Medicines management of type 2 diabetes

Professor Jonathan Shaw
Baker Heart and Diabetes Institute
Melbourne, Australia

Baker
HEART & DIABETES INSTITUTE

Disclosures

I have received honoraria for scientific advisory, lectures, and clinical research from Zuellig Pharma, Astra Zeneca; Sanofi; Novo Nordisk; Eli Lilly; Abbott; Mylan; Boehringer Ingelheim; Roche; Pfizer

Baker
HEART & DIABETES INSTITUTE

Role of medicines used to manage type 2 diabetes

- Glucose lowering
- Blood pressure lowering
- Lipid lowering

- Lifestyle is important for all of these
- Many people require multiple medications to control glucose and BP

Baker
HEART & DIABETES INSTITUTE

Role of medicines used to manage type 2 diabetes

- Glucose lowering – what are the aims?

Baker
HEART & DIABETES INSTITUTE

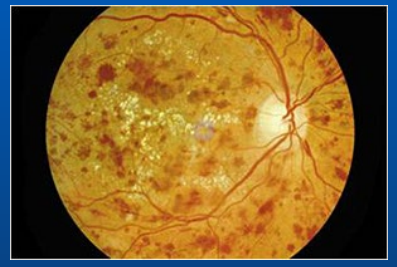
Chronic Diabetes Complications – traditional view

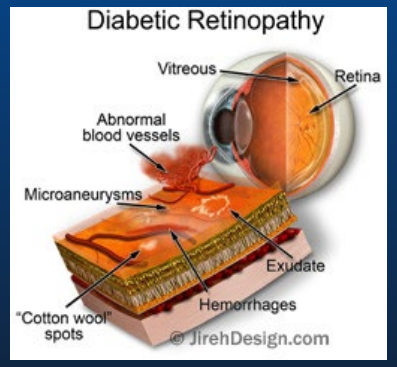
Microvascular Complications

'Pathognomonic' or characteristic of diabetes

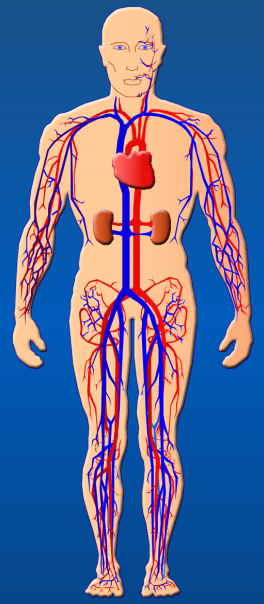
Directly due to prolonged hyperglycaemia

Prevented by good glycaemic control





Eye disease
Kidney disease
Nerve damage



Macrovascular Complications

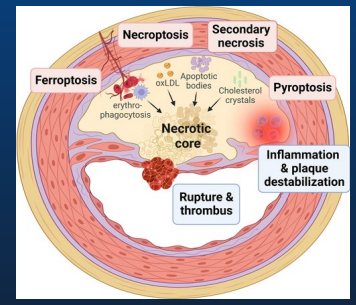
Can occur in people with or without diabetes

Risk is increased in diabetes

Many factors involved in aetiology

Good glycaemic control has only limited benefit

Heart attack
Stroke
Peripheral artery disease



Role of medicines used to manage type 2 diabetes

- Glucose lowering

‘Just’ lowering glucose is not enough to prevent the complications of diabetes

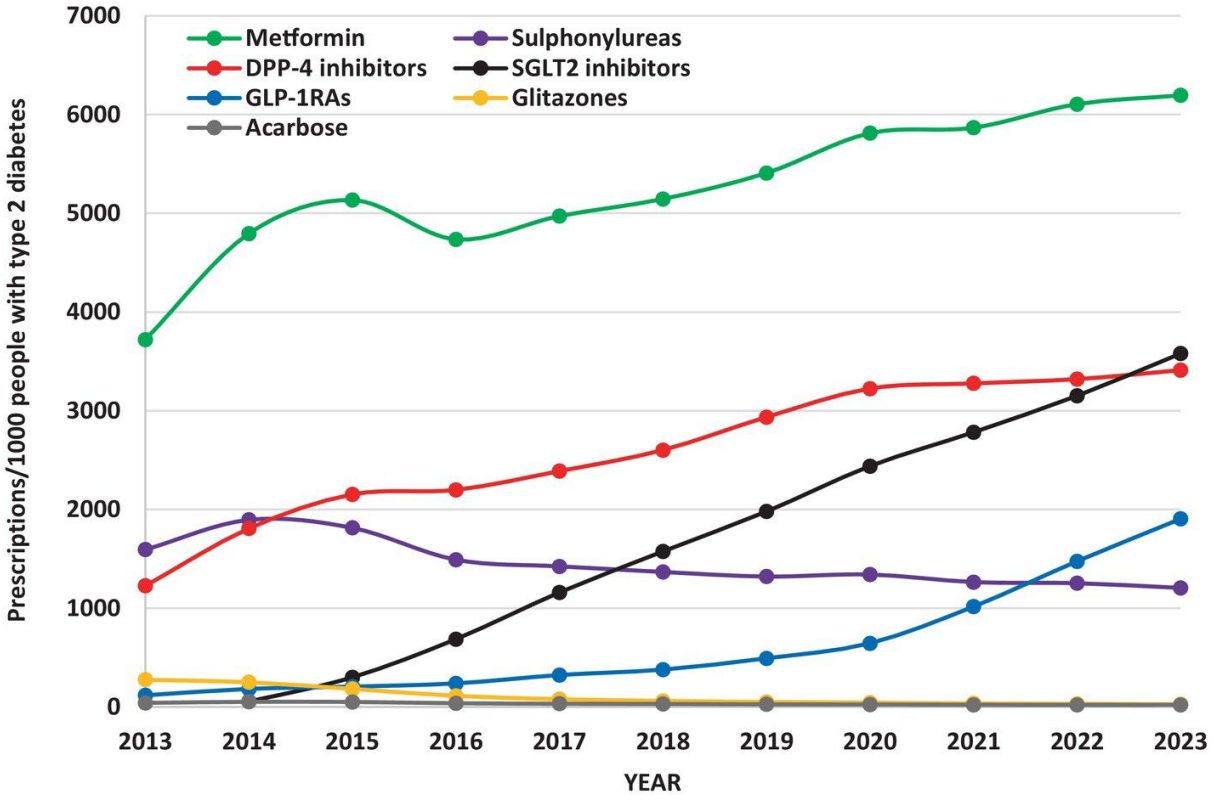
Baker
HEART & DIABETES INSTITUTE

Medicines used for T2DM – options and issues

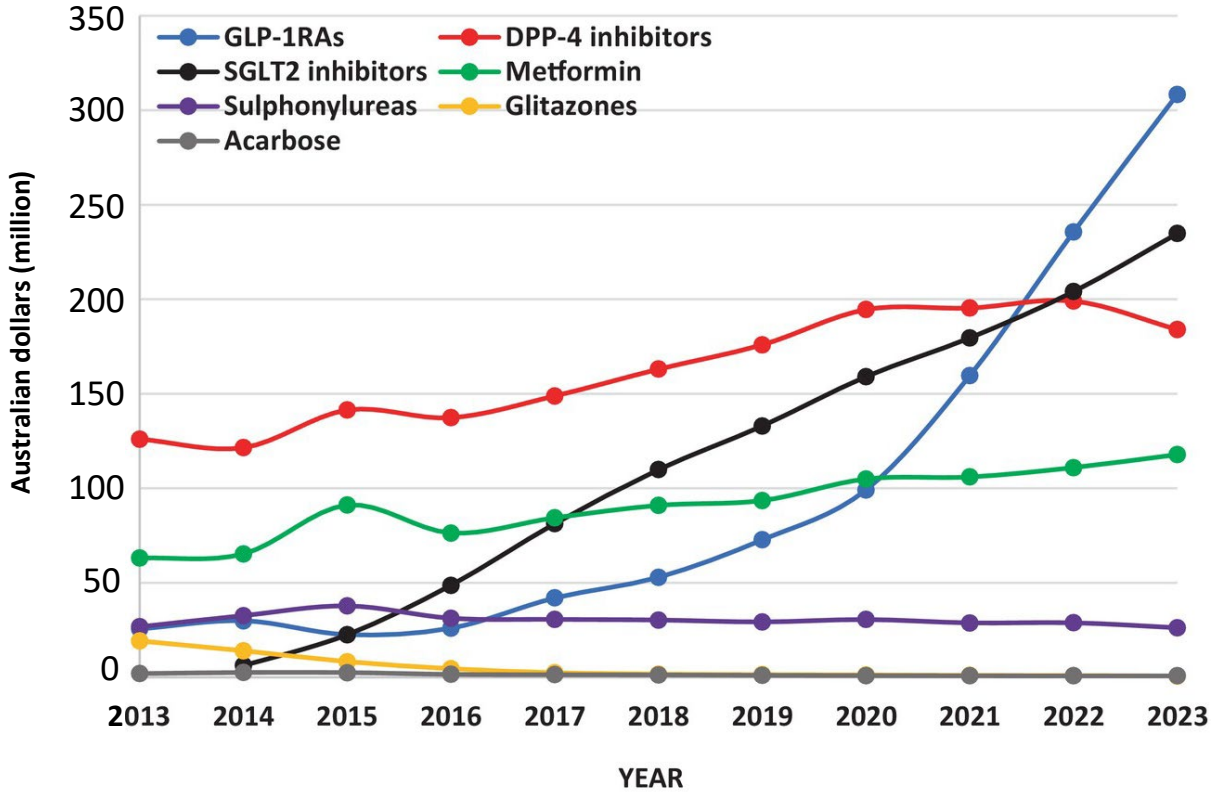
Baker
HEART & DIABETES INSTITUTE

Medicines used for T2DM

Usage



Cost



Baker HEART & DIABETES INSTITUTE

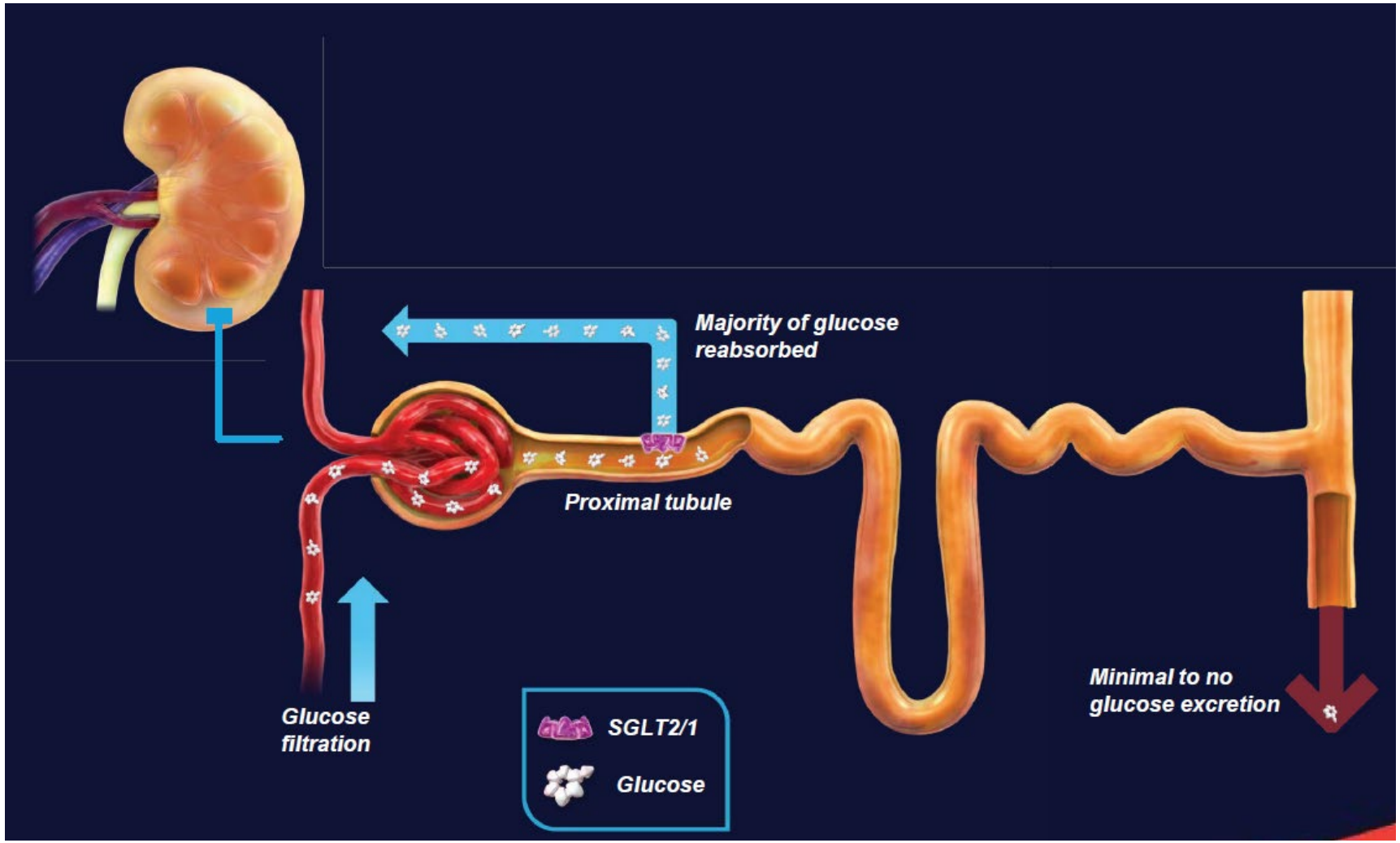
Hamblin. *Diabetes Obes Metab.* 2024;26:4924–4932

Medicines used for T2DM

- Multiple options – hard for primary care to keep up with best choices
- Frequent need for multiple drugs – adequate treatment vs polypharmacy
- Adherence
- Glucose-lowering vs impact on clinical outcomes (CVD, kidney etc)
- Cost (individual and to Medicare)
- Complexities of PBS

Baker
HEART & DIABETES INSTITUTE

SGLT2i



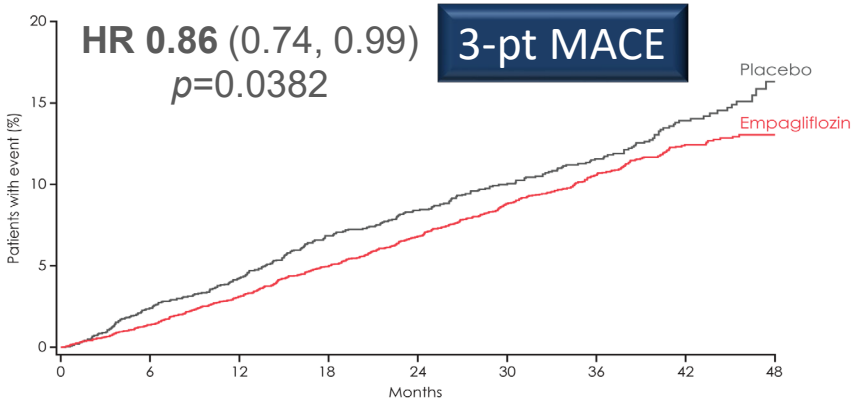
Baker
HEART & DIABETES INSTITUTE

Empagliflozin – CV outcome trial in T2DM

EMPA-REG OUTCOME®

HR 0.86 (0.74, 0.99)
p=0.0382

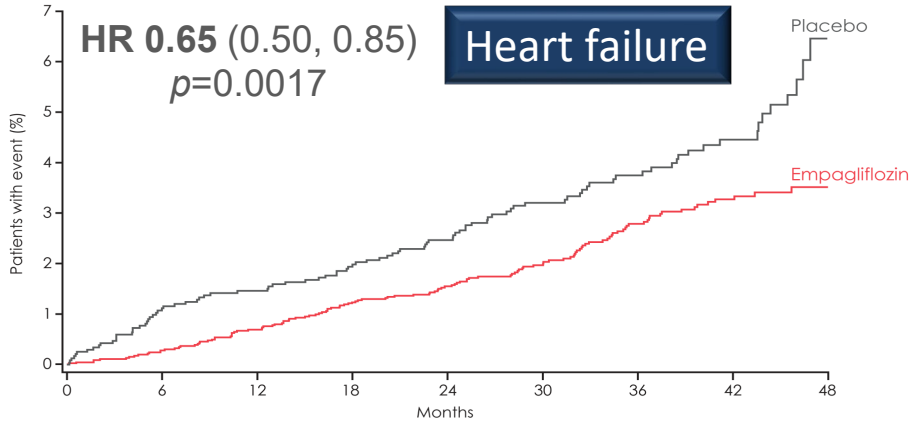
3-pt MACE



No. of patients									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

HR 0.65 (0.50, 0.85)
p=0.0017

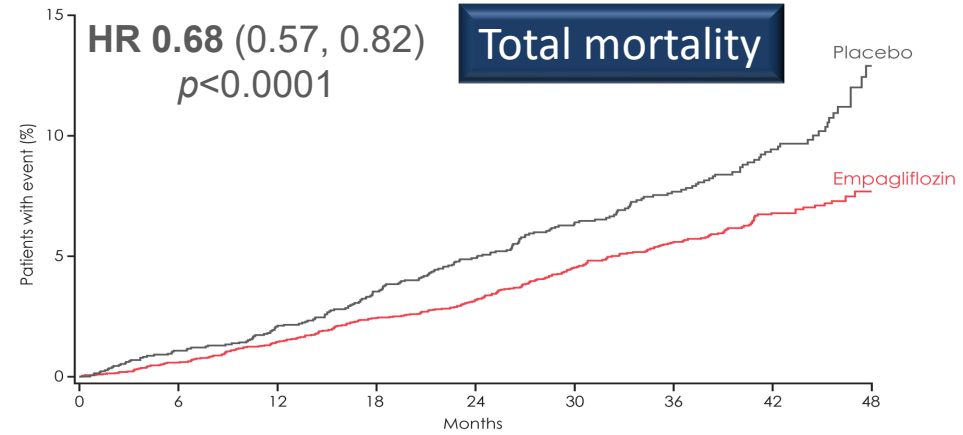
Heart failure



No. of patients									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

HR 0.68 (0.57, 0.82)
p<0.0001

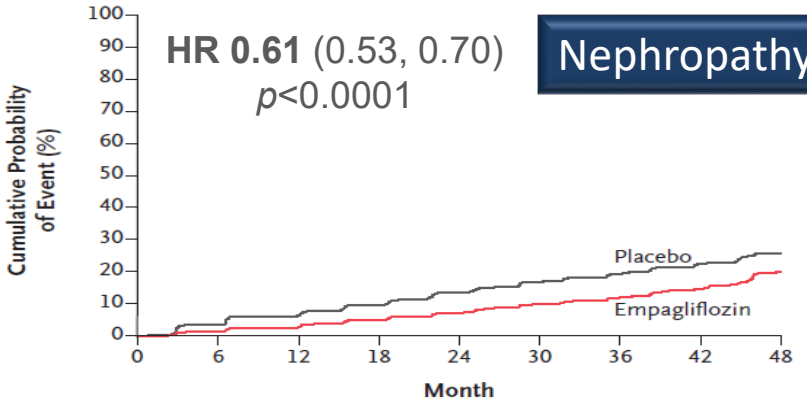
Total mortality



No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

HR 0.61 (0.53, 0.70)
p<0.0001

Nephropathy



lo. at Risk									
mpagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
lacebo	2061	1946	1836	1703	1433	1016	833	521	106

Baker HEART & DIABETES INSTITUTE

Zinman. *NEJM*. 2015;373(22):2117-28
Wanner. *N Engl J Med* 2016;375:323-34

CV and renal outcomes of SGLT2i in T2DM

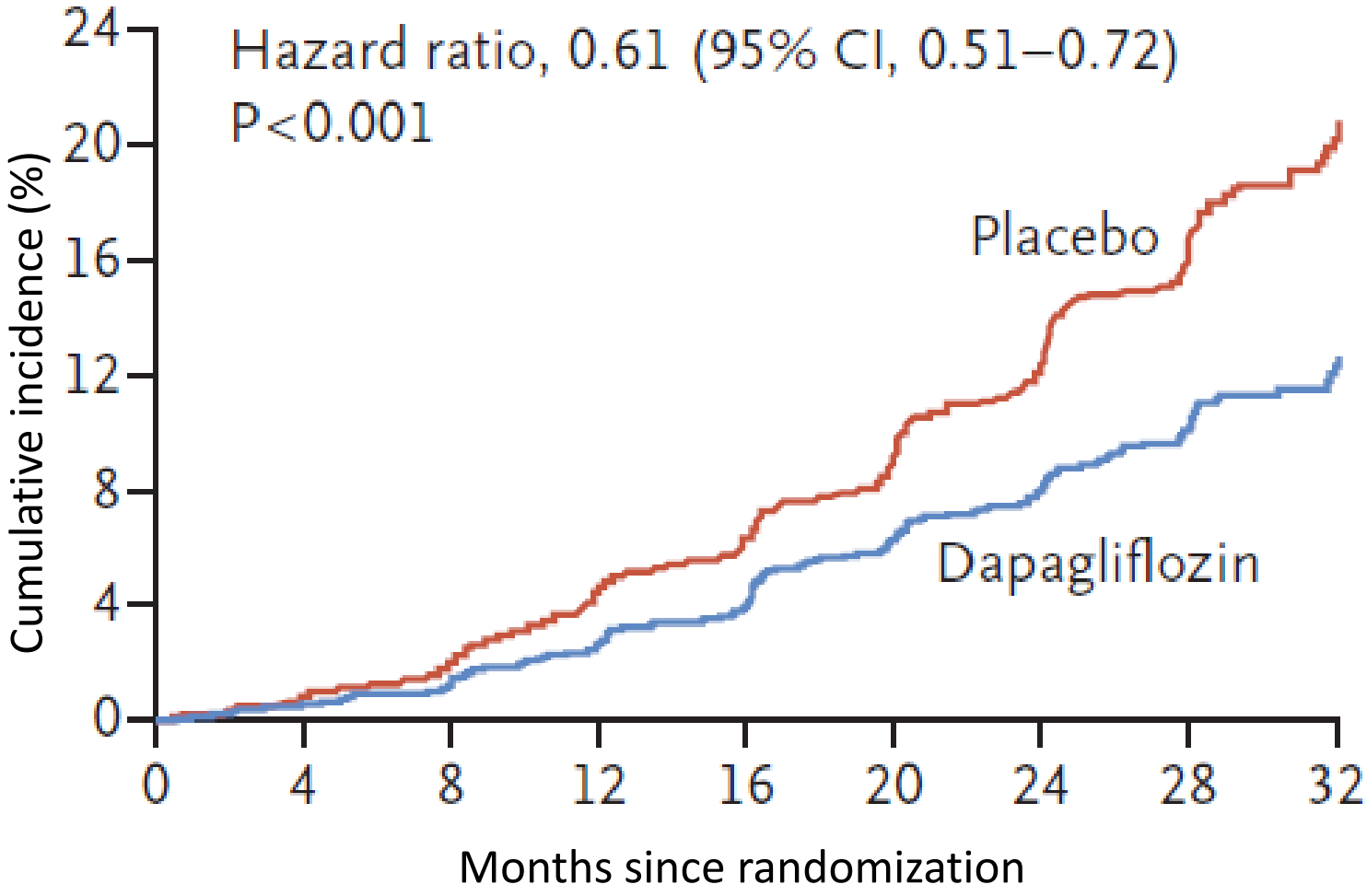
	MACE HR (95% CI)	CV Death HR (95% CI)	HHF HR (95% CI)	Renal HR (95% CI)
EMPA-REG OUTCOME[1]	**0.86** (0.74, 0.99)	**0.62** (0.49, 0.77)	**0.65** (0.50, 0.85)	**0.54 (0.40, 0.75)**
CANVAS Program[2]	**0.86** (0.75, 0.97)	**0.87** (0.72, 1.06)	**0.67** (0.52, 0.87)	**0.60 (0.47, 0.77)**
DECLARE-TIMI 58[3]	**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)	**0.81** (0.64, 1.03)

CV, cardiovascular; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events.

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.

Dapagliflozin – CKD with or without diabetes (Dapa CKD)

Outcome
50% decline in eGFR or ESKD or renal/CV death

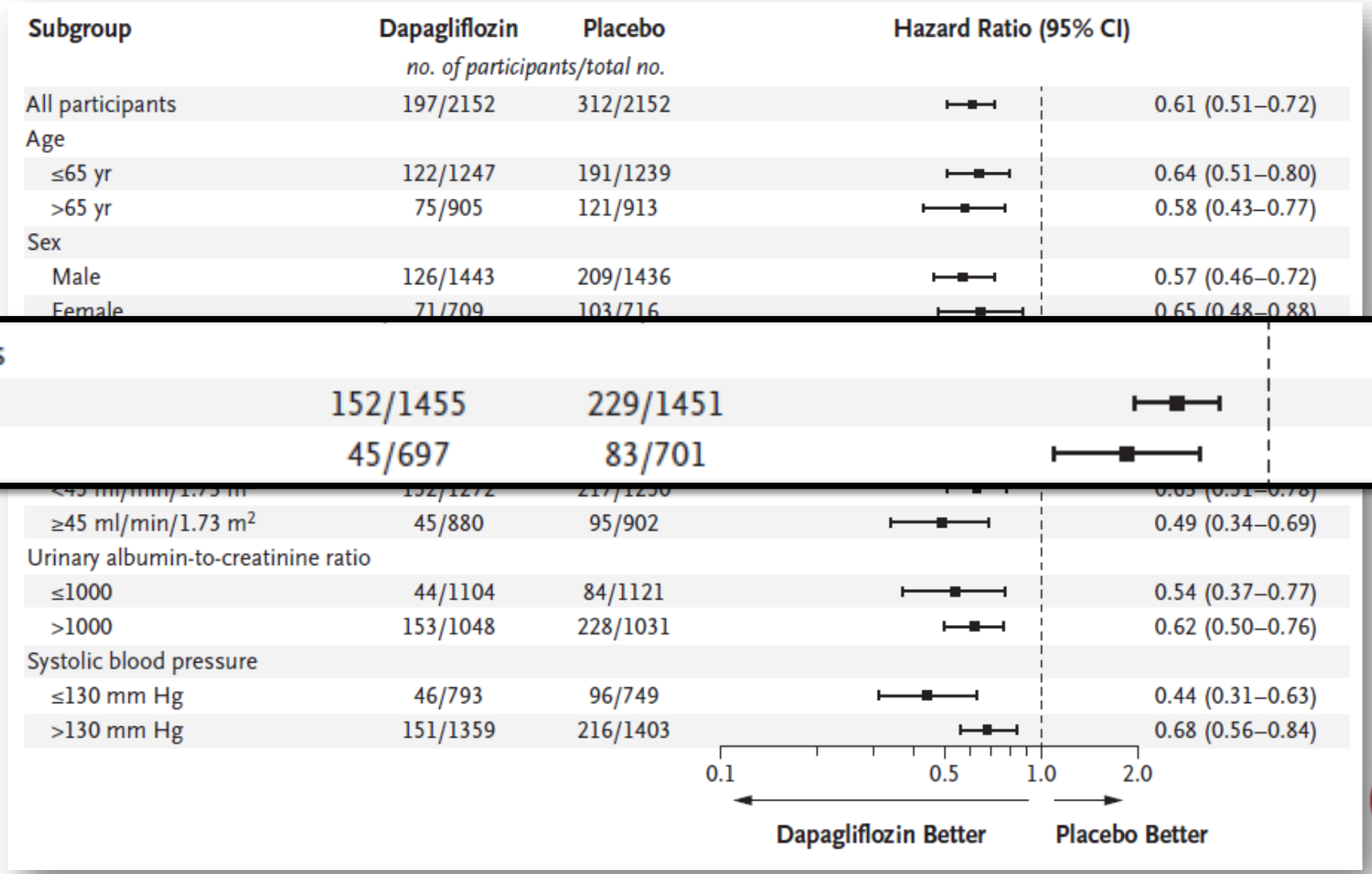


HR 0.61
(0.51-0.72)

Heerspink. *NEJM* 2020; 383:1436-46

Baker
HEART & DIABETES INSTITUTE

Dapagliflozin – CKD with or without diabetes (Dapa CKD)

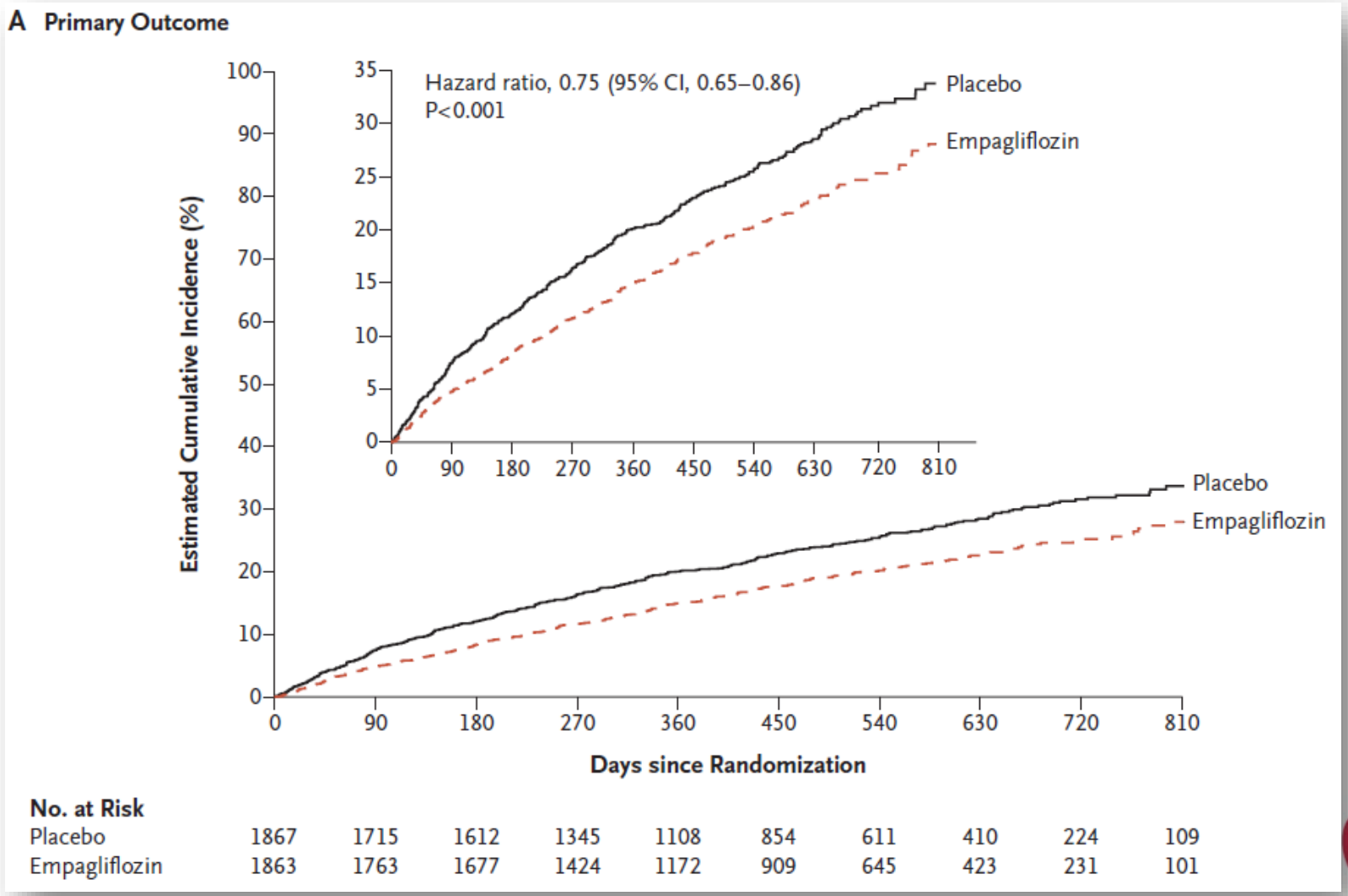


Heerspink. *NEJM* 2020; 383:1436-46

Baker HEART & DIABETES INSTITUTE

Empagliflozin – Heart failure with or without diabetes (EMPEROR Reduced)

Outcome
CVD death or HHF



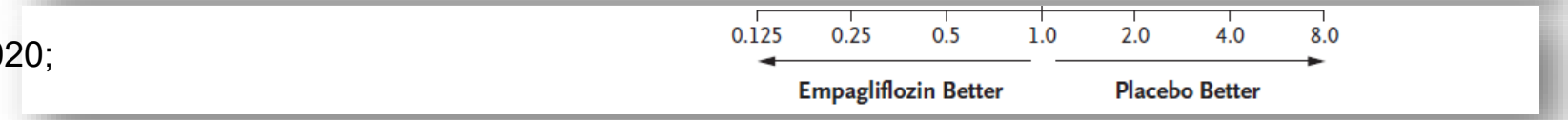
HR 0.75
(0.65-0.86)

Packer. *NEJM* 2020; 383:1413-24

Baker HEART & DIABETES INSTITUTE

Empagliflozin – Heart failure with or without diabetes

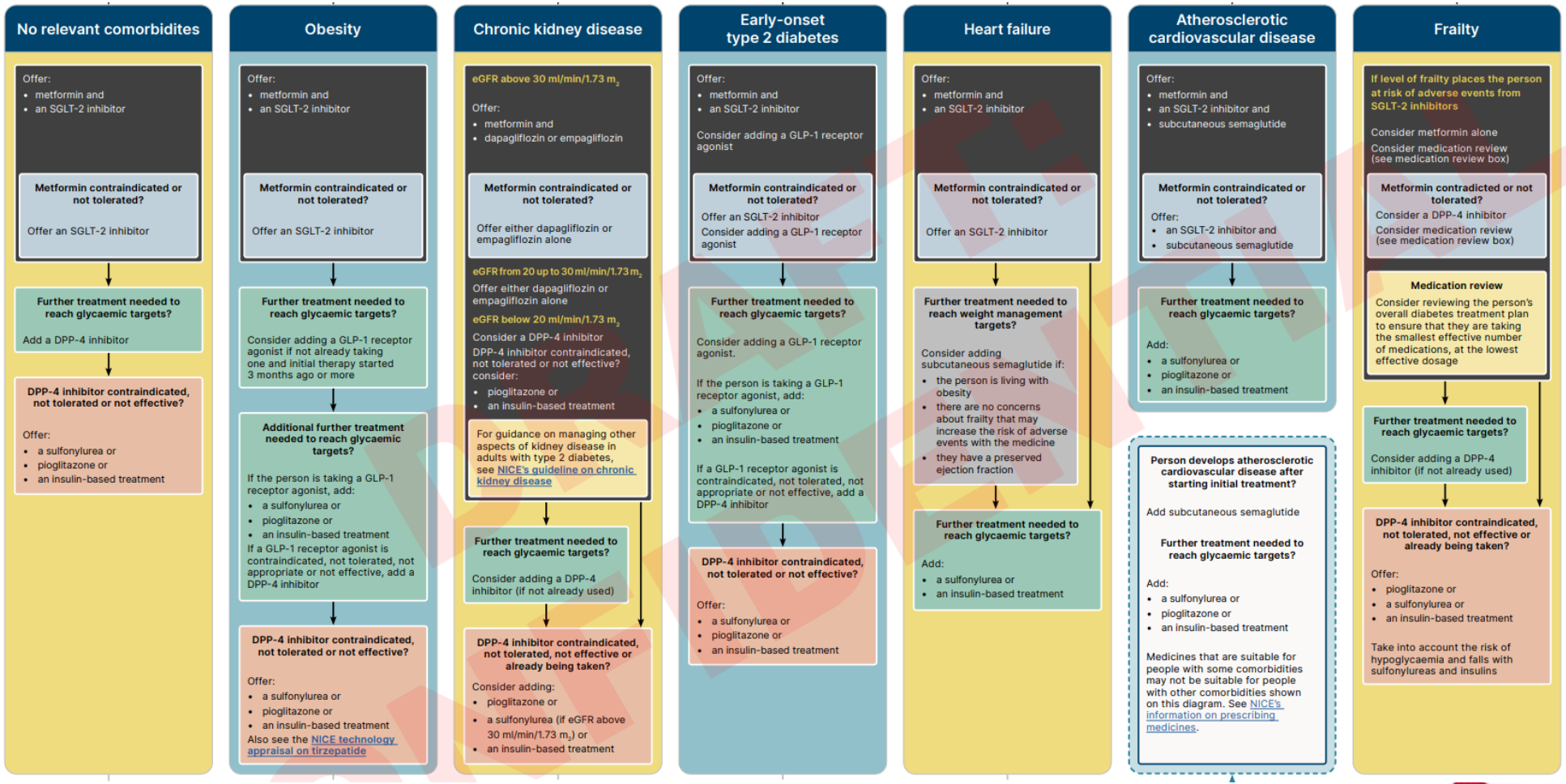
Subgroup	Empagliflozin (no. of patients with events/total no.)	Placebo (no. of patients with events/total no.)	Hazard Ratio (95% CI)
Baseline diabetes status			
Diabetes	200/927	265/929	0.72 (0.60–0.87)
No diabetes	161/936	197/938	0.78 (0.64–0.97)
≥65 yr	233/1188	269/1127	0.78 (0.66–0.93)
Sex			
Male	294/1426	353/1411	0.80 (0.68–0.93)
Female	67/437	109/456	0.59 (0.44–0.80)
Race			
White	264/1325	289/1304	0.88 (0.75–1.04)
Black	24/123	48/134	0.46 (0.28–0.75)
Asian	62/337	99/335	0.57 (0.41–0.78)
Other	5/51	14/63	0.41 (0.15–1.14)
Baseline body-mass index			
<30	226/1263	322/1300	0.70 (0.59–0.83)
≥30	135/600	140/567	0.85 (0.67–1.08)
Baseline eGFR (CKD-EPI)			
≥60	159/969	224/960	0.67 (0.55–0.83)
<60	202/893	237/906	0.83 (0.69–1.00)
HF hospitalization in ≤12 mo			
No	208/1286	285/1293	0.71 (0.60–0.85)
Yes	153/577	177/574	0.79 (0.64–0.99)
Cause of heart failure			



Packer. *NEJM* 2020; 383:1413-24

Baker HEART & DIABETES INSTITUTE

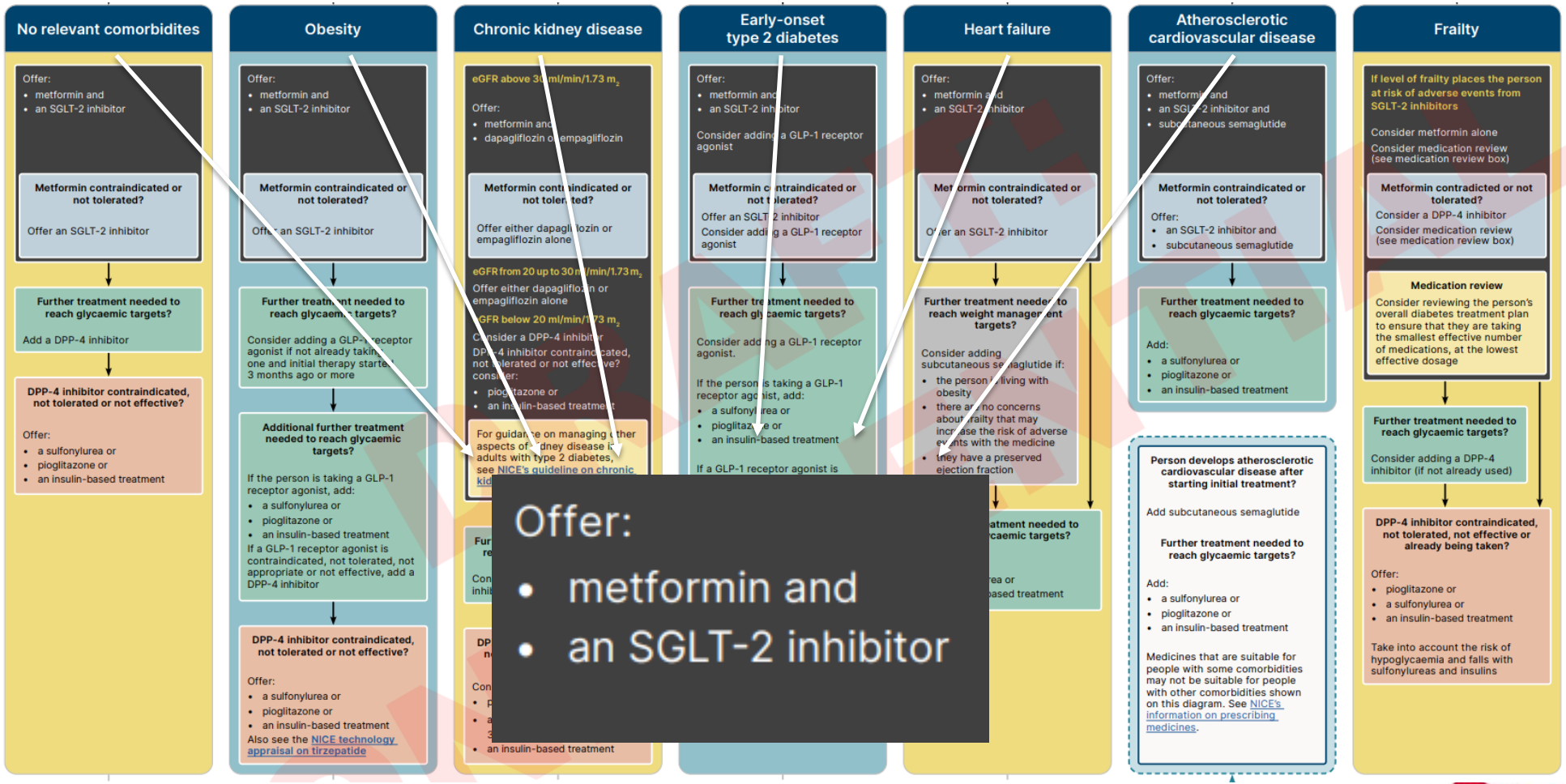
NICE 2025 draft guideline



https://www.nice.org.uk/guidance/indevelopment/gid-ng10336/documents

Baker HEART & DIABETES INSTITUTE

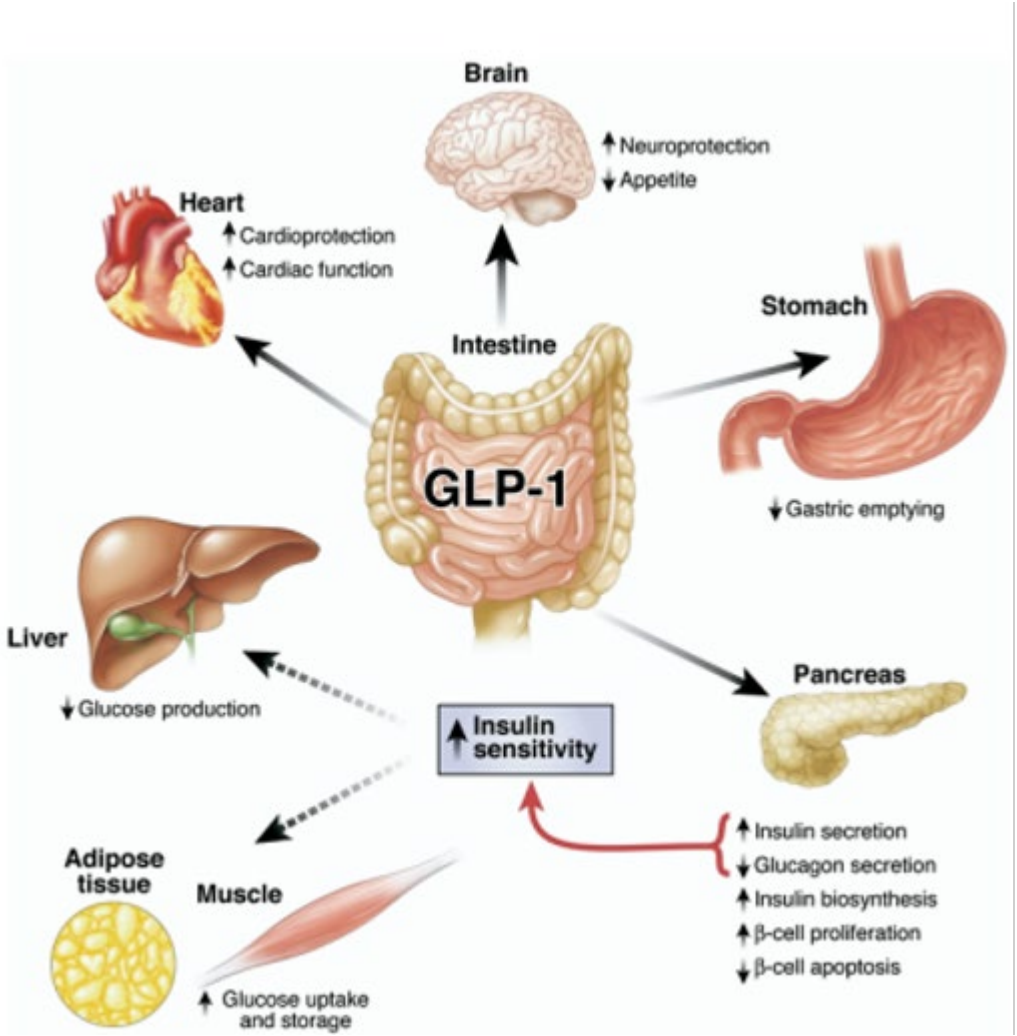
NICE 2025 draft guideline – all roads lead to Rome



https://www.nice.org.uk/guidance/indevelopment/gid-ng10336/documents

Baker HEART & DIABETES INSTITUTE

GLP1 receptor agonists



Baker HEART & DIABETES INSTITUTE

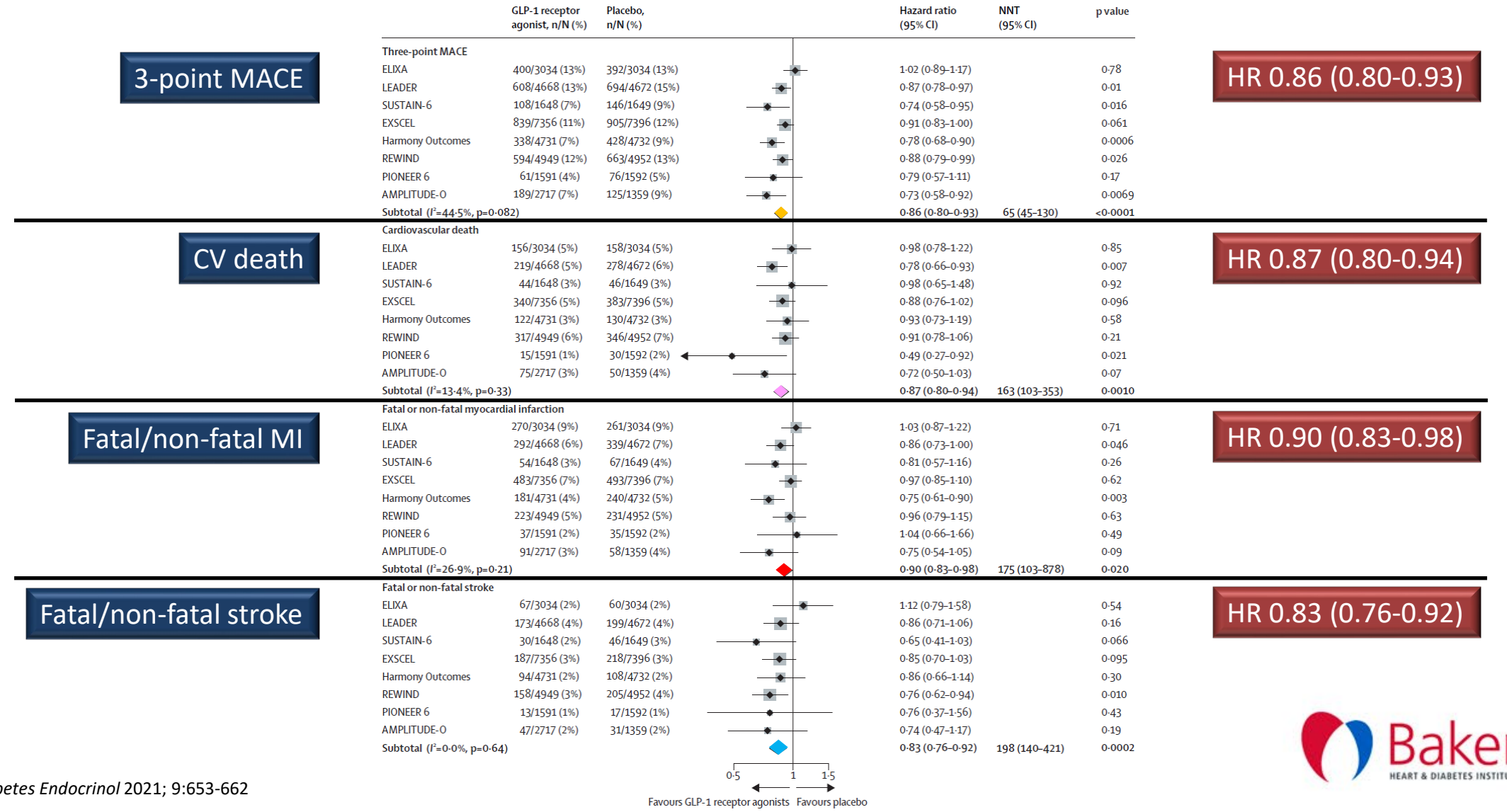
GLP1 Agonists and CV/renal outcomes in T2DM

3-point MACE

CV death

Fatal/non-fatal MI

Fatal/non-fatal stroke



HR 0.86 (0.80-0.93)

HR 0.87 (0.80-0.94)

HR 0.90 (0.83-0.98)

HR 0.83 (0.76-0.92)

Sattar. *Lancet Diabetes Endocrinol* 2021; 9:653-662

Baker HEART & DIABETES INSTITUTE

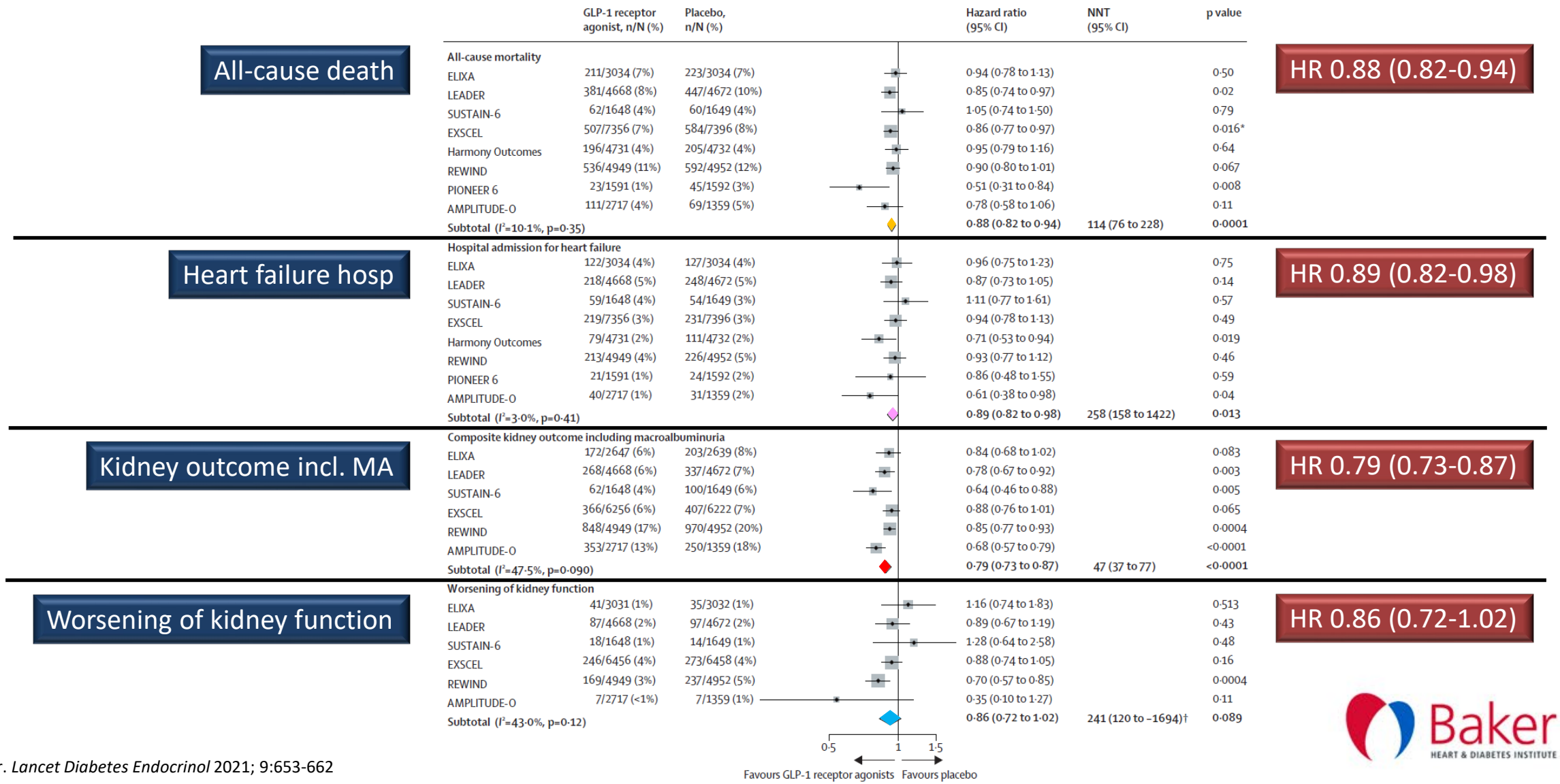
GLP1 Agonists and CV/renal outcomes in T2DM

All-cause death

Heart failure hosp

Kidney outcome incl. MA

Worsening of kidney function



HR 0.88 (0.82-0.94)

HR 0.89 (0.82-0.98)

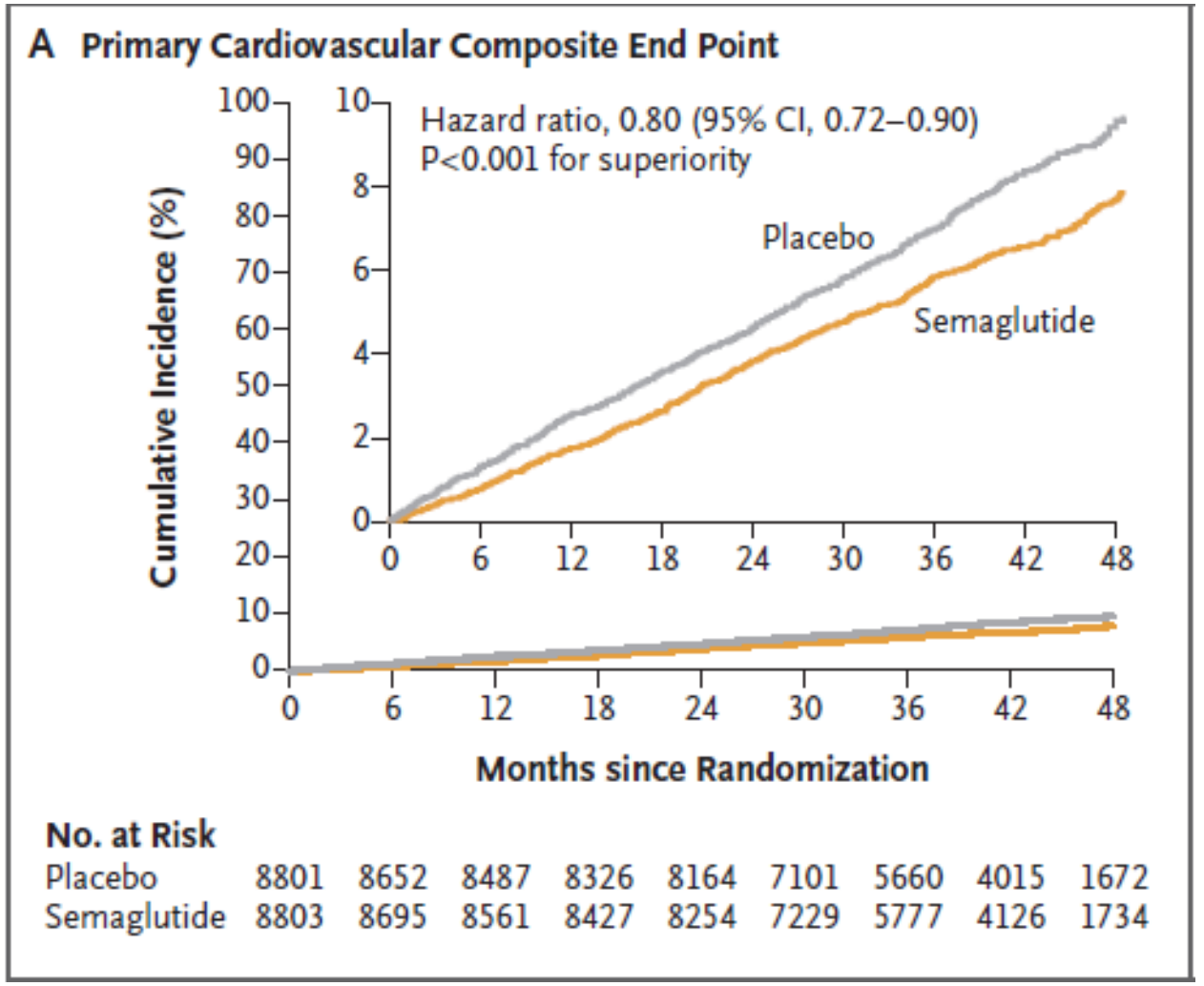
HR 0.79 (0.73-0.87)

HR 0.86 (0.72-1.02)

Sattar. *Lancet Diabetes Endocrinol* 2021; 9:653-662

Baker HEART & DIABETES INSTITUTE

Semaglutide in obesity without DM



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

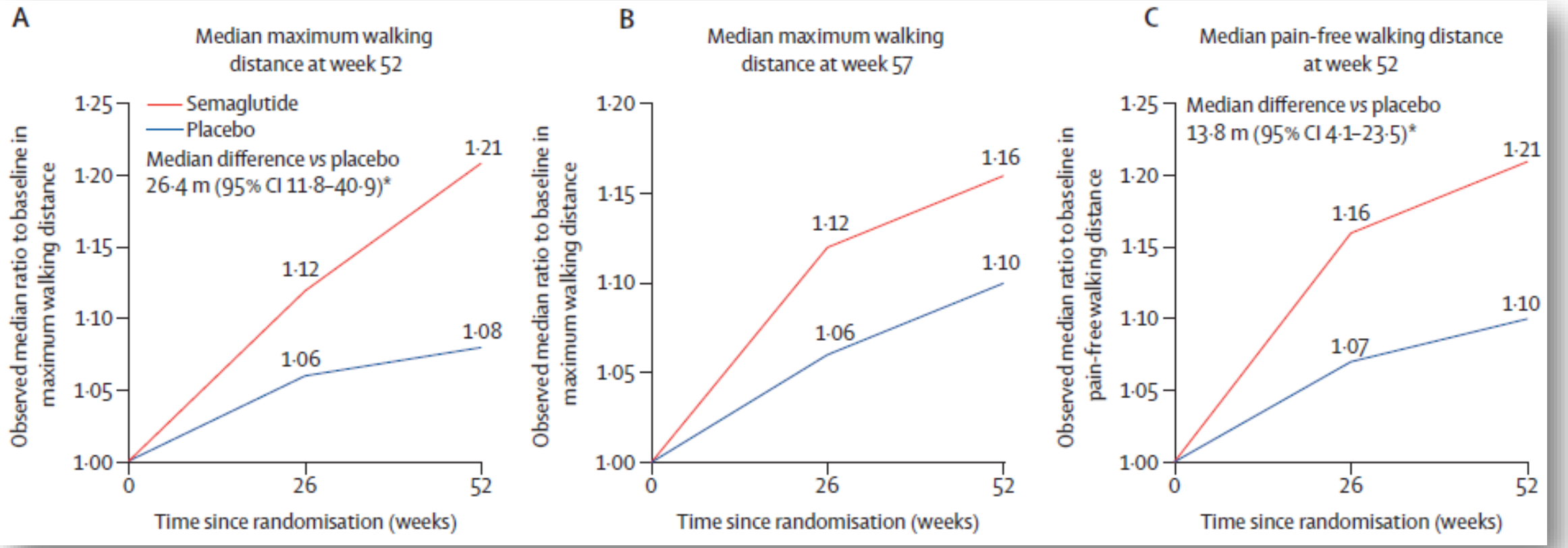
Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

Lincoff. *N Engl J Med*. 2023 Nov 11. doi: 10.1056/NEJMoa2307563

Baker HEART & DIABETES INSTITUTE

Semaglutide improves walking distance in PAD in T2DM



Bonaca. *Lancet* 2025; 405: 1580–93

Meta-analysis of RCTs shows benefits are not diminished in >75s

Table 2 – Meta-analysis results versus placebo for patients 75 years or older and patients younger than 75 years.

Outcome	Number of trials	Age categories (n events/N analyzed)[a]	HR	95% CI	P-interaction	I^2
GLP-1 receptor agonists versus placebo						
3-p MACE	2	All patients	0.87	0.79 to 0.97	0.07	40%
		<75 years (2598/22,006)	0.92	0.85 to 0.99		
		≥75 years (448/2086)	0.75	0.61 to 0.92		
SGLT2 inhibitors versus placebo						
3-p MACE	2	All patients	0.91	0.83 to 0.99	0.16	4%
		<75 years (2075/22,432)	0.93	0.85 to 1.02		
		≥75 years (256/1748)	0.77	0.60 to 0.99		
CVD	2	All patients	0.78	0.58 to 1.06	0.94	71%
		<75 years (691/22,432)	0.79	0.52 to 1.20		
		≥75 years (112/1748)	0.77	0.40 to 1.46		
CVDHHF	2	All patients	0.75	0.62 to 0.90	0.83	52%
		<75 years (1089/22,432)	0.76	0.63 to 0.91		
		≥75 years (187/1748)	0.71	0.40 to 1.27		
HHF	2	All patients	0.71	0.61 to 0.83	0.70	0%
		<75 years (607/22,432)	0.72	0.61 to 0.84		
		≥75 years (102/1748)	0.64	0.36 to 1.12		
Renal composite outcome	2	All patients	0.59	0.52 to 0.65	0.49	0%
		<75 years (1147/21,667)	0.59	0.51 to 0.68		
		≥75 years (133/1668)	0.51	0.36 to 0.65		

Abbreviations: HR, hazard ratio; CI, confidence interval; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter 2; 3-p MACE, 3-point composite of major adverse cardiovascular events; CVD, cardiovascular death; CVDHHF, cardiovascular death or hospitalization for heart failure; HHF, hospitalization for heart failure. [a]Number of events (n) and patients analyzed (N) are both for intervention and placebo arms.

Baker HEART & DIABETES INSTITUTE

Karigiannis. *DRCP* 174(2021)108737

TGA indications and PBS restrictions

Indication (TGA)	PBS	Key PBS restrictions
Ozempic		
T2DM for glucose lowering (incl. monotherapy)	✓	A1c >7.0% (excl. monotherapy) Not 1st line If SGLT2i can't be used
Wegovy		
Wt management CVD risk reduction	× ×	
Dapagliflozin/Empagliflozin		
T2DM for glucose lowering (incl. monotherapy) CV prevention CKD Heart failure	✓ ✓ ✓ ✓	A1c >7.0% (excl. monotherapy) DM plus high CV risk (no A1c limit) ACR 22.6-565 mg/mmol NYHA classes II, III or IV

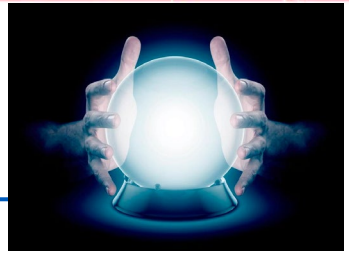
How should glucose-lowering drugs be selected?

- **For those at elevated CV or renal risk**
  - Add SGLT2i or GLP1-RA, irrespective of A1c – only partially supported by PBS

- **For 'pure' glucose lowering**
  - Most classes have a potential role
  - Avoidance of hypoglycaemia is valuable
  - Avoidance of weight gain is desirable, but not of proven benefit for hard outcomes

Baker
HEART & DIABETES INSTITUTE

What does the future hold?



- **Likely further evidence about the broader benefits of SGLT2i and GLP1-RA**
  - Liver disease, cognitive function
- **Better evidence about potential harms of GLP1-RA**
  - Eye complications, muscle loss
- **Oral GLP1-RA**
- **GLP-1-like drugs that preserve muscle mass/function**
- **Incorporation of technology (CGM and insulin pumps) into T2DM**

Baker
HEART & DIABETES INSTITUTE

Summary

- Multiple options for drug management of type 2 diabetes
- Glucose lowering by any means lowers risk of microvascular disease
- SGLT2i and GLP-1RA further lower renal and cardiovascular risk through non-glucose mechanisms
- SGLT2i and GLP1-RA often need to be used based on CV/renal risk, not just for HbA1c

Baker
HEART & DIABETES INSTITUTE

Resources

- **Royal Australian College of General Practitioners (RACGP) Guidelines**
  - https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/management-of-type-2-diabetes/introduction

- **Australian Diabetes Society (ADS) Clinical Guidelines**
  - https://www.diabetessociety.com.au/guideline/

Baker
HEART & DIABETES INSTITUTE