complete the Cardio-renal syndrome Puzzle : New Era of SGLT2 inhibitor

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Outline

- 2019-2020 Guideline for T2DM Management
- What is Cardio-renal syndrome (CRS)?
- The role of SGLT2 inhibitors in CRS
- Canaglu: the critical piece of CRS puzzle

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2019 ADA Updated Guideline

2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018.

A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Changes to consensus recommendations

General consideration

- In appropriate high-risk individuals with established type 2 diabetes, the decision to treat with a GLP-1 receptor agonist or SGLT2 inhibitor to reduce MACE, hHF, CV death or CKD progression should be considered independently of baseline HbA_{1c} or individualised HbA_{1c} target.
- Providers should engage in shared decision making around initial combination therapy in new-onset cases of type 2 diabetes.

GLP-1 receptor agonist recommendations

- For patients with type 2 diabetes and established atherosclerotic CV disease (such as those with prior myocardial infarction, ischaemic stroke, unstable angina with ECG changes, myocardial ischaemia on imaging or stress test, or revascularisation of coronary, carotid or peripheral arteries) where MACE is the gravest threat, the level of evidence for MACE benefit is greatest for GLP-1 receptor agonists.
- To reduce risk of MACE, GLP-1 receptor agonists can also be considered in patients with type 2 diabetes without established CVD with indicators of high risk, specifically, patients aged 55 years or older with coronary, carotid or lower extremity artery stenosis >50%, left ventricular hypertrophy, eGFR <60 ml min^{-1} [1.73 m]$^{-2}$ or albuminuria.

SGLT2 inhibitor recommendations

- For patients with or without established atherosclerotic CVD, but with HFrEF (EF <45%) or CKD (eGFR 30 to ≤60 ml min^{-1} [1.73 m]$^{-2}$ or UACR >30 mg/g, particularly UACR >300 mg/g), the level of evidence for benefit is greatest for SGLT2 inhibitors.
- SGLT2 inhibitors are recommended in patients with type 2 diabetes and HF, particularly those with HFrEF, to reduce hHF, MACE and CV death.
- SGLT2 inhibitors are recommended to prevent the progression of CKD, hHF, MACE and CV death in patients with type 2 diabetes with CKD.
- Patients with foot ulcers or at high risk for amputation should only be treated with SGLT2 inhibitors after careful shared decision making around risks and benefits with comprehensive education on foot care and amputation prevention.

1. Diabetologia (2020) 63:221–228

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

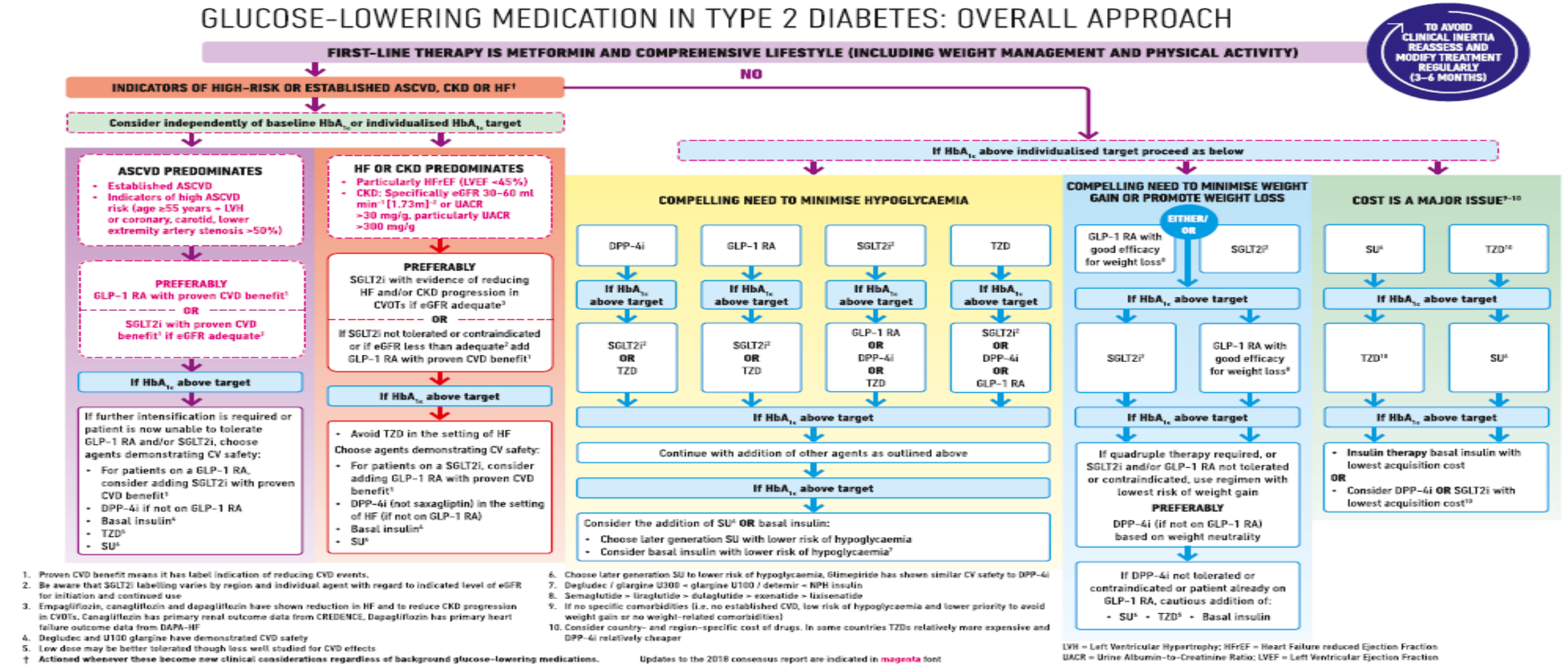

Fig. 1 Glucose-lowering medication in type 2 diabetes: overall approach. Modified from [2] with permission from Springer. ©European Association for the Study of Diabetes and American Diabetes Association 2018

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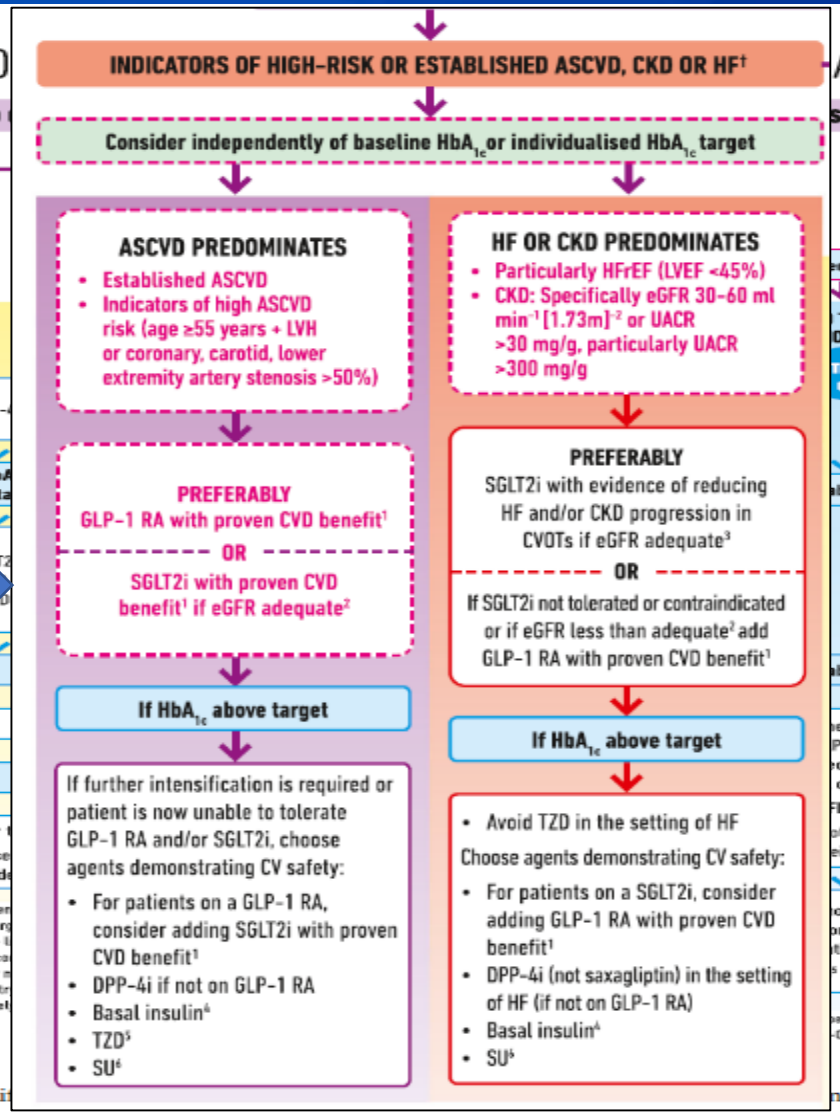

1. Proven CVD benefit means it has label indication of reducing CVD events.
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE, Dapagliflozin has primary heart failure outcome data from DAPA-HF
4. Degludec and U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

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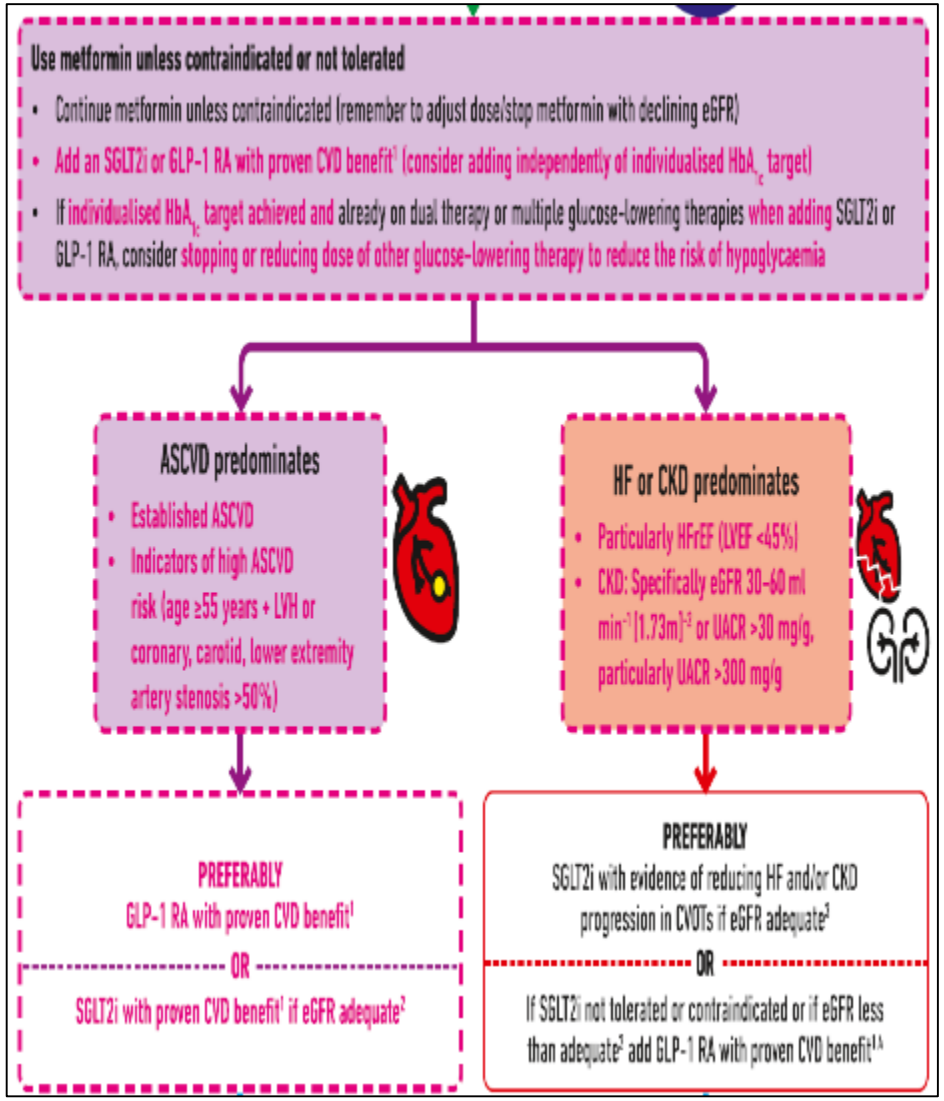
A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) - 2018



If individualised HbA1c 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 the risk of hypoglycemia.

ASCVD
Indicators of high ASCVD risk
- Age ≧ 55 yrs + LVH

or
- Coronary, carotid, lower extremity artery stenosis >50%

HF
- HFrEF (LVEF <45%)

CKD
- eGFR 30-60

or
- UACR >30 mg/g, particular UACR > 300mg/g

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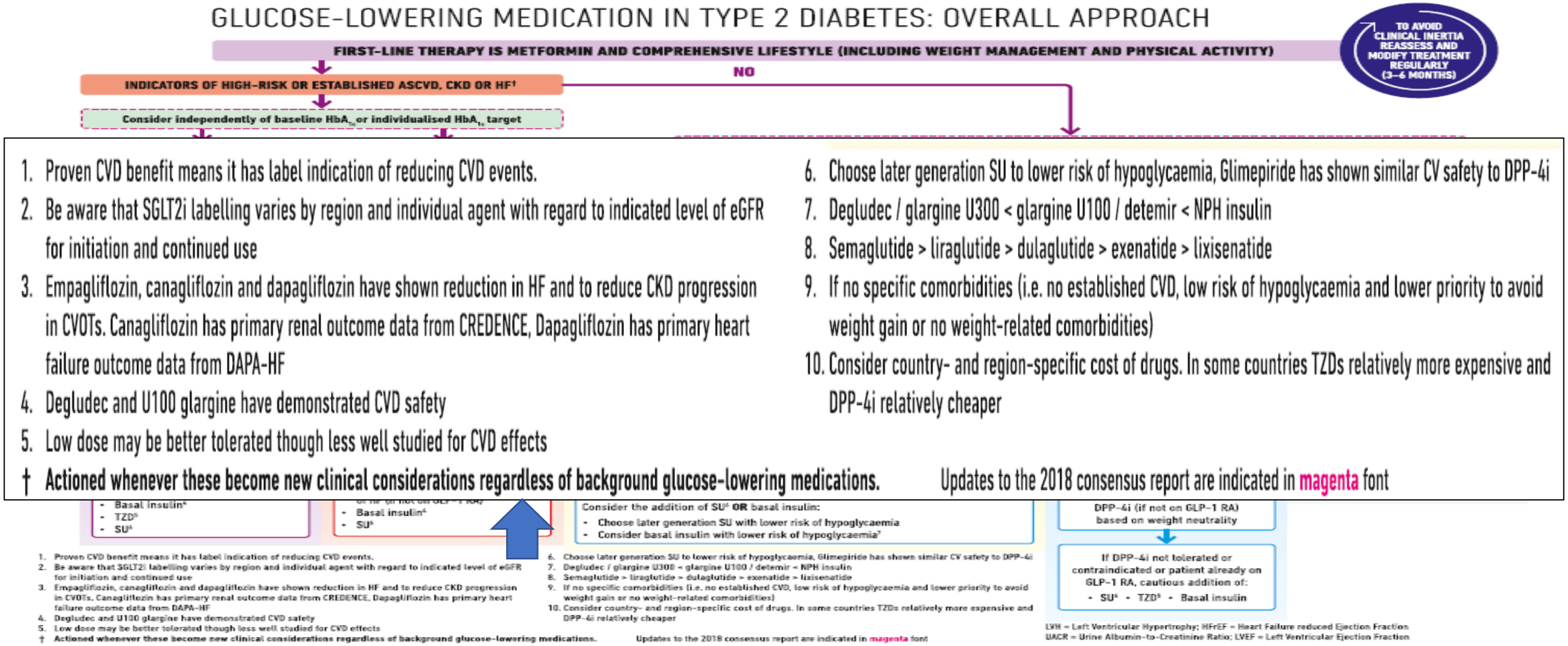

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4. Degludec and U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycaemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† **Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.** Updates to the 2018 consensus report are indicated in magenta font

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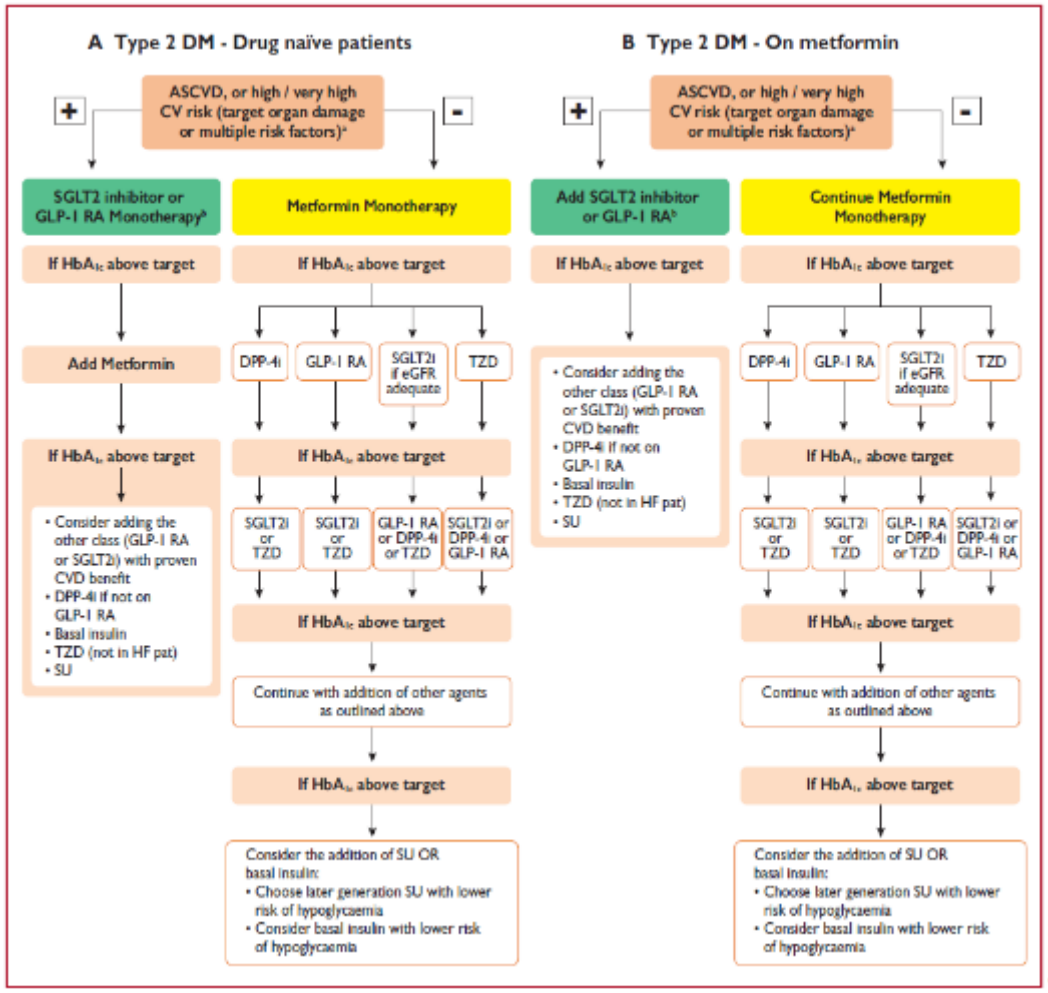
1. Diabetologia (2020) 63:221–228

2019 ESC Guideline

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD



ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)[a]

Table 7 Cardiovascular risk categories in patients with diabetes[a]

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

© ESC 2019

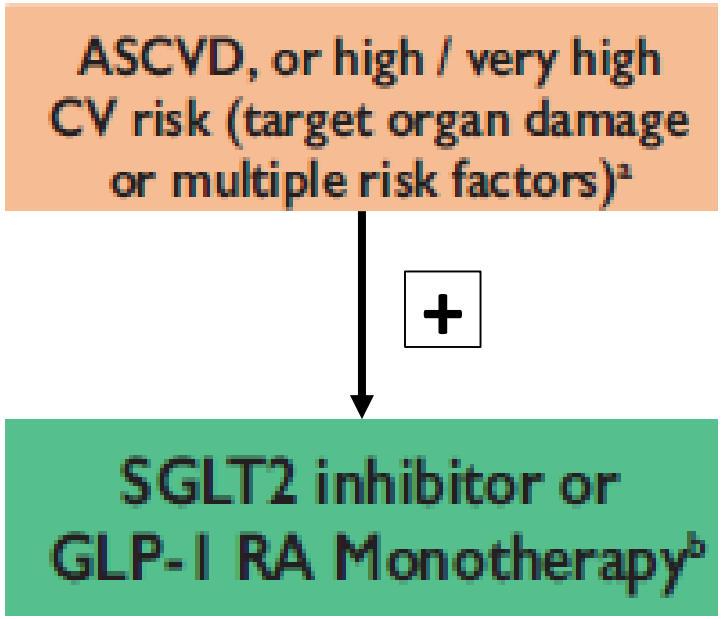
CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]

[b]Proteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.

[c]Age, hypertension, dyslipidemia, smoking, obesity.

2. Eur Heart J. 2020 Jan 7;41(2)255-323.

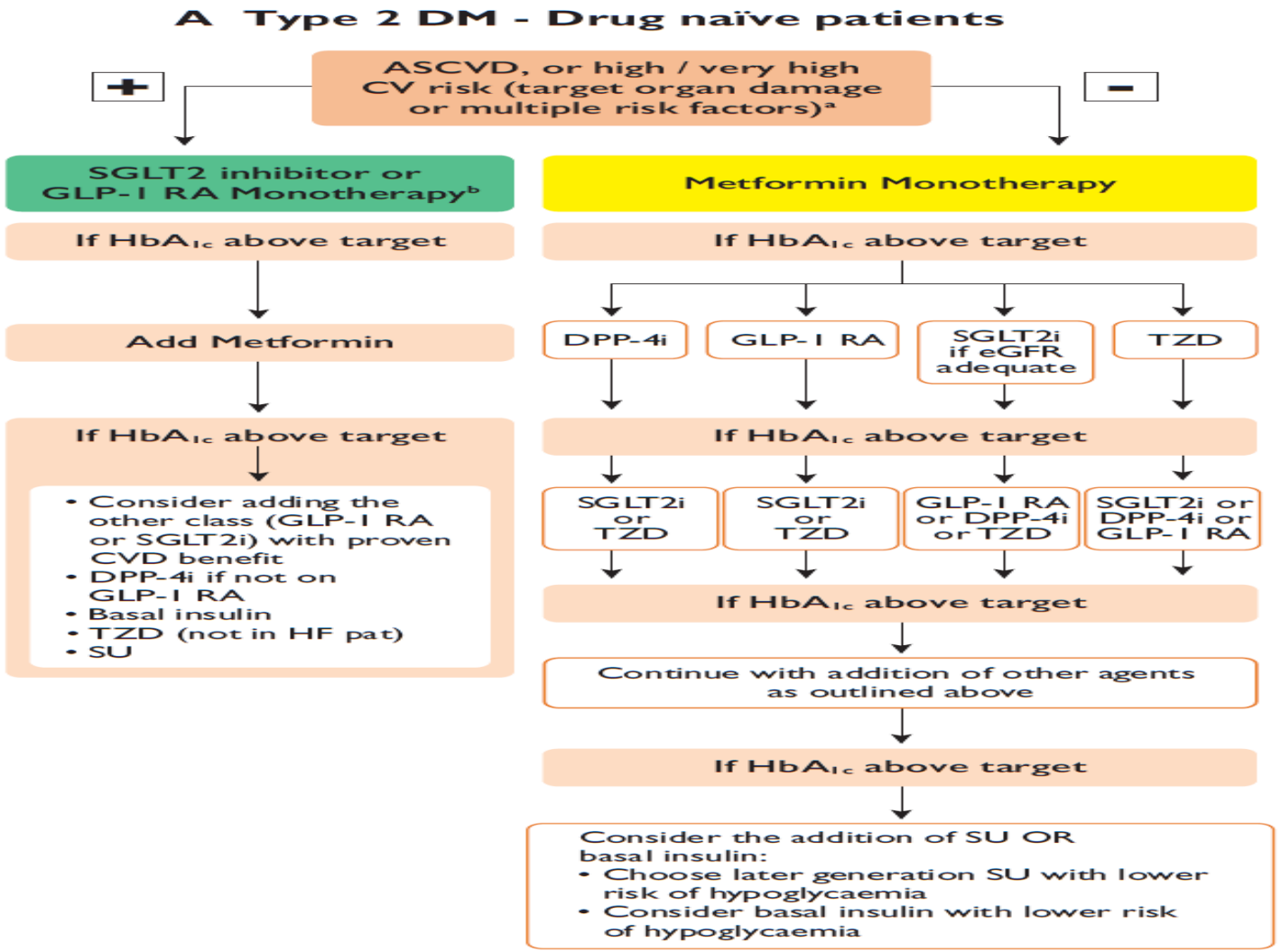


7.1.2.3
Implications of recent cardiovascular outcome trials

The results obtained from these trials, using both GLP1-RAs (LEADER, SUSTAIN-6, Harmony Outcomes, REWIND, and PIONEER 6) and SGLT2 inhibitors (EMPA-REG OUTCOME, CANVAS, DECLARETIMI 58, and CREDENCE), strongly suggest that these drugs should be recommended in patients with T2DM with **prevalent CVD or very high/high CV risk**, such as those with target-organ damage or several CVRFs, whether they are treatment naı¨ve or already on metformin.

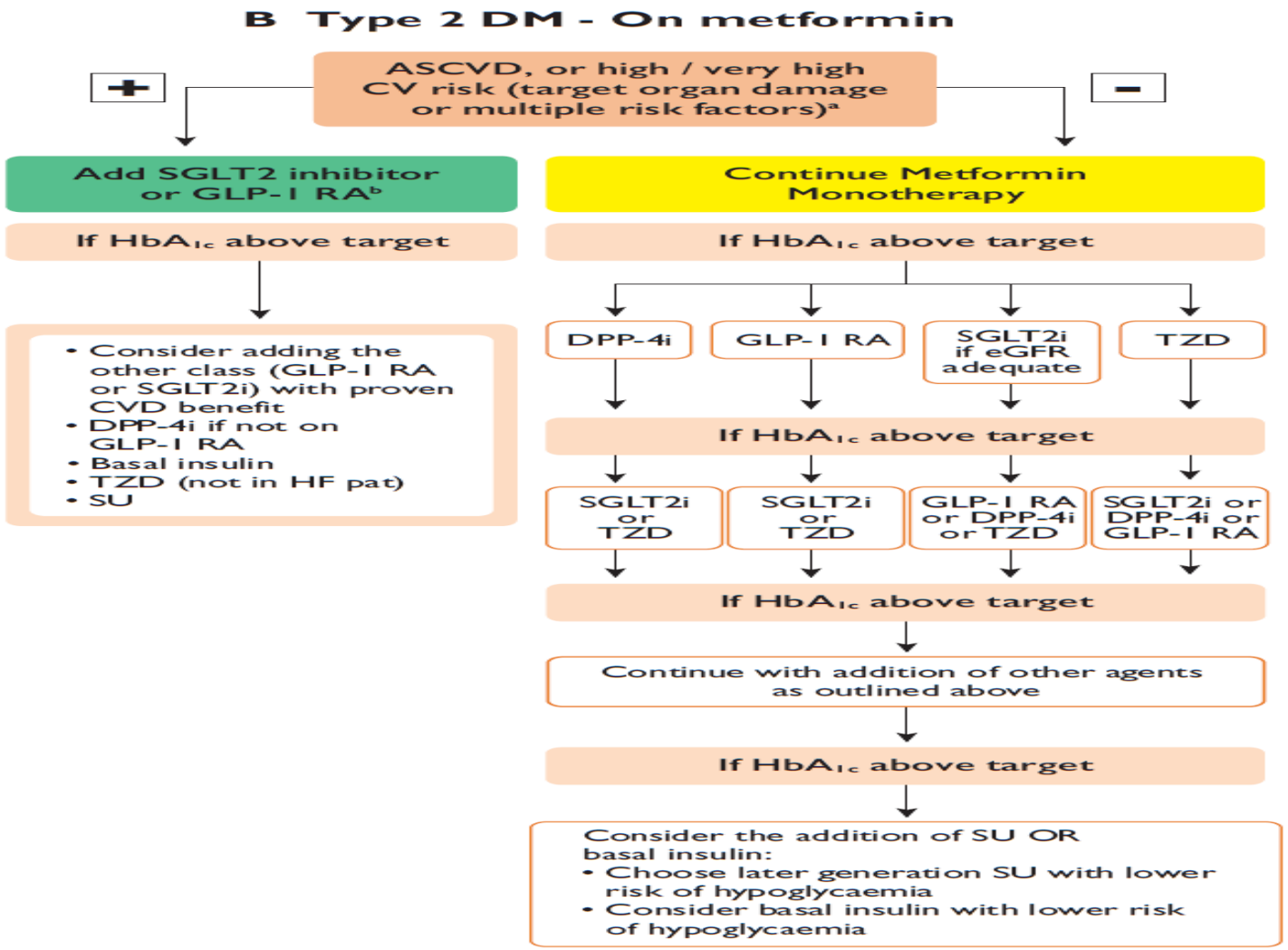
2. Eur Heart J. 2020 Jan 7;41(2)255-323.

Treatment algorithm in patients with type 2 diabetes mellitus - drug-naı¨ve



2. Eur Heart J. 2020 Jan 7;41(2)255-323.

Treatment algorithm in patients with type 2 diabetes mellitus - metformin-treated patients



2. Eur Heart J. 2020 Jan 7;41(2)255-323.

Recommendations for glucose-lowering treatment for patients with diabetes

Recommendations for glucose-lowering treatment for patients with diabetes

Recommendations	Class[a]	Level[b]
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[306,308,309,311]	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.[306]	I	B
GLP1-RAs		
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[176,299–300,302–303]	I	A
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce the risk of death.[176]	I	B
Biguanides		
Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk.[146,149]	IIa	C
Insulin		
Insulin-based glycaemic control should be considered in patients with ACS with significant hyperglycaemia (>10 mmol/L or >180 mg/dL), with the target adapted according to comorbidities.[260–262]	IIa	C
Thiazolidinediones		
Thiazolidinediones are not recommended in patients with HF.	III	A
DPP4 inhibitors		
Saxagliptin is not recommended in patients with T2DM and a high risk of HF.[291]	III	B

ACS = acute coronary syndromes; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; DPP4 = dipeptidyl peptidase-4; GLP1-RA = glucagon-like peptide-
1 receptor agonist; HF = heart failure; SGLT2 = sodium-glucose co-transporter 2; T2DM = type 2 diabetes mellitus.
a Class of recommendation.
b Level of evidence.

2. Eur Heart J. 2020 Jan 7;41(2)255-323.

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TYPE 2 DIABETES AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Microvascular complications of diabetes (retinopathy, nephropathy, and neuropathy) are directly related to the severity and duration of hyperglycaemia, as reflected by the HbA1c

Macrovascular complications are the primary cause of mortality, with myocardial infarction (MI) and stroke accounting for 80% of all deaths in T2DM patients

How about non-atherosclerotic cardiovascular disease? Such as Heart failure and death

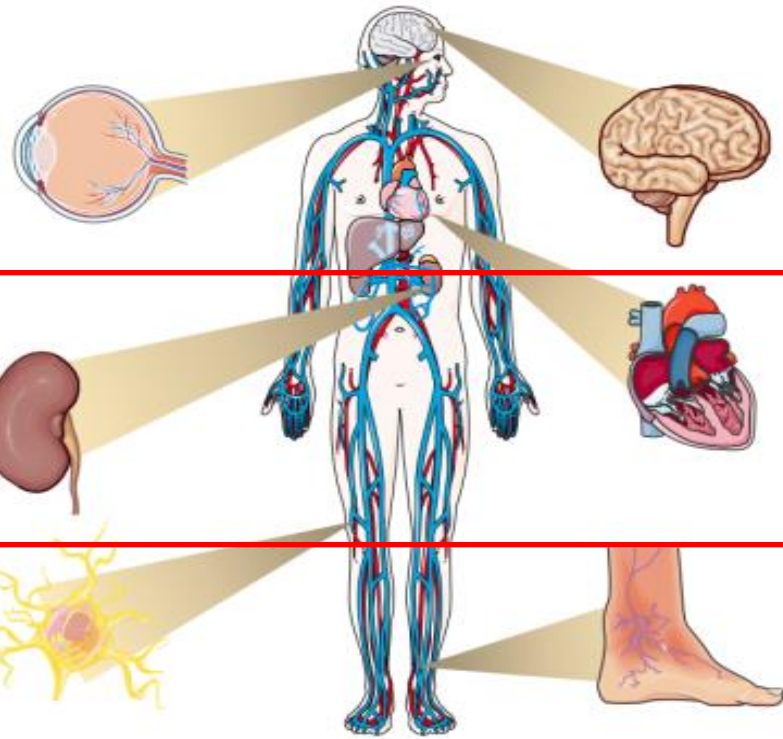
Major Complications of Diabetes

Microvascular

Eye
High blood glucose and high blood pressure can damage eye blood vessels, causing retinopathy, cataracts and glaucoma

Kidney
High blood pressure damages small blood vessels and excess blood glucose overworks the kidneys, resulting in nephropathy.

Neuropathy
Hyperglycemia damages nerves in the peripheral nervous system. This may result in pain and/or numbness. Feet wounds may go undetected, get infected and lead to gangrene.



Macrovascular

Brain
Increased risk of stroke and cerebrovascular disease, including transient ischemic attack, cognitive impairment, etc.

Heart
High blood pressure and insulin resistance increase risk of coronary heart disease

Extremities
Peripheral vascular disease results from narrowing of blood vessels increasing the risk for reduced or lack of blood flow in legs. Feet wounds are likely to heal slowly contributing to gangrene and other complications.

https://pdb101.rcsb.org/global-health/diabetes-mellitus/monitoring/complications
3. Diabetes Care, 37(1), 9–16. doi: 10.2337/dc13-2112
The Korean Journal of Physiology & Pharmacology, 18(1), 1. doi: 10.4196/kjpp.2014.18.1.1

Glucose-lowering studies confirmed benefit on microvascular complications but mixed results on macrovascular outcomes

Study[1]	Baseline HbA_{1c} Control vs intensive	Mean duration of diabetes at baseline (years)	Microvascular		CVD		Mortality	
UKPDS	9%→ 7.9% vs 7%	Newly diagnosed	↓	↓	↔	↓	↔	↓
ACCORD[1–3]	8.3%→ 7.5% vs 6.4%	10.0	↓*		↔		↑	
ADVANCE	7.5 %→ 7.3% vs 6.5%	8.0	↓	↔**	↔	↔	↔	↔
VADT	9.4 %→ 8.4% vs 6.9%	11.5	↓	?	↔	↓	↔	↔

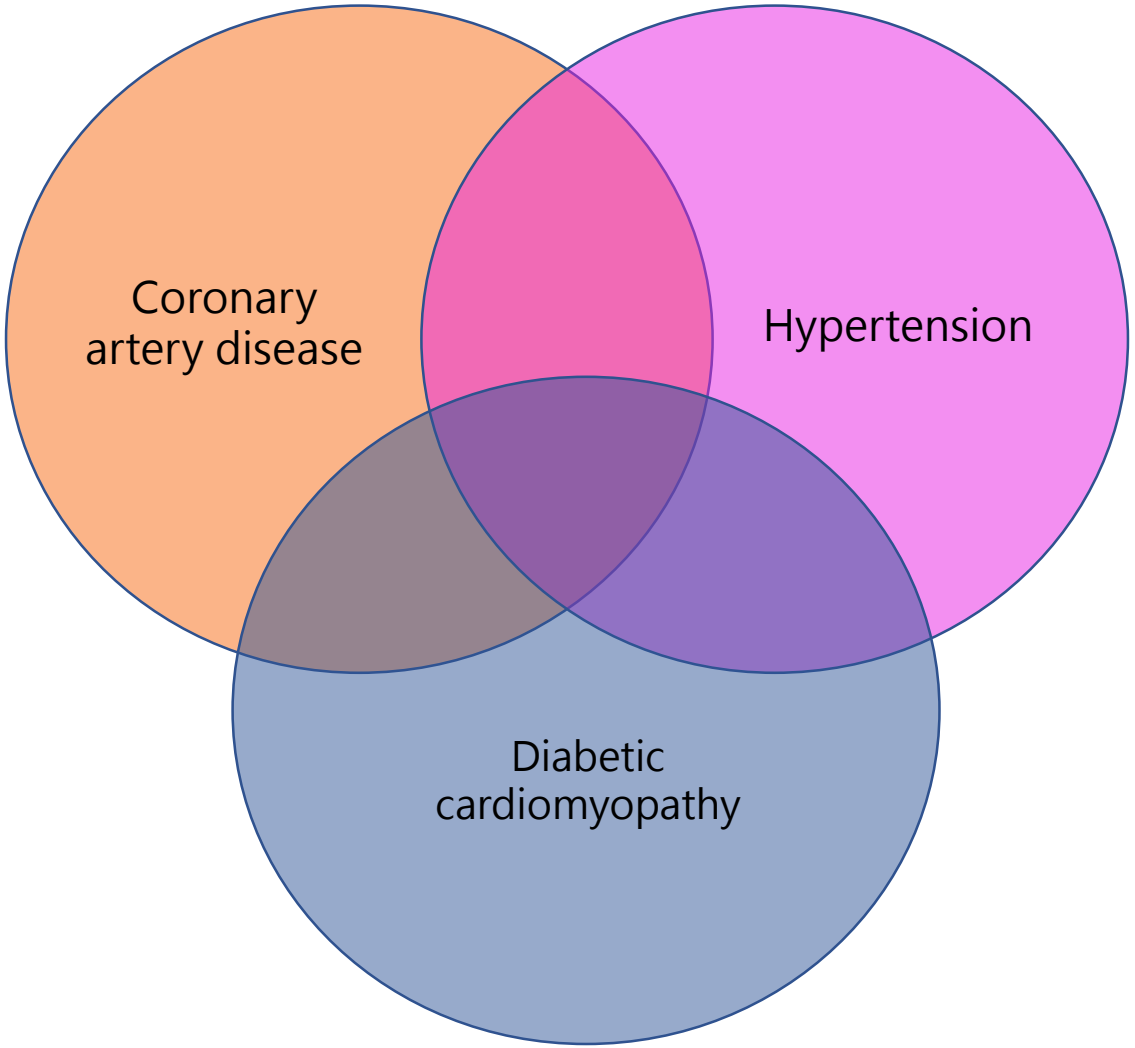
Long-term follow-up[1,4,5]

*No change in primary microvascular composite but significant decreases in micro/macroalbuminuria[2,3]

**No change in major clinical microvascular events but significant reduction in ESRD (p = 0.007)[5]

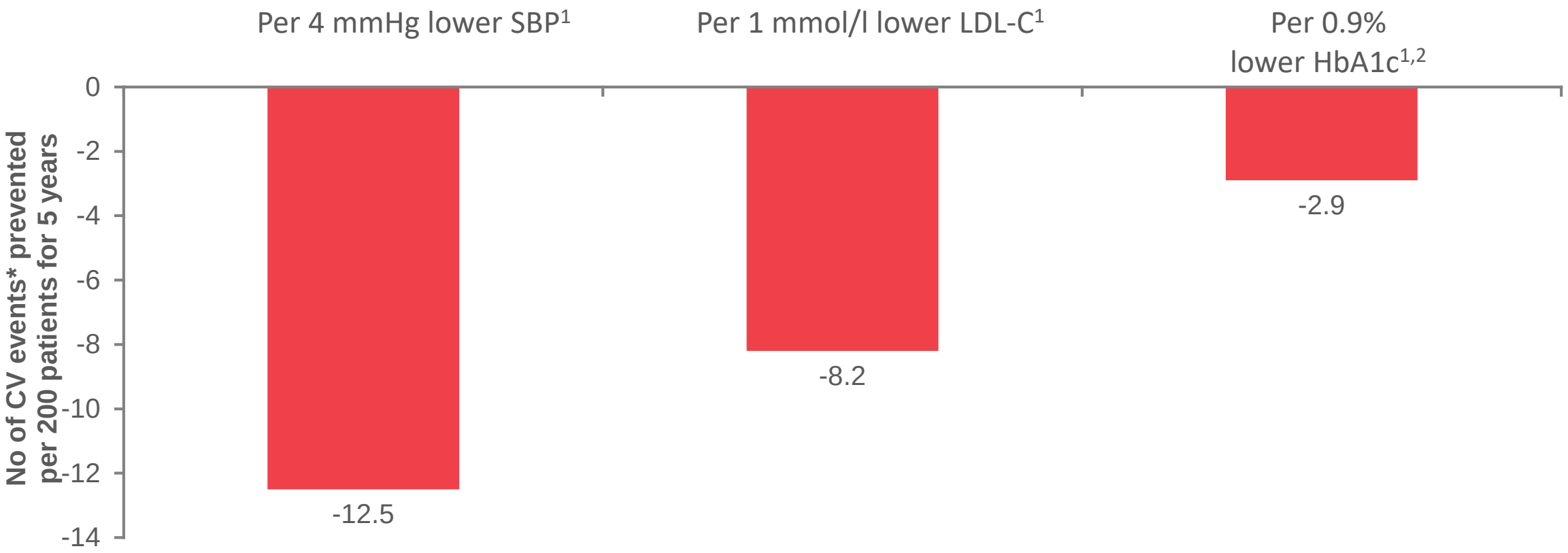
1. Table adapted from Bergenstal et al. Am J Med 2010;123:374.e9–e18. 2. Genuth et al. Clin Endocrinol Metab 2012;97:41–8.
3. Ismail-Beigi et al. Lancet 2010;376:419–30. 4. Hayward et al. N Engl J Med 2015;372:2197-206 (VADT). 5. Zoungas et al. N Engl J Med 2014;371:1392-406.

Toxic Triad of Heart Failure in Diabetes



4. Diabetes Care 26:2433–2441, 2003

CV risk reduction in T2D may require multiple interventions including BP and lipid management



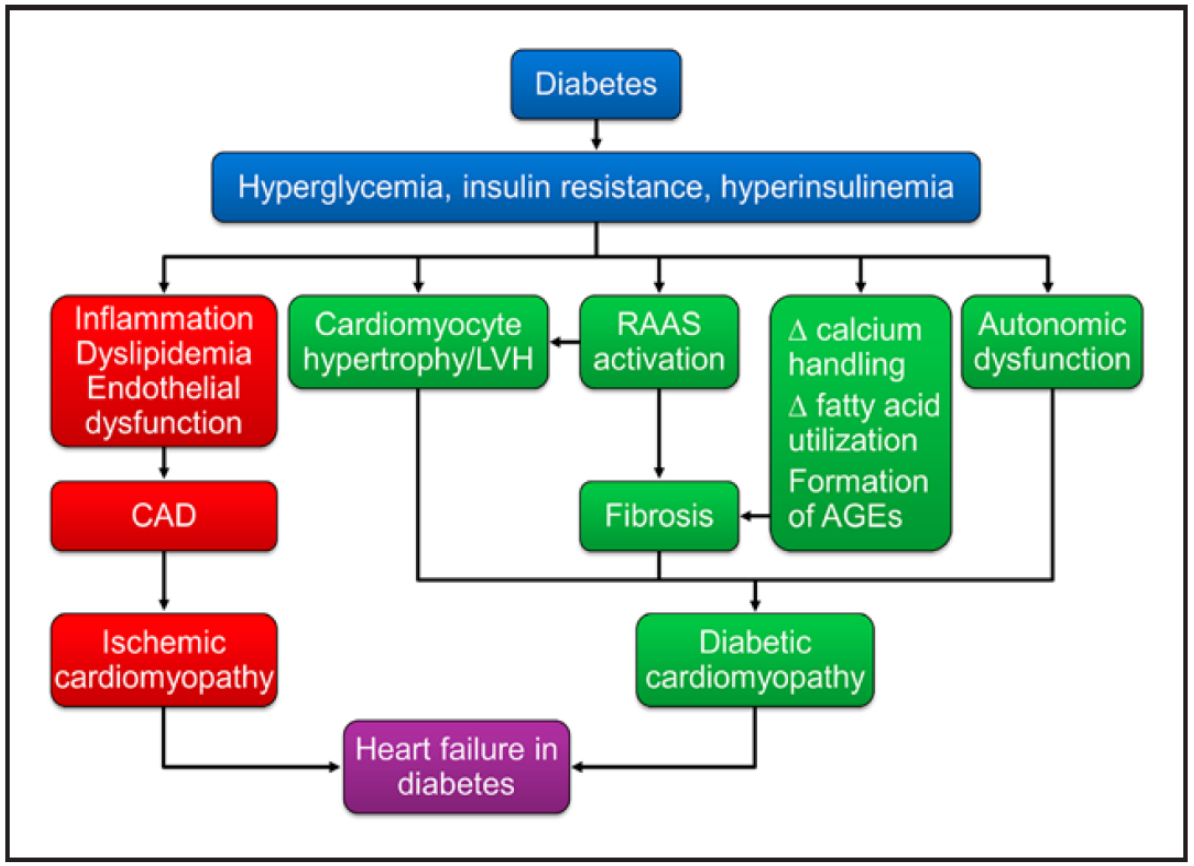
*Non-fatal MI, CHD, stroke and all-cause mortality

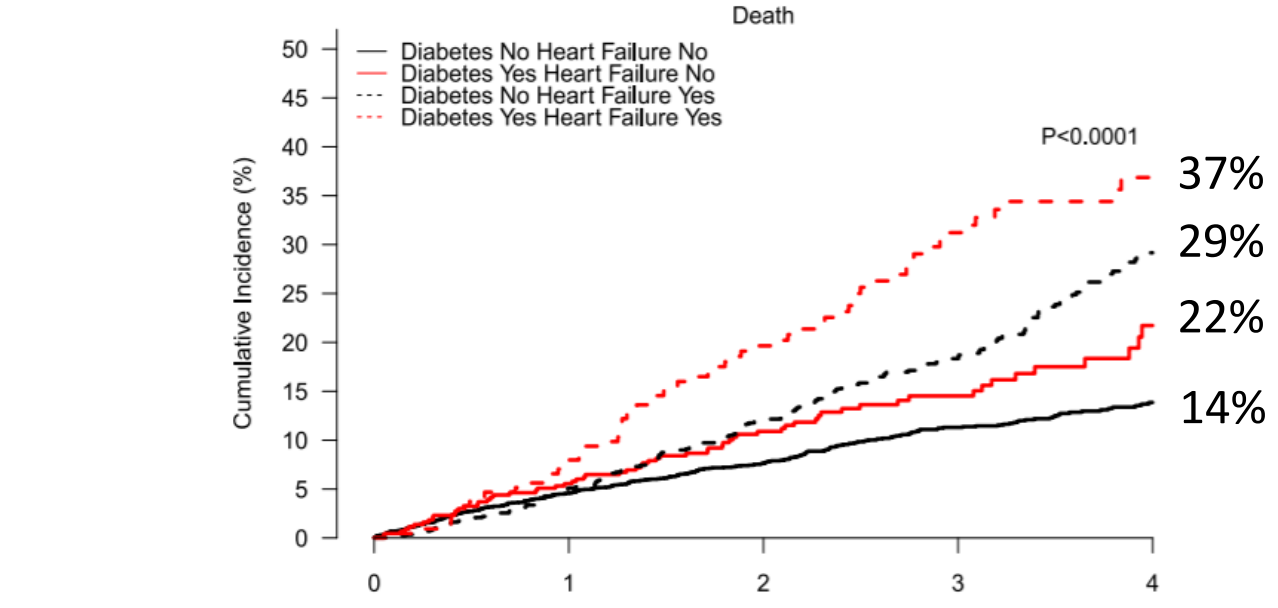
1. Sattar N. *Diabetologia* 2013;56:686; 2. Ray KK *et al. Lancet* 2009;373:1765

Diabetes and heart failure

- Heart failure is highly prevalent in patients with DM occurring in >1 in 5 patients aged over 65 yrs
- Patients with both DM and heart failure have a poor prognosis with a median survival 4 yrs
- Glucose lowering options for patients with type 2 DM and heart failure are limited .Meta-analysis of more or less intensive glucose control showed no benefit on heart failure hospitalization or death
- Specific glucose-lowering medications have not been shown to improve heart failure outcome and some may actually have deleterious effect (eg TZD)

Heart Failure increases Mortality





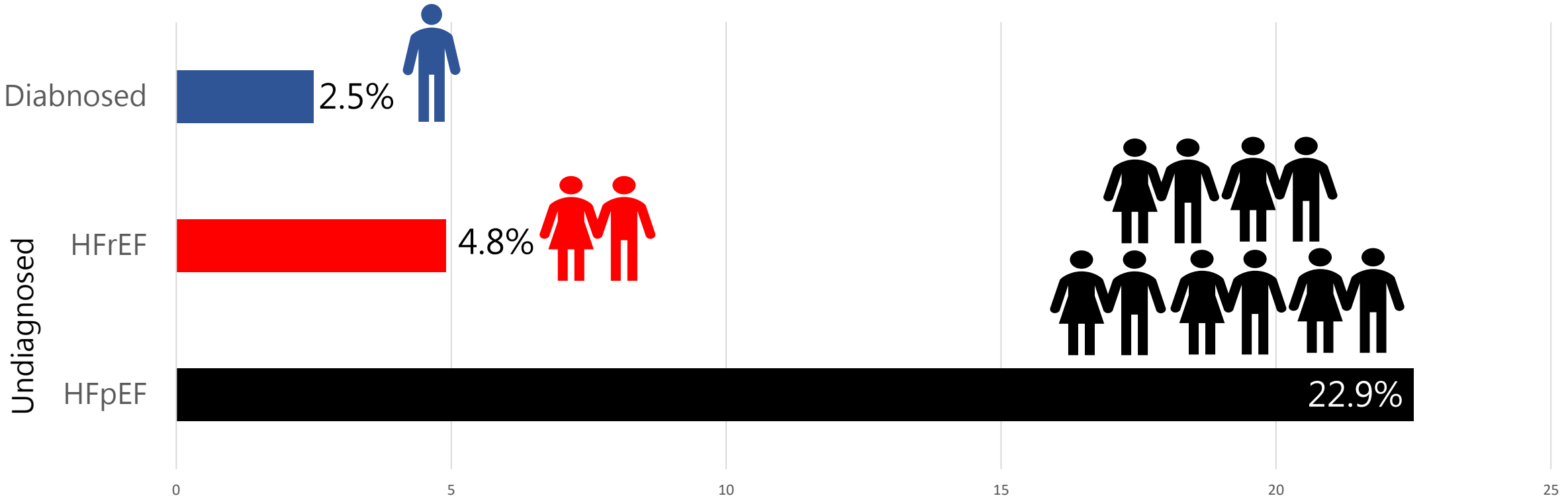
Population					
Diabetes No Heart Failure No:	2715	2588	2038	1188	519
Diabetes Yes Heart Failure No:	433	407	298	162	62
Diabetes No Heart Failure Yes:	861	816	669	450	209
Diabetes Yes Heart Failure Yes:	214	196	143	90	46

In unadjusted analyses, patients with diabetes had a higher risk of development of HF (hazard ratio 1.53 [95% CI 1.32–1.78]; P < 0.001), HF hospitalization (2.04 [1.65–2.52]; P < 0.0001)

5. Diabetes Care 2018;41:1285–1291
6 Circulation. 2019;140:e294–e324.

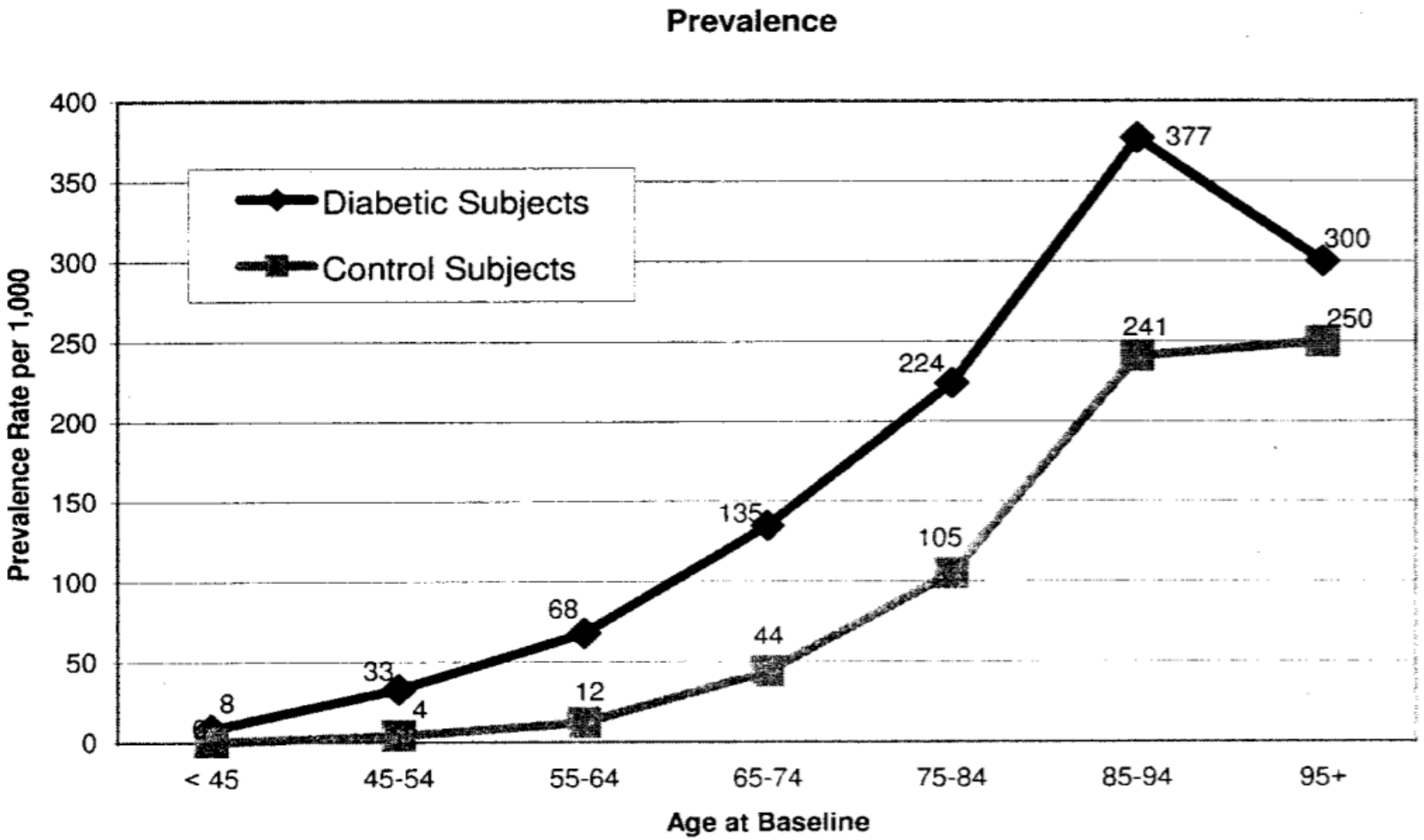
Prevalence of HF in DM2

605 DM2, age>60 years, Primary care, Zeeland
Symptoms, signs, echo, adjudication



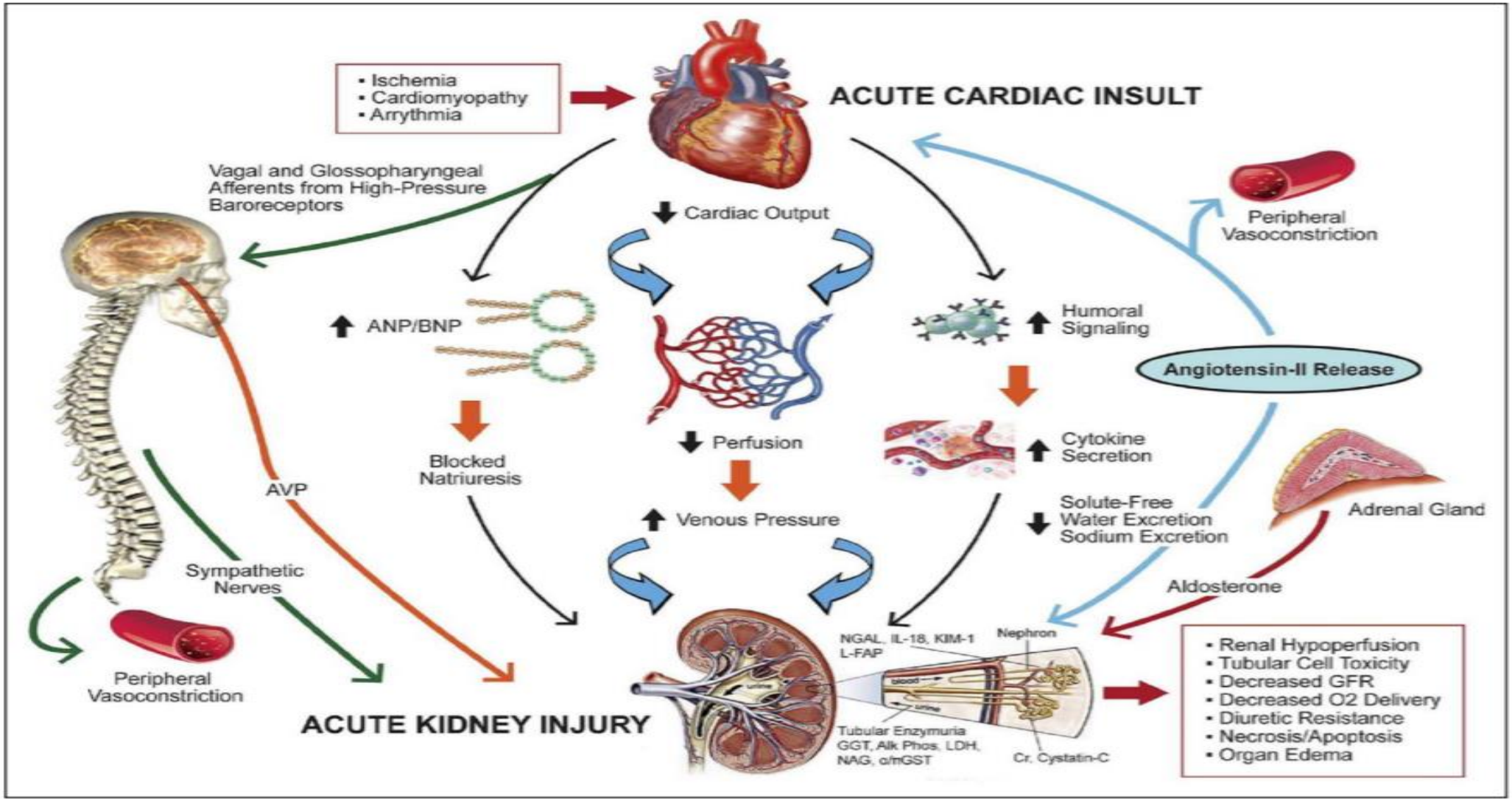
7 Diabetologia. 2012 Aug;55(8):2154-62

Heart Failure in Diabetes



8 Diabetes Care 2001 Sep; 24(9): 1614-1619.

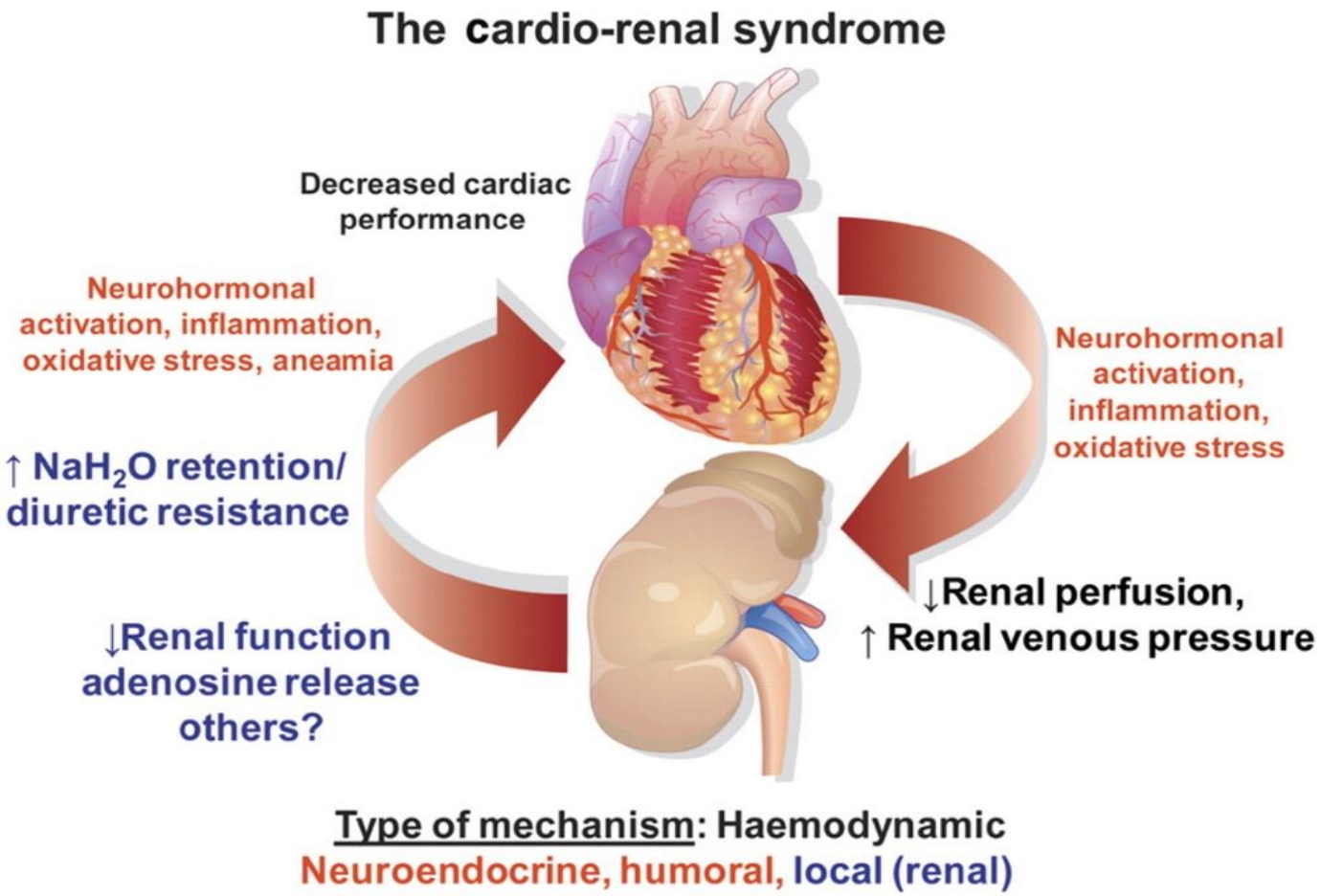
Pathophysiology of neurohumoral and inflammatory pathways involved in cardiorenal syndrome



9 Circulation. 2019;139:e840–e878.

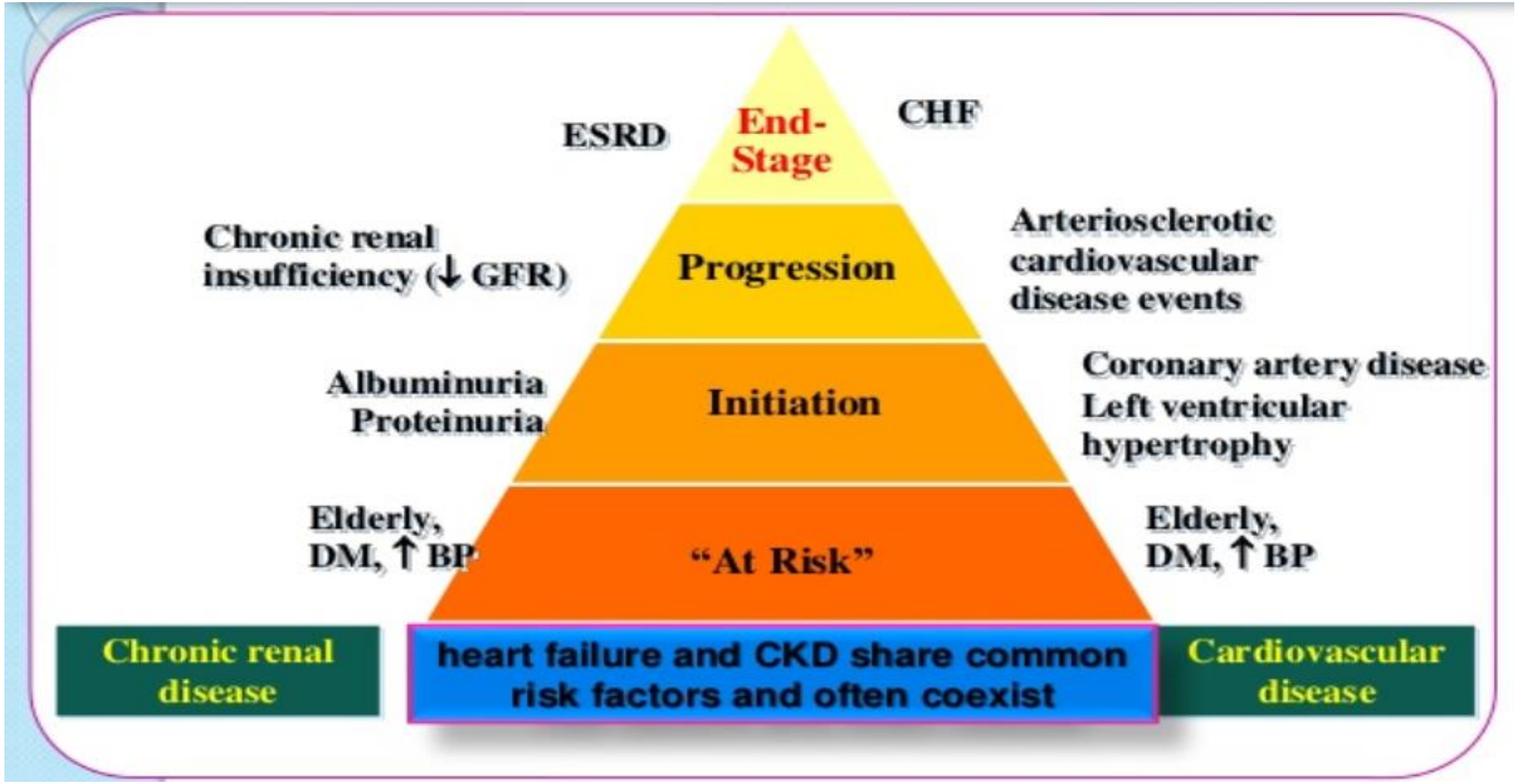
CAN-20200324.No2

Cardio-Renal Syndrome Does Matter



10 European Heart Journal (2012) 33, 2135–2143

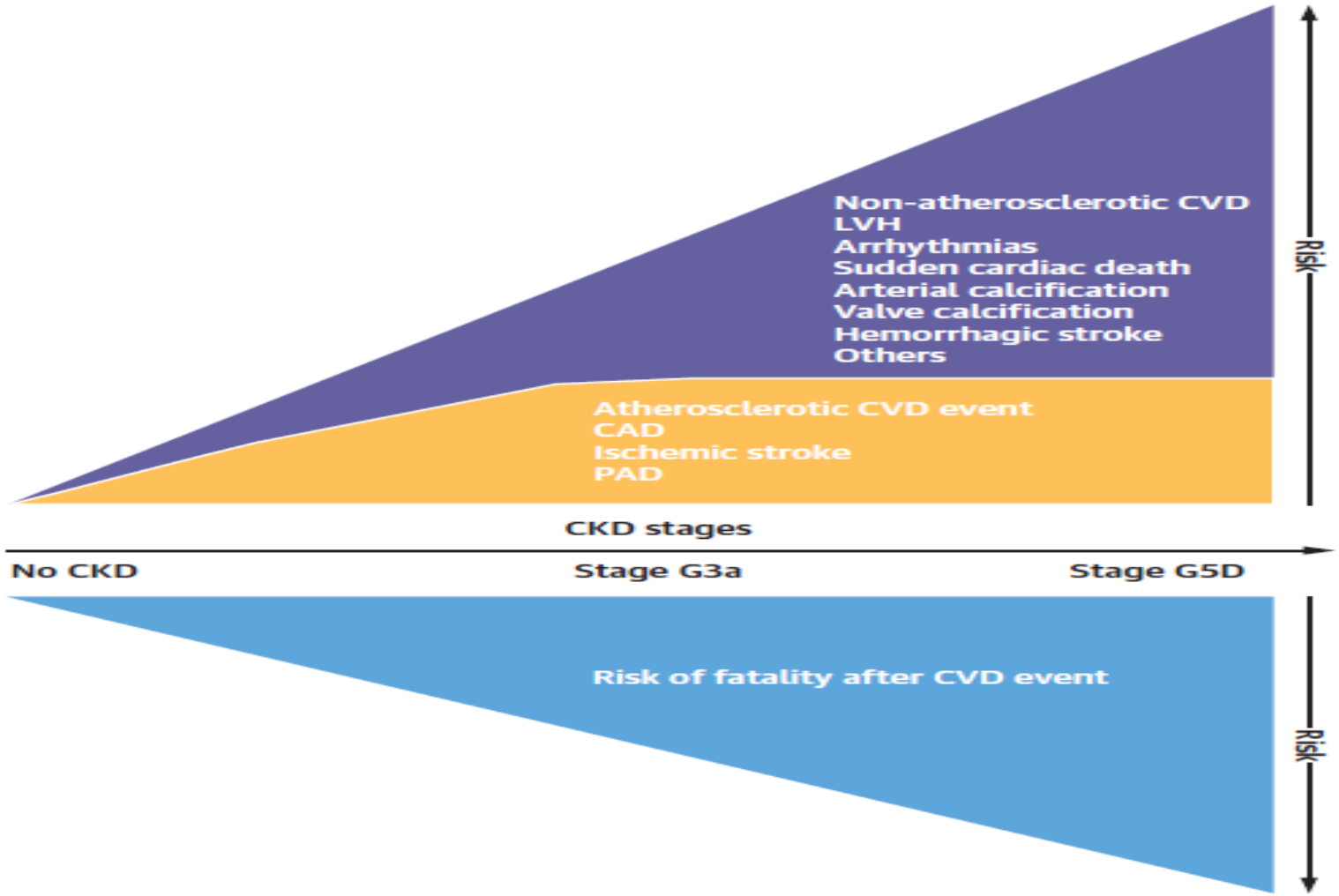
Cardiovascular and renal disease continuum



11 Am J Kidney Dis 2000; 35:S117-31

CAN-20200324.No2

Changes in Cardiovascular Disease Risk During Chronic Kidney Disease Progression



12 J Am Coll Cardiol. 2019;74(14):1823–38.

Classification of Cardio-Renal-Syndrome (CRS)

Table 1. Classification of CRS Based on the Consensus Conference of the Acute Dialysis Quality Initiative

Phenotype	Nomenclature	Description	Clinical Examples
Type 1 CRS	Acute CRS	HF resulting in AKI	ACS resulting in cardiogenic shock and AKI, AHF resulting in AKI
Type 2 CRS	Chronic CRS	Chronic HF resulting in CKD	Chronic HF
Type 3 CRS	Acute renocardiac syndrome	AKI resulting in AHF	HF in the setting of AKI from volume overload, inflammatory surge, and metabolic disturbances in uremia
Type 4 CRS	Chronic renocardiac syndrome	CKD resulting in chronic HF	LVH and HF from CKD-associated cardiomyopathy
Type 5 CRS	Secondary CRS	Systemic process resulting in HF and kidney failure	Amyloidosis, sepsis, cirrhosis

ACS indicates acute coronary syndrome; AHF, acute heart failure; AKI, acute kidney injury; CKD, chronic kidney disease; CRS, cardiorenal syndrome; HF, heart failure; and LVH, left ventricular hypertrophy.

13. Circulation. 2019;139:e840–e878.

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Compelling evidence of SGLT2i in cardiorenal benefits

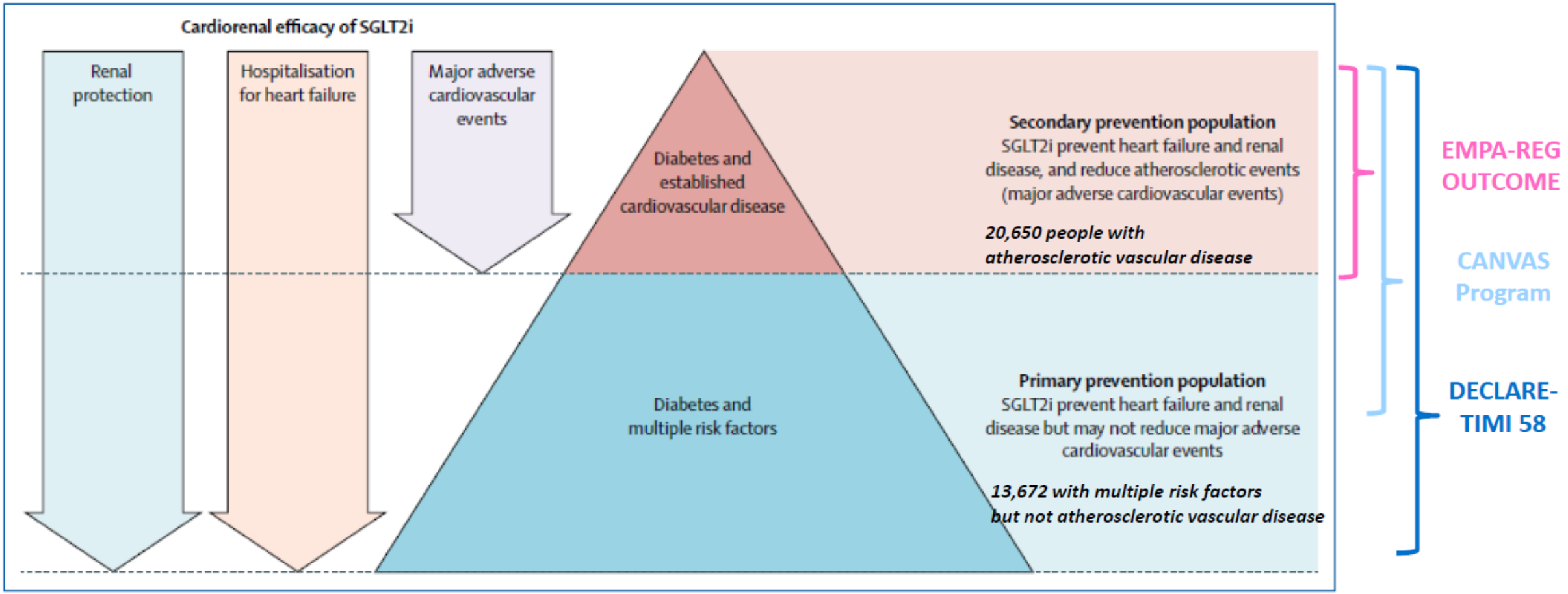
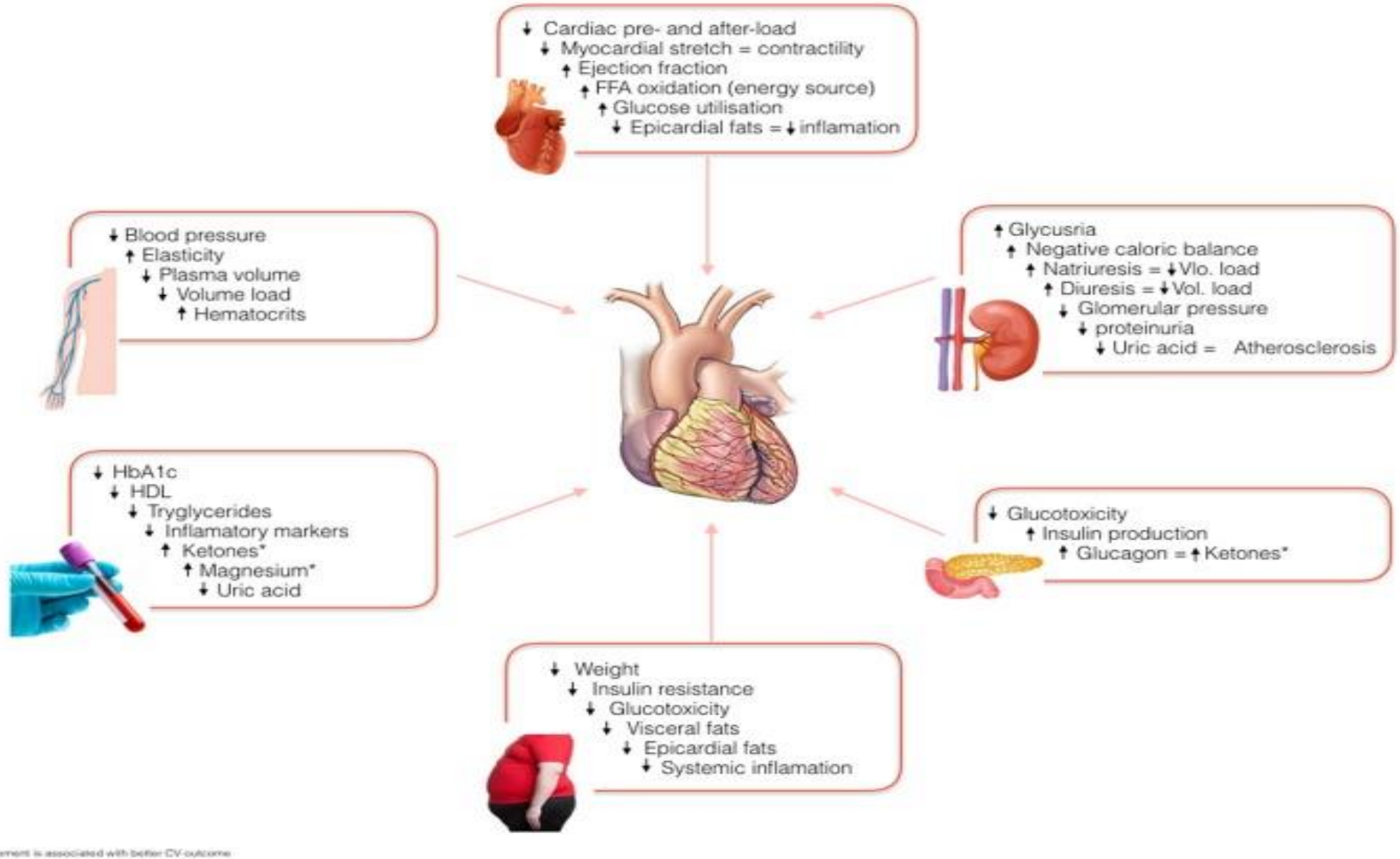


Figure: **Cardiorenal benefits of SGLT2i in different patient populations**
SGLT2i=sodium-glucose cotransporter-2 inhibitors.

Subodh Verma et al. Lancet 2018

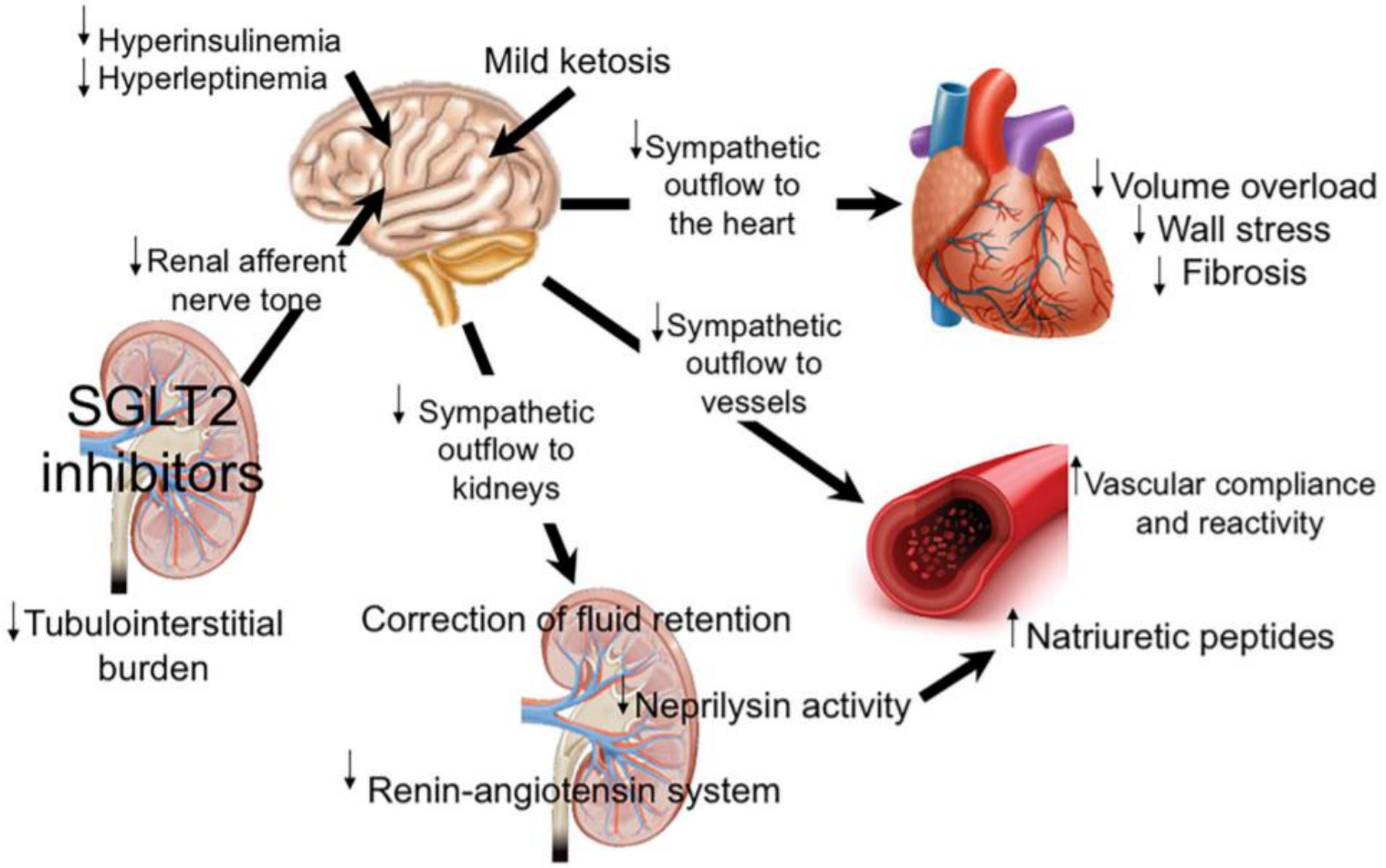
Current clinical hypothetical explanations for the cardioprotective effect of SGLT2 inhibitors



* Mild increment is associated with better CV outcome

14. J Clin Med Res. 2018 Aug;10(8):615-625

Proposed mechanism of cardiovascular protection by SGLT2 inhibitors



15. J Cardiol. 2018 May;71(5):471-476.

CAN-20200324.No2

The renal-cardio hypothesis for cardiovascular protection with SGLT2i: a nephrocentric perspective

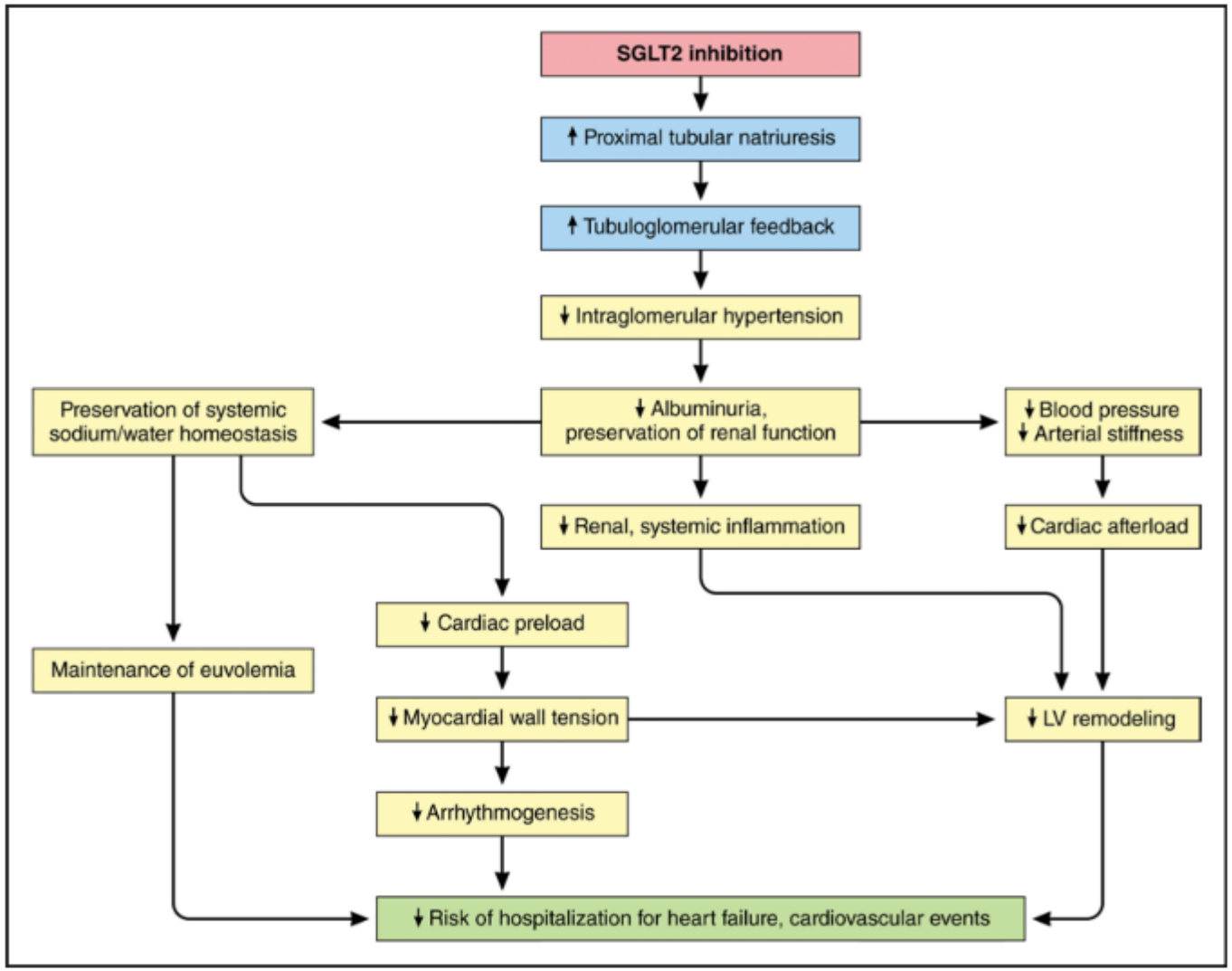


Figure 7. The renal-cardio hypothesis for cardiovascular protection with SGLT2 inhibition: a nephrocentric perspective.
LV indicates left ventricular; and SGLT2, sodium-glucose cotransporter-2.

16. Circulation. 2016;134:752–772.

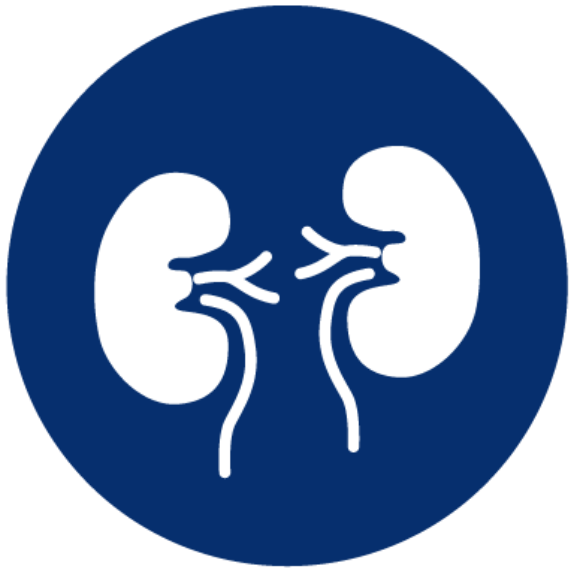
Many Renal Effects of SGLT2 Inhibition Have Been Proposed

↓ Intraglomerular pressure

↓ Glucose

↓ BP/arterial stiffness

↓ Volume



↓ Albuminuria

↓ Oxidant stress

↓ Intrarenal angiotensinogen upregulation

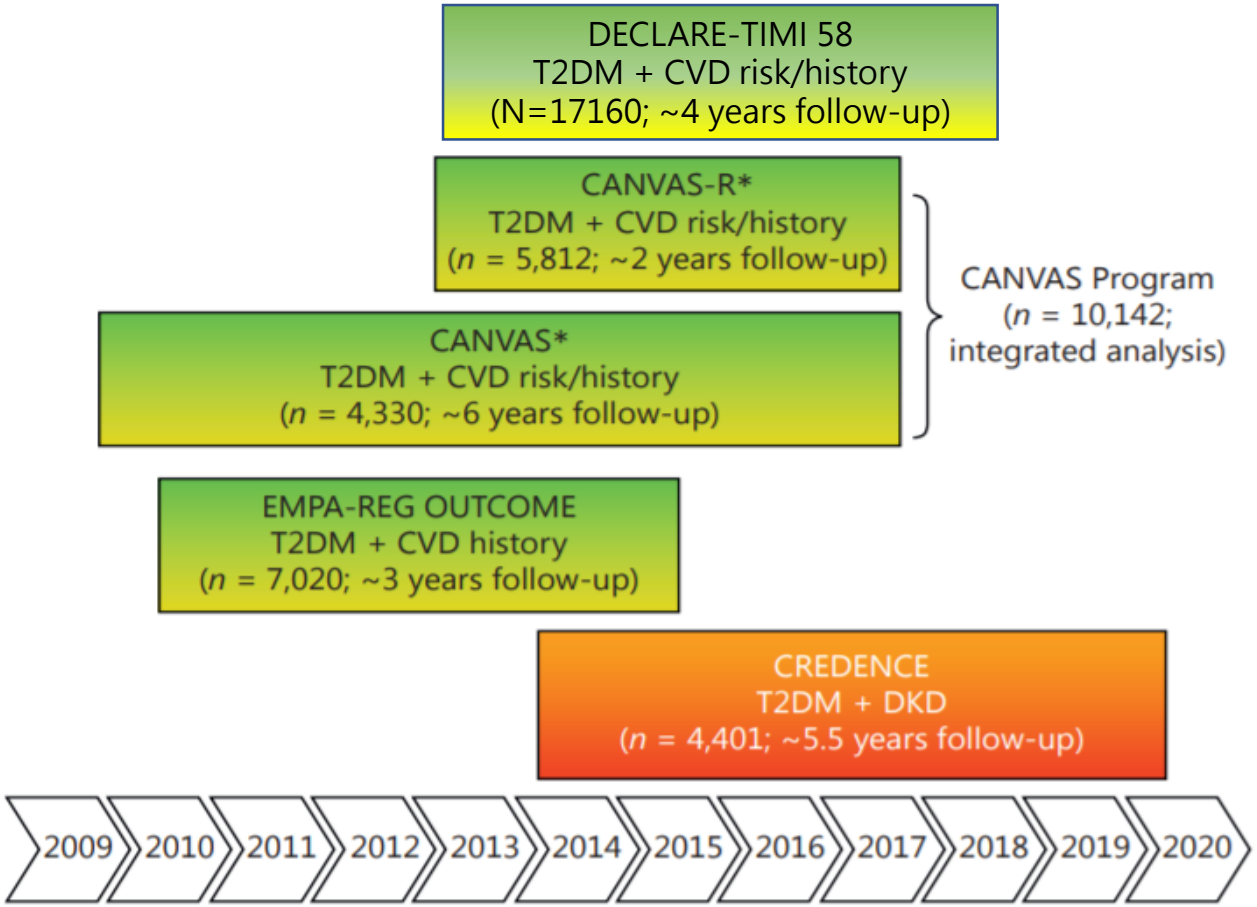
↓ Inflammation/fibrosis

And many others…

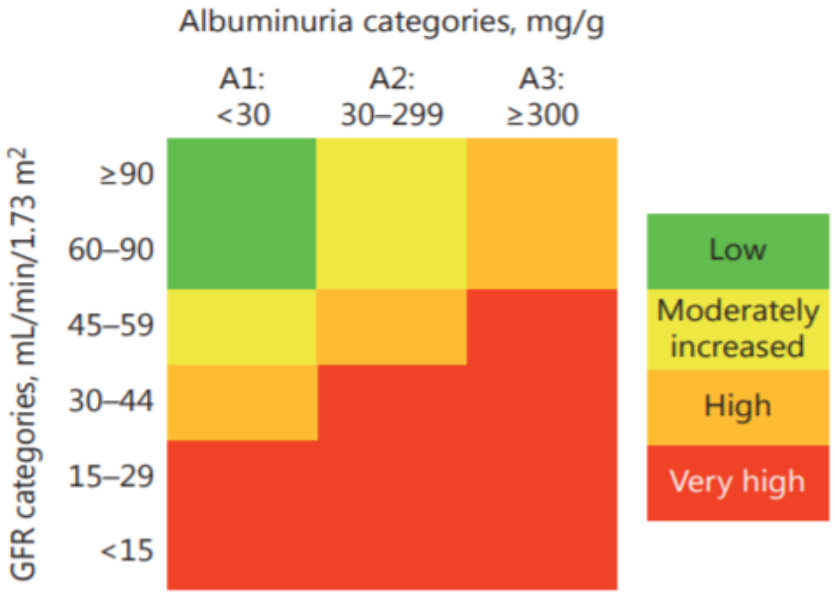
Presented at the 79th Scientific Sessions of the American Diabetes Association; June 11, 2019; San Francisco, CA.

CREDENCE

Timeline and population of major SGLT2 inhibitor outcome trials



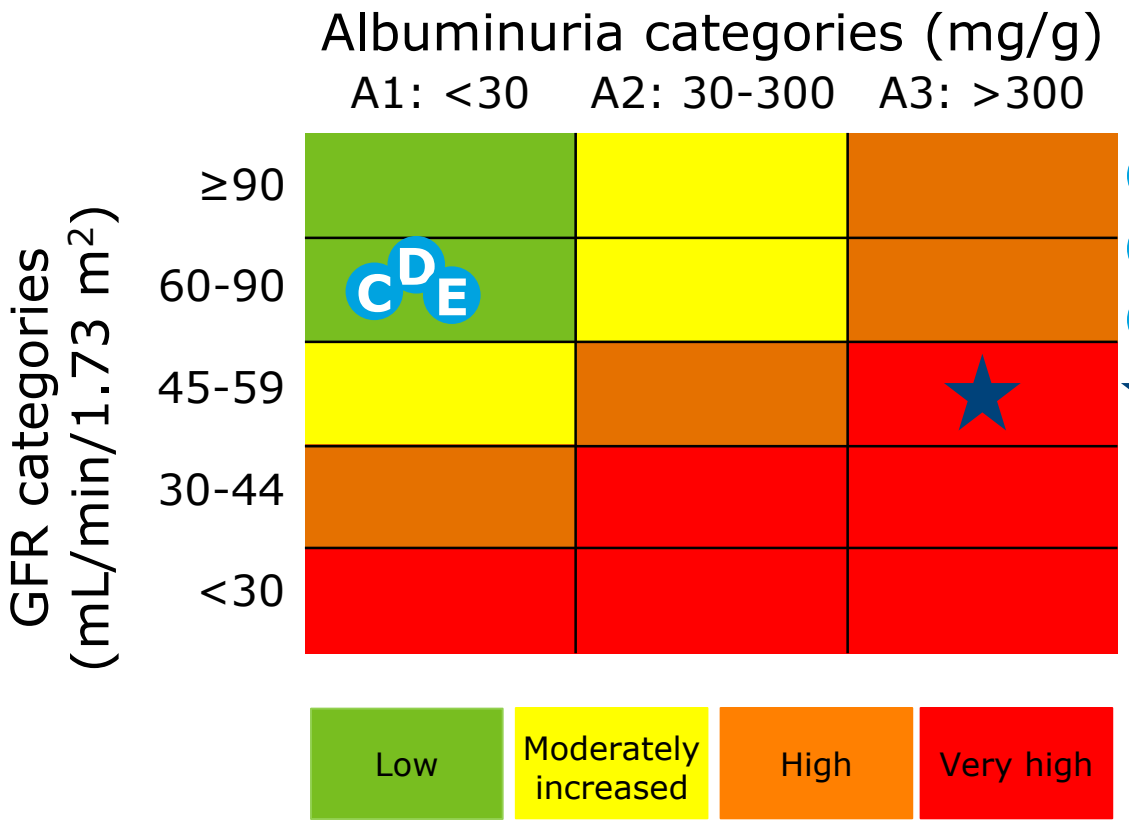
* Note that the patient populations in CANVAS and CANVAS-R are nearly identical to facilitate an integrated analysis of the data.



17 Am J Nephrol 2017;46:462–472

CAN-20200324.No2

Higher Renal Risk Population in CREDENCE



	Mean eGFR (mL/min/1.73 m²)	Median UACR (mg/g)
D DECLARE	85	13
C CANVAS Program	76	12
E EMPA-REG	74	18
★ OUTCOME	56	927
CREDENCE		

Events on dialysis, transplantation, or death due to kidney disease

Trial	Events	Patients
CREDENCE	183	4,401
DECLARE-TIMI 58	34	17,160
CANVAS Program	21	10,142
EMPA-REG OUTCOME	14	7,020

Weights were from random-effects meta-analysis. Data from DECLARE-TIMI 58 have not been previously reported. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

18. N Engl J Med 2015; 373:2117-2128
19. N Engl J Med 2017; 377:644-657
20. N Engl J Med 2019; 380:1880-1882
21. N Engl J Med 2019; 380:2295-2306

Cardio-Renal Syndrome Does Matter

	EMPA-REG	CANVAS	DECLARE	CREDENCE
CVD	99.2%	65.6%	40.6%	50.4%
non-CVD	0.8%	34.4%	59.4%	49.6%
Mean eGFR	74	76	85	56
Mean UACR	18	12	13	927

	EMPA-REG		**CANVAS**		**DECLARE**		**CREDENCE**	
	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
3P-MACE	37.4	**43.9**	26.9	**31.5**	22.6	**24.2**	38.7	**48.7**
HHF	9.4	**14.5**	5.5	**8.7**	6.2	**8.5**	15.7	**25.3**
CV death	12.4	**20.2**	11.6	**12.8**	7.0	**7.1**	19	**24.4**

no. of participants per 1000 patient-yr

18. N Engl J Med 2015; 373:2117-2128
19. N Engl J Med 2017; 377:644-657
20. N Engl J Med 2019; 380:1880-1882
21. N Engl J Med 2019; 380:2295-2306

Microalbuminuria: A Manifestation of Diffuse Endothelial Cell Injury

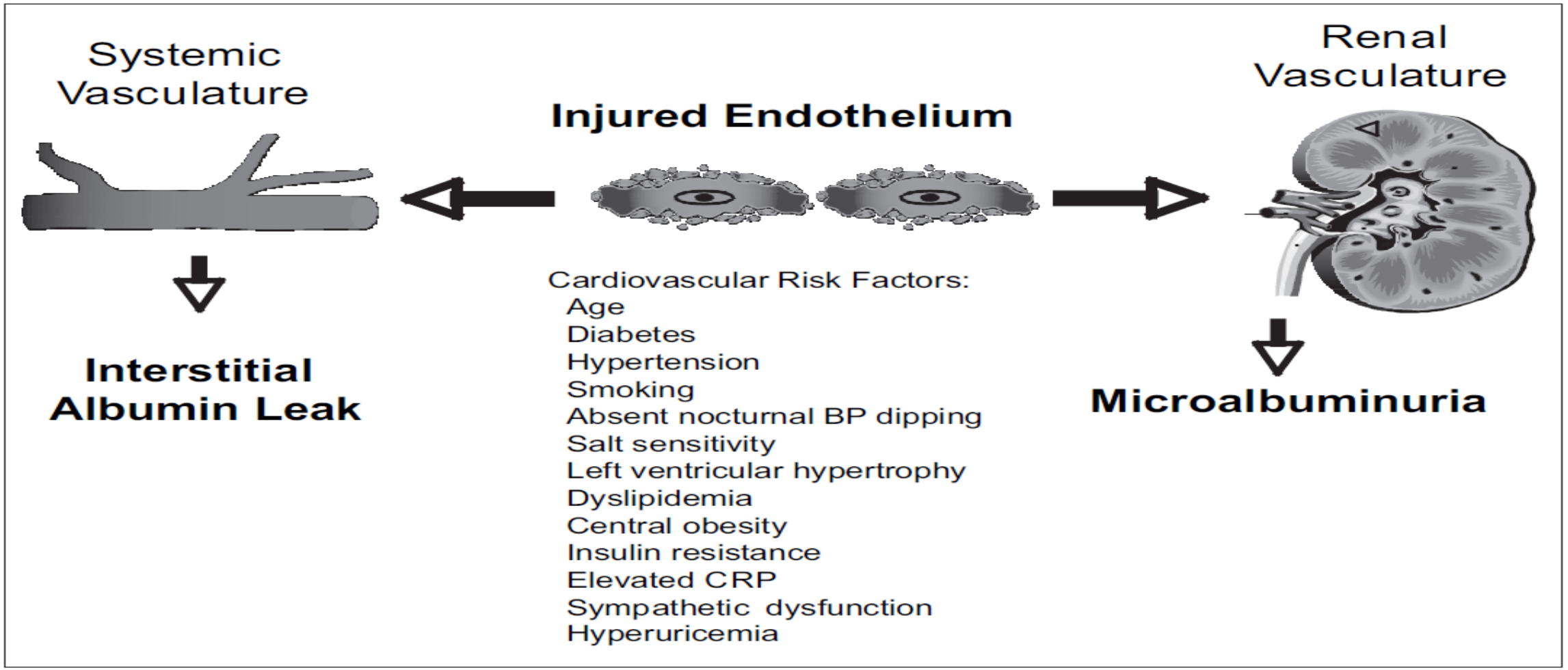
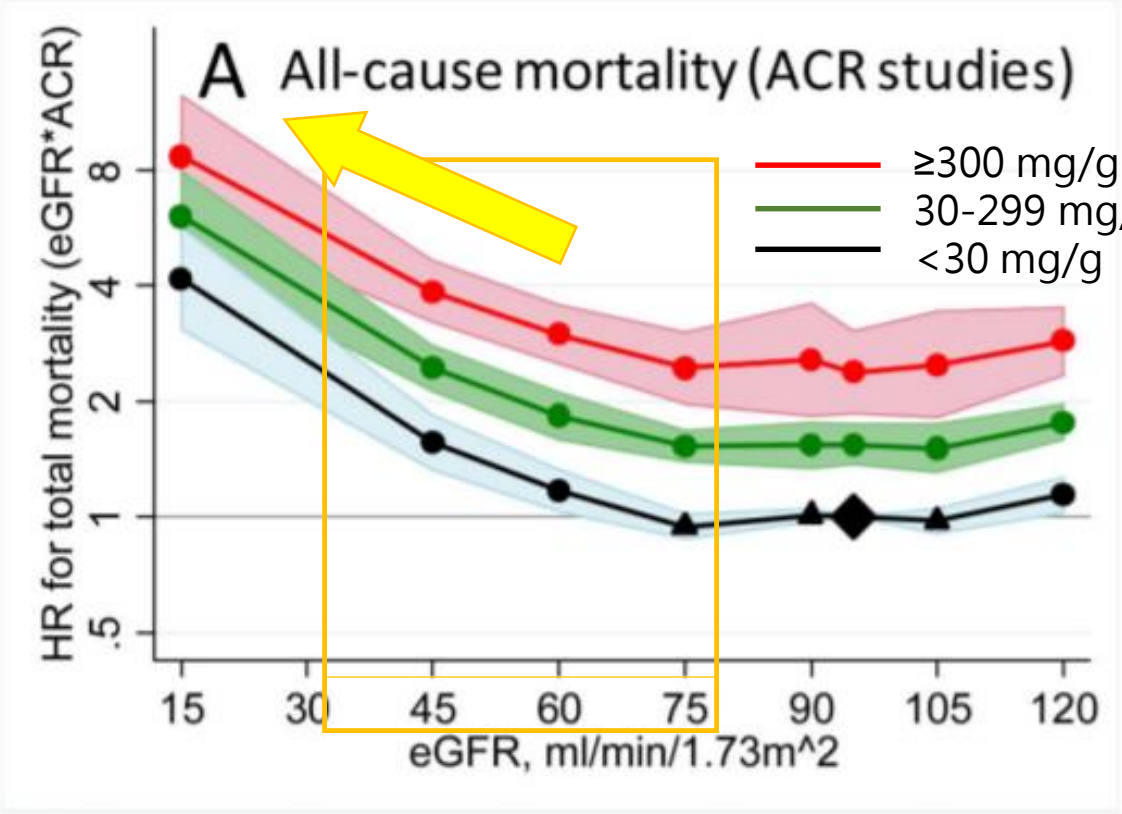
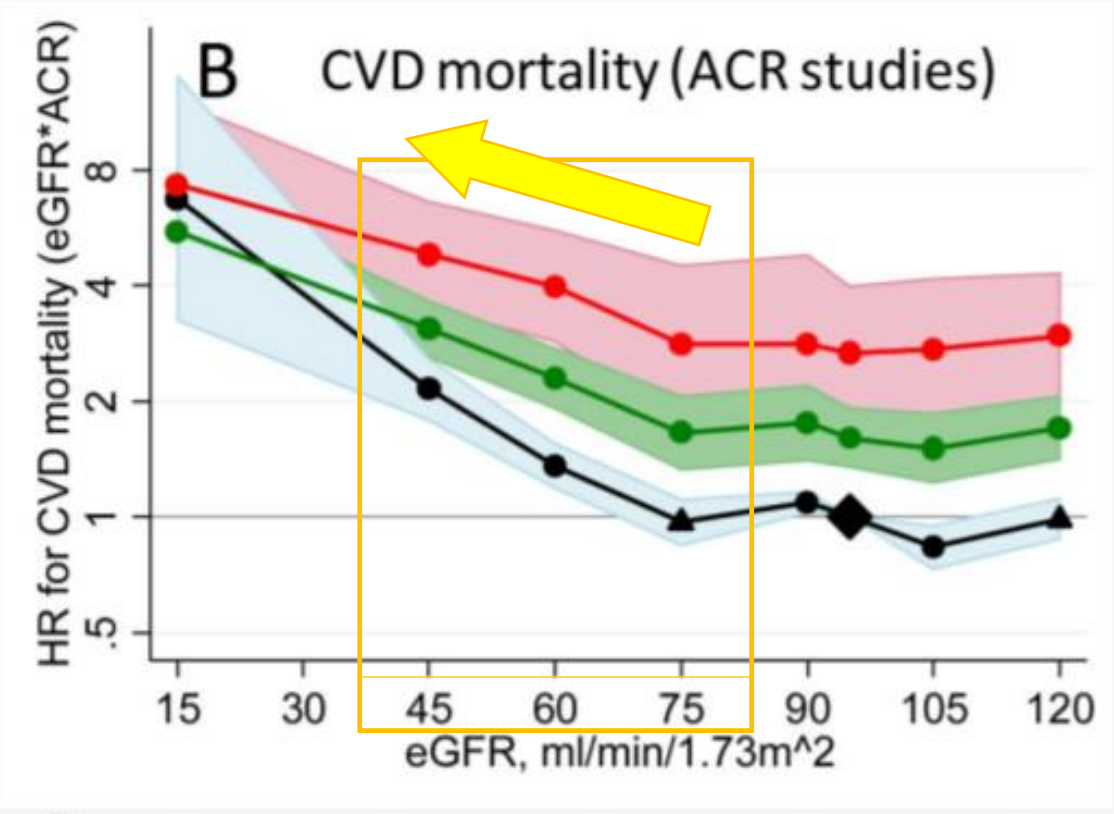


Figure 2. Microalbuminuria: manifestation of diffuse endothelial cell injury. BP=blood pressure; CRP=C-reactive protein

22. J Clin Hypertens. 2004; 6 (Suppl; 3):2-7

Association of eGFR and albuminuria with all-cause death and CV death

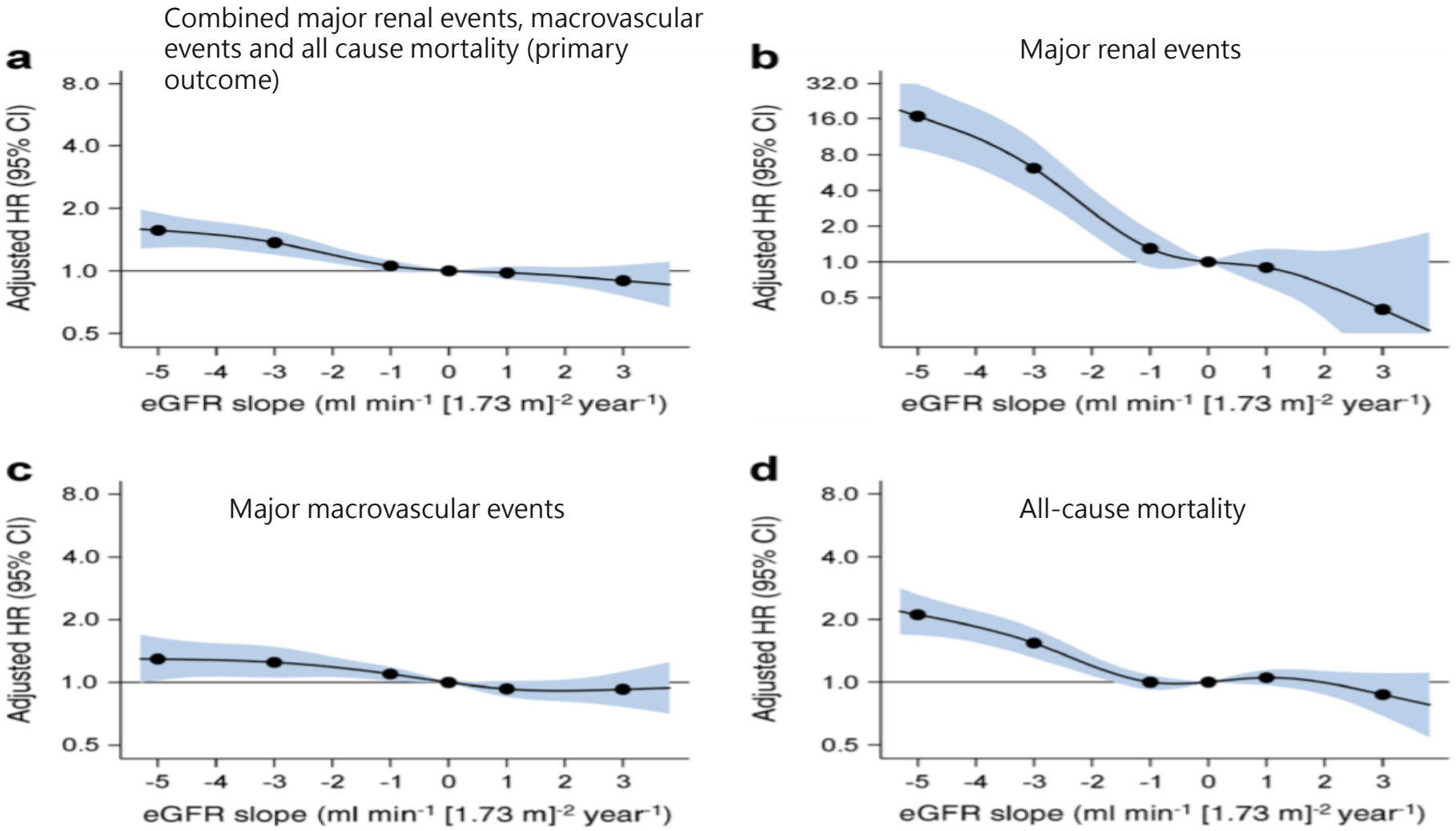




Early intervention is important to reduce mortality

23. Lancet. 2010 Jun 12;375(9731):2073-81.

The relationship between eGFR slope and subsequent risk of vascular outcomes and all-cause mortality in type 2 diabetes: the ADVANCE-ON study



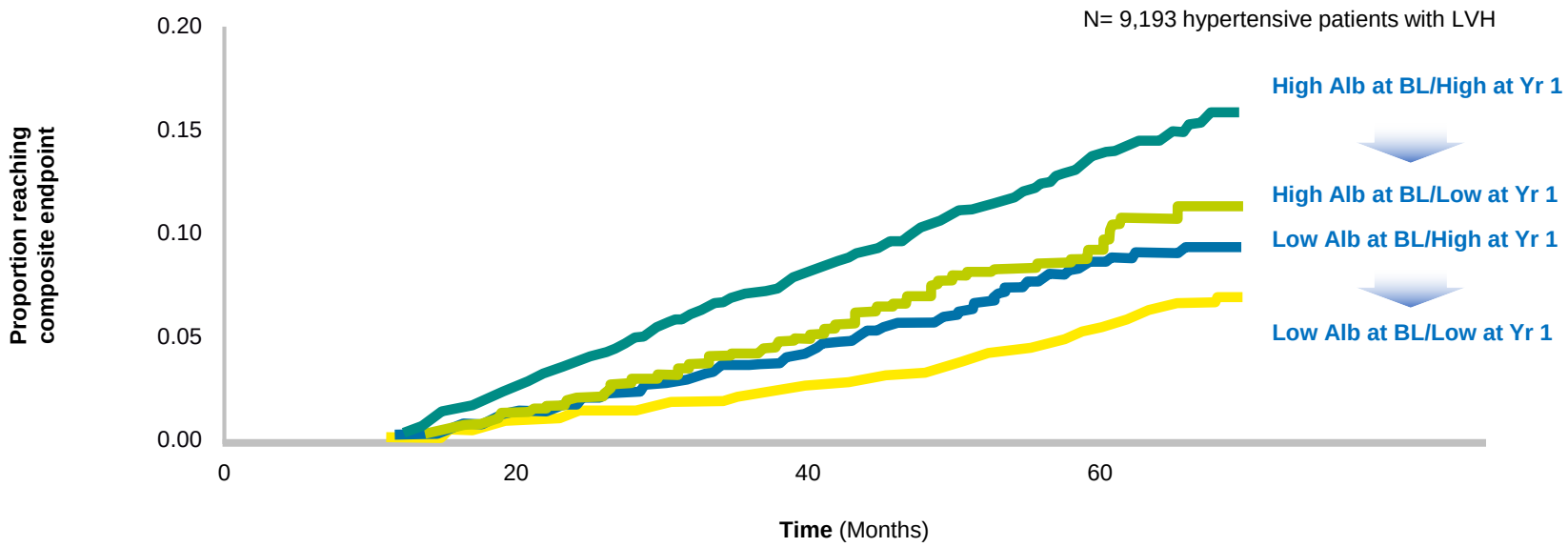
24. Diabetologia (2019) 62:1988–1997.

CAN-20200324.No2

Controlling progression of MAU as a means of reducing CV risk
The LIFE study

Prognosis after reduction of albuminuria

Composite endpoint of CV death, stroke and myocardial infarction



CV = cardiovascular; LVH = left ventricular hypertrophy; Ab at BL = albuminuria at baseline/value after 1 year (Yr 1)

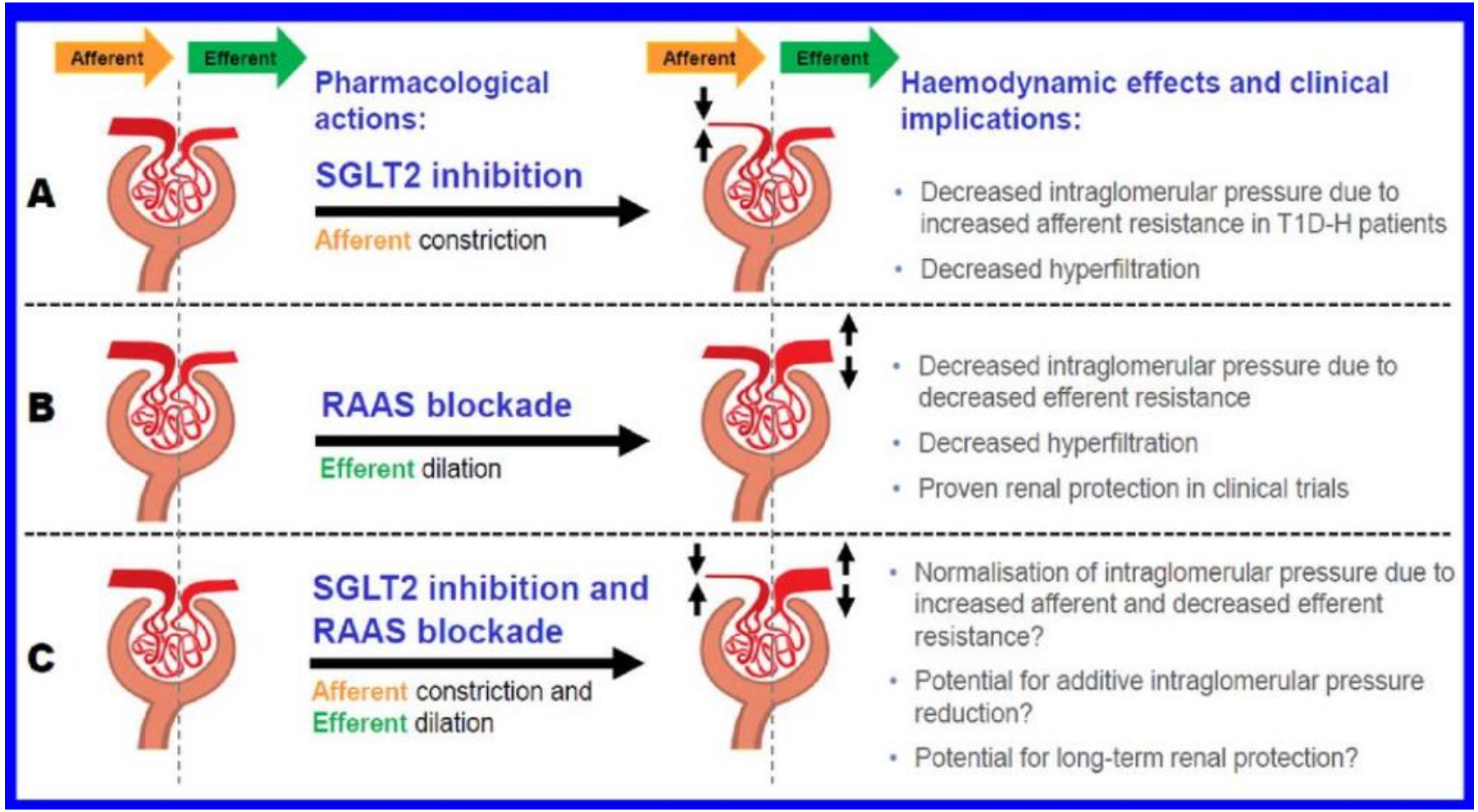
Reducing UACR during treatment is associated with a reduction in CV death, stroke and myocardial infarction in patients with hypertension

25. Hypertension 2005;45:198-202.

CAN-20200324.No2

MAU: microalbuminuria

SGLT2 Inhibition + RAAS Blockade = Afferent Constriction + Efferent Dilation



26. Diabetologia (2014) 57:2599–2602
27. Circulation. 2014 Feb 4;129(5):587-97.
Weber M et al. AHA 2013, Poster 2095

Physiological mechanisms implicated in changes in renal function following inhibition of SGLT2

T2DM

Proximal renal tubular epithelial cells are overloaded by excessive energy-dependent reabsorption of glucose

Changes of the microenvironment induce transformation of fibroblasts into myofibroblasts.

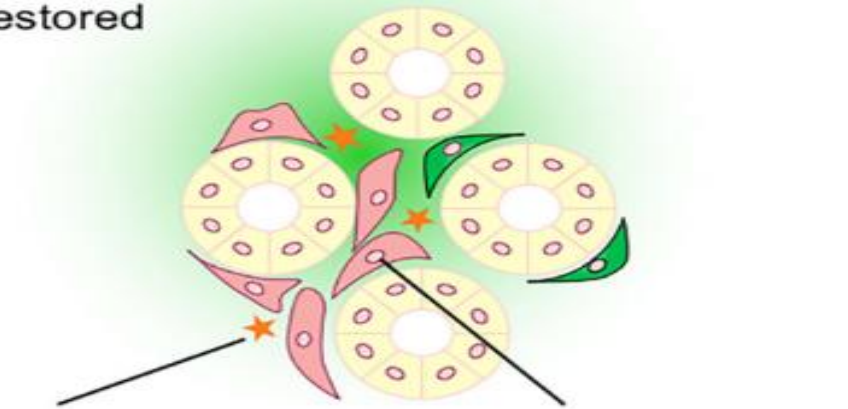
Interstitial fibrosis progresses and EPO production declines

Transformed fibroblasts

T2DM with SGLT2 inhibition

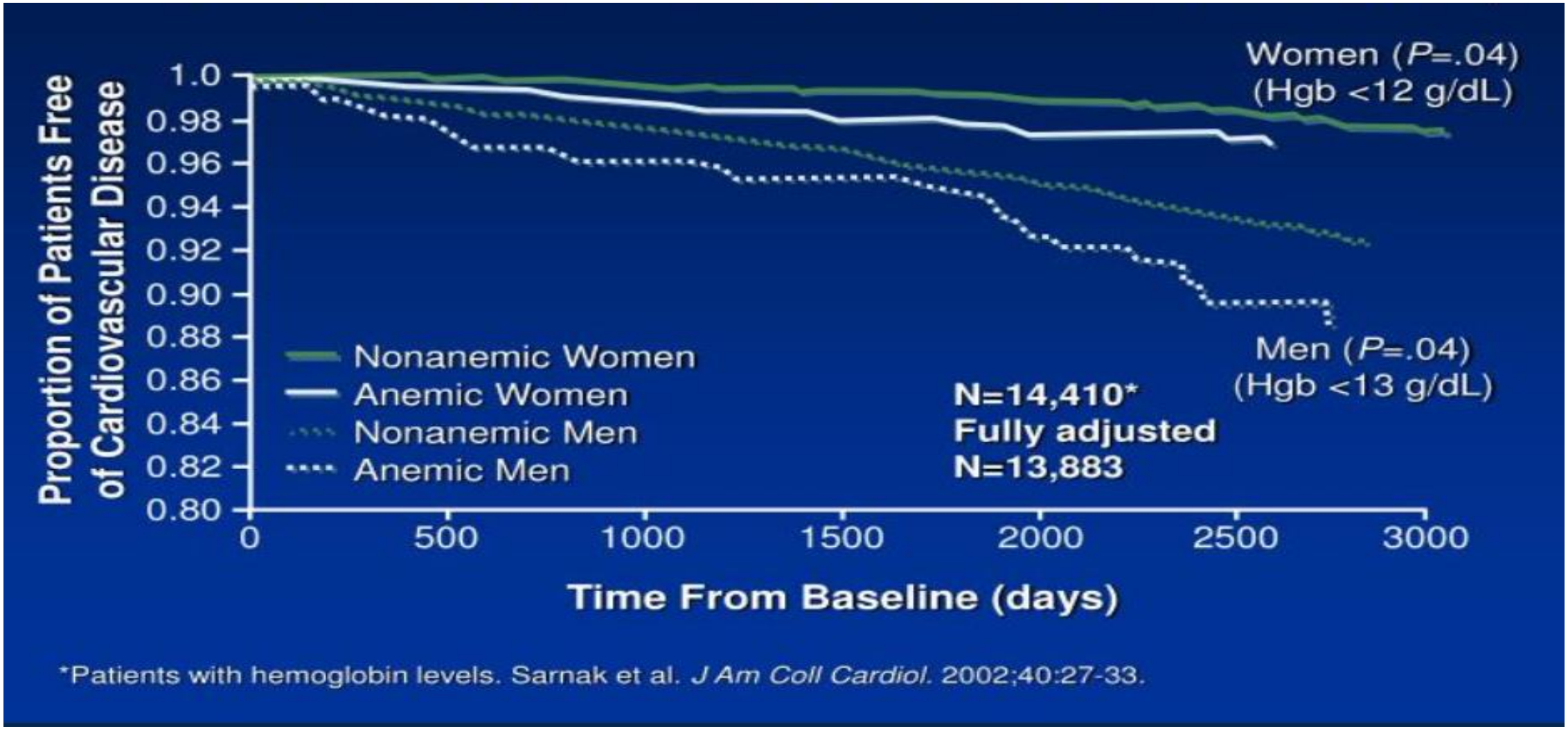
Proximal tubular epithelial cells are relieved from the burden of excessive reabsorption of glucose

Cortical tubulointerstitial damage recovers and EPO production by fibroblasts is restored

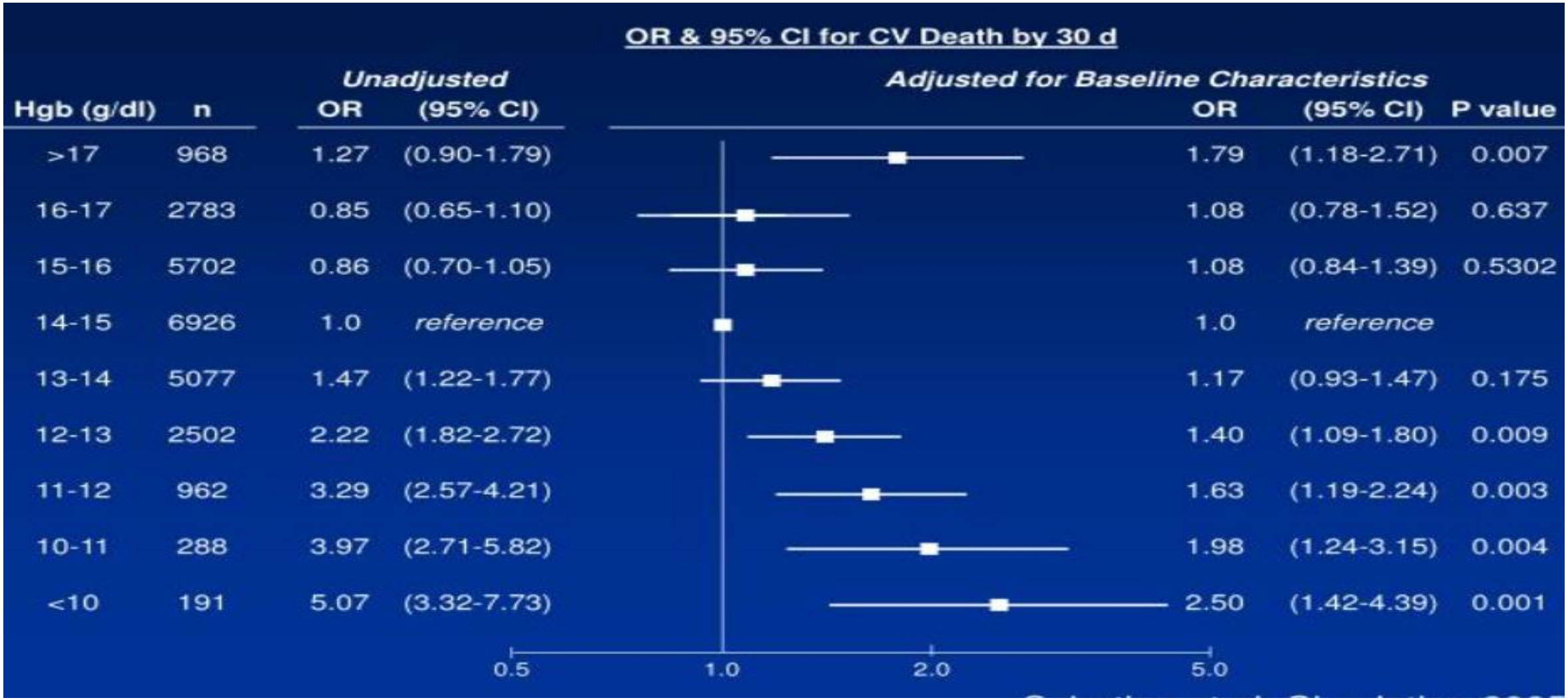


15. J Cardiol. 2018 May; 71(5): 471-476.

Anemia and Increased Cardiovascular Disease - ARIC Study

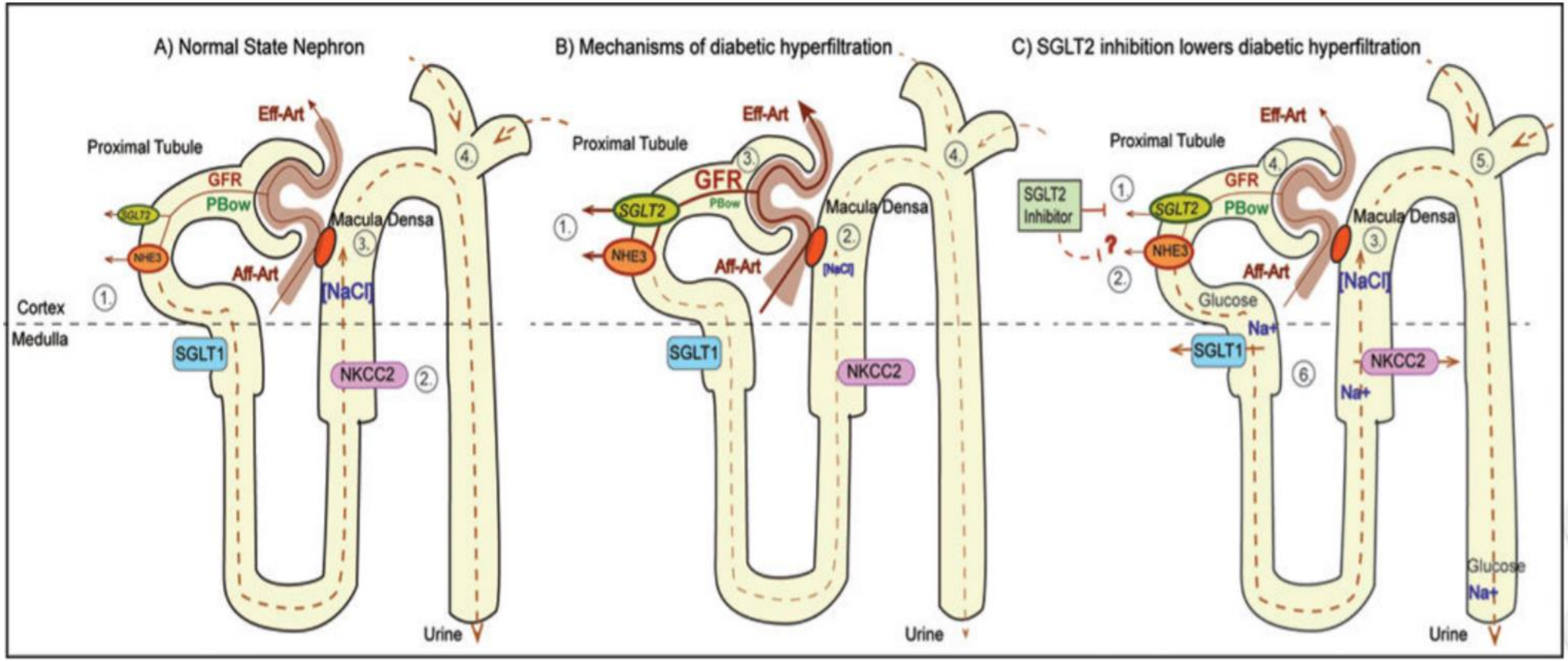


Anemia and CV Death in ACS



29. Circulation. 2005 Apr 26;111(16):2042-9.

The tubular hypothesis of diabetic glomerular hyperfiltration: effect of SGLT2 inhibition



30. Curr Opin Nephrol Hypertens. 2016 Jan;25(1):50-8.

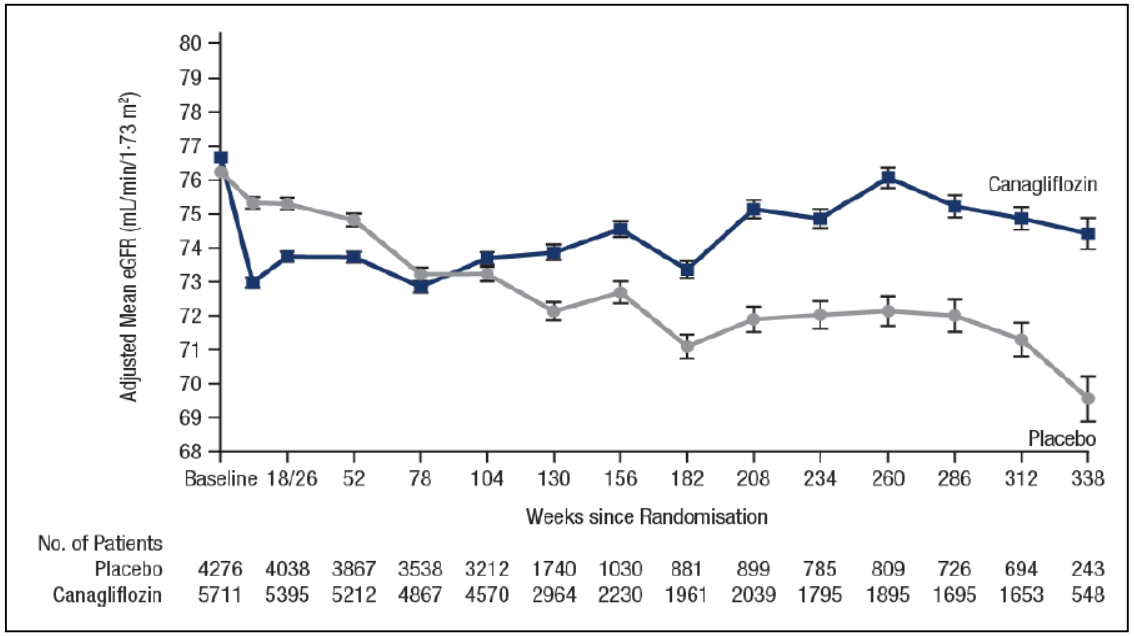
CAN-20200324.No2

Outline

- 2019-2020 Guideline for T2DM Management
- What is Cardio-renal syndrome (CRS)?
- The role of SGLT2 inhibitors in CRS
- Canaglu: the critical piece of CRS puzzle

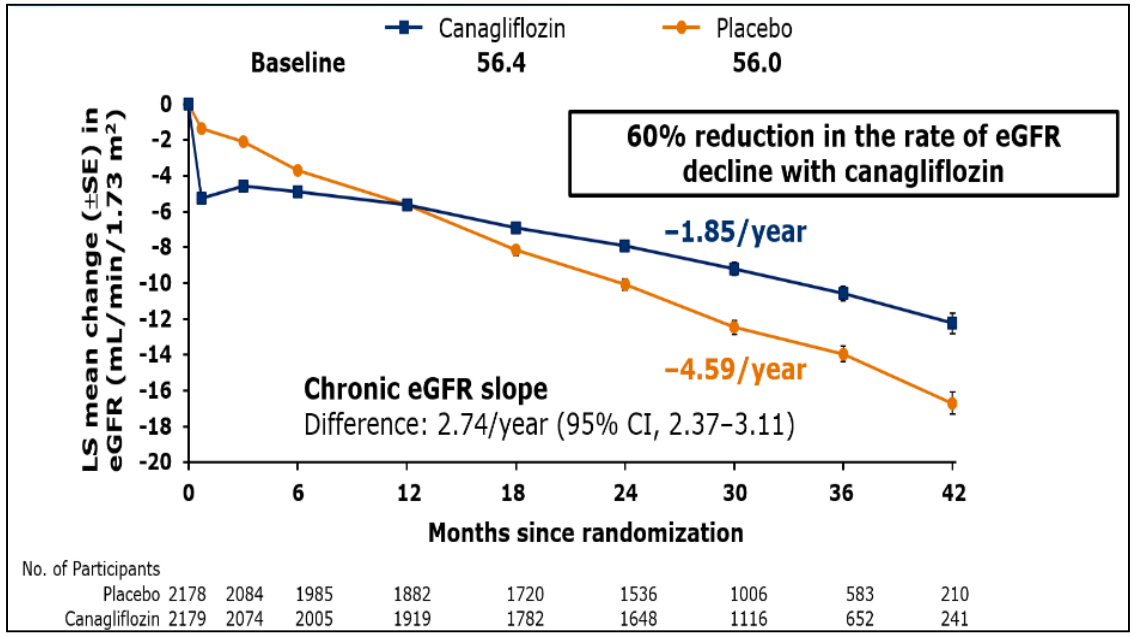
Canagliflozin can reduce eGFR slope

Secondary renal outcomes of the CANVAS/CANVAS R study



Mean eGFR 76 ml/min
Mean ACR 12mg/gCr

CREDENCE study

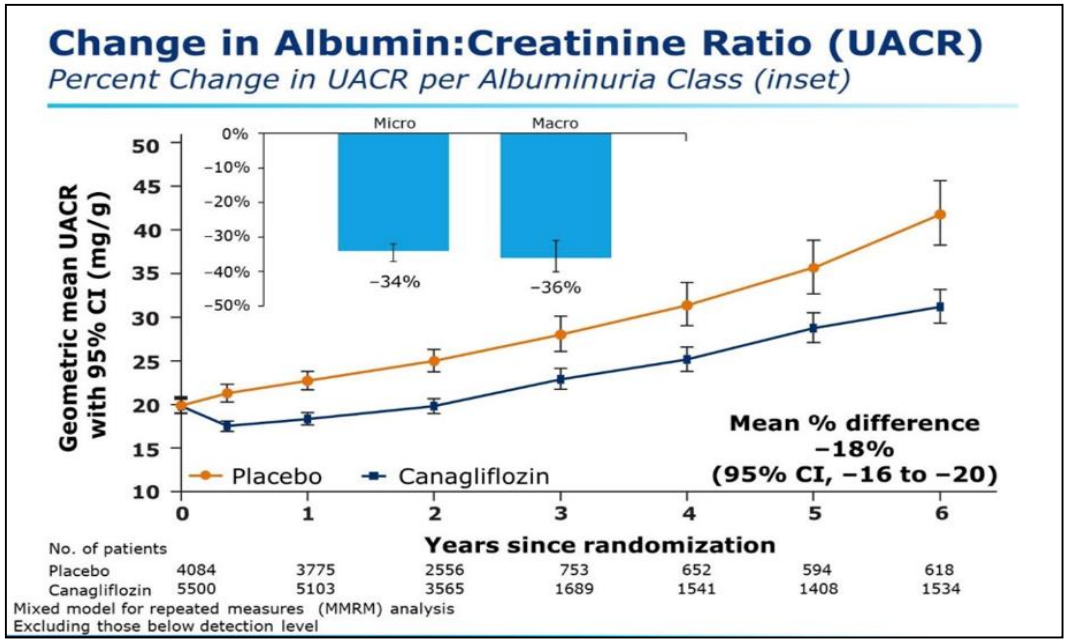


Mean eGFR 56 ml/min
Mean ACR 923 mg/gCr

19. N Engl J Med 2017; 377:644-657
21. N Engl J Med 2019; 380:2295-2306

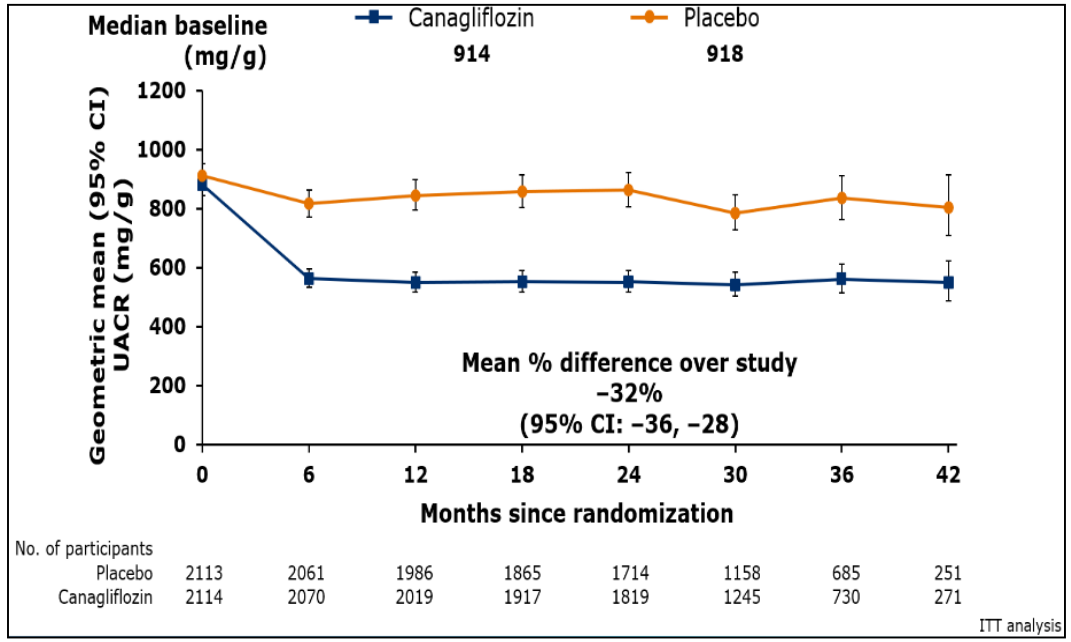
Canagliflozin can reduce UACR

Secondary renal outcomes of the CANVAS/CANVAS R study



Mean eGFR 76 ml/min
Mean ACR 12mg/gCr

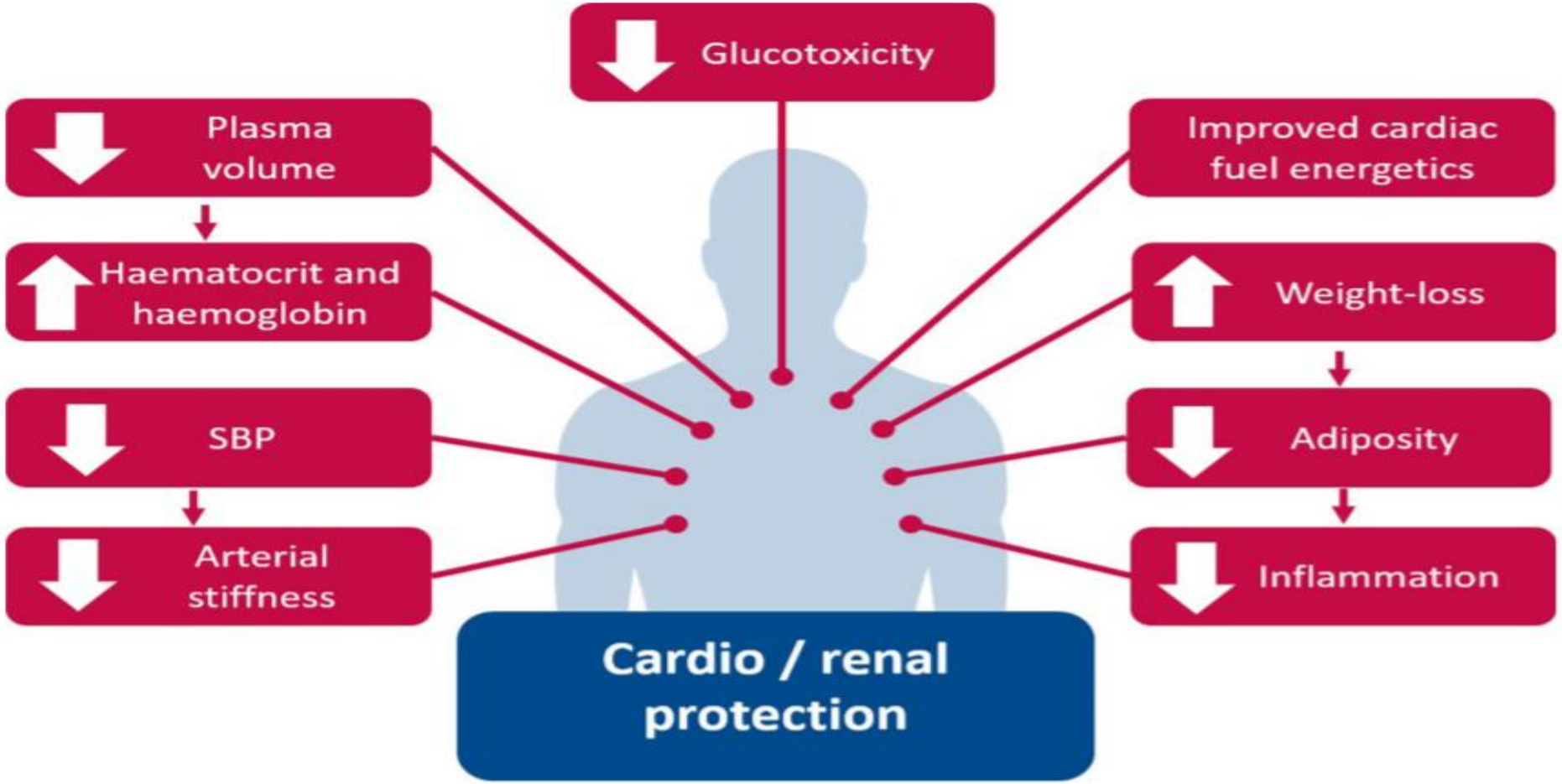
CREDENCE study



Mean eGFR 56 ml/min
Mean ACR 923 mg/gCr

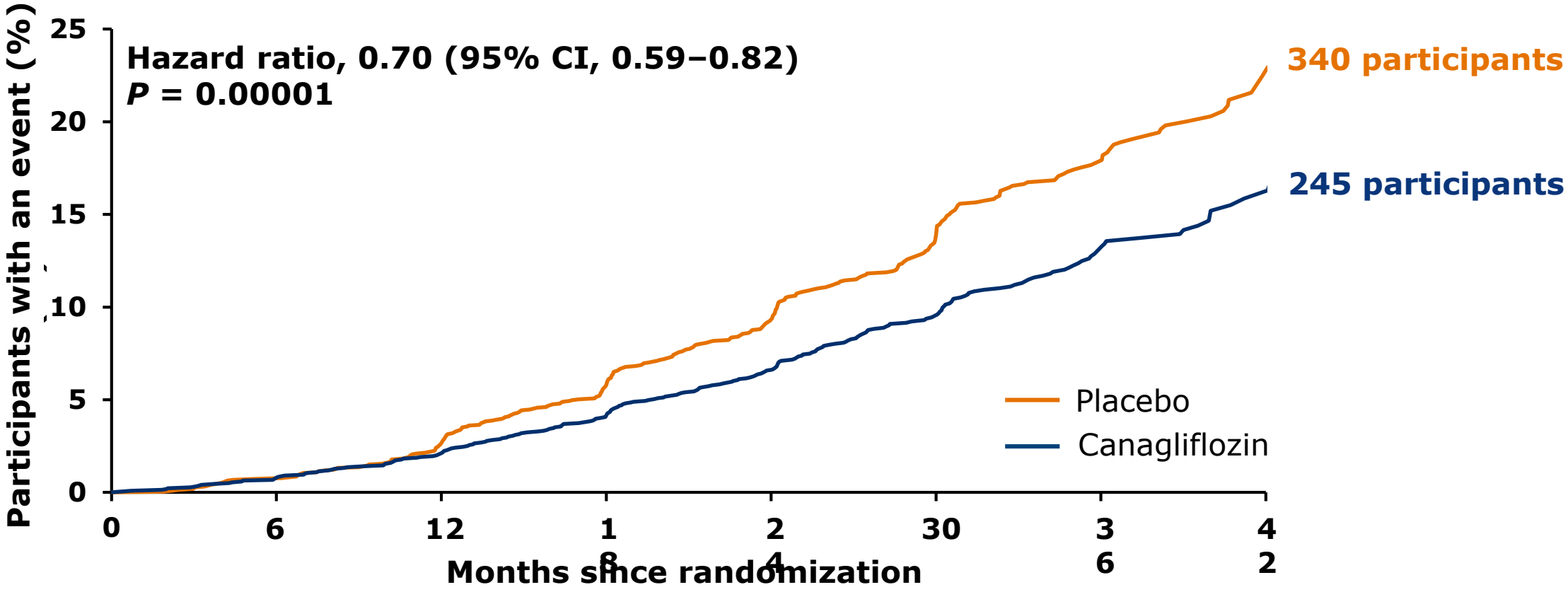
19. N Engl J Med 2017; 377:644-657
21. N Engl J Med 2019; 380:2295-2306

SGLT2 inhibitors cardiorenal protection mechanistic overview



31. Diabetes Ther (2019) 10:1719–1731

Primary Outcome:
ESKD, Doubling of Serum Creatinine, or Renal or CV Death



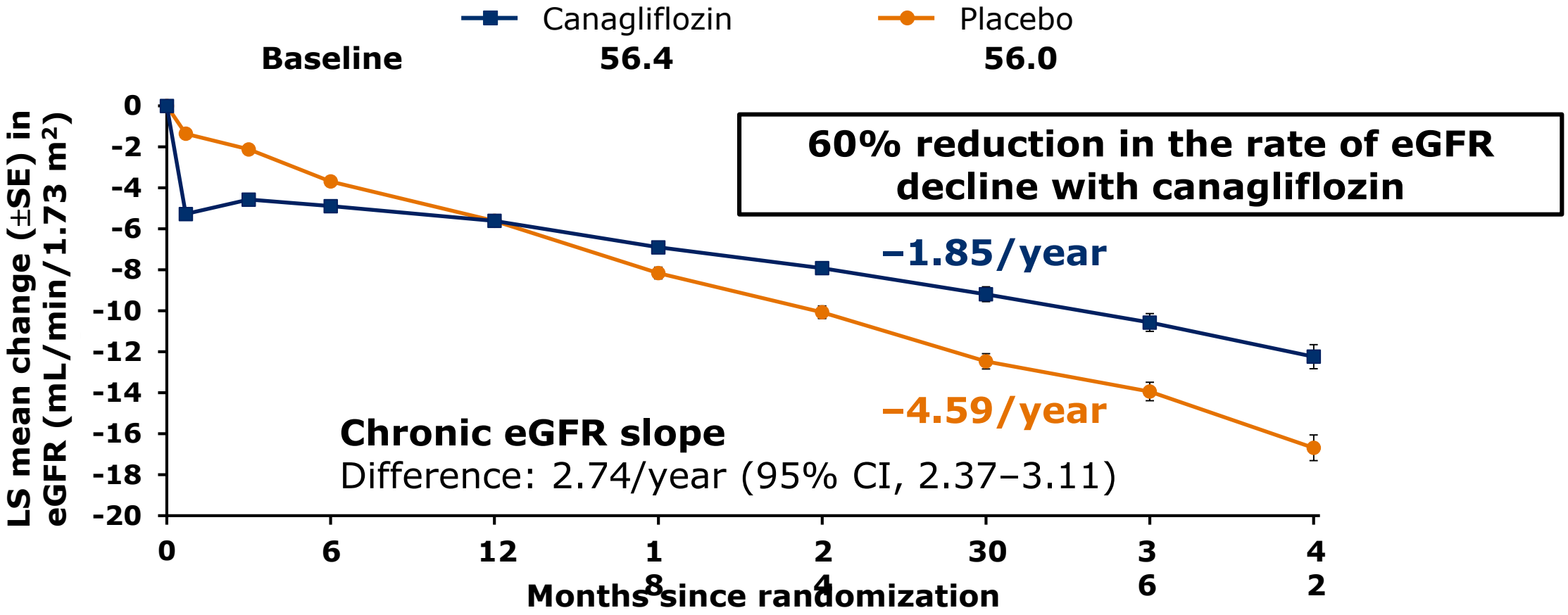
No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Perkovic V, et al. *N Engl J Med*. 2019. doi: 10.1056/NEJMoa1811744.

Presented at the 79th Scientific Sessions of the American Diabetes Association; June 11, 2019; San Francisco, CA.

CREDENCE

Acute and Long-term Effects on eGFR



No. of Participants

Placebo	2178	2084	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2074	2005	1919	1782	1648	1116	652	241

Perkovic V, et al. *N Engl J Med*. 2019. doi: 10.1056/NEJMoa1811744.

On treatment

Canagliflozin Improves Erythropoiesis in Diabetes Patients with Anemia of Chronic Kidney Disease

ORIGINAL ARTICLE

Canagliflozin Improves Erythropoiesis in Diabetes Patients with Anemia of Chronic Kidney Disease

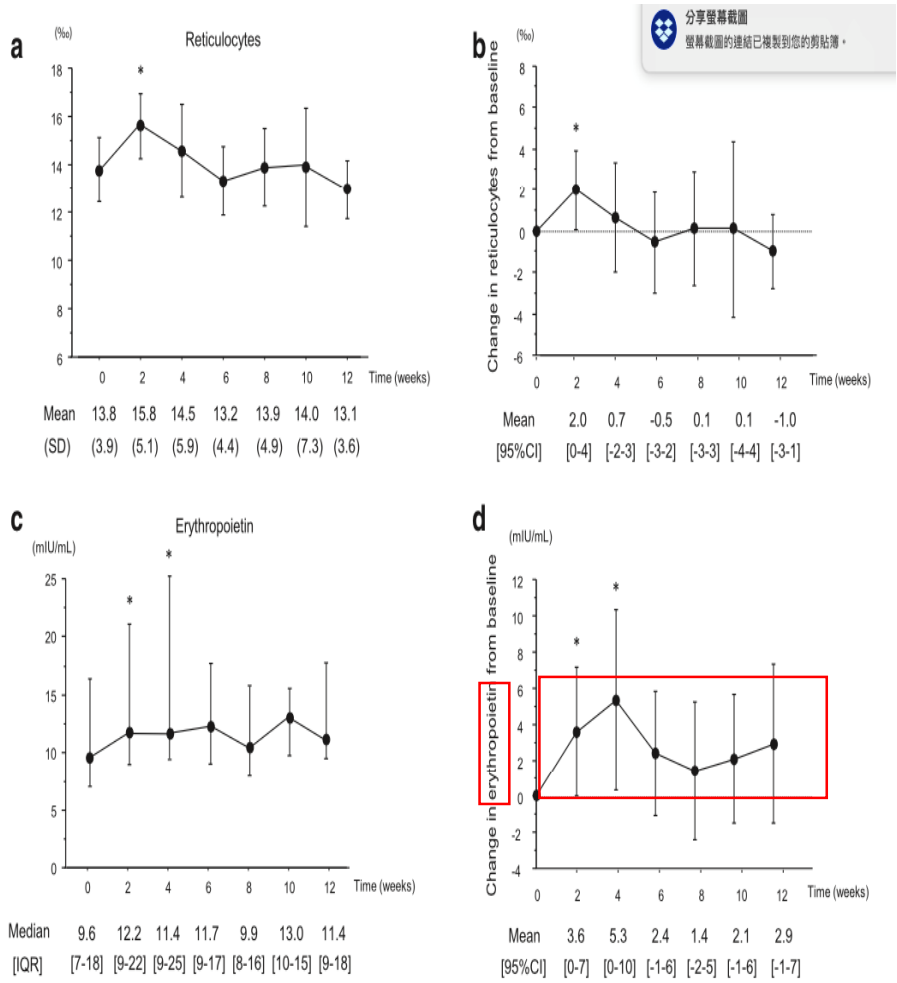
Abstract

Background: We evaluated the erythropoietic effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, in type 2 diabetes patients with anemia of chronic kidney disease.

Methods: Nine diabetes patients were enrolled and administered 100 mg canagliflozin once a day for 12 weeks. The patients received fixed doses of conventional antidiabetic drugs and renin-angiotensin system inhibitors for 8 weeks before enrollment; these drugs were continued during the study. Endpoints were changes in erythropoiesis parameters, including erythrocyte and reticulocyte count, hemoglobin, hematocrit, and serum erythropoietin (EPO) concentration from baseline to 12 weeks. All variables were measured every 2 weeks.

Results: Serum EPO concentration increased by 38 [15–62]% ($P=0.043$) between baseline and 2 and 4 weeks. Reticulocyte count transiently increased at 2 weeks. Erythropoiesis occurred after 2 weeks of canagliflozin treatment. Erythrocyte count (from $386\pm36\times10^4/\mu L$ to $421\pm36\times10^4/\mu L$; $P=0.0009$), hemoglobin (from 11.8 ± 0.6 g/dL to 12.9 ± 1.1 g/dL; $P=0.0049$), and hematocrit (from $37.1\pm2.3\%$ to $40.4\pm3.2\%$; $P=0.002$) increased from baseline to study completion. Although there were no significant changes in transferrin saturation, serum ferritin levels were decreased ($P=0.003$).

Conclusions: Canagliflozin treatment led to an improvement in erythropoiesis in patients with impaired kidney function. The effect on erythropoiesis appeared to be due to an EPO production-mediated mechanism and might be independent of glycemic control; however, further studies are needed to clarify this since the present study had a small sample size and no comparator group.



32. Diabetes Technol Ther. 2019 Dec;21(12):713-720.

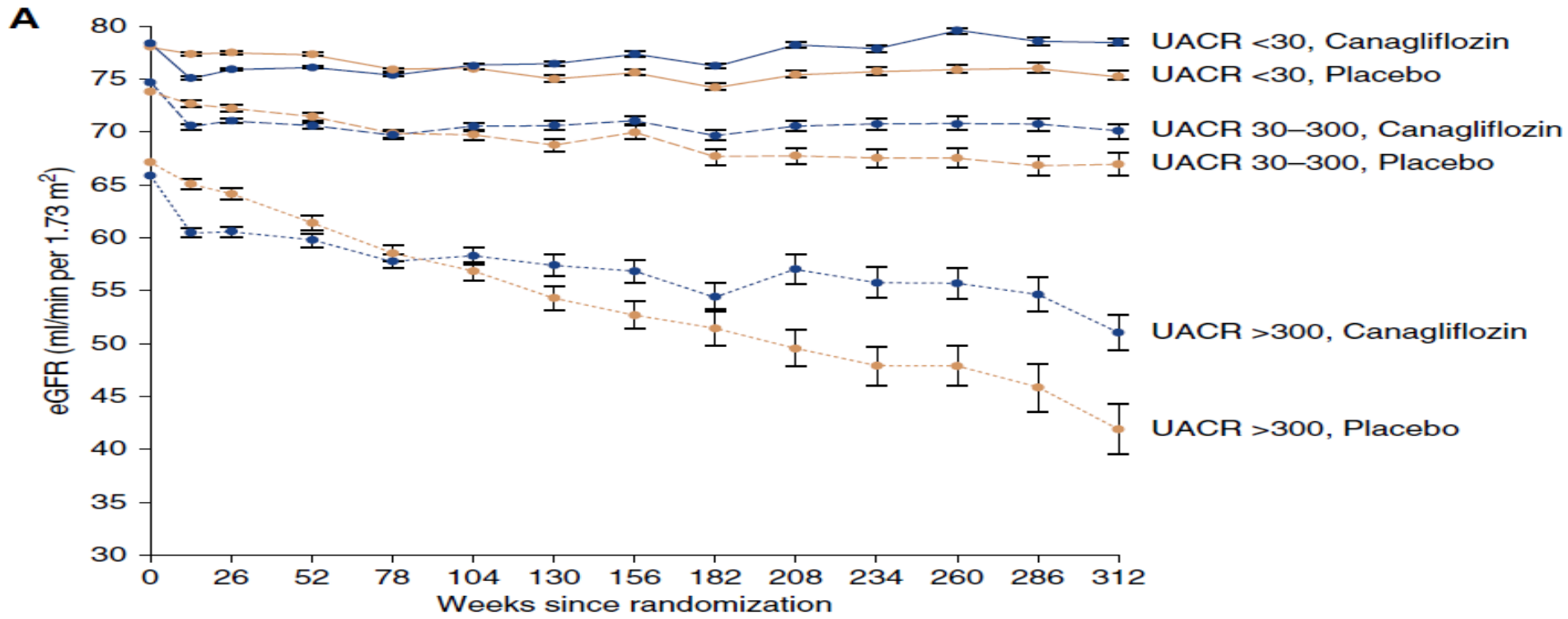
CAN-20200324.No2

Canagliflozin can reduce Cardiac and Renal Risk in T2DM

Trial	Recruit criteria	Primary endpoint	Result
CANVAS	• T2DM • HbA1c ≥ 7.0% to ≤ 10.5% • eGFR ≥30 mL/min/1.73 m2 • Age ≥30 years and history of prior CV event or Age 50 years with 2 CV risk factors	• CV death • Nonfatal MI • or nonfatal stroke	**-14%**
CREDENCE	• ≥30 years of age • T2DM and HbA1c 6.5% to 12.0% • eGFR 30 to 90 mL/min/1.73 m2 • UACR 300 to 5000 mg/g • Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks	• ESKD • Doubling of serum creatinine • or renal or CV death	**-30%**

19. N Engl J Med 2017; 377:644-657
21. N Engl J Med 2019; 380:2295-2306

Canagliflozin slowed the loss of kidney function across all UACR subgroups (Data from CANVAS trial)



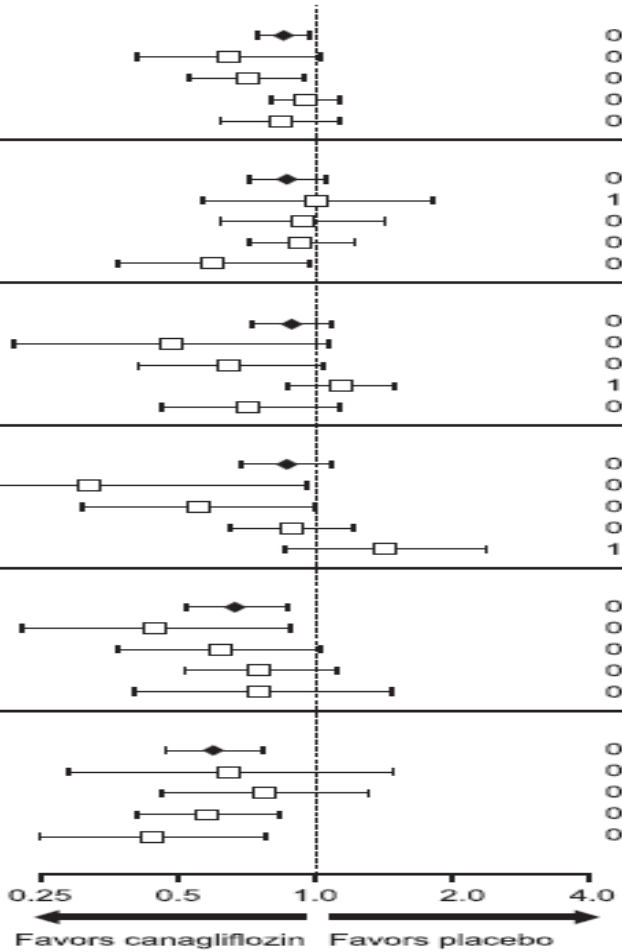
Participants, n													
UACR <30	Canagliflozin	3960	3739	3613	3390	3206	2126	1622	1433	1498	1327	1408	1264	1231
	Placebo	2947	2788	2677	2473	2263	1239	742	636	646	564	587	523	504
UACR 30–300	Canagliflozin	1300	1232	1181	1098	1030	645	499	435	454	387	407	358	349
	Placebo	933	876	837	759	680	352	225	193	200	178	183	170	159
UACR >300	Canagliflozin	398	373	368	331	287	157	97	82	77	72	68	64	63
	Placebo	344	325	306	263	227	110	58	49	48	40	34	30	26

33. JASN 30: 2229–2242, 2019

CAN-20200324.No2

Effects of canagliflozin on cardiovascular and renal outcomes in participants according to baseline eGFR categories (Data from CANVAS trial)

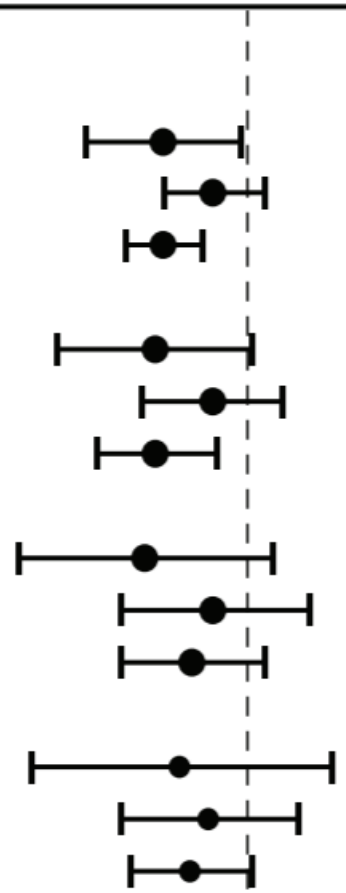
	Number of participants with an event	Patients with an event per 1000 patient-years		HR (95% CI)	Interaction *P* value
		Canagliflozin	Placebo		
MACE					
All	1011	26.9	31.5	0.86 (0.75, 0.97)	0.33
<45	82	44.7	63.3	0.65 (0.41, 1.03)	
45-<60	179	33.2	44.4	0.71 (0.53, 0.95)	
60-<90	563	26.8	29.0	0.95 (0.80, 1.13)	
≥90	187	20.8	23.6	0.84 (0.62, 1.13)	
CV death					
All	453	11.6	12.8	0.87 (0.72, 1.06)	0.53
<45	51	29.5	30.2	1.01 (0.57, 1.81)	
45-<60	96	19.4	18.6	0.94 (0.62, 1.42)	
60-<90	237	10.7	11.3	0.93 (0.72, 1.22)	
≥90	69	6.4	9.6	0.60 (0.37, 0.97)	
Fatal/nonfatal MI					
All	421	11.2	12.6	0.89 (0.73, 1.09)	0.08
<45	28	13.6	23.3	0.49 (0.22, 1.07)	
45-<60	74	12.8	19.0	0.65 (0.41, 1.04)	
60-<90	241	12.1	11.0	1.14 (0.87, 1.49)	
≥90	78	8.0	10.6	0.72 (0.46, 1.13)	
Fatal/nonfatal stroke					
All	309	7.9	9.6	0.87 (0.69, 1.09)	0.01
<45	16	5.2	16.8	0.32 (0.11, 0.96)	
45-<60	47	7.1	13.5	0.56 (0.31, 1.00)	
60-<90	173	7.7	9.3	0.89 (0.65, 1.21)	
≥90	73	9.5	6.6	1.42 (0.86, 2.36)	
Hospitalization for HF					
All	243	5.5	8.7	0.67 (0.52, 0.87)	0.62
<45	38	16.9	34.3	0.45 (0.23, 0.88)	
45-<60	60	9.6	16.5	0.62 (0.37, 1.03)	
60-<90	108	4.6	6.1	0.76 (0.52, 1.12)	
≥90	37	3.7	5.1	0.76 (0.40, 1.47)	
Renal composite*					
All	249	5.5	9.0	0.60 (0.47, 0.77)	0.59
<45	25	13.5	18.4	0.65 (0.29, 1.48)	
45-<60	58	10.6	13.9	0.78 (0.46, 1.31)	
60-<90	118	4.6	7.4	0.58 (0.41, 0.84)	
≥90	48	3.8	8.1	0.44 (0.25, 0.78)	



34. Circulation. 2018;138:1537–1550.

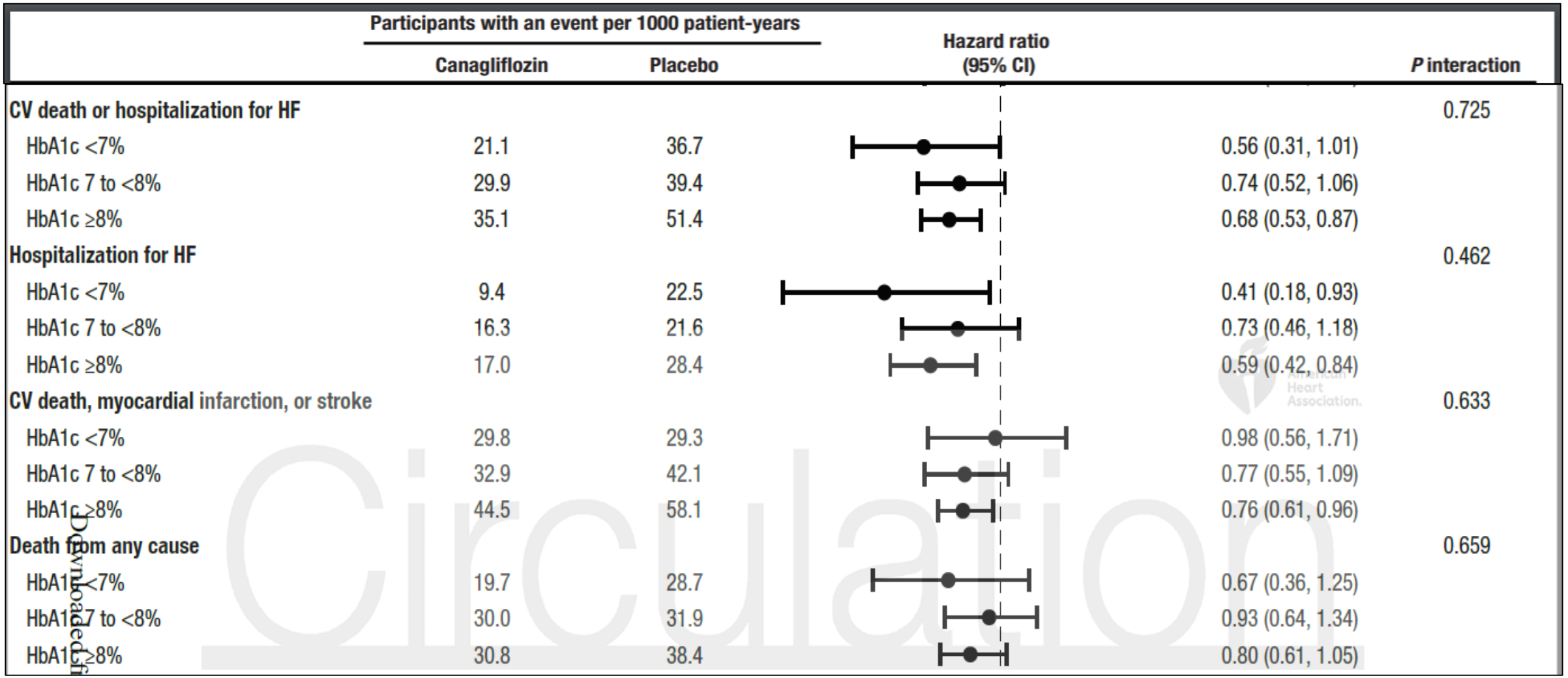
Canagliflozin reduced the risk of both CV and renal events in patients with T2DM and CKD without a significant interaction across the spectrum of baseline HbA1c values (Data from CREDENCE trial)

	Participants with an event per 1000 patient-years		Hazard ratio (95% CI)	*P* interaction
	Canagliflozin	Placebo		
Efficacy				
Primary composite outcome				0.277
HbA1c <7%	39.2	59.8	0.63 (0.41, 0.98)	
HbA1c 7 to <8%	44.8	52.3	0.84 (0.63, 1.13)	
HbA1c ≥8%	43.0	66.8	0.63 (0.51, 0.79)	
ESKD				0.505
HbA1c <7%	24.8	39.2	0.61 (0.35, 1.05)	
HbA1c 7 to <8%	22.8	27.1	0.83 (0.55, 1.25)	
HbA1c ≥8%	17.6	28.1	0.61 (0.43, 0.87)	
Dialysis initiated or kidney transplantation				0.733
HbA1c <7%	14.1	23.4	0.57 (0.28, 1.17)	
HbA1c 7 to <8%	13.5	15.9	0.84 (0.49, 1.43)	
HbA1c ≥8%	12.9	17.1	0.74 (0.49, 1.13)	
CV death				0.937
HbA1c <7%	12.8	17.2	0.72 (0.33, 1.57)	
HbA1c 7 to <8%	17.7	21.1	0.83 (0.52, 1.32)	
HbA1c ≥8%	21.3	28.1	0.76 (0.55, 1.04)	



35. Circulation. 2020 Feb 4;141(5):407-410.

Canagliflozin reduced the risk of both CV and renal events in patients with T2DM and CKD without a significant interaction across the spectrum of baseline HbA1c values (Data from CREDENCE trial)



35. Circulation. 2020 Feb 4;141(5):407-410.

CAN-20200324.No2

Take Home Message

- In appropriate high-risk individuals with established type 2 diabetes, the decision to treat with a GLP-1 receptor agonist or SGLT2 inhibitor to reduce MACE, hHF, CV death or CKD progression should be considered independently of base line HbA1c or individualized HbA1c target. [1]
- Cardio-renal interactions in heart failure and kidney disease. Most of the mechanisms may be activated by each of the two conditions and are able to affect both cardiac and renal function. [2]

1: 1. Diabetologia (2020) 63:221–228
2: 10 European Heart Journal (2012) 33, 2135–2143

財團法人振興醫院
CHENG HSIN GENERAL HOSPITAL

Thank You For Your Attention

Notice

- 提醒您Canagliflozin在台灣核准的仿單內容中，建議之劑量與應注意事項：

- Canagliflozin在台灣上市，核准可使用劑量僅為100mg。(Please be noted, canagliflozin approved dose in Taiwan is only 100mg.)

- 病人的eGFR 如果持續低於45 mL/min/1.73 m2，不建議使用 Canagliflozin；Canagliflozin 禁止用於 eGFR 低於30 mL/min/1.73 m2 的病人。(Initiation or use of canagliflozin is not recommended if eGFR is below 45 mL/min/1.73 m2. Canagliflozin is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m2)