

Update in Internal Medicine 2022

A Cardiologist's Perspective on Antihyperglycemic Therapy for Type 2 Diabetes

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Conflicts of Interest / Disclosures

- Clinical trials leadership:

- Merck & Co
- Pfizer
- AstraZeneca
- Lilly USA
- Boehringer Ingelheim
- Novo Nordisk
- Lexicon
- Eisai
- Sanofi
- CSL Behring

- Consultancy:

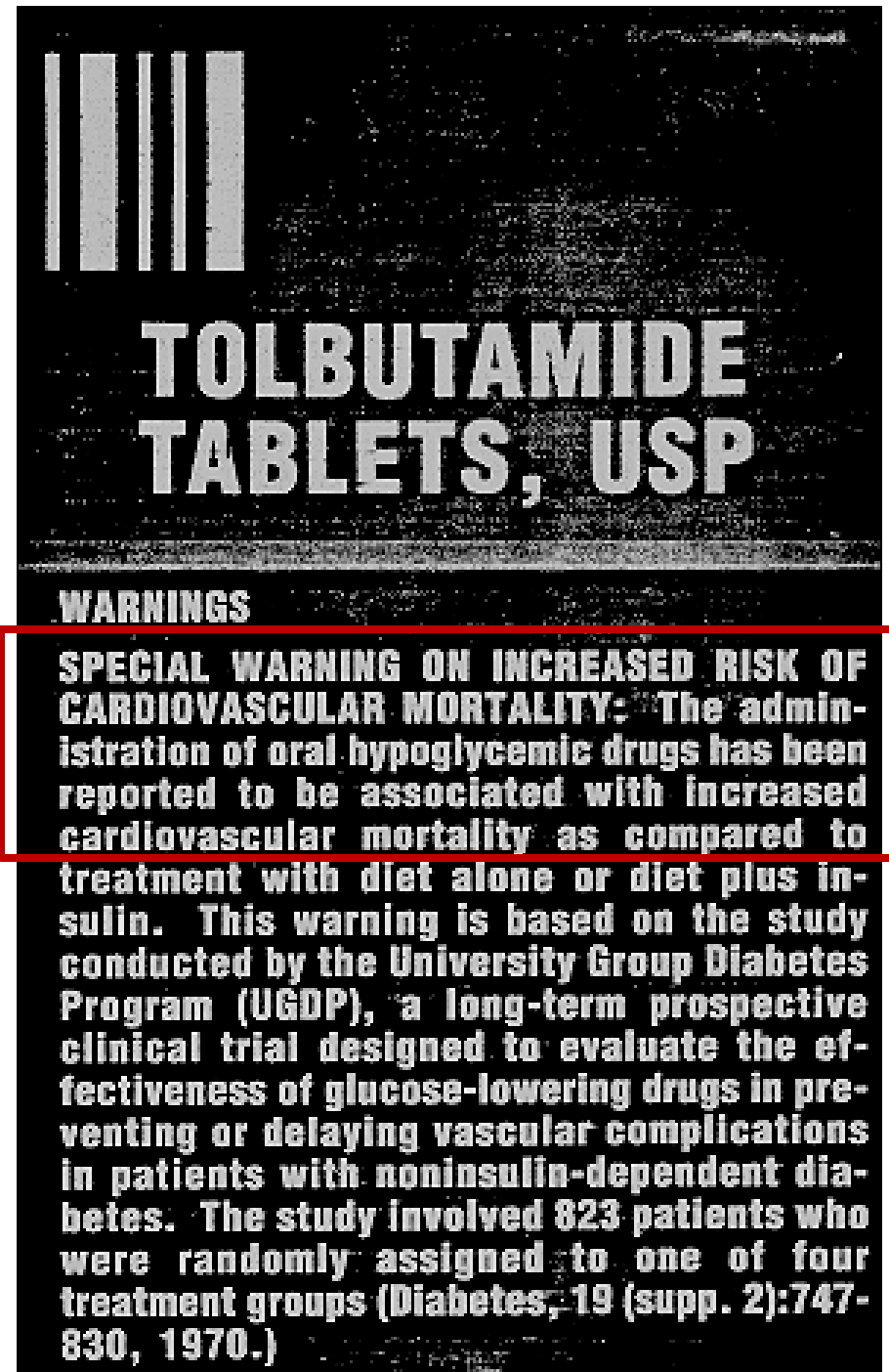
- Novo Nordisk
- Sanofi
- Boehringer Ingelheim
- Lilly USA
- Merck & Co
- Metavant
- Applied Therapeutics
- Lexicon
- Bayer

Regulatory Paradigm Shift 2008: Requires Proof of CV Safety of T2DM Medications

- Increasing incidence/prevalence of T2DM
 - >10% of US adult population
- Growing awareness of CV impact of T2DM
- Lack of proven CV safety or efficacy for more intense glucose control
- Proliferation of medications available
- Numerous examples of adverse drug effects
 - On target
 - Off target

Type 2 Diabetes Therapies: 1997

- Insulin
 - NPH; Regular; 70/30
- Sulfonylureas
 - tolbutamide, chlorpropamide, glyburide, glipizide, glimepiride
- Metformin



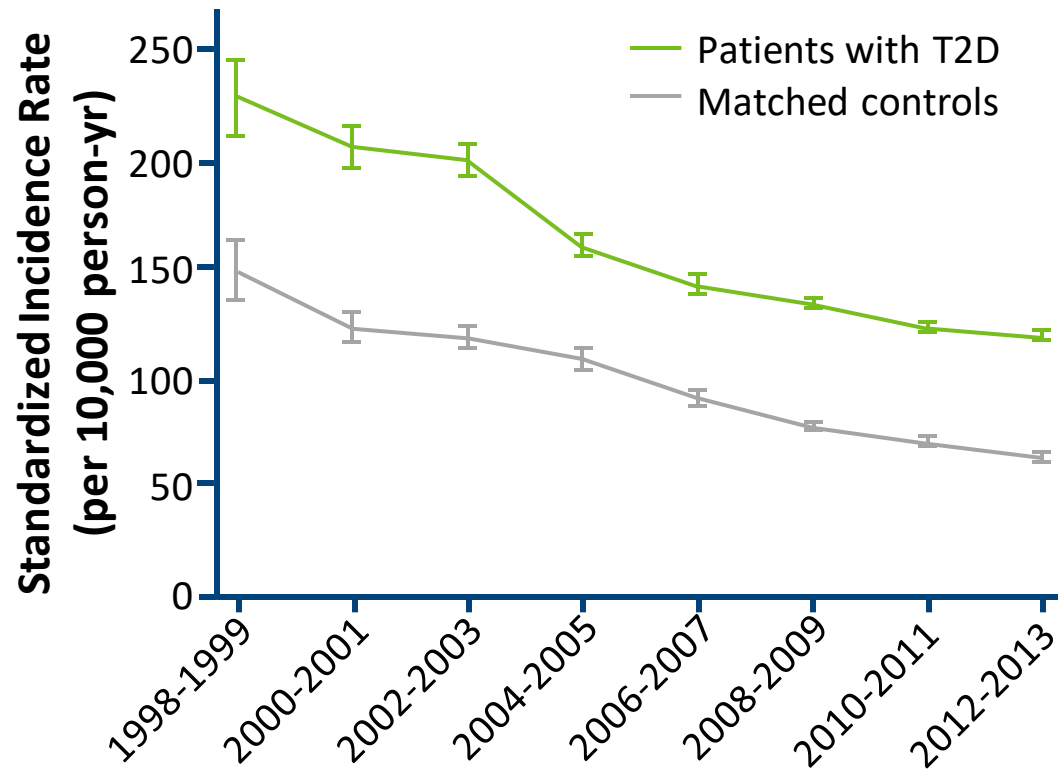
TOLBUTAMIDE TABLETS, USP

WARNINGS

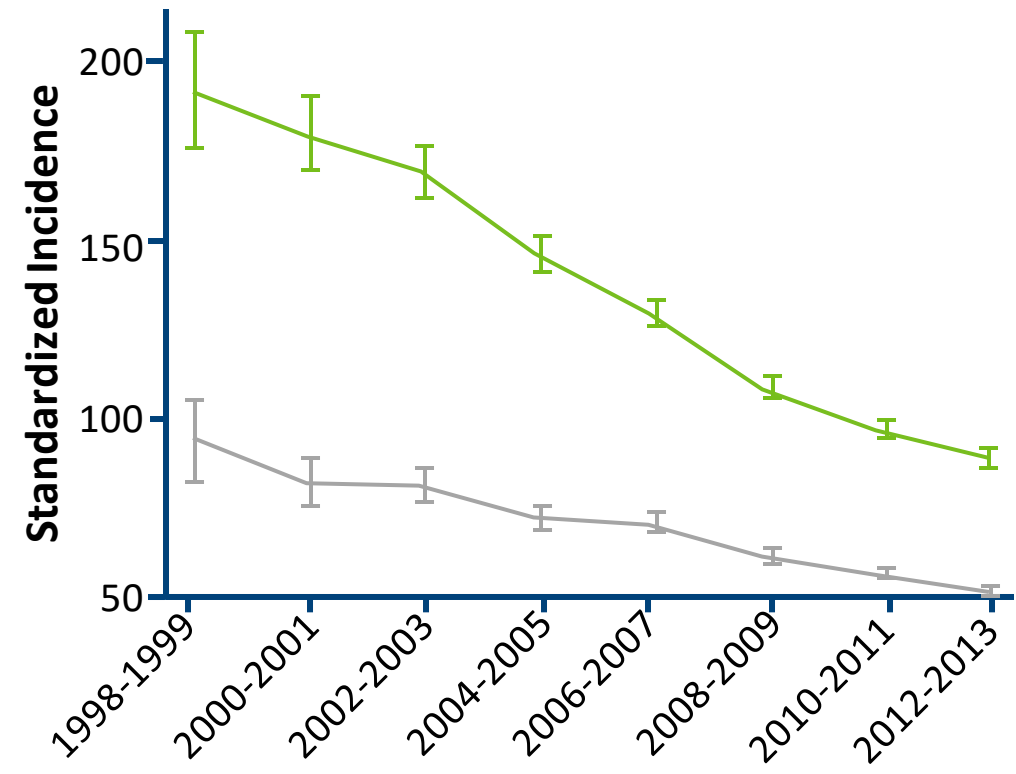
SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with noninsulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 19 (supp. 2):747-830, 1970.)

ASCVD Risk Associated with T2DM: Swedish National Registry Data 1998-2013

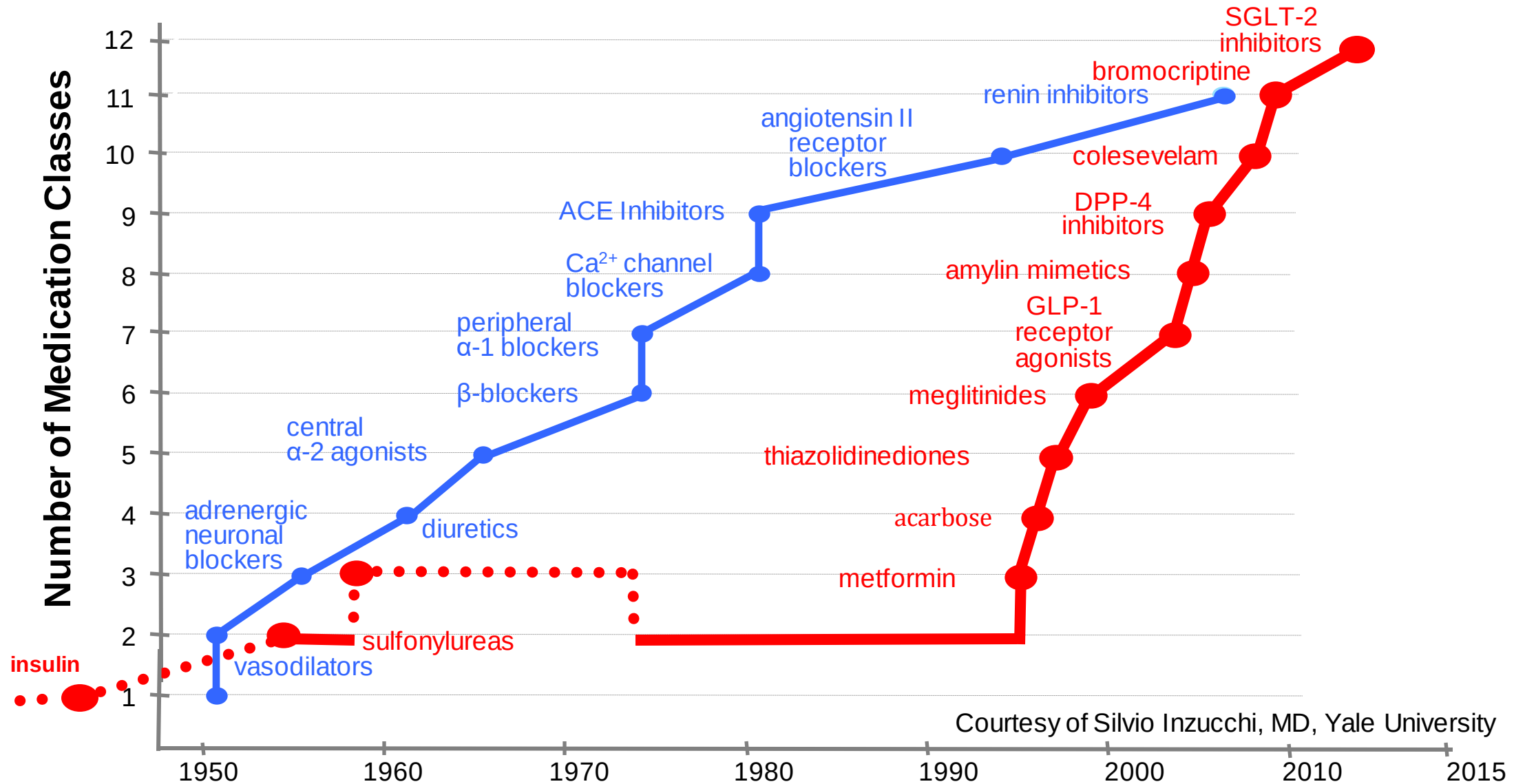
CV Death



Hospitalizations for MI



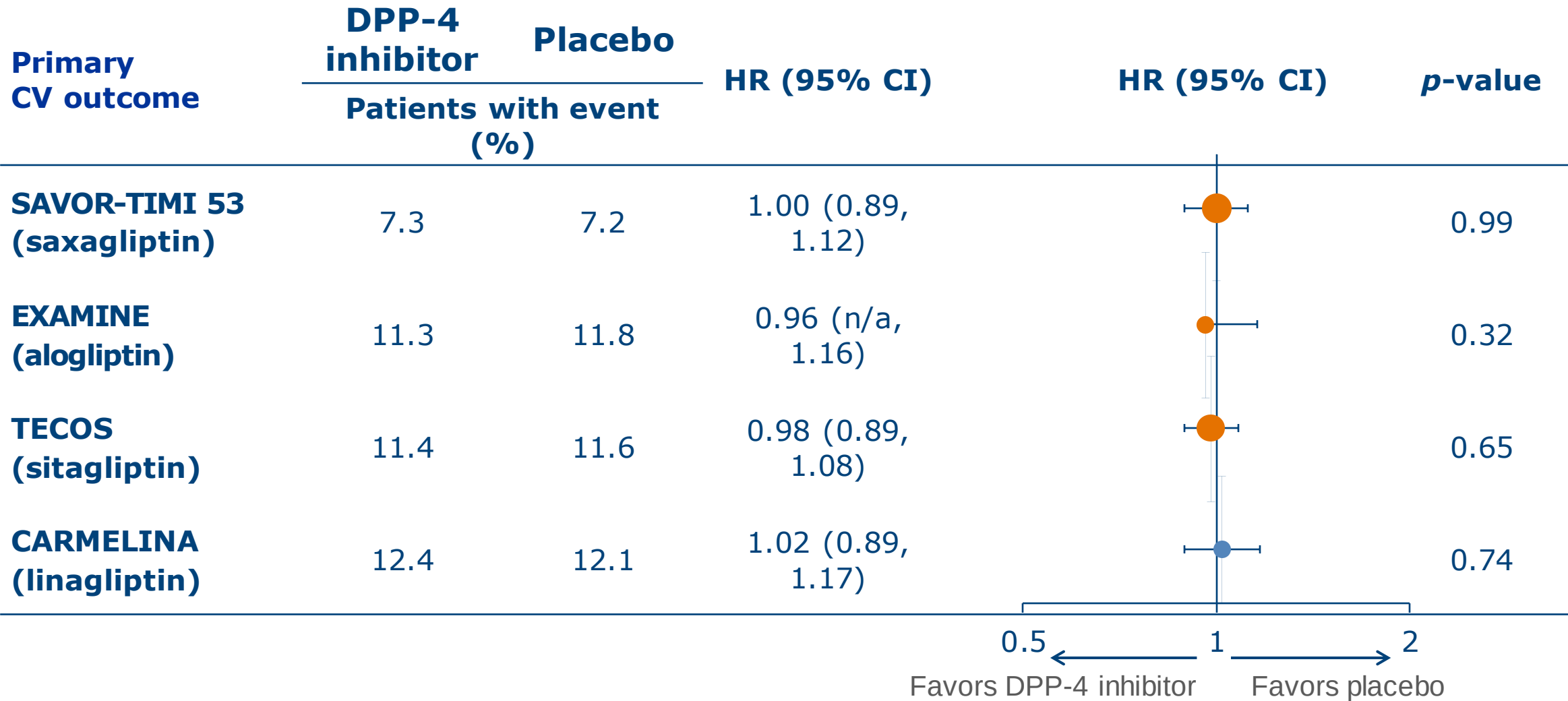
Half-Century of HTN & T2DM Medications in U.S.



DPP4 Inhibitors on the US Market

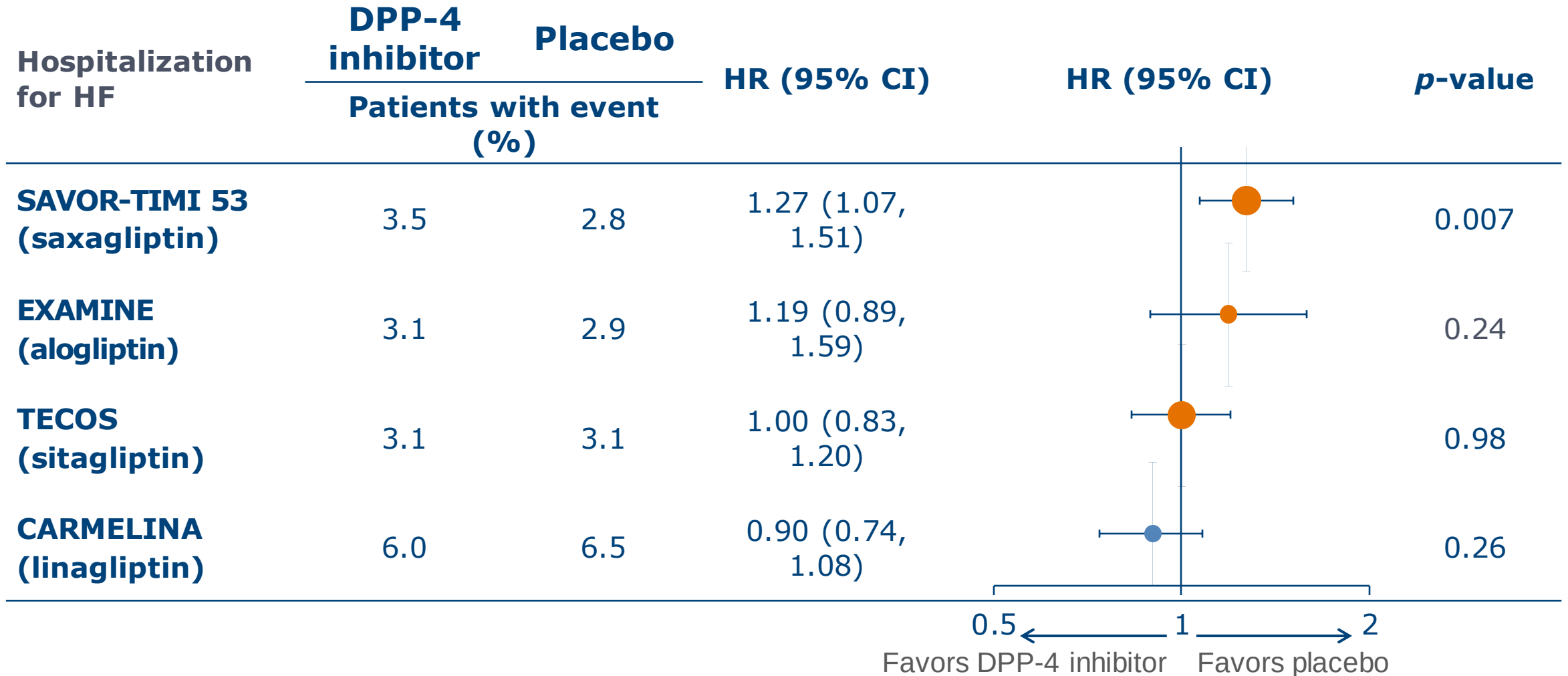
DPP4 inhibitors	sitagliptin
(tablets)	saxagliptin
	alogliptin
	linagliptin

Completed CVOTs of DPP4 Inhibitors: SAVOR-TIMI 53, EXAMINE, TECOS and CARMELINA



SAVOR-TIMI 53, EXAMINE, TECOS and CARMELINA:

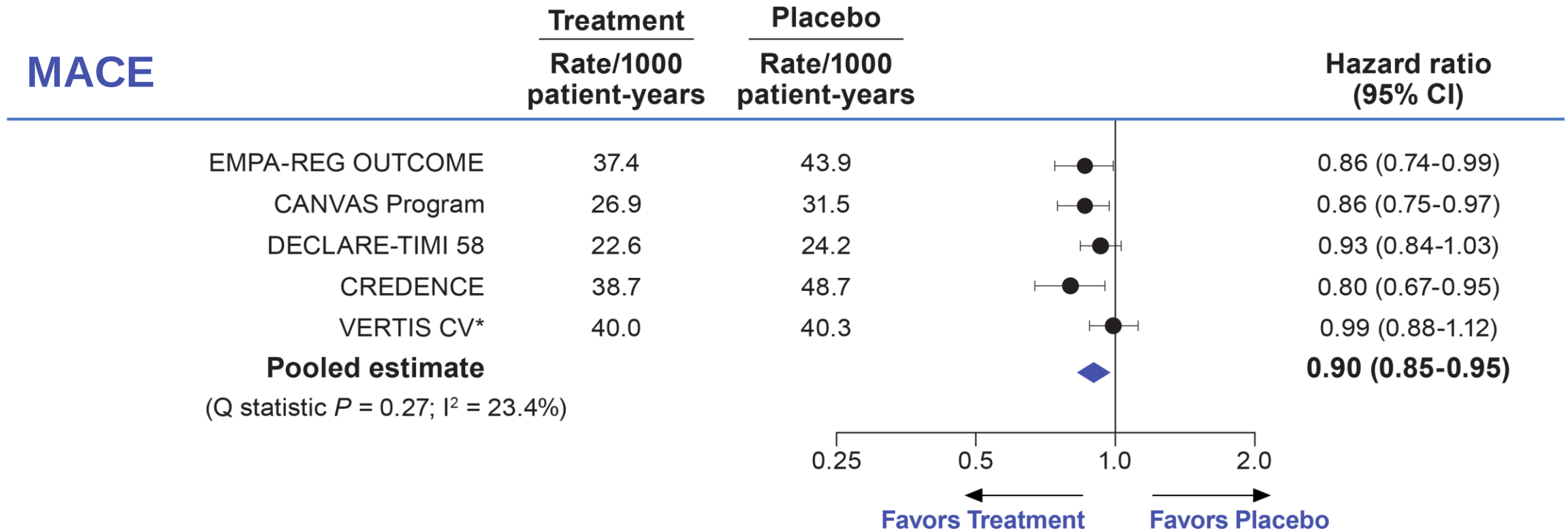
Hospitalization for Heart Failure



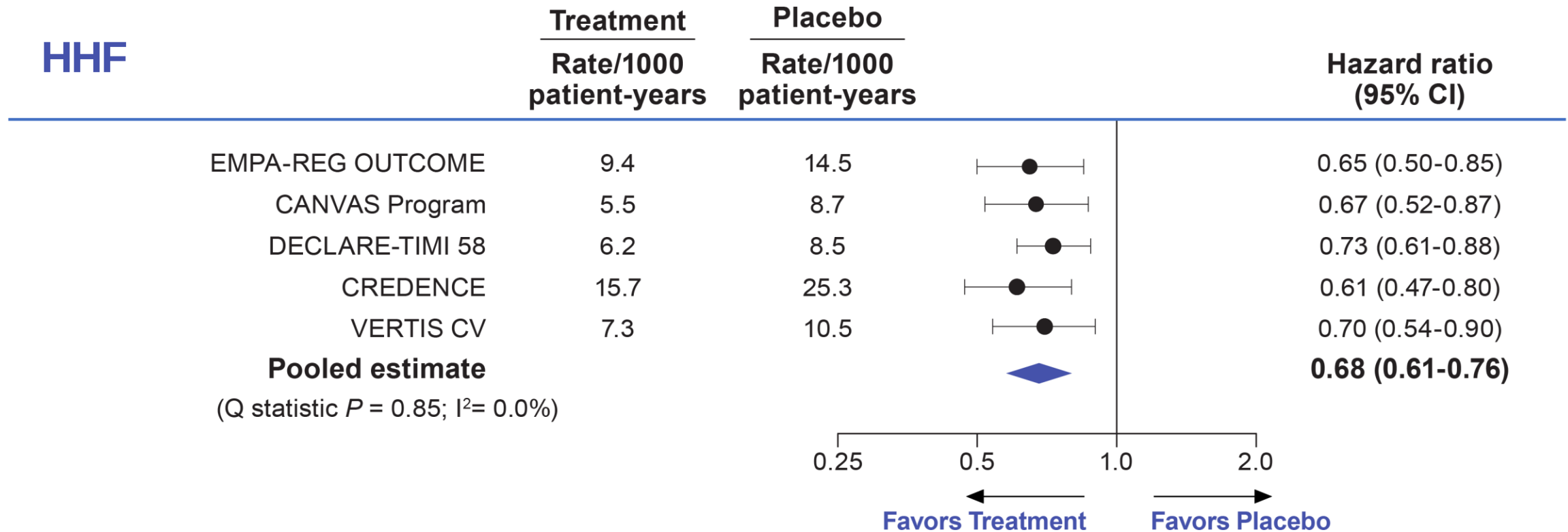
SGLT2 Inhibitors on the US Market

empagliflozin
canagliflozin
dapagliflozin
ertugliflozin

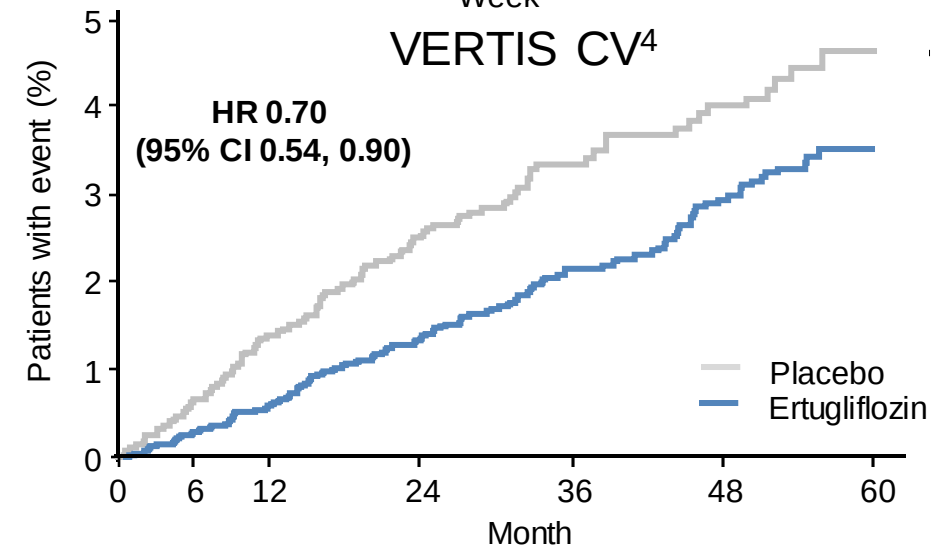
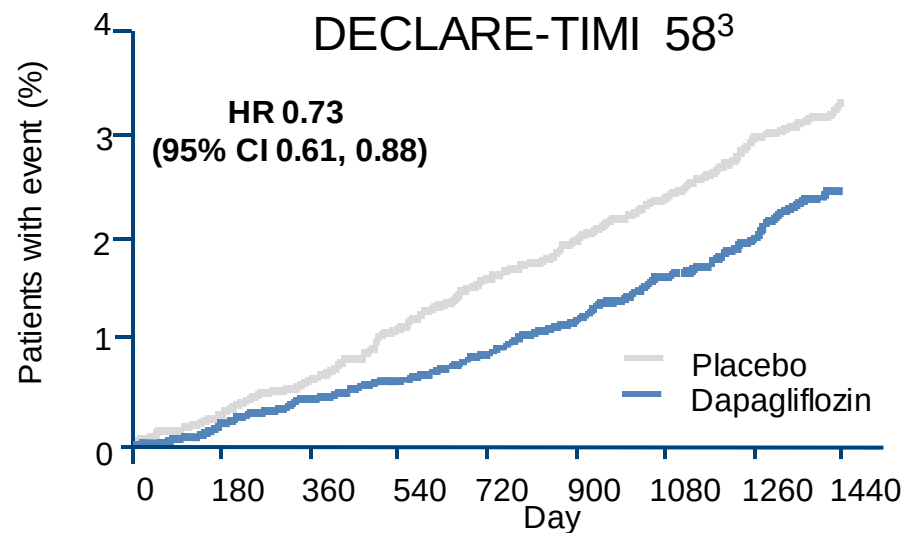
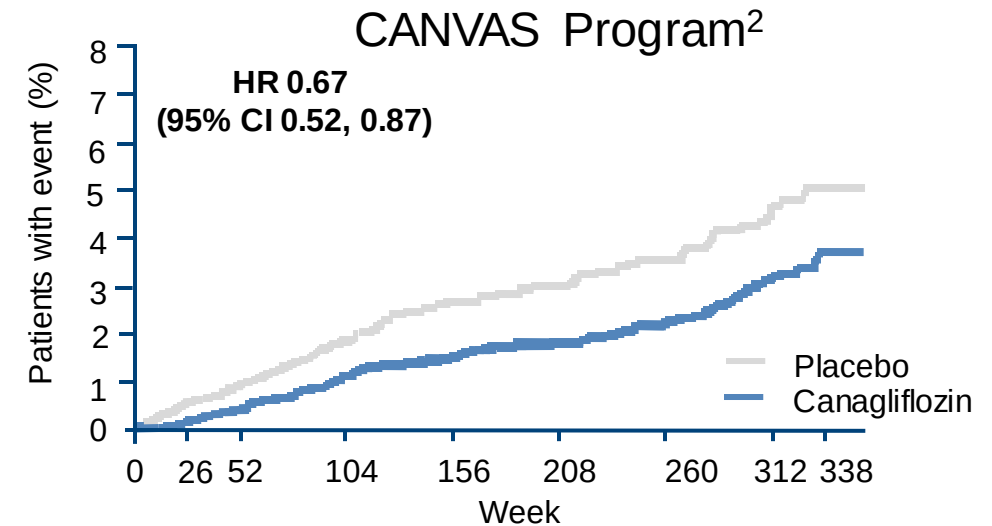
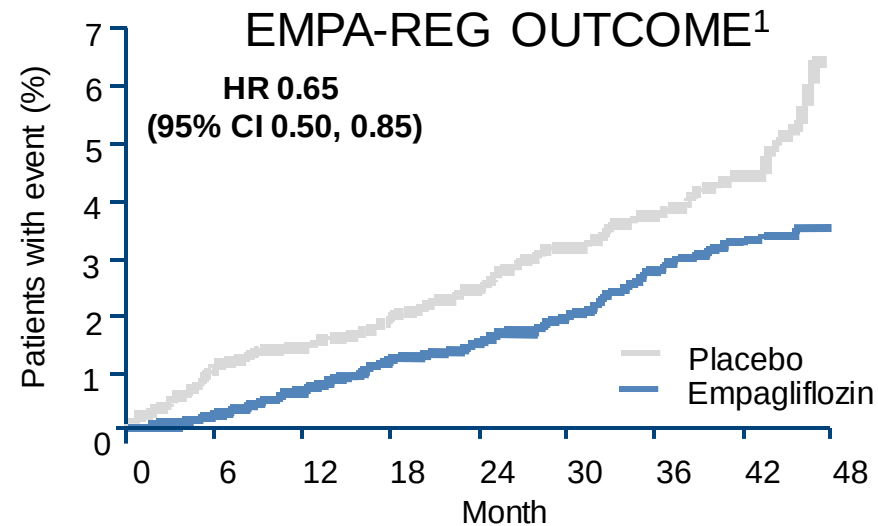
Meta Analysis of SGLT2 Inhibitor Trials: Time to first MACE



Meta Analysis of SGLT2 Inhibitor Trials: Time to first HHF



HHF outcomes in SGLT2 inhibitor CV outcomes trials



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.

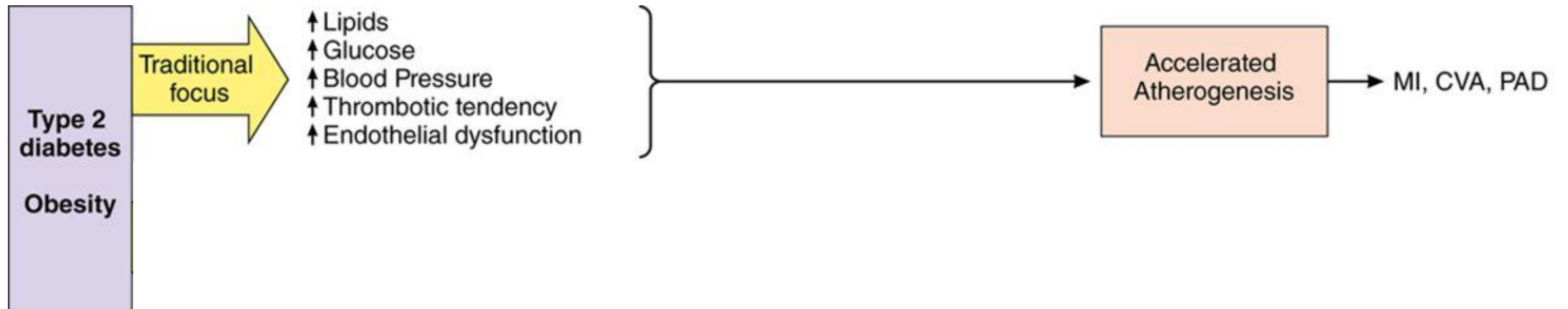
3. Wiviott SD et al. N Engl J Med 2019;380:347-357.

4. Cannon CP et al. N Engl J Med 2020;383:1425-1435.

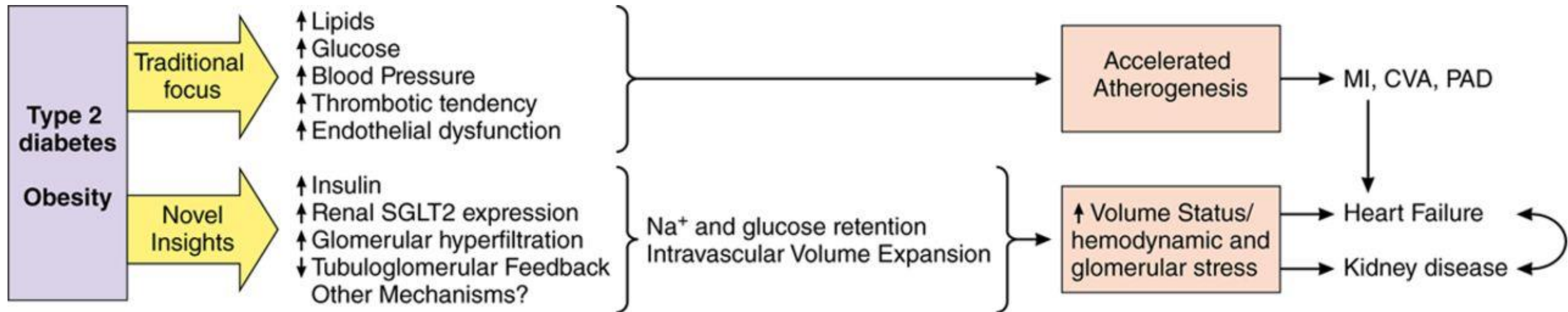
CV and Kidney Outcomes in Completed SGLT2 Inhibitor Outcome Trials of Patients with Type 2 Diabetes

	MACE HR (95% CI)	CV Death HR (95% CI)	HHF HR (95% CI)	Kidney Composite HR (95% CI)
EMPA-REG OUTCOME	0.86 (0.74, 0.99)	0.62 (0.49, 0.77)	0.65 (0.50, 0.85)	0.54 (0.40, 0.75)
CANVAS Program	0.86 (0.75, 0.97)	0.87 (0.72, 1.06)	0.67 (0.52, 0.87)	0.60 (0.47, 0.77)
DECLARE-TIMI 58	0.93 (0.84, 1.03)	0.98 (0.82, 1.17)	0.73 (0.61, 0.88)	0.53 (0.43, 0.66)
VERTIS CV	0.97 (0.85, 1.11)	0.92 (0.77, 1.11)	0.70 (0.54, 0.90)	0.66 (0.50, 0.88)

Redefining pathways to cardiorenal complications of type 2 diabetes mellitus



Redefining pathways to cardiorenal complications of type 2 diabetes mellitus



Potential Mediators of HF Risk Reduction of SGLT Inhibitors: Beyond diuresis...

- Reduced Myocardial Oxygen Demand:
 - Reduced intraventricular volumes
 - Reduced blood pressure/RAAS attenuation
 - Reduced heart rate/SNS withdrawal
 - Increased circulating ketones
- Increased myocardial oxygen supply
 - Increased Hgb/expanded RBC mass
- Direct myocardial effects
 - Positive inotropy
 - Na/H exchanger 1 inhibition
 - Anti-arrhythmic
 - Kv and late-Na channel inhibition
 - Anti-inflammatory
 - NLRP3 inhibition
- Other
 - Reduced body mass/adiposity
 - Reduced albuminuria
 - Stabilization of eGFR

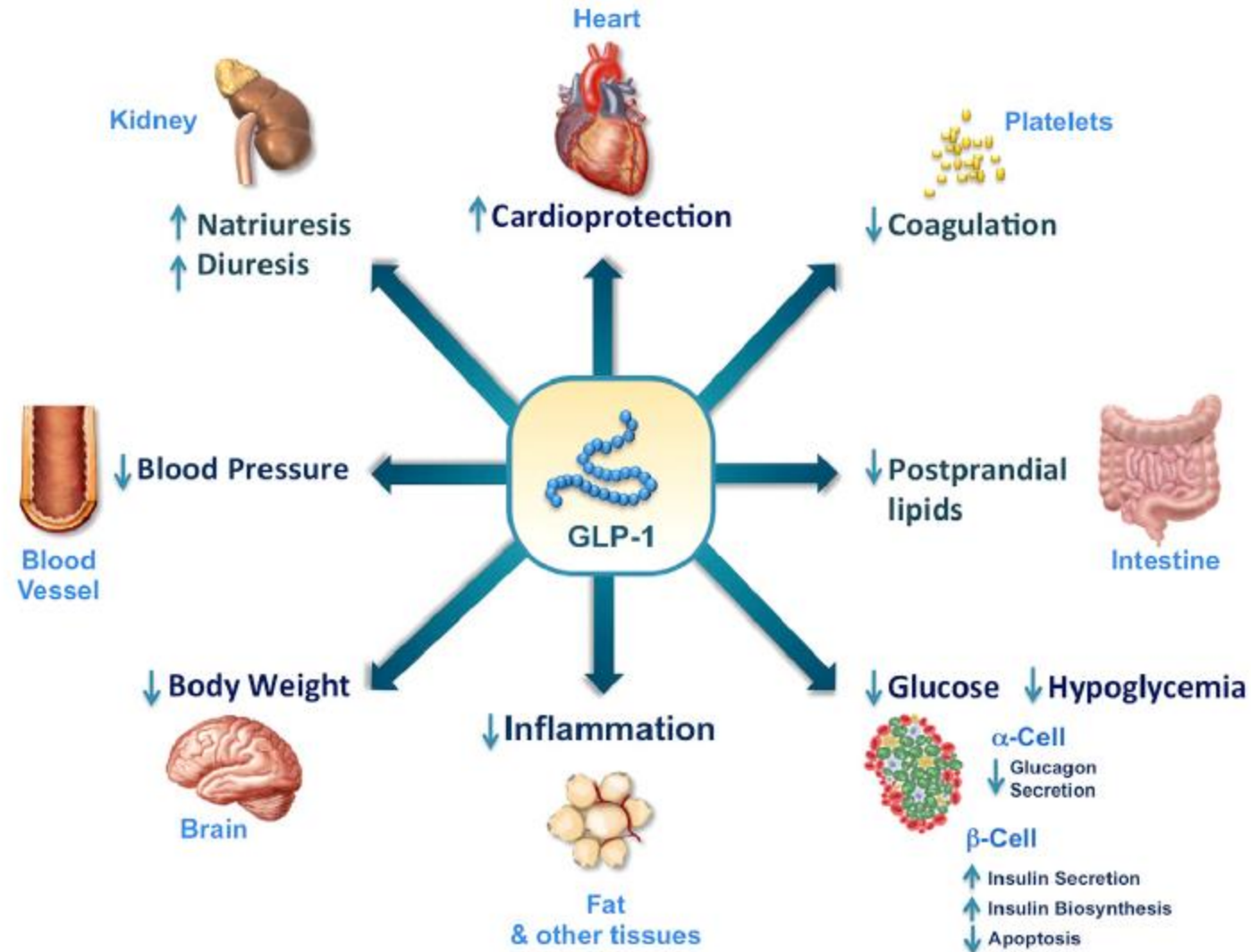
FDA CV Indications for GLP-1 Receptor Agonists

Labeled CV Indication	liraglutide
	semaglutide
	dulaglutide
Ongoing CVOTs	oral semaglutide
	SQ tirzepatide

Meta-Analysis of GLP1-RA CVOTs: Effects on MACE

	GLP-1 RA n/N (%)	Placebo n/N (%)		Hazard Ratio (95% CI)	NNT (95% CI)	P Value
3-point MACE						
ELIXA	400/3034 (13%)	392/3034 (13%)		1.02 (0.89-1.17)		0.78
LEADER	608/4668 (13%)	694/4672 (15%)		0.87 (0.78-0.97)		0.01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)		0.74 (0.58-0.95)		0.016
EXSCEL	839/7356 (11%)	905/7396 (12%)		0.91 (0.83-1.00)		0.061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)		0.78 (0.68-0.90)		0.0006
REWIND	594/4949 (12%)	663/4952 (13%)		0.88 (0.79-0.99)		0.026
PIONEER 6	61/1591 (4%)	76/1592 (5%)		0.79 (0.57-1.11)		0.17
AMPLITUDE-0	189/2717 (7%)	125/1359 (9%)		0.73 (0.58-0.92)		0.0069
Subtotal ($I^2 = 44.5\%$, $P = 0.082$)				0.86 (0.80-0.93)	65 (45-130)	<0.0001

GLP-1 RA Potential Mechanisms for CVD Benefit



ADA/EASD Society Recommendations

Use metformin unless contraindicated or not tolerated

- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- **Add an SGLT2i or GLP-1 RA with proven CVD benefit (consider adding independently of individualized A1C target)**
- If **individualized A1C target achieved and** already on dual therapy or multiple glucose-lowering therapies **when adding** SGLT2i or GLP-1 RA, consider **stopping or reducing dose of other glucose-lowering therapy to reduce risk of hypoglycemia**

ASCVD Predominates

- Established ASCVD
- Indicators of high ASCVD risk (age ≥ 55 years + LVH or coronary, carotid, lower extremity artery stenosis $>50\%$)



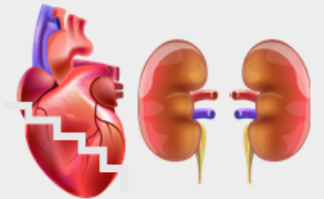
Preferably
GLP-1 RA with proven CVD benefit

OR

SGLT2i with proven CVD benefit if eGFR adequate

HF or CKD Predominates

- Particularly HFrEF (LVEF $<45\%$)
- CKD: Specifically, eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g



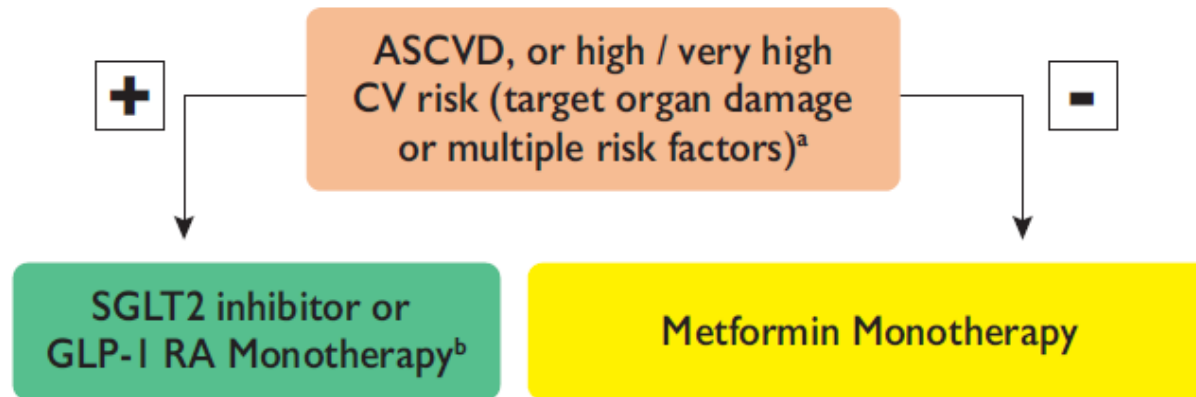
Preferably
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate

OR

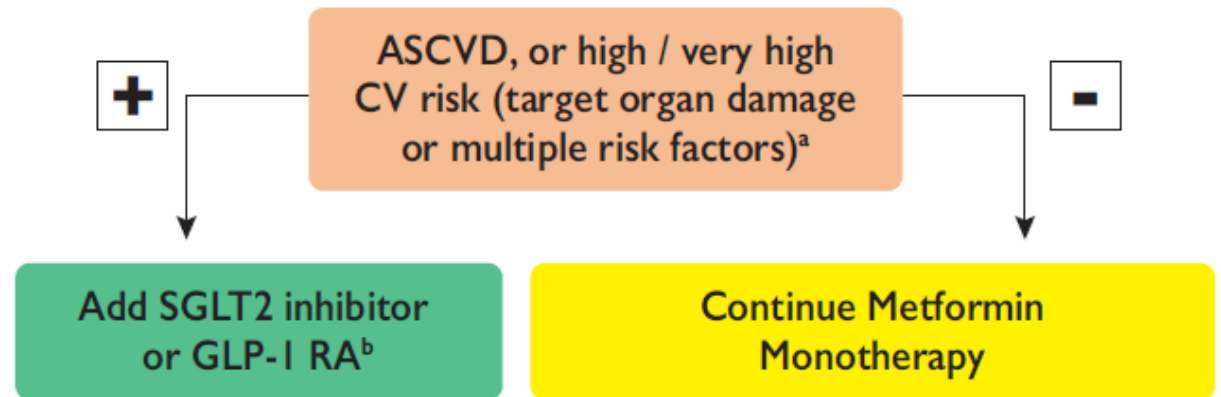
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate
add GLP-1 RA with proven CVD benefit

2019 ESC Guidelines for Type 2 Diabetes Treatment

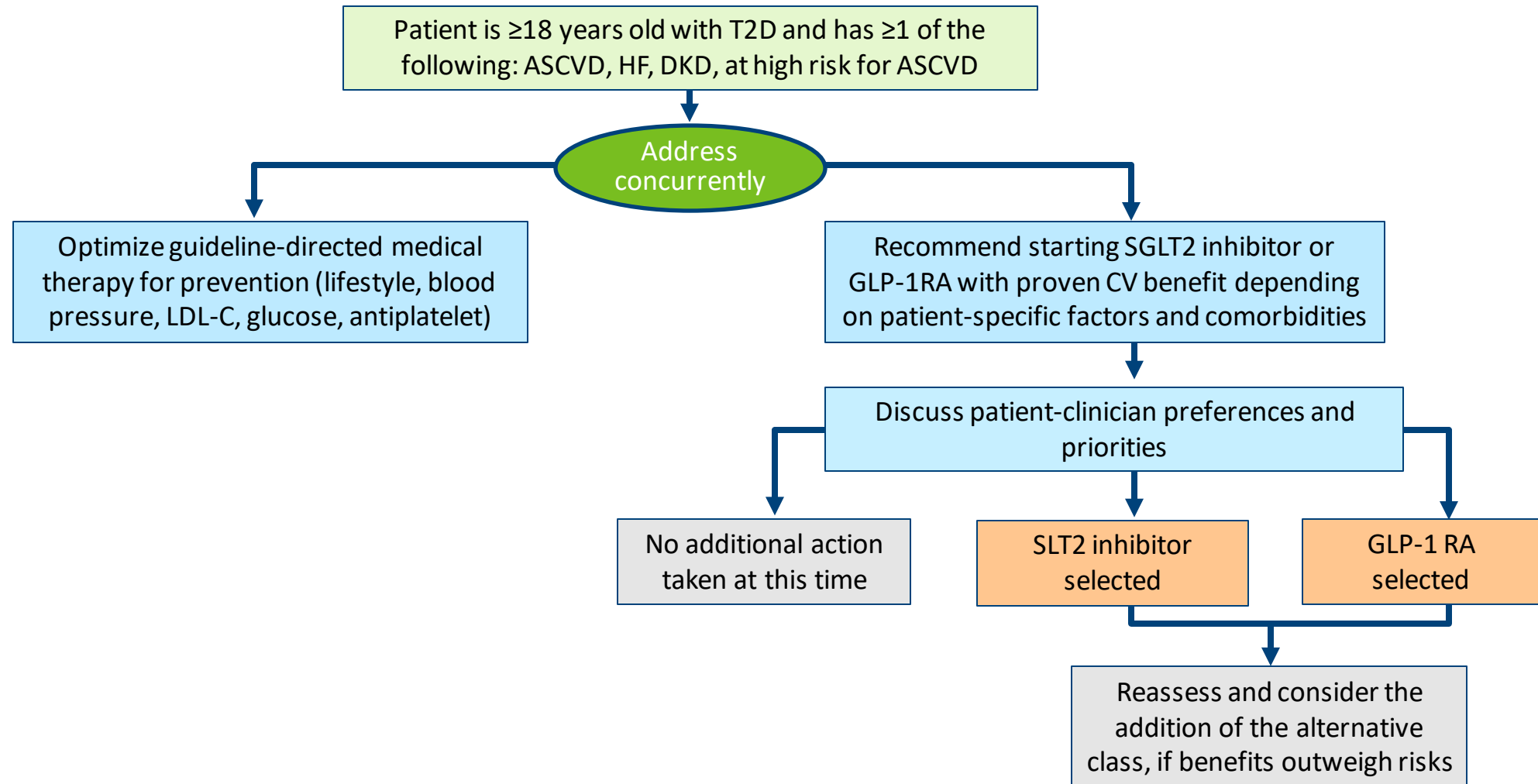
A Type 2 DM - Drug naïve patients



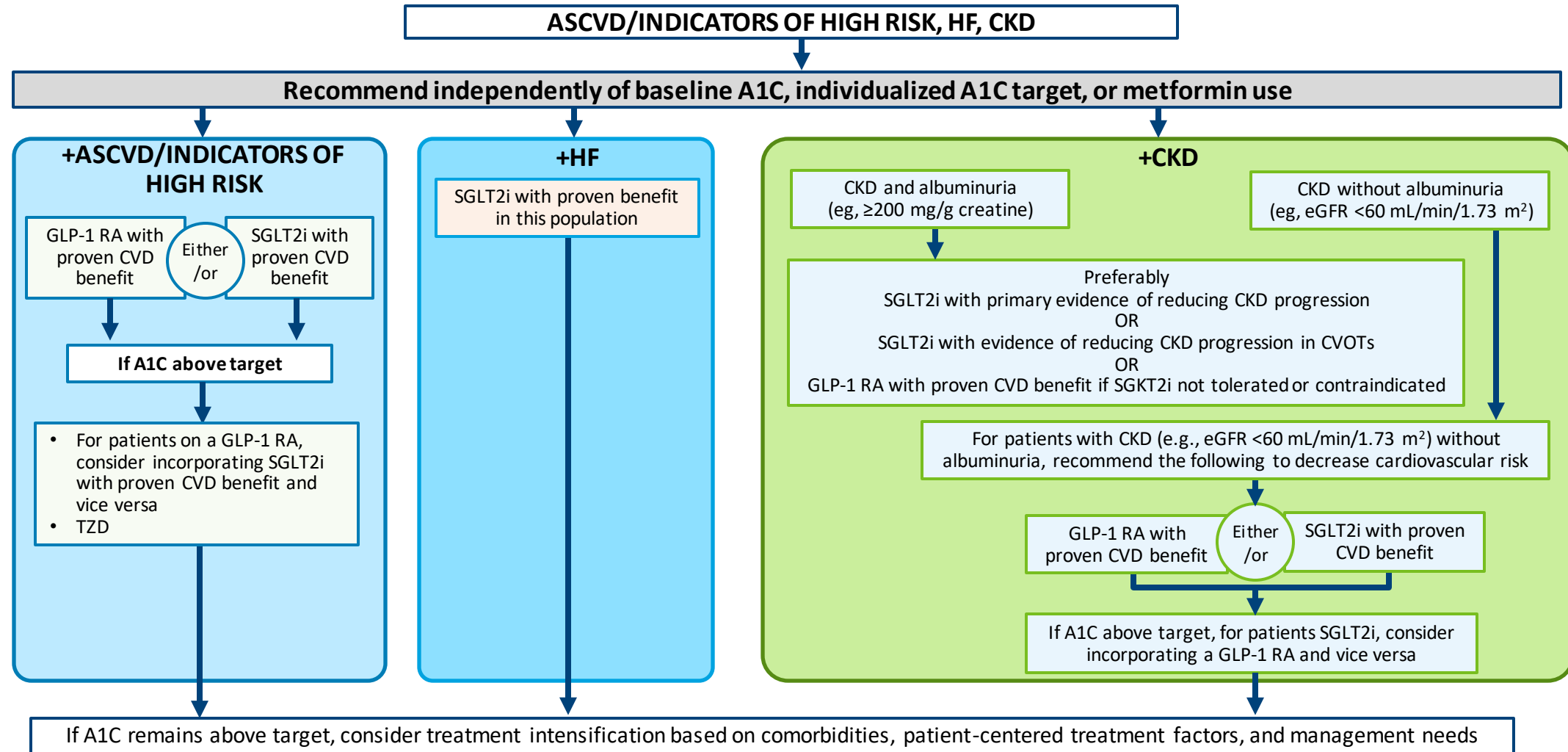
B Type 2 DM - On metformin



From Glucocentricity to CV Risk Mitigation: ACC Decision Pathway



ADA 2022 Standards of Medical Care for Diabetes



- CVOTs results have dramatically altered care of patients with T2DM
- Completed trials have demonstrated ASCVD safety of
 - saxagliptin*, alogliptin, sitagliptin, linagliptin
 - lixisenatide, exenatide ER, oral semaglutide
 - ertugliflozin
- Completed trials have reported CV benefit of
 - liraglutide, injectable semaglutide, dulaglutide, albiglutide
 - empagliflozin, canagliflozin, dapagliflozin
 - All SGLTi's with HF and kidney benefits
- Trial results have directly impacted contemporary T2DM guideline and society recommendations for mitigation of CV risk, independent of glucose control