# Type 2 Diabetes Management: A Case-Based Approach for Primary Care

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# Disclosure

Consultant: Bayer; Boehringer Ingelheim; Corcept Therapeutics; DIASOME; Eli Lilly; Merck; Novo Nordisk; Sanofi

Research Grant: Bayer; Eli Lilly; Merck; Novo Nordisk; Twin Health

Speaker's Bureau: AstraZeneca; Corcept Therapeutics; Novo Nordisk

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### Case 1

- A 62-year-old man presents for management of T2D, which was diagnosed 6 years ago.
- Patient takes metformin 1000 mg twice daily.
- Most recent A1C measurement was 9.1%.
- CAD diagnosed 3 years ago, for which he has undergone CABGX3.
- He denies any current symptoms of chest pain or shortness of breath.
- He recently underwent transthoracic echocardiography, and his LVEF was 50%.
- He has a 45 pack-year history of cigarette smoking, but he quit 3 years ago.
- He has HTN, treated with atenolol, 50 mg once daily, and lisinopril/hydrochlorothiazide, 20 mg/12.5 mg once daily, and hyperlipidemia controlled with atorvastatin, 80 mg daily.
- BP 138/84 mm Hg, HR 66 beats/min.
- Weight is 176 lb, BMI = 31 kg/m<sup>2</sup>.



## Additional Labs

- Total cholesterol = 112 mg/dL
- LDL cholesterol = 45 mg/dL
- HDL cholesterol = 35 mg/dL
- Triglycerides = 122 mg/dL
- eGFR= 35 mL/min per 1.73 m<sup>2</sup>
- UACR= 150 mg albumin/gram creatinine

#### Which of the Following Is the Next Best Step in Management of T2D?

- A. Start once daily insulin glargine
- B. Add once-weekly subcutaneous semaglutide (GLP-1RA)
- C. Add empagliflozin (SGLT-2i)
- D. Add glipizide XL

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- Of the options listed, the best next step is to add once-weekly subcutaneous semaglutide (Answer B)
- Semaglutide is approved to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in adults with T2D and established CVD
- Recently demonstrated renal outcome benefits in T2D and CKD (FLOW) and now has indication to reduce the risk of worsening kidney disease, kidney failure, and death due to cardiovascular disease in adults with T2D and CKD
- Oral semaglutide
  - CV safety of oral semaglutide established in PIONEER-6
  - SOUL study just finished and demonstrated oral version also affords CV risk reduction (not yet FDA approve/added to label)

Marso SP et al. N Engl J Med. 2016;375(19):1834-1844. Husain M et al. N Engl J Med. 2019; 381:841-851. McGuire DK et al. N Engl J Med. 2025 Mar 29. doi: 10.1056/NEJMoa2501006.

## GLP-1RA and Renal Benefit?

Trial	Year Published	Treatment (s)	Primary or Secondary	Kidney Outcome	Results
LEADER [39]	2016	Liraglutide vs. placebo	Secondary	Diabetic Nephropathy	HR 0.78 (95% CI 0.67-0.92
SUSTAIN-6 [40]	2016	Semaglutide vs. placebo	Secondary	Macroalbuminuria, doubling of serum creatinine, Creatinine clearance $\leq$ 45 mL/min or KRT	HR 0.64 (95% CI 0.46-0.88
AWARD-7 [41]	2018	Dulaglutide vs. insulin glargine	Secondary	eGFR and UACR	A decline in eGFR of the insulin arm but not in the higher-dose dulaglutide an
REWIND [42]	2019	Dulaglutide vs. placebo	Secondary	300 mg/g > UACR in lower baseline concentration, sustained 30% > eGFR decline, KRT	HR 0.85 (95% CI 0.77-0.9
Kristensen et. al. meta-analysis [43]	2019	GLP-1's	_	New-onset macroalbuminuria, decline in eGFR, progression of kidney disease or death of kidney cause	HR 0.83 (95% CI 0.78-0.89
AMPLITUDE-O [44]	2021	Efpeglenatide vs. placebo	Secondary	Incident microalbuminuria > 300mg/g, increase in UACR of at least 30% from baseline, sustained eGFR decrease > 40% for > 30 days, KRT for 90 days or more, eGFR < 15 for 30 days or more	HR 0.68 (95% CI 0.57–0.79

#### Sawaf H et al. J Clin Med. 2022;11(2):378.









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Aspect	GLP-1 Receptor Agonists	SGLT-2 Inhibitors
Mechanism of Action	Stimulate insulin secretion in response to glucose, suppress glucagon release, slow gastric emptying, and enhance satiety.	Inhibit sodium-glucose cotransporter 2 in the kidneys, preventing glucose reabsorption, leading to increased glucose excretion in urine.
Effect on Glycemic Control	- Significant reduction in HbA1c - Reduces postprandial and fasting blood glucose levels	<ul> <li>Significant reduction in HbA1c (eGFR ≥ 45)</li> <li>Reduces postprandial and fasting glucose levels, but largest effect is on lowering postprandial glucose</li> </ul>
Average HbA1c Change	- Reduces HbA1c by 1.0% to 1.8% (depending on the agent and dose)	- Reduces HbA1c by 0.5% to 1.2%
Effect on Weight Loss	- Significant weight loss (average of 5-10% body weight) due to appetite suppression and slower gastric emptying	<ul> <li>Moderate weight loss (3-5% body weight) due to caloric loss from glucose excretion in urine</li> </ul>
Onset of Action	<ul> <li>Onset of action can be gradual; typically takes a few weeks to months for optimal effects</li> </ul>	<ul> <li>Onset is generally quicker (within days), with sustained effects</li> </ul>
Side Effects	<ul> <li>Nausea, vomiting, diarrhea, constipation, risk of pancreatitis, possible risk of thyroid tumors (in animal studies)</li> </ul>	<ul> <li>Urinary tract infections, genital fungal infections, increased urination, dehydration, hypotension</li> </ul>
Cardiovascular Effects	<ul> <li>Some agents (e.g., liraglutide, dulaglutide, semaglutide) show positive effects on cardiovascular outcomes (e.g., reduced risk of cardiovascular events)</li> </ul>	<ul> <li>Proven benefits in reducing cardiovascular risk (e.g., empagliflozin, canagliflozin)</li> </ul>
Renal Effects	<ul> <li>Reduce albuminuria and reduce risk of progression of CKD</li> <li>Semaglutide</li> </ul>	- Reduce albuminuria and reduce risk of progression of CKD
Risk of Hypoglycemia	<ul> <li>Low risk of hypoglycemia when used alone, but risk increases when combined with other insulin-stimulating agents or insulin</li> </ul>	<ul> <li>Very low risk of hypoglycemia, as they don't increase insulir secretion, but background therapies (SFUs or insulin) may need adjusted</li> </ul>
Preferred Patient Populations	<ul> <li>Type 2 diabetes with obesity or those needing weight loss, particularly if cardiovascular protection (and/or CKD risk reduction) is needed</li> </ul>	- Type 2 diabetes with cardiovascular disease, heart failure, or CKD

•particularly in setting of lower eGFR values (< 45)

# SGLT-2i Efficacy and eGFR

**SGLT-2** inhibitors still offer moderate glycemic control benefits as eGFR drops, but their efficacy diminishes significantly at lower eGFR levels

- eGFR > 45-60 mL/min/1.73m<sup>2</sup>: SGLT-2 inhibitors are most effective in this range, with robust HbA1c lowering and additional benefits for kidney function
- eGFR 30-45 mL/min/1.73m<sup>2</sup>: The HbA1c lowering effect is reduced, but diabetic kidney disease and heart failure patients can still benefit, and careful monitoring is essential
- 3. eGFR < 30 mL/min/1.73m<sup>2</sup>: At this stage, SGLT-2i are added for CHF and CKD benefits, and can continued all the way down to start of dialysis
   However, eGFR > 20 at time of initiation recommended for empagliflozin and > 25 for dapagliflozin







## Randomized Controlled Trials of Intensive versus Standard Hypertension Treatment Strategies

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP (35)	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	SBP target: <120 mmHg Achieved (mean) SBP/DBP: 119.3/64.4 mmHg	SBP target: 130–140 mmHg Achieved (mean) SBP/DBP: 135/70.5 mmHg	<ul> <li>No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death</li> <li>Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment</li> <li>Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities</li> </ul>
ADVANCE (36)	11,140 participants with T2D aged ≥55 years with prior evidence of CVD or multiple cardiovascular risk factors	Intervention: a single- pill, fixed-dose combination of perindopril and indapamide Achieved (mean) SBP/DBP: 136/73 mmHg	Control: placebo Achieved (mean) SBP/DBP: 141.6/75.2 mmHg	<ul> <li>Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%)</li> <li>G-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (242)</li> </ul>
HOT (37)	18,790 participants, including 1,501 with diabetes	DBP target: ≤80 mmHg Achieved (mean): 81.1 mmHg, ≤80 group; 85.2 mmHg, ≤90 group	DBP target: ≤90 mmHg	<ul> <li>In the overall trial, there was no cardiovascular benefit with more intensive targets</li> <li>In the subpopulation with diabetes, an intensive DBP target was associated with a significantly reduced risk (51%) of CVD events</li> </ul>

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#### Randomized Controlled Trials of Intensive versus Standard Hypertension Treatment Strategies SPRINT (43) 9,361 participants SBP target: SBP target: Intensive SBP target lowered risk o without diabetes <120 mmHg <140 mmHg the primary composite outcome Achieved (mean): Achieved (mean): 25% (MLACS stroke heart failure 121.4 mmHg 136.2 mmHg and death due to CVD) Intensive target reduced risk of death 27% Intensive therapy increased risks of electrolyte abnormalities and AKI STEP (34) 8,511 participants aged SBP target: SBP target: Intensive SBP target lowered risk of <130 mmHg 60-80 years, <150 mmHg the primary composite outcome including 1,627 with Achieved (mean): Achieved (mean): 26% (stroke, ACS [acute MI and diabetes 127.5 mmHg 135.3 mmHg hospitalization for unstable angina], acute decompensated heart failure. coronary revascularization, atrial fibrillation, or death from cardiovascular causes) Intensive target reduced risk of cardiovascular death 28% • Intensive therapy increased risks of hypotension ACCORD BP, Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial; ACS, acute coronary syndrome; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; AKI, acute kidney injury; CVD, cardiovascular disease; DBP, diastolic blood pressure; HOT, Hypertension Optimal Treatment trial; MI, myocardial infarction; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; STEP, Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients; T2D, type 2 diabetes. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S158-S190







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#### Intensive Blood-Pressure Control in Patients with Type 2 Diabetes Adverse Events

Outcome				rd Treatment I = 6407)	Hazard Ratio (95% CI)	P Value
	No. of Events	Percentage of Participants	No. of Events	Percentage of Participants		
Serious adverse event†	2340	36.5	2328	36.3	1.00 (0.94–1.06)	0.96
Conditions of interest:						
Arrhythmia	69	1.1	68	1.1	1.01 (0.72–1.41)	0.95
Electrolyte abnormality	36	0.6	35	0.6	1.03 (0.65–1.64)	0.91
Injurious fall	65	1.0	61	1.0	1.06 (0.75–1.51)	0.74
Symptomatic hypotension	8	0.1	1	<0.1	7.92 (0.99–63.34)	0.05
Syncope	10	0.2	10	0.2	1.00 (0.41-2.39)	0.99
Acute renal failure	4	0.1	5	0.1	0.79 (0.21-2.95)	0.73
Clinical safety alerts§						
Serum sodium <130 mmol/liter	46	0.7	47	0.8	0.97 (0.65-1.46)	0.89
Serum sodium >150 mmol/liter	22	0.4	25	0.4	0.88 (0.49-1.56)	0.65
Serum potassium <3.0 mmol/liter	32	0.5	33	0.5	0.97 (0.60-1.58)	0.90
Serum potassium >5.5 mmol/liter	177	2.8	125	2.0	1.41 (1.12-1.77)	0.003

N Engl J Med 2025;392:1155-67.



















## Case 2: Current Meds

Metformin, 1000 mg twice daily Insulin aspart, 10 units before meals (3 times daily) Insulin degludec, 30 units at bedtime Lisinopril, 40 mg daily Aspirin, 81 mg daily Clopidogrel, 75 mg daily Metoprolol tartrate, 50 mg twice daily Chlorthalidone, 25 mg once daily Rosuvastatin, 10 mg once daily



#### Which of the Following Medications Should Be Started as the Best Next Step in This Patient's Treatment?

- A. Losartan
- B. Aliskiren
- C. Amlodipine
- D. Dapagliflozin

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### Other Answer Options

- A) In the ONTARGET trial, the combination of ACE/ARB was associated with more adverse events without an increase in benefit. For these reasons, addition of the ARB losartan is incorrect. ACE/ARB combination therapy is not recommended.
- B) Aliskiren, a direct renin inhibitor, should not be added to the regimen of a patient treated with an ACE inhibitor or ARB. The ALTITUDE study (Aliskiren Trial in T2D Using Cardiorenal Endpoints) failed to identify a benefit of aliskiren as an adjunct to therapy with an ACE inhibitor or an ARB and found that vs. placebo, aliskiren was associated with more cases of nonfatal stroke, renal complications, hyperkalemia, and hypotension.
- C) Amlodipine may lower BP < 130/80, but will not provide the significant reduction in UACR afforded by RAASi or SGLT-2i, and will not address the residual A1C elevation observed in this patient. If BP remained above target, despite SGLT-2i, this would be a reasonable option.

Parving H et al. N Engl J Med 2012; 367:2204-2213. Yusuf S et al. ONTARGET Investigators. N Engl J Med. 2008;358(15):1547-1559.

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# Glycemic Control Is Still Important!

- HbA1c: Average glycemia during the past 3 months
- Continuous glucose monitors provide real-time feedback to patients in terms of their BG control, and often pick up more detailed information regarding overall BG control, via Time-in-Range, than the HbA1c alone
- CGM allows one to identify the areas where improved glycemic control are necessary, or unrecognized hypoglycemia









Personal CGM Comparison						
	Dexcom G6	Dexcom G7	Libre 2+	Libre 3+	Guardian 4	Eversense 365
Туре	rtCGM	rtCGM	isCGM	rtCGM	rtCGM	rtCGM
Maximum wear time	10 days	10.5 days	15 days		7 days	365 days
Warm-up time	2 hours	<30 min	1 hour		<2 hours	24 hours
Calibrations	Optional	Optional	None		Optional	After 14 days, Weekly
Water Depth	8 feet, 24 hours	8 feet, 24 hours	3 feet 30 min		8 feet 30 min	3.28 feet 30 min
Data Platform	Dexcom Clarity		Libre View		Carelink	Eversense Data Management System

Rt: real time

Dexcom recently FDA approved for 15 days: https://www.diabetech.info/p/dexcom-g7-gets-fda-clearance-for-15-day-wear-but-will-it-actually-last-that-long

	Dexcom G6	Dexcom G7	Libre 2+ Libre 3+	Guardian 4	Eversense
FDA approved sites	Abdomen (ages2+) Upper buttocks (ages 2-17)	Upper arm (ages 7+) Upper buttocks (ages 2-6)	Upper arm	Upper arm, abdomen Upper buttocks (ages 2-13)	Upper arm
Approved in pregnancy	No	Yes	Yes	No	No
Transmitter	3 months	Disposable	Disposable	Charge weekly	Charge daily
FDA approved ages (years)	≥2	≥2	≥2	≥2	≥18
Drug interactions	Hydroxyurea	Hydroxyurea	Vitamin C	Acetaminophen Hydroxyurea	Tetracycline antibiotics, mannitol
Insulin Pump Compatibility	Omnipod 5, iLet, Mobi, T:Slim X2	Omnipod 5, iLet, Mobi, T:Slim X2	T:Slim X2 Omnipod 5, iLet	Medtronic 780G	Sequel Twist



65-ye	ar-old Woman, T2D, on MDI, A1c 6.5%
	Overview         III 0excom           Vication 100 (0.000)         100 (0.000)           Glucose         III 0excom
	Average Glucose Time in Range Sensor Usage           180         Sinsor Usage           overage Glucose         9% Very High         Days with CGM data           35% High         100 \lambda           5% In Range         14/14           0% Very Low         14/14
	Standard Deviation GM Target Name Arg calibrations per day 52 mg/st. 7.6 h To 10 mg/st. 0.0 Insulin
	42% Fast Acting 15.7 ufay 5% Long Acting 2.3 u/day Average Fast Acting 37.6 u/day 2.1 doses/day
	Bornie had a pattern of daytime highs
	The graph these store data areased one it. days The graph the graph th
Illustrates h	igher average glucose, time above range despite "well controlled A1c"





## Conclusions

- A1C reduction/goal attainment is STILL important
  - How you get there is important too!
- CV (and Renal) Risk Reduction with GLP-1RA
- CV, Renal, and HF risk reduction with SGLT-2i
- BP and LDL targets must be prioritized
- CGM can assist both patients and providers in improving glycemic control