Evolving Strategies for Kidney Protection in Type 2 Diabetes

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Disclosure

Consultant: Anji; Astra Zeneca; Bayer; Boehringer Ingelheim; Lilly; Novo Nordisk; Valo; Vertex

Grant Recipient: Bluedrop; Boehringer Ingelheim; Lilly

Research Grant: Merck; Roche

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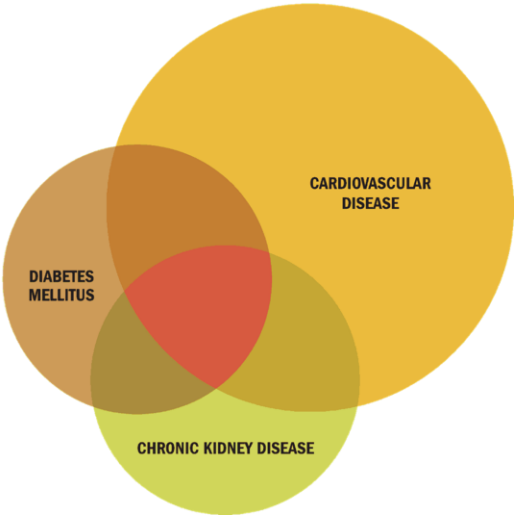
Residual Risk

- Diabetes, cardiovascular and kidney disease frequently coexist
- The presence of more than one condition increases the risk of adverse outcomes
- These risks are not fully addressed via traditional risk reduction strategies



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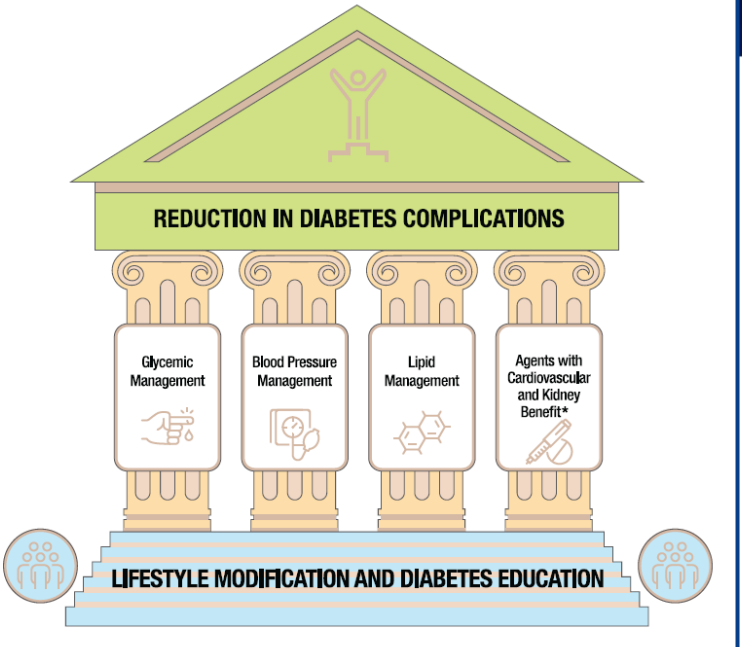

Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications. *Risk reduction interventions to be applied as individually appropriate.

Multifactorial Approach to Risk Reduction

Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes - 2022. Diabetes Care* 2022;45(Suppl. 1):S144-S174

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FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES
HEALTHY LIFESTYLE BEHAVIOURS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)
ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; 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; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.
* 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.
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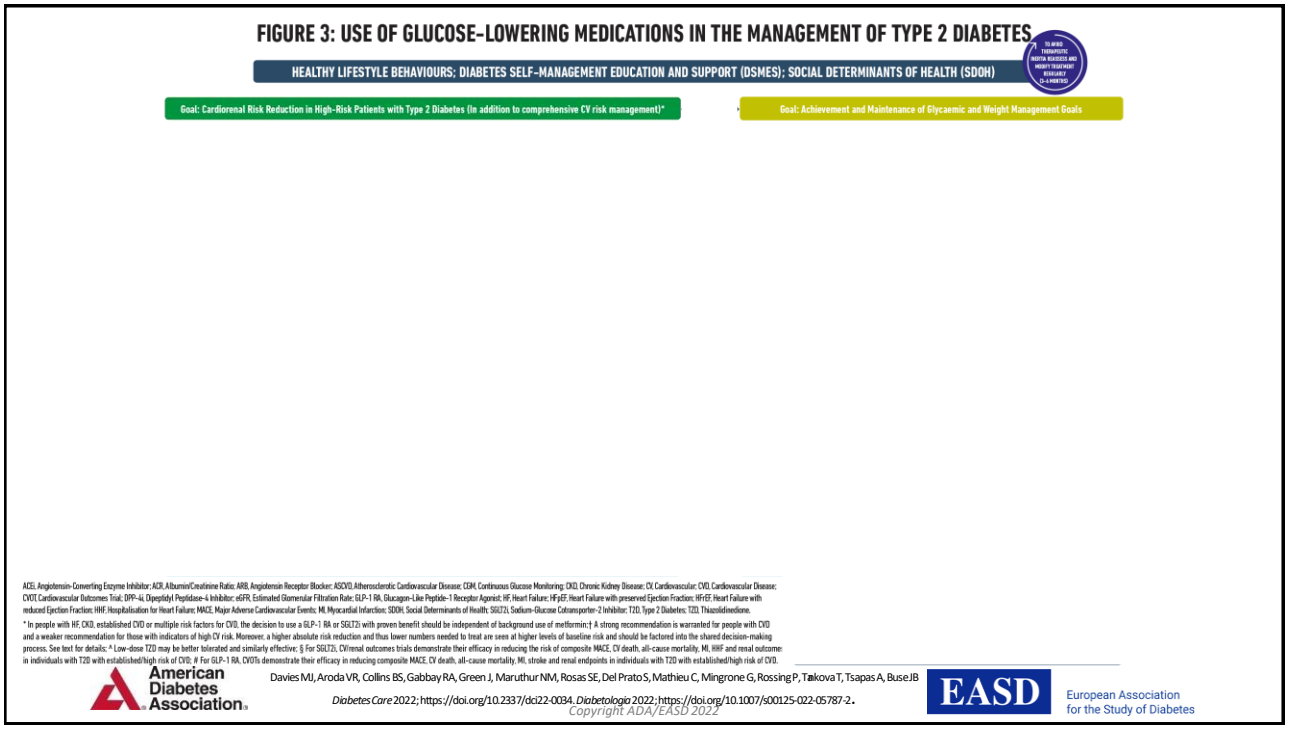
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Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (In addition to comprehensive CV risk management)*
Goal: Achievement and Maintenance of Glycaemic and Weight Management Goals
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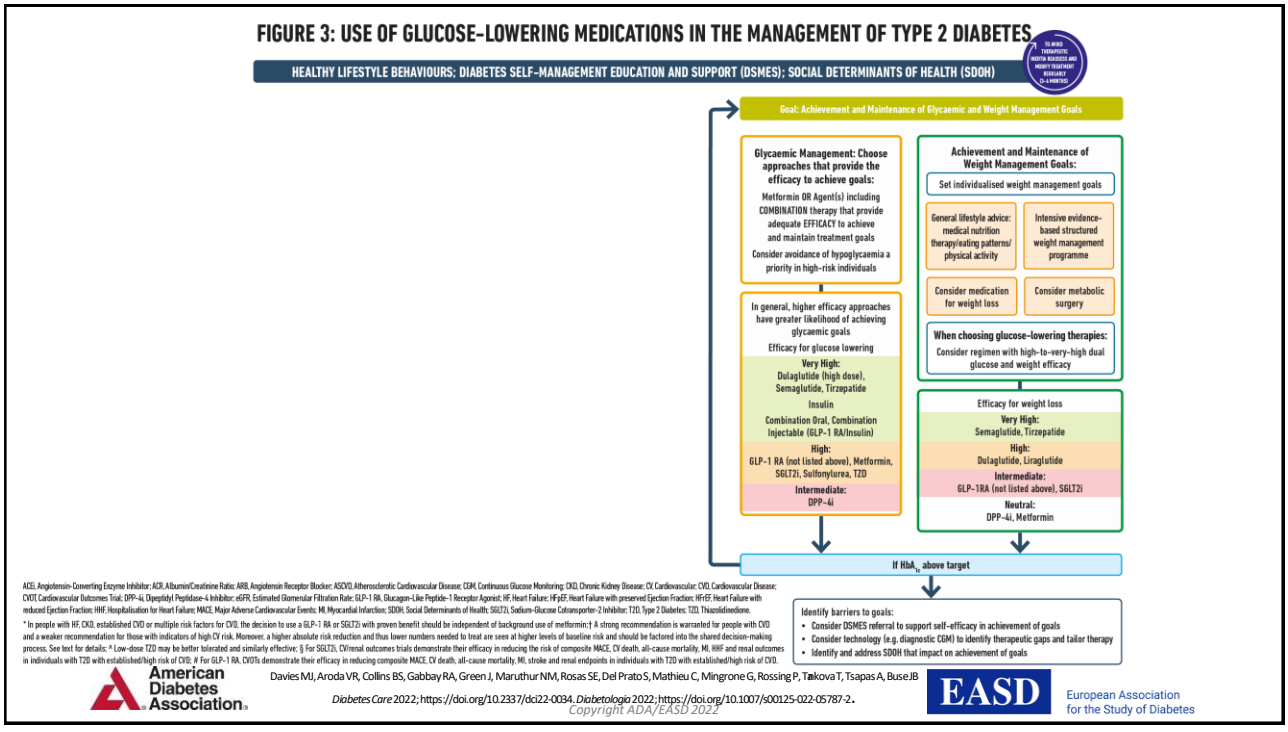
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Goal: Achievement and Maintenance of Glycaemic and Weight Management Goals
Glycaemic Management: Choose approaches that provide the efficacy to achieve goals:
Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals
Consider avoidance of hypoglycaemia a priority in high-risk individuals
In general, higher efficacy approaches have greater likelihood of achieving glycaemic goals
Efficacy for glucose lowering
Very High: Dulaglutide (high dose), Semaglutide, Tirzepatide
Insulin
Combination Oral, Combination Injectable (GLP-1 RA/Insulin)
High: GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD
Intermediate: DPP-4i
Achievement and Maintenance of Weight Management Goals:
Set individualised weight management goals
General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity
Intensive evidence-based structured weight management programme
Consider medication for weight loss
Consider metabolic surgery
When choosing glucose-lowering therapies:
Consider regimen with high-to-very-high dual glucose and weight efficacy
Efficacy for weight loss
Very High: Semaglutide, Tirzepatide
High: Dulaglutide, Liraglutide
Intermediate: GLP-1RA (not listed above), SGLT2i
Neutral: DPP-4i, Metformin
If HbA1c above target
Identify barriers to goals:
Consider DSMES referral to support self-efficacy in achievement of goals
Consider technology (e.g. diagnostic CGM) to identify therapeutic gaps and tailor therapy
Identify and address SDOH that impact on achievement of goals
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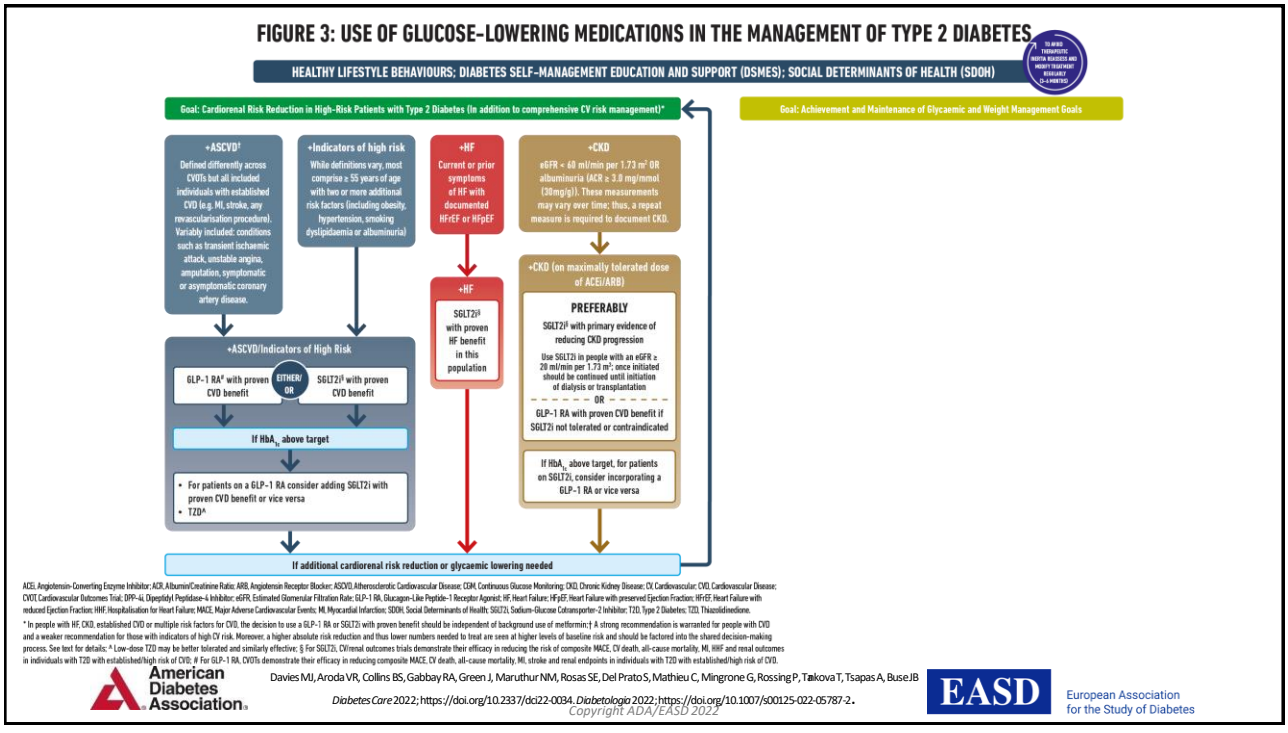
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Goal: Achievement and Maintenance of Glycaemic and Weight Management Goals
+ASCVD†
Defined differently across CVOTs but all included individuals with established CVD (e.g. MI, stroke, any revascularisation procedure). Variably included: conditions such as transient ischaemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.
+Indicators of high risk
While definitions vary, most comprise ≥ 55 years of age with two or more additional risk factors (including obesity, hypertension, smoking dyslipidaemia or albuminuria)
+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF
+CKD
eGFR < 60 ml/min per 1.73 m² OR albuminuria (ACR ≥ 3.0 mg/mmol (30mg/g)). These measurements may vary over time; thus, a repeat measure is required to document CKD.
+ASCVD/Indicators of High Risk
GLP-1 RA^ with proven CVD benefit
EITHER/ OR
SGLT2i§ with proven CVD benefit
If HbA1c above target
For patients on a GLP-1 RA consider adding SGLT2i with proven CVD benefit or vice versa
TZD^
+HF
SGLT2i§ with proven HF benefit in this population
+CKD (on maximally tolerated dose of ACEi/ARB)
PREFERABLY
SGLT2i§ with primary evidence of reducing CKD progression
Use SGLT2i in people with an eGFR ≥ 20 ml/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation
OR
GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated
If HbA1c above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa
If additional cardiorenal risk reduction or glycaemic lowering needed
ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; 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; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.
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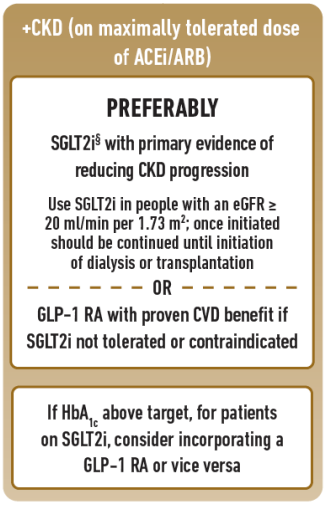
Choosing Glucose-lowering Medication in People with Chronic Kidney Disease



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Recommendations

- In people with CKD and eGFR≥ 20 ml/min per 1.73 m^2, an SGLT2i with proven benefit should be initiated to reduce risks of MACE, HF and kidney outcomes.
- If such treatment is not tolerated or is contraindicated, a GLP-1RA with proven CV outcomes benefit could be considered

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB
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Randomized Controlled Trials of SGLT2i in CKD

	CREDENCE[a-c]	DAPA-CKD[d-f]	EMPA-KIDNEY[g-h]
Population	DIABETIC KIDNEY DISEASE ✓ T2D x Non-DM x Non-Albuminuric	PROTEINURIC CHRONIC KIDNEY DISEASE ✓ T2D ✓ Non-DM x Non-Albuminuric	CHRONIC KIDNEY DISEASE ✓ T2D ✓ Non-DM ✓ Non-Albuminuric
No. of patients	4401[b,c]	4304	~6000
Key inclusion criteria	eGFR ≥30 to <90 and UACR >300 mg/g	eGFR ≥25 to ≤75 and UACR ≥200 mg/g	eGFR ≥20 to <45 or eGFR ≥45 to <90 and UACR ≥200 mg/g
Primary composite outcome	ESKD, doubling of creatinine, or renal/CV death	ESKD, ≥50% sustained eGFR decline, or renal/CV death	ESKD, or ≥40% sustained eGFR decline, or renal/CV death
Study start and stop date (announced or planned)	February 2014 [b] July 2018	February 2017 [d] March 2020	November 2018 [g] ~June 2022
Results	+ [c]	+ [f]	+ [g-i]

- DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; TBD, to be determined; UACR, urinary albumin:creatinine ratio.
a. Jardine MJ, et al. Am J Nephrol. 2017;46:462-472; b. ClinicalTrials.gov. Accessed November 09, 2021. https://clinicaltrials.gov/ct2/show/NCT02065791; c. Perkovic V, et al. N Engl J Med. 2019;380:2295-2306; d. ClinicalTrials.gov. Accessed November 09, 2021. https://clinicaltrials.gov/ct2/show/NCT03036150; e. Heerspink HJL, et al. Nephrol Dial Transplant. 2020;35:274-282; f. Heerspink HJL, et al. N Engl J Med. 2020;383:1436-1446; g. ClinicalTrials.gov. Accessed November 09, 2021. https://clinicaltrials.gov/ct2/show/ NCT03594110; h. Herrington WG, et al. Clin Kidney J. 2018;11:749-761. i. Herrington WG, Preiss D, Haynes R, et al. Clin Kidney J 2018;11:749–761; EMPA-KIDNEY Collaborative Group. N Engl J Med 2022 Nov 4. doi: 10.1056/NEJMoa2204233.

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EMPA-KIDNEY
The study of heart and kidney protection with empagliflozin

EMPA-KIDNEY Collaborative Group

OXFORD POPULATION HEALTH CTSU

MRC Population Health Research Unit

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EMPA-KIDNEY's Double-blind Placebo-controlled Design

Population: Designed to assess the effects of SGLT2 inhibition in a broad range of ~6000 patients with chronic kidney disease (CKD) at risk of progression, incl. ≥1/3rd with diabetes & ≥ 1/3rd without

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EMPA-KIDNEY's Double-blind Placebo-controlled Design

Population: Designed to assess the effects of SGLT2 inhibition in a broad range of ~6000 patients with chronic kidney disease (CKD) at risk of progression, incl. ≥1/3rd with diabetes & ≥ 1/3rd without

Adults with CKD-EPI estimated GFR (eGFR):

20 to <45 mL/min/1.73 m^2; or

45 to <90 mL/min/1.73 m^2 with a urinary ACR of ≥200 mg/g (≥22.6 mg/mmol)

Excluded patients with polycystic kidney disease or transplant

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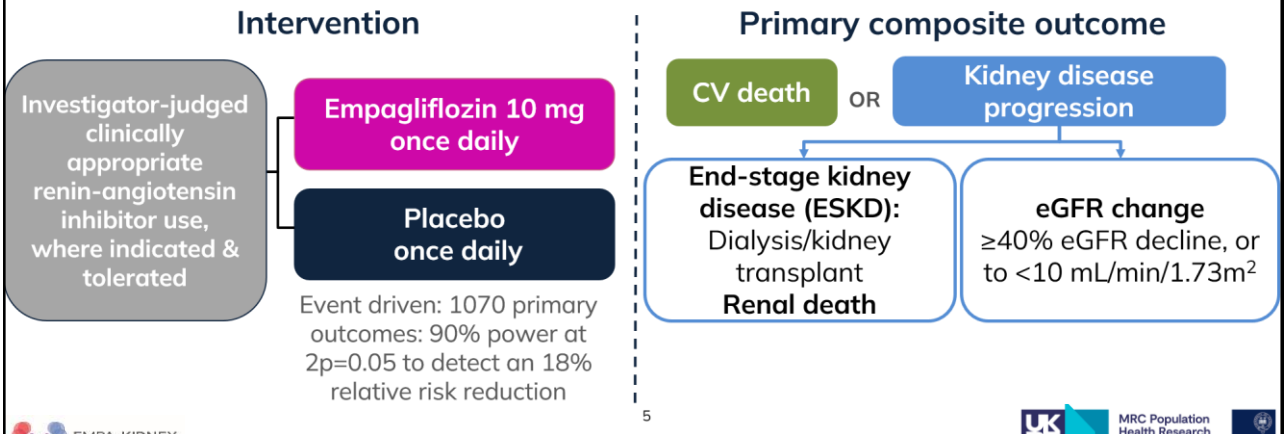

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Baseline Characteristics

	Empagliflozin (n=3304)	Placebo (n=3305)
Mean age at randomization (years)	63.9 ±13.9	63.8 ±13.9
Female	33%	33%
No prior diabetes	54%	54%
Mean estimated GFR (mL/min/1.73m²)	37.4 ± 14.5	37.3 ± 14.4
<30	34%	35%
Median urinary ACR (mg/g)	331 (46-1061)	327 (54-1074)
<300 (A1-A2)	48%	48%
Non-diabetic cause of CKD	69%	69%

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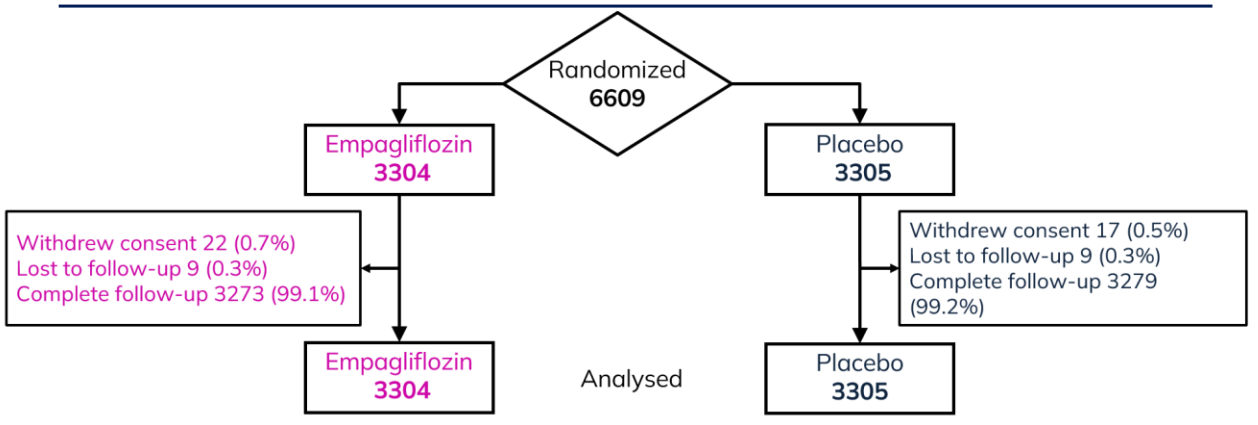
CONSORT



Median follow-up 2.0 (IQR 1.5-2.4) years
Adherence to study treatment at 12 months: 89.6% vs 90.3%
Final follow-up open-label SGLT2 inhibitor use: 18 (0.5%) vs 31 (0.9%)

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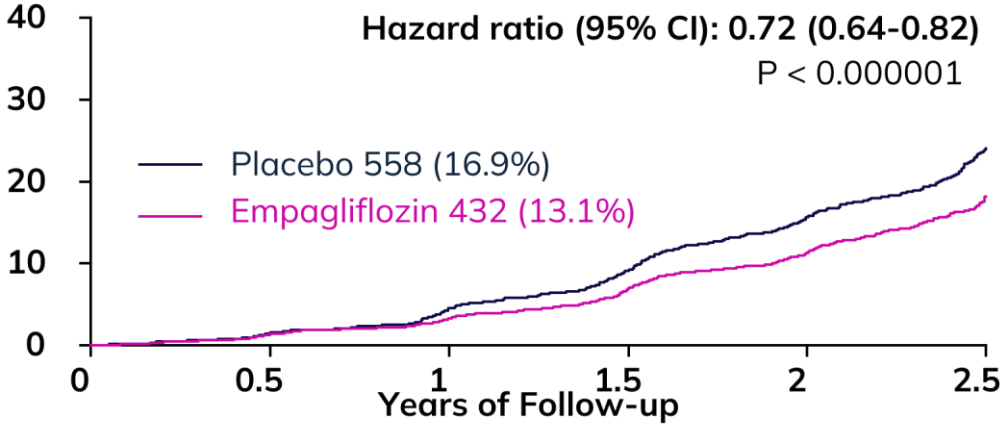
Primary Composite Outcome



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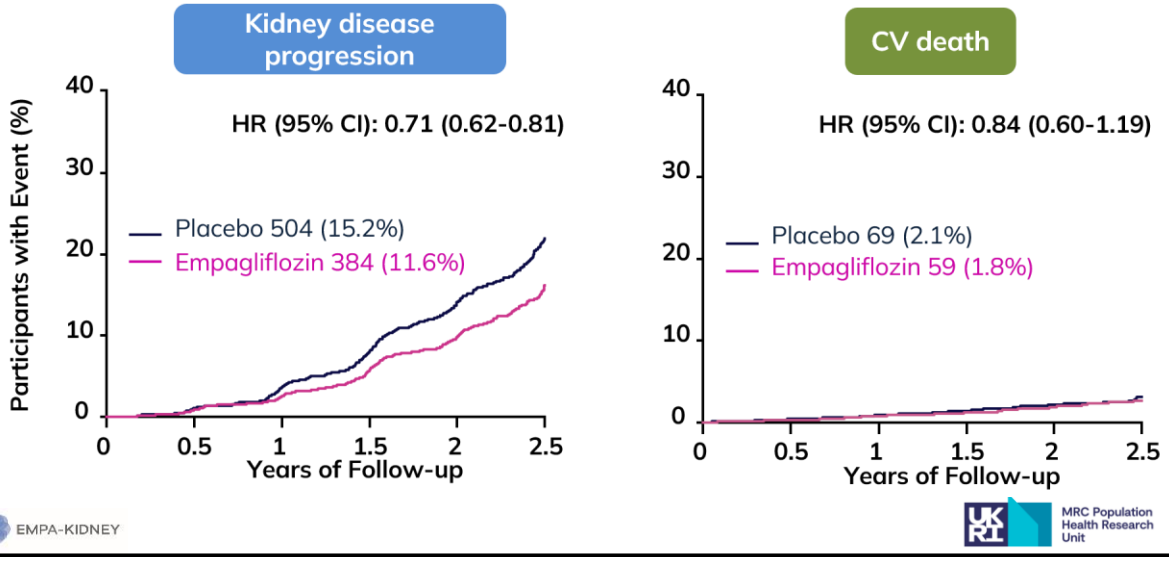
Components of the Primary Outcome



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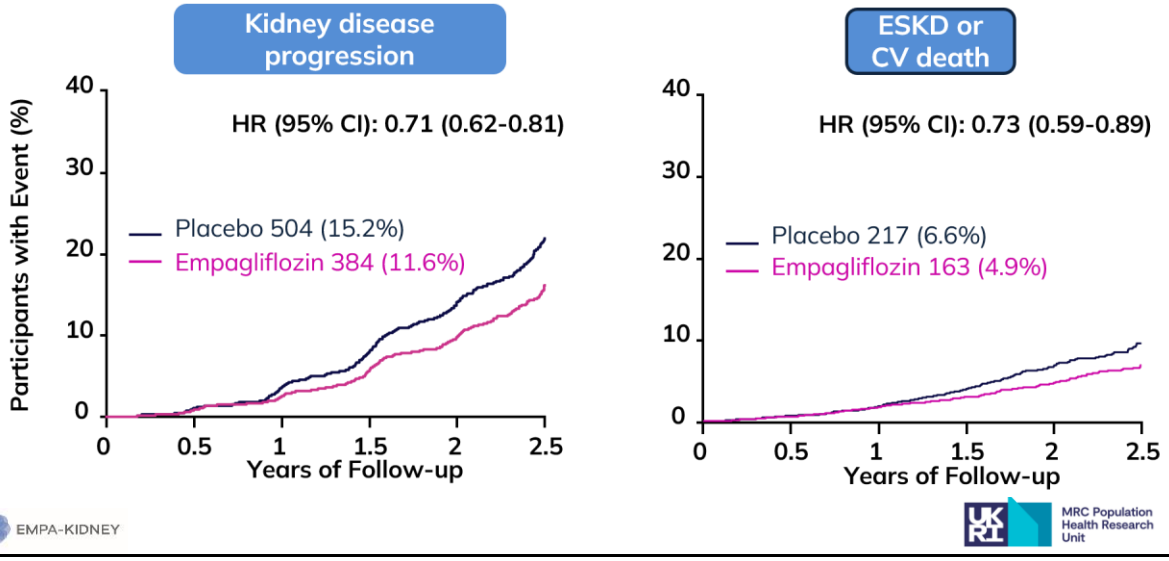

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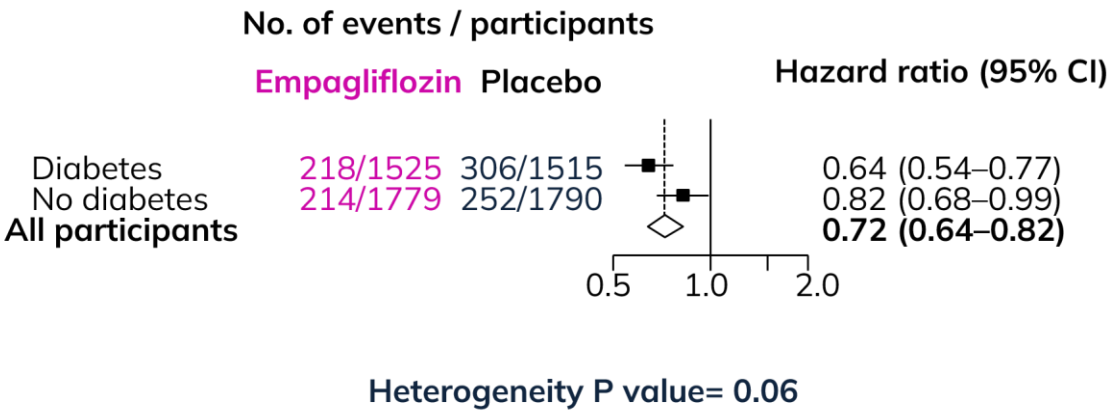
Primary Outcome by Diabetes



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Key Secondary Outcomes

	Empagliflozin (N=3304)	Placebo (N=3305)	Hazard ratio (95% CI)	P value
	n	n		
Hosp. for heart failure or CV death	131	152	0.84 (0.67-1.07)	0.15
Death from any cause†	148	167	0.87 (0.70-1.08)	0.21
	%/year	%/year		
All-cause hospitalization*	24.8	29.2	0.86 (0.78-0.95)	0.003

† 128/315 (41%) of deaths attributed to CV causes

* First & subsequent events (semi-parametric joint frailty model)

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Safety Outcomes

Serious adverse events	Empagliflozin (N=3304)	Placebo (N=3305)	Hazard ratio (95% CI)
Urinary tract infection	52	54	0.94 (0.64-1.37)
Hyperkalemia	92	109	0.83 (0.63-1.09)
Acute kidney injury	107	135	0.78 (0.60-1.00)
Ketoacidosis	6	1	-
Lower limb amputation	28	19	1.43 (0.80-2.57)

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EMPA-KIDNEY Conclusions

- Randomized 6609 patients with CKD with a broad range of causes, and large numbers with low levels of kidney function & albuminuria
- Empagliflozin safely reduced the composite primary outcome of kidney disease progression or CV death by **28% (95% CI 18-36%)**
- Relative benefits were consistent in the patients with & without diabetes, and across the range of eGFR studied (to at least 20 mL/min/1.73m^2)
- Slope analyses: Empagliflozin slowed chronic eGFR decline in all albuminuria subgroups

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Which of the Following Patients Should Be Screened Now for CKD, Including Measurement of Both eGFR and UACR?

A. Anyone with newly diagnosed Type 1 or Type 2 diabetes
B. An individual with newly diagnosed Type 2 diabetes
C. An individual with newly diagnosed Type 1 diabetes
D. An individual diagnosed with Type 1 diabetes two years ago

Screening and Diagnosis: KDIGO

Who and when to screen?

T1D Yearly starting 5 years after diagnosis

T2D Yearly starting at diagnosis

How to screen?

Spot urine ACR

and

eGFR

What to do with a positive result?

Repeat and confirm:
- Evaluate possible temporary or spurious causes
- Consider using cystatin C and creatinine to more precisely estimate GFR
- Only persistent abnormalities define CKD

Initiate evidence-based treatments

What defines CKD diagnosis?

Persistent urine ACR ≥30 mg/g

and/or

Persistent eGFR <60 mL/min/1.73 m^2

and/or

Other evidence of kidney damage

de Boer Ih et al. Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care. 2022 Oct 3:dci220027. doi: 10.2337/dci22-0027. Epub ahead of print. PMID: 36189689.

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73m^2) Description and range	G1	Normal to high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Risk of Chronic Kidney Disease (CKD) Progression, Frequency of Visits, and Referral to Nephrology According to Glomerular Filtration Rate (GFR) and Albuminuria.

Kidney Disease: *Standards of Medical Care in Diabetes - 2022. Diabetes Care* 2022;44(Suppl. 1):S175-S184

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ADA 2024: Chronic Kidney Disease and Risk Management

Chronic Kidney Disease—Treatment

- **As people with CKD and albuminuria are at increased risk for CV events and CKD progression, a nonsteroidal mineralocorticoid receptor antagonist (finerenone) is recommended** to reduce CKD progression and CV events if eGFR is ≥ 25. Potassium levels should be monitored. A

American Diabetes Association Professional Practice Committee. 11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S219-S230. doi:10.2337/dc24-S011

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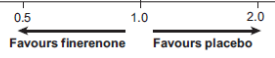
Finerenone Effects in Patients with T2DM and CKD

FIDELITY pooled analysis (FIDELIO + FIGARO)

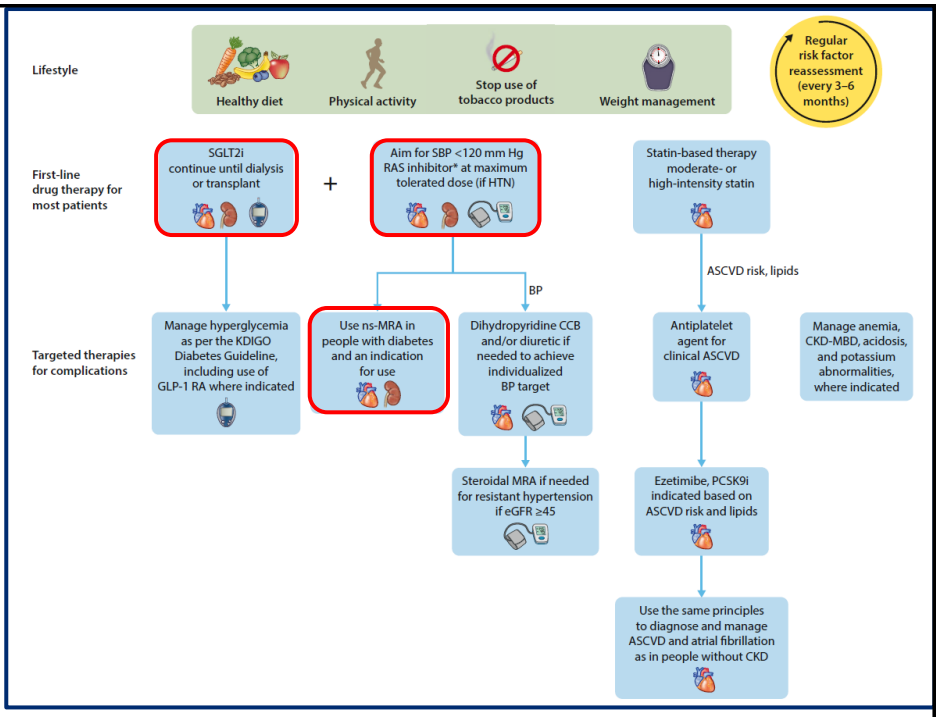
Outcome	Finerenone (n = 6519)		Placebo (n = 6507)		Hazard ratio (95% CI)	*P*-value[a]
	Number of patients with event (%)	Number of patients with event per 100 patient-years	Number of patients with event (%)	Number of patients with event per 100 patient-years		
Composite cardiovascular outcome[b]	825 (12.7)	4.34	939 (14.4)	5.01	0.86 (0.78–0.95)	0.0018
Death from cardiovascular causes	322 (4.9)	1.61	364 (5.6)	1.84	0.88 (0.76–1.02)	0.092
Non-fatal myocardial infarction	173 (2.7)	0.88	189 (2.9)	0.97	0.91 (0.74–1.12)	0.36
Non-fatal stroke	198 (3.0)	1.01	198 (3.0)	1.02	0.99 (0.82–1.21)	0.95
Hospitalization for heart failure	256 (3.9)	1.31	325 (5.0)	1.68	0.78 (0.66–0.92)	0.0030
eGFR ≥57% composite kidney outcome[c]	360 (5.5)	1.96	465 (7.1)	2.55	0.77 (0.67–0.88)	0.0002
Kidney failure	254 (3.9)	1.38	297 (4.6)	1.62	0.84 (0.71–0.99)	0.039
End-stage kidney disease[d]	151 (2.3)	0.76	188 (2.9)	0.96	0.80 (0.64–0.99)	0.040[e]
Sustained decrease in eGFR to <15 mL/min/1.73 m^2	195 (3.0)	1.06	237 (3.6)	1.29	0.81 (0.67–0.98)	0.026[e]
Sustained ≥57% decrease in eGFR from baseline	257 (3.9)	1.40	361 (5.5)	4.03	0.70 (0.60–0.83)	< 0.0001
Renal death	2 (<0.1)	0.01	4 (<0.1)	0.02	0.53 (0.10–2.91)	0.46[e]
eGFR ≥40% composite kidney outcome[f]	854 (13.1)	4.81	995 (15.3)	5.64	0.85 (0.77–0.93)	0.0004
Sustained ≥40% decrease in eGFR from baseline	817 (12.5)	4.60	962 (14.8)	5.45	0.84 (0.76–0.92)	0.0002
Death from any cause	552 (8.5)	2.76	614 (9.4)	3.10	0.89 (0.79–>1.00[g])	0.051[e]
Hospitalization for any cause	2836 (43.5)	19.04	2926 (45.0)	19.91	0.96 (0.91–1.01)	0.087[e]



Agarwal et al. European Heart Journal (2022) 43, 474–484 https://doi.org/10.1093/eurheartj/ehab777

29

KDIGO 2024: RASi and SGLT2i Should Be Used as First-line Therapy in Patients with CKD



Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;105(4S):S117-S314. doi:10.1016/j.kint.2023.10.018

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FLOW Study of Semaglutide in T2D with CKD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators*

N Engl J Med. 2024 May 24. doi: 10.1056/NEJMoa2403347. Online ahead of print. PMID: 38785209

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FLOW Study of Semaglutide in T2D with CKD

Methods

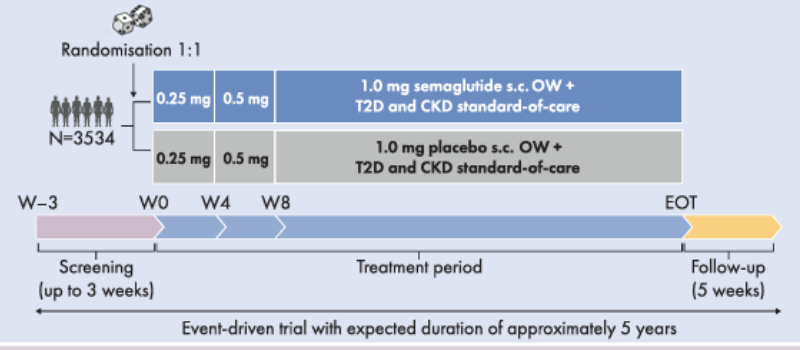
Participants:

- Adults with T2D
- eGFR ≥50 to ≤75 ml/min/1.73 m² and UACR >300 to <5000 mg/g OR
- eGFR ≥25 to <50 ml/min/1.73 m² and UACR >100 to <5000 mg/g

Composite primary endpoint:

Time to first occurrence of:

- Kidney failure (persistent eGFR <15 ml/min/1.73 m² or initiation of CKRT);
- Persistent ≥50% reduction in eGFR; or
- Death from kidney or CV causes



Baseline characteristics

68.2% at very high risk for CKD progression according to KDIGO categorisation, eGFR of 47.0 (15) ml/min/1.73 m²; median UACR of 568 (range: 2–11 852) mg/g

Advanced type 2 diabetes:
Mean age 66.6 years
Mean diabetes duration 17.4 years
Mean HbA_{1c} 7.8%

15.5% receiving SGLT-2is

CKD, chronic kidney disease; CKRT, chronic kidney replacement therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EOT, end of treatment; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; OW, once weekly; s.c., subcutaneous; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio; W, week.

Nephrol Dial Transplant. 2023 Aug 31;38(9):2041-2051. doi: 10.1093/ndt/gfad009. PMID: 36651820; PMCID: PMC10469096.

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FLOW Study of Semaglutide in T2D with CKD

Outcome	Semaglutide (N=1767)	Placebo (N=1766)	Hazard Ratio (95% CI)	Estimated Difference (95% CI)	P Value
Primary outcome: major kidney disease events — no. (%)†	331 (18.7)	410 (23.2)	0.76 (0.66 to 0.88)	—	0.0003
Components of primary outcome — no. (%)					
Persistent ≥50% reduction from baseline in eGFR	165 (9.3)	213 (12.1)	0.73 (0.59 to 0.89)	—	—
Persistent eGFR <15 ml/min/1.73 m²	92 (5.2)	110 (6.2)	0.80 (0.61 to 1.06)	—	—
Initiation of kidney-replacement therapy	87 (4.9)	100 (5.7)	0.84 (0.63 to 1.12)	—	—
Death from kidney-related causes	5 (0.3)	5 (0.3)	0.97 (0.27 to 3.49)	—	—
Death from cardiovascular causes	123 (7.0)	169 (9.6)	0.71 (0.56 to 0.89)	—	—
Composite of kidney-specific components of the primary outcome	218 (12.3)	260 (14.7)	0.79 (0.66 to 0.94)	—	—
Confirmatory secondary outcomes					
Mean annual rate of change in eGFR — ml/min/1.73 m²	−2.19	−3.36	—	1.16 (0.86 to 1.47)	<0.001
Major cardiovascular events — no. (%)	212 (12.0)	254 (14.4)	0.82 (0.68 to 0.98)	—	0.029
Death from cardiovascular causes	123 (7.0)	169 (9.6)	0.71 (0.56 to 0.89)	—	—
Nonfatal myocardial infarction	52 (2.9)	64 (3.6)	0.80 (0.55 to 1.15)	—	—
Nonfatal stroke	63 (3.6)	51 (2.9)	1.22 (0.84 to 1.77)	—	—
Death from any cause — no. (%)	227 (12.8)	279 (15.8)	0.80 (0.67 to 0.95)	—	0.01

median participant follow-up was 3.4 years

N Engl J Med. 2024 May 24. doi: 10.1056/NEJMoa2403347. Online ahead of print. PMID: 38785209

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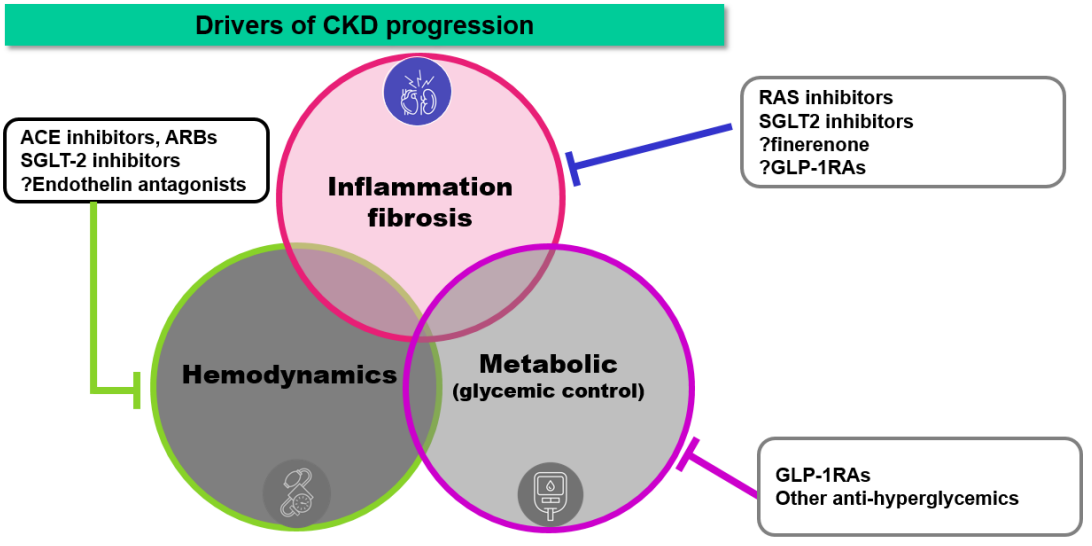
Kidney-Protective Mechanisms in Diabetes



From Cherney, D AJKD 2021

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Implementation

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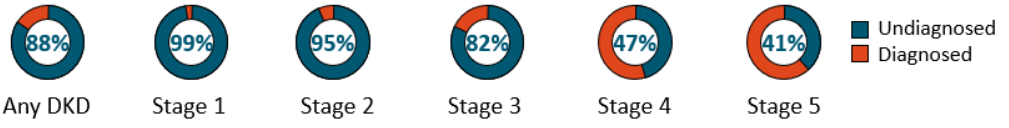
CKD Is Poorly Recognized in Patients with T2D

- 15-mo retrospective review of 5036 patients with T2D and DKD from 2011-2012 demonstrated following rates of diagnosis:



- Retrospective observational study of 123,169 patients with lab-positive T2D and DKD from 2010-2017 showed the following rate of undiagnosed patients with DKD:

Kern. Health Serv Res. 2006;41:56. Szczech. PLoS One. 2014;9:e110535. Bakris. 2019 National Kidney Foundation Spring Clinical Meetings.

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Guidelines and Gaps in Care for CKD in Diabetes

Recommendations	Indication	Implementation Rate	Implications
UACR testing	At least annually for most	**10-40%**	Underdiagnosis and Treatment of CKD
ACE or ARB	Albuminuria +/- HTN	**25-40%**	CKD progression, increased CV risk
SGLT2i	Most with CKD, particularly with albuminuria	**13%**	CKD progression, increased CV risk
Nonsteroidal MRA	CKD with elevated UACR	**unknown**	CKD progression, increased CV risk

Adapted from Tuttle KR et al. CJASN 2022; 17(7):1092-1103.

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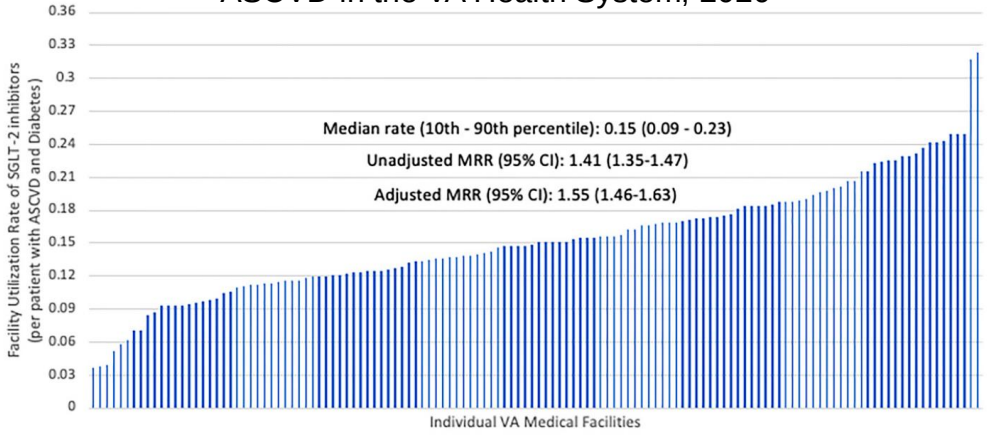
Clinical Inertia: Not Just an Access Issue

Utilization Rates of SGLT2i in Patients with T2DM and ASCVD in the VA Health System, 2020



Mahtta D et al. Diabetes Care. 2022 Feb 1;45(2):372-380. doi: 10.2337/dc21-1815. PMID: 35015080; PMCID: PMC8914426.

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What Is the Potential to Improve Outcomes?

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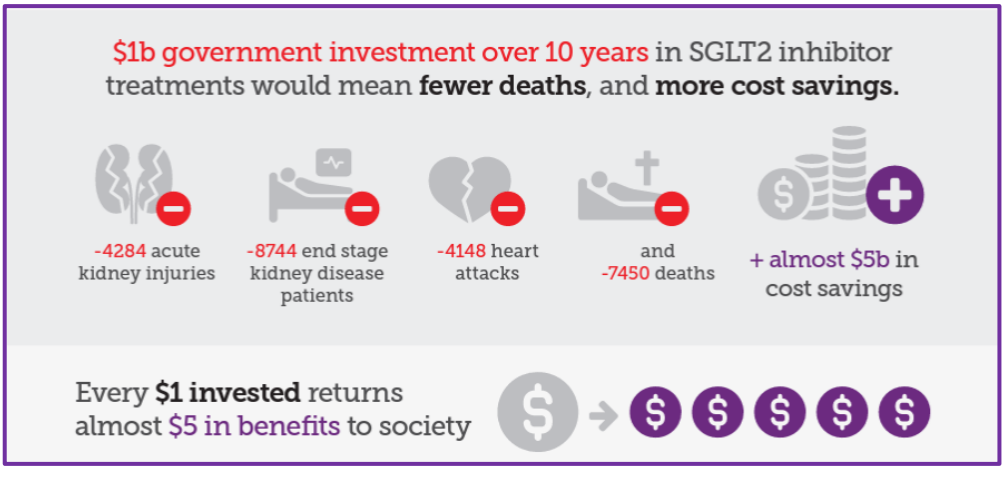
SGLT2i: Estimated Impact on Health

Assessed the impact of using SGLT2 inhibitors in Australian patients with T2DM, CKD and/or CVD



https://www.georgeinstitute.org/the-wider-benefits-of-sglt2-inhibitors

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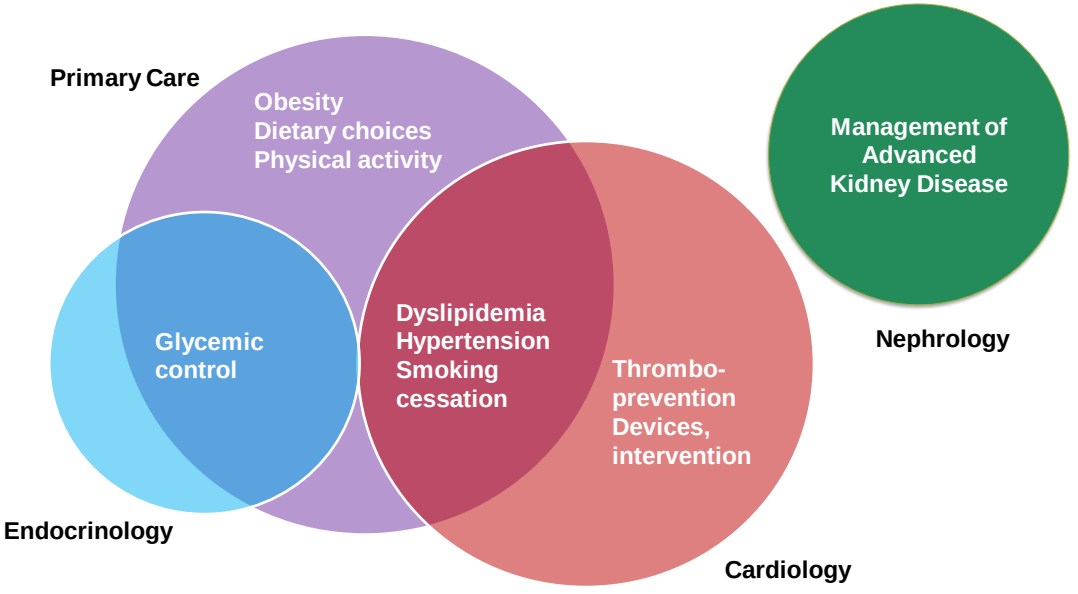
Traditional Care Silos in T2DM



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The Result

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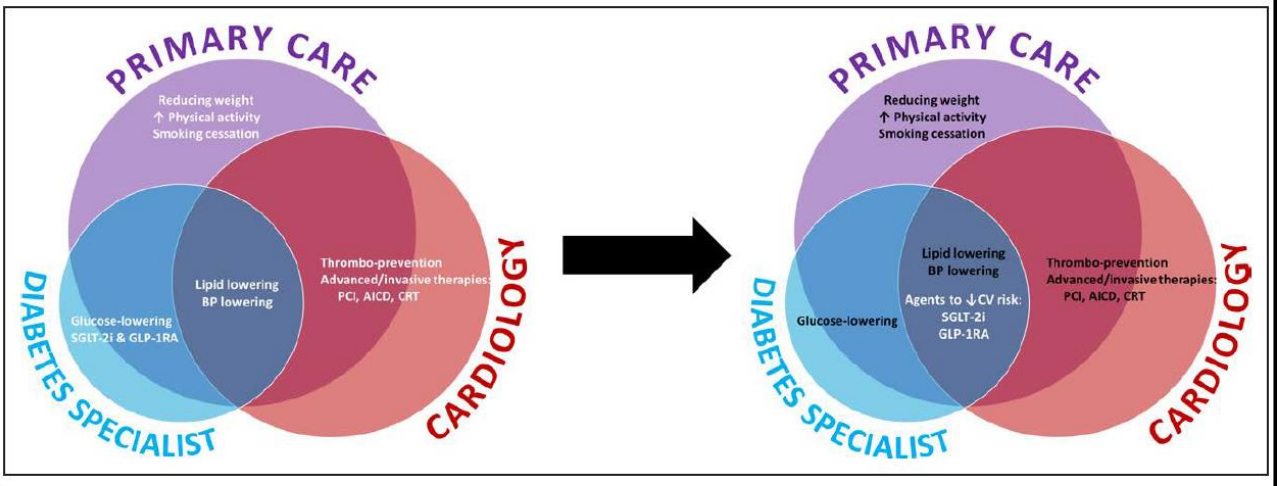
A New Paradigm Is Needed

Reframing cardio-renal risk reduction



Nelson et al. Circulation. 2021;144:74–84. DOI: 10.1161/CIRCULATIONAHA.121.053766

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Case Discussion

This 66-year-old woman with T2DM, HL and HTN has evidence of chronic kidney disease (eGFR 55, UACr 80). Her HbA1c is 7.3% on metformin and a DPP4i. She is on statin therapy and BP is controlled on a regimen which includes an ACE inhibitor.

What Would You Recommend at This Time?

A. No change in treatment
B. Sulfonylurea
C. SGLT2 inhibitor
D. Pioglitazone

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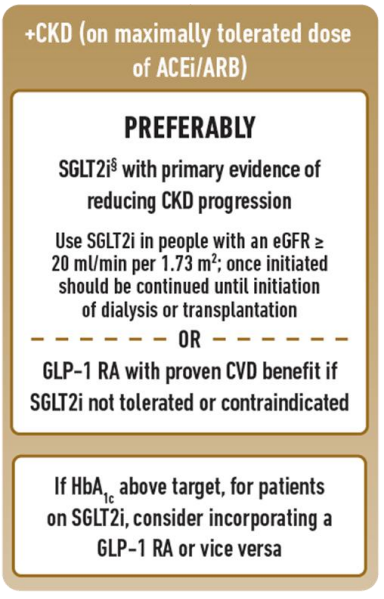
ADA 2024 Standards of Care

Add beneficial agent in high risk patients independent of HbA1c target and metformin use



American Diabetes Association Professional Practice Committee. 11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S219-S230. doi:10.2337/dc24-S011

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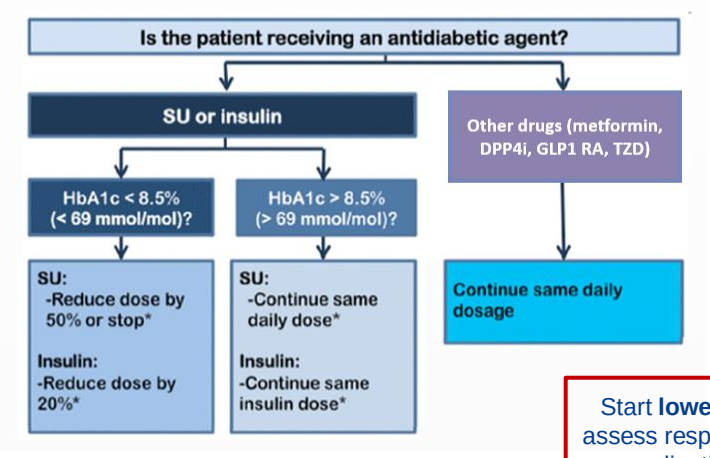
SGLT-2i: Starting with Other Diabetes Medications



Start **lowest dose** SGLT2i and assess response, make additional medication adjustments as necessary

*Avoid insulin withdrawal to minimize the risk of euglycemic diabetic ketoacidosis

Duke Clinical Research Institute

Adapted from Gomez-Peralta F et al. Diabetes Ther. 2017;8:953-62.

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Case Discussion

The same patient has been started on an SGLT2 inhibitor. At her follow up appointment, her BP is 108/70 mmHg and she notes occasional lightheadedness when rising from a seated position.

CONTINUING EDUCATION COMPANY

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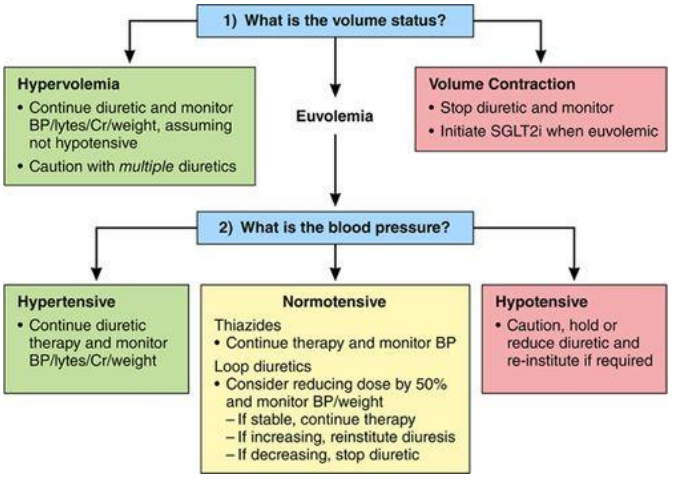
What Would You Recommend at This Time?

A. Increased intake of fluids
B. Discontinue HCTZ
C. Decrease dose of lisinopril
D. Discontinue SGLT2 inhibitor

SGLT-2i: If Patient on Diuretic Therapy



Cherney DZI and Udell JA. Circulation. 2016;134:1915-17.

Case Discussion

The 66-year-old woman with T2DM, HL, HTN and CKD is on a medication regimen which includes an SGLT2i. Her lightheadedness has resolved with discontinuation of HCTZ, but she now has a GU infection. Her last prior GU infection was about one year prior to initiation of the SGLT2i.

What Would You Recommend at This Time?

A. Fluconazole 150 mg single oral dose
B. Fluconazole 150 mg weekly for six months
C. Discontinue SGLT2 inhibitor
D. Change from SGLT2i to GLP-1 RA therapy

Genital Mycotic Infections (GMIs) with SGLT2 Inhibitors (Pooled 6 Month Data)

Adapted from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf, www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm262996.pdf, www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM378076.pdf and https://www.fda.gov/Drugs/DrugSafety/ucm617360.htm. Accessed 21st July, 2015; Nyirjesy P et al. Curr Med Res Opin. 2014;30(6):1109-19; Kim G et al. American Diabetes Association 73rd Scientific Sessions. 21st-25th June 2013. Chicago, IL.

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Case Discussion

How else might care be optimized for this patient with T2DM and chronic kidney disease?

Medications

Metformin 500 mg twice daily

SGLT2i

Atorvastatin 20 mg daily

Lisinopril 20 mg daily

Allergy: Aspirin

Clinical Data

Hemoglobin A_{1c} 7.1%

(4.0%-5.6%) (56 mmol/mol [20-38 mmol/mol])

Estimated GFR 53 mL/min per 1.73 m^2

(>60 mL/min per 1.73 m^2)

Total Cholesterol 167 mg/dL

Triglycerides 117 mg/dL

HDL Cholesterol 46 mg/dL

LDL Cholesterol 98 mg/dL

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Cardiovascular Disease and Risk Management

Statin Treatment—Secondary Prevention

- For people with diabetes aged 40-75 at higher CV risk, it is recommended to use high-intensity statin therapy to reduce LDL cholesterol by at least 50% from baseline and target an LDL cholesterol goal of <70 mg/dL. A

American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S179-S218. doi:10.2337/dc24-S010

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Summary

- Individuals with T2DM and CKD have cardiorenal risks that are not fully addressed with traditional care strategies
- Newer medications, including SGLT2i, finerenone and GLP-1RA, can significantly improve outcomes when added to standard care and may provide an additive benefit when used in combination
- Stay tuned to see how the guidelines include recent evidence of benefit to GLP-1RA therapy in CKD

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Summary

- Primary care has the potential to meaningfully improve the health of large populations of people with CKD
- Strategies to improve the early identification and treatment of patients with CKD are needed