

Stepwise Treatment of Type 2 Diabetes

Modified February 2026

Also see our resources, [Drugs for Type 2 Diabetes](#) and [Diabetes Medications: Cardiovascular and Kidney impact](#).

---Information pertains to **ADULTS** unless otherwise specified.---

Interactive Note: Additional information is available when hovering over text containing the magnify icon.  Best viewed in Adobe Acrobat.

STEP 1

Diagnosis of type 2 diabetes in nonpregnant patients

(in adults, A1C $\geq 6.5\%$ is diagnostic; A1C 5.7% to 6.4% indicates [prediabetes](#).^{1,5}):

Lifestyle changes to improve glycemia 
AND

Pharmacotherapy based on hyperglycemia and comorbidities.²
Consider combination therapy if A1C is $>1.5\%$ to 2% above goal.²

Is hyperglycemia severe or symptomatic? 

YES

Include insulin, at least initially. In pediatrics, insulin is the initial treatment of choice if A1C $\geq 8.5\%$ or if ketosis is present.⁷

Does the patient have heart failure history, chronic kidney disease, CV disease, or high CV risk? 

YES

Give priority to:

- **CV disease or high CV risk:** evidence-based GLP-1 agonist (dulaglutide, liraglutide, semaglutide) or SGLT2 inhibitor (canagliflozin, empagliflozin)^{2,12,13}
- **Heart failure history:** evidence-based SGLT2 inhibitor (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)²
- **Chronic kidney disease:** evidence-based SGLT2 inhibitor (canagliflozin, dapagliflozin, empagliflozin)²

THEN

Other comorbidities

Weight management focus:^{2,12}

- highest efficacy: semaglutide, tirzepatide
- high efficacy: dulaglutide, liraglutide
- moderate efficacy: exenatide, SGLT2 inhibitors
- weight neutral: metformin, DPP-4 inhibitor

Glycemic efficacy focus:²

- highest efficacy: dulaglutide (high dose), semaglutide, tirzepatide, combination therapy
- high efficacy: exenatide, liraglutide, metformin, pioglitazone, SGLT2, sulfonylurea
- moderate efficacy: DPP-4 inhibitor. Not first-line.

Metabolic liver disease:²

- See our resource, [Comparison of Medications for Metabolic Dysfunction-Associated Steatotic Liver Disease](#)

Pediatrics:

- Metformin is the first-line oral agent.^{7,10} Add to insulin if no acidosis or ketosis.¹⁰

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STEP 2

Assess and adjust treatment every three to six months (three months in pediatrics) based on efficacy, side effects, and new comorbidities.^{2,10}

- Goal: A1C (A1C $\leq$ 7% for many adult patients; A1C $\leq$ 6.5% for pediatrics).^{4,6,10} Individualize.

A **higher goal** may be appropriate for some patients.⁴ 

A **lower goal**, if it can be achieved without adverse effects (e.g., problematic hypoglycemia), may be appropriate for some patients.⁴ 

- » A tool for individualizing your patient's A1C target is available from Diabetes Canada at <https://www.diabetes.ca/managing-my-diabetes/tools--resources/individualizing-your-patient%E2%80%99s-a1c-target>.

De-escalate medications as appropriate.^{2,4}



- Give preference to deprescribing agents that cause hypoglycemia or that do not improve outcomes.²
- Attempt to transition youth to metformin over two to six weeks (once labs have stabilized) by decreasing insulin each time metformin is increased.⁷
- Discontinue DPP-4 inhibitors if a GLP-1 agonist  or intensive insulin regimen is started.⁴
- Discontinue sulfonylurea or meglitinide when intensive insulin regimen is started.⁴ Also  assess need for dose reduction as the patient ages and circumstances change.

Add medications as appropriate.



For help choosing, see options in Step 1 above, and our chart, [Drugs for Type 2 Diabetes](#) for med details.

- If escalating treatment in **pediatrics**:
 - » Add-ons to metformin and/or insulin in youth $\geq$ 10 years of age: canagliflozin, empagliflozin, liraglutide, or once-weekly exenatide.⁸⁻¹¹
 - » Pioglitazone could be considered if metformin is not tolerated and cardiac function is normal, given that youth tend to have severe insulin resistance. However, pioglitazone is **not preferred** due to weight gain (especially with insulin).⁷

Abbreviations: CV = cardiovascular; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium-glucose co-transporter 2; DPP-4 = dipeptidyl peptidase-4

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Diabetes Meds: Cardiovascular and Kidney Impact

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-- 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/1.73m², need for dialysis/transplant, or death from kidney causes (NNT = 67), driven by prevention of macroalbuminuria (NNT = 83).
Semaglutide injection  (MACE, ^e 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/1.73m², 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, $\geq 50\%$ 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 hospitalization²³ 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 HFpEF . 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 HFpEF . 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 m². EMPEROR-Reduced trial [Evidence Level A-1]; patients were receiving standard therapy for class II-IV HFrEF . 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 HFpEF . 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 HFpEF). 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}	

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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 m².³⁸ (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 m² 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>.]

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