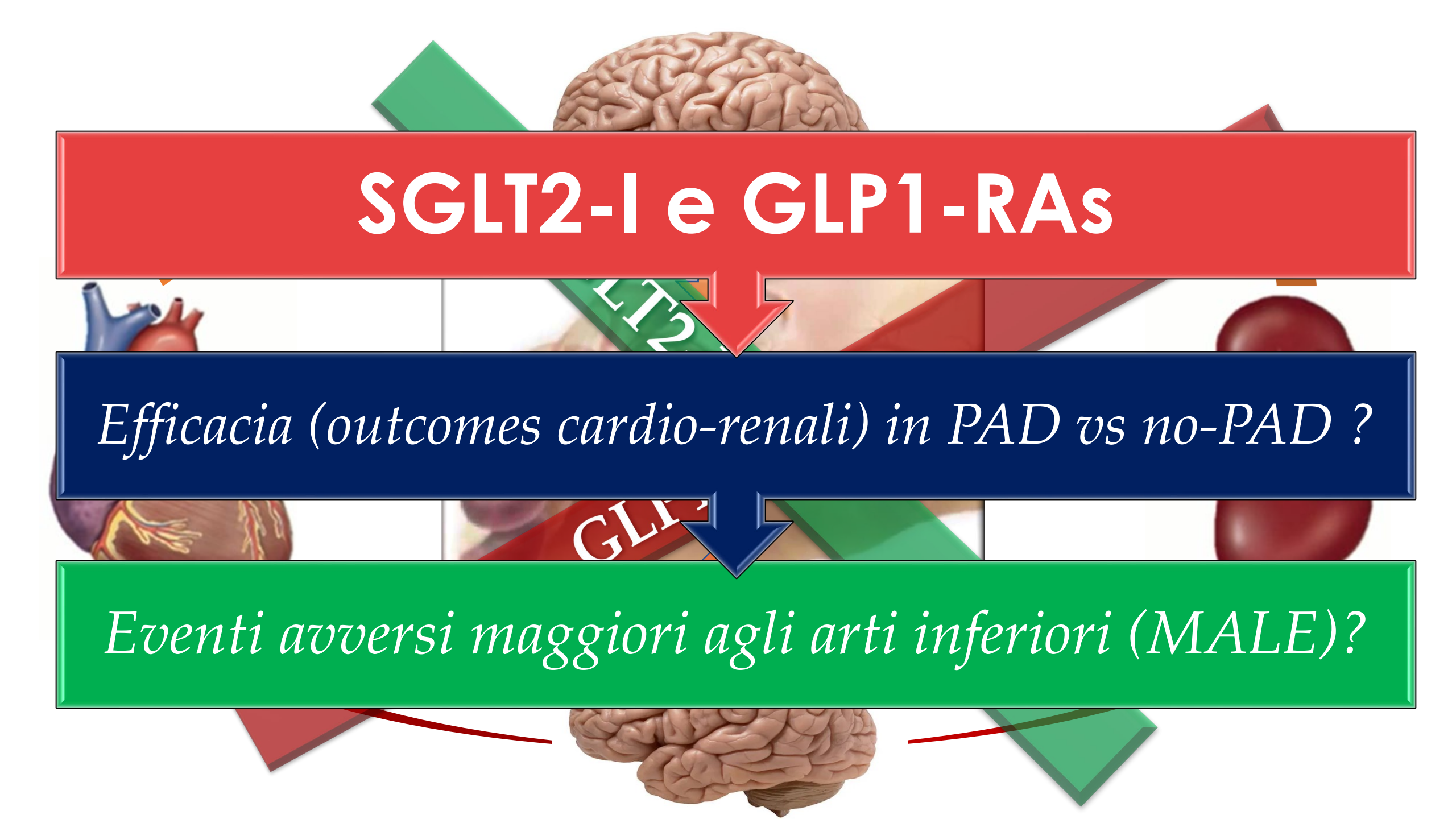
Cardiorenal Syndrome and PAD: the most frequent CVD manifestations in T2D



The cardio-renal metabolic continuum in T2D:

PAD as an «amplifier» of the CV risk at any stage



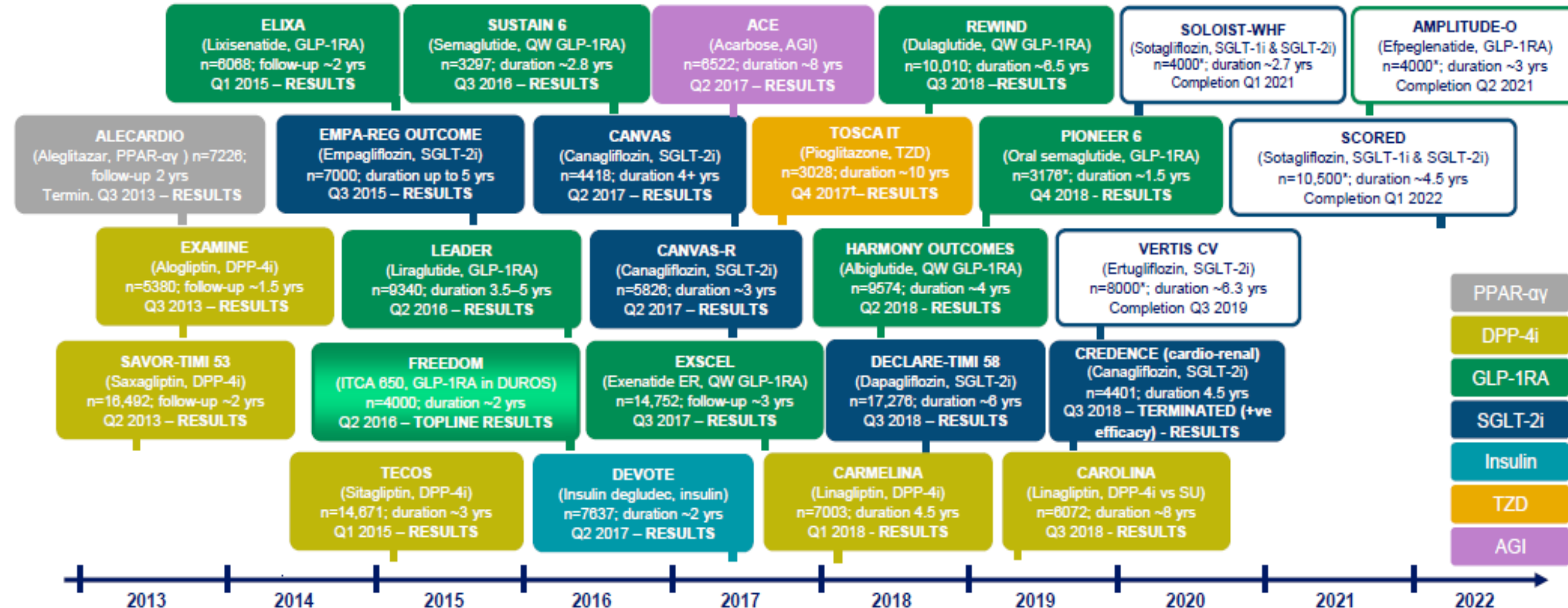


SGLT2-I e GLP1-RAs

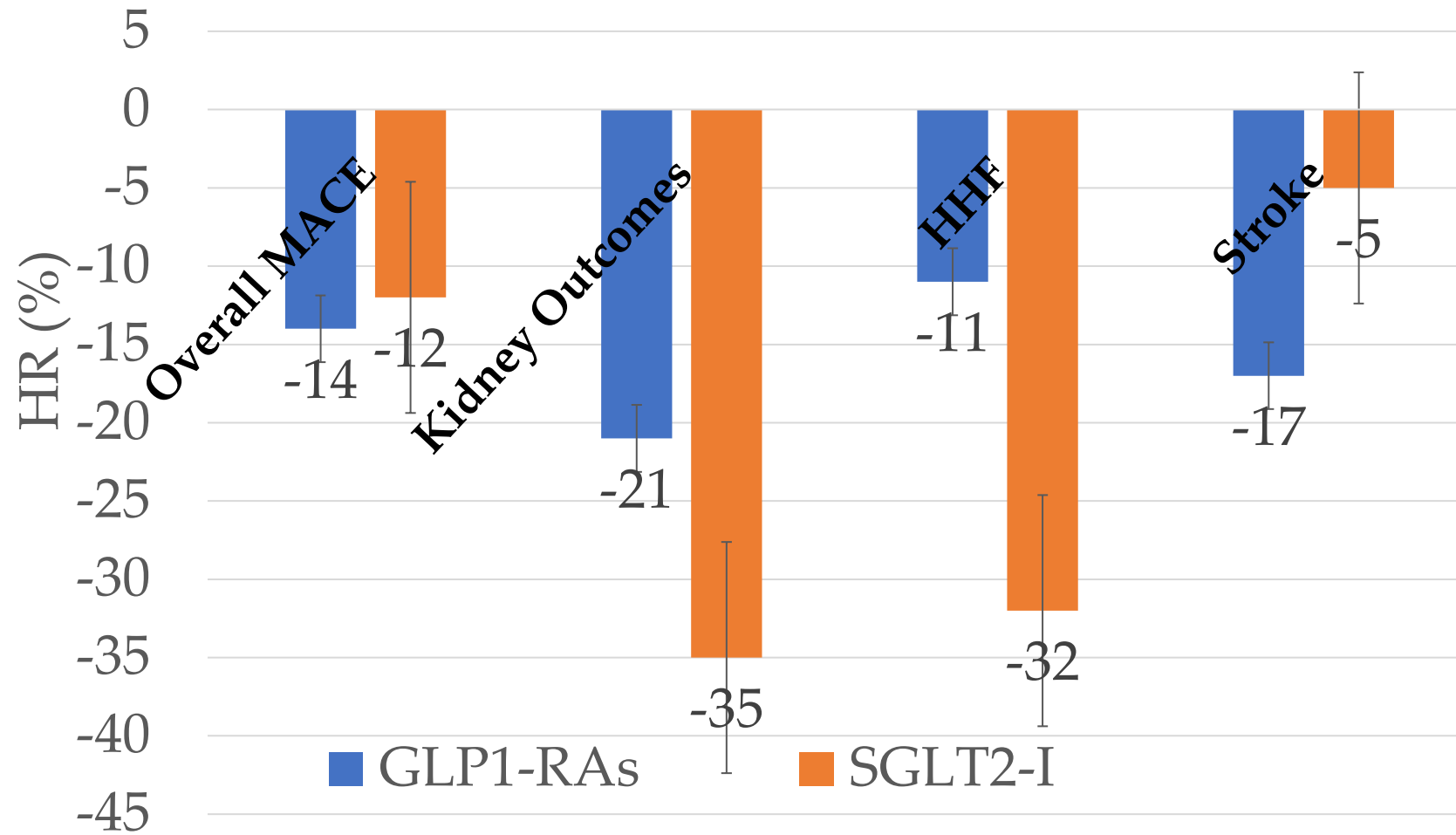
Efficacia (outcomes cardio-renali) in PAD vs no-PAD ?

Eventi avversi maggiori agli arti inferiori (MALE)?

A timeline of published diabetes CVOTs



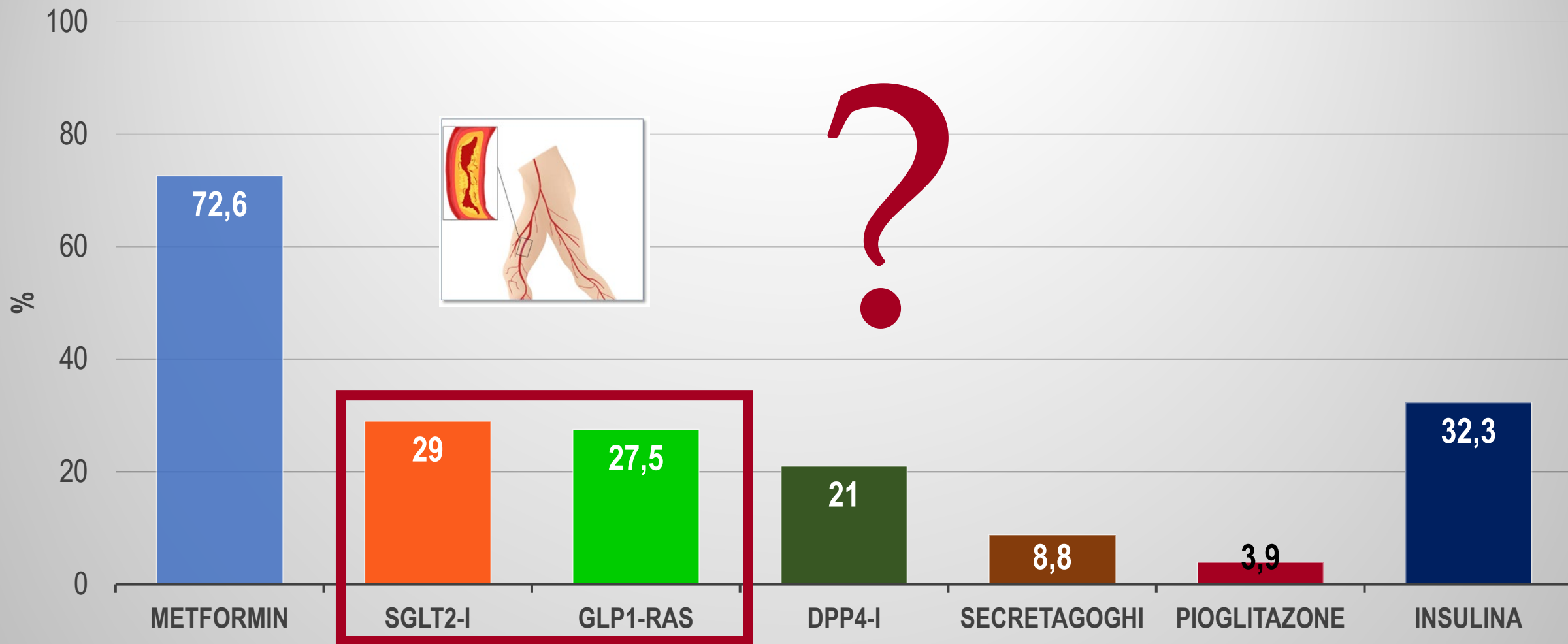
MACE and Cardio-Renal Outcomes with GLP1-RAs and SGLT2-I: *metanalyses of CVOTs*

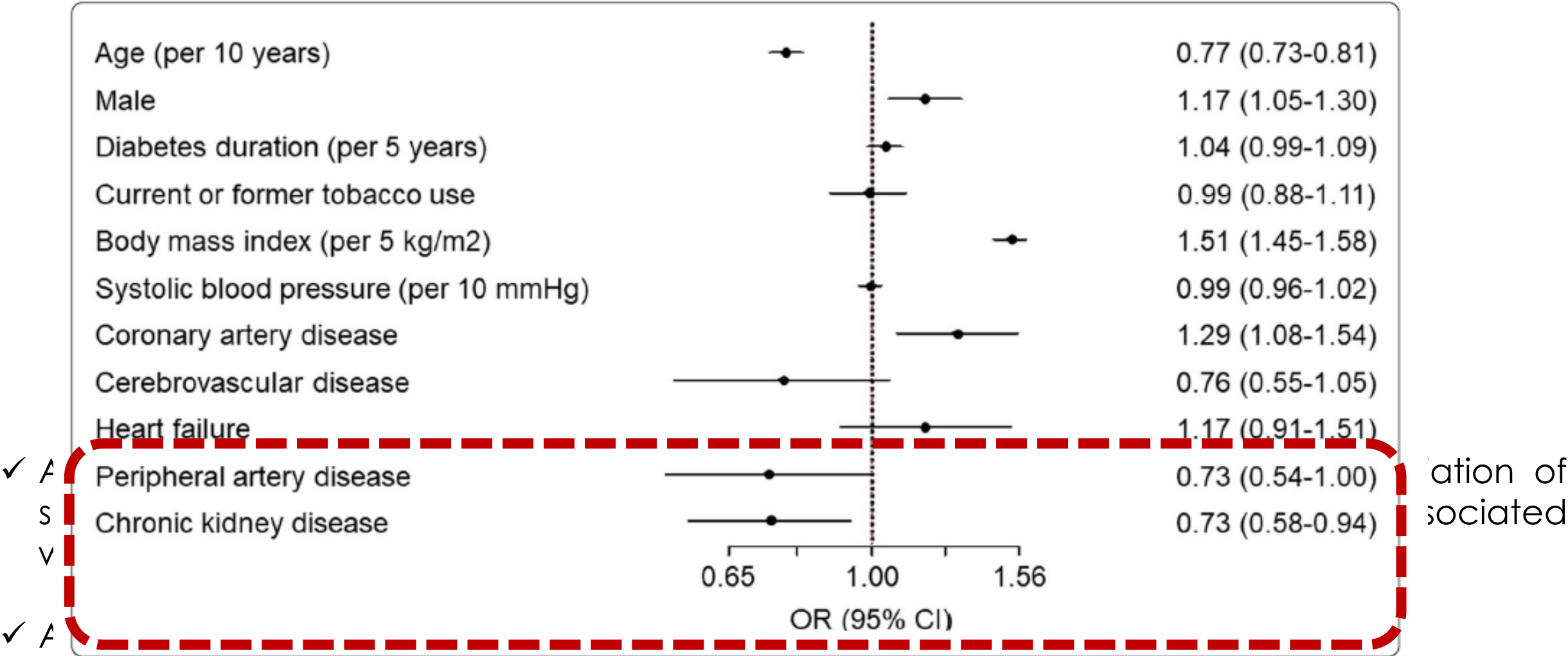


Sattar N. et al Lancet Diab Endocrinol 2021

Mc Guire D. et al JAMA Cardiol 2020

Prevalence of Use of Glucose-Lowering Drugs





- ✓ 10.6% were started on an SGLT2i or GLP-1RA at enrollment;
- ✓ over 3 yrs follow-up increasing to 16.1%

Guidelines on diagnosis, prognosis, and management of peripheral artery disease in patients with foot ulcers and diabetes (IWGDF 2019 update)

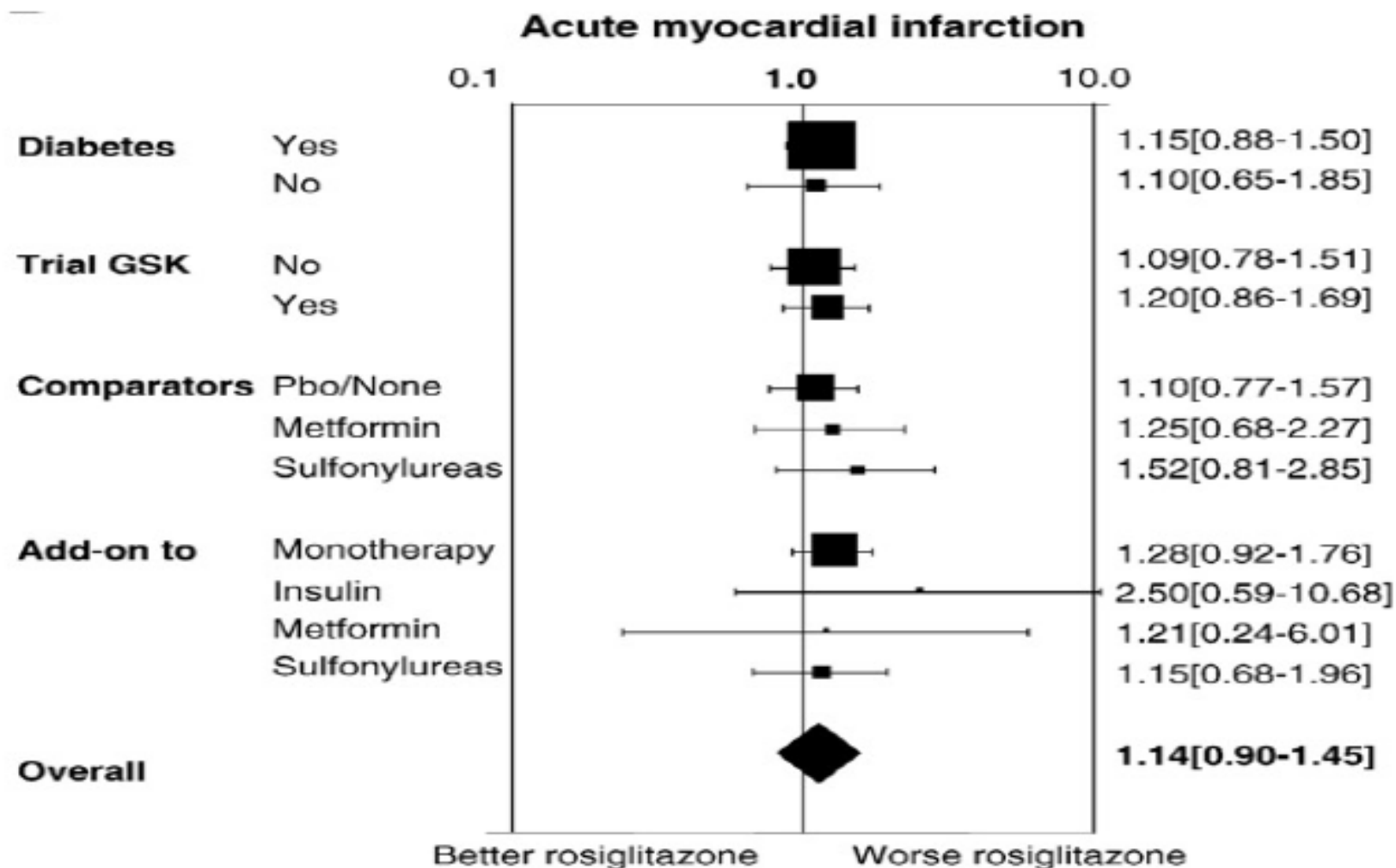
PICO: In patients with diabetes, foot ulceration and PAD, is it possible to reduce the risk of future cardiovascular events?

Recommendation 17: Provide intensive cardiovascular risk management for any patient with diabetes and an ischaemic foot ulcer, including support for cessation of smoking, treatment of hypertension, control of glycaemia and treatment with a statin drug as well as low-dose clopidogrel or aspirin. (Strong; Low)

Cardiac safety profile of rosiglitazone

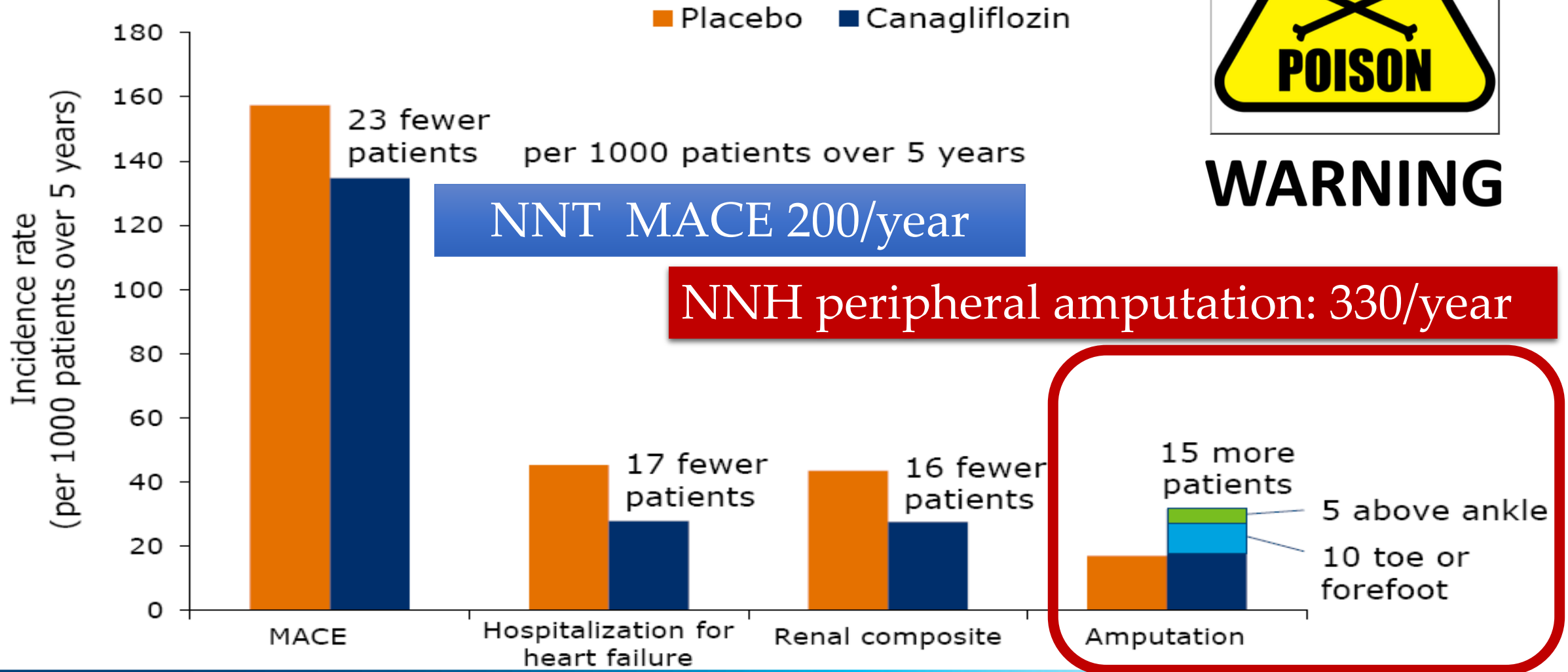
A comprehensive meta-analysis of randomized clinical trials

E. Mannucci et al. / International Journal of Cardiology 143 (2010) 135–140



Nissen's: 1.43

Benefits and risk

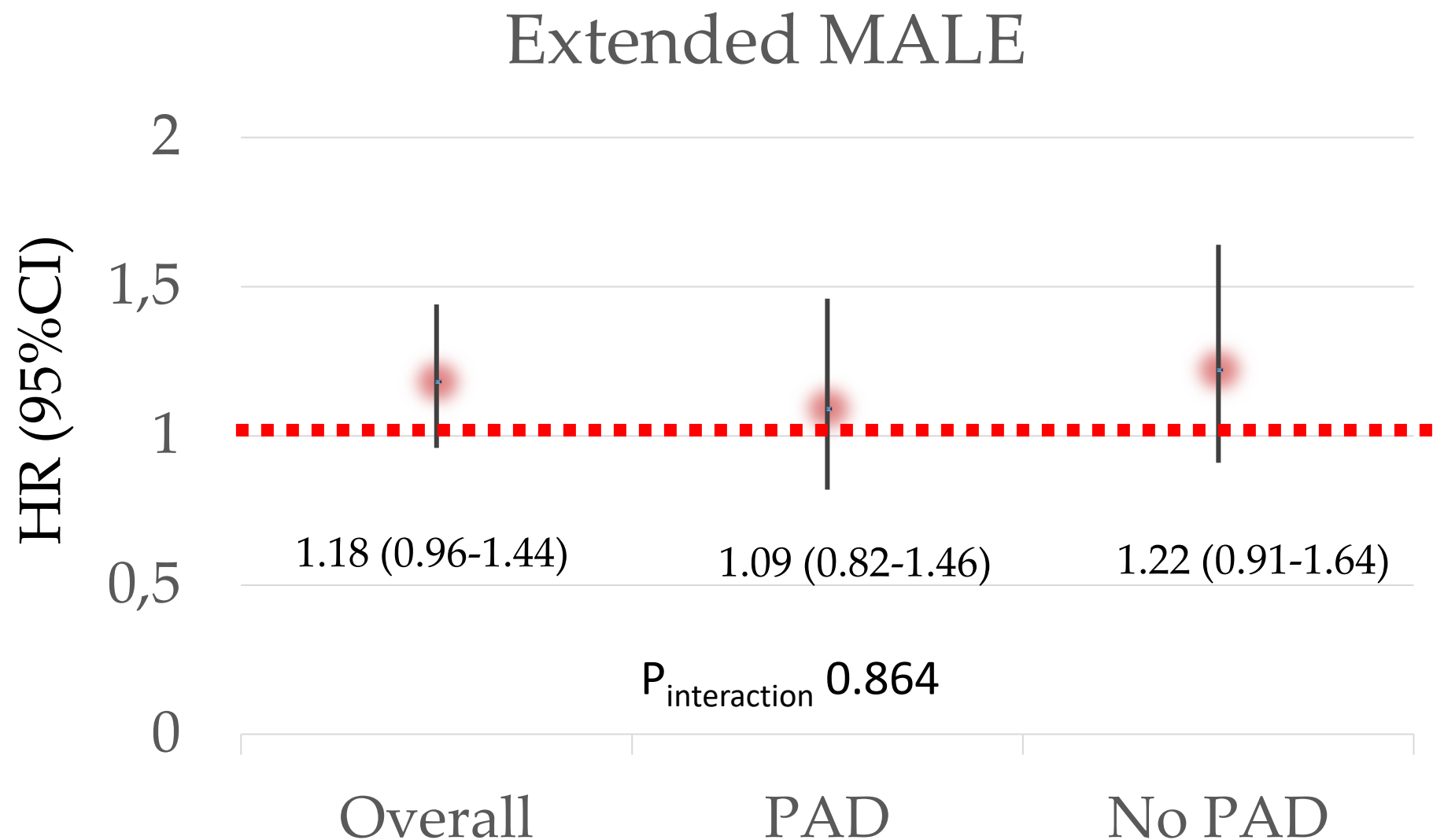


WARNING

ORIGINAL ARTICLE

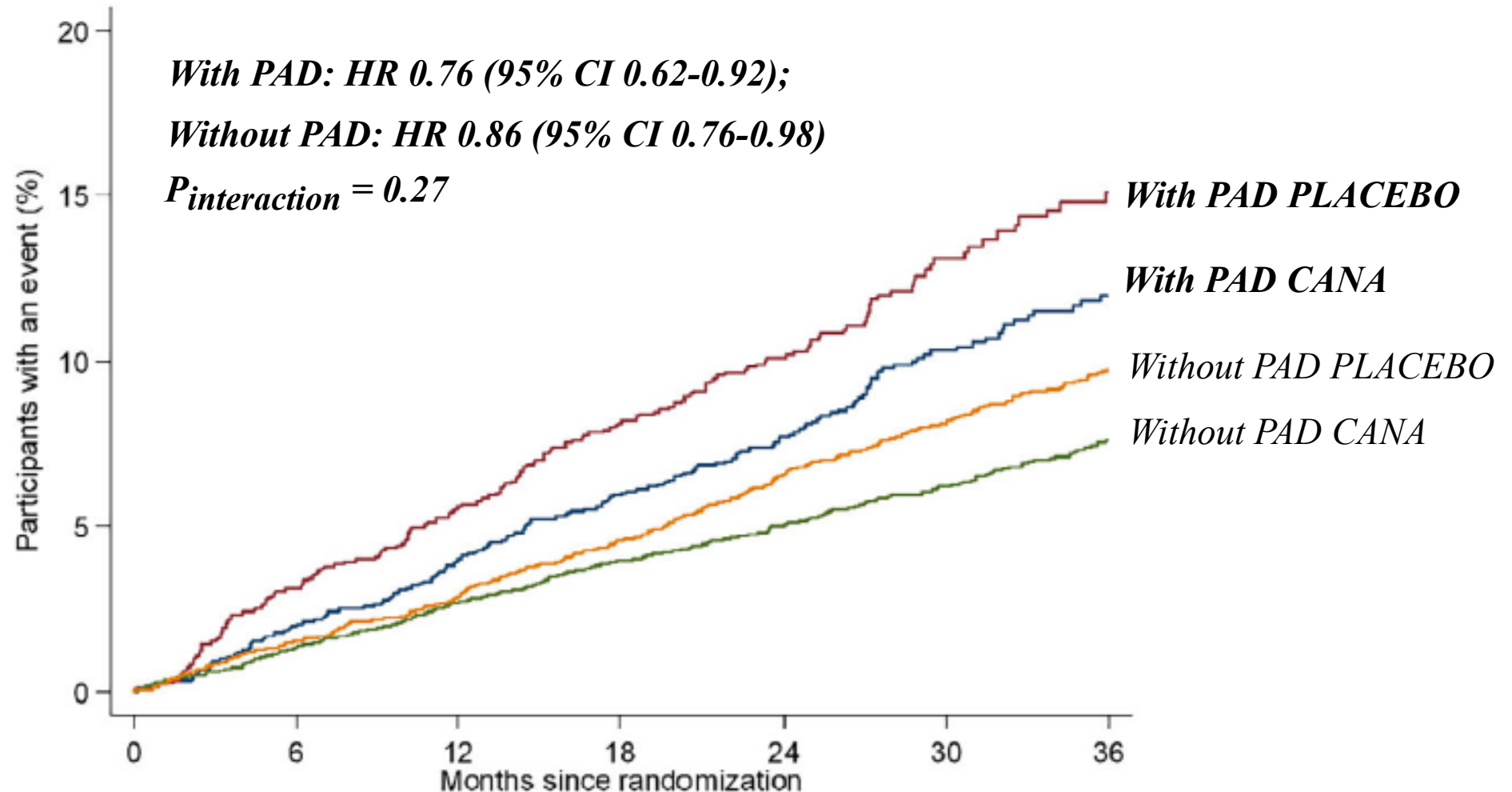
Cardiovascular and renal outcomes with canagliflozin in patients with peripheral arterial disease: Data from the CANVAS Program and CREDENCE trial

- ✓ *Post-hoc analysis of individual patient data from the CANVAS (n=10,142) and CREDENCE trial (n=4,401);*
- ✓ *Of 14,543 participants, 3,159 (21.7%) had PAD at baseline;*
- ✓ *Main outcomes: proportional and absolute benefits of canagliflozin in T2D pts with and without PAD:*
 - ✓ *MACE and Kidney outcomes;*
 - ✓ *Extended Major Adverse Limb Events (MALE)*



Extended MALE: **reported adverse events** because of PAD, peripheral artery occlusion, peripheral artery stenosis, peripheral ischaemia, peripheral vascular disorder, peripheral artery thrombosis, peripheral pulse decreased, peripheral restenosis and peripheral embolism or thrombosis.*

Rates of MACE in the pooled CANVAS Program and CREDENCE trial by PAD at baseline





FDA removes *Boxed Warning* about risk of leg and foot amputations for the diabetes medicine canagliflozin [REDACTED]

Based on our review of new clinical trial data

This information is an update to the [FDA Drug Safety Communication: FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin \[REDACTED\]](#) issued on May 16, 2017.

8-26-2020 FDA Drug Safety Communication

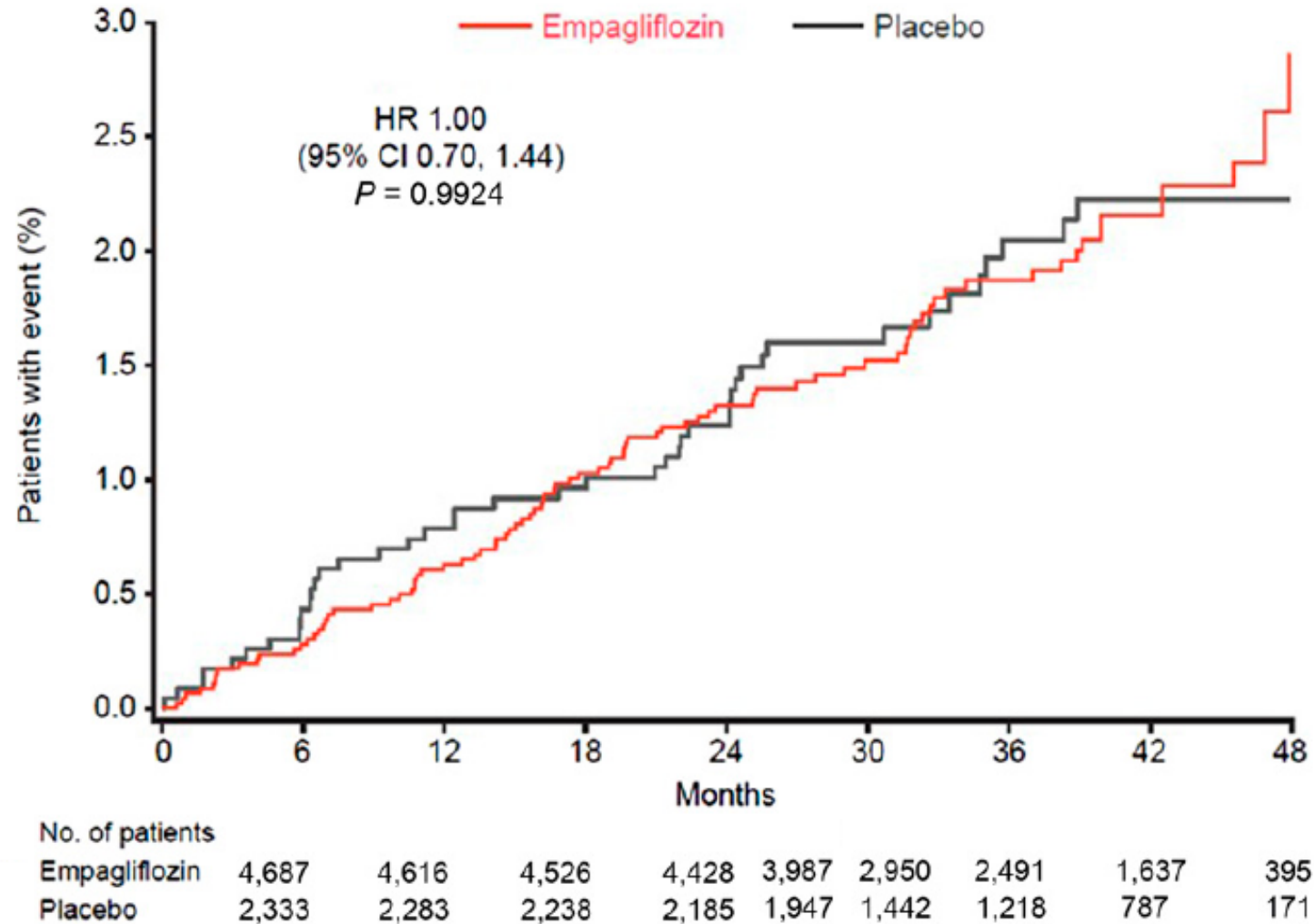
Based on a U.S. Food and Drug Administration (FDA) review of new data from three clinical trials, we have removed the *Boxed Warning* about amputation risk from the diabetes medicine canagliflozin [REDACTED] [prescribing information](#).

Time to first Lower Limb Amputation

Diabetes Care 2018;41:e4–e5



Empaglifloz
Lower-Limb
EMPA-REG



e 41, January 2018



to Iliev,²
rd Zinman³

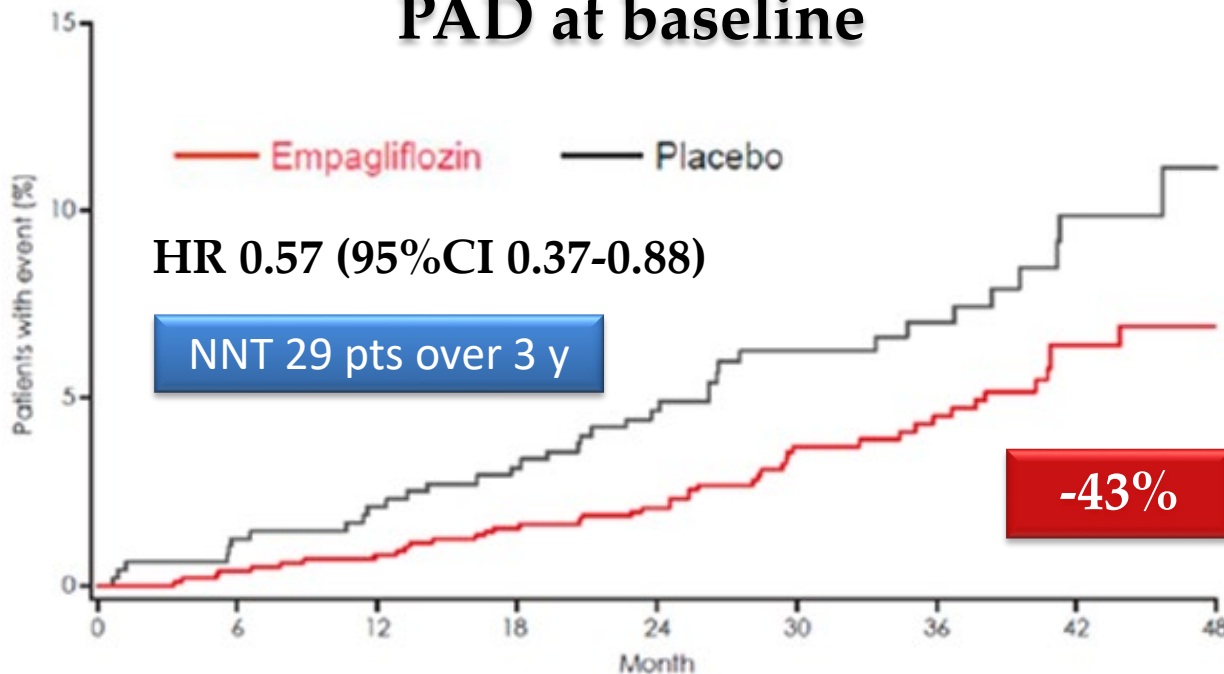
Cardiovascular outcomes, all-cause mortality, and incident or worsening nephropathy by PAD at baseline



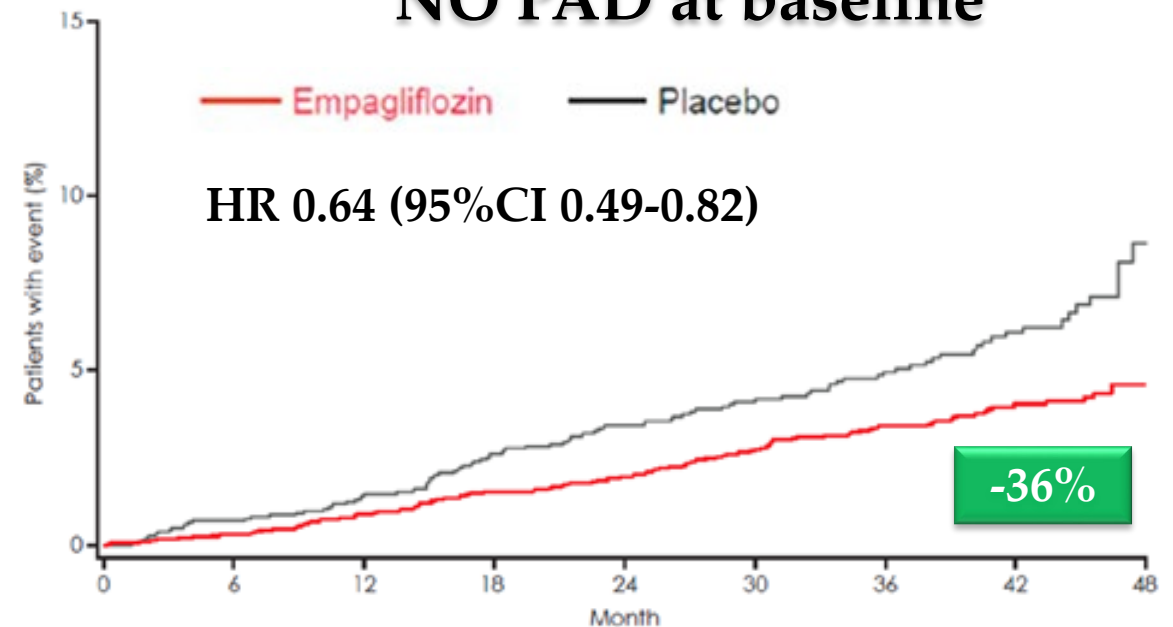
A sub-analysis of EMPAREG OUTCOME

- ✓ Of 7020 patients treated, 1461 (20.8%) *had PAD at baseline* (982 treated with EMPA, 479 treated with placebo).

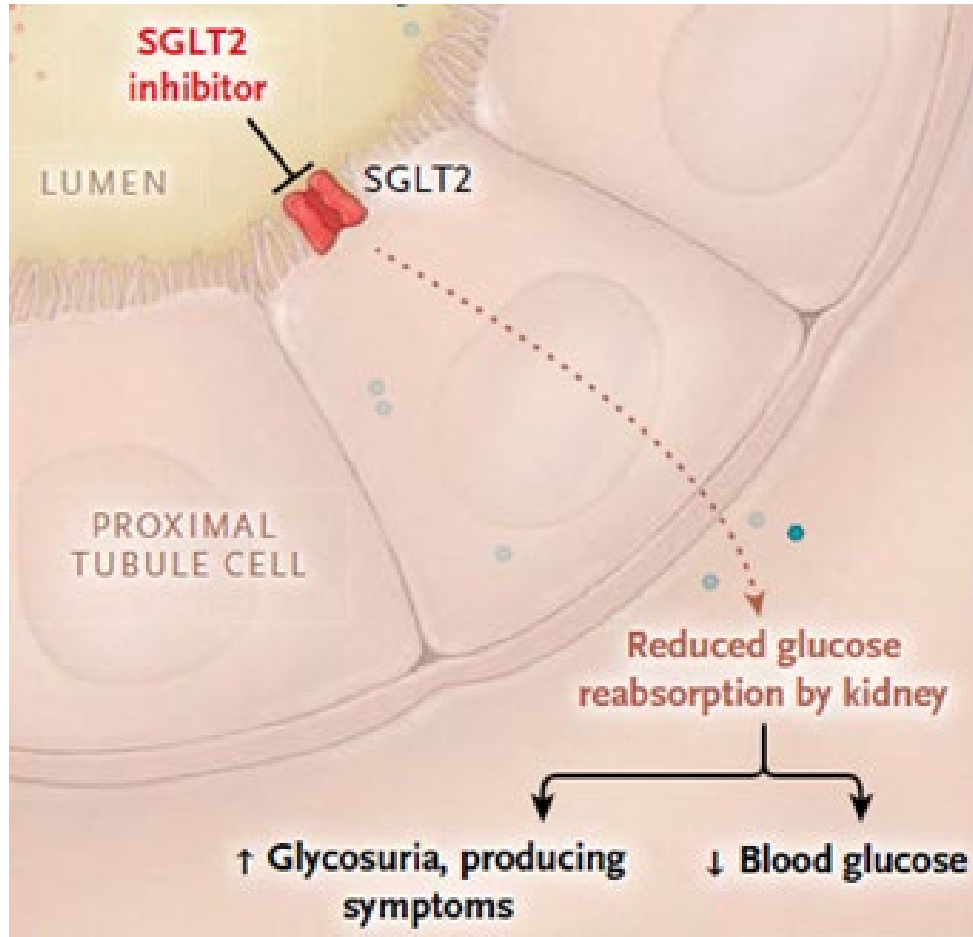
PAD at baseline



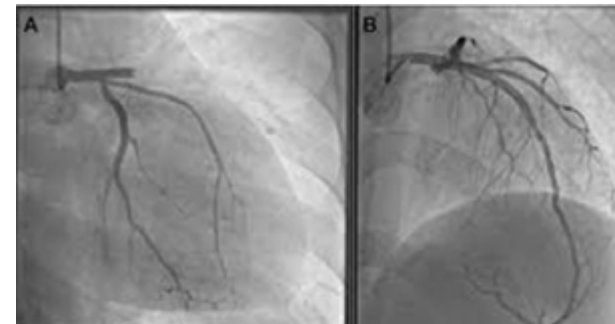
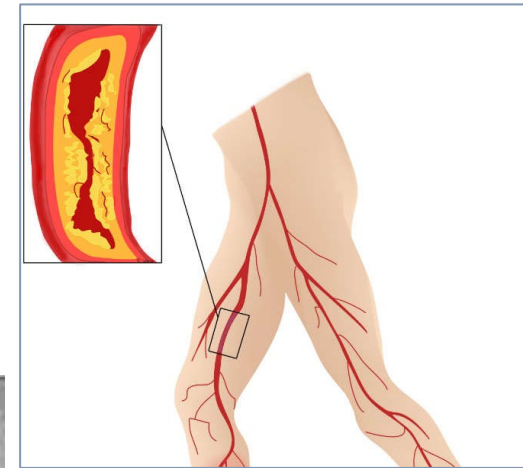
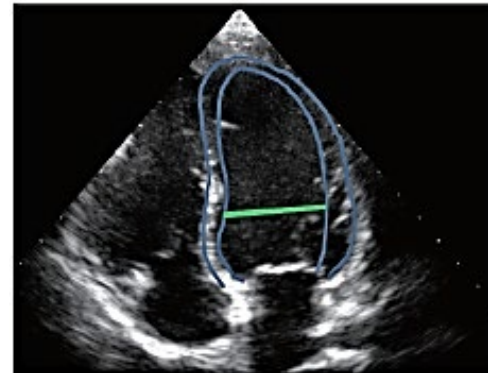
NO PAD at baseline



SGLT2-I in (sub)acute and post-acute settings: *unmet needs?*



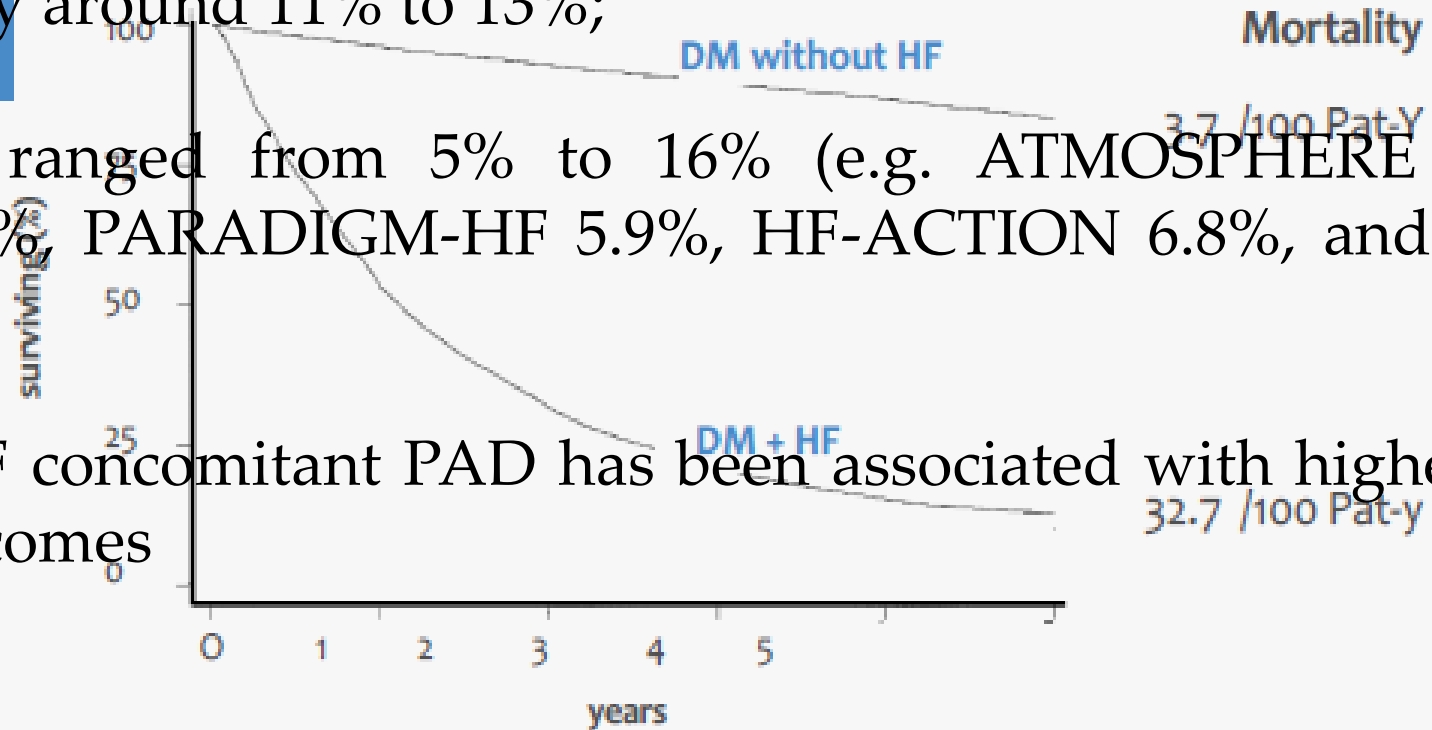
?



Heart failure and peripheral artery disease: a detrimental association

HF Predicts Higher Mortality in DM Patients

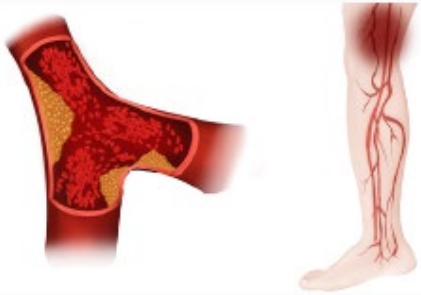
- ✓ The prevalence of clinically reported PAD among patients with HF in large registries is typically around 11% to 13%;
Population based study
Patients with DM: N=151,732
Age >65 years
- ✓ In prior trials, it ranged from 5% to 16% (e.g. ATMOSPHERE 5.1%, PARAGON-HF 5.4%, PARADIGM-HF 5.9%, HF-ACTION 6.8%, and BEST 16.4%);
- ✓ In patients with HF concomitant PAD has been associated with higher risk of poor clinical outcomes



Heart failure, peripheral artery disease, and amputation: a patient-level meta-analysis of DAPA-HF and DELIVER

11 005 patients in
DAPA-HF and DELIVER

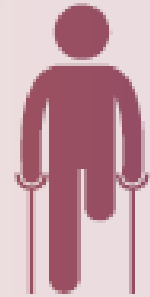
809 patients (7.4%) had a history of PAD
(LVEF $\leq 40\%$: 7.8%; LVEF $>40\%$: 7.0%)



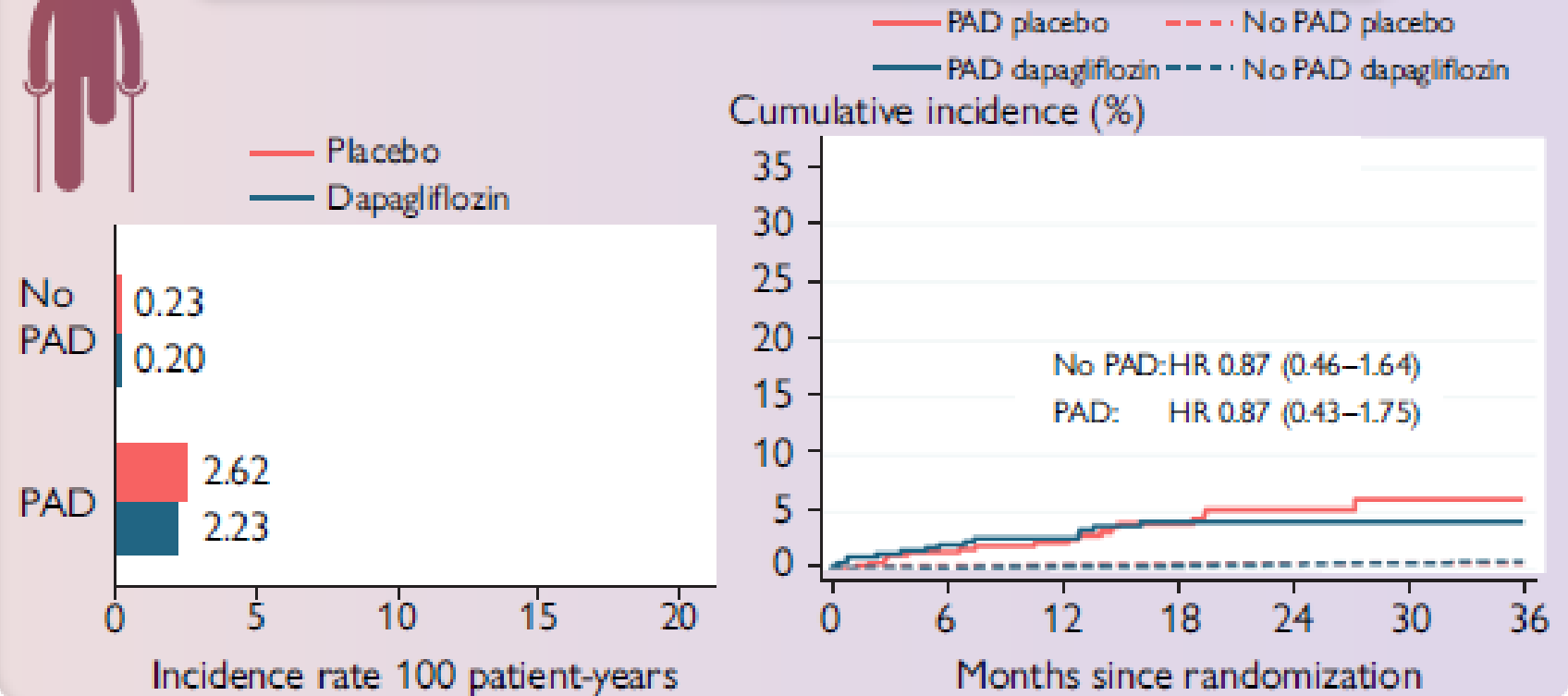
Characteristics of patients with
versus without PAD

↑ Male
↑ Smoker
↑ Hypertension
↑ Type 2 diabetes
↑ Atherosclerotic cardiovascular disease
↓ eGFR

Most measures of HF severity
not substantially worse



Amputation



✓ Because patients with PAD were at higher absolute risk, their absolute benefit was greater, reflected in a smaller NNT (17 in PAD vs. 24 in those without PAD)



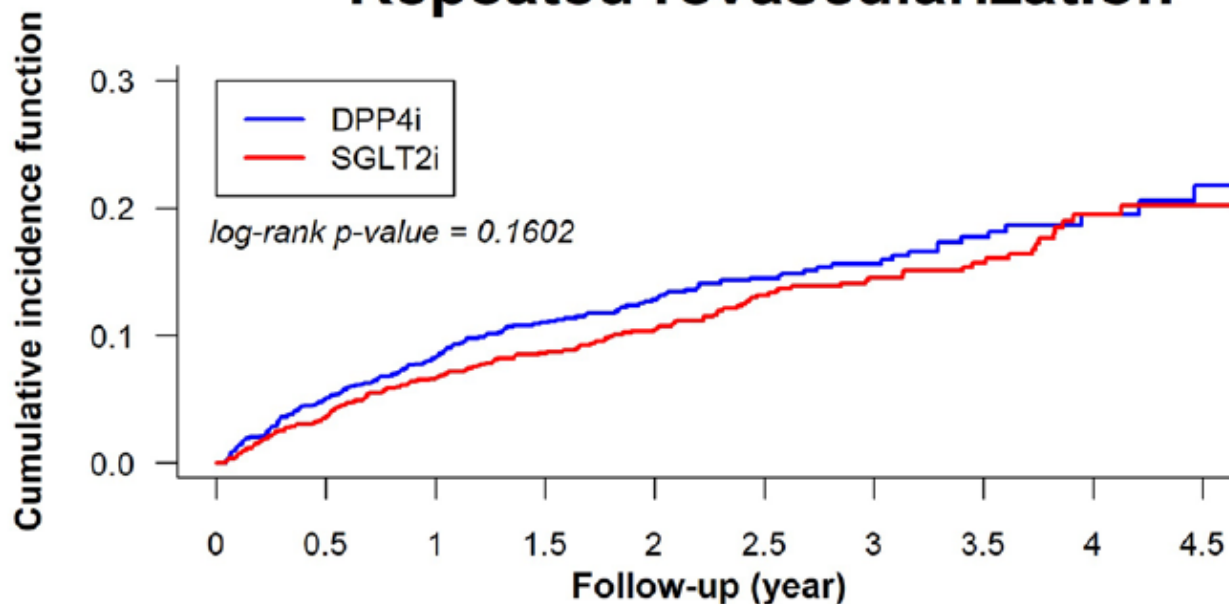
Adverse cardiovascular, limb, and renal outcomes in patients with diabetes after peripheral artery disease revascularization treated with sodium glucose cotransporter 2 inhibitors versus dipeptidyl peptidase-4 inhibitors

Lee et al. *Diabetology & Metabolic Syndrome* (2023) 15:8
<https://doi.org/10.1186/s13098-023-00982-6>

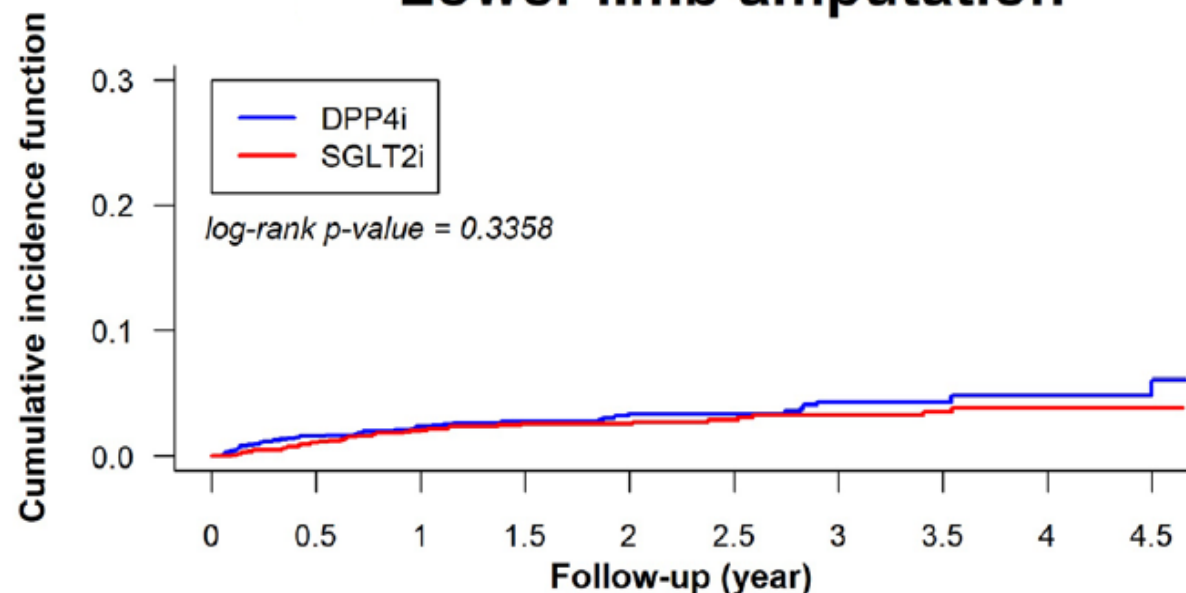
Hsin-Fu Lee^{1,2,3,4}, Chi Chuang^{1,2,3}, Pei-Ru Li⁵, Yung-Hsin Yeh^{2,3}, Yi-Hsin Chan^{2,3,6*} and Lai-Chu See^{5,7,8*}

- ✓ Nationwide retrospective cohort study (Taiwan National Health Insurance Research Database), of pts with T2D who had undergone PAD revascularization (43,568 pts) and received **first prescriptions for SGLT2i (2,455 pts) and DPP4i (8,695 pts)**, respectively;
- ✓ 1:1 propensity score matching (PSM) (1,598 SGLT2i matched with 1,598 DPP4i) to balance covariates between the two study groups;
- ✓ Aim: to compare cardiovascular, limb and renal outcomes after PAD revascularization treatment

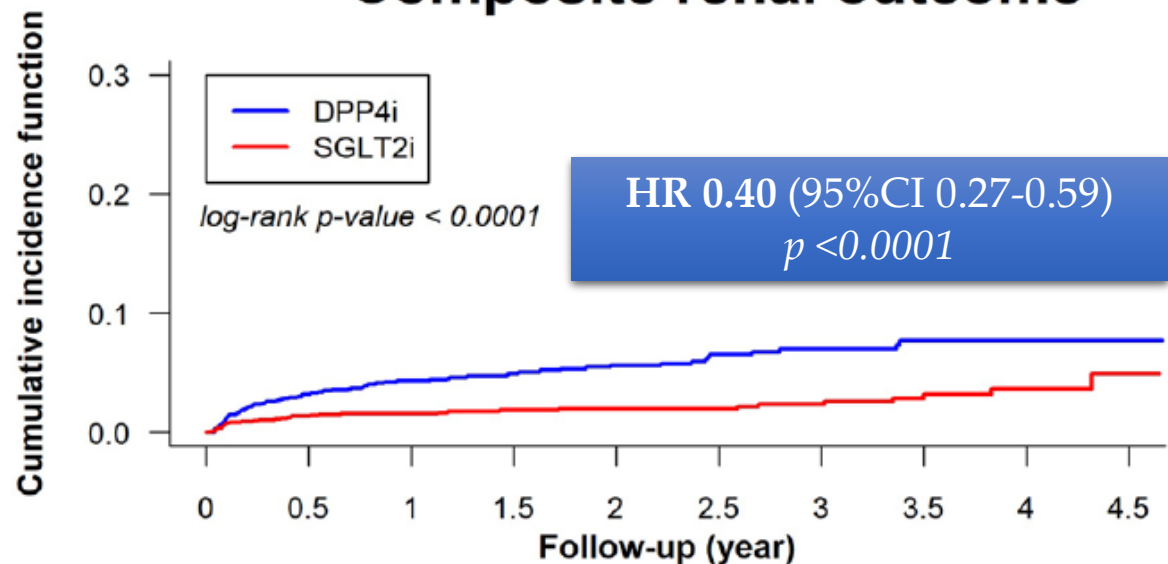
Repeated revascularization



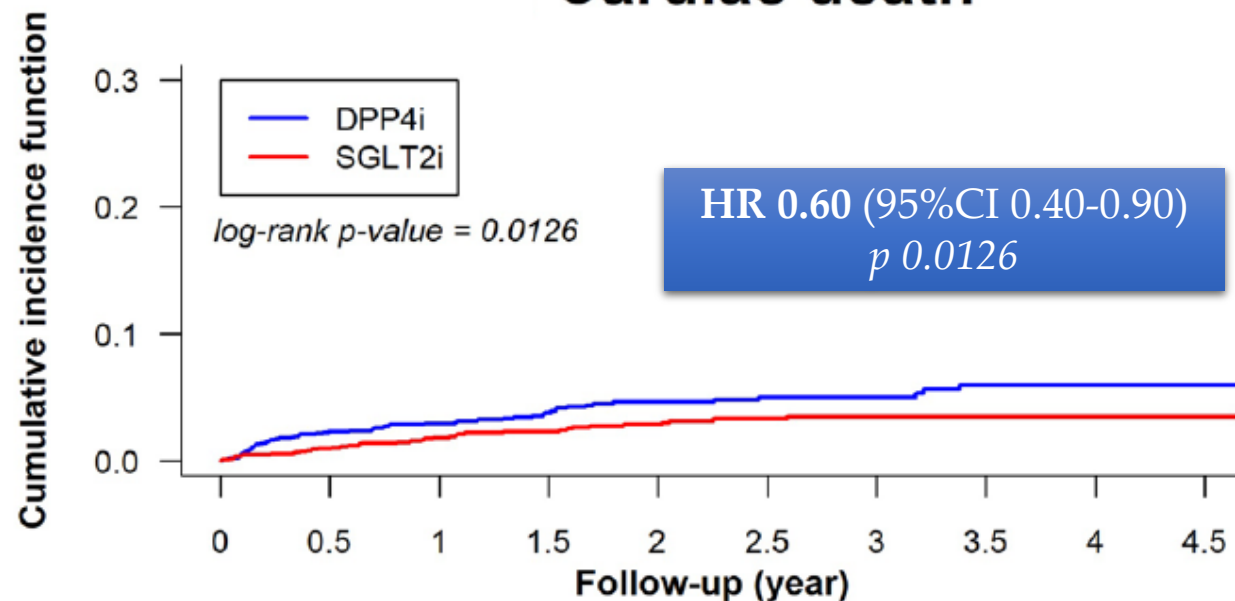
Lower limb amputation



Composite renal outcome



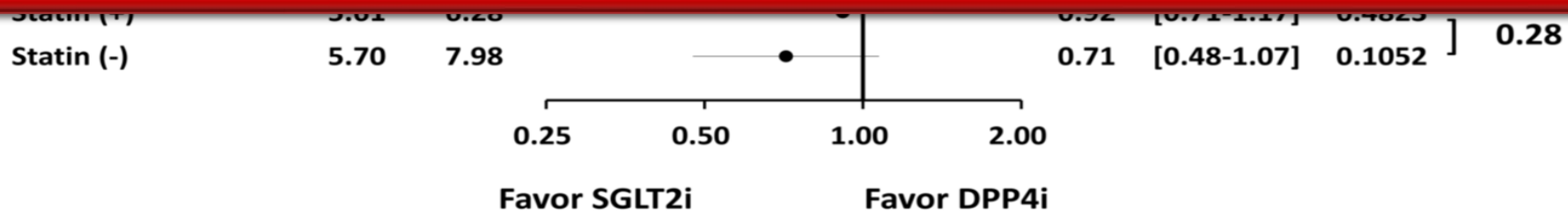
Cardiac death



Risk of repeated revascularization for SGLT2i vs DPP4i: subgroup analysis of patients with concomitant CKD

Repeated revascularization	Incidence rate (Per 100 PYs)		HR	95% CI	P value	P interaction
	SGLT2i	DPP4i				

In real-world setting, SGLT2i are “safe” glycemic control agents for pts with T2D and concomitant PAD, even after revascularization, and are associated with lower risk of cardio-renal outcomes when compared with DPP4i

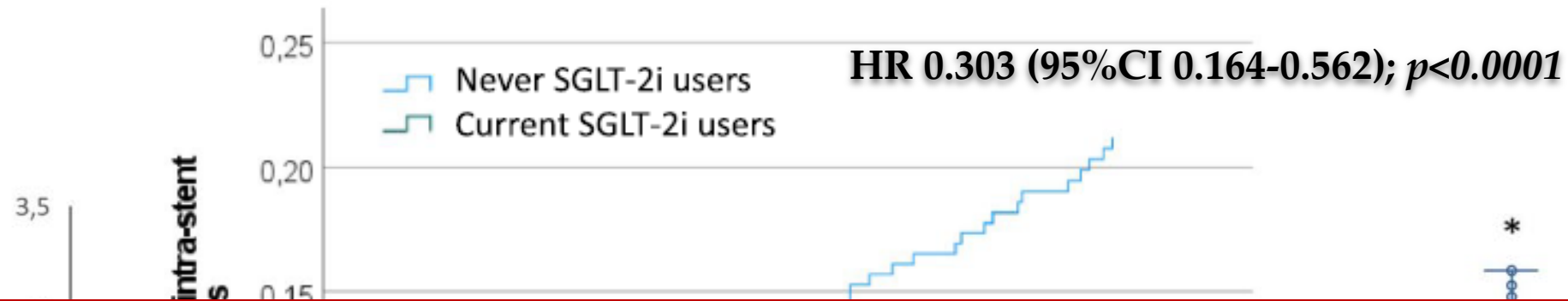




SGLT-2 inhibitors and in-stent restenosis-related events after acute myocardial infarction: an observational study in patients with type 2 diabetes

Raffaele Marfella^{1,2*†}, Celestino Sardu^{1†}, Nunzia D'Onofrio³, Carlo Fumagalli¹, Lucia Scisciola¹, Ferdinando Carlo Sasso¹, Mario Siniscalchi⁴, Ludovica Vittoria Marfella¹, Davide D'Andrea⁴, Fabio Minicucci⁴, Giuseppe Signoriello⁵, Arturo Cesaro⁶, Maria Consiglia Trotta⁷, Chiara Frigé⁸, Francesco Prattichizzo^{8*} , Maria Luisa Balestrieri³, Antonio Ceriello⁸, Paolo Calabrò⁶, Ciro Mauro⁴, Luca del Viscovo³ and Giuseppe Paolisso^{1,2}

- ✓ 377 patients with T2DM and AMI undergoing percutaneous coronary intervention (PCI);
- ✓ 200 pts “never SGT2i users” and 177 pts were “current SGLT2i users” before PCI;
- ✓ The primary outcome was MACE (cardiac death, re-infarction, and heart failure related to ISR);
- ✓ In pts without ISR, minimal lumen area and minimal lumen diameter were assessed by coronary CT-angiography at 1-year follow-up



- ✓ Treatment with SGLT2i is associated with a reduced risk of CV events related to In-Stent Restenosis after AMI in pts with T2D;
- ✓ These protective effects extend beyond glycemic control, suggesting either a direct anti-atherosclerotic effect of SGLT2-I or their potential use in a larger range of patients (acute settings ?)

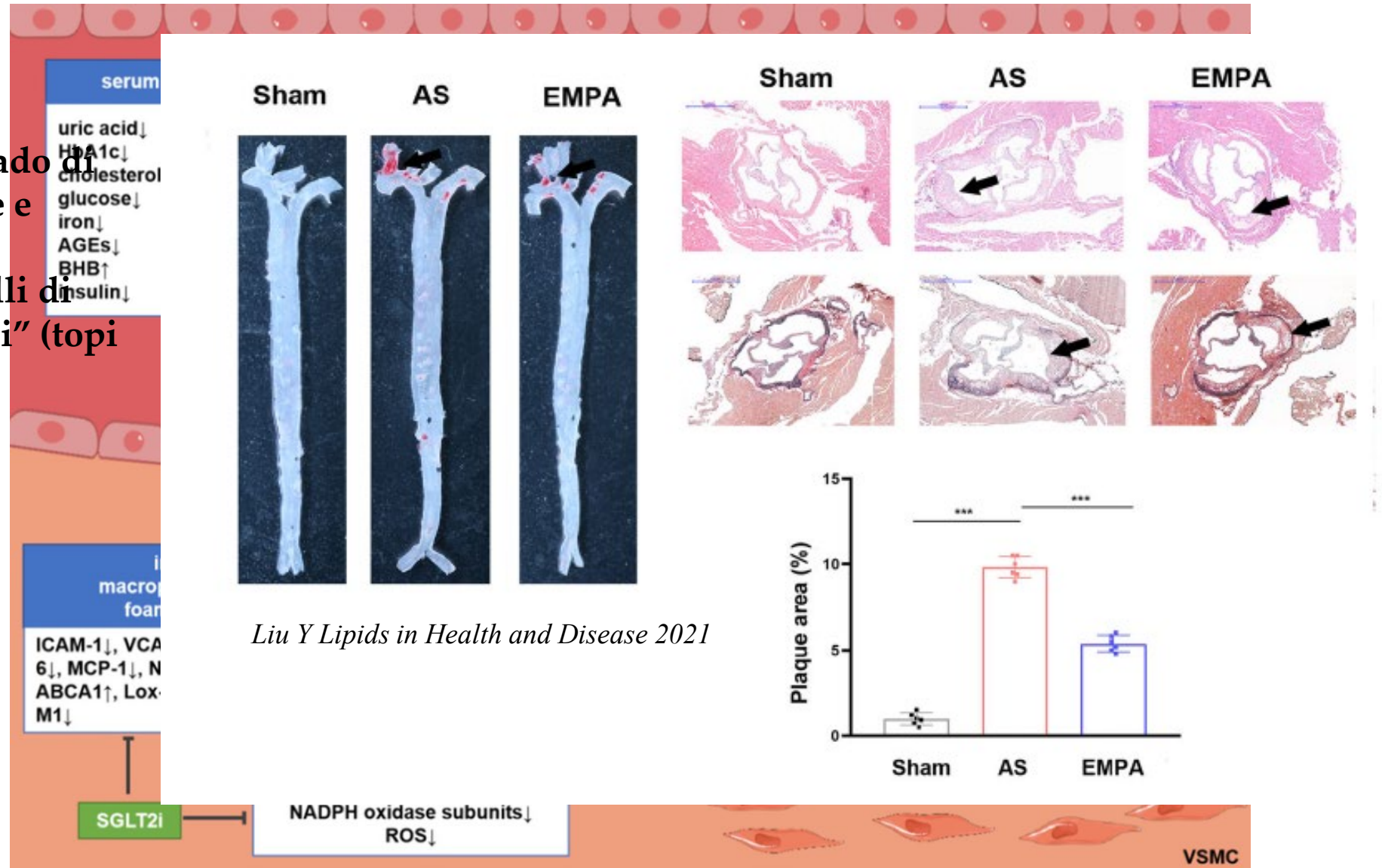
Figure 1: Time-dependent MACE risk analysis (adj. for admission, age, hypertension, smoking, BMI, HDL, LDL cholesterol, and diabetes) in pts with good glycemic control (1-year HbA1c mean < 7%)

A) of treated coronary artery disease patients at 1-year follow-up

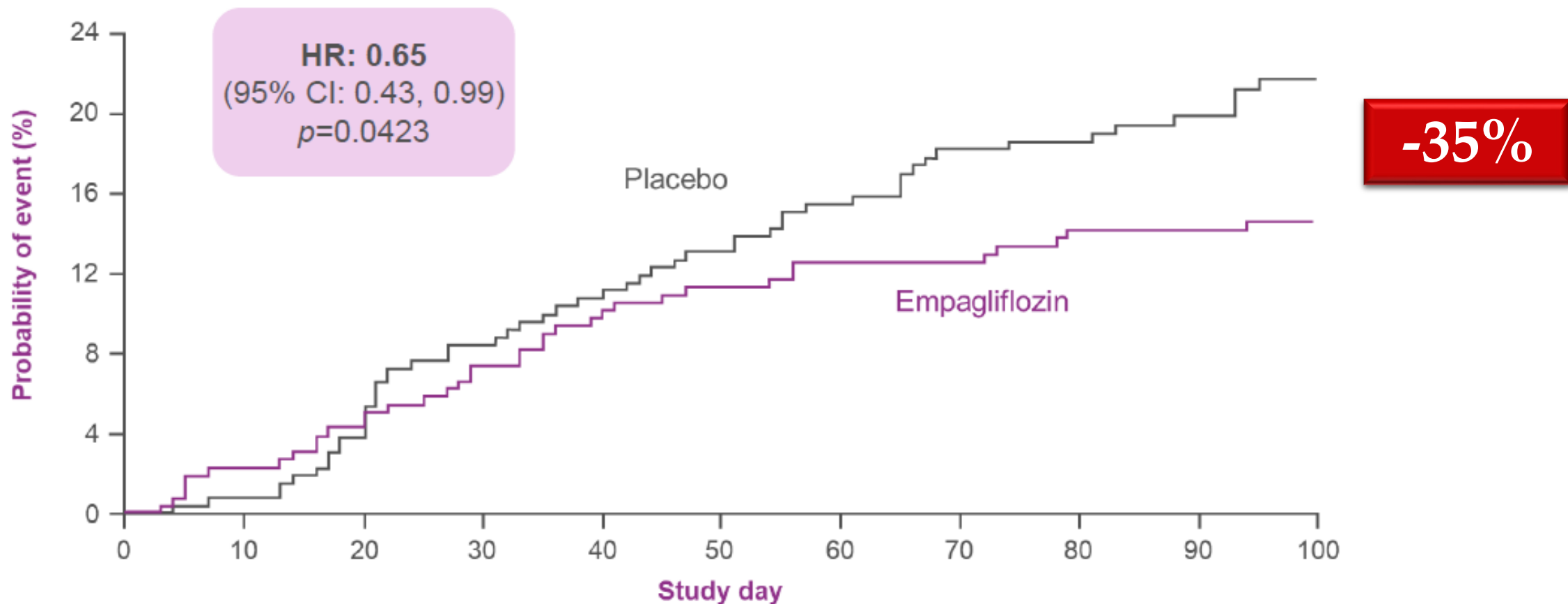
Figure 2: Time-dependent MACE risk analysis (adj. for admission, age, hypertension, smoking, BMI, HDL, LDL cholesterol, and diabetes) in pts with good glycemic control (1-year HbA1c mean < 7%)

Effetto Ateroprotettivo Diretto degli SGLT2-I

Empagliflozin è in grado di stabilizzare le placche e ridurre il processo di aterosclerosi in modelli di animali "non diabetici" (topi Apo E-/-)



EMPULSE: Time to all-cause death or first HFE



Median time from hospital admission
to randomization was **3 days**

*HF Events: HF hospitalizations; urgent HF visits
and unplanned outpatients HF visits

Empagliflozin following severe myocardial infarction

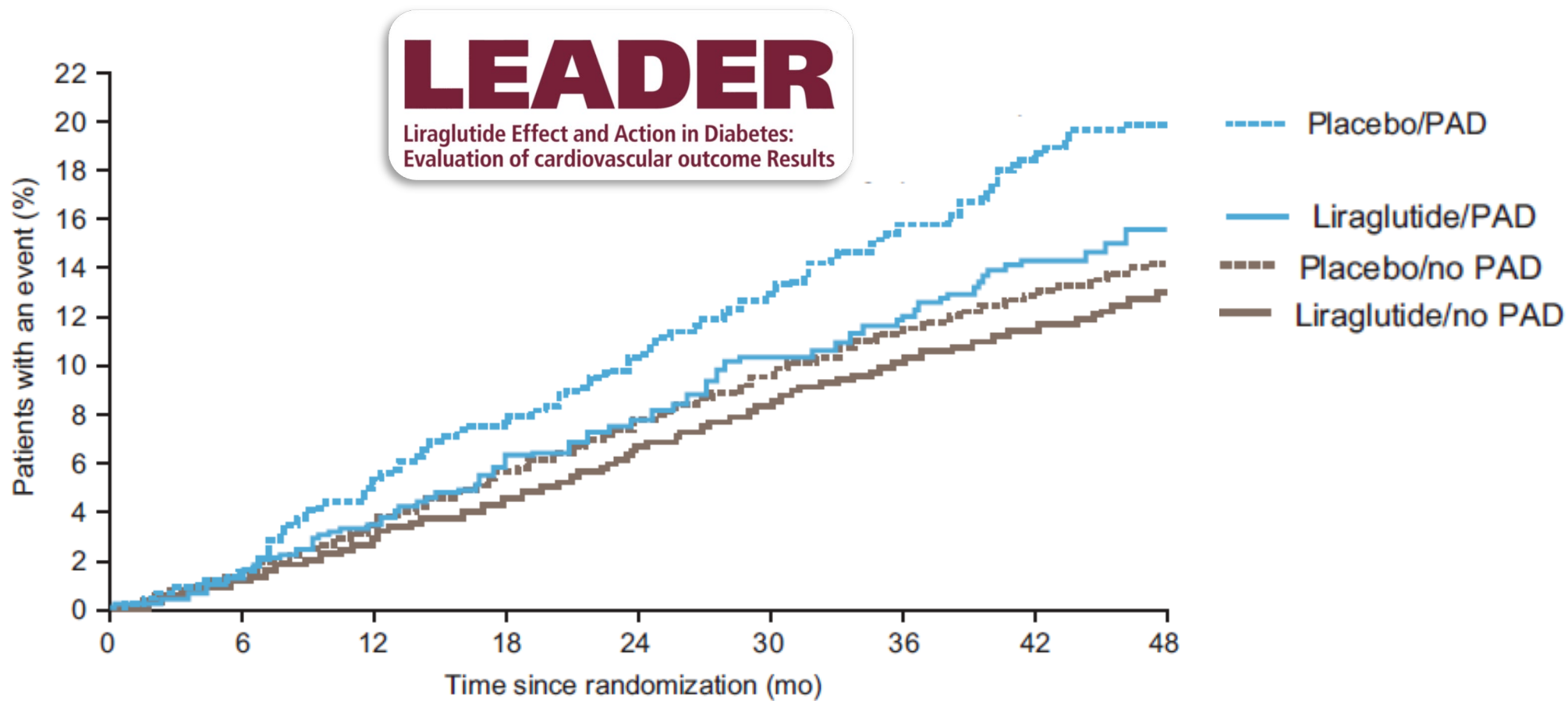
	EMPACT-MI	DAPA-MI
Initiation	2020	2020
Intervention	Empagliflozin 10 mg vs placebo	Dapagliflozin 10 mg vs placebo
Study population	Acute MI	Acute MI
Timing of therapy initiation	Within 14 d	Within 7-10 d
High-risk features	New LVEF <45% or signs/symptoms of congestion requiring treatment	New impaired regional or global LV systolic function or Q-wave MI on ECG
Inclusion of patients with T2DM	With and without T2DM	No, but patients with hyperglycemia without a prior diagnosis of T2DM are eligible
Primary outcome	Time to first HF hospitalization or all-cause death	Time to first HF hospitalization or cardiovascular death
Secondary outcomes	• Total HF hospitalizations or death • Total non-elective CV hospitalizations or death • Total non-elective all-cause hospitalizations or death • Total MI hospitalizations or death • Time to CV death	• Time to first MI, stroke, or CV death • Time to first fatal and nonfatal MI • Time to CV death • Time to all-cause death • Time to new-onset type 2 diabetes
Estimated duration of follow-up	~2 y	~3 y
Estimated sample size	5,000	6,400
Estimated completion	2023	2023

ORIGINAL ARTICLE

Cardiovascular efficacy of liraglutide and semaglutide in individuals with diabetes and peripheral artery disease

Subodh Verma MD¹  | Mohammed Al-Omran MD¹ | Lawrence A. Leiter MD¹ |
C. David Mazer MD¹  | Søren Rasmussen PhD² | Hans A. Saevereid MD² |
Maria Sejersten Ripa MD² | Marc P. Bonaca MD³

- ✓ LEADER and SUSTAIN 6 trials investigated sc liraglutide (≤ 1.8 mg/day) and semaglutide (0.5 or 1.0 mg/week), respectively, vs placebo in pts with T2D and high CV risk (median FU: 3.8 and 2.1 y, respectively);
- ✓ The primary outcome was a composite of CV death, non-fatal myocardial infarction or non-fatal stroke (MACE) according to the **presence of PAD at baseline**;
- ✓ Overall, **1184/9340 (12.7%) patients in LEADER and 460/3297 (14.0%) in SUSTAIN 6 had PAD at baseline.**



	HR (95%CI) LIRA vs PL	ARR (% point)	NNT	$P_{interaction}$
PAD (N.=1184)	0.77 (0.58-1.01) $P=0.06$	4.1	24	0.34
No PAD (N.=8156)	0.89 (0.79-1.00) $P=0.05$	1.4	70	

Recap

- ✓ *I dati dai CVOTs dimostrano come in pts con PAD (sia in fase cronica che dopo rivascolarizzazione) gli SGLT2-I come «classe» siano sicuri sul rischio amputativo e/o di MALE anche in setting «acuti», mantenendo l'efficacia nella protezione cardio-renale;*
- ✓ *I GLP1-RAs (dati limitati) riducono il rischio di amputazioni mantenendo il beneficio sulla riduzione del MACEs;*
- ✓ *Real World Evidence?*

ORIGINAL ARTICLE

WILEY

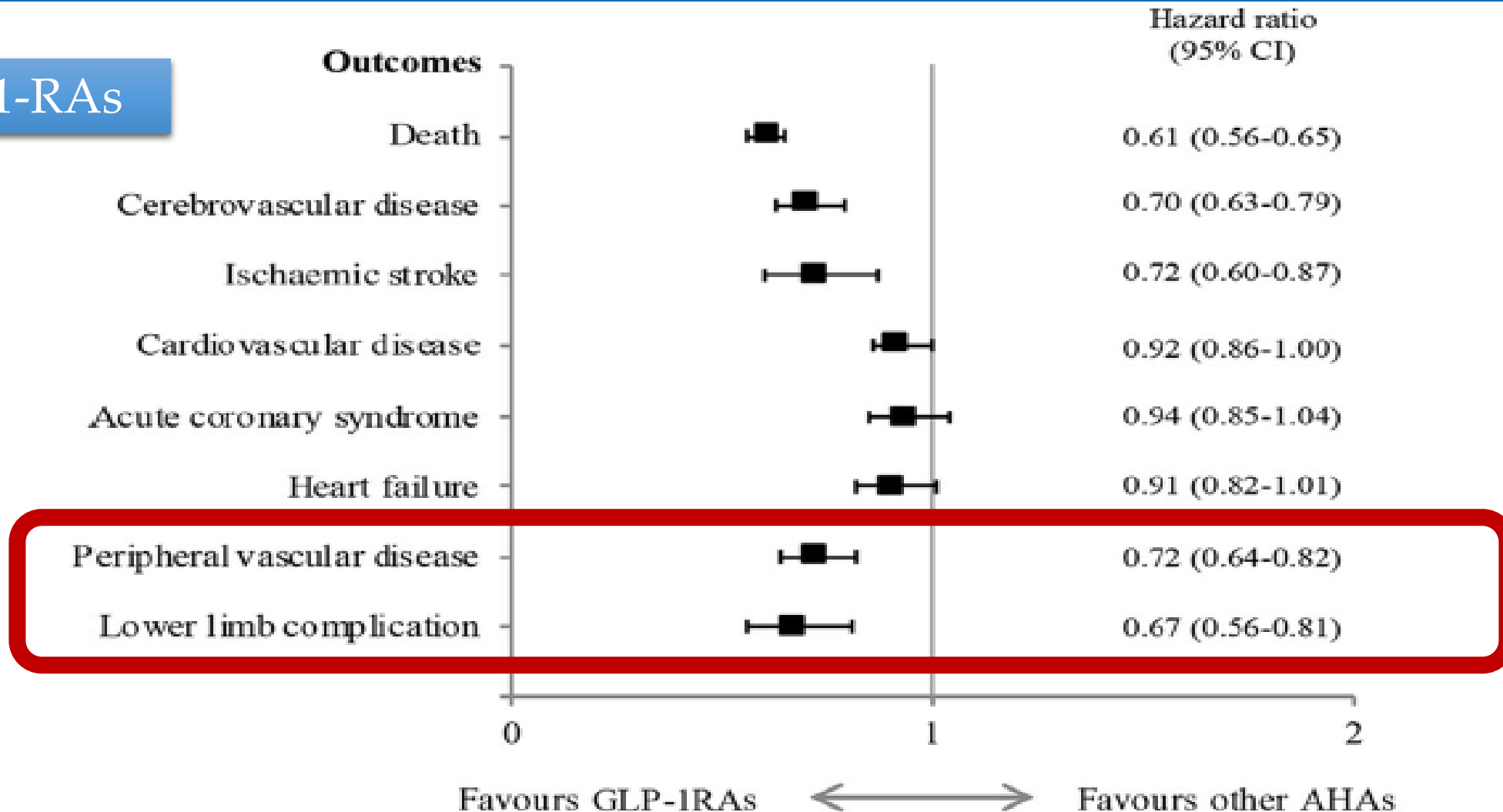
Lower risk of death and cardiovascular events in patients with diabetes initiating glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter-2 inhibitors: A real-world study in two Italian cohorts

Marta Baviera PharmD¹  | Stefano Genovese MD² | Vito Lepore MD^{3,4} |
Pierluca Colacioppo MSc¹ | Fabio Robusto MD³ | Mauro Tettamanti MSc⁵ |
Antonio D'Ettore MSc³ | Fausto Avanzini MD¹ | Ida Fortino MSc⁶ |
Antonio Nicolucci MD³  | Maria C. Roncaglioni MSc¹ | Francesco Giorgino MD⁷ 

*Observational cohort study of “first-time users” of GLP-1RAs, SGLT2-I or other AHAs conducted from 2010 to 2018;
(Lombardy cohort 60,798 pts; Apulia cohort 31,636 pts)*

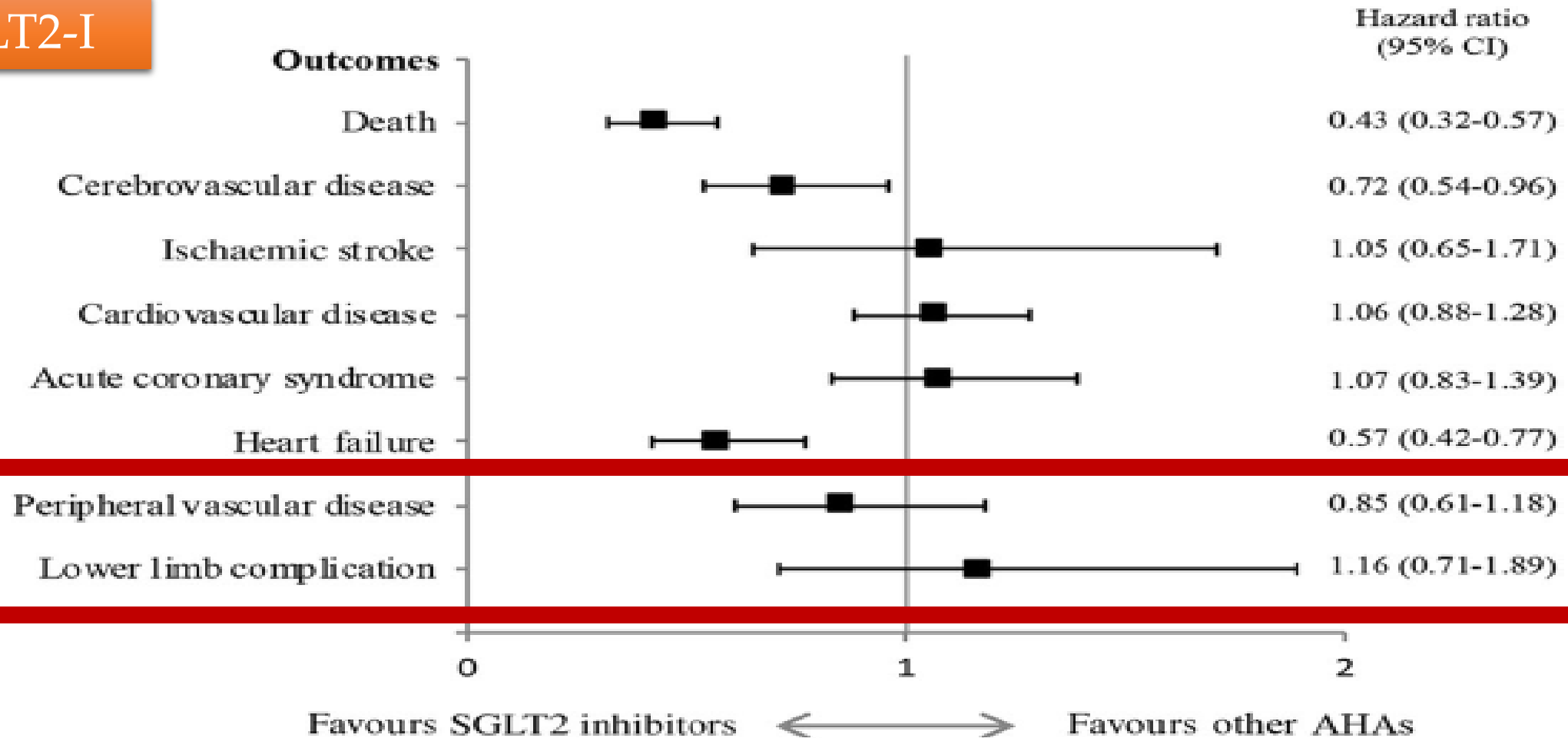
Hazard ratios for death and clinical events in matched populations according to treatment status in Lombardy

GLP1-RAs

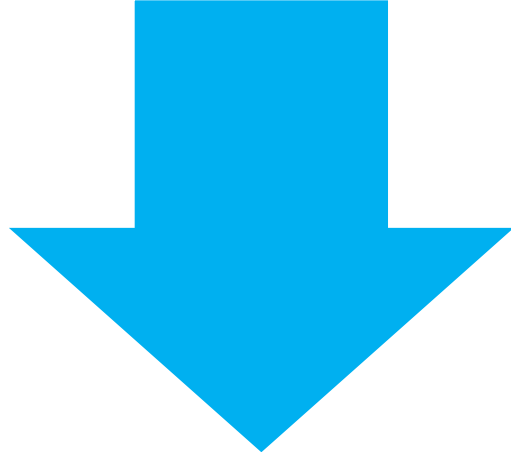


Hazard ratios for death and clinical events in matched populations according to treatment status in Apulia

SGLT2-I



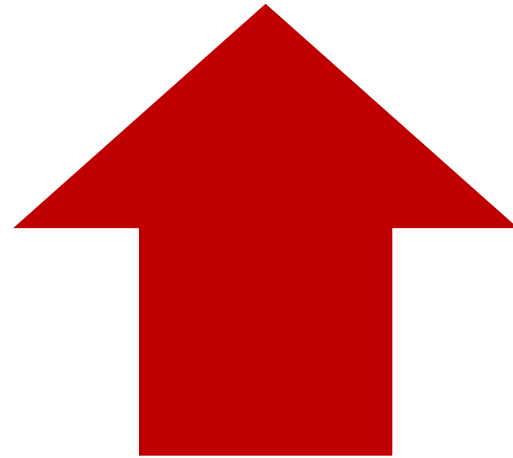
GLP1-RA



MACE



MALE



SGLT2i

287,091 patients

first treated with GLP1RA or SGLT2i
May 2016 until December 2019

1:4 Propensity score matching

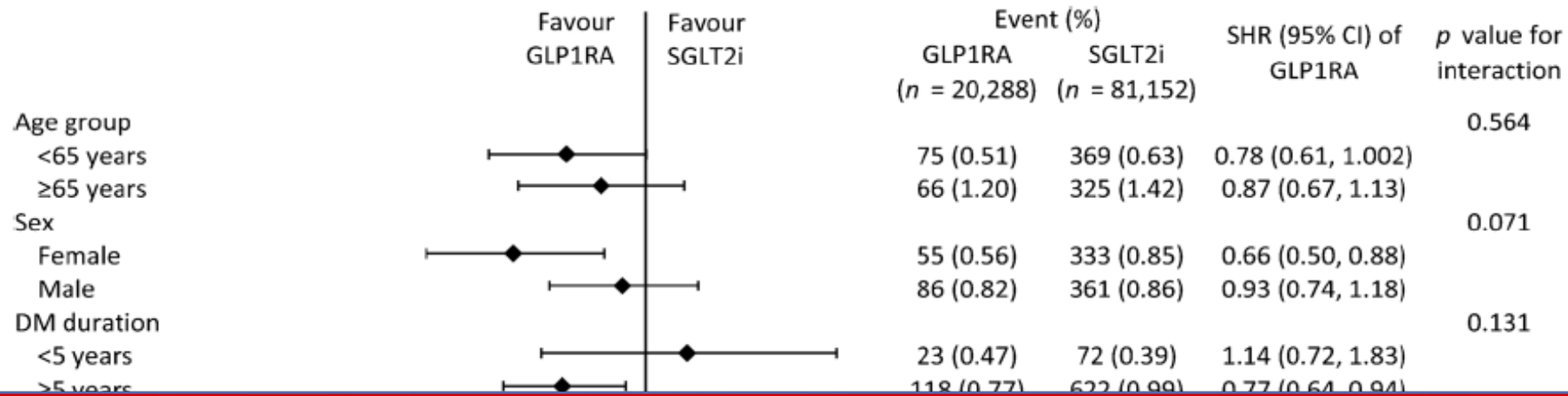


20,288
received GLP1RA

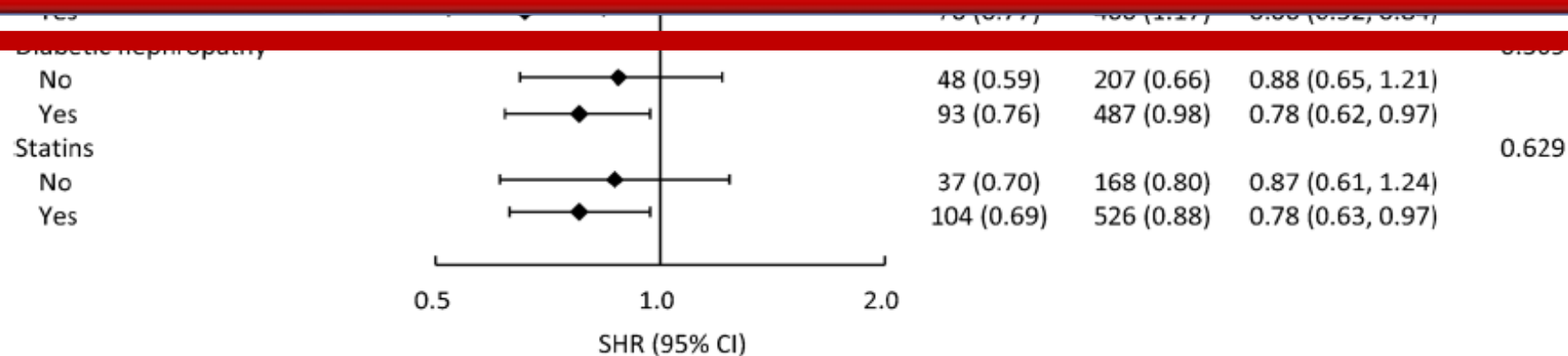


81,152
received SGLT2i

Mean follow-up of 1.96 years



GLP1RA use may be more favorable than SGLT2i in pts with peripheral neuropathy (high risk of adverse limb events)



Society Guidelines

Canadian Cardiovascular Society 2022 Guidelines for Peripheral Arterial Disease

RECOMMENDATION

10. We recommend that patients with PAD and type 2 diabetes should be offered a SGLT-2 inhibitor compared with usual diabetic control because of the reduction in MACE without any risk of increased amputation (Strong Recommendation; High-Quality Evidence).

11. We suggest that patients with PAD and diabetes might benefit from use of a GLP-1 agonist or DPP-4 inhibitor (Weak Recommendation; Low-Quality Evidence).

GLP1-RAs e/o SGLTs-I nella Sindrome da Piede Diabetico: come orientarsi ?

	GLP1-RAs	SGLT2-I	SGLT2-i+GLP1-RAs
PAD «masked»			
Neur. periferica			
HF			
CKD	 		 
CAD			 
Ater Car/Stroke			
Lesione/Ulcera		 	
PAD SGLT2-i			
HbA1c non a target			
Rivascolarizzazione			 
Cond. igieniche precarie		 	

**IO AMO
IL MARE
DELL'UMBRIA.**



Umbria. Cuore verde d'Italia.



Umbria

A scenic view of a coastal town with colorful buildings and a clear blue sea. The foreground shows the sandy beach and the shallow, clear water of the sea. In the background, there are buildings along the shore and mountains in the distance under a clear blue sky.

*..... ma il «mio» mare
è sempre più blu*

