SGLT Too? Updates in Heart Failure with Reduced Ejection Fraction

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Disclosure

- The speaker has no conflicts of interest to disclose
- Non-FDA approved indications may be discussed

Learning Objectives

1. Outline current guideline-directed medical therapy for heart failure with reduced ejection fraction (HFrEF)
2. Evaluate the literature regarding SGLT2 inhibitors and their role in patients with HFrEF
3. Identify optimal patients to initiate on SGLT2 inhibitors

Pre-Assessment Question #1

Which of the following is true regarding guideline-directed medical therapy in patients with heart failure with reduced ejection fraction?

a) Ivabradine has been shown to decrease incidence of cardiac death in patients with HFrEF
b) Hydralazine/isosorbide nitrate has been shown to decrease morbidity and mortality in various demographics of patients with HFrEF regardless of whether they are on an ACEi/ARB
c) ACEi/ARBs, ARNIs, and digoxin have been shown to decrease morbidity and mortality in patients with HFrEF
d) Beta-blockers are one of the first-line options in patients with HFrEF and have been shown to decrease morbidity and mortality

Pre-Assessment Question #2

In patients with heart failure with reduced ejection fraction (HFrEF), the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure recommends that:

a) An SGLT2 inhibitor can be initiated irrespective of the presence of type 2 diabetes
b) An SGLT2 inhibitor may be started in all patients regardless of eGFR
c) Any SGLT2 inhibitor can be given as a part of guideline-directed medical therapy
d) SGLT2 inhibitors should be given in HFrEF stages B and C

Pre-Assessment Question #3

Various trials regarding SGLT2 inhibitors have shown that:

a) These medications cause an increased risk of lower extremity amputations as a class effect
b) Dapagliflozin and empagliflozin both have cardiovascular benefit in patients with and without type 2 diabetes
c) Empagliflozin lowers the risk of cardiovascular death and hospitalization for heart failure without increasing the incidence of genital tract infections
d) Dapagliflozin can decrease the risk of MACE outcomes but leads to a higher risk of volume depletion

Pre-Assessment Question #4

RM is a 55-year-old female who has a history of HF (EF = 32%) and T2D. Her current therapy includes metoprolol succinate 100 mg daily, lisinopril 40 mg daily, spironolactone 25 mg daily, furosemide 20 mg twice a day, and metformin 1000 mg twice a day. Her PCP wants to start her on an SGLT2i as an addition to her heart failure therapy. Which of the following is true regarding therapy changes for RM after the addition of an SGLT2i?

a) SGLT2 inhibitors have been shown to cause hyperkalemia and a dose reduction of spironolactone must be considered
b) SGLT2 inhibitors may cause hypoglycemia and metformin must be dose reduced
c) SGLT2 inhibitors have a modest diuretic effect and a decrease in the furosemide dose may be considered
d) SGLT2 inhibitors may cause hypotension and lisinopril must be dose reduced

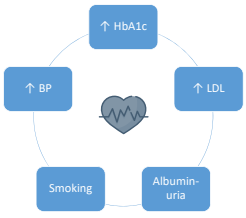
Pre-Assessment Question #5

The addition of an SGLT2 inhibitor should be considered in:

a) A 58-year-old male patient with a history of HFrEF and pre-diabetes
b) A 33-year-old female patient with a history of type 2 diabetes and no other comorbidities
c) A 64-year-old male patient with a history of HFpEF and type 2 diabetes
d) Addition of an SGLT2 inhibitor should be considered in all of the above patients

Heart Failure

- Heart failure (HF) begins with an initial insult which leads to myocardial injury
- Various risk factors: age > 65 years, African American race, obesity, comorbidities
- Heart failure with reduced ejection fraction (HFrEF, EF ≤ 40%)
- Heart failure with preserved ejection fraction (HFpEF, EF ≥ 50%)



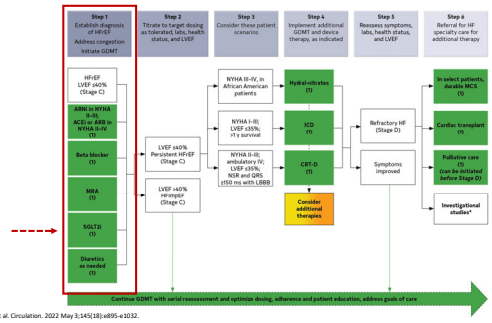
Schmidt AM. Arterio, Thromb, and Vasc Bio. 2019;39:558–568. Ziaeian B, Fonarow GC. Nat Rev Cardiol. 2016 Jun;13(6): 368–378.

Classifications of Heart Failure

NYHA Classification (Functional Status)	
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.

HF Staging (Objective Assessment)	
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experience symptoms even while at rest.

Classes of Heart Failure, American Heart Association



Heidenreich PA, et al. Circulation. 2022 May 3;145(18):e895-e1032.

Guideline Directed Medical Therapy

ACEi/ARB/ARNI
↓ morbidity and mortality

Results in vasodilation and improved EF

Beta-Blocker
↓ morbidity and mortality

Controls heart rate and reduces arrhythmia risk

MRA
↓ morbidity and mortality

Competes with aldosterone for receptor sites

SGLT2i
↓ morbidity and mortality

Stimulates natriuresis, decreases preload and afterload

Heidenreich PA, et al. Circulation. 2022 May 3;145(18):e895-e1032.

Guideline Directed Medical Therapy

Hydral-Nitrates

↓ morbidity and mortality*

Hydralazine as arterial vasodilator, nitrate as venous vasodilator

Ivabradine

↓ risk of HF hospitalizations

For use in patients on GDMT with resting HR ≥ 70 in sinus

Digoxin

↓ risk of HF hospitalizations

For use in symptomatic patients despite optimal GDMT

Loop Diuretics

Improves symptoms

Improves edema and congestion

*in African American patients when added to optimized GDMT

Heidenreich PA, et al. Circulation. 2022 May 3;145(18):e895-e1032.

SGLT2 Inhibitors

Sodium-Glucose Cotransporter-2 Inhibitors

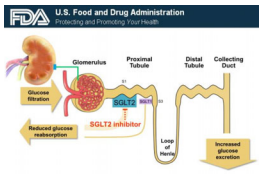
Cardiovascular Benefits of Diabetes Medications?

- FDA Guidance
  - Prior to 2008, evaluation of adverse cardiovascular events of diabetes medications was based on reported adverse events
  - FDA issued a guidance for industry to perform cardiovascular outcome trials for all new diabetes medications
  - Medications studied included:

DPP-4 Inhibitors | GLP-1 Agonists | SGLT-2 Inhibitors

FDA Guidance for Industry. 2008.

SGLT2 Inhibitors



Drugs	Canagliflozin Ertugliflozin Dapagliflozin Sotagliflozin* Empagliflozin Bexagliflozin
HbA1c Reduction	0.5-1%
Mechanism	Inhibits SGLT2 in the proximal renal tubules, thus reducing the reabsorption of filtered glucose
Side Effects	Risk of UTI, increased urination, dehydration
Notes	- Previous canagliflozin BBW for lower extremity amputations removed August 2020 -

Canagliflozin; Dapagliflozin; Empagliflozin. Lexicomp.
US Food and Drug Administration.

*not FDA approved; SGLT2 and SGLT1 inhibitor

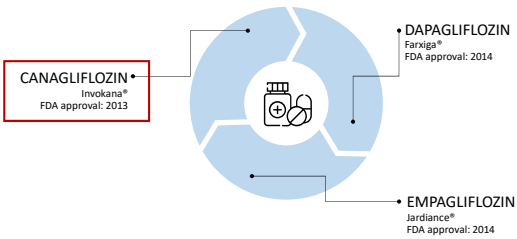
Mechanism

- SGLT2 inhibitors may exert cardio-protective effects through several distinct mechanisms:

Stimulation of natriuresis
Stimulation of osmotic diuresis
Improved systolic and diastolic function
Decreased preload and afterload
Improved endothelial function
Increased cardiac output, HR, O_2 consumption, coronary blood flow mediated by increased levels of circulating glucagon

Lam CSP, et al. J Am Heart Assoc. 2019 Oct 15;8(20):e013389.

SGLT2 Inhibitors



CANVAS

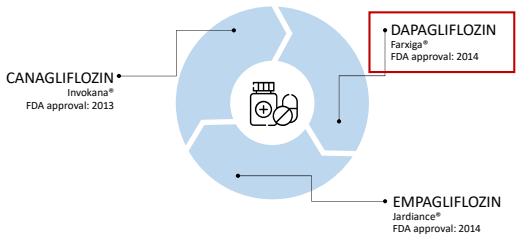
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Inclusion	Type 2 diabetes and high cardiovascular risk
Intervention	Canagliflozin 100 mg daily vs matching placebo
Outcome	Composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke
N	10,142
Results	- Lower incidence of the primary endpoint in the canagliflozin group (26.9 vs 31.5; p = 0.02) - Increased risk of amputations in canagliflozin group (6.3 vs 3.4; p < 0.001)
Conclusion	In patients with T2D and an elevated CV ri treatment with canagliflozin had a signific lower rate of CV events but a higher risk o amputation when compared to placebo

Cardiovascular benefit
BUT
↑ risk of amputation

Bruce Neal MB, et al. N Engl J Med 2017; 377:644-657.

SGLT2 Inhibitors



DECLARE-TIMI 58

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

Objective	• Assess the cardiovascular safety profile of dapagliflozin in patients with type 2 diabetes
Design	• Randomized, double-blind, multinational, placebo-controlled, phase 3 trial
Inclusion	• Type 2 diabetes and age ≥ 40 years • HbA1c 6.5-12% • CrCl ≥ 60mL/min • Multiple risk factors for atherosclerotic cardiovascular disease (ASCVD) or had established ASCVD
Interventi on	• Dapagliflozin 10 mg daily vs matching placebo

Wiviott SD, et al. N Engl J Med 2019; 380:347-357.

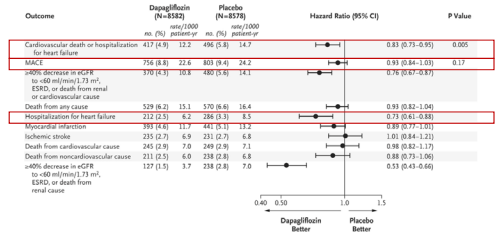
DECLARE-TIMI 58

Baseline Characteristics	Dapagliflozin (N=8582)	Placebo (N=8578)
Age, yr	63.9±6.8	64.0±6.8
Female Sex, n (%)	3171 (36.9)	3251 (37.9)
HbA1c, %	8.3±1.2	8.3±1.2
eGFR, mL/min/1.73m^2	85.4±15.8	85.1±16.0
Established ASCVD, n (%)	3474 (40.5)	3500 (40.8)
ACEi or ARB, n (%)	6977 (81.3)	6973 (81.3)
Beta-blocker, n (%)	4498 (52.4)	4532 (52.8)
History of HF, n (%)	***852 (9.9)***	***872 (10.2)***

Wiviott SD, et al. N Engl J Med 2019; 380:347-357.

DECLARE-TIMI 58

- Primary outcomes: major adverse cardiovascular events (MACE) and a composite of cardiovascular death or hospitalization for heart failure



Wiviott SD, et al. N Engl J Med 2019; 380:347-357.

DECLARE-TIMI 58

Outcome	Results (dapa vs placebo)
Primary efficacy outcome of MACE (CV death, MI, ischemic stroke)	8.8% vs 9.4%, p < 0.001*
Primary efficacy outcome of CV death or hospitalization for HF	4.9% vs 5.8%, p = 0
Hospitalizations for HF	2.5% vs 3.3%, HR 0. 0.61-0.88)

*p for non-inferiority

Cardiovascular benefit

- Dapagliflozin non-inferior to placebo with respect to MACE
- Dapagliflozin lowered rate of CV death or hHF when compared to placebo
- Majority of patients did not have a history of HF

Wiviott SD, et al. N Engl J Med 2019; 380:347-357.

DAPA-HF

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

Objective	• Assess the effects of dapagliflozin in patients with HFrEF regardless of diagnosis of type 2 diabetes
Design	• Phase 3, randomized, placebo-controlled trial
Inclusion	• Age ≥ 18 years • Ejection fraction ≤ 40% • NYHA class II-IV symptoms • NT-proBNP cut offs
Exclusion	• eGFR < 30 ml/min/1.73m²
Intervention	• Dapagliflozin 10 mg daily vs matching placebo

McMurray JJV, et al. N Engl J Med 2019; 381:1995-2008.

DAPA-HF

Baseline Characteristics	*Dapagliflozin (N=2373)*	*Placebo (N=2371)*
Age, yr	66.2±11.0	66.5±10.8
Female Sex, n (%)	564 (23.8)	545 (23.0)
NYHA Class II, n (%)	1606 (67.7)	1597 (67.4)
Ejection Fraction, %	31.2±6.7	30.9±6.9
eGFR, mL/min/1.73m²	66.0±19.6	65.5±19.3
HF Medication, n (%)		
- Diuretic	2216 (93.4)	2217 (93.5)
- ACEi/ARB/ARNI	2257 (95.1)	2219 (93.6)
- Beta-blocker	2278 (96.0)	2280 (96.2)
- MRA	1696 (71.5)	1674 (70.6)

McMurray JJV, et al. N Engl J Med 2019; 381:1995-2008.

DAPA-HF

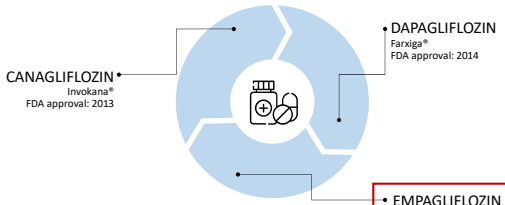
Outcome	*Dapagliflozin, n (%) (N = 2373)*	*Placebo, n (%) (N = 2371)*	*Hazard or Rate Ratio (95% CI)*
Primary composite outcome (worsening HF or CV death)	386 (16.3)	502 (21.2)	0.74 (0.65-0.85) p = < 0.001
Hospitalization or urgent visit for HF	237 (10.0)	326 (13.7)	0.70 (0.59-0.83)
Hospitalization for HF	231 (9.7)	318 (13.4)	
Urgent HF visit	10 (0.4)	23 (1.0)	
Cardiovascular death	227 (9.6)	273 (11.5)	0.82 (0.69-0.98)

Cardiovascular benefit

- Risk of worsening HF or CV death lower in the dapagliflozin group (NNT = 21)
- Benefit was seen in patients with or without type 2 diabetes
- Safety outcomes between the two arms did not differ
  - No differences in urinary tract infections, volume depletion, and major hypoglycemia

McMurray JJV, et al. N Engl J Med 2019; 381:1995-2008.

SGLT2 Inhibitors



- CANAGLIFLOZIN
  Invokana®
  FDA approval: 2013
- DAPAGLIFLOZIN
  Farxiga®
  FDA approval: 2014
- EMPAGLIFLOZIN
  Jardiance®
  FDA approval: 2014

EMPA-REG OUTCOME

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Objective	• Evaluate the effects of empagliflozin on CV morbidity and mortality in patients with T2D at high CV risk
Design	• Randomized, double-blind, placebo-controlled trial
Inclusion	• Age ≥ 18 years • Type 2 diabetes • BMI ≤ 45 • eGFR ≥ 30 ml/min/1.73m² • Established cardiovascular disease
Interventi	• Empagliflozin 10 mg or 25 mg daily vs matching placebo

Zinman B, et al. 2128.

EMPA-REG OUTCOME

Baseline Characteristics	*Empagliflozin, pooled (N=4687)*	*Placebo (N=2333)*
Age, yr	63.1±8.6	63.2±8.8
Male Sex, n (%)	3336 (71.2)	1680 (72.0)
HbA1c, %	8.07±0.85	8.08±0.84
eGFR, mL/min/1.73m²	74.2±21.6	73.8±21.1
ACEi or ARB, n (%)	3798 (81.0)	1868 (80.1)
Beta-blocker, n (%)	3056 (65.2)	1498 (64.2)
History of HF, n (%)	*462 (9.9)*	*244 (10.5)*

Zinman B, et al. ed 2015; 373:2117-2128.

EMPA-REG OUTCOME

Outcome	Empagliflozin, n (%) (N = 4687)	Placebo, n (%) (N = 2333)	p-value
Primary composite outcome (CV death, nonfatal MI, nonfatal stroke)	490 (10.5)	282 (12.1)	0.04
Death			
From any cause	296 (5.7)	194 (8.3)	
From CV cause	172 (3.7)	137 (5.9)	
Hospitalization for HF	126 (2.7)	95 (4.1)	0.002

Cardiovascular benefit

- Empagliflozin resulted in a lower rate of the primary outcome, death from any cause, death from CV cause, and hospitalization for HF
- Empagliflozin caused a higher incidence of genital infection (6.4% vs 1.8%)
- Majority of patients did not have a history of HF

Zinman B, et al. N Engl J Med 2015; 373:2117-2128.

EMPEROR-REDUCED

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

Objective	• Assess the effects of empagliflozin in patients with HFrEF
Design	• Randomized, double-blind, parallel-group, placebo-controlled, event-driven trial
Inclusion	• Age ≥ 18 years • HF (NYHA class II-IV) • LVEF ≤ 40% on GDMT • Additional criteria if LVEF > 30%
Exclusion	• eGFR < 20 ml/min/1.73m^2
Interventi on	• Empagliflozin 10 mg daily vs matching placebo

Packer M, et al. N Engl J Med 2020; 383:1413-1424.

EMPEROR-REDUCED

Baseline Characteristics	Empagliflozin (N=1863)	Placebo (N=1867)
Age, yr	67.2±10.8	66.5±11.2
Female Sex, n (%)	437 (23.5)	456 (24.4)
NYHA Class II, n (%)	1399 (75.1)	1401 (75.0)
Ejection Fraction, %	27.7±6.0	27.2±6.1
eGFR, mL/min/1.73m^2	61.8±21.7	62.2±21.5
HF Medication, n (%)		
- ACEi/ARB/ARNI	1654 (88.8)	1673 (89.6)
- Beta-blocker	1765 (94.7)	1768 (94.7)
- MRA	1306 (70.1)	1355 (72.6)
History of T2D, n (%)	**927 (49.8)**	**929 (49.8)**

Packer M, et al. N Engl J Med 2020; 383:1413-1424.

EMPEROR-REDUCED

Outcome	Empagliflozin, n (%) (N = 1863)	Placebo, n (%) (N = 1867)	Hazard Ratio (95% CI)
Primary composite outcome (worsening HF or CV death)	361 (19.4)	462 (24.7)	0.75 (0.65-0.86) p = <0.001
Hospitalization for HF	246 (13.2)	342 (18.3)	0.69 (0.59-
Cardiovascular death	187 (10.0)	202 (10.8)	1.12)
Total HF hospitalizations	388	553	0.7 (0.58-0.85) p = 0.001

Cardiovascular benefit

- Empagliflozin resulted in a lower risk of CV death or hHF (composite)
- Benefit was seen in patients with or without type 2 diabetes
- Genital infection reported more frequently with empagliflozin (1.7% vs 0.6%)
- No differences in safety outcomes of volume depletion and hypoglycemia

Packer M, et al. N Engl J Med 2020; 383:1413-1424.

Nov 2015
EMPA-REG OUTCOME

Aug 2017
CANVAS

Jan 2019
DECLARE-TIMI 58

Nov 2019
DAPA-HF

Oct 2020
EMPEROR-Reduced

What About Us?

Ertugliflozin

- Steglatro®
- FDA approval: 2017
- VERTIS CV: ertugliflozin non-inferior to placebo with respect to MACE, no difference in death from CV causes or hHF (no statistical significance); CV benefit data lacking

Sotagliflozin

- Zynquista®
- FDA approval: N/A
- SOLOIST-WHF: lower incidence of CV death, hHF, and urgent visits for HF when sotagliflozin started shortly after an episode of decompensated HF, compared to placebo; trial terminated early

Bexagliflozin

- Brenzavvy®
- FDA approval: 2023
- BEST: bexagliflozin non-inferior to placebo with respect to MACE, no difference in CV death and hHF (no statistical significance); CV benefit data lacking

Cannon CP, et al. N Engl J Med 2020; 383:1425-1435. Bhatt DL, et al. N Engl J Med 2021; 384:117-128. McMurray JJV, et al. Diabetes 2020;69(Supplement_1):32-OR.

What Would be an Ideal HFrEF Therapy to Implement?

- One pill, once per day, with no dose titration
- Substantially improves survival and prevents hospitalization
- Meaningfully improves quality of life and functional status
- Benefits appear rapidly within days to few weeks of initiation
- Exceptionally well tolerated and safe
- Does not lower blood pressure or does so very minimally
- No adverse renal effects, and instead preserves kidney function and prevents dialysis
- Affordable and accessible

Khan MS, et al. Circ Heart Fail. 2020 Dec;13(12):e008030.

Initiating SGLT2 Inhibitor Therapy

FDA Approved Indications

Canagliflozin	Dapagliflozin	Empagliflozin
• Type 2 DM • Type 2 DM with CV disease • Diabetic kidney disease	• Type 2 DM • Diabetic kidney disease • Chronic kidney disease • **HFrEF**	• Type 2 DM • Type 2 DM with CV disease • **HFrEF**/HFpEF

Canagliflozin; Dapagliflozin; Empagliflozin. Lexicomp.

Who Should get an SGLT Too…?

Assessment	Intervention	Follow-Up
Eligible Patients - eGFR ≥ 30 ml/min/1.73m² - Optimized on GDMT (ACEi/ARB/ARNI + β-Blocker ± MRA) Potential Contraindications - Genital infection risk - Diabetic ketoacidosis - Foot ulcers	Low-dose SGLT2 inhibitor with proven benefits ~~- Canagliflozin 100 mg~~ - Dapagliflozin 10 mg - Empagliflozin 10 mg Education - Sick day protocol - Perioperative care - Adherence	- Assess adverse effects - Watch for hypoglycemia and volume depletion - Review knowledge

Dixit NM, et al. US Card Rev 2021;15:e07. Zoungas S, et al. Clin J Am Soc Nephrol. 2021 Apr 7;16(4):631-633.

Assessment	Intervention	Follow-Up
Hypoglycemia risk? - Insulin or sulfonylurea - History of severe hypoglycemia - HbA1c at or below goal	Education - Hypoglycemia symptoms - Glycemia monitoring - Consider insulin/ sulfonylurea dose reduction	- Ask about hypoglycemia - Reduce sulfonylurea or insulin if needed

If high

Assessment	Intervention	Follow-Up
Volume depletion risk? - Concurrent diuretic use - Tenuous volume status - History of acute kidney injury	Education - Volume depletion symptoms - Consider diuretic dose reduction	- Re-assess volume - Reduce concomitant diuretic if needed

Dixit NM, et al. US Card Rev 2021;15:e07. Zoungas S, et al. Clin J Am Soc Nephrol. 2021 Apr 7;16(4):631-633.

Practical Considerations

SGLT2i + Diuretics

- Modest diuretics effect
- Actively monitor volume status after initiation
- Consider decreasing loop diuretic dose

SGLT2i + GDMT

- Causes minimal blood pressure lowering
- Not associated with hyperkalemia
- SGLT2i's decrease MRA-induced hyperkalemia

SGLT2i + DM Therapy

- Modest glycemic effect in diabetes
- Sulfonylureas, prandial and basal insulin may need dose reduction

Khan MS, et al. Curr Diab Rep. 2020 Oct 11;20(11):63.

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Western Pharmacy Exchange 2023
presented by california pharmacists association