Addressing cardiorenal outcomes in CKD and T2D: What are the key considerations for daily practice?

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What is the link between T2D and CKD, and what are the pathophysiological drivers behind the progression of CKD?

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The epidemiology of CKD/T2D

40% of patients with T2D develop CKD[1]

T2D with CKD can shorten the life expectancy of patients by **16 years,** relative to those with neither disease[2]

Patients with CKD/T2D are at **2x greater risk** of developing heart failure and **3x more likely** to die of CV-related causes than patients with T2D alone[3,4]

Diabetes exacerbates progression of CKD[5]

	Stage 3a	Stage 3b	Stage 4	Stage 5
Median time in CKD stage (yrs)	7.9	5.0	4.2	0.8
	↓ -1.8	↓ -1.4		↓ -0.1
Median time in CKD stage with poorly controlled diabetes (yrs)	6.1	3.6	–	0.7

CKD, chronic kidney disease; CV, cardiovascular; T2D, type 2 diabetes; yrs, years.

1. Alicic RZ, et al. *Clin J Am Soc Nephrol*. 2017;12:2032–45; 2. Wen CP, et al. *Kidney Int*. 2017;92:388–96; 3. Birkeland K, et al. *Diabetes Obes Metab*. 2020;22:1607–18; 4. Afkarian M, et al. *J Am Soc Nephrol*. 2013;24:302–8; 5. Ku E, et al. *Clin J Am Soc Nephrol.* 2018;13:693–701.

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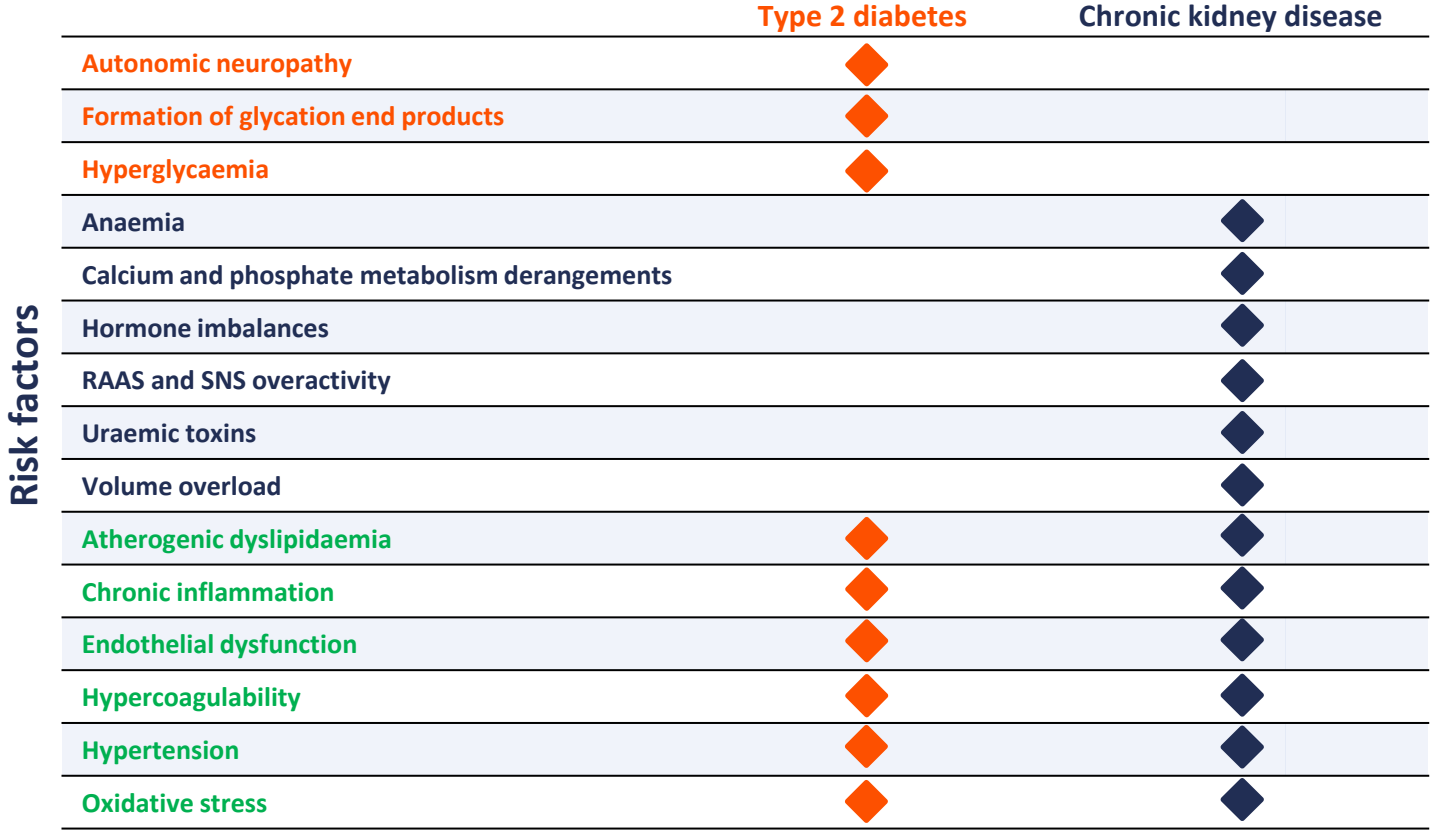
The association between T2D, CKD and CVD



CKD, chronic kidney disease; CVD, cardiovascular disease; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system; T2D, type 2 diabetes.

Pálsson R, Patel UD. *Adv Chronic Kidney Dis.* 2014; 21:273–80.

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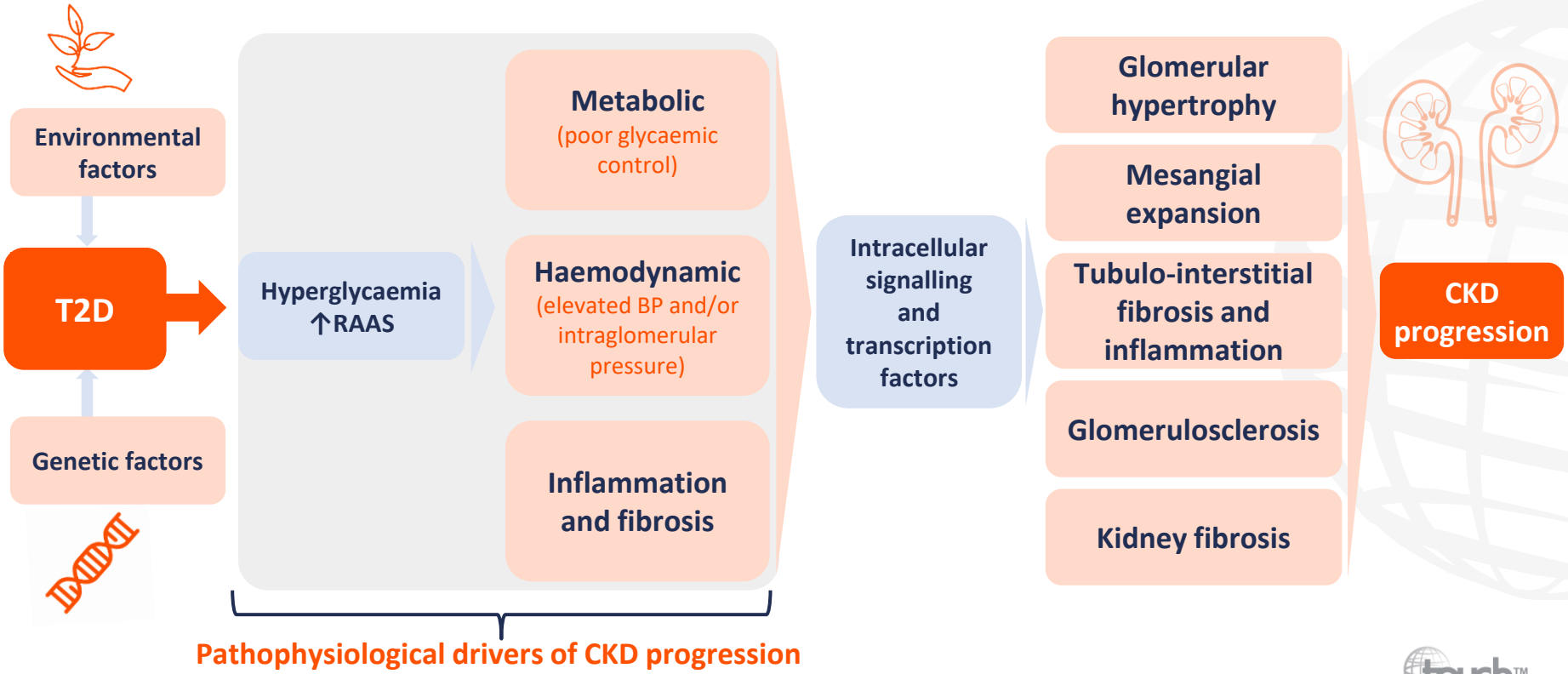
Pathophysiological drivers of CKD progression in T2D[1,2]



BP, blood pressure; CKD, chronic kidney disease; RAAS, renin–angiotensin–aldosterone system; T2D, type 2 diabetes.

1. Alicic RZ, et al. *Clin J Am Soc Nephrol*. 2017;12:2032–45; 2. Mora-Fernández C, et al. *J Physiol.* 2014;592:3997–4012.

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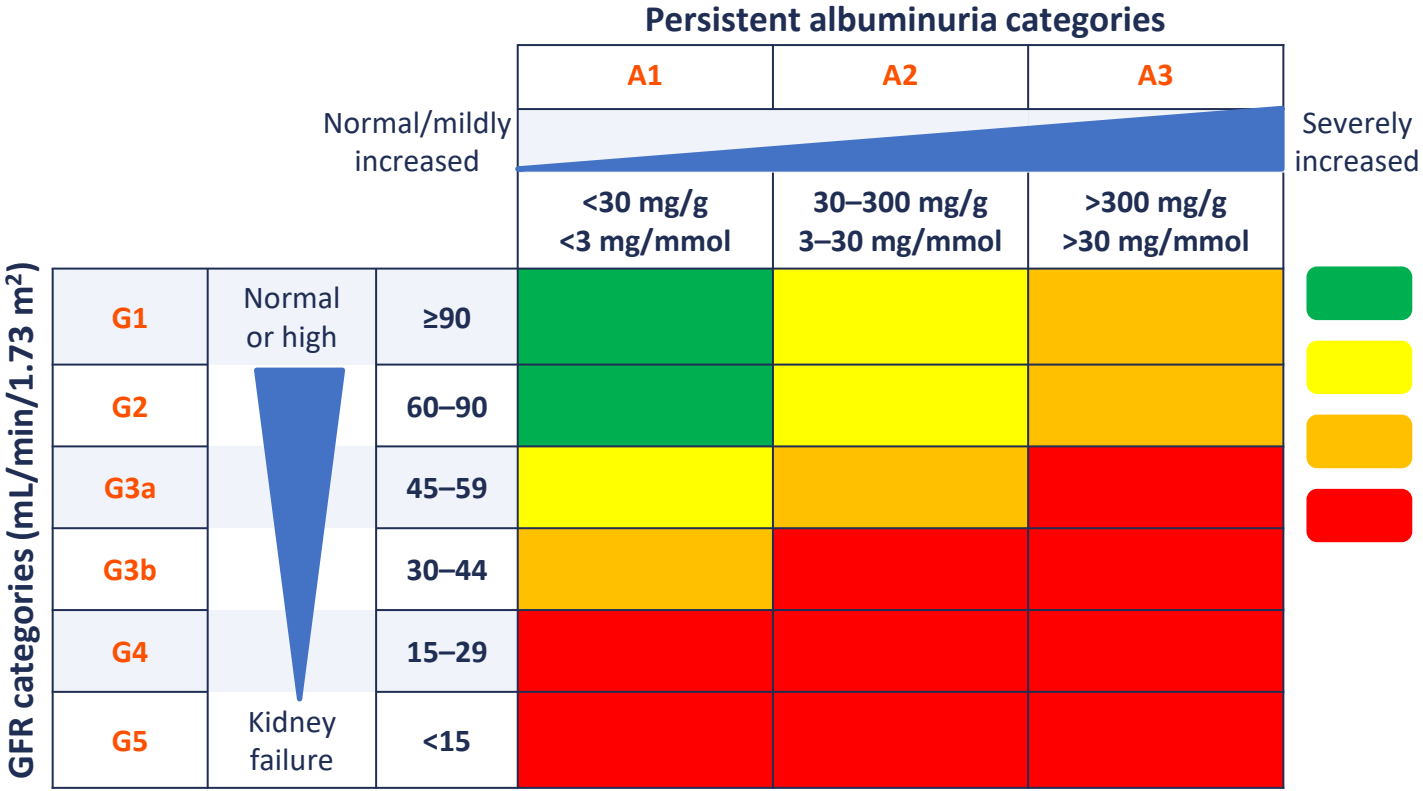
Prognosis of CKD by GFR and albuminuria categories



CKD, chronic kidney disease; GFR, glomerular filtration rate.

Adapted from: KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int.* 2020;98:S1–S115, with permission from KDIGO.

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What are the cardiorenal risks associated with CKD and T2D and how can they be addressed?

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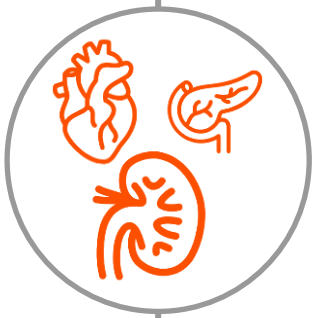
Cardiorenal outcomes in T2D/CKD[1,2]

Cardiovascular

- Heart failure
- Myocardial infarction
- Peripheral artery disease
- Stroke
- Cardiovascular death



Kidney

- Albuminuria
- ESKD
- Renal replacement therapy
- Renal death

Progressive GFR decline → **Increased cardiorenal mortality**

CKD, chronic kidney disease; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; T2D, type 2 diabetes.

1. Folkerts K, et al. *Nephron*. 2021;145:342–52; 2. Lai AC, et al. *J Am Coll Cardiol.* 2021;77:1470–9.

Approved therapies with evidence for reducing cardiorenal outcomes in CKD/T2D (1/2)

SGLT2i

	CANVAS[1]	CREDENCE[2]	DAPA-CKD[3]	DECLARE-TIMI 58[4]	EMPA-REG[5]
Treatment	**Canagliflozin vs PBO**	**Canagliflozin vs PBO**	**Dapagliflozin vs PBO**	**Dapagliflozin vs PBO**	**Empagliflozin vs PBO**
Number of participants	10,142	4,401	4,304[§]	17,160	7,020
Median observation time (years)	3.6*	2.6	2.4	4.2	3.1
eGFR criteria (mL/min/1.73 m²)	≥30	30–90	25–75	CrCl ≥60 mL/min 45% of pts had eGFR 60–90	≥30
Key composite cardiovascular outcomes	**↓ Risk of MACE[†]** (HR 0.86, p=0.02[‡])	**↓ Risk of CV death or HHF** (HR 0.69, p<0.001)	**↓ Risk of CV death or HHF** (HR 0.71, p=0.009)	**Risk of MACE,[‖] NS change** (HR 0.93, p=0.17[‡]) **↓ Risk of HHF or CV death** (HR 0.83, p=0.005[‡])	**↓ Risk of MACE[†]** (HR 0.86, p=0.04[‡])
Key composite kidney outcomes	**↓ Risk of sustained 40% decline in eGFR, RRT or renal death** (HR 0.60, 95% CI 0.47–0.77)	**↓ Risk of ESKD, doubling of SCr or renal death** (HR 0.66, p<0.001)	**↓ Risk of sustained ≥50% decline in eGFR, ESKD or renal death** (HR 0.56, p<0.001)	**↓ Risk of sustained ≥40% decline in eGFR, new ESKD or renal death** (HR 0.76, 95% CI 0.67–0.87)	—

* Mean; [†] CV death, non-fatal MI, or non-fatal stroke; [‡] for superiority; [§] with and without type 2 diabetes; [‖] CV death, MI, or ischemic stroke.
CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; NS, not significant; PBO, placebo; pts, patients; RRT, renal replacement therapy; SCr, serum creatinine; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.

1. Neal B, et al. *N Engl J Med*. 2017;377:644–57; 2. Perkovic V, et al. *N Engl J Med.* 2019;380:2295–306; 3. Hiddo JL, et al. *N Engl J Med*. 2020;383:1436–46; 4. Wiviott SD, et al. *N Engl J Med.* 2019;380:347–57; 5. Zinman B, et al. *N Engl J Med.* 2015;373:2117–28.

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Approved therapies with evidence for reducing cardiorenal outcomes in CKD/T2D (2/2)

	SGLT2i	Non-steroidal mineralocorticoid receptor antagonist	GLP-1 RA		
	VERTIS CV[1]	FIDELITY[2]	REWIND[3]	LEADER[4]	SUSTAIN-6[5]
Treatment	**Ertugliflozin vs PBO**	**Finerenone vs PBO**	**Dulaglutide vs PBO**	**Liraglutide vs PBO**	**Semaglutide SC vs PBO**
Number of participants	8,246	13,026	9,901	9,340	3,297
Median observation time (years)	3.5*	3.0	5.4	3.8	2.1
eGFR criteria (mL/min/1.73 m²)	≥30	≥25	≥15	≥30	—
Key composite cardiovascular outcomes	**↔ Risk of MACE†** (HR 0.97, p<0.001‡) **↓ Risk of CV death, HHF** (HR 0.88, p=0.11§)	**↓ Risk of MACE‖** (HR 0.86, p=0.0018)	**↓ Risk of MACE†** (HR 0.88, p=0.026§)	**↓ Risk of MACE†** (HR 0.87, p=0.01§)	**↓ Risk of MACE†** (HR 0.74, p=0.02§)
Key composite kidney outcomes	**↓ Risk of renal death, RRT or doubling of SCr** (HR 0.81, 95% CI 0.63–1.04)	**↓ Risk of KF, sustained ≥57% decline in eGFR or renal death** (HR 0.77, p=0.0002)	**↓ Risk of new macroalbuminuria¶, sustained ≥30% decline in eGFR or RRT** (HR 0.85, p=0.0004)	**↓ Risk of new macroalbuminuria¶, doubling of SCr, eGFR of ≤45, RRT or renal death** (HR 0.78, p=0.003)	**↓Risk of macroalbuminuria¶, doubling of SCr or RRT** (HR 0.64, p=0.005)

* Mean; † CV death, non-fatal MI, or non-fatal stroke; ‡ for non-inferiority; § for superiority; ‖ CV death, non-fatal MI, non-fatal stroke or HHF; ¶ severely increased albuminuria.
CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HHF, hospitalization for heart failure; HR, hazard ratio; KF, kidney failure; MACE, major adverse cardiovascular event; PBO, placebo; RRT, renal replacement therapy; SC, subcutaneous; SCr, serum creatinine; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.

1. Cannon CP, et al. *N Engl J Med.* 2020;383:1425–35; 2. Agarwal R, et al. *Eur Heart J.* 2022;43:474–84; 3. Gerstein HC, et al. *Lancet.* 2019;394:121–30; 4. Marso SP, et al. *N Engl J Med.* 2016;375:311–22; 5. Marso SP, et al. *N Engl J Med.* 2016;375:1834–44.

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Highlights from EASD and ESC 2022 (1/2)

CANVAS	• Higher levels of IL-6 is associated with increased risk of adverse CV outcomes in patients with T2D at high CV risk ($p<0.01$); the association is stronger when eGFR <60[1]
CANVAS and CREDENCE	• Canagliflozin reduced the risk of MACE,* HHF, CV death and ESKD, regardless of risk factor control[2] • Canagliflozin demonstrates early benefits (at 6 months' treatment) and was associated with reduced risk of CV and kidney outcomes and all-cause mortality[3]
DECLARE-TIMI 58 and DAPA-CKD	• Dapagliflozin consistently reduced the risk of HHF/CVD and kidney events regardless of baseline eGFR and UACR[4] • Large absolute risk reductions in patients with lower eGFR and higher UACR[4]
EMPA-REG	• Empagliflozin had 30% lower odds of worsening and >50% higher odds of improvement in KDIGO CKD risk groups[5]

* Death from CV causes, non-fatal MI, non-fatal stroke.

CKD, chronic kidney disease; CV, cardiovascular; CVD, CV disease; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; ESKD, end-stage kidney disease; HHF, heart failure hospitalization; IL-6, interleukin 6; KDIGO, Kidney Disease Improving Global Outcomes; MACE, major adverse cardiovascular event; MI, myocardial infarction; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

1. Koshino A, et al. Presented at: EASD, Stockholm. 19–23 Sept 2022. Abstr. 553; 2. Seufert J, et al. Presented at: EASD, Stockholm. 19–23 Sept 2022. Abstr. 551; 3. Ang G, et al. Presented at: ESC 2022, Barcelona. 26–29 Aug 2022. Science box 3; 4. Moura F, et al. Presented at: ESC 2022, Barcelona. 26–29 Aug 2022. Science box 3; 5. Inzucchi SE, et al. Presented at: EASD, Stockholm. 19–23 Sept 2022. Abstr. 88.

Highlights from EASD and ESC 2022 (2/2)

FIDELITY	• Effect of finerenone on composite CV and kidney outcomes not modified by waist:hip ratio[1] • Cardiorenal risk reductions with finerenone is independent of BL HbA_{1c}, HbA_{1c} variability or duration of diabetes[2] • Benefits of finerenone on composite CV and kidney outcomes consistent irrespective of GLP-1 RA use at BL, with greater effects on UACR reduction with GLP-1 RA use[3] • In patients with T2D, CKD is a modifiable CV risk factor, mediated partly by mineralocorticoid receptor overactivation[4]
REWIND	• Dulaglutide associated with 9% reduced index of atherosclerosis in patients with T2D and CVD/high CV risk[5]
SUSTAIN-6 and PIONEER-6	• Effect of semaglutide on MACE* consistent across BL HbA_{1c} ($p>0.05$)[6] • Semaglutide reduces MACE* risk across eGFR and UACR subgroups[7]
VERTIS CV	• Efficacy of ertugliflozin in preventing first HHF generally comparable across the spectrum of pre-trial ejection fraction[8]

* Death from CV causes, non-fatal MI, non-fatal stroke.

BL, baseline; CKD, chronic kidney disease; CV, cardiovascular; CVD, CV disease; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; HHF, heart failure hospitalization; MACE, major adverse cardiovascular event; MI, myocardial infarction; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

1. Billings LK, et al. Presented at: EASD, Stockholm. 19–23 Sept 2022. Abstr. 618; 2. McGill JB, et al. Presented at: EASD, Stockholm. 19–23 Sept 2022. Abstr. 620; 3. Caramori ML, et al. Presented at: EASD, Stockholm. 19–23 Sept 2022. Abstr. 593; 4. Agarwal R, et al. Presented at ESC 2022, Barcelona. 26–29 Aug 2022. Station 4; 5. Ferrannini G, et al. Presented at: ESC 2022, Barcelona. 26–29 Aug 2022. Station 4; 6. Mellbin LG, et al. Presented at EASD, Stockholm. 19–23 Sept 2022. Abstr. 594; 7. Rossing P, et al. Presented at EASD, Stockholm. 19–23 Sept 2022. Abstr. 45; 8. Pandey A, et al. Presented at: ESC 2022, Barcelona. 26–29 Aug 2022. Science box 2.

How can the latest clinical guidelines for treating patients with CKD and T2D be applied in daily practice?

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Latest clinical guidelines for the management of CKD and T2D

	ADA 2022[1]	ESC/EASD 2019[2]	KDIGO 2020[3]
When to screen for CKD	Screen patients with T2D annually	Screen patients with T2D annually	Screen patients with T2D annually
Screening tests	eGFR and UACR	eGFR and UACR	eGFR and UACR
Diagnosis	• eGFR* persistently <60 • UACR ≥30 mg/g in two of three specimens within 3–6 months	• eGFR* <60 and/or persistent proteinuria, sustained >90 days	Any of the following for >3 months: • eGFR* <60 • UACR ≥30 mg/g
	RAAS blocker, plus:		
First-line recommendation	**SGLT2i** when eGFR* is ≥25 and UACR is ≥300 mg/g	**SGLT2i** when eGFR* is 30 to <90	**Metformin and an SGLT2i** when eGFR* is ≥30 (Do not initiate a SGLT2i when eGFR* is <30)
Other recommendations	**Non-steroidal mineralocorticoid receptor antagonist** in those: • Unable to use a SGLT2i • At increased risk of CV events and CKD progression	**GLP-1 RA** if eGFR* >30	**GLP-1 RA** in those: • Not achieving individualized glycaemic targets with metformin + SGLT2i • Unable to use SGLT2i

* mL/min/1.73 m^2.

ADA, American Diabetes Association; CKD, chronic kidney disease; CV, cardiovascular; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; GLP-1 RA, glucagon-like peptide-1 receptor agonist; KDIGO, Kidney Disease Improving Global Outcomes; RAAS, renin–angiotensin–aldosterone system; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatine ratio.

1. American Diabetes Association Professional Practice Committee. *Diabetes Care.* 2022;45(Suppl. 1):S175–84; 2. Cosentino F, et al. *Eur Heart J.* 2020;41:255–323;
3. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. *Kidney Int.* 2020;98(Suppl. 4):S1–115.

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