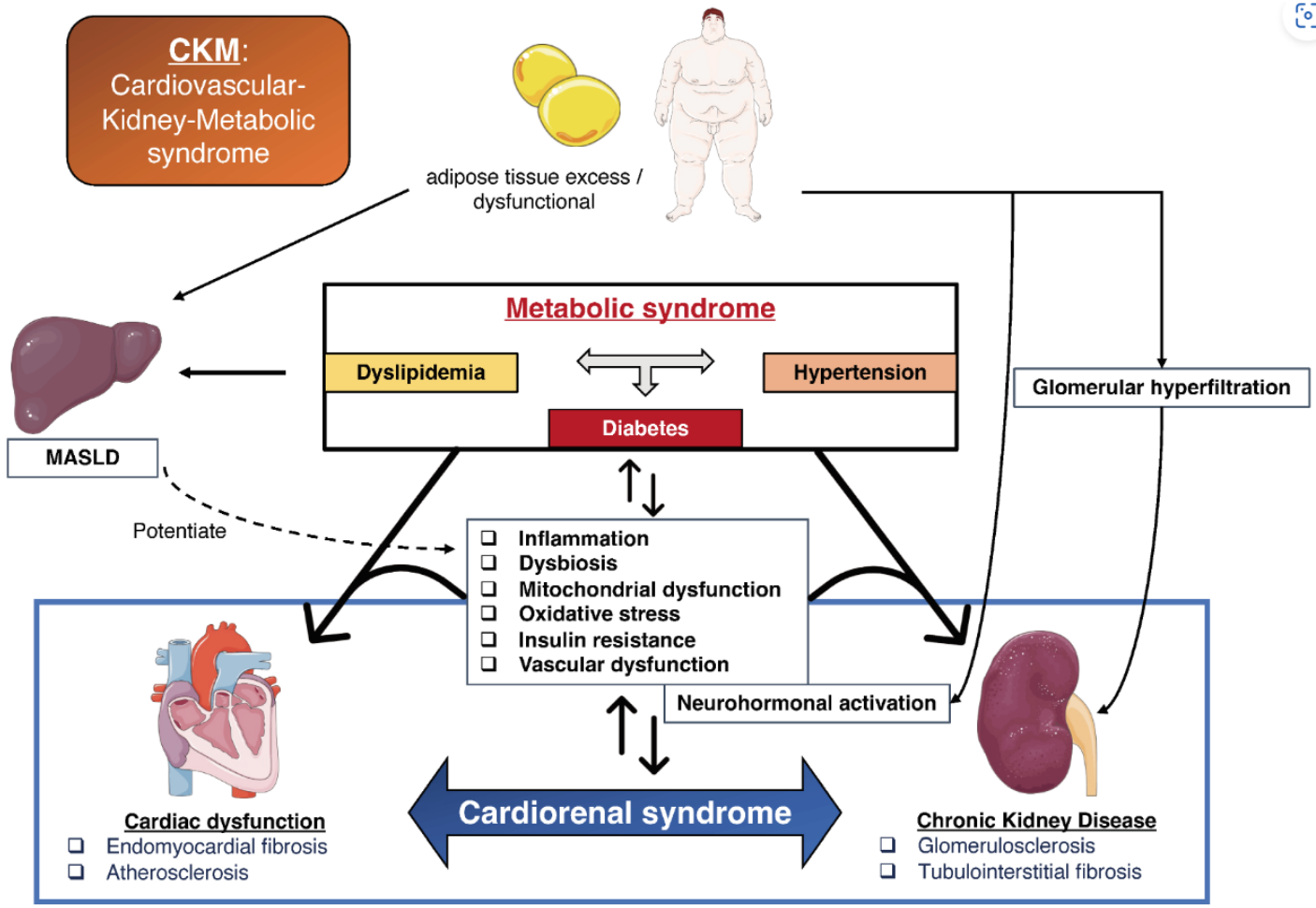
Definition of Cardio-Kidney-Metabolic syndrome

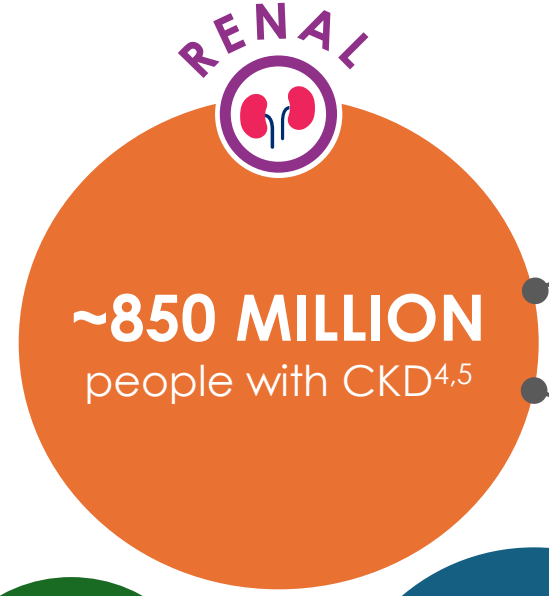
The Cardio-Renal Metabolic syndrome (CRM), or as the Anglo-Saxons call it, Cardio-Kidney-Metabolic syndrome (CKM), is a **systemic disorder** characterized by **pathophysiological interactions among metabolic risk factors, CKD, and the cardiovascular system leading to multiorgan dysfunction and a high rate of adverse cardiovascular outcomes.** CRM syndrome includes both individuals at risk for CVD due to the presence of metabolic risk factors, CKD, or both and individuals with existing CVD that is potentially related to or complicates metabolic risk factors or CKD. The increased likelihood of CRM syndrome and its adverse outcomes is further **influenced by** unfavorable conditions for **life style** and **self-care resulting from policies, economics and the environment.**



Concept of Cardio-Kidney-Metabolic syndrome, a broad physiopathological entity promoting CRS. Inspired by Ndumele et al. from AHA Circulation 2023 [19].Bedo, D.; Beaudrey, T.; Florens, N. Unraveling Chronic Cardiovascular and Kidney Disorder through the Butterfly Effect. Diagnostics 2024, 14, 463.

1 CKM, cardio-kidney- metabolic; CRM, cardio-renal- metabolic; CVD, cardio-vascular disease; MASLD: metabolic dysfunction-associated steatotic liver disease T2DM, type 2 diabetes mellitus. Fig adapted from M. Kambay et al European Journal of Internal Medicine127(2024)1–14; Ndumele CE. et al. Circulation. 2023;148:1606–1635

Cardiovascular, Renal and Metabolic conditions pose a high disease burden globally

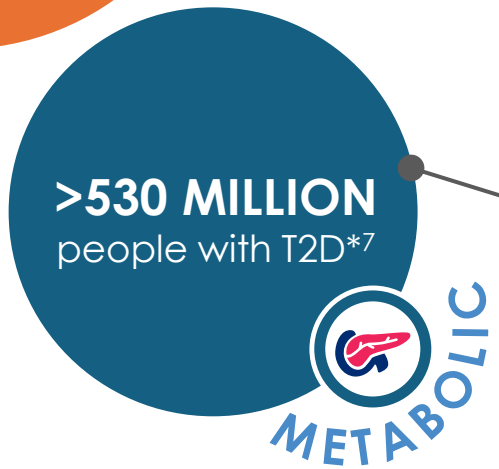


The estimated global **prevalence** of CKD is **>11%**[5]

CKD is asymptomatic in its early stages, which contributes to **low awareness** of the disease in people with CKD and clinicians[6]

Approximately **50% of people** diagnosed with HF will die within 5 years of diagnosis[1]

There is a large **unmet need in HF,** with a scarcity of approved therapies in some forms of HF (e.g. HFpEF)[2]



The **prevalence** of T2D is high and **rising across all regions**[7]

*Adults 20–79 years old

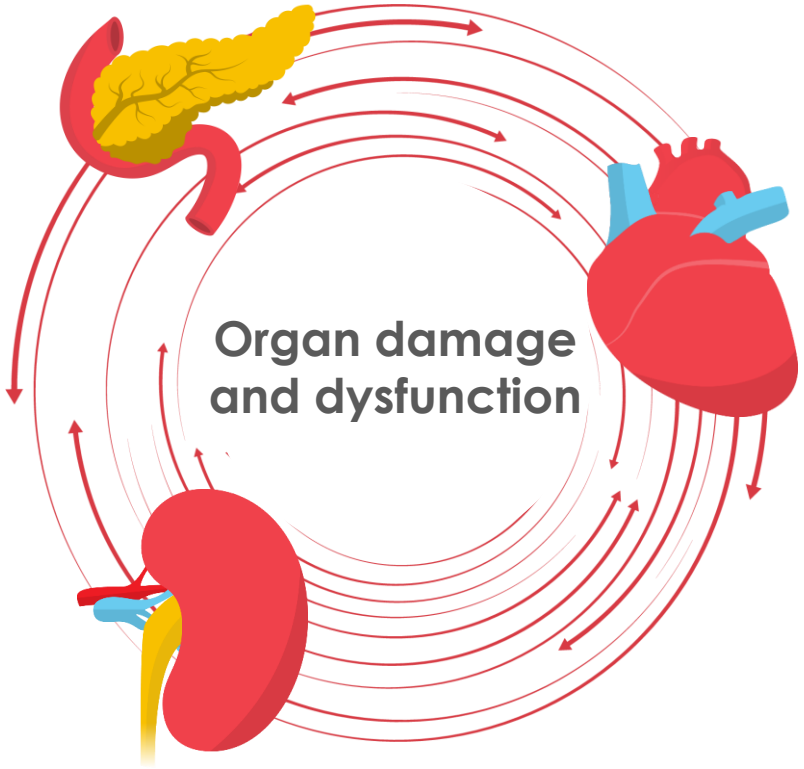
CKD, chronic kidney disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; T2D, type 2 diabetes

1. Tsao CW *et al. Circulation* 2022;145:e153; 2. Heidenreich PA *et al. J Am Coll Cardiol* 2022;79:e263; 3. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. *Lancet* 2017;390:1211; 4. ASN. The hidden epidemic: worldwide, over 850 million people suffer from kidney diseases. 2018. https://www.asn-online.org/news/2018/0626-Joint_Hidden_Epidem.pdf (accessed Mar 2023); 5. Jager KJ *et al. Nephrol Dial Transplant* 2019;34:1803; 6. Shlipak MG *et al. Kidney International* 2021;99:34; 7. International Diabetes Federation Diabetes Atlas 10th edition 2021. Available here: https://diabetesatlas.org/atlas/tenth-edition/ (accessed Mar 2023)

Disorders of the Cardio-Renal-Metabolic systems affect more than 1 billion people worldwide and often co-exist[1,2]

T2D + CVD

~One-third of patients with T2D have CV disease[1,2]



T2D + CVD/HF

CV disease is the **leading cause of mortality** in patients with T2D[5,6]

Up to 40% of patients with HF have T2D[7]

T2D + CKD/ESKD

~37% of adults with diabetes have been diagnosed with CKD*[3]

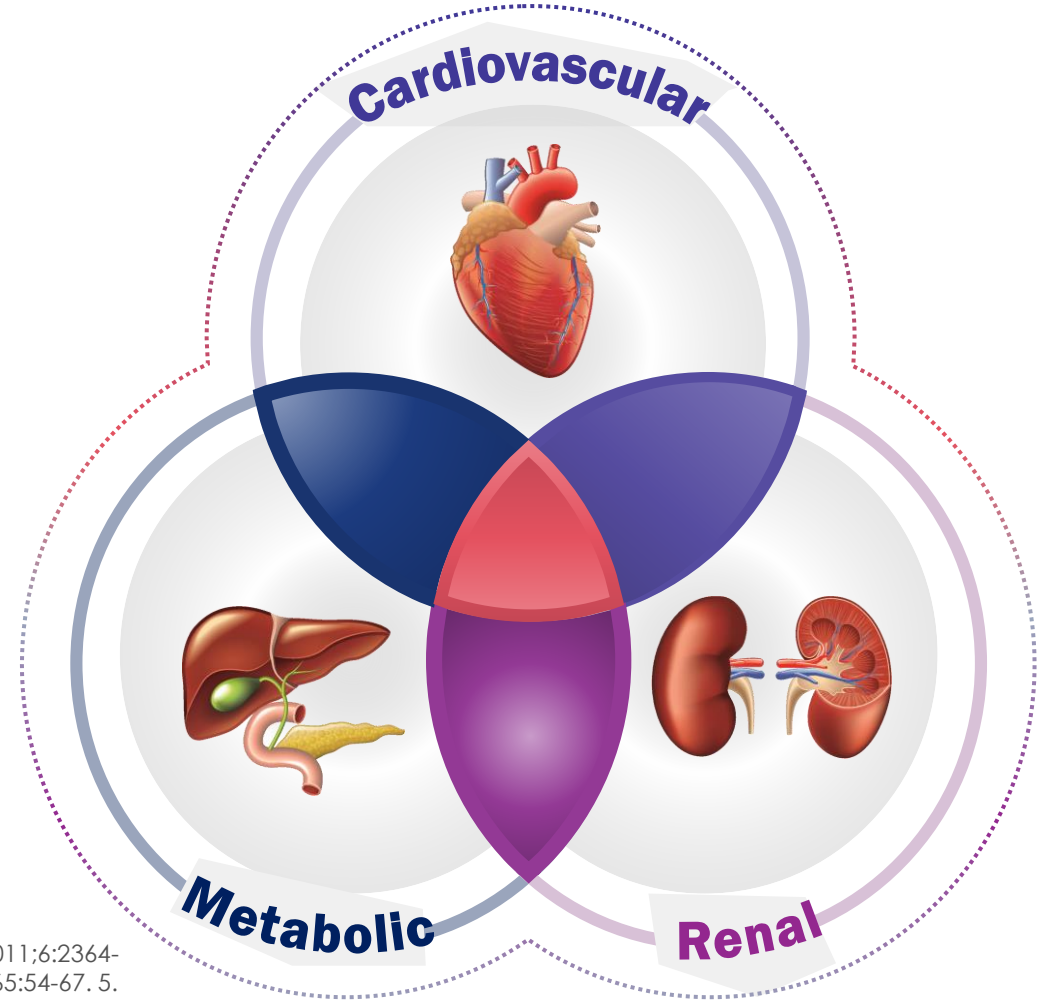
Diabetes and/or hypertension are the primary causes of **~75% of ESKD** prevalent cases in the US[4]

CKD + HF

20–67% of patients with HF are estimated to have CKD[8]

Dysfunction of the heart, kidneys, or metabolism may contribute to the dysfunction of the others[1,2]

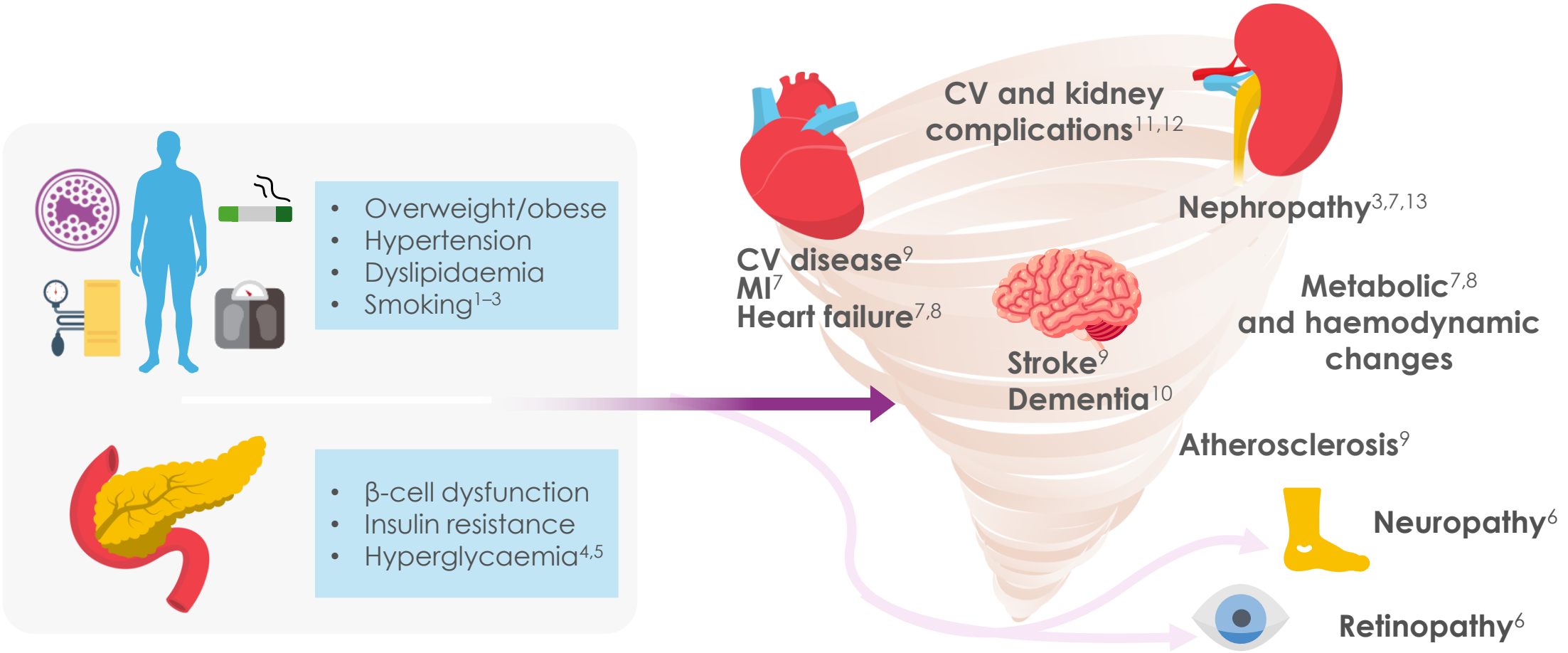
- Disorders affecting the CRM systems share many of the same risk factors[3]
- Dysfunction in one system can set off a cascade of multisystem dysfunction[4]
- This can lead to interrelated diseases such as T2DM, CV disease, HF, and CKD, which in turn lead to an increased risk of CV death[5]



CV, cardiovascular; HF, heart failure; T2DM, type 2 diabetes mellitus.

1. García-Donaire JA, et al. *Int J Nephrol*. 2011;2011:975782. 2. Thomas G, et al. *Clin J Am Soc Nephrol*. 2011;6:2364-2373. 3. Sarafidis PA, et al. *J Cardiometab Syndr*. 2006;1:58-65. 4. Ronco C, et al. *Contrib Nephrol*. 2010;165:54-67. 5. Leon BM, et al. *World J Diabetes*. 2015;6:1246-1258.

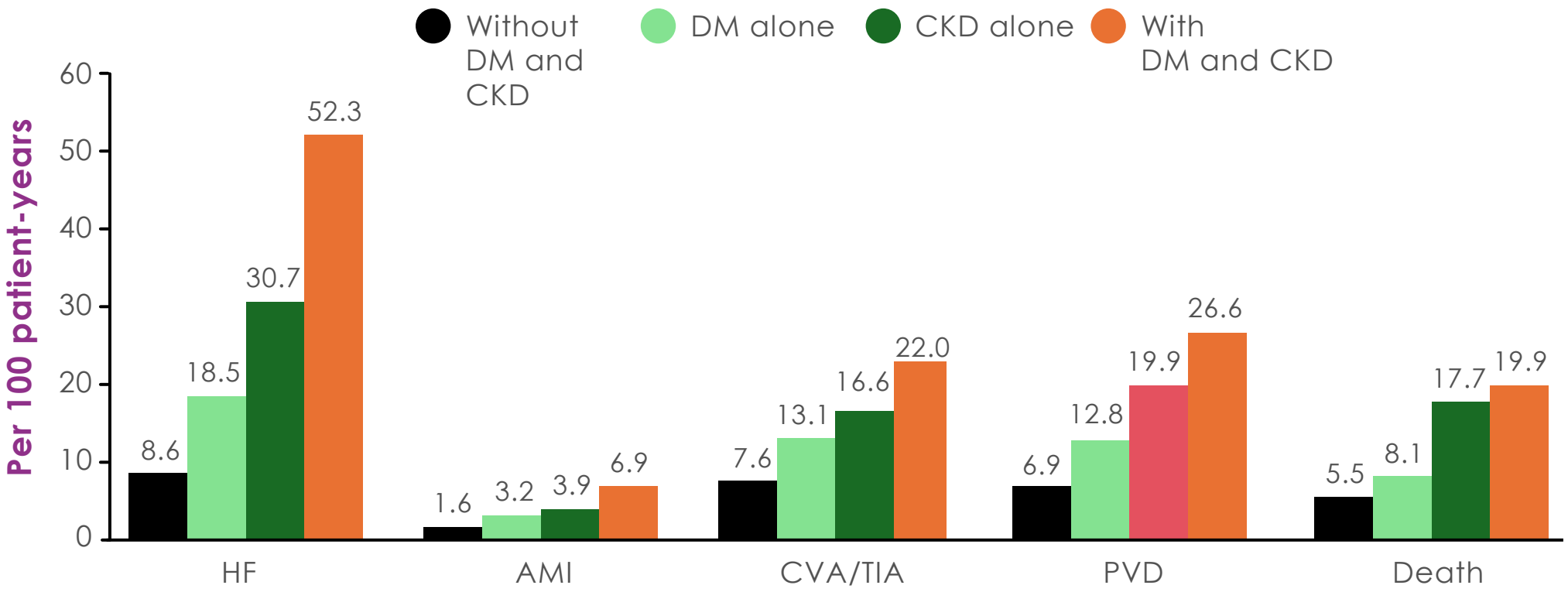
A patient with early T2D is at an increased risk of complications due to metabolic disturbances and interconnected risk factors[1–10]



Leading hypotheses shown; additional factors may contribute to progression of complications. CV, cardiovascular; T2D, type 2 diabetes; MI, myocardial infarction. 1. Leon BM & Maddox TM. *World J Diabetes* 2015;6:1246; 2. Sposito AC *et al. Cardiovasc Diabetol* 2018;17:157; 3. Cade WT. *Phys Ther* 2008;88:1322; 4. Marwick TH *et al. J Am Coll Cardiol* 2018;71:339; 5. DeFronzo RA *et al. Diabetes* 2009;58:773; 6. Fowler MJ. *Clinical Diabetes* 2011;29:116; 7. Song MK *et al. J Diabetes Res* 2014;2014:e313718; 8. Bugger H & Abel ED. *Diabetologia* 2014;57:660; 9. Galicia-Garcia U *et al.* Int *J Mol Sci* 2020;21:6275; 10. Hayden MR *et al. Cardiorenal Med* 2013;3:265; 11. Ronco C *et al. J Am Coll Cardiol* 2008;52:1527; 12. McCullough PA *et al. Contrib Nephrol* 2013;182:82; 13. Chen Y *et al. Kidney Dis* 2020;6:225

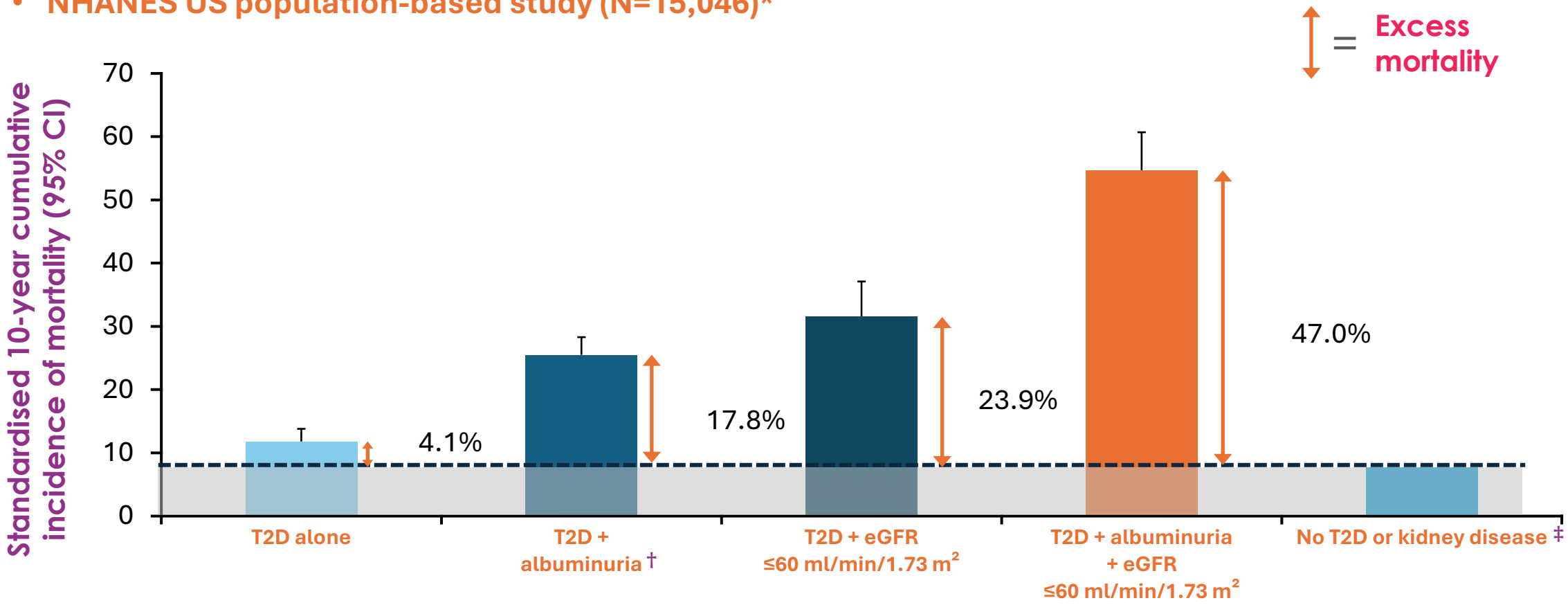
Correlation evidence: CKD is associated with an increased risk of CV events and death

- **The risk is amplified in patients with CKD and diabetes**



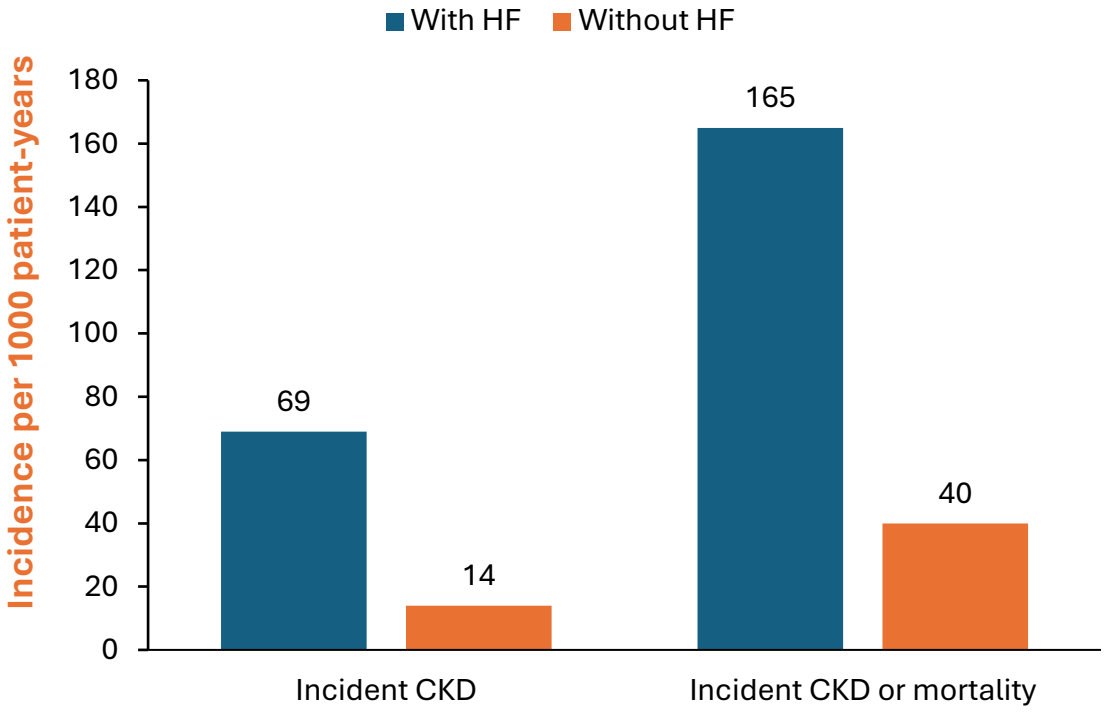
The coexistence of T2D and kidney disease is associated with increased mortality

- **NHANES US population-based study (N=15,046)***

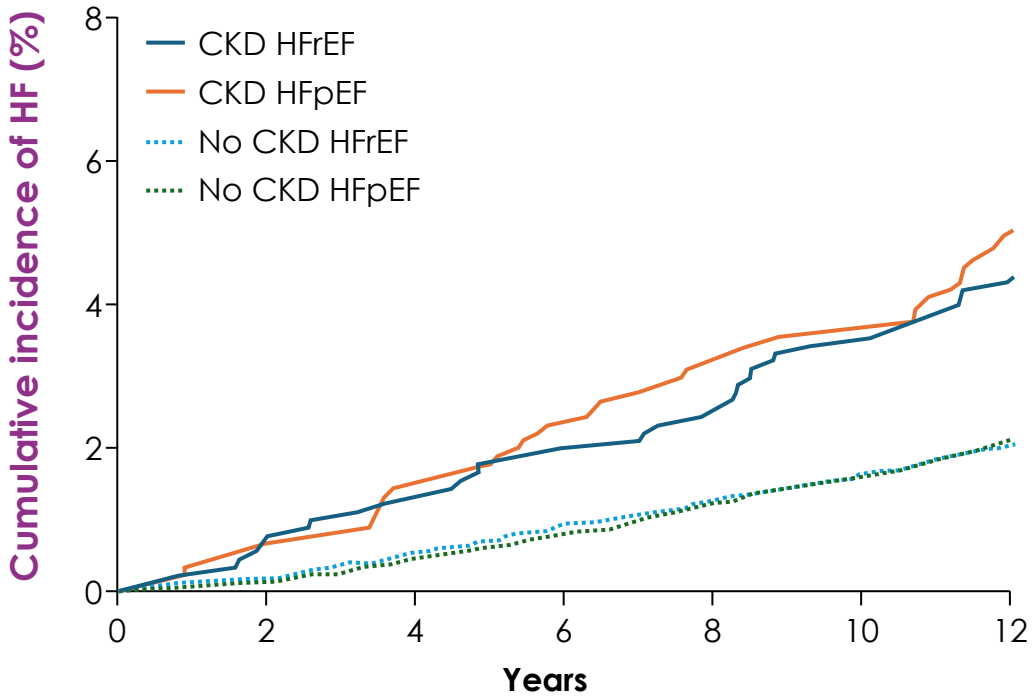


HF and kidney function decline are interconnected complications, with one often exacerbating the other[1,2]

HF is associated with significantly higher risk of incident CKD* and incident CKD or mortality[1]



Incidence rates of HF are higher in those with CKD compared with those without[2]

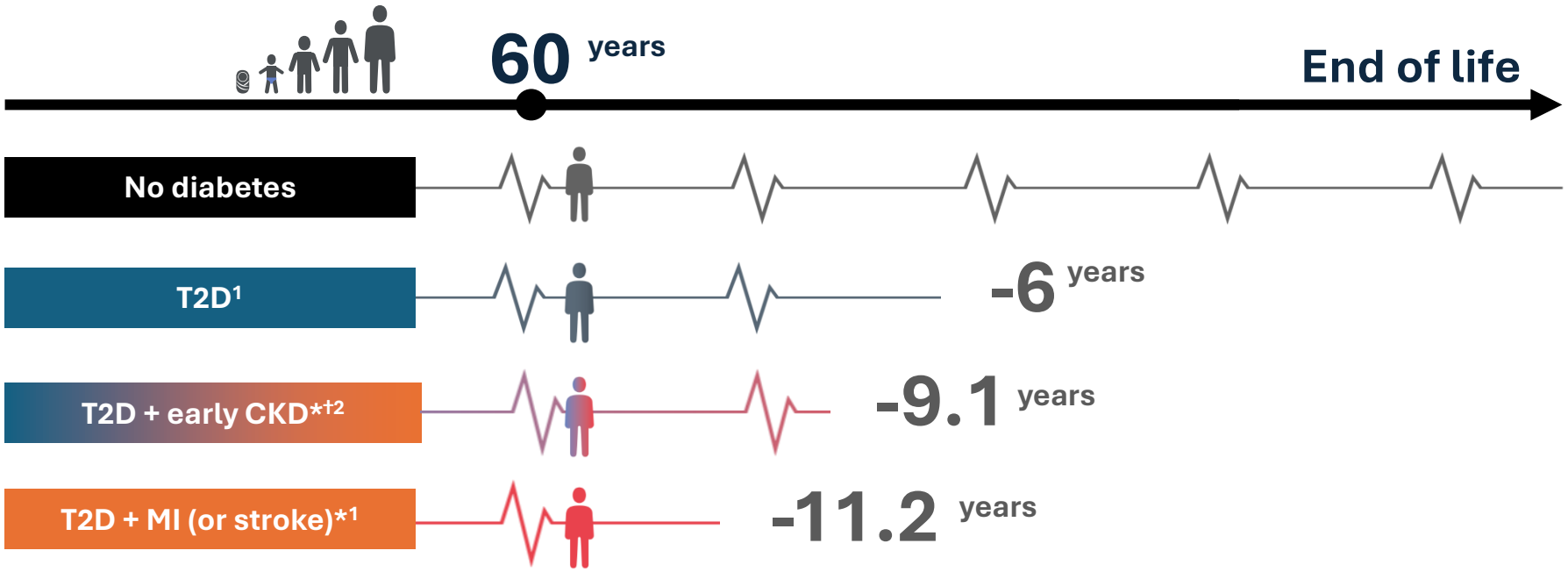


*Incident CKD was defined as two eGFR values of <60 mL/min/1.73 m^2 occurring ≥3 months apart and a decrease from baseline eGFR of at least 25%

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction

1. George LK et al. *Circ Heart Fail* 2017;10:e003825; 2. Nayor M et al. *Eur J Heart Fail* 2017;19:615–623

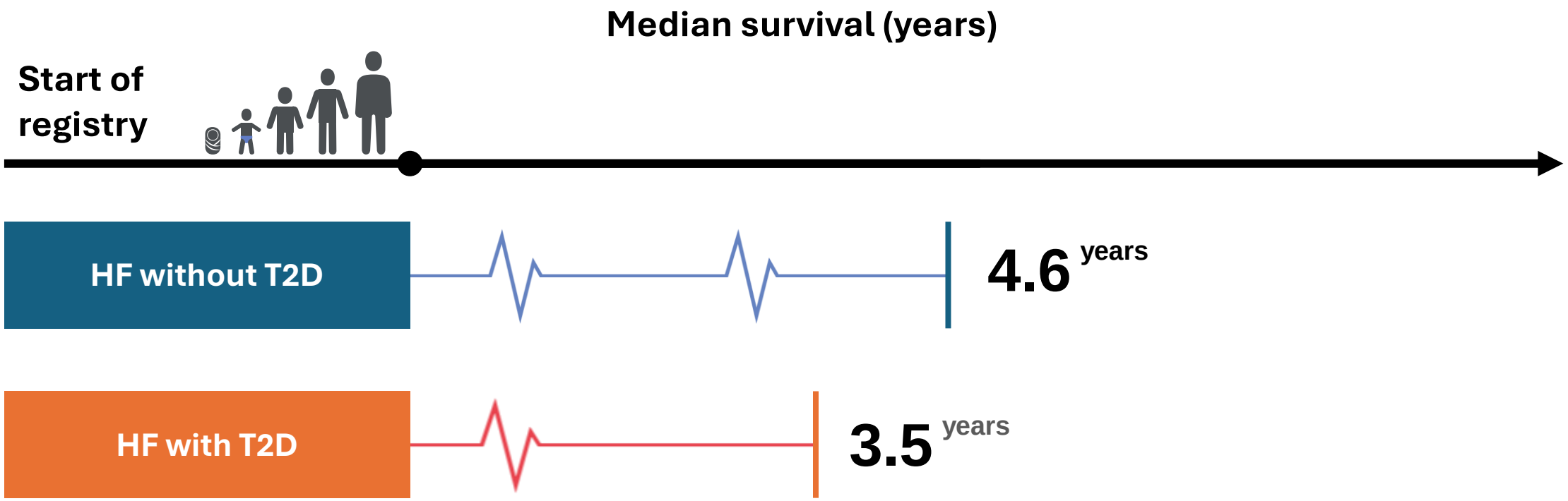
Life expectancy is reduced by 11.2 years in patients with T2D and CV disease[1]



*A 60-year-old man with diabetes and CVD or CKD; †CKD stages 1–3
CRM, cardio-renal-metabolic; CVD, cardiovascular disease
1. The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52; 2. Wen C *et al. Kidney Int* 2017;92:388

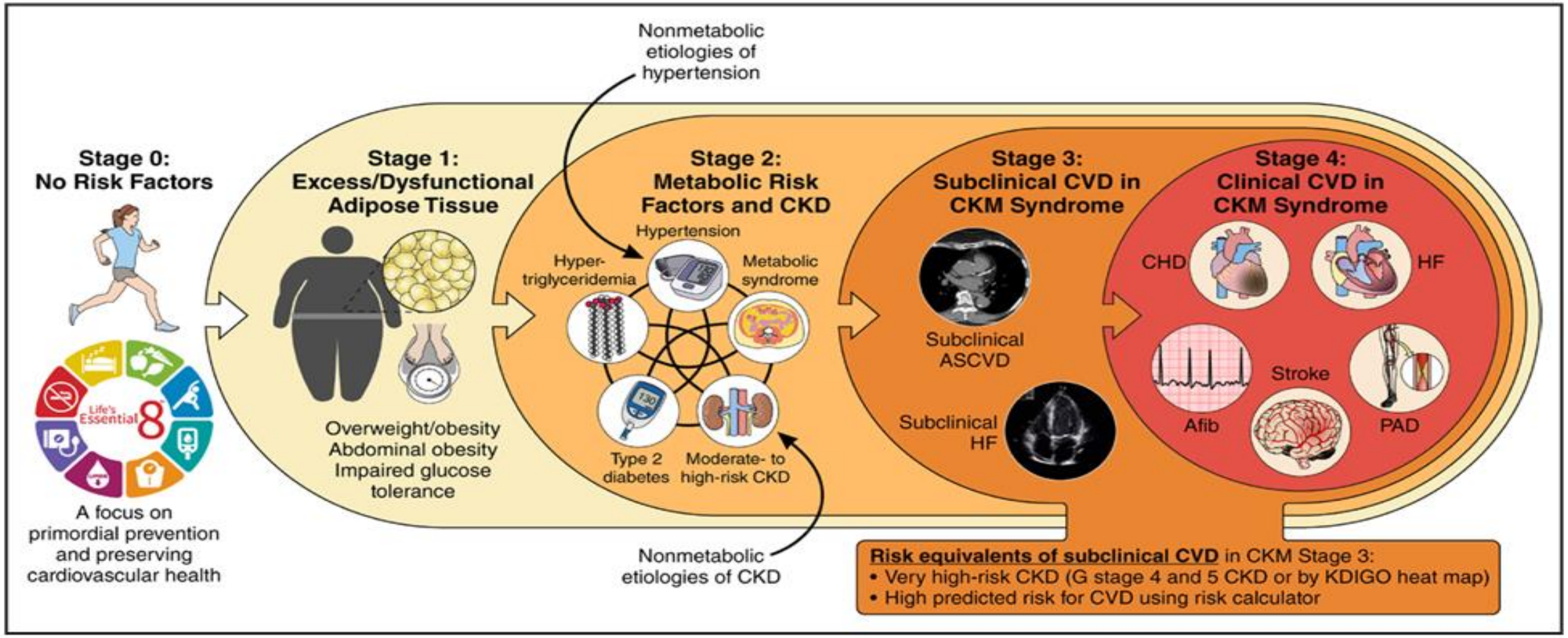
Patients with HF and T2D have reduced life expectancy

- **Long-term follow-up of patients with HF in a large, nationwide registry study***



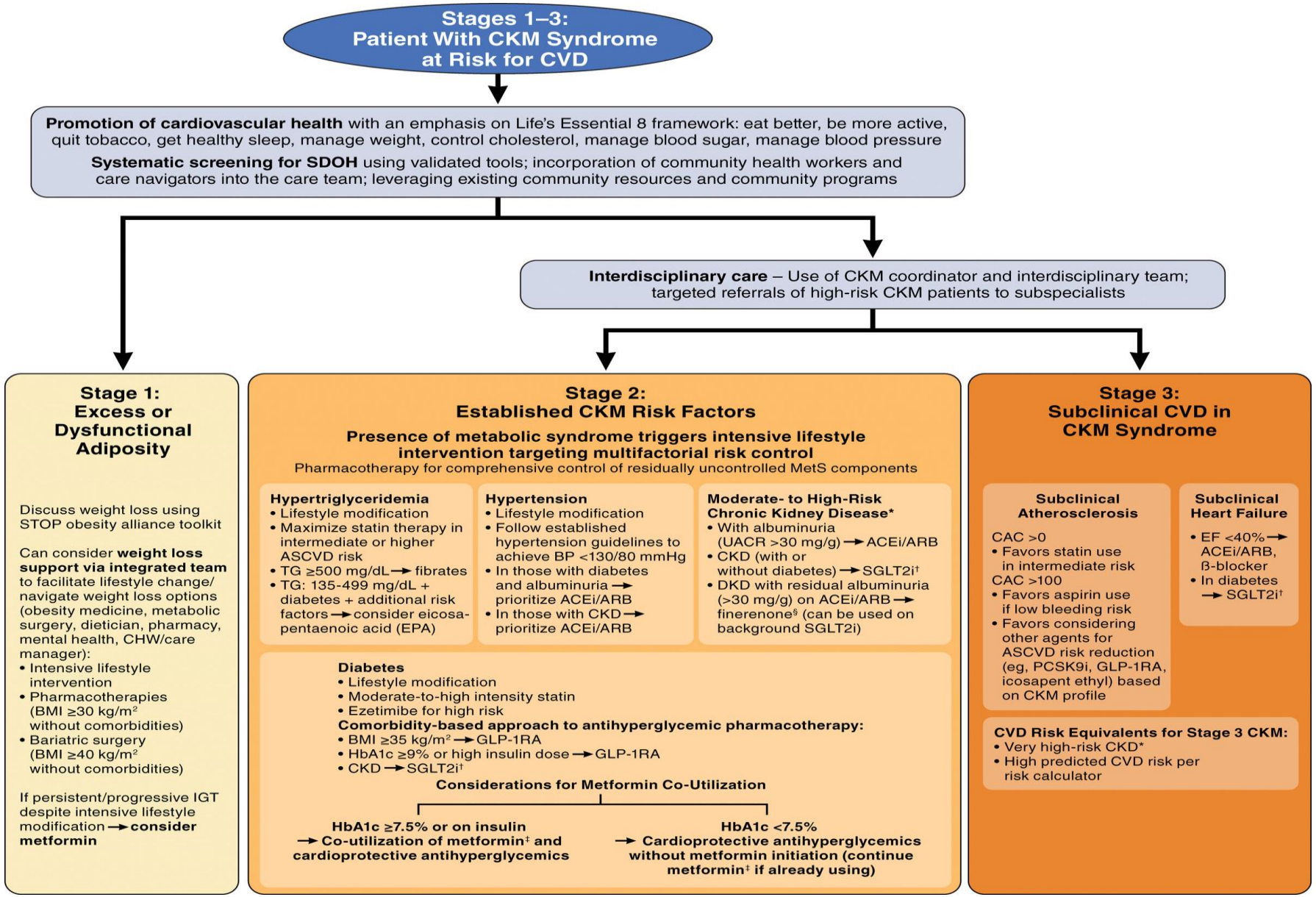
*Patients with previously diagnosed HF in the Swedish Heart Failure Registry (S-HFR) between 2003 and 2011 (N=36,274); median follow-up 1.9 years
Johansson I *et al*. *Eur J Heart Fail* 2014;16:409

Novel Cardio-Kidney-Metabolic staging model



Afib, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; CKM, cardiovascular-kidney-metabolic; CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; KDIGO, Kidney Disease Improving Global Outcomes; and PAD, peripheral artery disease. Ndumele CE. et al. Circulation. 2023;148:1606–1635

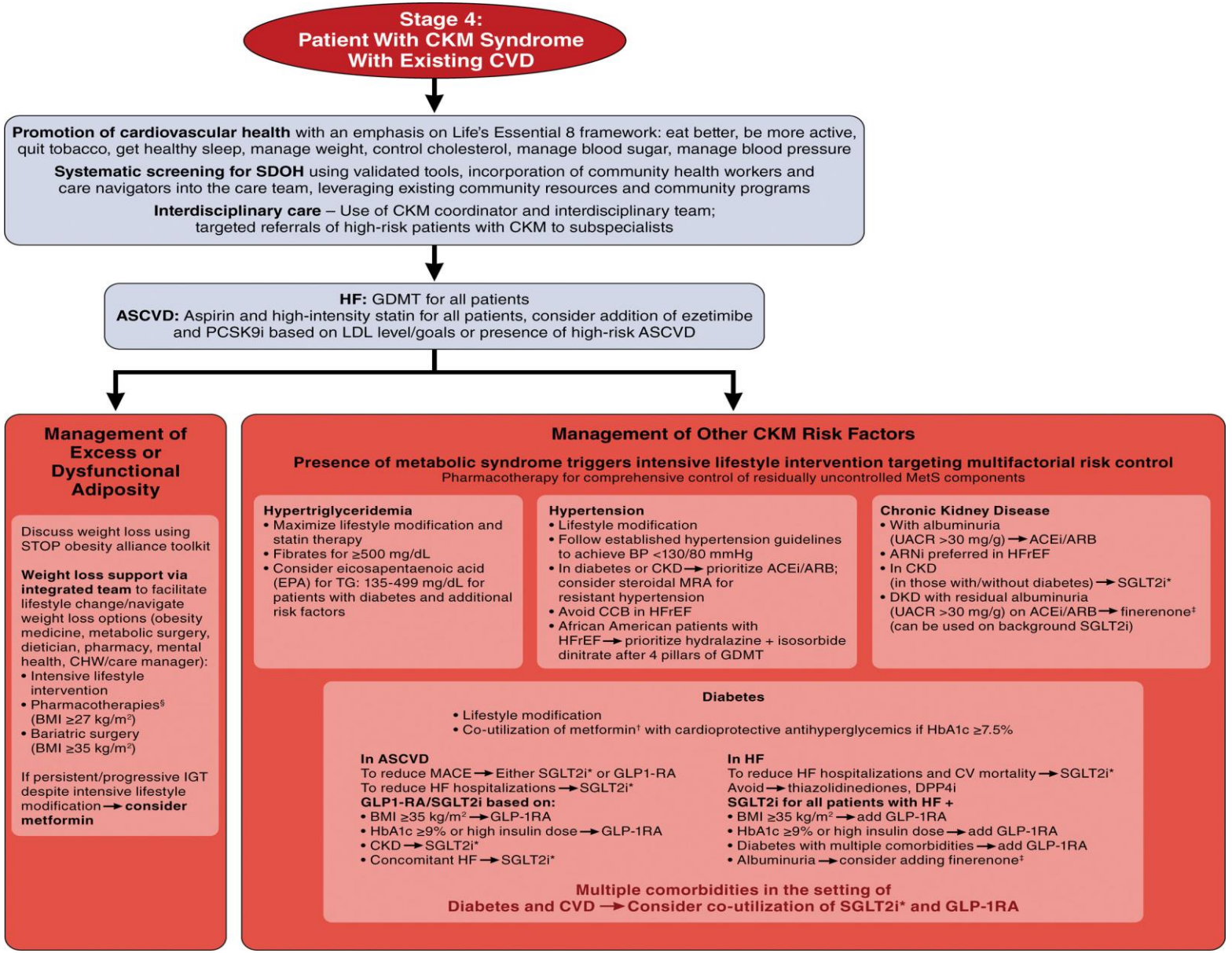
AHA – Cardio-Kidney-Metabolic Health:
Algorithm for the management of patients with Cardio-Kidney-Metabolic syndrome Stages 1-3



*Per Kidney Disease Improving Global Outcomes heat map.
†SGLT2i can be safely initiated for patients with estimated glomerular filtration rate (eGFR) ≥20 mL · min−1 · 1.73 m−2.
‡Metformin can be also be used in patients with eGFR ≥30 mL · min−1 · 1.73 m−2.
§Finerenone can likely be initiated on background SGLT2i for those with eGFR >25 mL · min−1 · 1.73 m−2 and potassium <5 mEq/L

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor/neprilysin inhibitor; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcium; CHD, coronary heart disease; CHW, community health worker; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CRM, cardio-renal-metabolic; CVD, cardiovascular disease; DKD, diabetic kidney disease; DM, diabetes; EF, ejection fraction; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA1c, hemoglobin A1c; HF, heart failure; IGT, impaired glucose tolerance; MetS, metabolic syndrome; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; P2Y12i, P2Y12 inhibitor; SDOH, social determinants of health; SGLT2i, sodium-glucose transport protein 2 inhibitors; STOP, Strategies to Overcome and Prevent; TG, triglycerides; and UACR, urine albumin-creatinine ratio. Ndumele CE. et al. Circulation. 2023;148:1606–1635

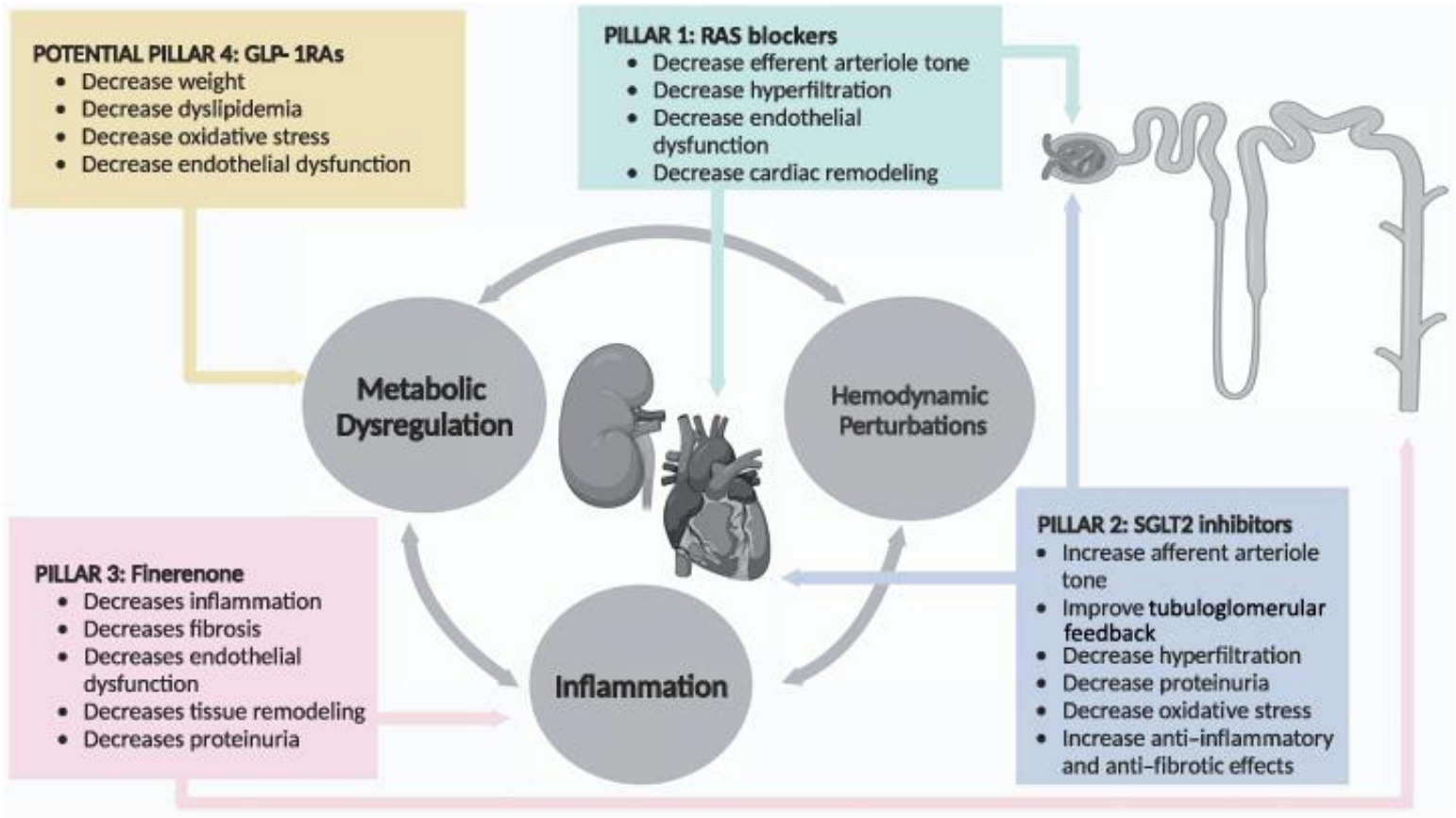
AHA – Cardio-Kidney-Metabolic Health:
Algorithm for the management of patients with Cardio-Kidney-Metabolic syndrome Stage 4



*SGLT2i can be safely initiated for patients with estimated glomerular filtration rate (eGFR) ≥20 mL·min−1·1.73 m−2. †Metformin can be also be used in patients with eGFR ≥30 mL·min−1·1.73 m−2 and without unstable or decompensated HF. ‡Finerenone can likely be initiated on background SGLT2i for those with eGFR >25 mL·min−1·1.73 m−2 and potassium <5 mEq/L.
§Pending the full results of the SELECT trial (Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity), high-dose GLP-1RA may become frontline therapy in patients with obesity and established CVD.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor/neprilysin inhibitor; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; BMI, body mass index; CCB, calcium channel blocker; CHD, coronary heart disease; CHW, community health worker; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CRM, cardio-renal-metabolic; CV, cardiovascular; CVD, cardiovascular disease; DKD, diabetic kidney disease; DM, diabetes; DPP4i, dipeptidyl peptidase 4 inhibitor; EF, ejection fraction; GDMT, guideline-directed medical therapy; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA1c, hemoglobin A1c; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event; MetS, metabolic syndrome; MRA, mineralocorticoid receptor antagonist; P2Y12i, P2Y12 inhibitor; SDOH, social determinants of health; SGLT2i, sodium-glucose transport protein 2 inhibitors; STOP, Strategies to Overcome and Prevent; TG, triglycerides; and UACR, urine albumin-creatinine ratio. Ndumele CE. et al. Circulation. 2023;148:1606–1635

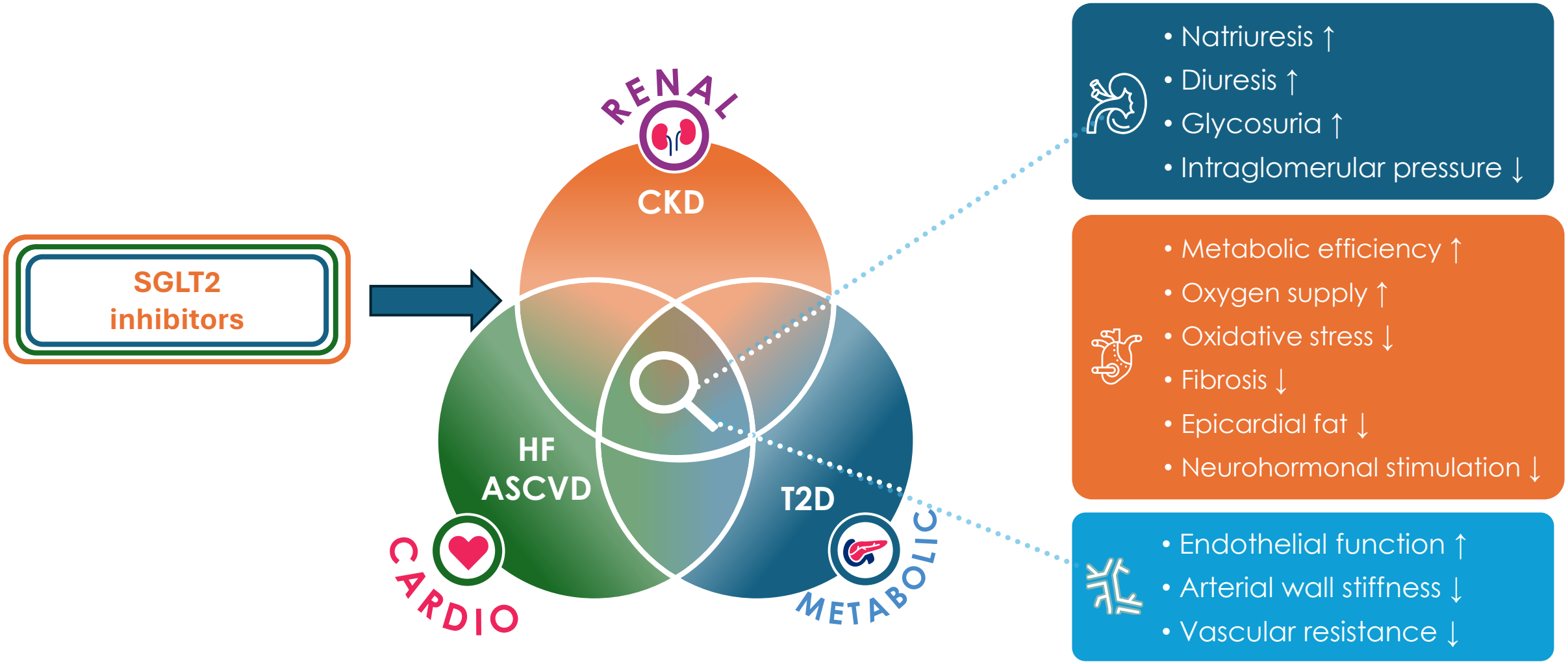
New pharmaceutical therapies and evolution of standard of Care for **Cardio-Kidney-Metabolic syndrome**



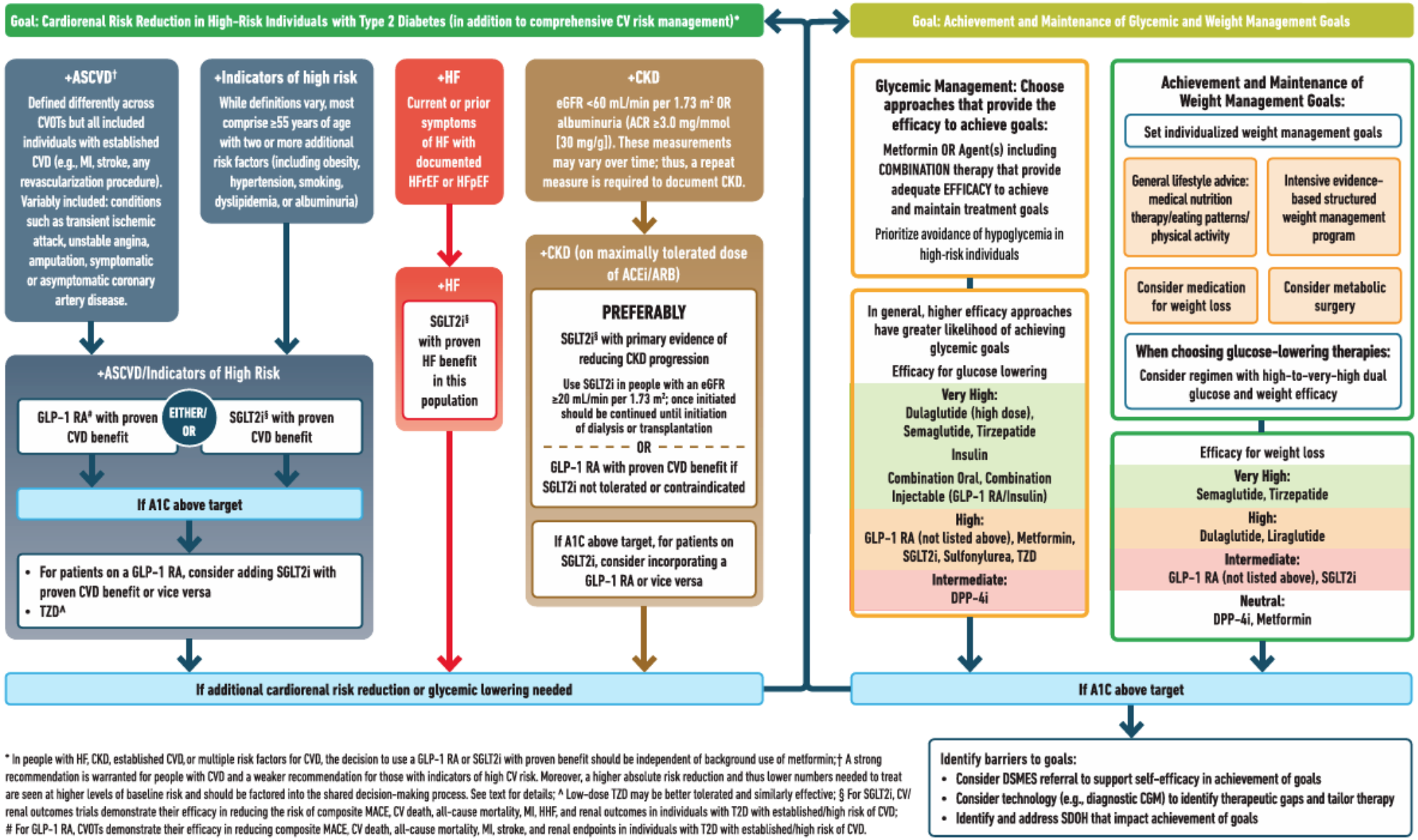
GLP1-Ras, glucagon-like peptide 1 receptor agonists; RAS, renin-angiotensin system; SGLT2i,
Sandra C. Naaman and George L. Bakris. Diabetes Care 2023;46(9):1574–1586

SGLT2 inhibitors positively impact multiple mechanisms beyond haemodynamic improvement across the cardio, renal and metabolic spectrum

- **Possible mechanisms driving the cardio, renal and metabolic effects of empagliflozin[1,2,3]**



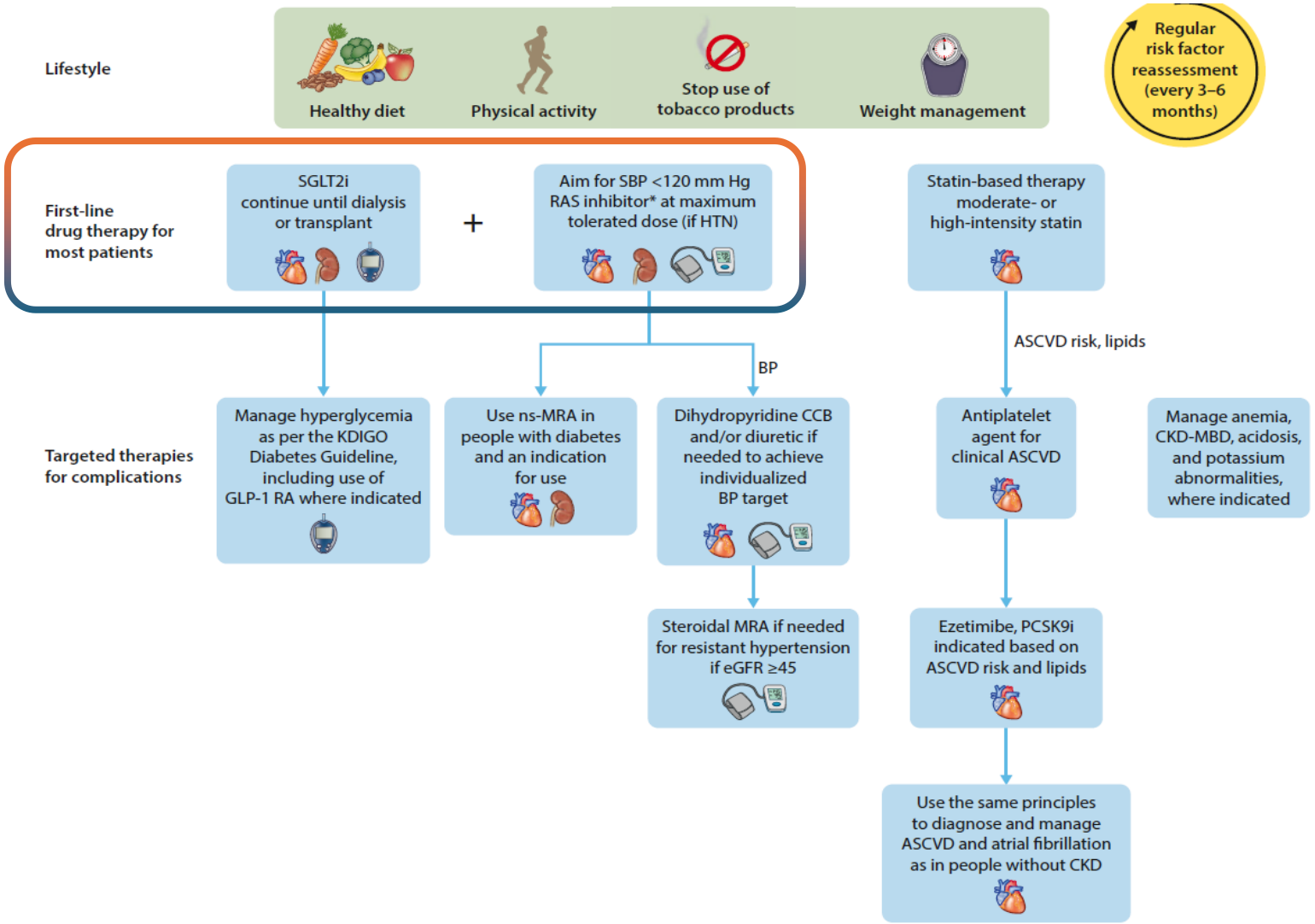
ADA 2024 Guidelines recommends SGLT2 inhibitors for management of T2DM



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

The KDIGO 2024 CKD guideline recommends SGLT2 inhibitors for their CV and kidney benefits for the treatment of people with CKD

Holistic approach to CKD treatment and risk modification

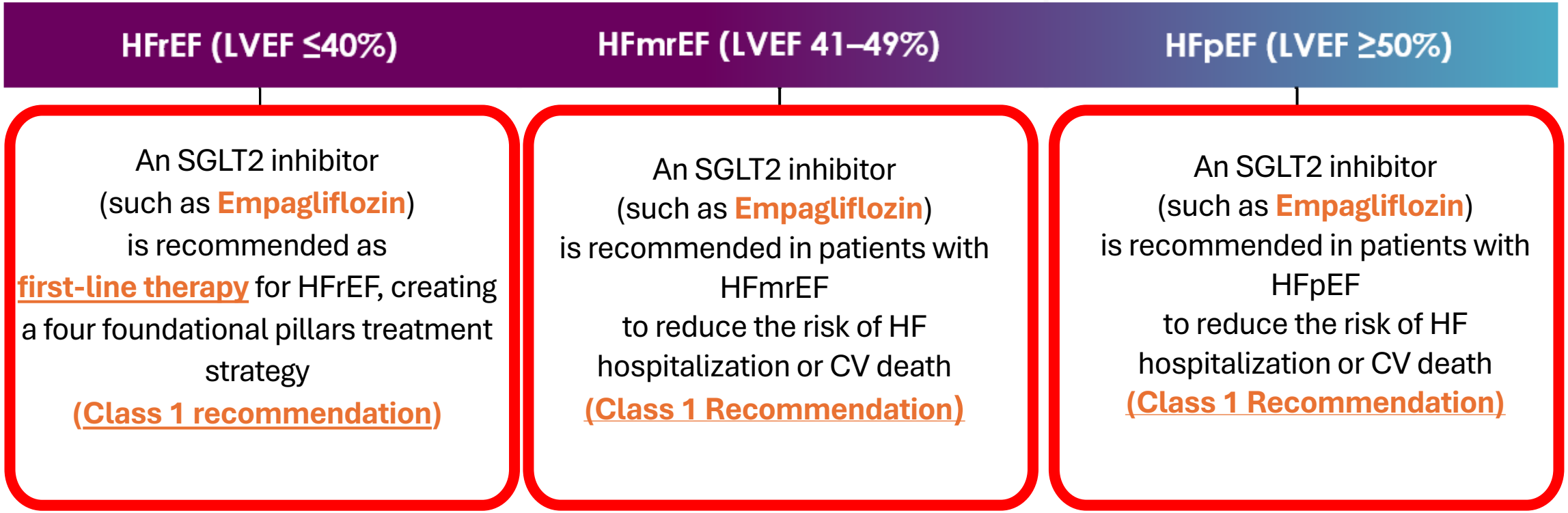


Practice Points are consensus-based statements representing the expert judgment of the Work Group and are not graded. Users should consider the Practice Point as expert guidance and use it as they see fit to inform the care of patients

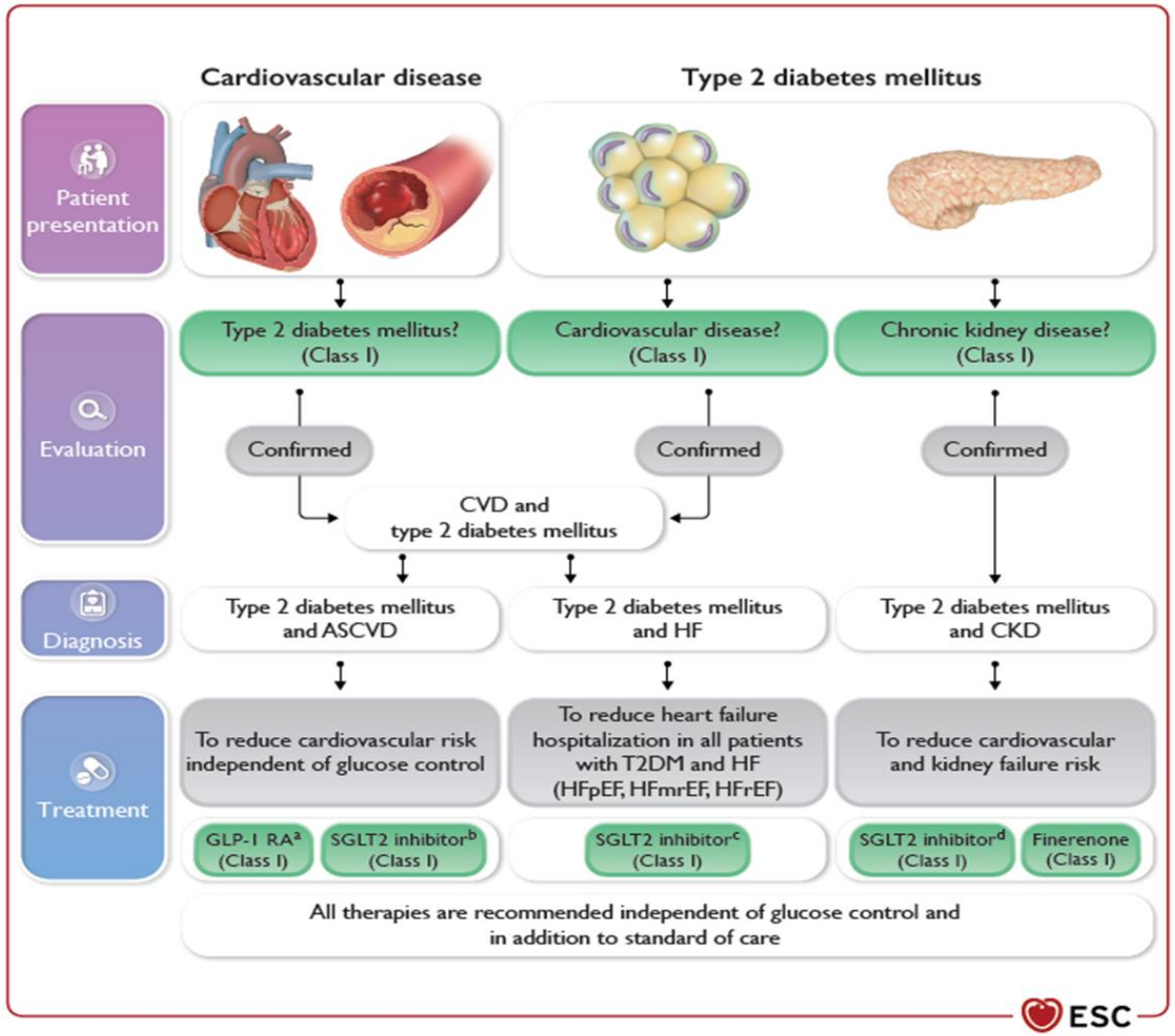
ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blockers; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HTN, hypertension; KDIGO, Kidney Disease: Improving Global Outcomes; MBD, mineral bone disease; MRA, mineralocorticoid receptor antagonist; ns-MRA, non-steroidal mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin–angiotensin–aldosterone system ; SBP, systolic blood pressure; SGLT2, sodium-glucose co-transporter-2

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int* 2024;105(Suppl. 4S):S117

SGLT2-Inhibitors, like Empagliflozin, has the highest recommendation in the treatment of Heart Failure based from the ESC 2023 Guidelines



ESC 2023 Guidelines recommends SGLT2 inhibitors for management of cardiovascular disease in patients with type 2 diabetes



ASCVD, atherosclerotic cardio vascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; T2DM, type 2 diabetes mellitus

Marx N. et al. Eur Heart J. 2023 doi.org/10.1093/eurheartj/ehad192

The **ESC 2024 Guidelines** guideline also recommends SGLT2 inhibitors **for manegement of BP in patients with Heart Failure**

Heart failure					
In patients with HFrEF, it is recommended that BP-lowering treatment comprises an ACE inhibitor or ARB, a beta-blocker and diuretic and/or MRA if required.	I	A	In patients with symptomatic HFrEF/HFmrEF, the following treatments with BP-lowering effects are recommended to improve outcomes: ACE inhibitors (or ARBs if ACE inhibitors are not tolerated) or ARNi, beta-blocker, MRA, and SGLT2 inhibitors.	I	A
In patients with HFpEF, because no specific drug has proven its superiority, all major agents can be used.	I	C	In hypertensive patients with symptomatic HFpEF, SGLT2 inhibitors are recommended to improve outcomes in the context of their modest BP-lowering properties.	I	A
			In patients with symptomatic HFpEF who have BP above target, ARBs and/or MRAs may be considered to reduce heart failure hospitalizations and reduce BP.	IIb	B

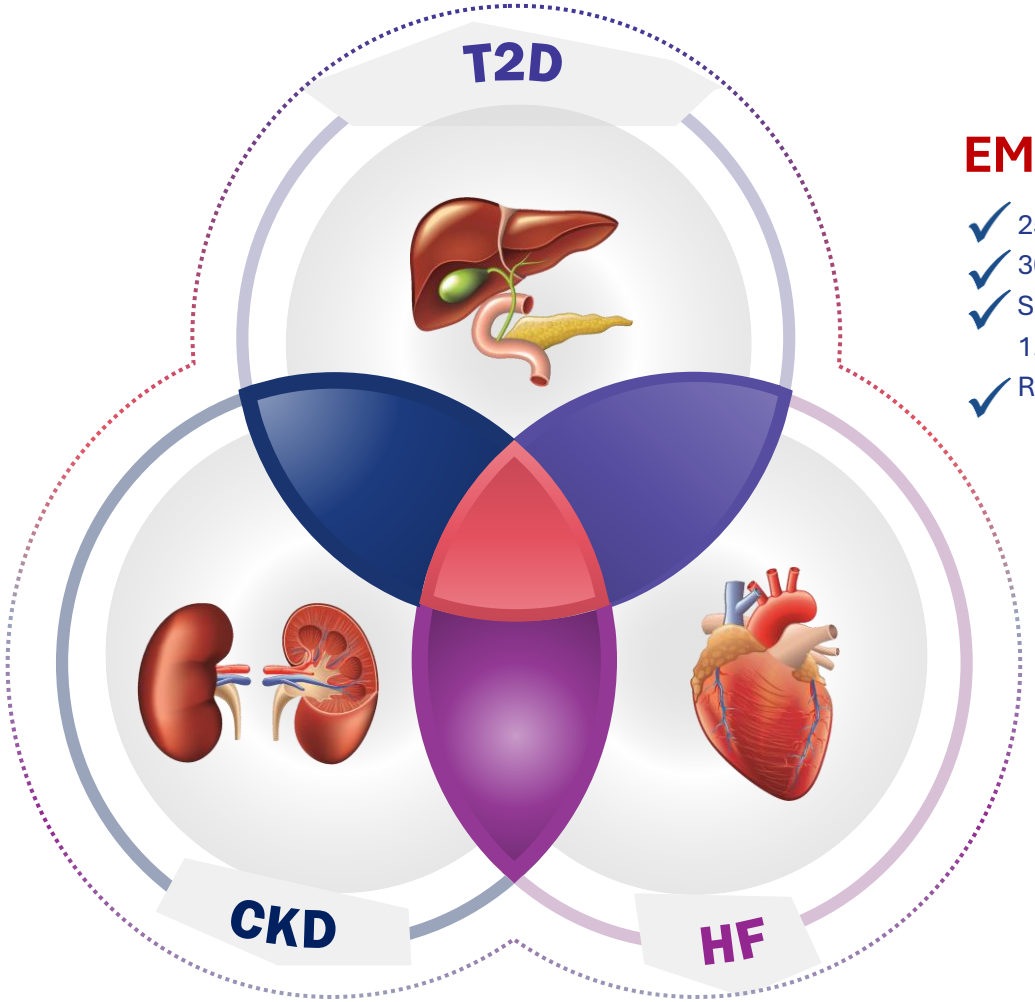
Empagliflozin component provides consistent Cardio-Renal-Metabolic benefit across a broad range of patients

EMPA-REG OUTCOME[1]

- ✓ Unique 38% RRR in CV Death
- ✓ 14% RRR in 3P-MACE
- ✓ 35% RRR in HHF
- ✓ 32% RRR in all-cause mortality
- ✓ 39% RRR in worsening nephropathy

EMPEROR-Reduced[2]

- ✓ 25% RRR in composite CV death or HHF
- ✓ 30% RRR in total hospitalizations
- ✓ Slowed down eGFR decline by 1.73 mL/min/1.73 m2 per year
- ✓ Reduced kidney outcomes by 50%



EMPA-KIDNEY[4]

- ✓ 28% RRR CV death or Kidney disease progression
- ✓ 14% RRR All-Cause Hospitalization
- ✓ 13% Nominal RRR All-Cause Mortality
- ✓ 16% Nominal RRR CV death or HHF

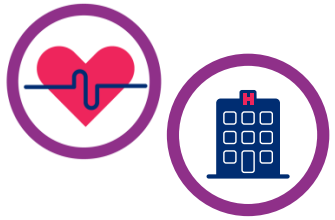
EMPEROR-Preserved[3]

- ✓ 21% RRR in composite death or HHF
- ✓ 27% RRR in total hospitalizations
- ✓ Slowed down eGFR decline by 1.36 mL/min/1.73 m2 per year

1. Zinman, *et al*. N Engl J Med. 2015;373:2117–28. 2. Packer, *et al*. NEJM 2020. DOI: 10.1056/NEJMoa2022190. 3. Anker S, *et al.* N Engl J Med. 2021;DOI:10.1056/NEJMoa2107038.
4. The EMPA-KIDNEY Collaborative Group. [Published online ahead of print March 3 2022]. Nephrol Dial Transplant. 2022. DOI:10.1093/ndt/gfac040.

In 2015, EMPA-REG OUTCOME was the first SGLT2 inhibitor CVOT to demonstrate CV and kidney benefits in people with T2D and established CV disease

Significant relative risk reduction with empagliflozin[1,2]:

3P-MACE*	CV death†	HHF†	CV death or HHF†	Kidney outcomes†§[2]
				
14%	**38%**	**35%**	**34%**	**39%**
(0.86) *p*=0.04	**(0.62) *p*<0.001‡**	**(0.65) *p*=0.002‡**	**(0.66) *p*<0.001‡**	**(0.61) *p*<0.001‡**
ARR=1.6%; NNT=63	ARR=2.2%; NNT=46	ARR=1.4%; NNT=71	ARR=2.8%; NNT=36	ARR=7.4%; NNT=14

Reductions in CV, HHF, CV death or HHF and kidney outcomes were **generally consistent across subgroup analyses**

% values represent relative risk reduction; values in parentheses are HR
*Primary endpoint, *p*-values are for superiority; †Secondary or exploratory endpoints as defined in the study protocols; ‡Nominal *p*-value; §Incident or worsening nephropathy, defined as progression to macroalbuminuria (UACR >300 mg/g), doubling of serum creatinine (accompanied by eGFR [MDRD] ≤45 ml/min/1.73 m^2), initiation of RRT or death from kidney disease
3P-MACE, 3-point major adverse cardiovascular events; ARR, absolute risk reduction; CV, cardiovascular; CVOT, cardiovascular outcomes trial; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; MDRD, Modification of Diet in Renal Disease; NNT, number needed to treat; RRT, renal replacement therapy; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio
1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Wanner C *et al. N Engl J Med* 2016;375:323

EMPEROR-Reduced investigated the safety and efficacy of empagliflozin versus placebo in patients with HF with reduced ejection fraction

Significant relative risk reduction with empagliflozin[1]:

Adjudicated CV death or heart failure hospitalisation*	Adjudicated total HHF (first and recurrent)†	Kidney outcomes: Slope of change in eGFR from baseline†	Composite renal endpoint †$
			
25% **(0.75) p<0.001** ARR=5.2%; NNT=19	**30%** **(0.70) p<0.001**	**+1.73** **mL/min/1.73 m2 per year**	**50%** **(0.50)** ARR=1.5%;

Empagliflozin reduces CV death or HHF in patients with **LVEF ≤40%** and protects the kidney by slowing the progression of kidney disease

% values represent relative risk reduction; values in parentheses are HR
*Primary endpoint, *p*-values are for superiority; †Secondary or exploratory endpoints as defined in the study protocols; $Composite renal endpoint is defined as chronic dialysis, renal transplant, sustained reduction of ≥40% eGFR or sustained eGFR <15 ml/min/1.73 m² for patients with eGFR ≥30 ml/min/1.73 m² at baseline (<10 ml/min/1.73 m² for patients with eGFR <30 ml/min/1.73 m² at baseline). Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days.
ARR, absolute risk reduction; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; NNT, number needed to treat; SGLT2, sodium-glucose co-transporter-2;
Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190

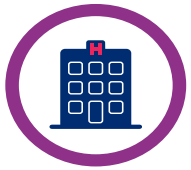
EMPEROR-Preserved investigated the safety and efficacy of empagliflozin compared with placebo in patients with HF with preserved ejection fraction.

Significant relative risk reduction with empagliflozin[1]:

Adjudicated CV death or HHF*

21%
(0.79) *p*<0.001
ARR=3.3%; NNT=31

Adjudicated total HHF (first and recurrent)†



27%
(0.73) *p*<0.001

Kidney outcomes: Slope of change in eGFR from baseline†

+1.36
mL/min/1.73 m2 per year

Empagliflozin reduces CV death or HHF in patients with **LVEF >40%** and protects the kidney by slowing the progression of kidney disease

% values represent relative risk reduction; values in parentheses are HR
*Primary endpoint, *p*-values are for superiority; †Secondary or exploratory endpoints as defined in the study protocols; ARR, absolute risk reduction; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; NNT, number needed to treat; SGLT2, sodium-glucose co-transporter 2;
1: Anker S *et al. N Engl J Med.* 2021;385:1451.

EMPA-KIDNEY investigated the safety and efficacy of empagliflozin compared with placebo in patients with CKD

Significant relative risk reduction with empagliflozin[1]:

CV death or kidney disease progression (first)*

28%
(0.72) p<0.001
ARR=3.6%; NNT=28

All-cause hospitalization (first and recurrent)†

14%
(0.86) p<0.003

Empagliflozin reduced the relative risk of kidney disease progression or CV death in a broad range of patients with CKD. Treatment effect was demonstrated irrespective of underlying cause of CKD across a broad range of eGFR

% values represent relative risk reduction; values in parentheses are HR
*Primary endpoint, *p*-values are for superiority; †Secondary or exploratory endpoints as defined in the study protocols; ARR, absolute risk reduction; CV, cardiovascular; eGFR, estimated glomerular filtration rate; NNT, number needed to treat; Kidney disease progression defined as end-stage kidney disease, a sustained decline in eGFR to <10 ml/min/1.73 m^2, renal death, or a sustained decline of ≥40% in eGFR from randomization

1: The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2023;388:117