Second step therapy in the treatment of Type 2 diabetes mellitus: National Guideline Program review of medication benefits and risks

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Guideline Update Timeline

- 2018
  - Consensus Statement posted in response to published ADA Consensus Report (Nov)
  - External evidence review by Kaiser Permanente Research Affiliates for SGLT-2/GLP-1s, CV subpopulations/outcomes and overall harms (Nov)
- 2019
  - Internal evidence review SGLT-2/GLP-1s, renal and HF subpopulations and outcomes (Jan-Jul); CREDENCE published in May
  - REWIND published in June, PIONEER-6 published in August
  - Updated external evidence review by Kaiser Permanente Research Affiliates for GLP-1s, CV subpopulation/outcomes (Aug)
  - Recommendations drafted (Mar, Apr, Jun, Sep, Oct)
    - GDT Meetings (March, April)
  - Algorithm drafted/revised (May-Sep)
  - GDT review/approval recs + algorithm (October)
  - NGD/GQ approval (November)→Posting to Clinical Library (December)

What we will cover today

- SGLT-2 inhibitors and GLP-1 inhibitors
  - Benefits (*absolute* reduction of these outcomes):
    - Composite cardiovascular outcome (required for FDA approval): nonfatal MI + nonfatal stroke + CV death
    - Composite renal outcome: 40% sustained increase in creatinine + need for renal replacement therapy + renal-related death
    - Heart failure hospitalizations
  - Harms (complications, side effects, contraindications)
  - **Net benefit =** balance of benefits and harms (including cost)
- Guidelines prioritize populations most likely to experience net benefit
  - Selected subgroups require the lowest number-needed-to-treat

Question 1

You evaluate a 51-year-old woman at a follow-up visit after diagnosing her with type 2 diabetes mellitus 6 months ago. Her initial hemoglobin A_{1c} level was 8.3%. She subsequently tried immediate release metformin but discontinued it due to diarrhea. She also began an exercise program and made dietary changes and has lost 4.5 kg (10 lb). Family history includes that her father had a myocardial infarction at the age of 52. Remaining family and medical history are otherwise unremarkable.

On physical examination, blood pressure is 132/82 mm Hg and pulse is 72/min. BMI is 29. The examination is otherwise unremarkable.

Her repeat hemoglobin A_{1c} level today is 7.8%; she would like it lower than this. Results of other laboratory studies are within normal ranges.

Next Slide for ARS question

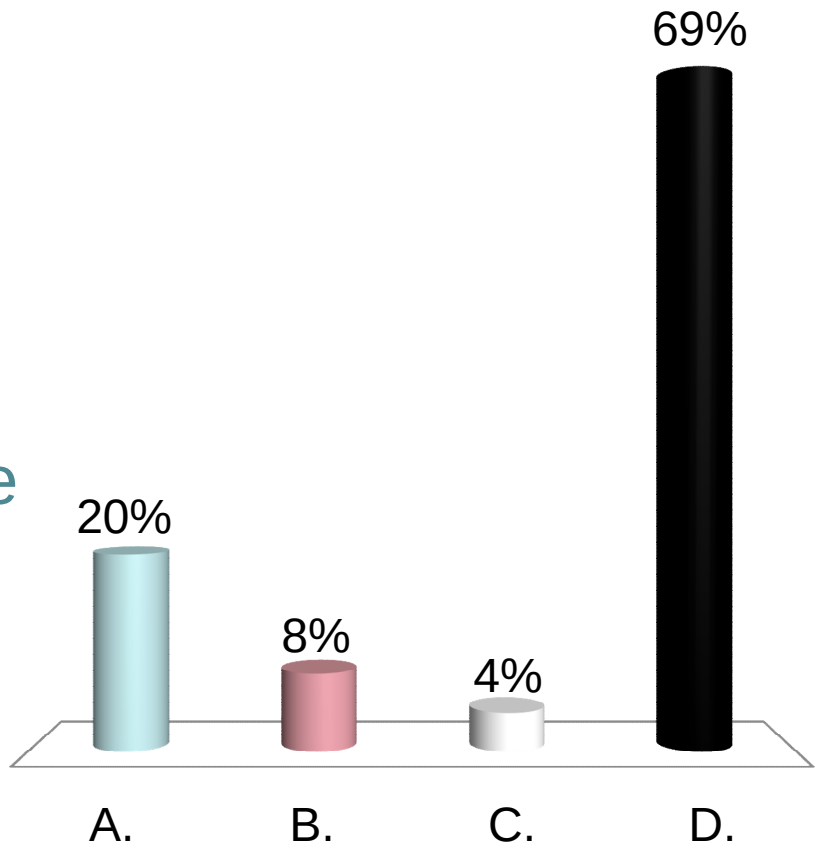
ARS 1: Which of the following is the most appropriate management?

A. Recommend continuing current efforts with lifestyle changes

B. Recommend empagliflozin

C. Recommend liraglutide

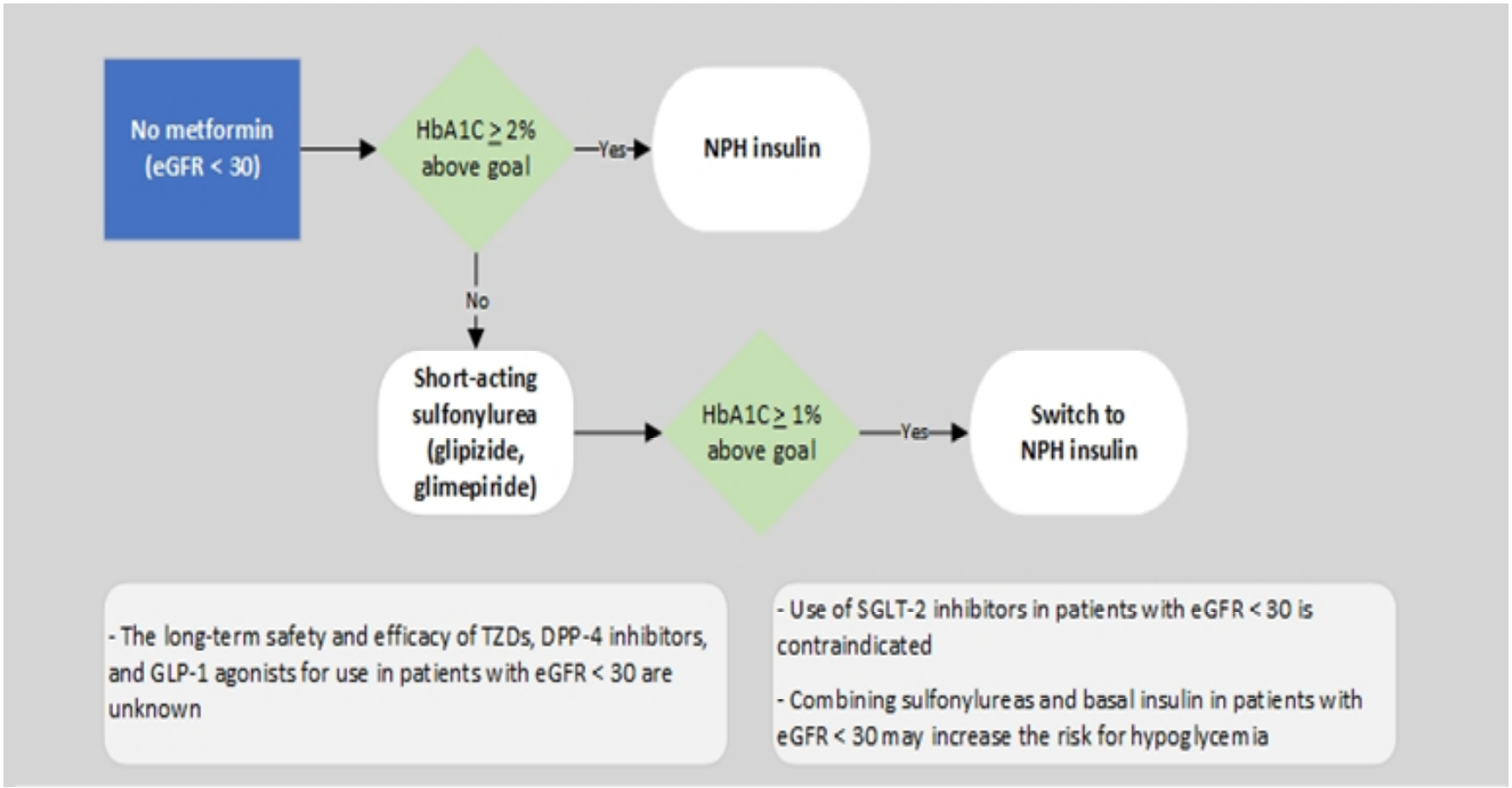
D. Recommend extended-release metformin



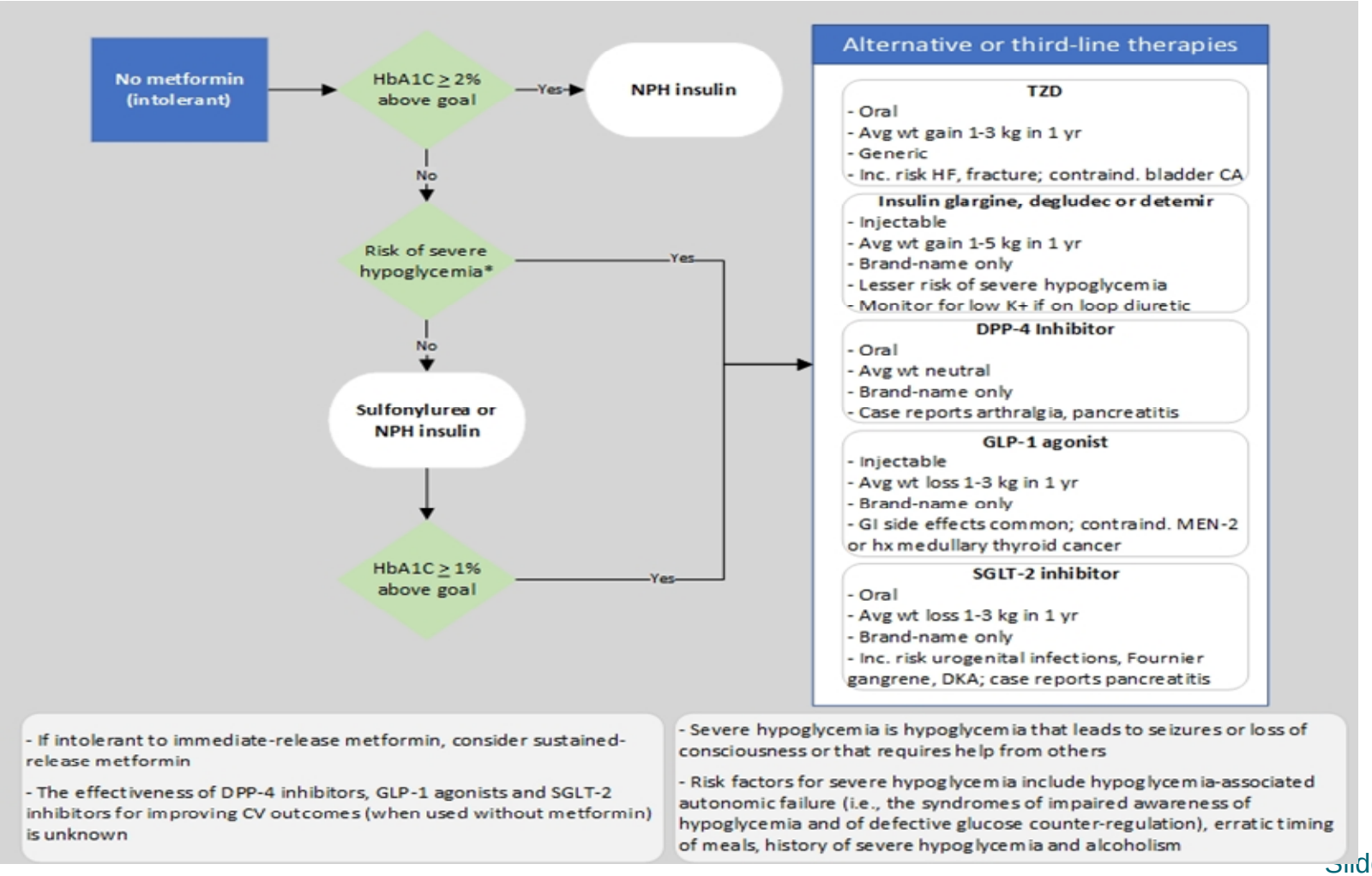
General design characteristics of RCTs of SGLT-2i's and GLP-1a's

- RCTs all vs. placebo
- SGLT-2s: 4 trials
  - Most patients on metformin
  - A1C is not controlled, mean A1Cs across trials 8.1-8.3%
- GLP-1 agonists: 6 trials
  - Most patients on metformin
  - A1C is not controlled, mean A1C across trials 7.3-8.7%
- Patients with eGFR < 30 were excluded from trials of SGLT-2 inhibitors and GLP-1 agonists

Clinician Guide for eGFR < 30



Clinician Guide metformin intolerance



Question 2

You evaluate a 64-year-old woman in a routine office visit for a physical examination. Medical history is significant for hypertension, Type 2 diabetes diagnosed 6 years ago, history of stroke with residual left leg weakness, history of tobacco use, history of biliary pancreatitis and hyperlipidemia.

Medications are aspirin, losartan, amlodipine, metformin, metoprolol, and rosuvastatin. On physical examination, she has a foot drop on the left side for which she wears a brace. BMI is 30. Blood pressure is 134/84 and other vital signs are normal. The remainder of the examination is unremarkable.

Results of laboratory studies show a hemoglobin A_{1c} of 8.1%.

Chemistry panel and creatinine levels are normal.

Next slide for ARS question

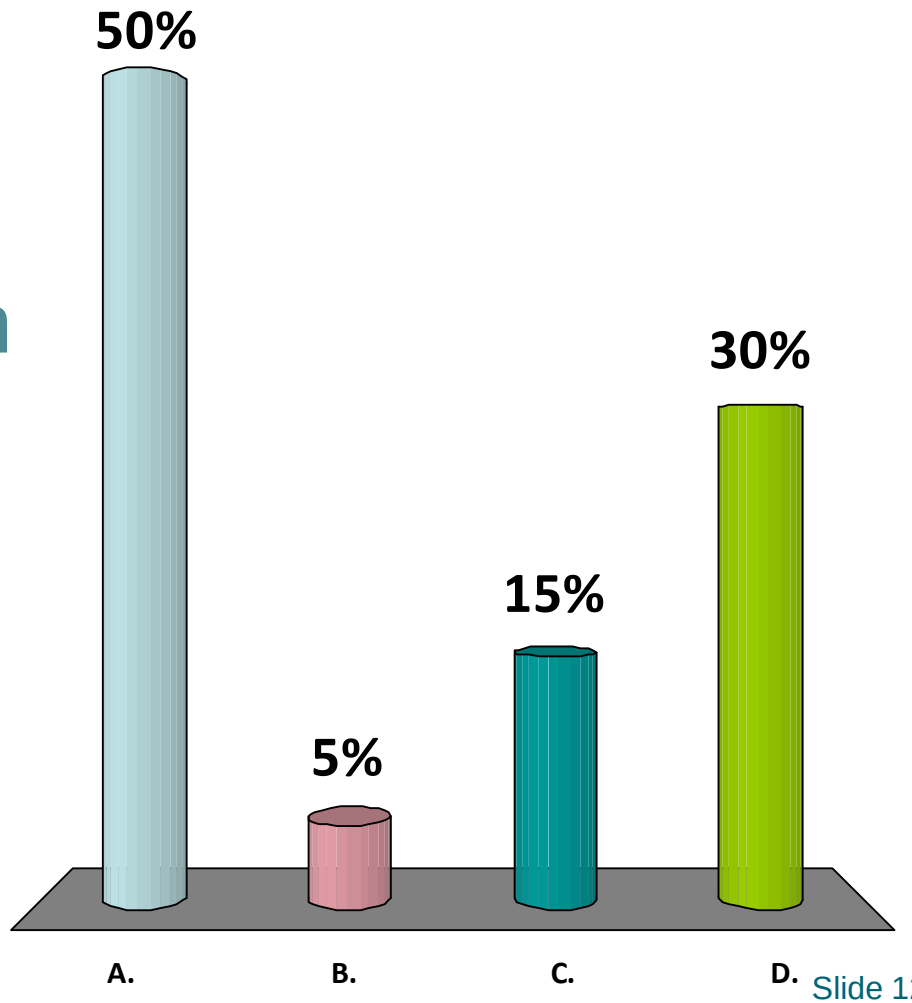
ARS 2: Which of the following is the most appropriate management for this patient's diabetes?

A. Offer glipizide

B. Offer liraglutide

C. Offer empagliflozin

D. Offer NPH insulin



Comparative effectiveness of SGLT-2 inhibitors in lowering the risk of CV events

SGLT-2 inhibitors exert effects via osmotic diuresis

- Inhibit sodium-glucose cotransporter 2 (SGLT2) in the proximal renal tubules
  - reduce reabsorption of filtered glucose from the tubular lumen and
  - lower the renal threshold for glucose (RT_G), thereby
  - Increasing urinary excretion of glucose.

SGLT-2 inhibitors vs. placebo and reduction of composite CV outcome

SGLT-2 inhibitors for diabetics with clinical ASCVD: MACE (Zelniker, 2019)

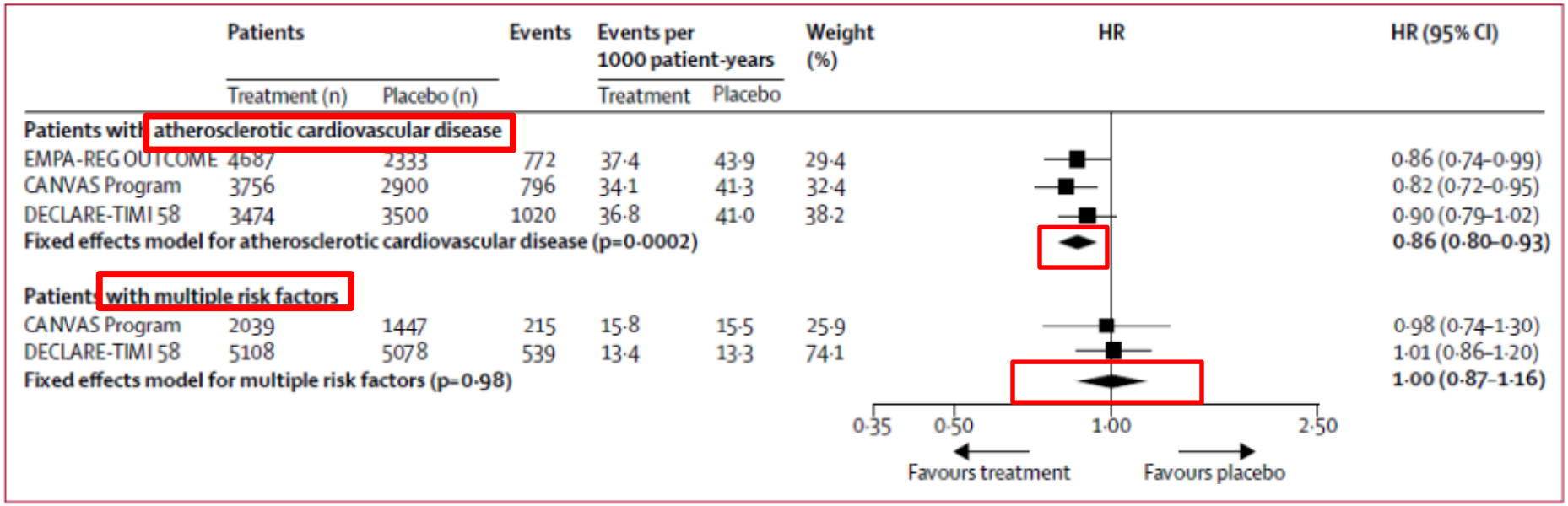


Figure 1: **Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease**

No heterogeneity was found in terms of between-study variance in the subgroups (atherosclerotic cardiovascular disease: Q statistic=0·94, p=0·63, I^2=0%; multiple risk factors: Q statistic=0·03, p=0·86, I^2=0%). Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. The p value for subgroup differences was 0·0501. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

SGLT-2 inhibitors compared to other drug classes for CV event reduction

- In trials, patients in the placebo group were often taking other second-step diabetes medicines (i.e. sulfonylurea, DPP-4 inhibitor, etc.) in addition to metformin—not truly vs. placebo
  - Study researchers were also allowed to adjust drugs as needed to reach A1C targets
  - Not an ideal, direct comparison between classes, but close
- No single network meta-analysis compares all drugs within a class and includes all applicable trials (new trials keep being published)
- Large-scale observational studies need careful design to avoid confounding

Question 3

You evaluate a 58-year-old man in the hospital for nausea, vomiting, and abdominal pain two weeks after sigmoid colectomy. He was diagnosed with type 2 diabetes 2 years ago. In addition to type 2 diabetes, medical history is significant for hypertension, and dyslipidemia. Medications are aspirin, lisinopril, metformin, metoprolol, atorvastatin, and canagliflozin.

On physical examination, temperature is normal, blood pressure is 90/58 mm Hg, pulse rate is 120/min, and respiration rate is 28/min.

Dry mucous membranes are noted.

There is diffuse abdominal tenderness to palpation without guarding.

The remainder of the examination is normal.

Next slide for ARS question

Laboratory studies:	
Hgb A1C	9.8%
Sodium	133 mEq/L (133 mmol/L)
Bicarbonate	10 mEq/L (10 mmol/L)
Glucose	150 mg/dL (8.3 mmol/L)
Anion gap	17 mEq/L (16 mmol/L)
Creatinine	1.17 mg/dL (103 μmol/L)
Urine ketones	Elevated

Peters, 2015

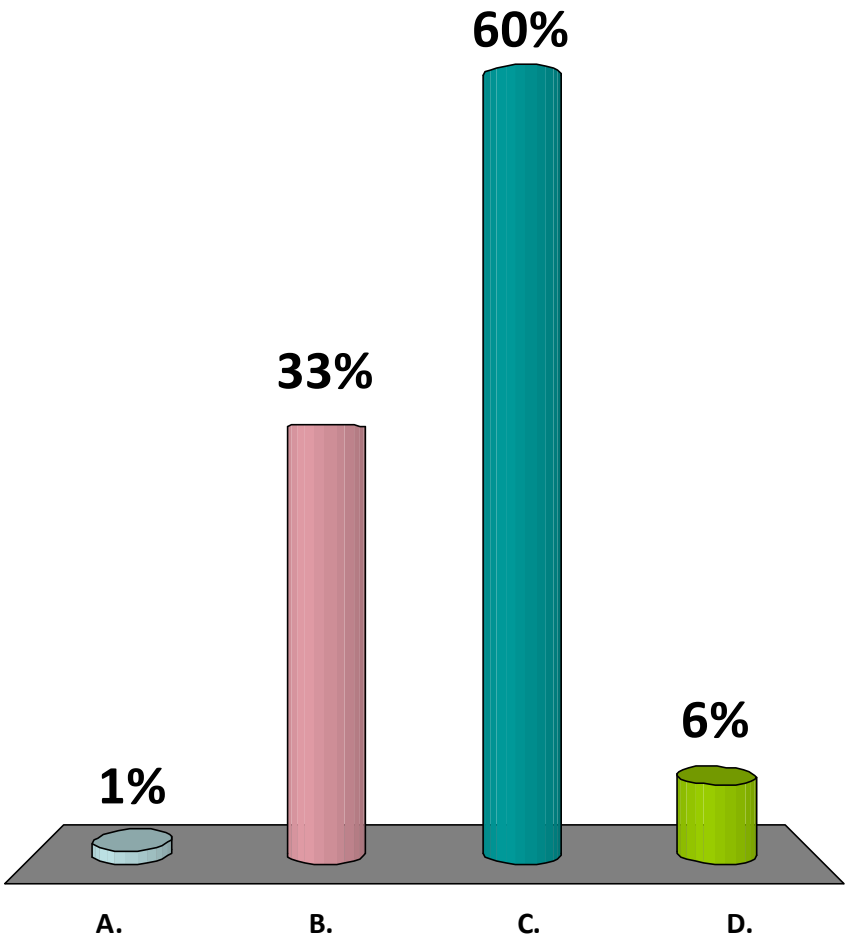
ARS 3: Which of the following is most likely responsible for the patient's findings?

A. Atorvastatin

B. Metformin

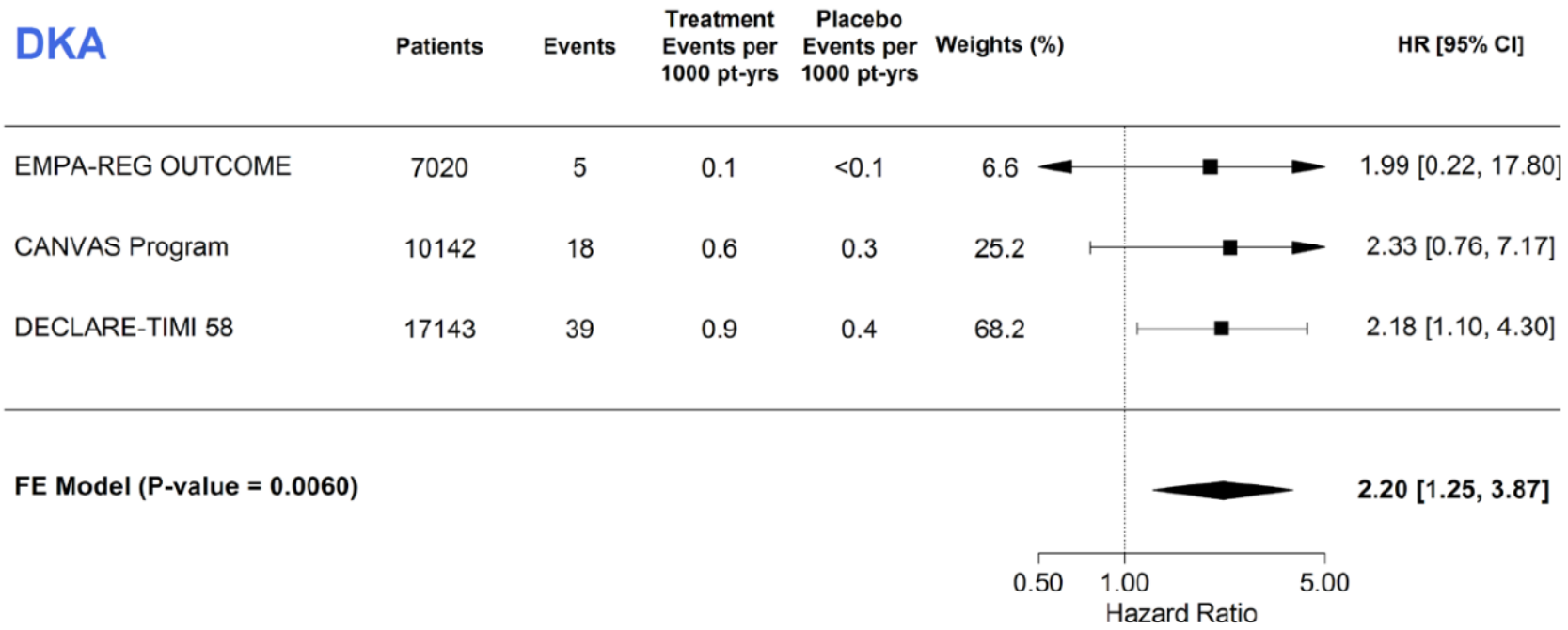
C. Canagliflozin

D. Lisinopril



SGLT-2 inhibitors increase the risk for diabetic ketoacidosis

Figure S20: Risk of diabetic ketoacidosis



Q statistic = 0·02, p=0·99, I^2= 0%

Zelniker, 2019

DKA from SGLT-2 inhibitors can occur with relatively low serum BG

In a review of DKA cases occurring with SGLT-2 use, mean BG was 265.6 (+/- 140.7) mg/dL

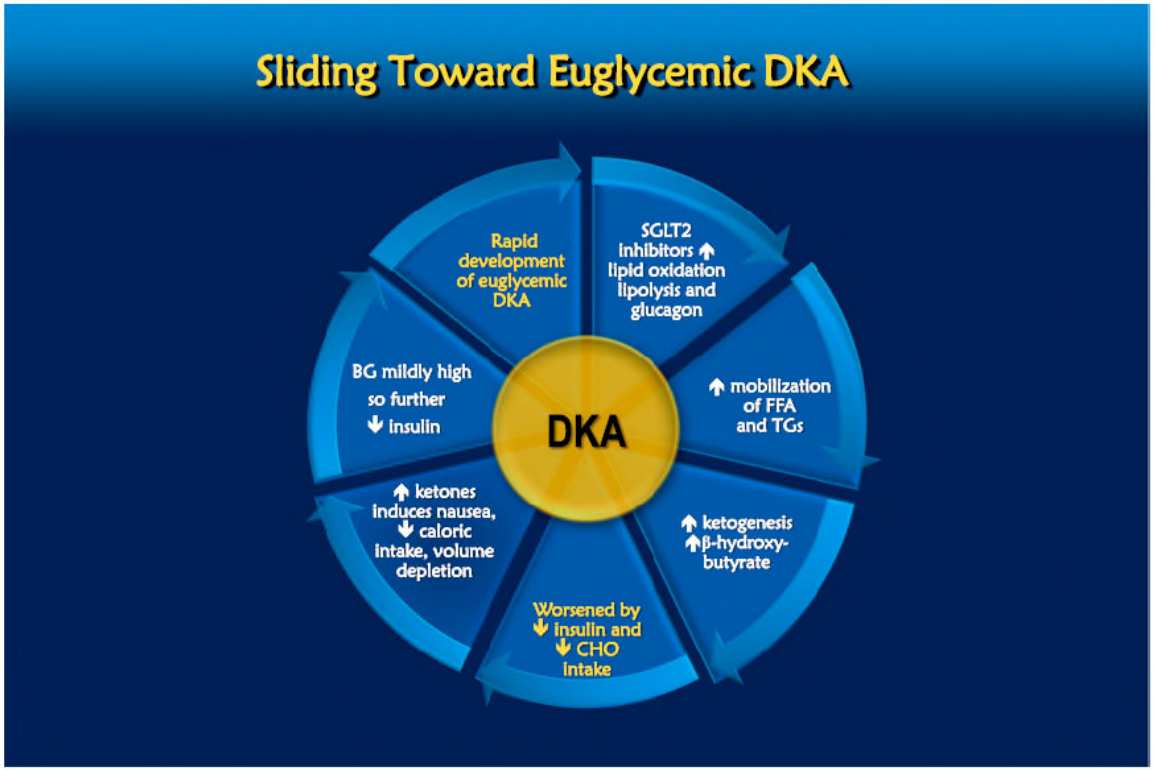


Figure 2—Demonstration of the cascade of clinical events and metabolic changes that contribute sequentially to progressive clinical deterioration and development of full-blown episodes of euDKA. BG, blood glucose; CHO, carbohydrate; TGs, triglycerides.

Clinicians should check serum ketones in patients if clinical suspicion is high (i.e., symptoms and risk factors are present), even if BG is only mildly elevated

Rosenstock et al., 2015
Burke et al., 2017

SGLT-2 agonists and CV event reduction

Benefits

- When used as second-step therapy (after metformin) in Type 2 diabetes for patients with ASCVD, SGLT-2 inhibitors perform better than placebo (and possibly better than other drugs) for reducing CV events (NNT = 167 per year)
  - Reduction in weight and blood pressure in the treatment group across all trials

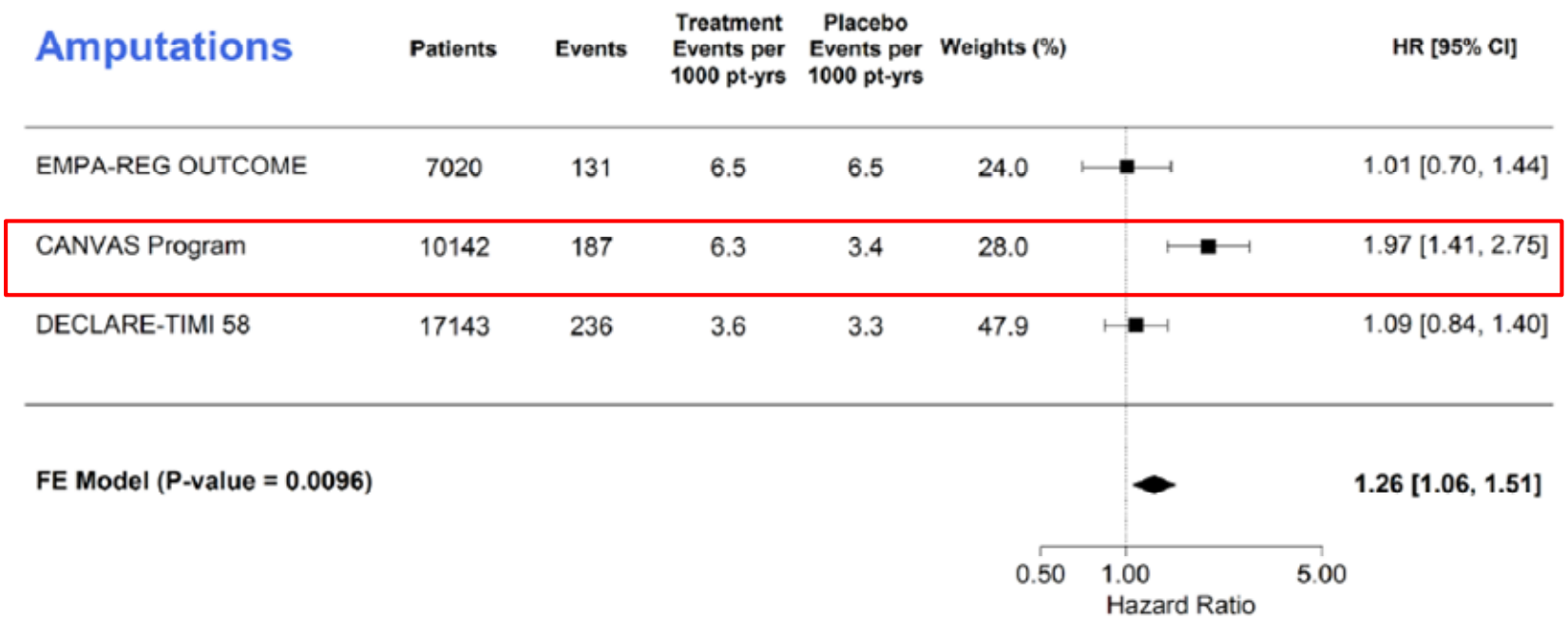
Risks

- Associated with genital infections and Fournier gangrene
  - FG 1.6 cases per 100,000 men (peak 3 per 100,000 men ages 50-74)
- Associated with increased risk for diabetic ketoacidosis
- Drug class is still too new to know full risk profile

Lin et al., 2018
Bersoff-Matcha et al., 2019
Zelniker et al., *Lancet.* 2019

SGLT-2 inhibitors may increase the risk for amputation in some patients

Risk of amputations possibly higher among patients taking SGLT-2 inhibitors

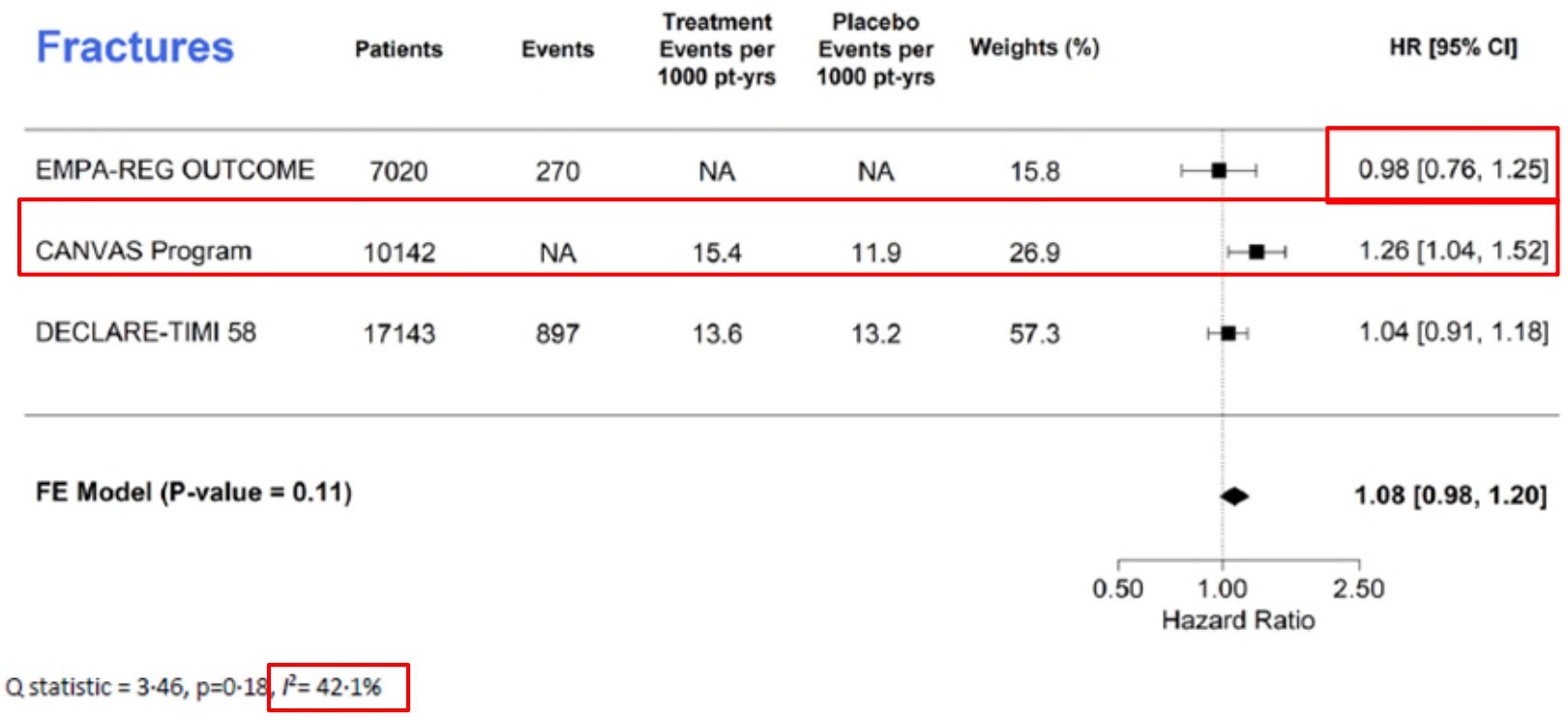


Zelniker, 2019

High heterogeneity across studies. Results mainly driven by CANVAS trial.

Insufficient evidence for SGLT-2 inhibitors increasing risk for fracture

Risk of fractures possibly higher among patients taking SGLT-2 inhibitors



Zelniker, 2019

Moderate heterogeneity across studies. Results mainly driven by CANVAS trial. Non-significant decrease among patients taking empagliflozin.

Recommendation

- For people with type 2 diabetes not controlled on metformin monotherapy and with clinical ASCVD, consider prescribing an SGLT-2 inhibitor to reduce the risk of cardiovascular events (myocardial infarction or stroke) or cardiovascular death
- (Conditional Recommendation)

Question 4

You evaluate a 45-year-old woman for management of her type 2 diabetes mellitus. She was diagnosed with type 2 diabetes 8 years ago after having gestational diabetes but did not make efforts to treat it for several years. Medical history is also significant for hypertension, hyperlipidemia, history of tobacco use, diabetic retinopathy, diabetic polyneuropathy, recurrent vaginal yeast infections and chronic kidney disease stage G3b. Medications are metformin, lisinopril, HCTZ, amlodipine, atorvastatin and aspirin.

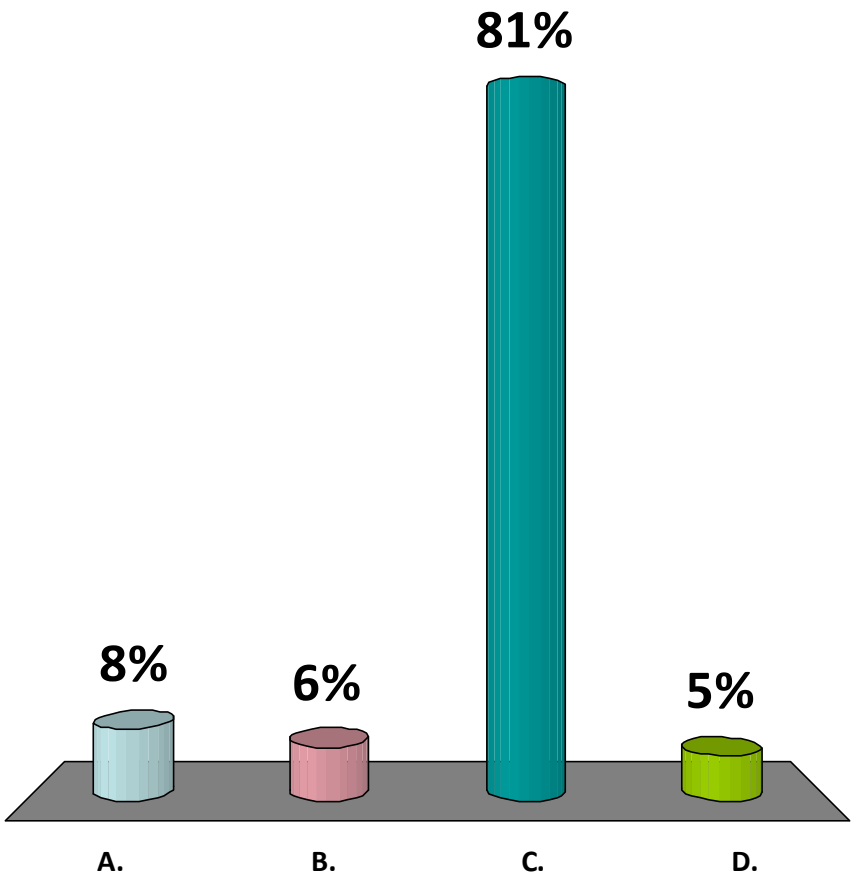
On physical examination, vital signs are normal. BMI is 42. A foot examination reveals an insensate foot with intact skin. The remainder of the physical examination is normal.

Results of laboratory studies show a hemoglobin A_{1c} of 10.5% and serum creatinine level of 1.4 mg/dL (123.8 mmol/L). Estimated glomerular filtration rate (eGFR) is 44 mL/min/1.73 m^2. Urine albumin-to-creatinine ratio is 400.

Next slide for ARS question

ARS 4: Which of the following is the most appropriate management of this patient's diabetes?

A. Discontinue metformin
B. Offer empagliflozin
C. Offer NPH insulin
D. Offer glipizide

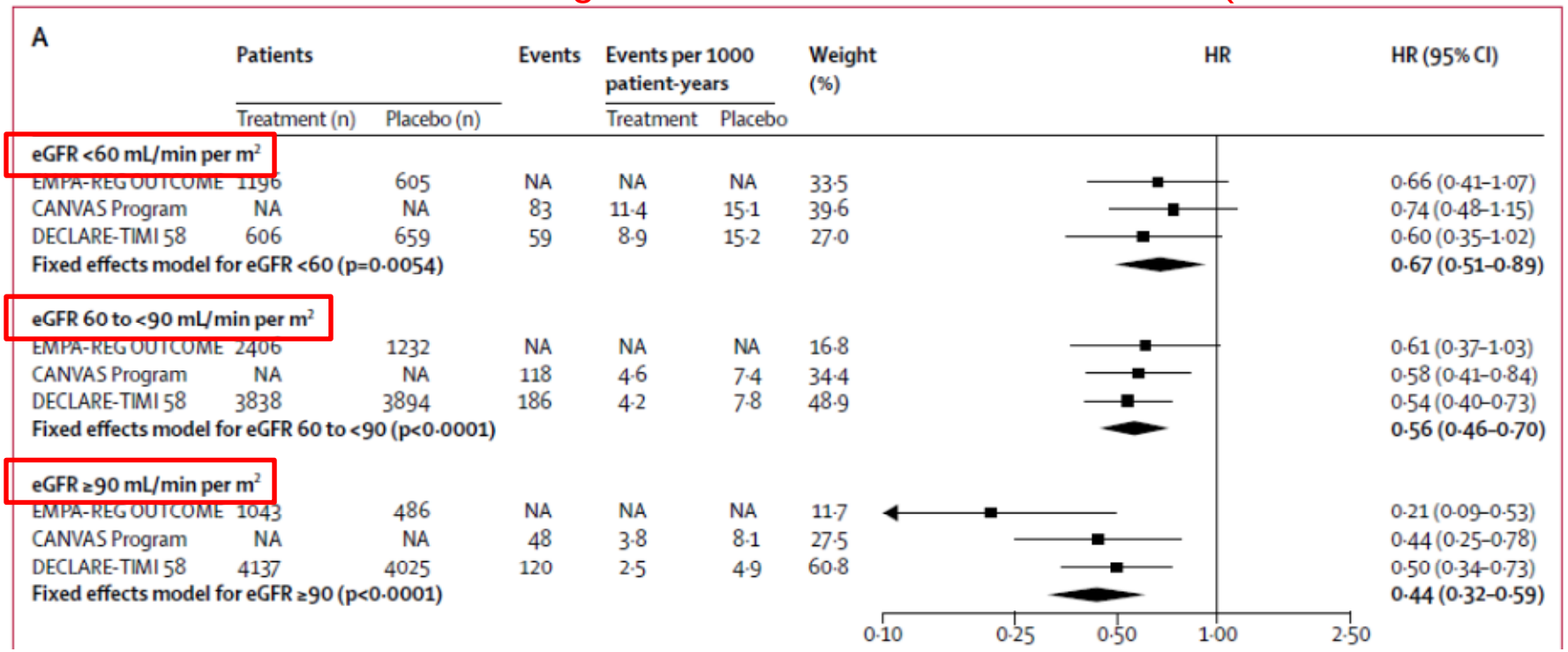


Comparative effectiveness of SGLT-2 inhibitors in lowering the risk of worsening renal disease, end-stage renal disease or renal death

SGLT-2 inhibitors vs. placebo and reduction of renal outcomes

SGLT-2 inhibitors for reduction of renal events and mortality (Zelniker, 2019)

The *absolute* risk reduction is greatest for those with eGFR < 60 (NNT = 167 to 250)



A	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
eGFR <60 mL/min per m²								
EMPA-REG OUTCOME	1196	605	NA	NA	NA	33·5		0·66 (0·41–1·07)
CANVAS Program	NA	NA	83	11·4	15·1	39·6		0·74 (0·48–1·15)
DECLARE-TIMI 58	606	659	59	8·9	15·2	27·0		0·60 (0·35–1·02)
Fixed effects model for eGFR <60 (p=0·0054)								**0·67 (0·51–0·89)**
eGFR 60 to <90 mL/min per m²								
EMPA-REG OUTCOME	2406	1232	NA	NA	NA	16·8		0·61 (0·37–1·03)
CANVAS Program	NA	NA	118	4·6	7·4	34·4		0·58 (0·41–0·84)
DECLARE-TIMI 58	3838	3894	186	4·2	7·8	48·9		0·54 (0·40–0·73)
Fixed effects model for eGFR 60 to <90 (p<0·0001)								**0·56 (0·46–0·70)**
eGFR ≥90 mL/min per m²								
EMPA-REG OUTCOME	1043	486	NA	NA	NA	11·7		0·21 (0·09–0·53)
CANVAS Program	NA	NA	48	3·8	8·1	27·5		0·44 (0·25–0·78)
DECLARE-TIMI 58	4137	4025	120	2·5	4·9	60·8		0·50 (0·34–0·73)
Fixed effects model for eGFR ≥90 (p<0·0001)								**0·44 (0·32–0·59)**

While all subgroups experience a *relative* reduction in the risk of renal outcomes…

Recommendation

- For people with type 2 diabetes not controlled on metformin monotherapy, with eGFR 30 to 59 ml per minute per 1.73 m^2, consider prescribing an SGLT-2 inhibitor to reduce (1) progression of renal disease and/or (2) death from renal causes.
- (Conditional Recommendation)

CREDENCE: N = 4,401 with median follow-up 2.6 years

- Study Population:
  - Type 2 diabetes not controlled on metformin monotherapy, with eGFR pf 30 to <90 and macroalbuminuria (urinary albumin-to-creatinine ratio, >300 to 5000)
  - All participants required to be on ACE or ARB for 4+ weeks prior to randomization
  - About 30% of participants had eGFR 30-45

Reduction in composite renal outcome for those with urine a/c > 300

CREDENCE

Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no./total no.		*events/ 1000 patient-yr*			
Efficacy						
Primary composite outcome	245/2202	340/2199	43.2	61.2	0.70 (0.59–0.82)	0.00001

The absolute reduction in risk of a renal outcome among those with macroalbuminuria is also relatively high (NNT = 77 per year; one study)

SGLT-2 agonists and reduction of renal events and renal death

Benefits

- When used as second-line therapy (after metformin) in Type 2 diabetes for patients with ASCVD or multiple risk factors and urine a/c > 300, **canagliflozin and empagliflozin** perform better than placebo (and possibly other drugs) for reducing renal outcomes
  - Reduction in weight and blood pressure in the treatment group across all trials

Risks

- Associated with genitourinary infections and Fournier gangrene
  - FG 1.6 cases per 100,000 men (peak 3 per 100,000 men ages 50-74)
- Associated with increased risk for diabetic ketoacidosis
  - eGFR 30-45 + urine A/C > 300 on ACE or ARB may be an additional risk factor
- Drug class is still too new to know full risk profile

Recommendation

- For people with type 2 diabetes not controlled on metformin monotherapy, with macroalbuminuria (urinary albumin-to-creatinine ratio, >300 to 5000), consider prescribing canagliflozin or empagliflozin to reduce (1) progression of renal disease and/or (2) death from renal causes
- (Conditional Recommendation)

eGFR 30-59 or urine A/C >300

Who is most eligible for an SGLT-2 inhibitor?

- The A1C should be within 2% of goal on metformin alone
- Measure the urine albumin-to-creatinine ratio and consider SGLT-2 if already taking an ACE or an ARB
- Optimize the dosage of an ACE or ARB as much as possible also
- Right now the drug monographs recommend against starting or continuing empagliflozin for patients with an eGFR of 30-44
  - The regions are still examining how to operationalize the guideline given this caveat
- Conclusion: For those with an eGFR of 30-59 and/or urine albumin-to-creatinine ratio >300, an SGLT-2 inhibitor **reduces the risk of important renal outcomes**

Question 5

You evaluate a 67-year-old man for management of his type 2 diabetes mellitus, which was diagnosed 6 years ago. Medical history is also significant for hypertension, atrial fibrillation and systolic heart failure with an ejection fraction of 45%. Medications are lisinopril, atorvastatin, metformin, metoprolol, furosemide and warfarin. He walks on a treadmill most days for 30 minutes at a moderate pace.

On physical examination, blood pressure is 112/64, pulse is irregularly irregular with an auscultated rate of 68. BMI is 34. The rest of the physical examination is unremarkable.

Results of laboratory studies show a hemoglobin A_{1c} of 8.3%. INR is 2.7. Remaining laboratory results are normal.

Next slide for ARS question

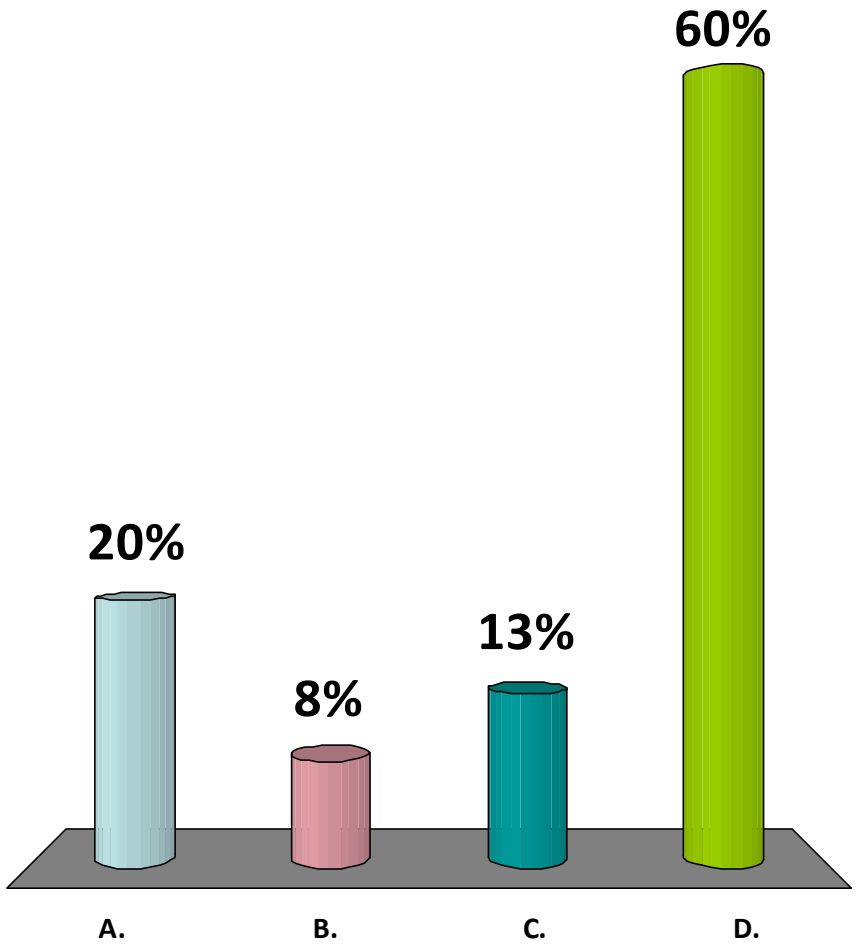
ARS 5: Which of the following is the most appropriate management of this patient's diabetes?

A. Offer glipizide

B. Offer pioglitazone

C. Offer liraglutide

D. Offer empagliflozin

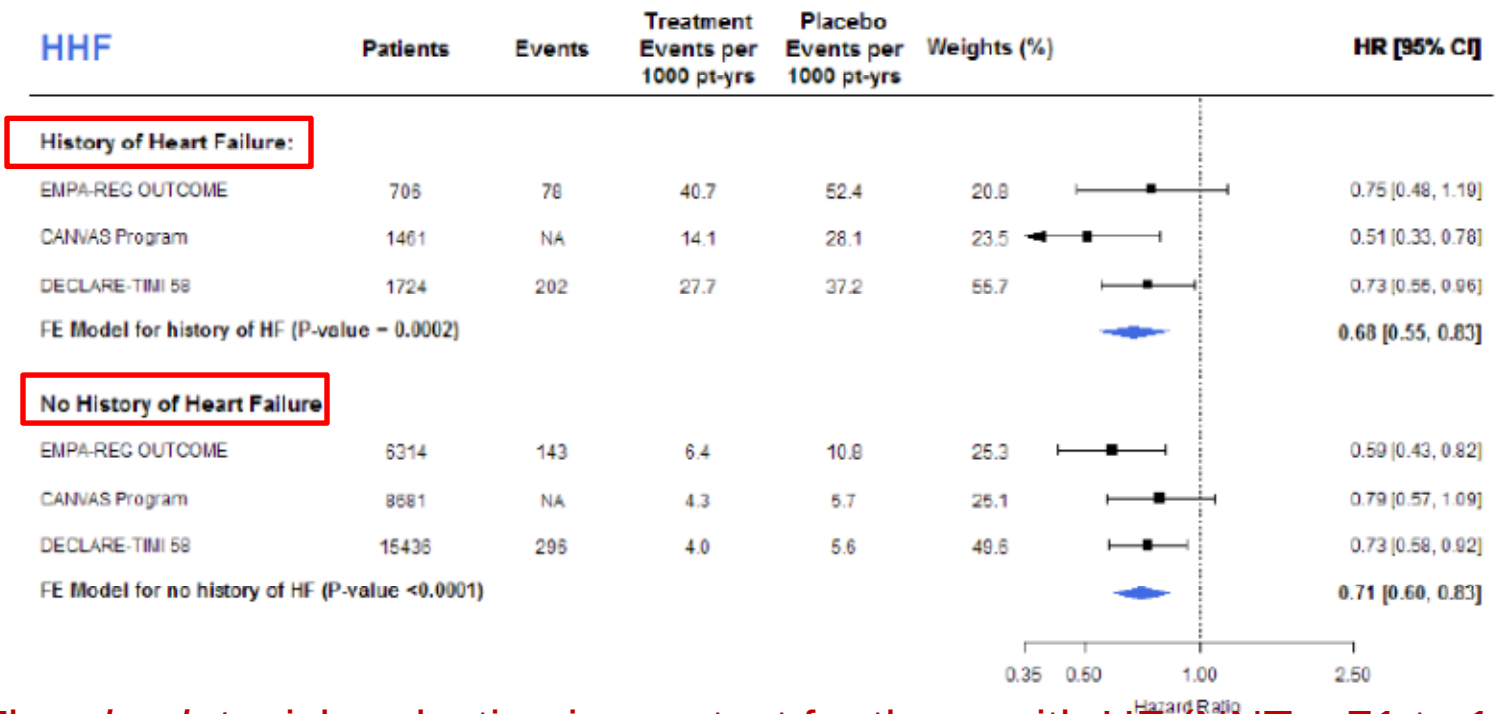


Comparative effectiveness of SGLT-2 inhibitors in lowering the risk of heart failure hospitalizations

SGLT-2 inhibitors vs. placebo for reduction of HF hospitalizations (with and without HF at baseline)

SGLT-2 inhibitors for reduction of heart failure hospitalizations (Zelniker, 2019)

Figure S13: Treatment effect on hospitalization for heart failure stratified by history of heart failure



The *absolute* risk reduction is greatest for those with HF (NNT = 71 to 100)

Prior HF: Q statistic = 2·14, p=0·34, I^2= 6·6%
No HF: Q statistic = 1·73, p=0·42, I^2= 0%
P-value for subgroup differences: 0·76

Recommendation

For people with type 2 diabetes not controlled on metformin monotherapy, with a history of heart failure, consider prescribing an SGLT-2 inhibitor to reduce heart failure hospitalizations.

(Conditional Recommendation)

Cardiovascular, renal and heart failure benefits of SGLT-2 inhibitors *across* high risk subgroups

Cross-subgroup benefits of SGLT-2 inhibitors

- Patients with diabetes and existing cardiovascular disease experience renal and heart failure preventive benefits
  - Pooled studies: Patients with diabetes and ASCVD taking SGLT-2 inhibitors also experienced an absolute reduction in risk of composite renal outcomes (NNT = 200-250) and of heart failure hospitalizations (NNT = 250-333)

Cross-subgroup benefits of SGLT-2 inhibitors

- Patients with diabetes and existing renal disease experience cardiovascular and heart failure preventive benefits
  - Pooled studies: Patients with diabetes and eGFR 30-59 taking SGLT-2 inhibitors also experienced an absolute reduction in risk of composite cardiovascular outcomes (NNT = 77-125) and of heart failure hospitalizations (NNT = 100-142)

Cross-subgroup benefits of SGLT-2 inhibitors

- Patients with diabetes and existing renal disease experience cardiovascular and heart failure preventive benefits
  - CREDENCE: Patients with diabetes and macroalbuminuria taking SGLT-2 inhibitors also experienced an absolute reduction in risk of composite cardiovascular outcomes (NNT = 100) and of heart failure hospitalizations (NNT = 100)

Cross-subgroup benefits of SGLT-2 inhibitors

- Patients with existing heart failure may experience cardiovascular and renal benefits, though pooled studies do not report these outcomes
- DAPA-HF (4,744 with HFrEF), 18 mo f/u
  - HR 0.82 (06.9 to 09.8) for CV death in dapaglifozin group

Final recommendations (combined)

For people with type 2 diabetes not controlled on metformin monotherapy, with ASCVD, consider prescribing an SGLT-2 inhibitor to reduce the risk of (1) cardiovascular events (myocardial infarction or stroke) or cardiovascular death, (2) progression of renal disease and/or (3) death from renal causes, and/or (4) heart failure hospitalizations.

(Conditional Recommendation)

For people with type 2 diabetes not controlled on metformin monotherapy, with eGFR 30 to 59 ml per minute per 1.73 m^2, consider prescribing an SGLT-2 inhibitor to reduce the risk of (1) cardiovascular events (myocardial infarction or stroke) or cardiovascular death, (2) progression of renal disease and/or (3) death from renal causes, and/or (4) heart failure hospitalizations.

(Conditional Recommendation)

Final recommendations (combined)

For people with type 2 diabetes not controlled on metformin monotherapy, with macroalbuminuria (urinary albumin-to-creatinine ratio, >300), consider prescribing canagliflozin or empagliflozin to reduce the risk of (1) cardiovascular events (myocardial infarction or stroke) or cardiovascular death, and/or (2) progression of renal disease and/or (3) death from renal causes and/or (4) heart failure hospitalizations.
(Conditional Recommendation)

For people with type 2 diabetes not controlled on metformin monotherapy, with a history of heart failure, consider prescribing an SGLT-2 inhibitor to reduce the risk of heart failure hospitalizations.
(Conditional Recommendation)

Question 6

You evaluate a 59-year-old man during a routine office visit. He was diagnosed with type 2 diabetes mellitus 6 years ago. Medical history is significant for coronary artery disease, hypertension, hyperlipidemia, hidradenitis suppurativa and groin abscess. Medications are lisinopril, metoprolol, metformin, aspirin, and atorvastatin.

On physical examination, vital signs are normal. BMI is 38. The remainder of the examination is normal.

Laboratory studies show a hemoglobin A_{1c} level of 8.2%.

Next slide for ARS question

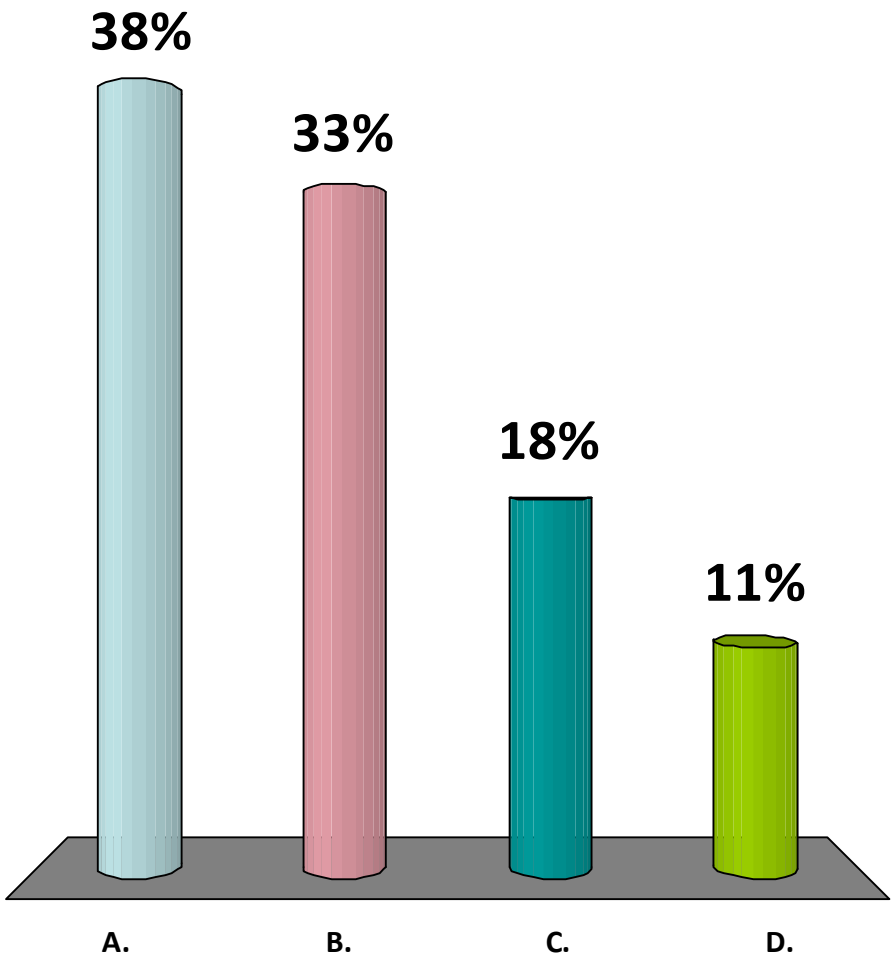
ARS 6: Which of the following is the most appropriate management of this patient's diabetes?

A. Offer empagliflozin

B. Offer glipizide

C. Offer liraglutide

D. Offer linagliptin



Comparative effectiveness of GLP-1 agonists in lowering the risk of CV events

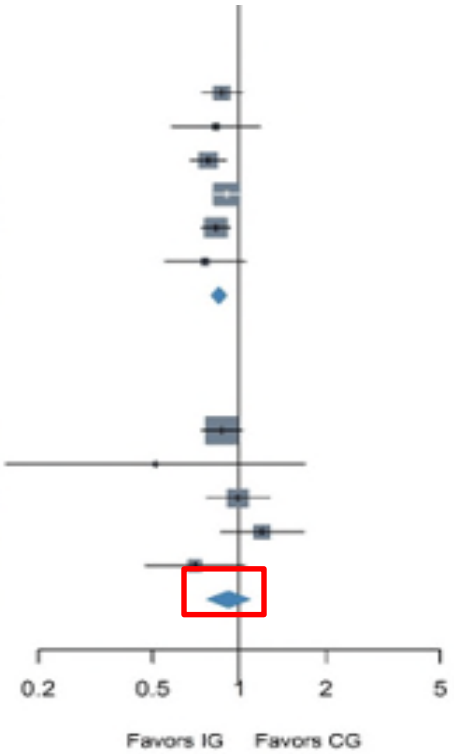
Mechanism of action of GLP-1 agonists

- Analog of human glucagon-like peptide-1 (GLP-1) (an incretin hormone)
  - Increases glucose-dependent insulin secretion,
  - Decreases inappropriate glucagon secretion,
  - Increases B-cell growth/replication,
  - Slows gastric emptying, and
  - Decreases food intake.

GLP-1 agonists vs. placebo for composite CV outcome

GLP-1 agonists for diabetics with and without clinical ASCVD (Lin, 2019)

Participants with CVD								
Dulaglutide	REWIND	2019	5.4 years	100	280/1560 (17.9%)	315/1554 (20.3%)	0.87	[0.74; 1.02]
Semaglutide (oral)	PIONEER 6	2019	1.3 years	100	57/1350 (4.2%)	68/1345 (5.1%)	0.83	[0.58; 1.18]
Albiglutide	HARMONY	2018	1.6 years	100	338/4731 (7.1%)	428/4732) (9.0%)	0.78	[0.68; 0.90]
Exenatide	EXSCEL	2017	3.2 years	100	722/5394 (13.4%)	786/5388 (14.6%)	0.90	[0.82; 1.00]
Liraglutide	LEADER	2016	3.8 years	100	536/3831 (14.0%)	629/3767 (16.7%)	0.83	[0.74; 0.93]
Semaglutide (injection)	SUSTAIN-6	2016	2.1 years	100	66/673 (9.8%)	88/694 (12.7%)	0.76	[0.55; 1.05]
Overall							**0.85**	**[0.80; 0.90]**
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.60$								
Participants without CVD								
Dulaglutide	REWIND	2019	5.4 years	0	277/3093 (8.9%)	317/3128 (10.1%)	0.87	[0.74; 1.02]
Semaglutide (oral)	PIONEER 6	2019	1.3 years	0	4/241 (1.7%)	8/247 (3.2%)	0.51	[0.15; 1.69]
Exenatide	EXSCEL	2017	3.2 years	0	117/1962 (6.0%)	119/2008 (5.9%)	0.99	[0.77; 1.28]
Liraglutide	LEADER	2016	3.8 years	0	72/837 (8.6%)	65/905 (7.2%)	1.20	[0.86; 1.67]
Semaglutide (injection)	SUSTAIN-6	2016	2.1 years	0	42/975 (4.3%)	58/955 (6.1%)	0.70	[0.47; 1.04]
Overall							**0.92**	**[0.77; 1.08]**
Heterogeneity: $I^2 = 33\%$, $\tau^2 = 0.01$, $p = 0.20$								



- ELIXA trial excluded due to differences in study population compared to other GLP-1 trials

GLP-1 agonists and CV outcome reduction

Benefits

- When used as second-line therapy (after metformin) in Type 2 diabetes for patients with ASCVD, GLP-1 agonists perform better than placebo (and possibly other drugs) for reducing CV events (NNT unknown)
- GLP-1 agonists are associated with weight loss, which varies according to the specific agent

Harms

- May be discontinued due to minor side effects (more so than SGLT-2 inhibitor)—gastrointestinal side effects most common
- There have been case reports of biliary disease, pancreatitis
- Contraindicated in MEN-2 and/or if there is a history of medullary thyroid cancer (animal studies)
- Mostly injectable (liraglutide: daily; dulaglutide: weekly)

Final recommendation

- For people with type 2 diabetes not controlled on metformin monotherapy and with clinical ASCVD who cannot or prefer not to take an SGLT-2 inhibitor, consider prescribing GLP-1 agonists to reduce the risk of cardiovascular events (myocardial infarction or stroke) or cardiovascular death.
- (Conditional Recommendation)

DPP-4 inhibitors and CV outcomes

- 4 trials of DPP-4 vs. placebo, all added to metformin
  - CARMELINA (N = 6,991), linagliptin
  - TECOS (N = 14,671), sitagliptin
  - SAVOR TIMI 53 (N = 16,492), saxagliptin
  - EXAMINE (N = 5,380), alogliptin
- All trials found that the rates of MACE were not increased in the intervention arm vs. placebo (non-inferiority demonstrated)

Sulfonylureas and CV outcomes

- CAROLINA trial (N = 6,033), f/u 6.3 yr
  - Linagliptin vs. glimepiride (added to metformin)
  - No sig. difference between treatments in CV event incidence

Comparative effectiveness of GLP-1 agonists in lowering the risk of worsening renal disease, end-stage renal disease or renal death

Little evidence for GLP-1 agonists reducing risk of key renal outcomes

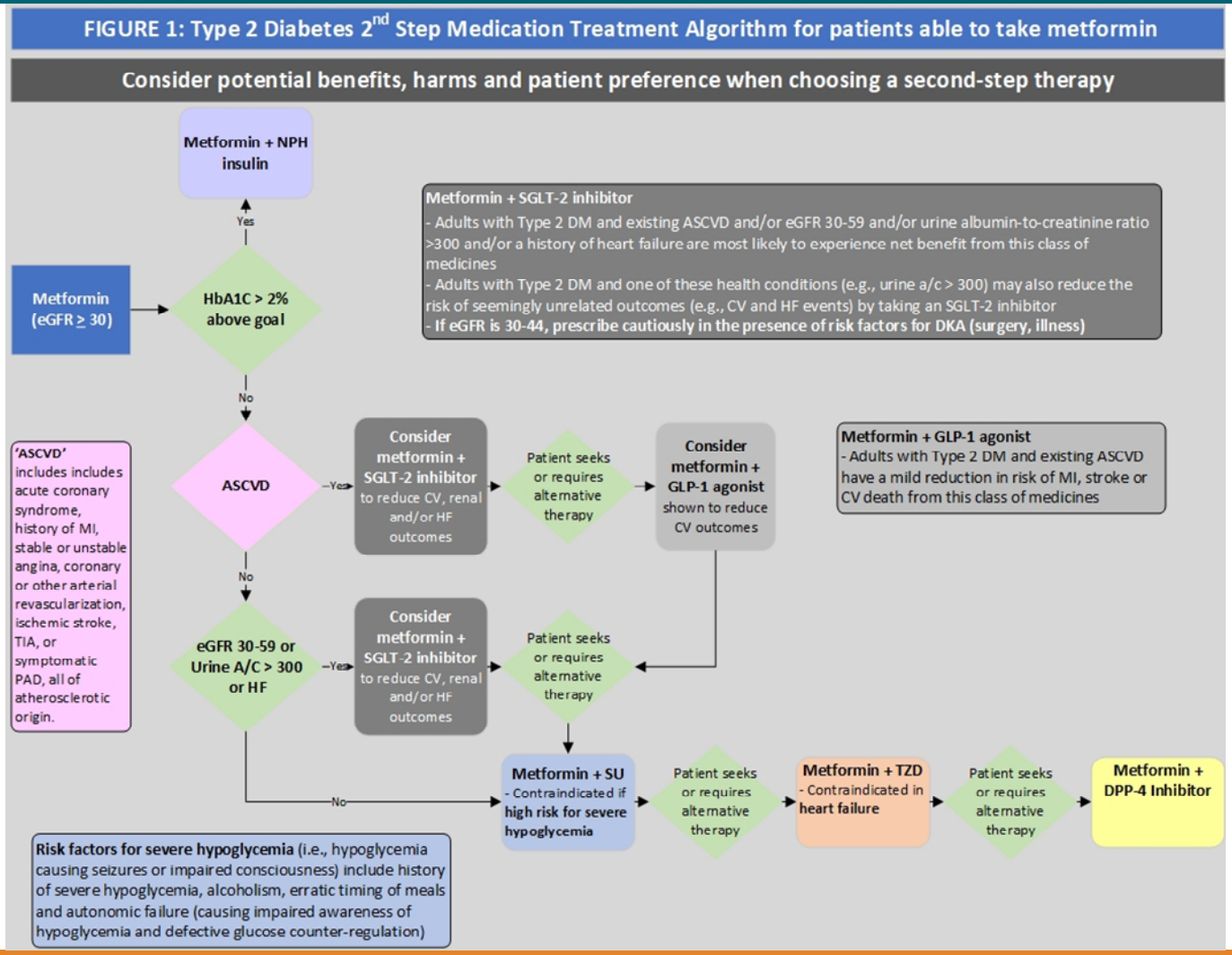
- One meta-analysis comparing trials of GLP-1 agonists vs. placebo reports renal outcomes
  - Kristensen, 2019
  - No significant difference between GLP-1 agonists vs placebo for hard outcomes of end stage kidney disease and renal death
  - Reported results heavily driven by intermediate outcomes
- One trial (REWIND: dulaglutide) of GLP-1 agonist vs. placebo reports incidence of renal outcomes by eGFR subgroups
  - Composite outcome differs from that reported in SGLT-2 studies—renal death not included
  - Results by subgroup differ from those reported in SGLT-2 studies—unclear why
- Evidence remains insufficient

Comparative effectiveness of GLP-1 agonists in lowering the risk of heart failure hospitalizations

No evidence for GLP-1 agonists

- There is no reduction in heart failure hospitalization when comparing the intervention group to the placebo group in any GLP-1 agonist study, regardless of heart failure status at baseline.

Diabetes Treatment Algorithm



Graphical Decision Aid

Benefits and risks of second-step medications for Type 2 diabetes not adequately controlled on metformin*										
Drug class	**Drug names (examples)**	**Hgb A_{1c} lowering**	**Cardiovascular problems**	**Kidney problems**	**Heart failure problems**	**Hypoglycemia potential**	**Other common effects (5-30%)**	**Rare complications or risks (<1%)**	**Other possible risks (not proven)**	**Cost**
NPH insulin	Humulin N	++++ (unlimited)	Neutral	Neutral	Neutral	High	Weight gain (1-5 kg)	Severe hypoglycemia	None	Low
Sulfonylurea	glipizide, glimepiride	++ (1-2%)	Neutral	Neutral	Neutral	Moderate	Weight gain (1-3 kg)	Severe hypoglycemia	Avoid if severe sulfa allergy	Low
SGLT-2 inhibitor	empagliflozin	+ (0.5-1%)	Prevents for some	Prevents for some	Prevents for some	Low	Genital infections, weight loss (1-3 kg)	DKA, pancreatitis, Fournier gangrene	Amputation, fracture	High
GLP-1 agonist	liraglutide, exenatide ER	+ (1%)	Prevents for some	?	Neutral	Low	Nausea, diarrhea, weight loss (1-3 kg)	Pancreatitis, biliary disease	Medullary thyroid cancer	High
TZD	pioglitazone	+ (1%)	?	Neutral	Worsens for some	Low	Weight gain (1-3 kg), edema	Fracture	Bladder cancer	Low
DPP-4 inhibitor	linagliptin	+ (0.5%)	Neutral	Neutral	Neutral	Low	None	Arthralgia, pancreatitis	None	High

**The above table was adapted with permission from the Diabetes Medication Choice Decision Aid by the Mayo Clinic Shared Decision-Making National Resource Center*

Benefits of SGLT-2i's and GLP-1a's

Absolute and relative benefits of SGLT-2 inhibitors and GLP-1 agonists within high-risk subgroups			
Outcome	**High-risk subgroups**	**Absolute events prevented per 1,000 persons per year of use (events per year)**	**Relative events prevented per type of event (range)**
SGLT-2 inhibitors			
Cardiovascular health events (myocardial infarction, stroke or CV-related death)	ASCVD	6-7 of 43-44	14-31% prevention of cardiovascular events
	eGFR 30-59	6-8 of 43-60	
	Urine A/C > 300	10 of 49	
Kidney health events (significant worsening of kidney function, need for dialysis or kidney-related death)	ASCVD	4-5 of 8-12	34-44% prevention of kidney health events
	eGFR 30-59	4-6 of 15	
	Urine A/C > 300	13 of 40	
Heart failure hospitalizations	ASCVD	3-5 of 11-14	29-40% prevention of heart failure hospitalizations
	eGFR 30-59	7-10 of 19-26	
	Urine A/C > 300	10 of 25	
	HF	10-14 of 28-52	
GLP-1 agonists			
Cardiovascular health events (myocardial infarction, stroke, or CV-related death)	ASCVD	Not reported	15% prevention of cardiovascular events

Thank you