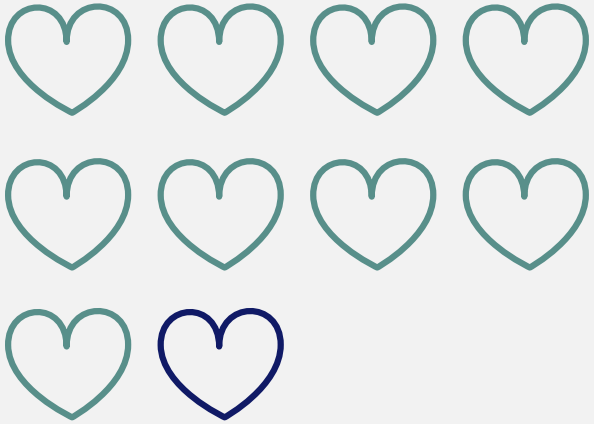
Impatto dei nuovi farmaci sugli aspetti cardio-renali

Dott. Olga Eugenia Disoteo

CAPTURE study shows the high incidence of CVD in people with T2D

The study found that **1/3 of people** with T2D have established cardiovascular disease[1]



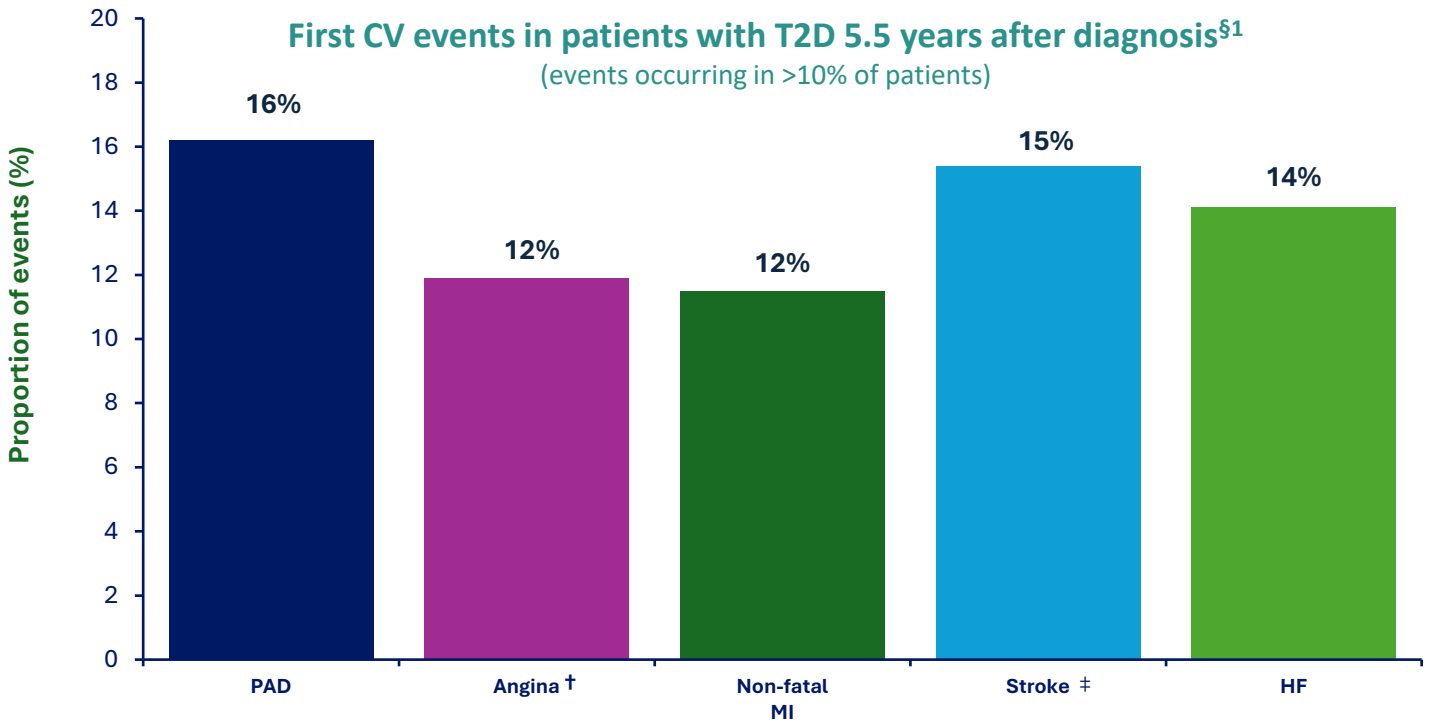
9/10 people with T2D and established CVD have ASCVD[1].

ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; T2D, type 2 diabetes.

1. Mosenzon O, et al. Cardiovasc Diabetol. 2021;20:154.

18% of people with T2D experience their first CV event within the first 5–6 years post diagnosis[1]

Cohort study of 34,198 patients with T2D*

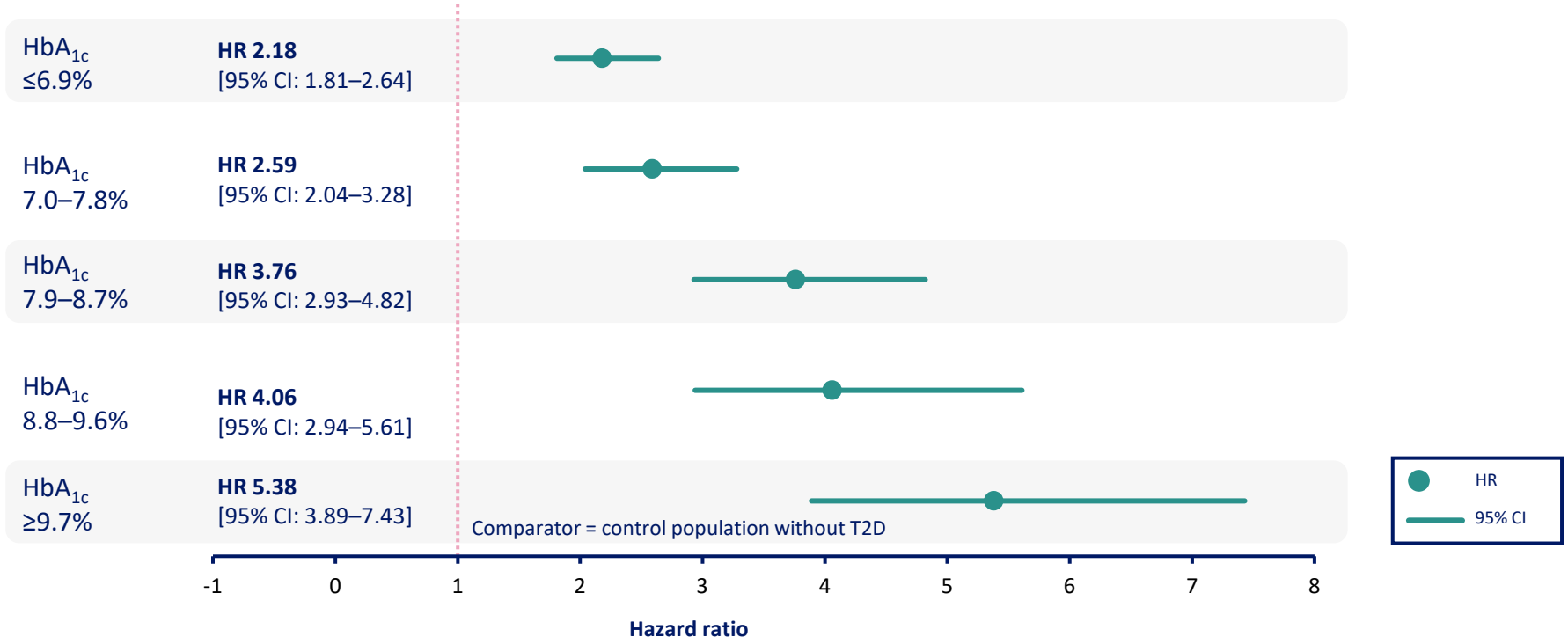


Heart attacks and strokes occur over **10 years earlier** in people with T2D than those without and will occur with greater severity[2,3]

CV, cardiovascular; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; T2D, type 2 diabetes; UK, United Kingdom.
**Full cohort including non-diabetic population ~1.9 million patients; †Includes stable and unstable angina; ‡Includes ischaemic stroke and stroke not further specified. §Results rounded up or down to nearest percentage point*
1. Shah AD et al. Lancet Diabetes Endocrinol 2015;3:105–113; 2. Low Wang CC et al. Circulation 2016;133:2459–2502; 3. Echouffo-Tcheugui JB et al. Eur Heart J 2018;39:2376–2386.

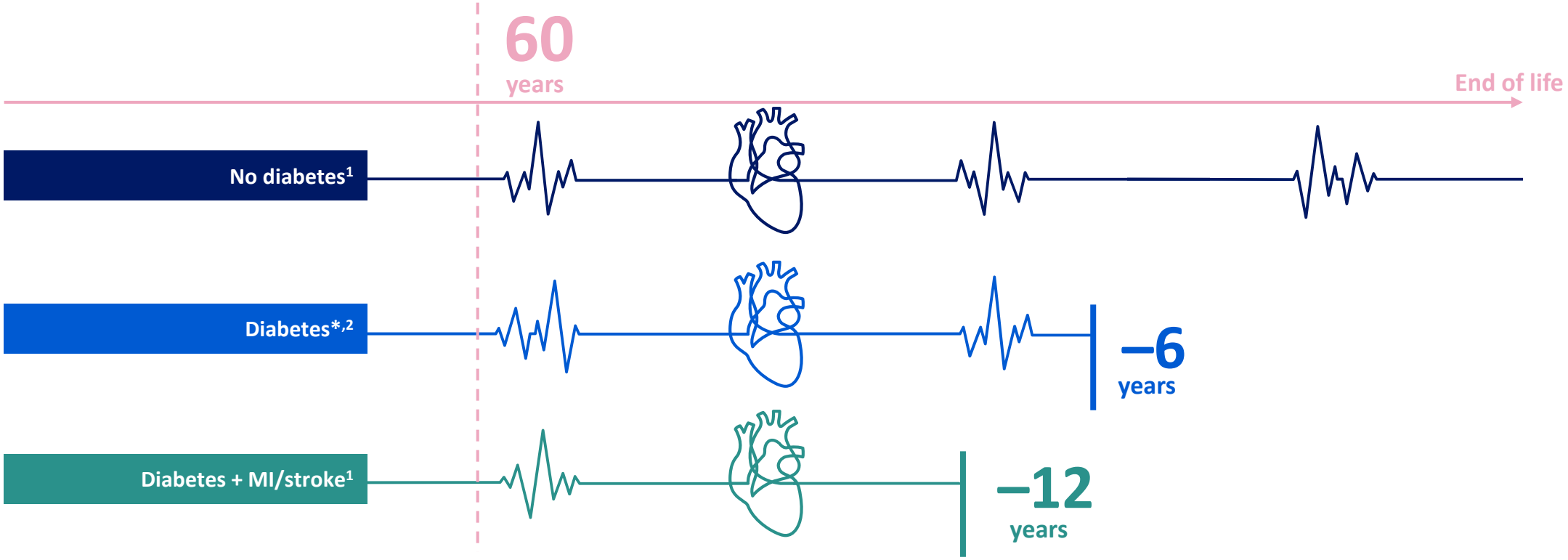
CV mortality risk increases with increasing HbA_{1c}

Association between T2D and CV mortality (<55 years), n = 78,086[1]



Data for people with T2D from the Swedish National Diabetes Register and controls without T2D matched for age, sex and county with 4.6 years mean follow-up.
Multivariate analysis, adjusting for various CVD risk factors.
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CVD, cardiovascular disease; HbA_{1c}, glycated haemoglobin; HR, hazard ratio; T2D, type 2 diabetes.
1. Tancredi M et al. N Engl J Med 2015;373:1720–1732.

Life expectancy is reduced by 12 years in people with diabetes with pre-existing ASCVD[1,2]

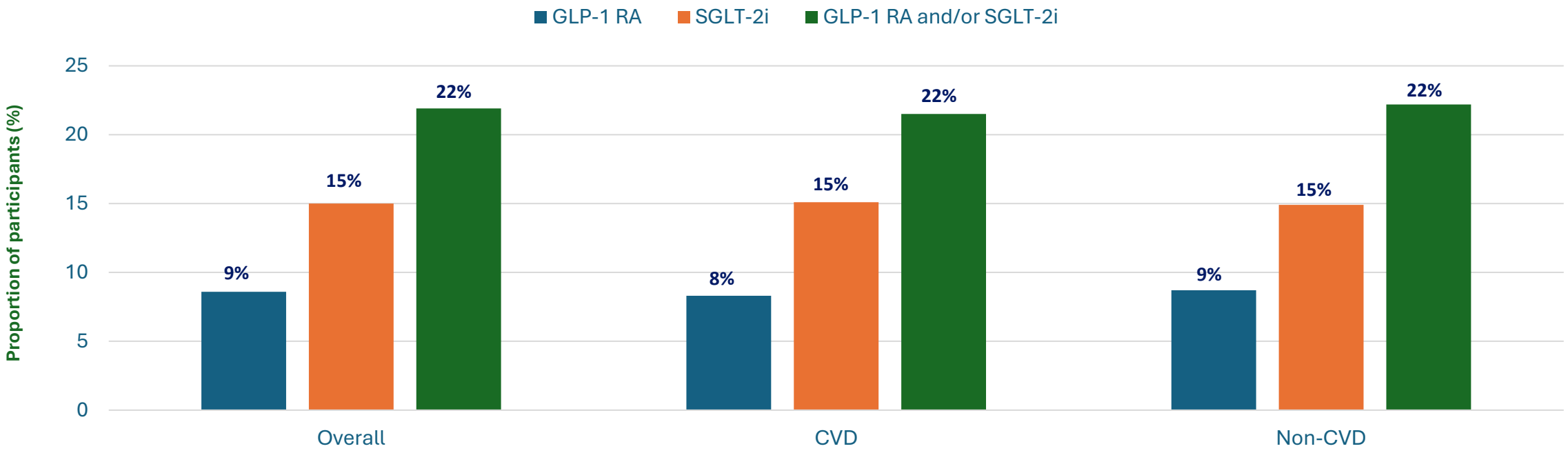


Early screening and further management of cardiovascular risk among younger and newly diagnosed people with T2D is required to protect them from the risk of stroke[1,2].

ASCVD, atherosclerotic cardiovascular disease; MI, myocardial infarction; T2D, type 2 diabetes.
**Diagnosed at age 45.*
1. Di Angelantonio E et al. JAMA 2015;314:52–60; 2. Sattar N et al. Circulation 2019;139:2228–2237.

Only 2 in 10 people with T2D and CVD or CV risk factors receive treatment proven to reduce the risk of ASCVD[1]

Use of glucose-lowering agents with demonstrated CV benefit[1].

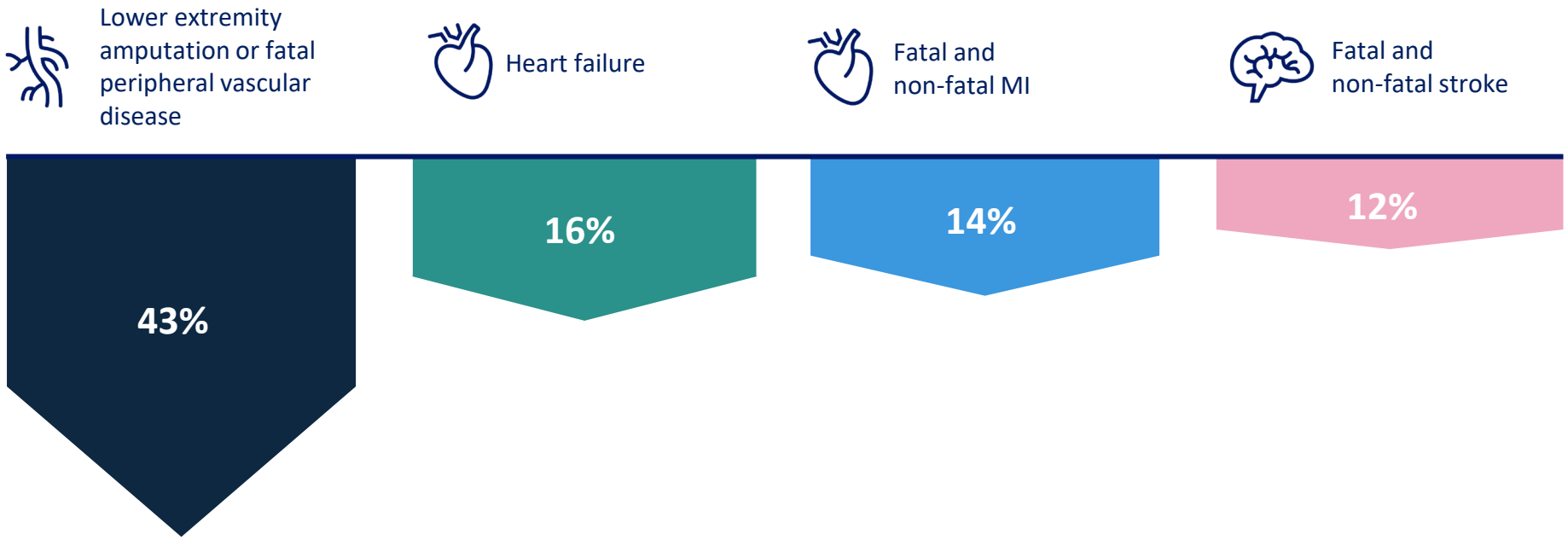


ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes.
GLP-1RAs included dulaglutide, liraglutide and semaglutide; and SGLT2is: canagliflozin, dapagliflozin and empagliflozin.

1. Mosenzon O et al. Cardiovasc Diabetol 2021;20:154.

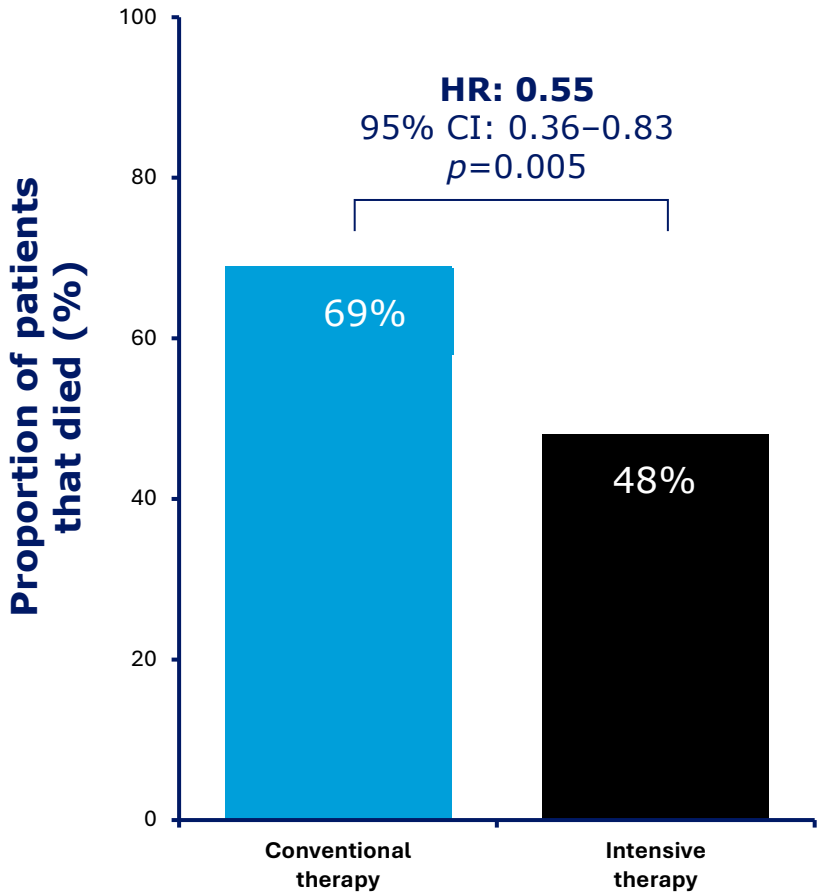
Better HbA1c control is associated with reductions in CV events

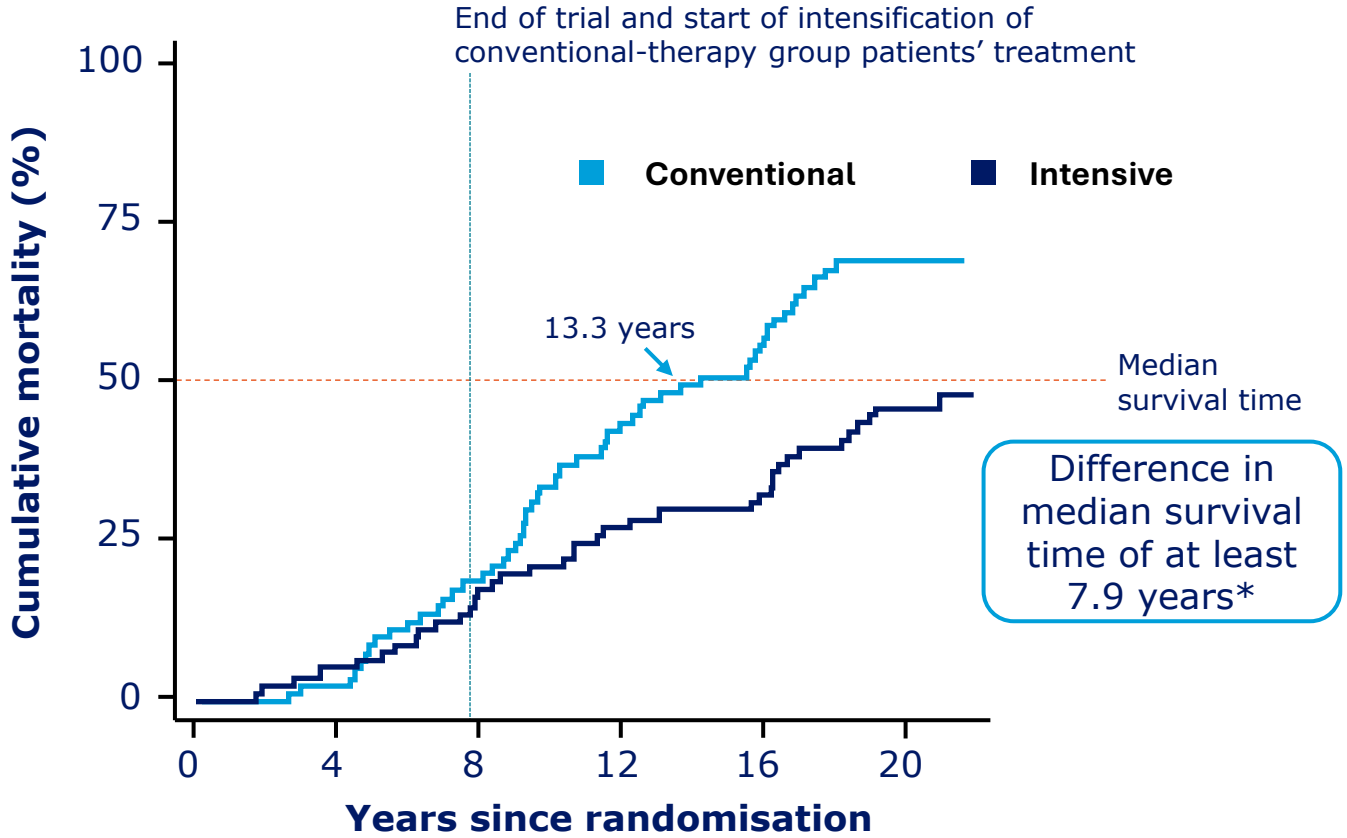
Every 1% drop in HbA_{1c} can reduce long-term diabetes complications[1]



CV, cardiovascular; HbA1c, glycated haemoglobin; MI, myocardial infarction.
1. Stratton IM, et al. BMJ. 2000; 321:405–412.

STENO-2: Mortality at 21 years' follow-up





Difference in median survival time of at least 7.9 years*

Patients at risk

Intensive	80	76	66	58	54	43
Conventional	80	78	65	45	34	24

*No formal calculation possible as <50% mortality in intensive therapy group. CI, confidence interval; HR, hazard ratio

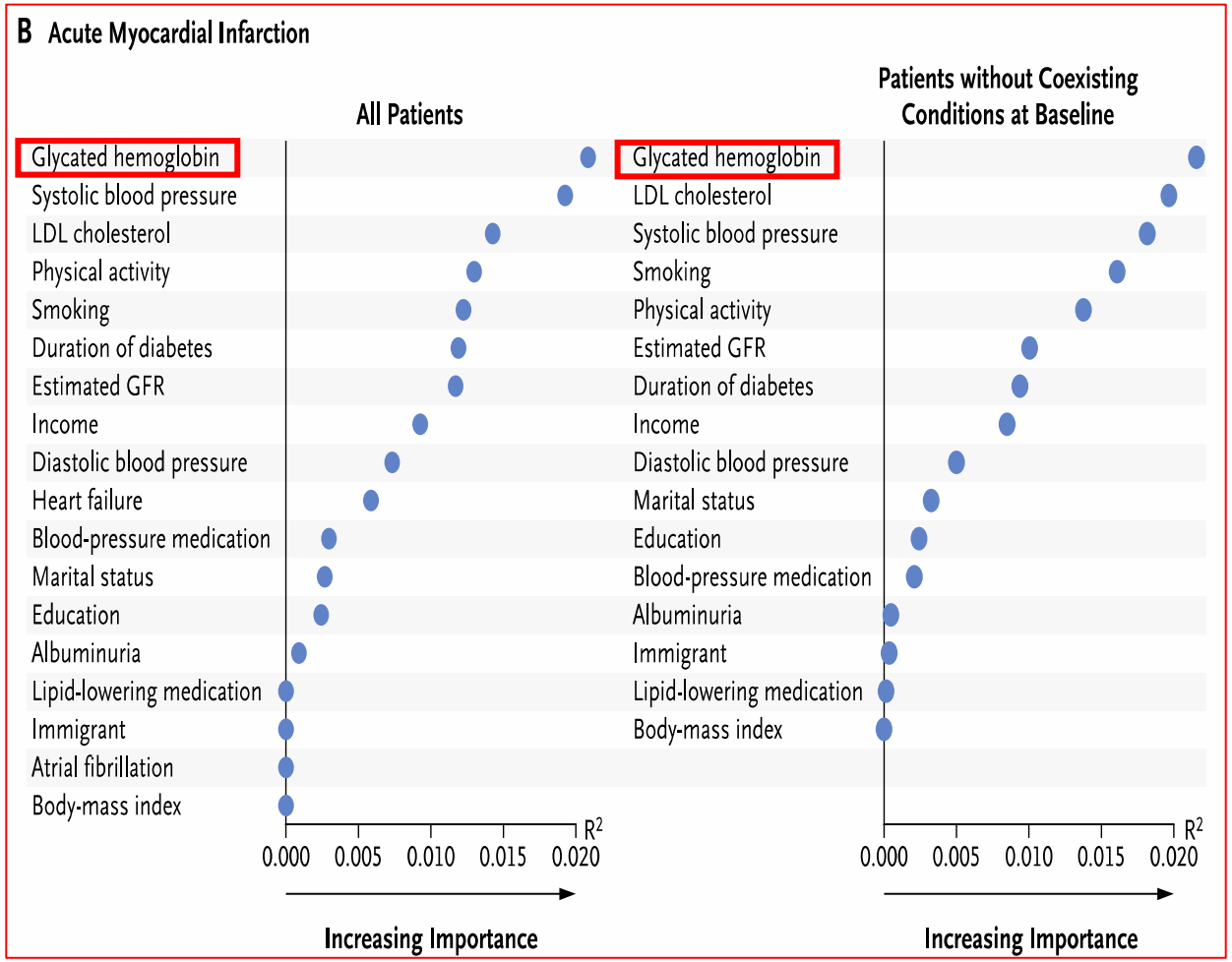
Gæde P et al. *Diabetologia* 2016;59:2298–2307

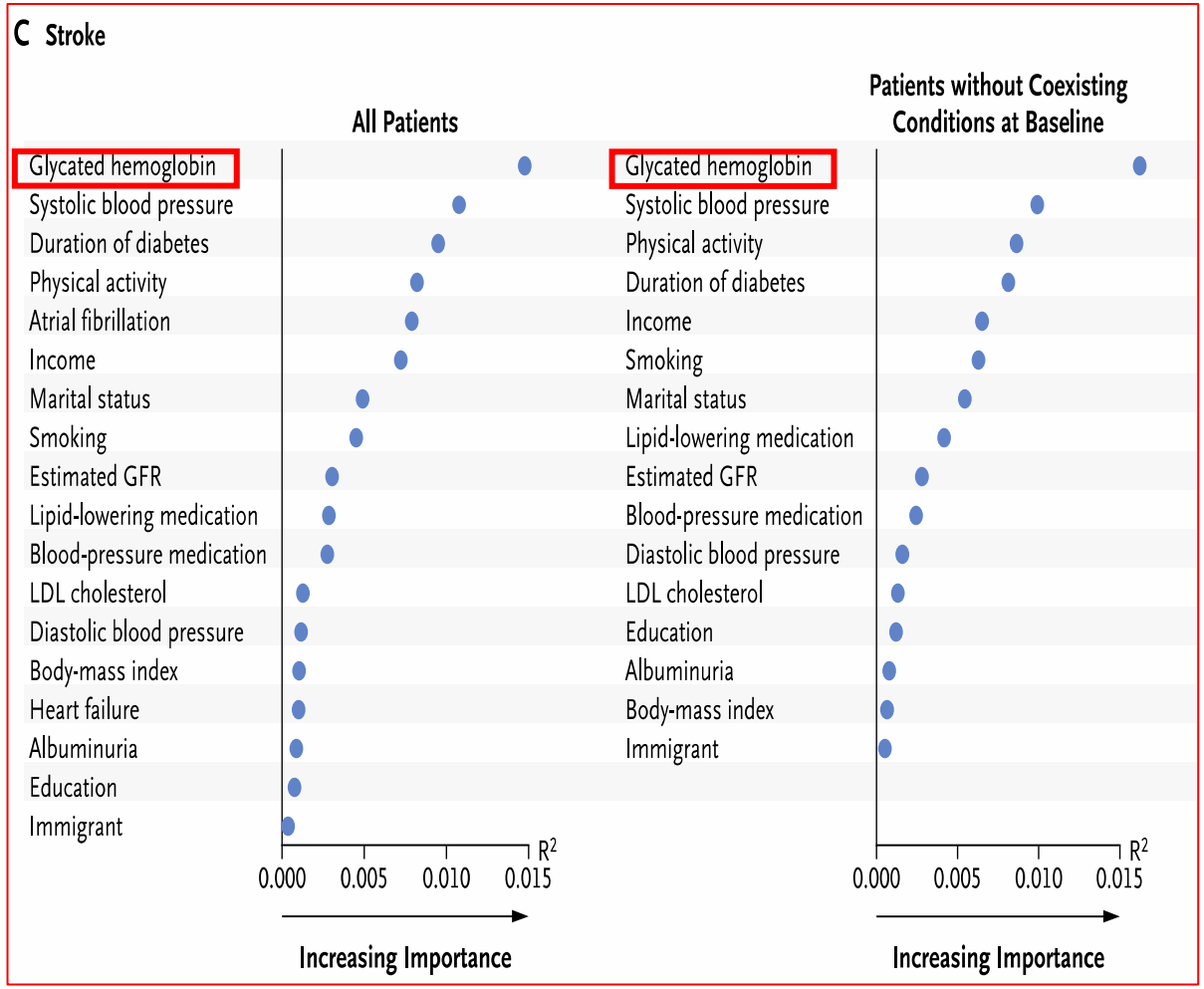
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

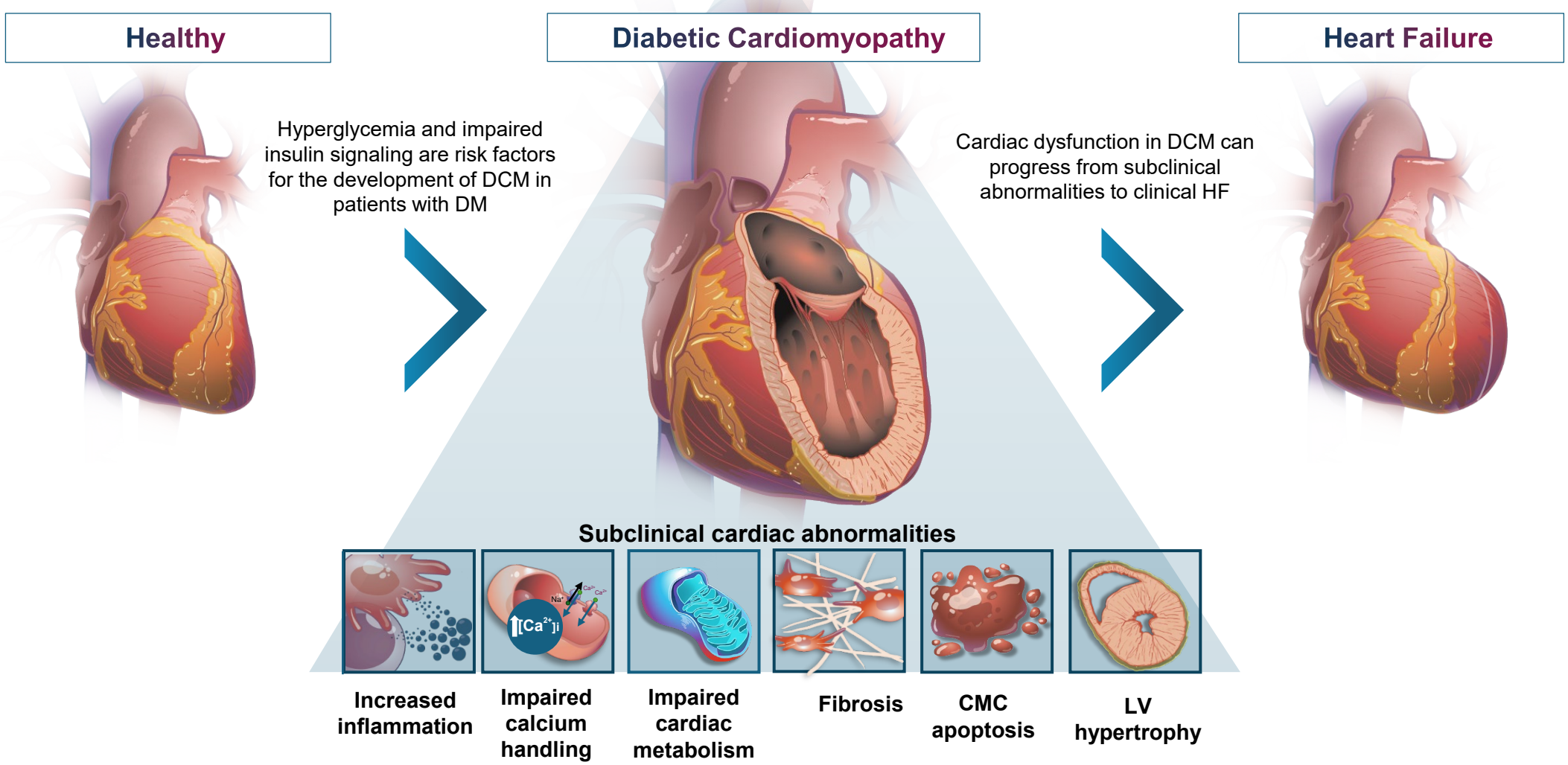
Rawshani A et al. *N Engl J Med* 2018;379:633–644

Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes





Cardiac Abnormalities of Type 2 Diabetes Increase the Risk for Heart Failure

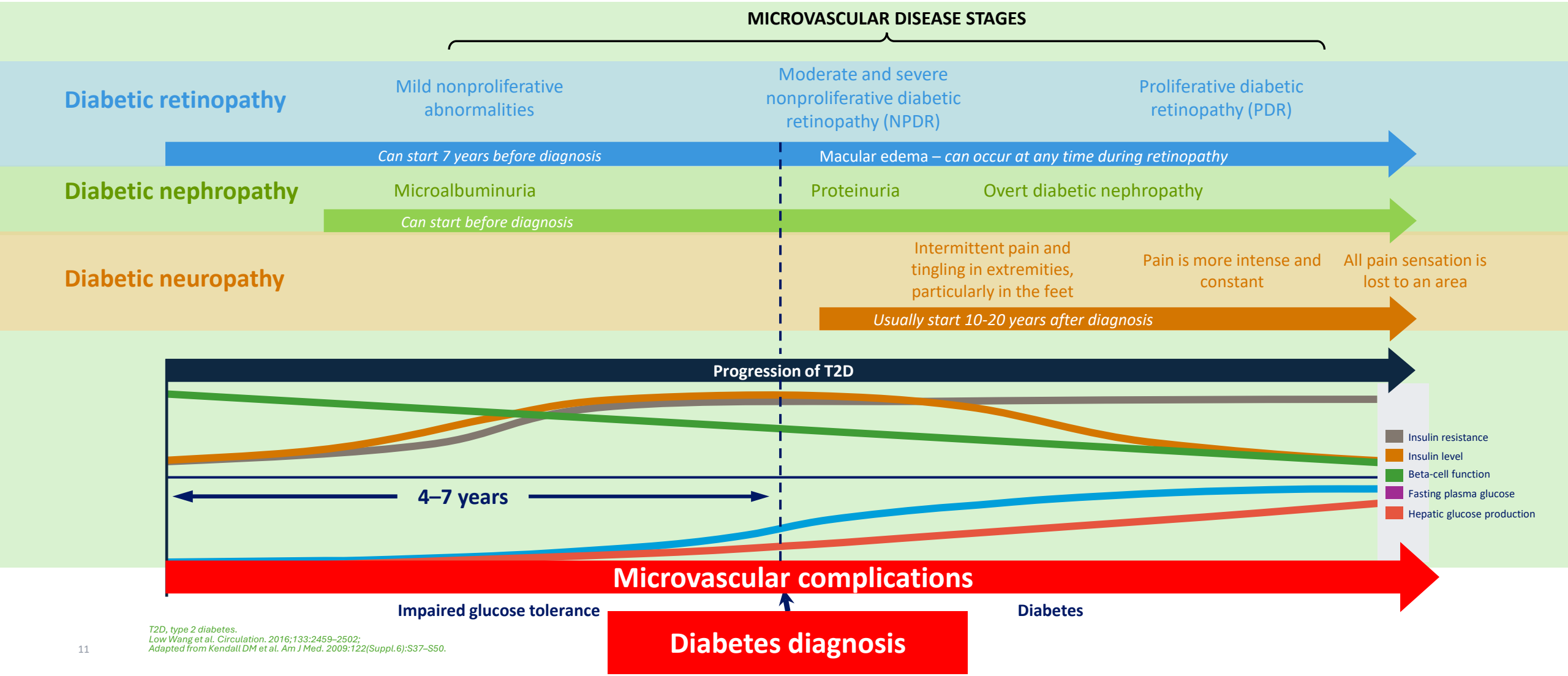


[Ca2+]i=intracellular calcium; CMC=cardiomyocyte; DCM=diabetic cardiomyopathy; DM=diabetes mellitus; HF=heat failure; LV=left ventricular.

Jia J et al. Circ Res. 2018;122(4):624-638.

Microvascular complications may predate T2D diagnosis

Timeline of microvascular disease in T2D



T2D, type 2 diabetes.
Low Wang et al. Circulation. 2016;133:2459–2502;
Adapted from Kendall DM et al. Am J Med. 2009:122(Suppl.6):S37–S50.

Microvascular complications of T2D

Microvascular complications
Damage to **small blood vessels** caused by severe and prolonged hyperglycaemia

Diabetic retinopathy

~25%

of patients with T2D have retinopathy and the risk increases over time[1]

Chronic kidney disease

~7%

of patients with T2D already have **microalbuminuria** at the time of diagnosis[2]

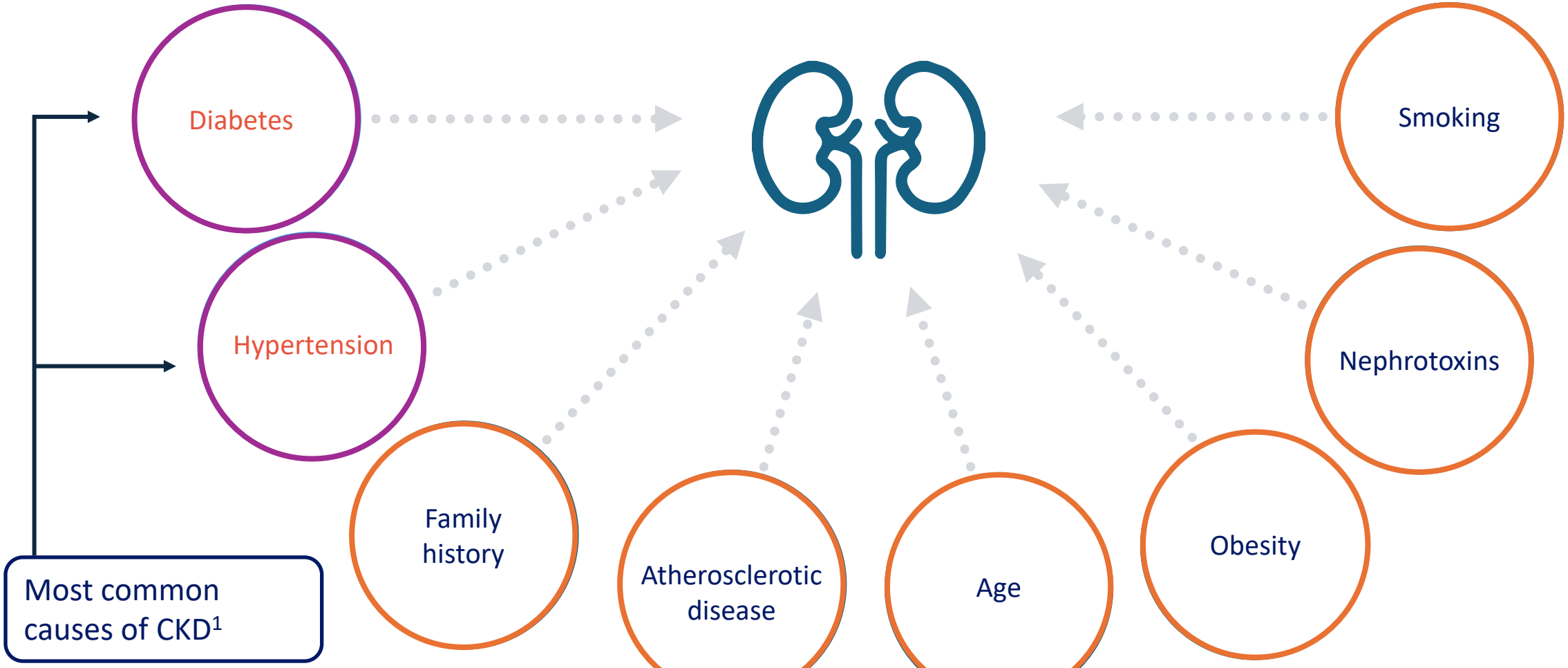
Diabetic neuropathy

45%

incidence of neuropathy for patients with T2D[3]

1. Yau JWY et al. *Diabetes Care* 2012;35:556–564; 2. Gross JL et al. *Diabetes Care* 2005;28:164–176; 3. Russell KW, Zilkoa LA. *Continuum (Minneap Minn)* 2014;20:1236–1240

CKD risk factors and causes

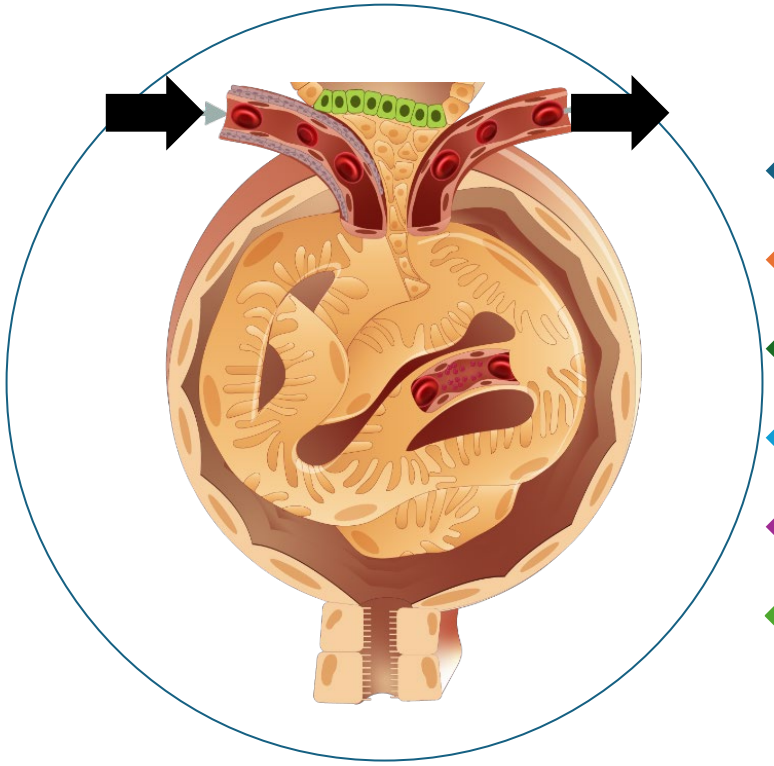


CKD, chronic kidney disease

1. NIDDK. Available from: Causes of Chronic Kidney Disease | NIDDK (nih.gov) accessed May 2021; 2. Kazancioğlu R. Kidney Int Suppl (2011) 2013; 3(4):368–371; 3. Woolfson R. Postgrad Med J 2001; 77(904):68–74; 4. Hall ME et al. Int J Nephrol Renovasc Dis 2014; 7:75–88; 5. Orr SE et al. Int J Mol Sci 2017; 18:pii: E1039

Kidney hyperfiltration is a common feature and driver of disease progression across the diverse CKD etiologies

Diabetes and hypertension are responsible for **more than half** of all cases of CKD[1]

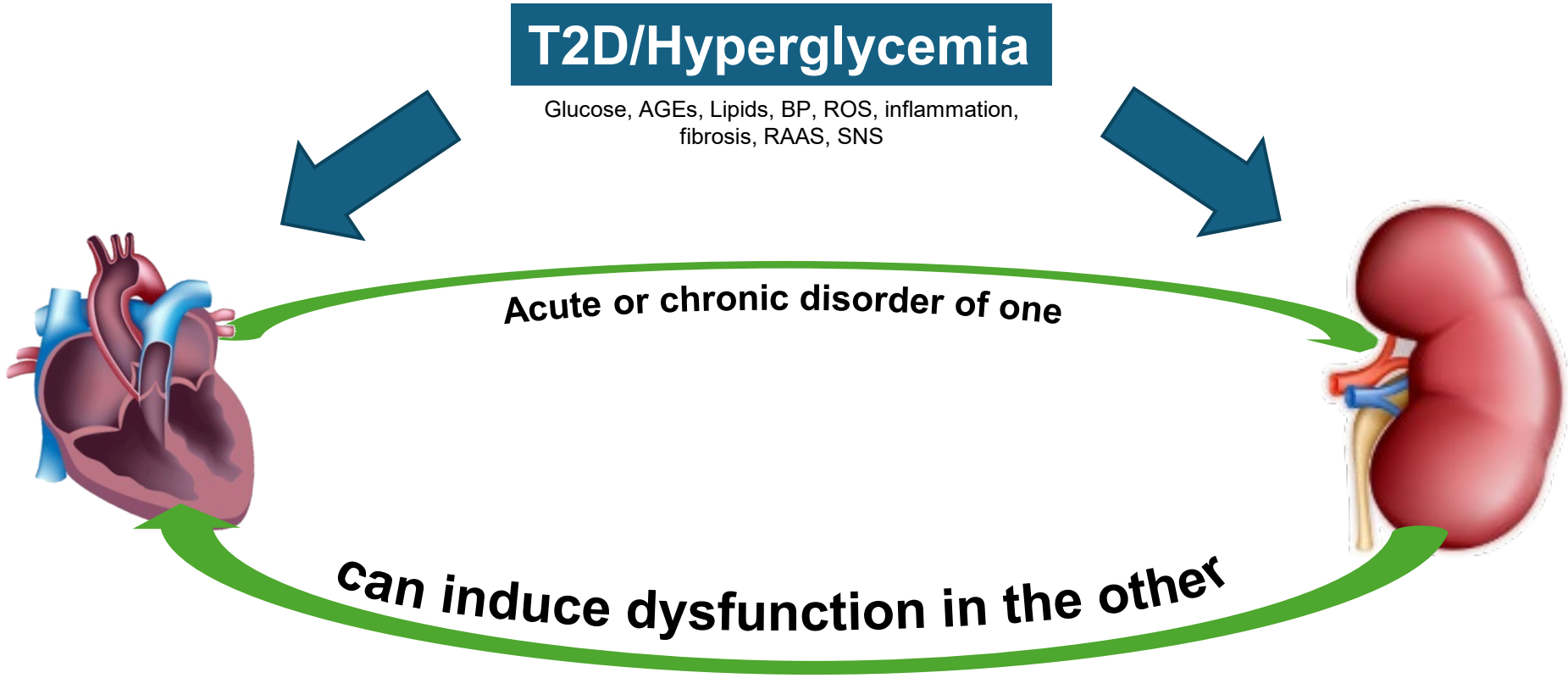


- Diabetic nephropathy[2]
- Hypertensive nephrosclerosis[3]
- IgA nephropathy[4]
- Focal segmental glomerulosclerosis[5]
- Obesity[2]
- Polycystic kidney disease[2]

CKD = chronic kidney disease; IgA = immunoglobulin A.

1. Xie Y et al. Kidney Int. 2018;94:567–581; 2. Helal I et al. Nat Rev Nephrol. 2012;8:293–300; 3. Palatini P. Nephrol Dial Transplant. 2012;27:1708–1714; 4. Coppo R. Nephrol Dial Transplant. 2019;34:1832–1838; 5. Rosenberg AZ et al. Clin J Am Soc Nephrol. 2017;12:502–517.

Type 2 diabetes, cardiovascular and renal disease are closely interconnected



Renal and cardiac systems are inextricably linked and should be considered together

AGEs = advanced glycation end-products; BP = blood pressure; RAAS = renin angiotensin aldosterone system; ROS = reactive oxygen species; SNS = sympathetic nervous system; T2D = type 2 diabetes.

1. Maqbool M et al. *Semin Nephrol*. 2018;38:217-232; 2. Ronco C et al. *J Am Coll Cardiol*. 2008;52:1527-39.

Early and effective control can reduce complication risks

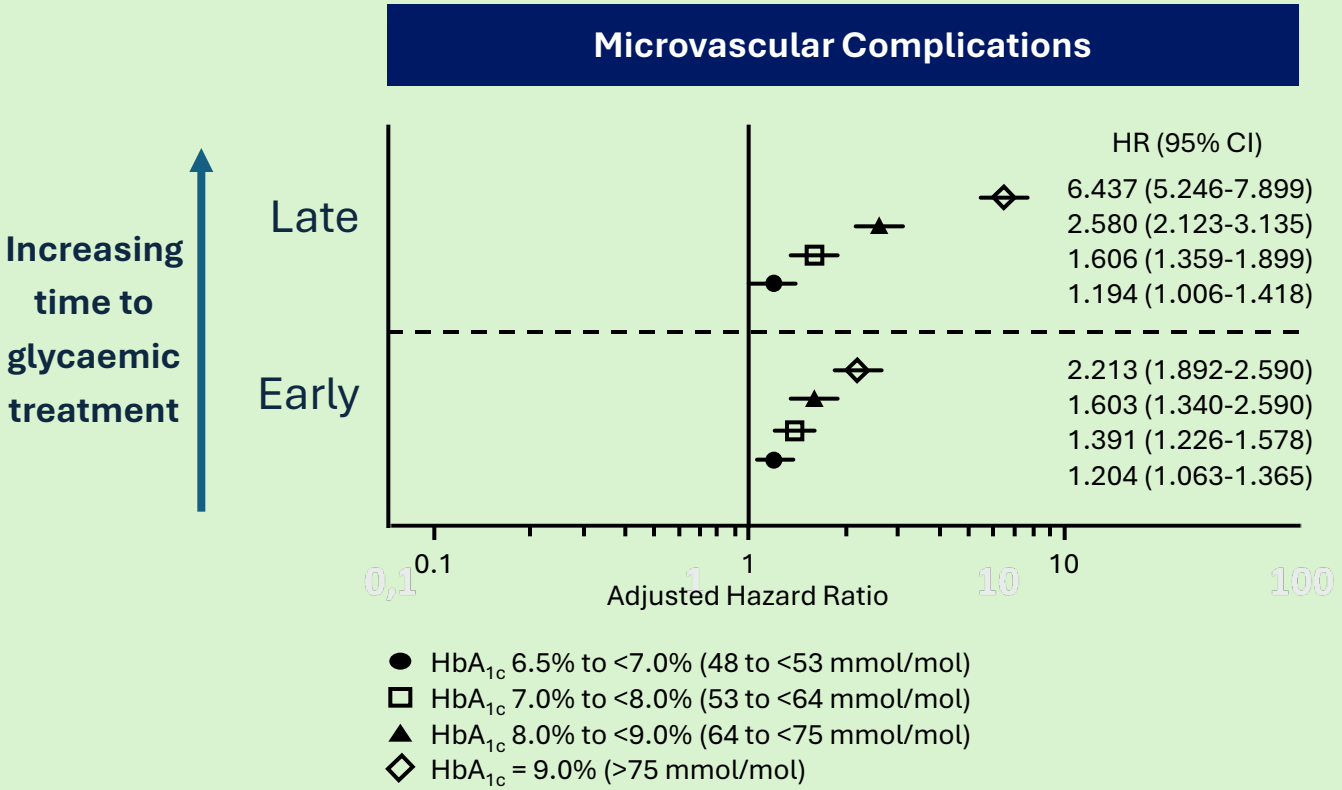
Treating additional risk factors further reduces risks or microvascular and macrovascular complications

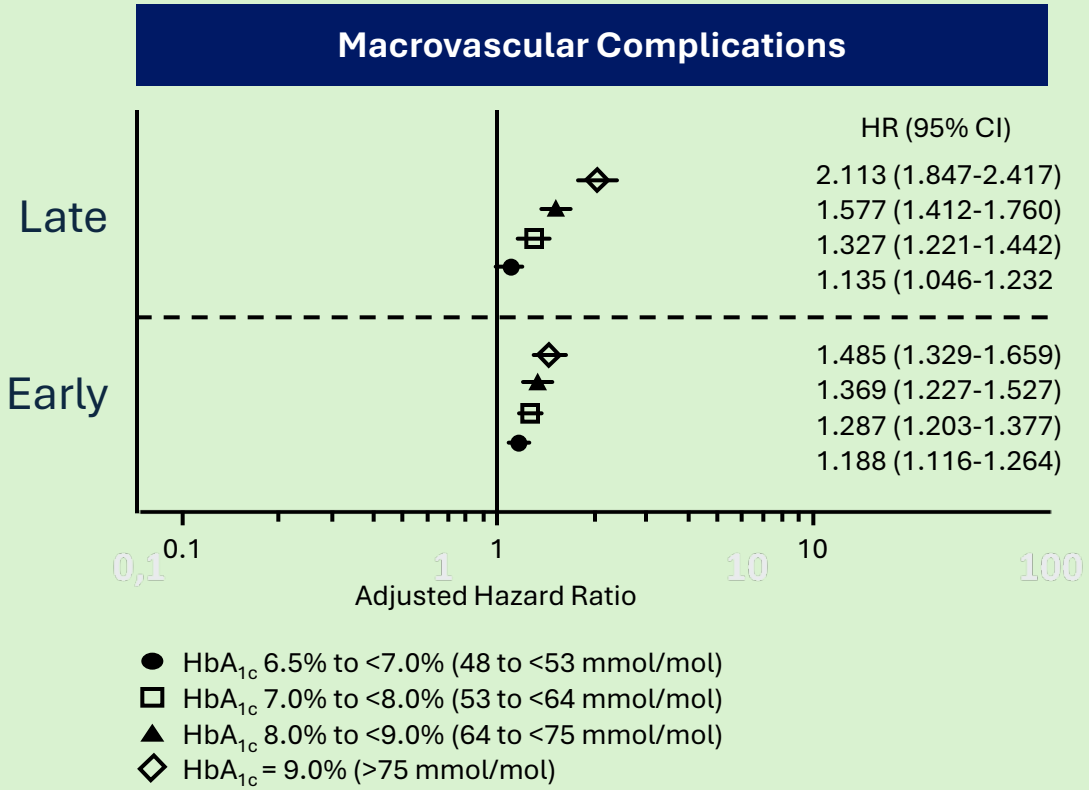
- Tight glucose control early in the course of T2D can reduce long-term CV outcomes
- HbA_{1c} <7% is associated with lower risk of microvascular events
- International practice guidelines encourage early glucose lowering to achieve near-normal HbA_{1c} targets

HbA_{1c}, glycosylated haemoglobin; T2D, type 2 diabetes.
1. UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:837853; 2. Holman RR et al. N Engl J Med. 2008;359:15771589; 3. Laiteerapong N et al. Diabetes Care. 2019;42:416426; 4. Cosentino F et al. Eur Heart J. 2019;00:1–69; 5. Diabetes Care. 2021;44 (Suppl. 1): S73-S84. 5. The DCCT Research Group. N Engl J Med. 1993;329:977–86.

Early and effective glycaemic control associated with lower microvascular and macrovascular complication risks

Diabetes and Aging Study

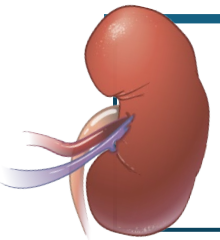




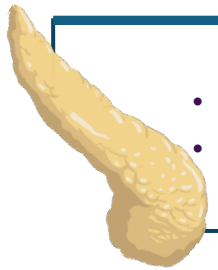
HbA_{1c}, glycosylated haemoglobin.
Adapted from Laiteerapong N et al. Diabetes Care. 2019;42(3):416-426.

ISGLT 2

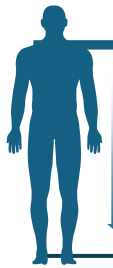
Evidence Supports Glycemic and Non-glycemic Effects of SGLT-2i



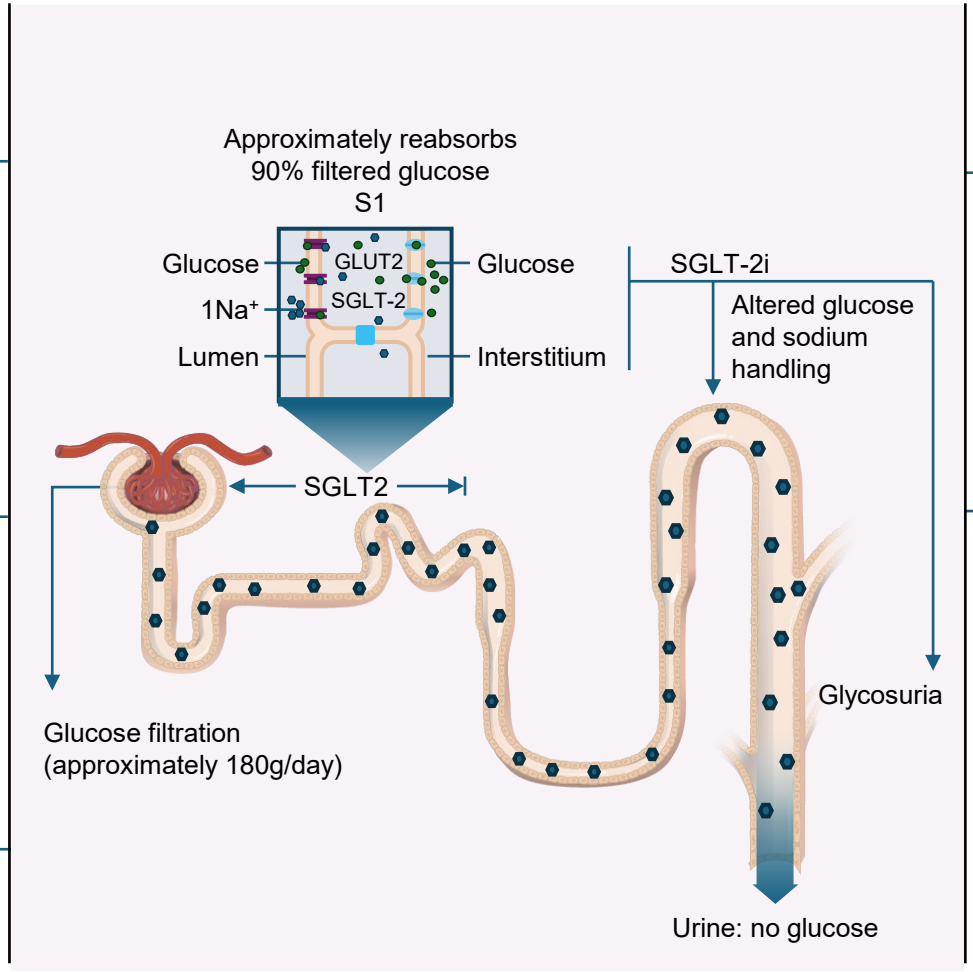
- Decreased glucose and sodium reabsorption[1,2]
- Increased delivery of sodium to the distal tubule[1]



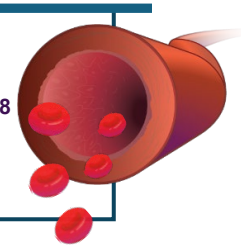
- Decreased plasma glucose[3,4]
- Increased β-cell function[3,4]



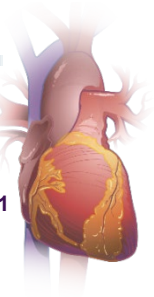
- Decreased body weight[5,6]
- Decreased fat mass[5,6]
- Increased insulin sensitivity[7]



- Decreased blood pressure[7]
- Decreased plasma volume[6,8]
- Increased hematocrit[6]



- Decreased preload and afterload[6]
- Increased cardiac efficiency[9,10]
- Decreased cardiac remodeling[10,11]



Potential mechanisms by which SGLT-2 inhibition reduces risk for heart failure hospitalization are not fully understood and research is under way

Dapagliflozin is not indicated for weight loss or hypertension.

1. FARXIGA® (dapagliflozin) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; May 2020. 2. Eickhoff MK, et al. J Clin Med. 2019;8(6);779. 3. Merovci A, et al. J Clin Endocrinol Metab. 2015;100(5):1927-1932. 4. Kaneto H, et al. J Diabetes. 2017;9(3):219-225. 5. Bolinder J, et al. J Clin Endocrinol Metab. 2012;97(3):1020-1031. 6. Heerspink HJL, et al. Kidney Int. 2018;94(1):26-39. 7. Kalra S, et al. Indian J Endocrinol Metab. 2017;21(1):210-230. 8. Lambers Heerspink HJ, et al. Diabetes Obes Metab. 2013;15(9):853-862. 9. Verma S, et al. JACC Basic Transl Sci. 2018;3(5):575-587. 10. Tamargo J. Eur Cardiol. 2019;14(1):23-32. 11. Lee TM, et al. Free Radic Biol Med. 2017;104:298-310.

SGLT2 inhibitors offer early metabolic benefits in patients with T2D[1–4]

SGLT2 inhibitor on top of metformin	Empagliflozin 25 mg[1]	Canagliflozin 100 mg[2]	Dapagliflozin 10 mg[3]	Ertugliflozin 5 mg[4]
HbA1c, %	-0.77*	-0.73†	-0.84‡	-0.7§
Weight, kg	-2.46*	-3.3†	-2.9‡	-3.0§
Systolic blood pressure, mmHg	-5.2*	-3.5†	-5.1¶	-4.4§
Diastolic blood pressure, mmHg	-1.6*	-1.8†	-1.8¶	-1.6§

SGLT2 inhibitors reduce the development and progression of HF and CKD in patients with T2D across the CV and kidney risk continuum[1]

↓ Reduced risk	CANVAS Program[2,3] (canagliflozin)	DECLARE-TIMI 58[4] (dapagliflozin)	EMPA-REG OUTCOME[5,6] (empagliflozin)	VERTIS CV[7–9] (ertugliflozin)	CREDENCE[10]* (canagliflozin)
	T2D + ASCVD or ≥2 CV risk factors	T2D + established ASCVD or multiple risk factors	T2D + CVD	T2D + established ASCVD	T2D + albuminuric CKD
3P-MACE†	↓ ***p*=0.02**	*p*=0.17	↓ ***p*=0.04**	**p=0.001 for non-inferiority**	↓ ***p*=0.01**
CV death or HHF‡	↓ ***p*=0.002**§	↓ ***p*=0.005**¶	↓ ***p*<0.001**§	*p*=0.11	↓ ***p*<0.001**
CV death‡	*p*=NR**	*p*=NR**	↓ ***p*<0.001**§	*p*=NR**	↓ ***p*=0.05**
HHF‡	↓ ***p*=0.002**§	↓ *p*=NR**	↓ ***p*=0.002**§	↓ ***p*=0.006**	↓ ***p*<0.001**
Composite kidney outcome‡,‡‡	↓ *p*=NR‡**	↓ *p*=NR‡**	↓ ***p*<0.001**‡§	↓ *p*<0.01	↓ *p*=0.00001††

Cells coloured light blue indicate that the upper bound limit of the confidence interval for the active versus placebo comparison is below unity (<1.00)

3P-MACE, 3-point major adverse cardiovascular events; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HF, heart failure; HHF, hospitalisation for heart failure; NR, not reported; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes

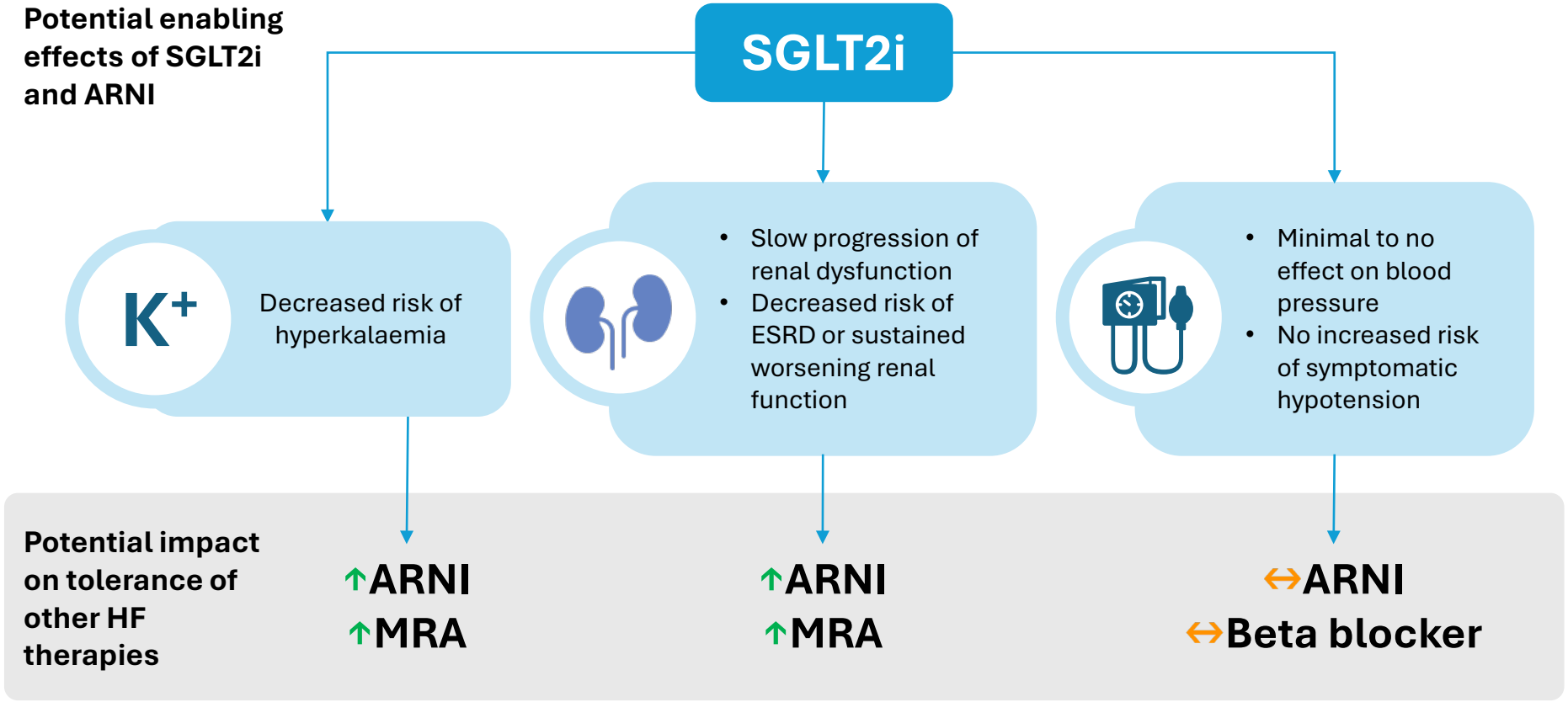
1. McGuire DK et al. JAMA Cardiol 2021;6:148 2. Neal B et al. N Engl J Med 2017;377:644 3. Radholm K et al. Circulation 2018;138:458 4. Wiviott S et al. N Engl J Med 2019;380:347 5. Zinman B et al. N Engl J Med 2015;373:2117 6. Wanner C et al. N Engl J Med 2016;375:323 7. Cannon CP et al. N Engl J Med 2020;383:1425 8. Cosentino F et al. Circulation 2020;142:2205 9. Cherney DZI et al. Diabetologia 2021;64:1256 10. Perkovic V et al. N Engl J Med 2019;380:2295

SGLT2 inhibitors have an established safety profile across the CV and kidney risk continuum and are well tolerated[1–5]

	CANVAS Program*[1]		DECLARE-TIMI[2]		EMPA-REG OUTCOME[3,4]		VERTIS CV[5]	
	Placebo	Canagliflozin	Placebo (n=8569)	Dapagliflozin (n=8574)	Placebo (n=2333)	Pooled empagliflozin (n=4687)	Placebo (n=2745)	Pooled ertugliflozin (n=5493)
	n (%)	n (%)	n (%)	n (%)	Event rate per 1000 PY	Event rate per 1000 PY	n (%)	n (%)
Patient population	T2D + ASCVD or ≥2 CV risk factors		T2D + established ASCVD or multiple risk factors		T2D + CVD		T2D + established ASCVD	
Hypoglycaemia	46.4	50.0	NR	NR	650 (27.9)	1303 (27.8)	790 (28.8)	1496 (27.2)
Hypoglycaemia requiring assistance	NR	NR	83 (1.0)	58 (0.7)	36 (1.5)	63 (1.3)	162 (5.9)	285 (5.2)
Diabetic ketoacidosis	0.3	0.6	12 (0.1)	27 (0.3)	1 (<0.1)	4 (0.1)	2 (0.1)†	19 (0.3)†
Urinary tract infection	37.0	40.0	133 (1.6)	127 (1.5)	423 (18.1)	842 (18.0)	279 (10.2)	666 (12.1)
Genital infection	10.8§	34.9‡§	9 (0.1)	76 (0.9)‡	42 (1.8)	301 (6.4)‡	42 (1.5)	297 (5.4)
Volume depletion	18.5	26.0‡	207 (2.4)	213 (2.5)	115 (4.9)	239 (5.1)	106 (3.9)	236 (4.3)
Bone fractures	11.9	15.4	440 (5.1)	457 (5.3)	91 (3.9)	179 (3.8)	98 (3.6)†	201 (3.7)†
Acute kidney injury	4.1	3.0	175 (2.0)	125 (1.5)‡	37 (1.6)	45 (1.0)‡	60 (2.2)	101 (1.8)
Lower limb amputation	3.4	6.3‡	113 (1.3)	123 (1.4)	46 (1.1)	47 (1.1)**	45 (1.6)††	111 (2.0)††

1. Neal B *et al. N Engl J Med* 2017;377:644; 2. Wiviott S *et al. N Engl J Med* 2019;380:347; 3. Zinman B *et al. N Engl J Med* 2015;373:2117; 4. Kohler S *et al. Adv Ther* 2017;34:1707; 5. Cannon CP *et al. N Engl J Med* 2020;383:1425; 6. Empagliflozin summary of product characteristics; 7. Canagliflozin summary of product characteristics; 8. Dapagliflozin summary of product characteristics; 9. Ertugliflozin summary of product characteristics.

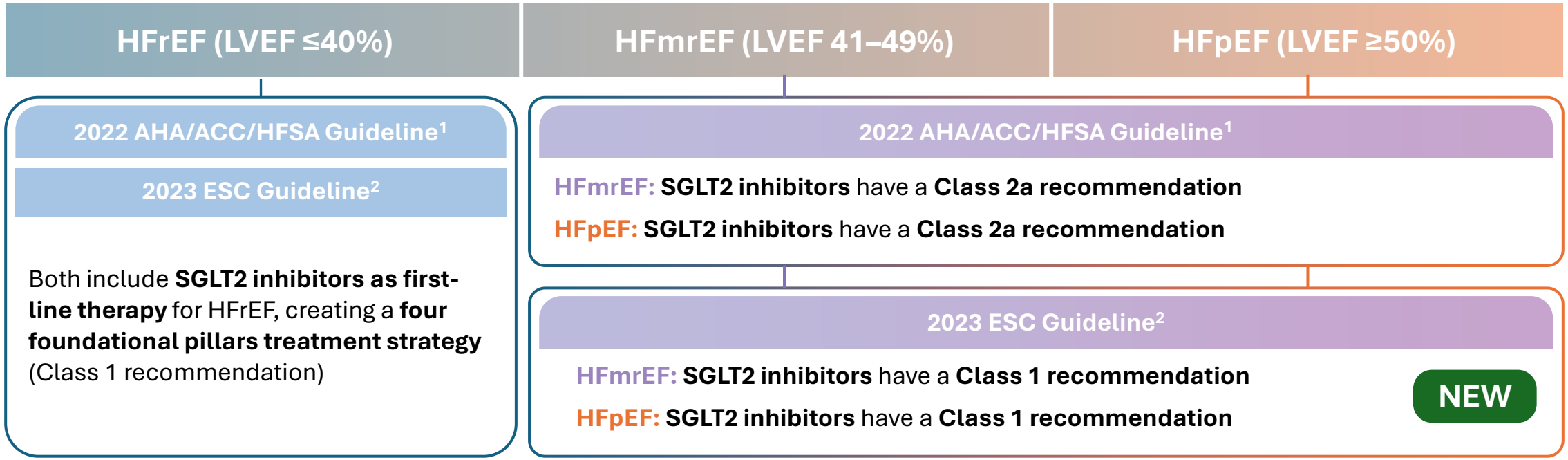
SGLT2 inhibitors may improve tolerance of other heart failure therapies



ARNI, angiotensin receptor–neprilysin inhibitor; ESRD, end-stage renal disease; HF, heart failure; MRA, mineralocorticoid receptor antagonist; SGLT2(i), sodium-glucose co-transporter-2 (inhibitor).

Greene SJ *et al. Eur J Heart Fail.* 2021;23:1525.

International guidelines support the use of SGLT2 inhibitors for patients with heart failure regardless of LVEF, including in the hospital setting



Treatment for heart failure should be started regardless of LVEF

ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFSA, Heart Failure Society of America; LVEF, left ventricular ejection fraction; SGLT2, sodium-glucose co-transporter-2.

1. Heidenreich PA et al. J Am Coll Cardiol. 2022;79:e263; 2. McDonagh T et al. Eur Heart J. 2023: doi.org/10.1093/eurheartj/ehad195

2023 KDIGO CKD Guideline: SGLT2 Inhibitors in CKD

Preview Presented at 2023 ERA Congress[1]

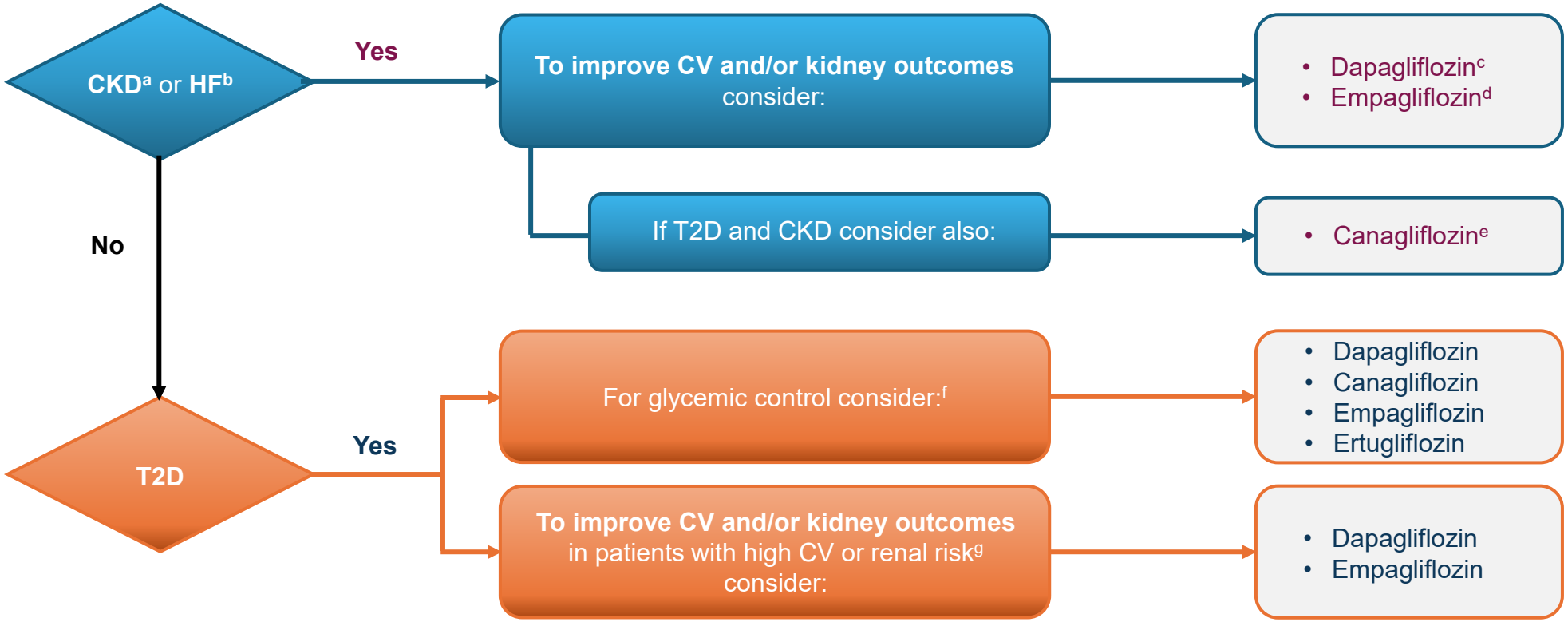
- **Recommendation 3.6.1:** We recommend treating adults with CKD and heart failure or eGFR ≥20 mL/min/1.73 m^2 with UACR ≥200 mg/g with an SGLT2 inhibitor (1A)
- **Recommendation 3.6.2:** We suggest treating adults with eGFR ≥20-45 mL/min/1.73 m^2 with UACR <200 mg/g with an SGLT2 inhibitor (2B)

Note: Level 1 = "We recommend" and Grade A = High quality of evidence; Level 2 = "We suggest" and Grade B = Moderate quality of evidence.[2]

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ERA = European Renal Association; KDIGO = Kidney Disease: Improving Global Outcomes; SGLT2 = sodium-glucose cotransporter 2; UACR = urine albumin-to-creatinine ratio.

1. Madero M. Presented at: 60th ERA Congress; June 15-18, 2023; Milan, Italy and Virtual; 2. KDIGO. KDIGO methods manual for guideline development – December 2022.

2023 ERA Consensus Paper: Algorithm for Selection of SGLT2i in Patients With CKD, HF, or T2D

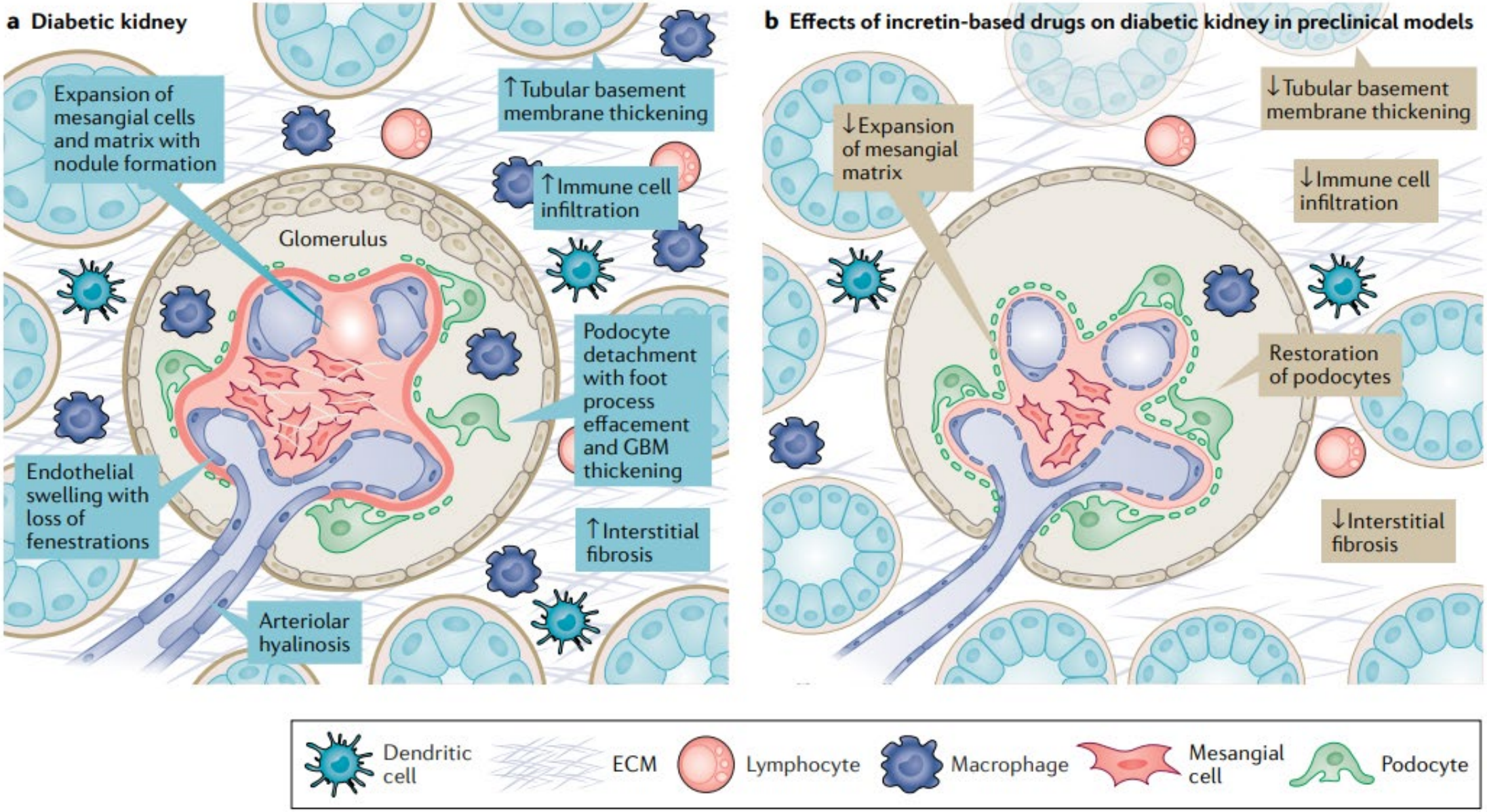


[a]eGFR <60 mL/min/1.73 m^2 or UACR >30 mg/g; [b]With reduced or preserved ejection fraction; [c]Start if eGFR ≥25 mL/min/1.73 m^2 and continue until start of KRT; [d]Start if eGFR ≥20 mL/min/1.73 m^2; [e]Start if eGFR ≥30 mL/min/1.73 m^2 and continue until start of KRT; [f]While all 4 drugs may be used for glycemic control with eGFR ≥45 mL/min/1.73 m^2, an SGLT2i that has improved outcomes in CKD randomized controlled trials would be preferable if eGFR is 45-60 mL/min/1.73 m^2; [g]Established atherosclerotic CV disease (coronary, peripheral vascular, or cerebral artery disease).

Mark PB et al. Online ahead of print. *Nephrology Dial Transplant*. 2023;gfad112.

AGLP 1

Effetti dei GLP1RA sul danno renale della DKD

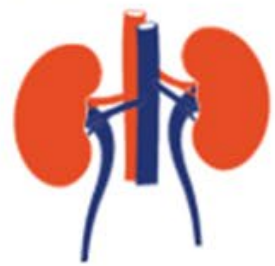


Alicic RZ et al. Nat Rev Nephrol 2020 Nov 20

Three mechanisms may drive the effect of GLP-1 on natriuresis (1/2)[1,2]

1. Inhibition of the **tubular sodium-hydrogen exchanger isoform 3 (NHE3)**
2. Inhibitory effects on the **renin-angiotensin-aldosterone system (RAAS)**
3. Indirect effects via **neuronal pathways**

Natriuresis and diuresis



GLP-1, glucagon-like peptide-1

1. Muskiet MHA et al. *Nat Rev Nephrol* 2017;13:605–628; 2. Skov J. *Rev Endocr Metab Disord* 2014;15:197–207;

Potential renoprotective effect of GLP1 RA

Indirect effects

CKD, chronic kidney disease; CV, cardiovascular; CVOT, cardiovascular outcomes trial; GLP-1RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes

1. Zoungas S et al. *Lancet Diabetes Endocrinol* 2017;5:431–437; 2. de Galan BE et al. *J Am Soc Nephrol* 2009;20:883–892; 3. Adler AL et al. *BMJ* 2000;321:412–419; 4. Bolignano D and Zoccali C. *Nephrol Dial Transplant* 2013;28 Suppl 4:iv82-98; 5. Marso SP et al. *N Engl J Med* 2016;375:311–322; 6. Marso SP et al. *N Engl J Med* 2016;375:1834–1844; 7. Mann JFE et al. *N Engl J Med* 2017;377:839–848

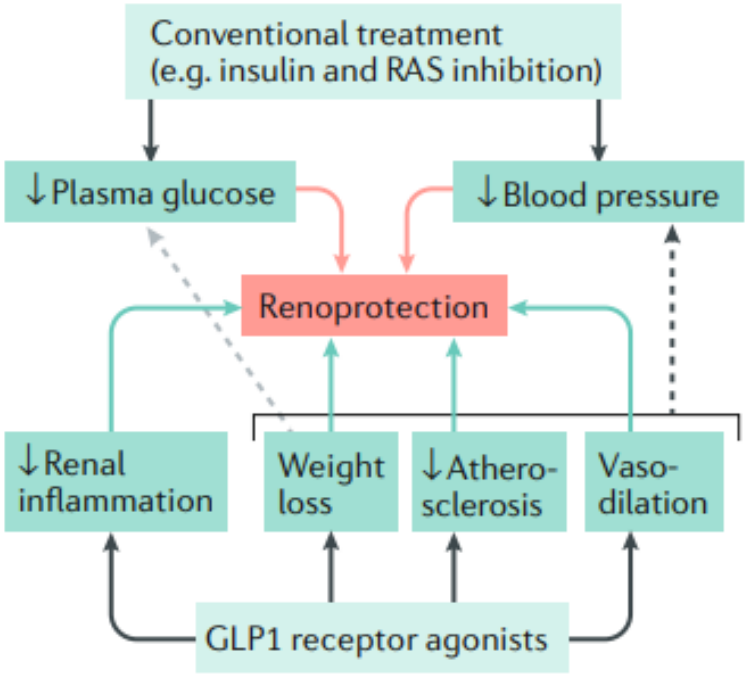
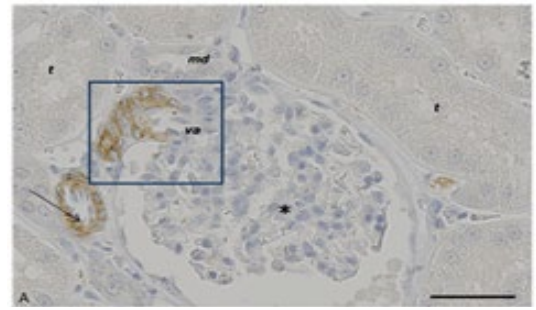


Fig. 1 | **Potential renoprotective effects of GLP1 receptor agonists.** The renoprotective effects of glucagon-like peptide 1 (GLP1) receptor agonists and of conventional treatments for type 2 diabetes mellitus are additive. GLP1 receptor agonists can reduce blood pressure and plasma glucose directly (not shown), as well as indirectly (dashed arrows) via effects on body weight, atheroclerosis and the renal vasculature. RAS, renin–angiotensin system.

Effects of GLP-1 in the kidney: Outline



Renal outcomes with liraglutide and semaglutide

Direct effects of GLP-1 in the kidney

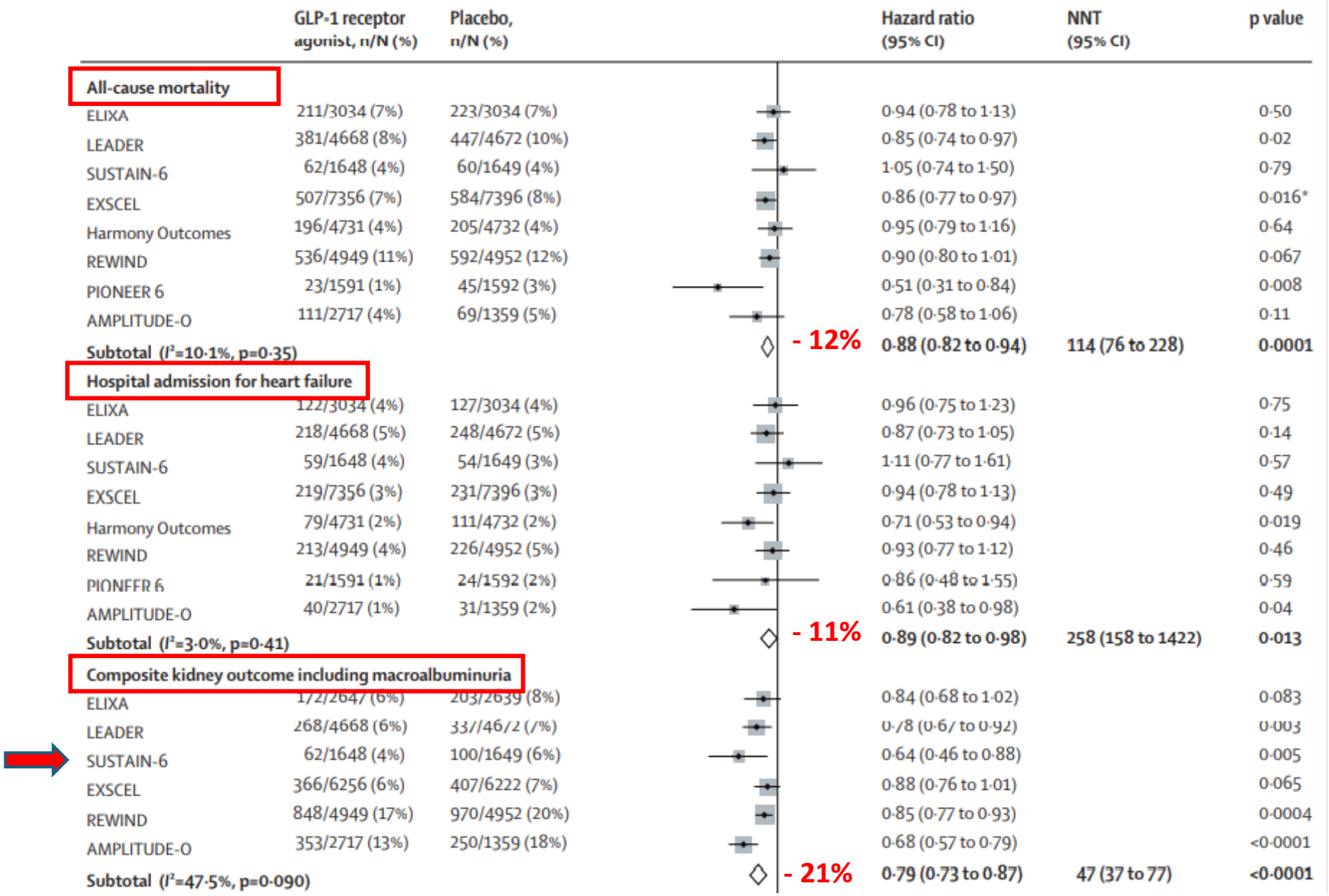
- Natriuresis
- Haemodynamic effects in the setting of diabetic glomerular hyperfiltration
- Effects on the renin-angiotensin-aldosterone system
- Reduced oxidative stress
- Anti-inflammatory effects
- Summary of the effects of liraglutide and semaglutide

Indirect effects of GLP-1 in the kidney

GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; RAAS, renin-angiotensin-aldosterone system

1. Pyke C et al. *Endocrinology* 2014;155:1280–1290; 2. Skov J. *Rev Endocr Metab Disord* 2014;15:197–207; 3. Jensen EP et al. *Am J Physiol Renal Physiol* 2015;308:F867–F877; 4. Fujita H et al. *Kidney Int* 2014;85:579–589

GLP1RA, Hospitalization for HF and CKD



	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
All-cause mortality					
ELIXA	211/3034 (7%)	223/3034 (7%)	0·94 (0·78 to 1·13)		0·50
LEADER	381/4668 (8%)	447/4672 (10%)	0·85 (0·74 to 0·97)		0·02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	1·05 (0·74 to 1·50)		0·79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0·86 (0·77 to 0·97)		0·016*
Harmony Outcomes	196/4731 (4%)	205/4732 (4%)	0·95 (0·79 to 1·16)		0·64
REWIND	536/4949 (11%)	592/4952 (12%)	0·90 (0·80 to 1·01)		0·067
PIONEER 6	23/1591 (1%)	45/1592 (3%)	0·51 (0·31 to 0·84)		0·008
AMPLITUDE-O	111/2717 (4%)	69/1359 (5%)	0·78 (0·58 to 1·06)		0·11
Subtotal (I^2=10·1%, p=0·35)			**- 12%** **0·88 (0·82 to 0·94)**	**114 (76 to 228)**	**0·0001**
Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0·96 (0·75 to 1·23)		0·75
LEADER	218/4668 (5%)	248/4672 (5%)	0·87 (0·73 to 1·05)		0·14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1·11 (0·77 to 1·61)		0·57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0·94 (0·78 to 1·13)		0·49
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0·71 (0·53 to 0·94)		0·019
REWIND	213/4949 (4%)	226/4952 (5%)	0·93 (0·77 to 1·12)		0·46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0·86 (0·48 to 1·55)		0·59
AMPLITUDE-O	40/2717 (1%)	31/1359 (2%)	0·61 (0·38 to 0·98)		0·04
Subtotal (I^2=3·0%, p=0·41)			**- 11%** **0·89 (0·82 to 0·98)**	**258 (158 to 1422)**	**0·013**
Composite kidney outcome including macroalbuminuria					
ELIXA	172/2647 (6%)	203/2639 (8%)	0·84 (0·68 to 1·02)		0·083
LEADER	268/4668 (6%)	337/4672 (7%)	0·78 (0·67 to 0·92)		0·003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0·64 (0·46 to 0·88)		0·005
EXSCEL	366/6256 (6%)	407/6222 (7%)	0·88 (0·76 to 1·01)		0·065
REWIND	848/4949 (17%)	970/4952 (20%)	0·85 (0·77 to 0·93)		0·0004
AMPLITUDE-O	353/2717 (13%)	250/1359 (18%)	0·68 (0·57 to 0·79)		<0·0001
Subtotal (I^2=47·5%, p=0·090)			**- 21%** **0·79 (0·73 to 0·87)**	**47 (37 to 77)**	**<0·0001**

Sattar et al, Lancet Diabetes Endocrinol 2021

ORIGINAL INVESTIGATION Open Access

GLP-1 receptor agonists and cardiorenal outcomes in type 2 diabetes: an updated meta-analysis of eight CVOTs

Dario Giugliano[1,2*†], Lorenzo Scappaticcio[1,2†], Miriam Longo[1,2†], Paola Caruso[1,2], Maria Ida Maiorino[3], Giuseppe Bellastella[1], Antonio Ceriello[4], Paolo Chiodini[5] and Katherine Esposito[2,3]

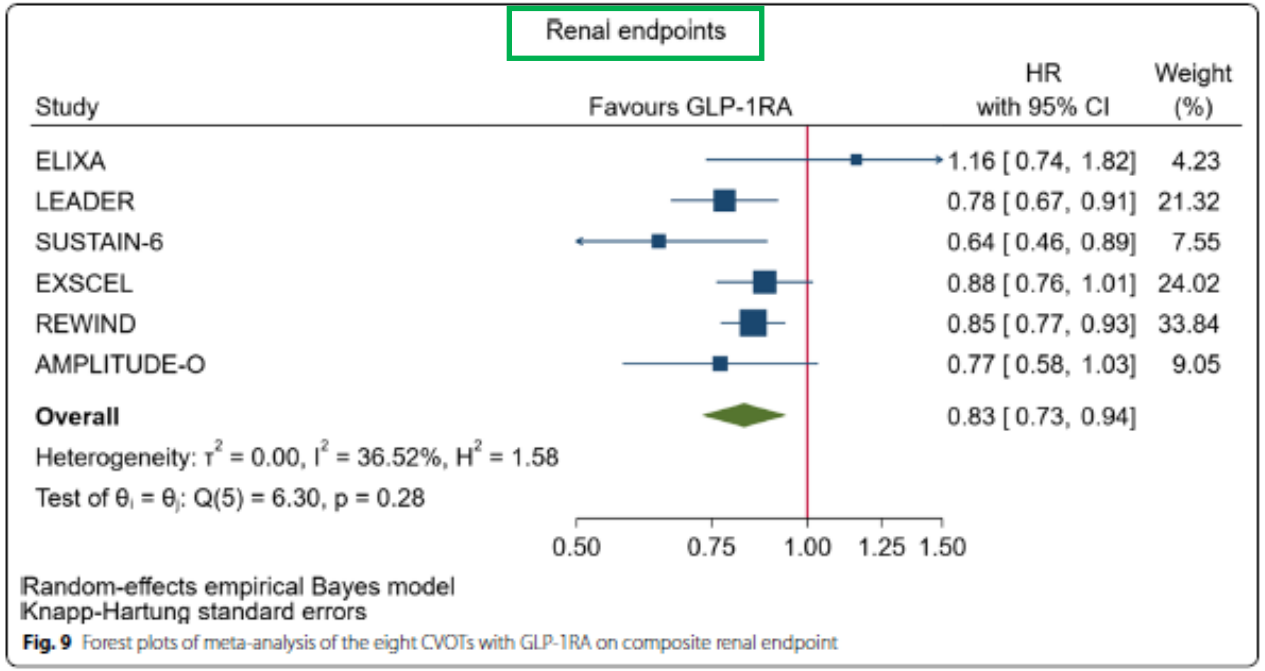


Fig. 9 Forest plots of meta-analysis of the eight CVOTs with GLP-1RA on composite renal endpoint

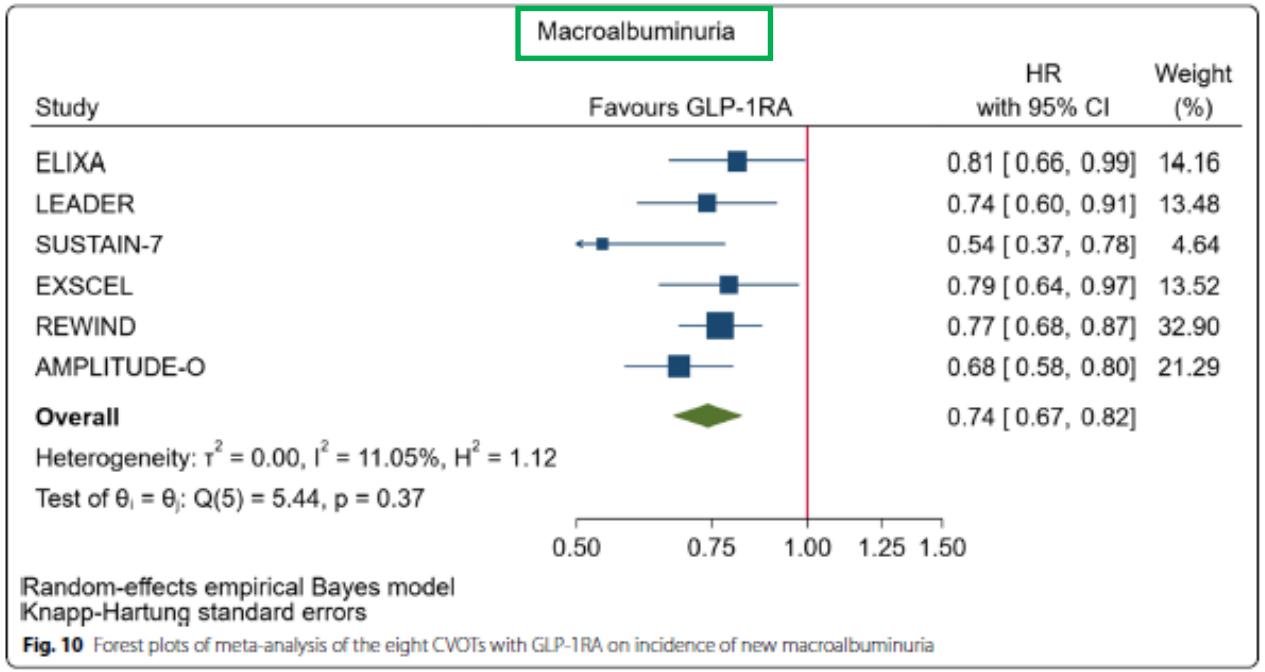
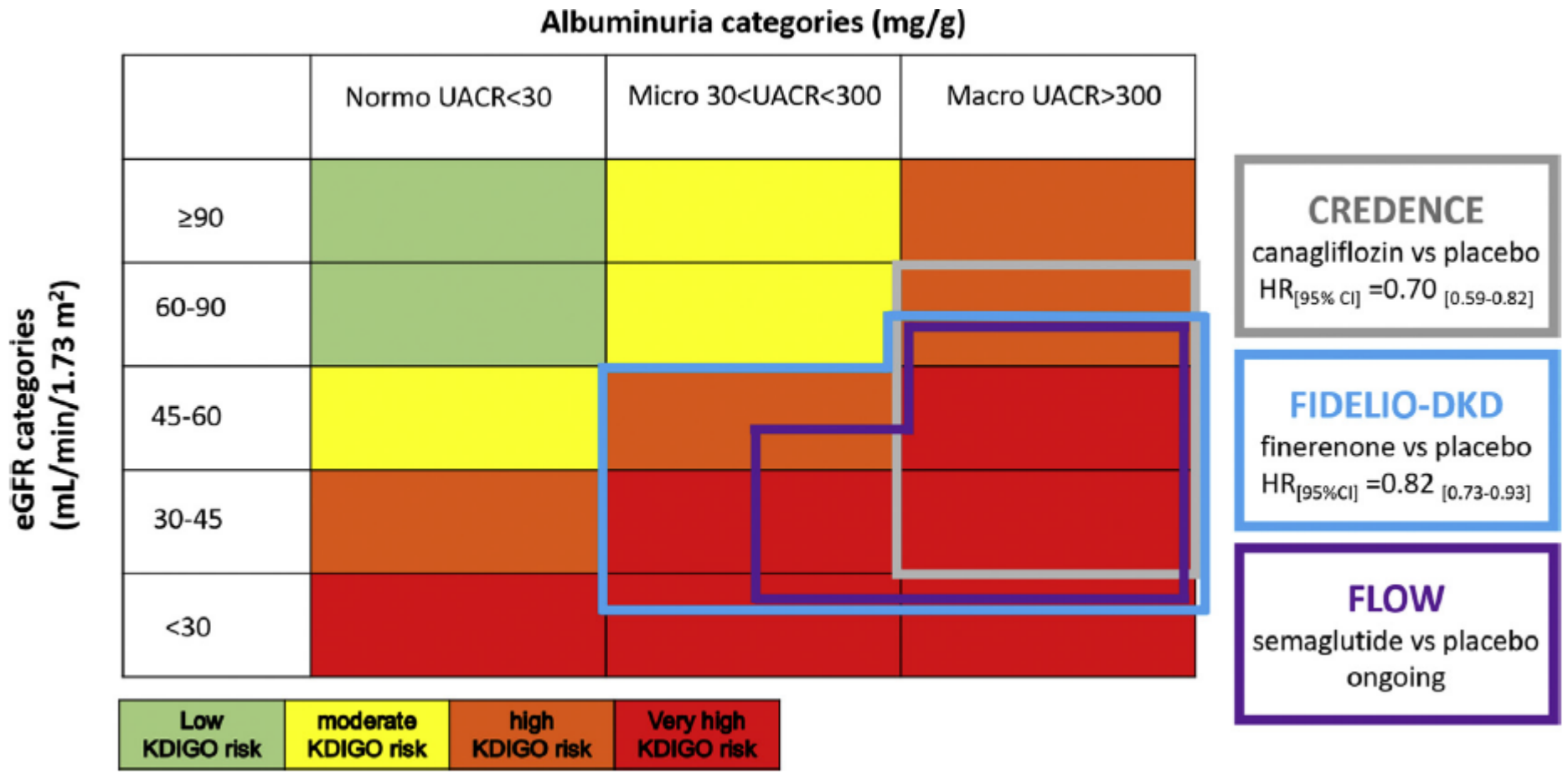


Fig. 10 Forest plots of meta-analysis of the eight CVOTs with GLP-1RA on incidence of new macroalbuminuria

Kidney Outcomes With Glucagon-Like Peptide-1 Receptor Agonists in Patients With Type 2 Diabetes

Ofri Mosenzon,[1] Meir Schechter,[1] and Gil Leibowitz



Summary of the 2023 ADA Standards of Care in Diabetes

- The choice of pharmacologic agents should be guided by a person-centered approach including comorbidities and treatment goals.
- In adults with T2D and **HF, CKD, and/or established/high risk of ASCVD**, the treatment regimen should **include agents that reduce cardiorenal risk** independent of background use of metformin or baseline HbA1c.

Recommended Therapy	T2D Population	Rationale
SGLT2 inhibitor[a]	**HF** Current/prior HF symptoms with reduced or preserved EF	Reduce the risk of worsening HF and CV death, improve symptoms, physical limitations, and quality of life
	CKD[b] eGFR <60 mL/min/1.73 m^2 OR urinary albumin ≥30 mg/g creatinine	Reduce CKD progression and CV events
	Established ASCVD, multiple ASCVD risk factors, or CKD	Reduce the risk of MACE and/or hHF
GLP-1 RA[c]	**CKD** (if SGLT2 inhibitor not tolerated) eGFR <60 mL/min/1.73 m^2 OR urinary albumin ≥30 mg/g creatinine	Reduce the risk of CV events
	Established ASCVD or multiple ASCVD risk factors	Reduce the risk of MACE

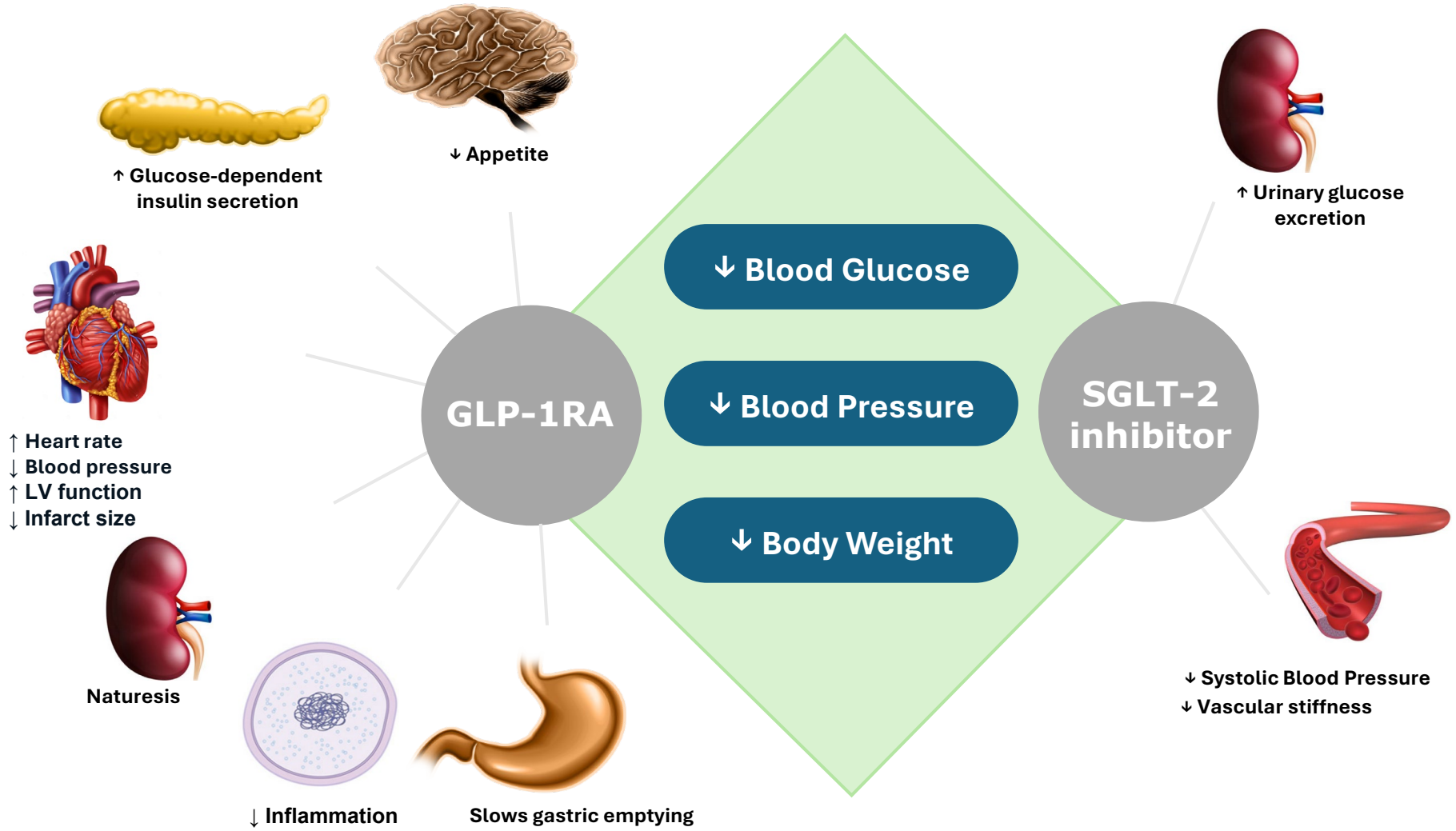
[a]Use agent with proven benefit in HF population, agent with evidence of reducing CKD progression in CKD population, and agent with proven CV disease benefit in patients with established ASCVD/multiple ASCVD risk factors/CKD; [b]Recommended for use in patients with eGFR ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine (Level of evidence A). Recommended for use in patients with eGFR ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine (Level of evidence B); [c]Use agent with demonstrated CV benefit in those with established ASCVD or multiple risk factors for ASCVD.

ADA = American Diabetes Association; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; EF = ejection fraction; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; HF = heart failure; hHF = heart failure hospitalization; MACE = major adverse cardiovascular event; SGLT2 = sodium-glucose cotransporter 2; T2D = type 2 diabetes.

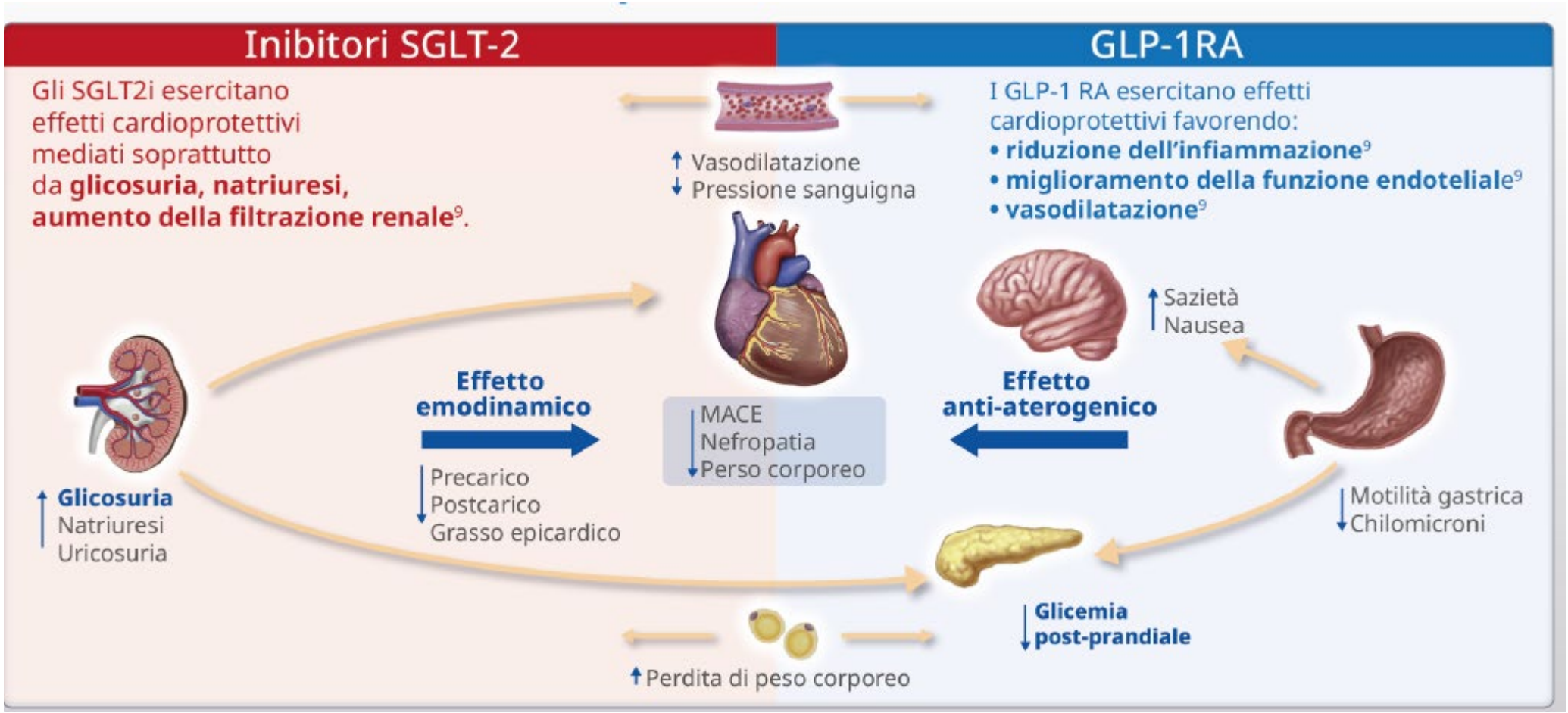
American Diabetes Association. *Diabetes Care*. 2023;46(suppl 1):S1-S298.

Associare

GLP1 RA and SGLT-2 Inhibitors Address a Broad Range of Pathophysiologic Defects Associated With T2D[1-10]



1. Drucker DJ Diabetes. 2015;64:317-326. 2. Campbell JE et al. Cell Metab. 2013;17:819-837. 3. Baggio LL et al. Gastroenterology. 2007;132:2131-2157. 4. Ussher JR et al. Circ Res. 2014;114:1788-1803 5. Bays H. Curr Med Res Opin. 2009;25;671-681. 6. Abdul-Ghani MA et al. Endocr Pract. 2008;14:782-790. 7. Marsenic O. Am J Kidney Dis. 2009;53:875-883. 8. Mather A et al. Kidney Int. 2011;79(suppl 120):S1-S6. 9. FARXIGA PI. 6. Inzucchi SE. Diab Vasc Dis Res. 2015;12(2):90-100. 10. Asano T et al. Curr Med Chem. 2004;11:2717-2724



#Expert Consensus ottenuta con metodo Delphi in un Panel di 80 Diabetologi italiani con solida esperienza clinica nel campo del diabete.
Lo statement citato (n. 24) ha ottenuto un livello di agreement del 76%, in accordo con la letteratura che dimostra le proprietà anti-aterosclerotiche dei GLP-1RA.

GLP1RA, agonista del recettore del peptide 1 simile al glucagone; MACE, eventi cardiaci avversi maggiori; SGLT2i, inibitore del cotrasportatore sodio-glucosio 2.

Wilcox T et al. Diabetic Agents, From Metformin to SGLT2 Inhibitors and GLP1 Receptor Agonists. JACC 2020 Apr 28;75(16):1956-1974

Grazie