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Diabetes Meds: Cardiovascular and Kidney Impact

Modified October 2025

-- See footnote b for additional kidney protection strategies --

Medication	Pertinent Studies[a]
GLP-1 Agonists with Cardiovascular and Kidney Benefit (also see Neutral Effects section)	
Dulaglutide (MACE,[c,d] kidney benefit)	REWIND [Evidence Level A-1]; **patients had CV disease or CV risk**.[12] Over ~5.4 years, reduced a composite of: • nonfatal MI, nonfatal stroke, and death from CV or unknown causes [NNT = 71]. Only nonfatal stroke reduction was significant. • new macroalbuminuria, 30% decrease in eGFR, or dialysis/transplant [NNT= 40], **driven by prevention of macroalbuminuria** (exploratory analysis).[35]
Liraglutide (MACE,[c,d] kidney benefit)	LEADER [Evidence Level A-1]; **patients had CV disease or high CV risk**.[14] Over ~4 years, reduced: • death from CV causes, NNT = 77; death of any cause, NNT = 71; composite of CV death, nonfatal MI, or nonfatal stroke, NNT = 53. • new macroalbuminuria or doubling of SCr plus eGFR ≤45 mL/min/1.73m^2, need for dialysis/transplant, or death from kidney causes (NNT =67), **driven by prevention of macroalbuminuria** (NNT = 83).
Semaglutide injection (MACE,[c] kidney benefit[e] [including CKD])	SUSTAIN-6 [Evidence Level A-1]; **patients had CV disease, CV risk, or CKD**.[16] Over ~2 years, reduced a composite of: • CV death, nonfatal MI, or nonfatal stroke (NNT = 44). Only nonfatal stroke reduction was significant. • new onset macroalbuminuria or doubling of SCr plus eGFR ≤45 mL/min/1.73m^2, need for dialysis/transplant, or death from kidney causes (NNT = 44), **driven by prevention of macroalbuminuria**. FLOW [Evidence Level A-1]; patients had **CKD** with albuminuria ≥100 mg/g.[2] Over ~3 years, reduced a composite of: • kidney failure, ≥50% reduction in eGFR, kidney or CV death (NNT = 20; NNT = 42 for kidney-specific outcomes). STRIDE [Evidence Level A-1]; patients had symptomatic **PAD**.[44] Over one year, increased: • walking distance by 13% vs placebo. SELECT [Evidence Level A-1]; **patients had obesity and CV disease without DM**.[45] Over ~3 years, decreased: • a composite of CV death, nonfatal MI, or nonfatal stroke (NNT = 67).
Semaglutide, oral (MACE benefit)	SOUL [Evidence Level A-1]; **patients had CV disease and/or chronic kidney disease**.[17] Over ~4 years, reduced: • a composite of CV death, nonfatal MI, or nonfatal stroke (NNT = 56) PIONEER [Evidence Level A-1]; **most patients had CV disease**; others had CKD, HF, or high CV risk.[47] Over 16 months, reduced: • MACE (NNT = 100).
GIP/GLP-1 Receptor Agonist	
Tirzepatide (HF benefit)	SUMMIT [Evidence Level A-1]; **patients had HFpEF and obesity**, and about half had DM.[43] Over ~2 years, reduced: • a composite of CV death or worsening HF (NNT ~ 15 [patients with DM], or NNT ~ 23 [patients without DM]).
SGLT2 Inhibitors with Kidney and/or Cardiovascular Benefit (also see Neutral Effects section)	
Canagliflozin (MACE,[c,d] HF, kidney benefit[e,f])	CANVAS and CREDENCE [Evidence Level A-1]; **patients had very high CV risk**.[21,22,32] Reduced a composite of: • CV death, nonfatal MI, or nonfatal stroke (26.9 vs 31.5/1,000 patient-years; individual endpoints were not significantly improved).[21] • ESKD, SCr doubling, or death from kidney causes, driven by doubling of SCr (NNT = 31 over ~2.6 years in CKD patients on RAAS blocker).[22,32]
Dapagliflozin (HF,[g,h] kidney benefit[e])	DECLARE-TIMI 58 trial [Evidence Level A-1]; **patients had CV disease or high CV risk**. • Reduced HF hospitalization[23] **Neutral** effect on CV death, MI, or ischemic stroke (composite).[23] Secondary analysis shows kidney benefit.[33] Dapa-HF [Evidence Level A-1]; patients were on standard therapy for class II-IV **HF*r*EF**.[25] Over ~1.5 years: • reduced a composite of HF hospitalization/need for intravenous HF therapy or CV death (NNT ~18 [patients with DM] or NNT ~22 [patients without DM]. DELIVER trial [Evidence Level A-1]; patients were on standard therapy for **HF*p*EF**. Over ~2.3 years, reduced: • a composite of HF urgent visit/hospitalization or CV death (NNT = 33), driven by reduction in worsening HF (NNT = 37) over ~2.3 years. Results were similar for patients with and without DM.[41]

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Medication	Pertinent Studies[b]
SGLT2 Inhibitors with Kidney and/or Cardiovascular Benefit, continued	
Dapagliflozin (HF,[g,h] kidney benefit[e])	Dapa-CKD trial [Evidence Level A-1]; patients had CKD and were on standard kidney protective therapy.[24] Over ~2.4 years, reduced: • a composite of sustained eGFR decline of at least 50%, progression to ESKD, or death from kidney or CV causes (NNT ~19 [patients with DM], NNT ~25 [patients without DM] over ~2.4 years). Of the individual endpoints, only eGFR decline and delayed progression to ESKD were significant.[24]
Empagliflozin (MACE,[c,d] HF,[g,h] kidney benefit[e,f])	EMPA-REG OUTCOME [Evidence Level A-1; **patients had CV disease**.[26] Over ~3 years, reduced a composite of: • CV death, nonfatal MI, and nonfatal stroke (NNT = 62). EMPA-KIDNEY [Evidence Level A-1; patients had **CKD**, and about half had DM].[40] Over ~2 years, reduced: • a composite of progression of kidney disease and risk of CV death (NNT = 26). Effective with eGFR as low as 20 mL/min/1.73 m^2. EMPEROR-Reduced trial [Evidence Level A-1]; patients were receiving standard therapy for **class II-IV HF*r*EF**.[27] Over ~16 months, reduced: • a composite of HF hospitalization or CV death (NNT ~14 [patients with DM] or NNT ~26 [patients without DM]).[27] Composite endpoint driven by HF hospitalizations.[27] EMPEROR-Preserved trial [Evidence Level A-1]; patients were on standard therapy for **class II-IV HF*p*EF**.[28] Over ~2 years, reduced: • a composite of CV death or HF hospitalization (NNT ~29 [patients with DM], or NNT ~33 [patients without DM]), driven by reduction in HF-related hospitalizations (NNT ~31).[28]
Sotagliflozin (HF benefit[g])	SOLOIST-WHF trial [Evidence Level A-1]; added to usual therapy **post-HF hospitalization** (few patients had HF*p*EF).[42] Over ~9 months, reduced: • a composite of CV death, HF hospitalization, urgent visit for HF (NNT = 6), driven by reduction in HF hospitalization/urgent visit.[42] SCORED [Evidence Level A-1]; **patients had CKD and high CV risk**).[36] Over ~16 months, reduced: • a composite of CV death and HF hospitalization/urgent visit (NNT ~41), driven by reduction in HF hospitalization/urgent visit.
Medications that POTENTIALLY Improve Outcomes	
Metformin	• Possibly reduces CV mortality (UKPDS subanalysis; pooled data [Evidence Level B-2]).[4,5] • Possibly reduces risk of progression to ESKD [Evidence Level B-3].[34,46]
Pioglitazone	IRIS trial [Evidence Level A-1]; patients with **prediabetes** and TIA or stroke history with mild impairment. Over ~5 years may reduce: • the risk of a future stroke or MI (NNT = 36 over ~5 years).[29] PROactive trial [Evidence Level A-1]: patients with **macrovascular disease** (e.g., MI, stroke, PCI). Over~3 years may reduce: • a composite secondary endpoint of all-cause mortality, non-fatal MI, and stroke (NNT = 50).[30] • risk of recurrent fatal or nonfatal stroke (NNT = 22) in patients with previous stroke (subgroup analysis).[31] A meta-analysis suggests reduced albuminuria [Evidence Level B-2].[37]
Medications with NEUTRAL Effects	
• **Acarbose**: neutral CV effect (ACE trial [Evidence Level A-1]; patients had impaired glucose tolerance and coronary heart disease).[3] • **DPP-4 inhibitors: INCREASED HF admission**: with recent ACS (**alogliptin**, NNH = 167) or with high CV risk (**saxagliptin**, NNH = 143)(EXAMINE; SAVOR-TIMI 53 [Evidence Level A-1]);[6-8] Neutral CV effect: **linagliptin**, **sitagliptin** (CARMELINA; CAROLINA [Evidence Level A-1].[9-11] • **Insulin**: neutral CV effect (insulin **glargine** use over ~6 years (ORIGIN [Evidence Level A-1])[18] • **GLP-1 agonists** with neutral effects (also see Benefit Section, above): **exenatide weekly** (note reduced death from any cause [NNT = 341]), **oral semaglutide** (kidney).[13,17,36] • **Nateglinide**: neutral CV effect (NAVIGATOR trial [Evidence Level A-1]. Patients had **impaired glucose tolerance** and high CV risk) • **SGLT2 inhibitors** (also see Benefits sections, above): **bexagliflozin** (neutral CV effect);[15] **ertugliflozin** (neutral CV and kidney effect;[19] note that a secondary endpoint suggests ertugliflozin may reduce the risk of HF-related hospitalizations [NNT = 29].[20]) • **Sulfonylureas**: neutral CV effect (glimepiride; CAROLINA [Evidence Level A-1]) and kidney effect.[1,11]	

Diabetes Meds: Cardiovascular and Kidney Impact

Modified October 2025

Footnotes

a. Patients in studies had type 2 diabetes and were receiving standard treatment, unless otherwise noted.
b. Other strategies to reduce kidney risk:

- Optimize blood pressure and glycemic control.[38,39]
- Add an ACEI or ARB for patients with hypertension and albumin/creatinine ratio ≥30 mg/g, and especially if albumin/creatinine ratio ≥300 mg/g or eGFR <60 mL/min/1.73 m^2.[38] (Canada: Patients with CKD with hypertension or albuminuria.[39])
- For patients with CKD at increased risk for CV events or kidney disease progression, consider adding **finerenone** to optimized ACEI or ARB if eGFR ≥25 mL/min/1.73 m^2 and serum potassium ≤4.8 mEq (mmol)/L.[38]
  - Spironolactone and eplerenone reduce albuminuria.[38]
  - Safety and additive efficacy of finerenone, spironolactone, or eplerenone combined with an SGLT2 inhibitor or GLP-1 agonist are unknown.

c. FDA-approved MACE benefits.
d. Health Canada-approved MACE benefits.
e. FDA-approved kidney benefits.
f. Health Canada-approved kidney benefit.
g. FDA-approved HF benefit.
h. Health Canada-approved HF benefit.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; DM = diabetes mellitus; DPP-4 inhibitor = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; ESKD = end-stage kidney disease; HF = heart failure; MACE = major adverse cardiovascular events; MI = myocardial infarction; NNH = number needed to harm; NNT = number needed to treat; PAD = peripheral artery disease; RAAS = renin-angiotensin-aldosterone system; SCr = serum creatinine; SGLT2 = sodium-glucose co-transporter 2.

Levels of Evidence

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*	1.High-quality randomized controlled trial (RCT) 2.Systematic review (SR)/Meta-analysis of RCTs with consistent findings 3.All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*	1.Lower-quality RCT 2.SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3.Cohort study 4.Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

*Outcomes that matter to patients (e.g., morbidity, mortality, symptom improvement, quality of life).
[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician 2004;69:548-56. https://www.aafp.org/pubs/afp/issues/2004/0201/p548.html.]

Diabetes Meds: Cardiovascular and Kidney Impact

Modified October 2025

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