ashp MIDYEAR 2018
Clinical Meeting & Exhibition

Examining the Influence of Cardiovascular Outcome Trials: Is It the Heart of Diabetes?

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Learning Objectives

- Evaluate the potential benefits of antidiabetic therapy beyond A1c lowering effects.
- Given a case study, analyze the results from antidiabetic therapy cardiovascular outcome clinical trials (CVOT).
- Given a case study, design an individualized, evidence-based pharmacotherapeutic plan for a patient with type 2 diabetes.
- Given a scenario, recommend strategies for identifying and integrating into practice the results of new CVOT literature involving antidiabetic drug therapy.

Disclosure

- Melody Hartzler – Janssen & Valeritas (Speaker's Bureau)
- All other planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.

Session Announcements

Beyond A1c: Possible CV Benefits

- Reductions in glucose variability
- Reductions in uric acid [Sodium-glucose cotransporter-2 inhibitors (SGLT2i)]
- Weight loss
- BP reduction (SGLT2i)
- Increased cardiac contractility (GLP-1 Receptor Agonist)
- Reduction in preload and afterload (SGLT2i)
- Reduction in arterial stiffness (SGLT2i)

Ferrannini E, DeFronzo RA. *Eur Heart J*. 2015;36(34):2288-96.

Meet CJ

- 55-year-old African American male with a history of CABG x 3
- Type 2 DM x 15 years
- HTN
- Hyperlipidemia (high TG and LDL)

- Current medications include:
  - Clopidogrel 75 mg orally daily
  - ASA 325 mg orally daily
  - Metformin 1,000 mg orally twice daily
  - Glipizide 5 mg orally twice daily
  - Lisinopril/HCTZ 20-12.5, two tablets orally daily
  - Metoprolol 25 mg ER orally daily
  - Atorvastatin 40 mg orally daily

Meet CJ

- Height 5 ‘ 9”
- Weight 260 lb
- BMI: 38.4 kg/m^2

- BP today is 145/87 mm Hg, Pulse of 62 bpm

- Today CJ is here for follow-up for his diabetes. A1c is 9.5%, other labs are WNL, including renal function.

- During your initial review of systems with CJ you learn that his blood glucose levels are fluctuating anywhere from 55 to 400 mg/dL in a given day.

Question 1

Which of the following cardiovascular (CV) risk reduction strategies should we think about first for CJ?

a) Reductions in glucose variability
b) Weight loss
c) BP reduction
d) Reduction in uric acid

Answer to Question 1

Which of the following cardiovascular (CV) risk reduction strategies should we think about first for CJ?

a) Reductions in glucose variability

- First we should work on decreasing glucose variability (GV), which has been linked to inflammation, elevated C-reactive protein, insulin resistance, and all-cause mortality.
- His weight and BP need improvement as well, but they may improve with diabetes treatment added to reduce GV.

Nyiraty S et al. *Front Endocrinol. 2018; 9:174.;* Farkouh M. *JACC Cardiovasc Interv.* 2015; 8(5):812–3.; Liang S et al. *J Diabetes Metab Disord.* 2017; 16:45.; Zinman B et al. *Diabetologia.* 2018; 61: 48–5.; Natsuaki M et al. *Circulation.* 2015; 79: 972-973.

Glucose Variability

- GV is also associated with:
  - Cardiovascular autonomic neuropathy in patients with type 1 diabetes[1]
  - Worse outcomes for MI patients undergoing PCI[2]
  - Increased production of reactive oxygen species leading to detrimental effect on endothelial tissue[3]

1. Nyiraty S et al. *Front Endocrinol. 2018; 9:174.*
2. Farkouh M. *JACC Cardiovasc Interv.* 2015; 8(5):812–3.
3. Liang S et al. *J Diabetes Metab Disord.* 2017; 16(45):1-9.

Glucose Variability

- A recent meta-analysis showed minimizing GV is accompanied by a reduction of carotid intima-media thickness with an estimated magnitude between 0.09 and 0.47 mm.
  - This is consistent with an estimated 11% to 59% reduction in risk of MI and a 13% to 70% reduction in risk of stroke.
  - Minimizing GV also resulted in an improvement in insulin resistance measures.

Liang S et al. *J Diabetes Metab Disord.* 2017; 16(45):1-9.

Glucose Variability

- DEVOTE-2[1]
  - High day-to-day fasting glycemic variability is associated with increased risks of severe hypoglycemia and all-cause mortality.
- Higher level of variability could be the cause of left ventricular remodeling in the chronic phase in patients with acute MI regardless of the level of A1c[2]

1. Zinman B et al. *Diabetologia.* 2018; 61: 48–5.
2. Natsuaki M et al. *Circulation.* 2015; 79: 972-973.

Uric Acid

- Studies are mixed
  - Some studies that have controlled for multiple risk factors suggest that elevated uric acid may be an independent risk factor for both cardiovascular disease and kidney disease
  - Other studies have shown that an elevated level of uric acid predicts the development of hypertension, obesity, kidney disease, and diabetes
  - Some reports of cardiovascular and renal benefits when lowering uric acid in preliminary clinical trials
- We need to understand more about its role
  - Uric acid can be pro-inflammatory in adipocytes and vascular tissue but also can function as an antioxidant and have beneficial effects for neurological conditions

Feig D et al. *N Engl J Med.* 2008;359:1811-21.

Cardiovascular Risk Data for Diabetes Medications

Metformin

Proposed CV Benefits

- Studies have demonstrated that metformin improves CV outcomes outcomes compared with sulfonylureas.
- Proposed mechanisms for CV protective effect of metformin[1]:
  - Improved glucose control, reduction in methylglyoxal levels, decrease in VLDL secretion and plasma triglyceride levels, and reduced postprandial lipemia

Evidence

- UKPDS showed metformin significantly decreased:
  - MI, coronary deaths, and all-cause mortality in newly diagnosed T2DM patients (n = 753) with low CVD risk whose body weight was >120% of their ideal weight.[2,3]
- 10-year follow-up of UKPDS, metformin-treated obese T2DM patients (n=342) continued to show a reduction in MI and death from any cause[4]

1. Ferrannini E, DeFronzo RA. *Eur Heart J.* 2015;36(34):2288-96.; 2. UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998; 352:837-853.; 3. UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352:854–865.; 4. Holman RR et al. *N Engl J Med.* 2008;359:1577–1589.

Sulfonylurea (SU) CVD Data

- Controversial
  - UKPDS,[1] ADVANCE[2] and ACCORD[3] failed to demonstrate an increase in either CVD mortality or morbidity in sulfonylurea-treated T2DM patients.
  - In the ADVANCE trial, severe hypoglycemia was associated with a significant increase in major macrovascular events and death from a cardiovascular cause[2]
- Results of meta-analyses of studies of CV effects of SU are mixed[4]
- In a recent study the AGi, acarbose, was compared with SU as add-on therapy with metformin – significantly lower risks[5]
- During a mean follow-up of 1.1 years, SU monotherapy versus metformin monotherapy, was associated with[6]:
  - an increased risk of MI, all-cause mortality, and severe hypoglycemia
  - a trend towards increased risks of ischemic stroke and cardiovascular death

1.UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352:837–853.;
2. Patel A et al. *N Engl J Med.* 2008; 358:2560–2572.; 3. Action to Control Cardiovascular Risk in Diabetes Study Group. *N Engl J Med.* 2008;358:2545–2559.; 4. Ferrannini E, DeFronzo RA. *Eur Heart J*. 2015;36(34):2288-96.; 5. Hsu P et al. *J Clin Endocrinol Metab.* 2018; DOI: 10.1210/jc.2018-00040.; 6. Douros A et al. *BMJ.* 2018;362:k2693.

Pioglitazone and CV Impact

- Concerns with pioglitazone:
  - Fluid retention and ↑heart failure
- Proposed benefits:
  - BP regulation - ↓ BP
  - Improved endothelial function
  - Reduced vascular inflammation
  - Lipid metabolism - ↑HDL (~15%), ↓ TG
  - Reduced smooth muscle cell proliferation
  - Reduced fibrinolysis
  - ↓ C-reactive protein
- In patients with diabetes, pioglitazone compared with glimepiride:
  - Slows increase in carotid intima-media thickness and progression of coronary atherosclerosis

Lincoff AM et al. *JAMA.* 2007;298:1180-1188.
Wilcox R et al. *Stroke.* 2007;38:865-873.
Lee M et al. *Stroke.* 2017;48:388-393.

Pioglitazone CVD Data

- PROactive included patients with T2DM, evidence of extensive macrovascular disease[1,2]
  - **Primary outcome** – MACE + leg revascularization and major leg amputation - Not significantly different
- IRIS included patients with insulin resistance, recent ischemic stroke or TIA[3]
  - **Primary outcome** - Fatal or nonfatal stroke or MI occurred in 9.0% of pioglitazone group vs. 11.8% of placebo group (HR 0.76; 95% CI, 0.33 to 0.69; p<0.001) - **NNT – 36**
  - **Safety outcomes** occurring more in pioglitazone group- weight gain, edema, bone fracture requiring surgery or hospitalization

1. Dormandy JA et al. *Lancet*. 2005;366:1279-1289.; 2. Wilcox R et al. *Stroke*. 2007;38:865-873.;
3. Kernan WN et al. *N Engl J Med*. 2016;374:1321-1331.; 4. Lincoff MA et al. *JAMA*. 2007;298:1180-1188.

Pioglitazone CVD Data

- 3 Meta-analyses from 2017:
  - Systematic review included patients with insulin resistance, prediabetes, and T2DM[1] - decreased risk of major adverse cardiac events (MACE) (RR 0.83; 95% CI, 0.72 to 0.97)
  - Systematic review focused on secondary stroke prevention[2] – decreased risk of recurrent stroke (HR 0.68; 95% CI, 0.50 to 0.92; p=0.01) and risk of all major vascular outcomes (HR 0.75; 95% CI, 0.64 to 0.87; p=0.001)
  - Focused on patients with CVD[3] – decreased risk of recurrent MACE (RR 0.74; 95% CI, 0.60 to 0.92)

1. Liao HW et al. *BMJ Open*. 2017;7:e013927.
2. Lee M et al. *Stroke.* 2017;48:388-393.
3. de Jong M et al. *Cardiovasc Diabetol*. 2017;12:134.

Meet SM

- 62-year-old African American female with a past medical history of T2DM, hyperlipidemia, HTN, vitamin D deficiency, and PAD.
- BMI 32.1 kg/m^2, Basic metabolic panel WNL

- She reports checking BG sometimes daily or every other day with fasting
- BG ranging 150 – 170 mg/dL.

- Current medications include:
  - metformin 1000 mg po twice a day
  - rosuvastatin 5 mg po daily
  - aspirin 81 mg po daily
  - vitamin D 1000 IU 2 tabs po daily
  - amlodipine 5 mg po daily
  - lisinopril 20 mg po daily
  - coral calcium 1000 mg po BID
  - esomeprazole 40 mg po daily

A1c today is 7.7%

Question 2

Knowing the potential for CV benefits, adding which of the following medications is the next best step for managing SM's T2DM?

a) Acarbose
b) Bromocriptine
c) Glimepiride
d) Pioglitazone

Answer to Question 2

Knowing the potential for CV benefits, adding which of the following medications is the next best step for managing SM's T2DM?

d) Pioglitazone

- Although pioglitazone can increase weight and SM is obese, the potential for pioglitazone to decrease the risk of recurrent MACE would make it the best choice.
- Additionally remember that pioglitazone has neutral effects on hypoglycemia and is administered orally once a day.

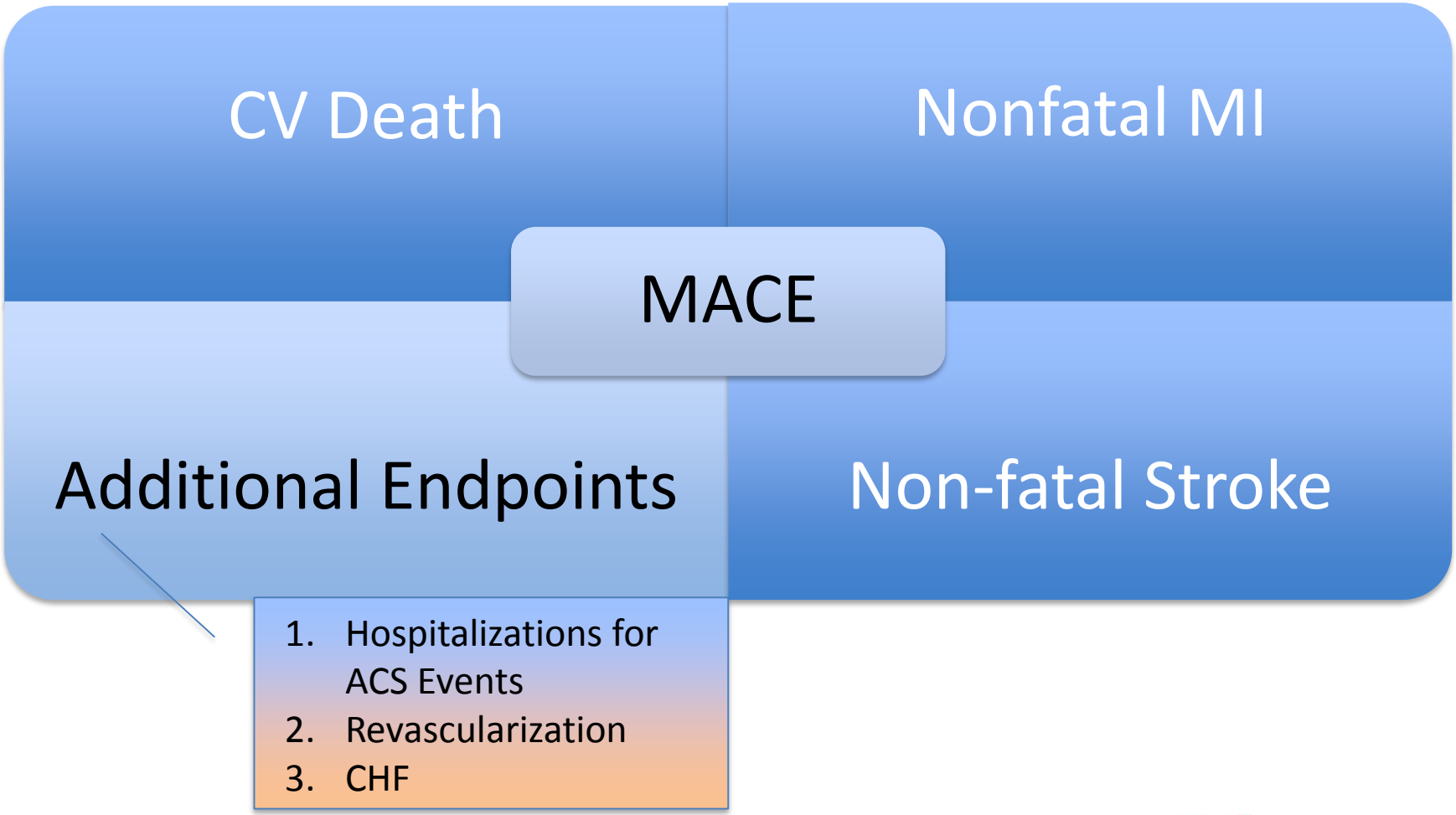
Liao HW et al. *BMJ Open*. 2017;7:e013927.; Lee M et al. *Stroke.* 2017;48:388-393.; Cefalu WT et al. *Diabetes Care.* 2018;41:14-31.; Dormandy JA et al. *Lancet*. 2005;366:1279-1289.; Wilcox R et al. *Stroke*. 2007;38:865-873.; de Jong M et al. *Cardiovasc Diabetol*. 2017;12:134.

Cardiovascular Outcomes Trial (CVOT) Design

FDA Guidance on CVOTs

- To adequately evaluate the CV safety of type 2 diabetes drugs in development, future development programs should include:
  - Phase 2 and 3 trials that include patients at higher risk for CV events, are of sufficient size and duration to enable enough CV events to allow for a meaningful evaluation of CV risk
  - Be designed to facilitate later meta-analysis
  - The CV events should include CV mortality, MI, and stroke
  - Can also include hospitalization for ACS, urgent revascularization procedures, and other end points, such as HF hospitalization

Cefalu WT et al. *Diabetes Care.* 2018;41:14-31.



Cefalu WT et al. *Diabetes Care.* 2018;41:14-31.

FDA Guidance on CVOTs

- Independent adjudication of CV events
- Meta-analysis of the phase 2 and 3 trials at the end of the research program
  - following a protocol developed in advance that prespecifies the end points to be assessed and the statistical methods
- Analysis of premarketing data comparing the CV events occurring with the agent to those occurring with the control group and demonstrating that the upper limit of a two-sided 95% CI of the estimated risk ratio is <1.8
  - If this cannot be done through the meta-analysis described above, it should be accomplished in a separate, large CV safety trial

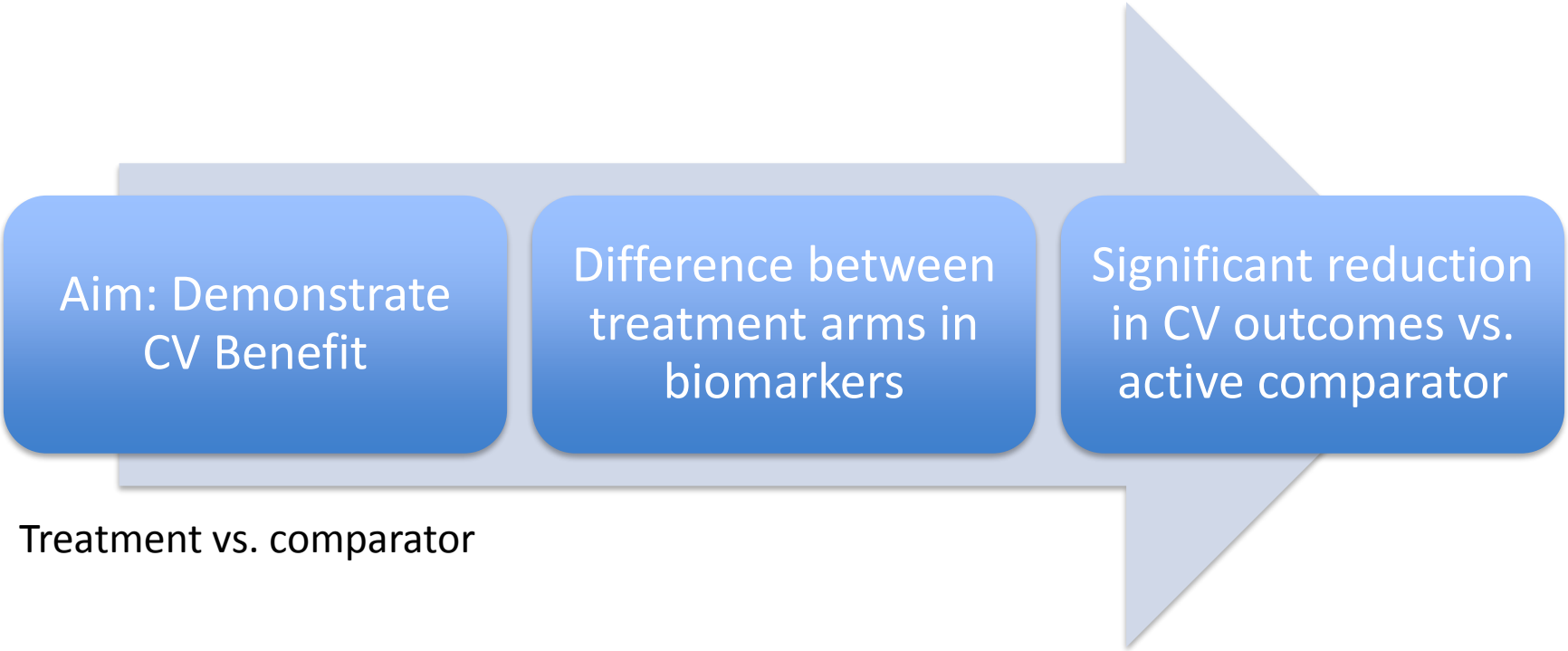
Cefalu WT et al. *Diabetes Care* 2018;41:14-31.
Hirshberg B, Katz A. *Diabetes Care.* 2013; 36(Supplement 2): S253-S258.

FDA Guidance on CVOTs

- For agents whose 95% CI upper limit falls between 1.3 and 1.8 in premarketing analysis, completion of a post-marketing trial or continuation of a premarketing trial after approval may be needed to conclusively show that the upper limit of the two-sided 95% CI is <1.3 with a "reassuring" point estimate of overall CV risk
  - It has been proposed that the required number of events for such a trial would be 600–700
- If 95% CI is <1.3, no further study may be necessary.
- Relative Risk should not be more than 1

Cefalu WT et al. *Diabetes Care.* 2018;41:14-31.
Hirshberg B, Katz A. *Diabetes Care.* 2013; 36(Suppl. 2): S253-S258.

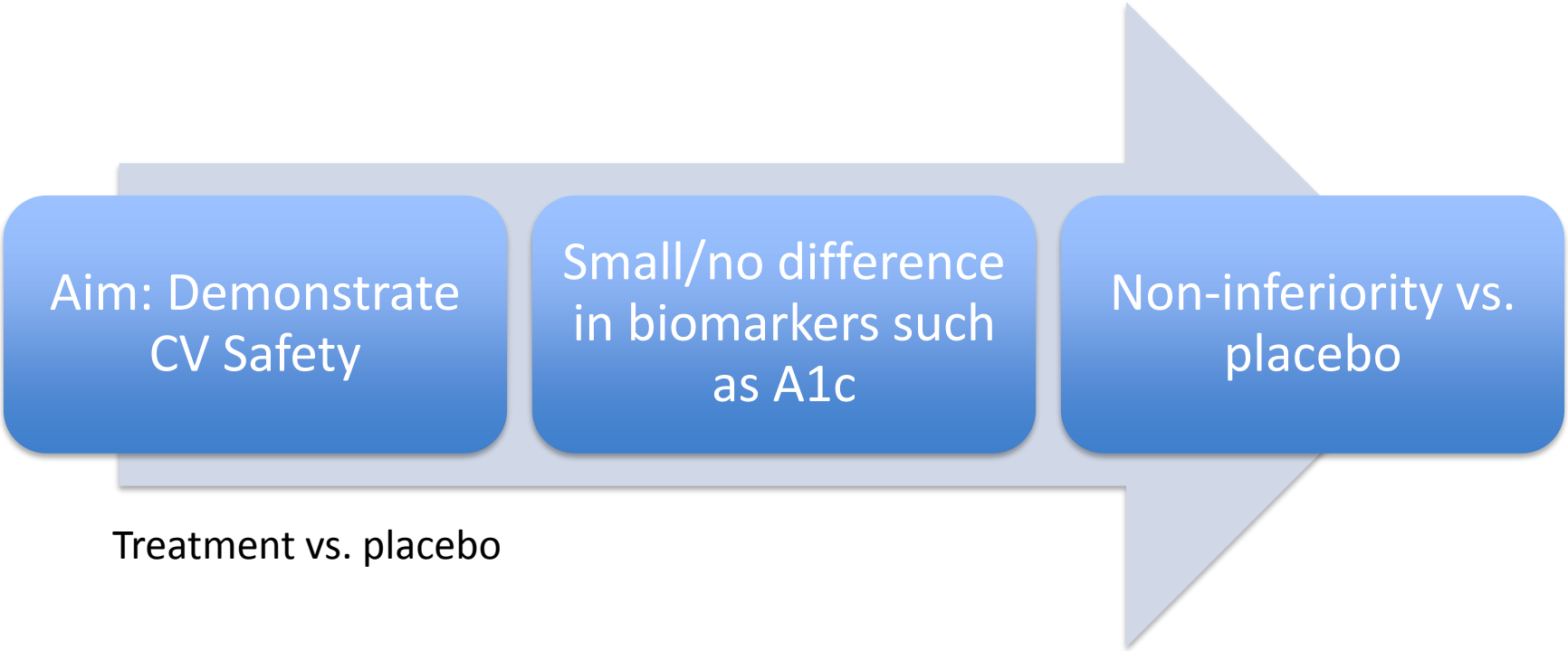
Cardiovascular Outcomes Trials - Efficacy



Treatment vs. comparator

Hirshberg B, Katz A. *Diabetes Care*. 2013; 36(Suppl. 2): S253-S258.

Cardiovascular Outcomes Trials - Safety



Treatment vs. placebo

Hirshberg B, Katz A. *Diabetes Care.* 2013; 36(Suppl. 2): S253-S258.

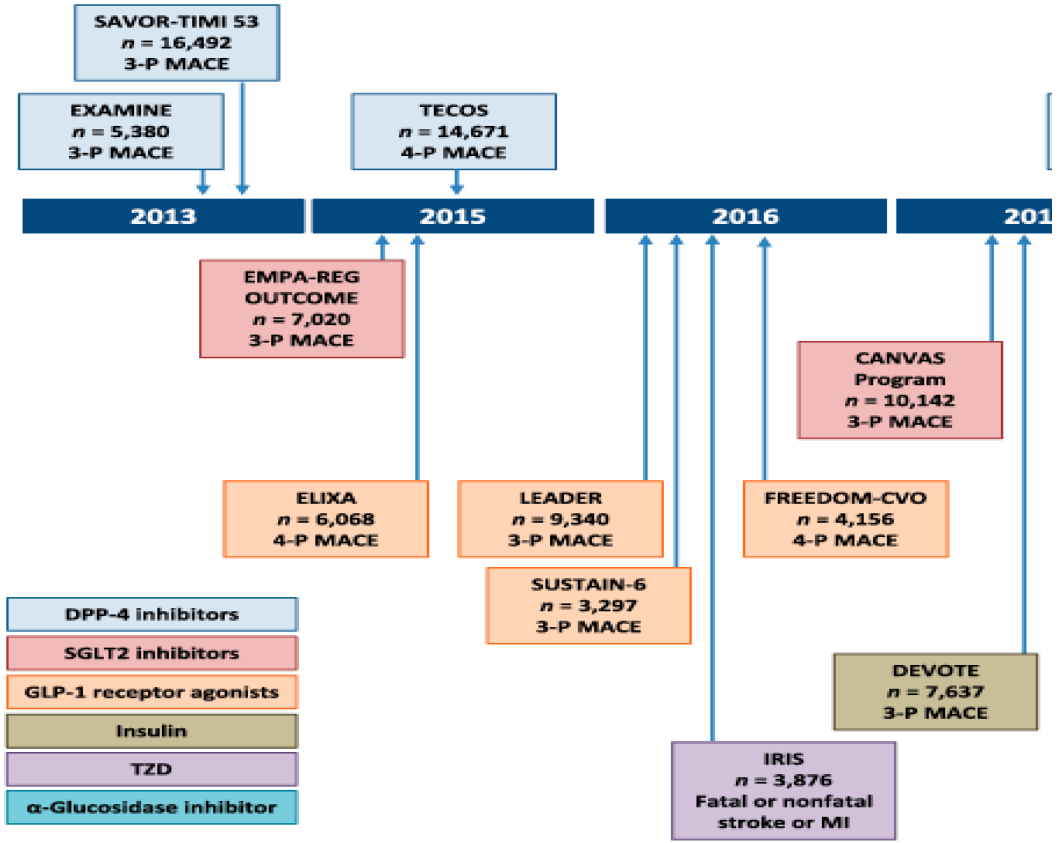
Major Trials with Intensive Glycemic Control & Long-Term Follow-up of Cardiovascular Outcomes

Study	Diabetes Type	CV Composite	MI	CV Mortality	All-cause Mortality
DCCT/EDIC	Type 1	⬇			⬇
UKPDS	Type 2		⬇		⬇
ACCORD	Type 2	↔	↔	⬆	↔
ADVANCE	Type 2	↔	↔	↔	↔
VADT	Type 2	⬇	↔	↔	↔

↔ = Neutral Effect, ⬆ increase, ⬇ decrease

Modified from Table 1. Cefalu WT et al. *Diabetes Care.* 2018;41:14-31.

Diabetes CVOT Trials



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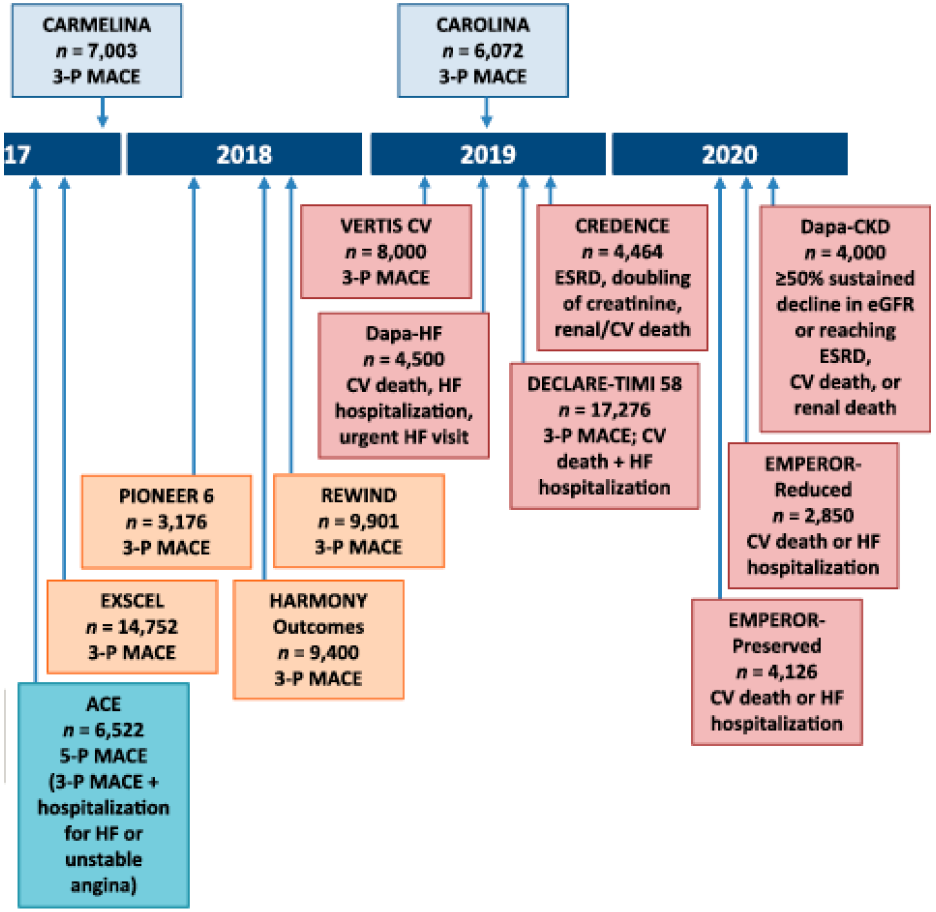

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Primary literature results from antidiabetic therapy Cardiovascular Outcomes Trials (CVOT)

DPP-4 Inhibitors (DPP-4i) and Proposed CV Benefits

- Potential direct effects on:
  - Heart
    - ↑ glucose uptake, ↑ ischemia tolerance
  - Peripheral arteries
    - ↓ intima media thickness progression, improved endothelial function?

- Other impacts on CV function:
  - Renal function
    - ↓ albumin excretion
  - Inflammatory responses
    - ↓ expression of inflammatory cytokines (TNF-α, IL-1β, and others), ↓ C-reactive protein
  - Platelet function
    - ↓ platelet aggregation?

- ↑ rate of hospitalization for congestive heart failure – saxagliptin (significant) vs. alogliptin (non-significant)

Zhang Z et al. *Cardiovasc Diabetol.* 2017;16:31.
Nauck MA et al. *Circulation.* 2017; 136:849-870.

Baseline Characteristics of DPP-4i CVOTs

	EXAMINE (alogliptin)	SAVOR-TIMI 53 (saxagliptin)	TECOS (sitagliptin)
N	5,380	16,492	14,724
Mean age, yr	61	65	66
Mean BMI, kg/m^2	28.7	31	30.2
Previous CV Disease, %	100	78.4	74
Mean A1c %	8	8	7.2
Mean duration of diabetes, yr	7.2	11.9	11.6
Insulin use, %	29.9	40.9	23.2

White W et al. (EXAMINE) *N Engl J Med*. 2013;369:1327-1335.; Scirica B et al. (SAVOR-TIMI 53) *N Engl J Med*. 2013;369:1317-1326.; Green J et al. (TECOS) *N Engl J Med*. 2015;373:232-242.

Other Study Design for DPP-4i CVOTs

	EXAMINE (alogliptin)	SAVOR-TIMI 53 (saxagliptin)	TECOS (sitagliptin)
CV Risk status	CVD history	CVD history or risk factors	CVD history or risk factors
Median (max) time to follow-up, yr	1.5 (3.3)	2.1 (2.9)	3.0
MACE (events)	621	1,222	1,690

White W et al. (EXAMINE) *N Engl J Med*. 2013;369:1327-1335.
Scirica B et al. (SAVOR-TIMI 53) *N Engl J Med*. 2013;369:1317-1326.
Green J et al. (TECOS) *N Engl J Med*. 2015;373:232-242.

Results for DPP-4i CVOTs

	EXAMINE (alogliptin)	SAVOR-TIMI 53 (saxagliptin)	TECOS (sitagliptin)
Primary outcome	3-point MACE	3-point MACE	4-point MACE
Results of primary outcome	Occurred in 11.3% (alogliptin) and in 11.8% (placebo); (HR alogliptin, 0.96; upper boundary of one-sided repeated CI, 1.16; p<0.001 noninferiority; p=0.32, superiority)	Occurred in 7.3% (saxagliptin) and in 7.2% (placebo); (HR saxagliptin, 1.00; 95% CI, 0.89 to 1.12; p<0.001 noninferiority, p=0.99 superiority)	Occurred in 11.4% of (sitagliptin) and in 11.6% (placebo); (HR sitagliptin, 0.98; 95% CI, 0.88 to 1.09; p<0.001 noninferiority)

White W et al. (EXAMINE) *N Engl J Med*. 2013;369:1327-1335.; Scirica B et al. (SAVOR-TIMI 53) *N Engl J Med*. 2013;369:1317-1326.; Green J et al. (TECOS) *N Engl J Med*. 2015;373:232-242.

Question 3

The prescriber wants to know what trial's results will provide him with additional information regarding the CV safety of using linagliptin when compared to an active control. For which of the following trial results should the prescriber watch?

a) CARMELINA
b) CAROLINA
c) EXAMINE
d) TECOS

Answer to Question 3

The prescriber wants to know what trial's results will provide him with additional information regarding the CV safety of using linagliptin when compared to an active control. For which of the following trial results should the prescriber watch?

b) CAROLINA

- CAROLINA is a recently completed CVOT designed to establish the noninferiority of linagliptin compared with glimepiride (active control) using a 3-point MACE primary endpoint with results that have not yet been published.

Cefalu WT et al. *Diabetes Care* 2018;41:14-31.; CAROLINA. https://clinicaltrials.gov/ct2/show/NCT01243424 (Accessed 2018 Sept 9).
Marx N et al. *Diab Vasc Dis Res*. 2015;12:164-174.;CARMELINA. https://clinicaltrials.gov/ct2/show/NCT01897532 (Accessed 2018 Sept 9).

Recently Completed DPP-4i CVOTs

Drug	Study	Main inclusion criteria	Median follow-up	Primary outcome
Linagliptin vs. glimepiride	CAROLINA[1-3]	T2DM + history of CVD OR diabetes end-organ damage OR age ≥ 70 yr OR ≥ 2 risk factors for CVD (n = 6,072)	~ 8.3 yr (enrollment ended 2012)	3-point MACE *Completed 2018*
Linagliptin vs. placebo	CARMELINA[1,4,5]	T2DM + high CV risk (confirmed CVD) and/or presence of CKD (n = 7.003)	4.5 yr	3-point MACE *Completed 2018*

1. Cefalu WT et al. *Diabetes Care* 2018;41:14-31.; 2. CAROLINA https://clinicaltrials.gov/ct2/show/NCT01243424 (Accessed 2018 Sept 9); 3. Marx N et al. *Diab Vasc Dis Res*. 2015;12:164-174.; 4. CARMELINA https://clinicaltrials.gov/ct2/show/NCT01897532 (Accessed 2018 Sept 9); 5. Rosenstock J et al. *Cardiovasc Diabetol.* 2018; 17:39.

Meet JJ

- 52-year-old African-American male, BMI 32.1 kg/m^2
- A1c 8%, SCr 0.9 mg/dL, Basic metabolic panel WNL
- Past Medical History:
  - Type 2 DM (x 1 yr)
  - Stroke
- JJ's BG log book reveals:

Timing of BG values	Range of BG values (mg/dL)
Fasting BG	120 – 150
2-hr postprandial	210 - 250

- Current medications:
  - Metformin 1000 mg orally twice daily
  - Atorvastatin 40 mg orally nightly
  - Aspirin 81 mg orally daily

Question 4

In addition to encouraging intensive lifestyle modifications, which of the following would be the BEST option to optimize JJ's T2DM management and minimize his risk for heart failure?

a) Alogliptin
b) Linagliptin
c) Saxagliptin
d) Sitagliptin

Answer to Question 4

In addition to encouraging intensive lifestyle modifications, which of the following would be the BEST option to optimize JJ's T2DM management and minimize his risk for heart failure?

d) Sitagliptin

- In TECOS, a placebo-controlled CVOT of sitagliptin, no significant differences in the primary outcome (4-point MACE) or rate of hospitalization were demonstrated.

Green J et al. (TECOS) *N Engl J Med*. 2015;373:232-242.
Cefalu WT et al. *Diabetes Care* 2018;41:14-31.

GLP-1 RA and Proposed CV Benefit

- Effects may vary depending on the particular GLP-1 RA
  - Different characteristics of GLP-1 RA thought to be related to differences in GLP-1 RA CVOT results beyond ↓ glucose variability
  - Decreased CV events noted with GLP-1 RA that result in greater decreased in A1c, body weight, and SBP
  - Less risk of severe hypoglycemia

- GLP-1 RA address other CV risk factors by decreasing:
  - SBP by 2-3 mm Hg
  - Cholesterol – LDL, TC, TG
  - Body weight
  - Waist circumference

Zhang Z et al. *Cardiovasc Diabetol.* 2017;16:31.
Nauck MA et al. *Circulation.* 2017; 136:849-870.

GLP-1 RA and Proposed CV Benefit

- Potential direct effects on:
  - Heart
    - Increasing myocardial contractility, glucose uptake, and ischemia tolerance
  - Peripheral arteries
    - Increasing endothelial function and plaque stability
    - Decreasing arterial stiffness and vascular inflammation/inflammatory responses
- Other impacts on CV function:
  - Renal function
    - May see acute increase in glomerular filtration
    - Emerging evidence shows GLP-1 RA decrease albumin excretion
  - Decreased inflammatory responses
    - Reactive oxygen species, expression of inflammatory cytokines (TNF-α, IL-1β, and others),
    - C-reactive protein
  - Platelet function
    - Decreased platelet aggregation

Zhang Z et al. *Cardiovasc Diabetol.* 2017;16:31.
Nauck MA et al. *Circulation.* 2017; 136:849-870.

Baseline Characteristics of GLP-1 RA CVOTs

	ELIXA (lixisenatide)	EXSCEL (exenatide)	LEADER (liraglutide)	SUSTAIN-6 (semaglutide)	Harmony Outcomes (albiglutide)
N	6,075	14,000	9,340	3,297	9,463
Mean age, yr	60	62	65	64.6	64.1
Mean BMI, kg/m^2	30	31.8	32.5	32.8	32.3
Previous CV Disease, %	100	73.1	81	83	70
Mean A1c %	7.7	8	8.7	8.7	8.7
Mean duration of diabetes, yr	9.3	12	12.8	8.1	14.1
Insulin use, %	37.8	46.3	44.5	58	60

Pfeffer M et al. (ELIXA) *N Engl J Med*. 2015;373:2247-2257.; Holman R et al. (EXSCEL) *N Engl J Med.* 2017;377:1228-1239.; Marso SP et al. (LEADER) *N Engl J Med.* 2016;375:311-322.; Marso SP et al. (SUSTAIN-6) *N Engl J Med.* 2016;375:1834-1844.; Hernadez AF et al. (Harmony Outcomes) *Lancet.* 2018; http://dx.doi.org/10.1016/S0140-6736(18)32261-x.

Other Study Design for GLP-1 RA CVOTs

	ELIXA (lixisenatide)	EXSCEL (exenatide)	LEADER (liraglutide)	SUSTAIN-6 (semaglutide)	Harmony Outcomes (albiglutide)
CV Risk status	CVD history	CVD history or risk factors	CVD history or risk factors	CVD history or risk factors	CVD history
Median (max) Time to follow-up, yr	1.9 (3.9)	3.2 (4.4)	3.8	2.1	1.6 (2.6)
MACE (events)	805	1,744	1,302	254	766

Pfeffer M et al. (ELIXA) *N Engl J Med*. 2015;373:2247-2257.; Holman R et al. (EXSCEL) *N Engl J Med.* 2017;377:1228-1239.; Marso SP et al. (LEADER) *N Engl J Med.* 2016;375:311-322.; Marso SP et al. (SUSTAIN-6) *N Engl J Med.* 2016;375:1834-1844.; Hernadez AF et al. (Harmony Outcomes) *Lancet.* 2018; http://dx.doi.org/10.1016/S0140-6736(18)32261-x

ELIXA (lixisenatide)

Type 2 DM and acute coronary event within 180 days of screening

Multicenter, randomized, double-blind, placebo-controlled

Primary Outcome: 4-point MACE-CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina. Powered for noninferiority and superiority.

lixisenatide

The primary outcome occurred in 13.4% of the lixisenatide group and in 13.2% of the placebo group (HR in the lixisenatide group, 1.02; 95% CI, 0.89 to 1.17; p<0.001 noninferiority, p=0.81 superiority).

Showed noninferiority but not superiority

Pfeffer M et al. (ELIXA) *N Engl J Med*. 2015;373:2247-2257.

ELIXA Renal Outcomes

- Lixisenatide was associated with:
  - A reduction in urinary albumin-to-creatine ratio (UACR) of 39.18% for the macroalbuminuria group (HR 14.97; -68.53 to -9.84; p = 0.007) from baseline to week 108
  - Significant reduction in new onset macroalbuminuria (HR 0.815; 95% CI: 0.665-0.999; p = 0.0491) when adjusted for baseline and on-trial A1c
- No significant differences in eGFR decline were identified between treatment groups in any UACR subgroup

Muskiet MHA et al. *Lancet Diabetes Endocrinol.* 2018; http://dx.doi.org/10.1016/S2213-8587(18)30291-2.

EXSCEL (exenatide)

Type 2 DM +/- previous CV disease (70% previous disease/30% no previous disease)

Multicenter, randomized, double-blind, placebo-controlled

Primary Outcome: 3-point MACE-CV death, nonfatal MI, nonfatal stroke. Powered for noninferiority and superiority.

exenatide

The primary outcome occurred in 11.4% of the exenatide group and in 12.2% of the placebo group (HR in the exenatide group, 0.91; 95% CI, 0.83 to 1.00; p<0.001 noninferiority, p=0.06 superiority).

Showed noninferiority but not superiority

Holman R et al. (EXSCEL) *N Engl J Med.* 2017;377:1228-1239.

LEADER (liraglutide)

Type 2 DM, previous CV disease or CV risk factor

Multicenter, randomized, double-blind, placebo-controlled

Primary Outcome: 3-point MACE-CV death, nonfatal MI, nonfatal stroke. Powered for noninferiority and superiority.

liraglutide

The primary outcome occurred in 13.0% of the liraglutide group and in 14.9% of the placebo group

(HR in the liraglutide group, 0.87; 95% CI, 0.78 to 0.97; p=0.01 superiority).

NNT for primary outcome = 53

Marso SP et al. (LEADER) *N Engl J Med.* 2016;375:311-322.

LEADER (liraglutide): Secondary Outcomes

- Lower rates in liraglutide vs. placebo - significant findings
  - Expanded composite (3-point MACE + coronary revascularization or hospitalization for unstable angina pectoris or heart failure) – 20.3% vs. 22.7% (HR, 0.88; 95% CI, 0.81 to 0.96; p=0.005)
  - Death from any cause – 8.2% vs. 9.6% (HR, 0.85; 95% CI, 0.74 to 0.97; p=0.02)
  - Death from CV causes – 4.7% vs. 6.0% (HR, 0.78; 95% CI, 0.66 to 0.93; p=0.007)
  - Microvascular event – 7.6% vs. 8.9% (HR, 0.84; 95% CI, 0.73 to 0.97; p=0.02)
    - Nephropathy – 5.7% vs. 7.2% (HR, 0.78; 95% CI, 0.67 to 0.92; p=0.003)

- Nonsignificant findings
  - Prespecified – nonfatal stroke; coronary revascularization, hospitalization for unstable angina pectoris, hospitalization for heart failure; retinopathy
  - Not-prespecified - MI – fatal, silent; fatal stroke; TIA

Marso SP et al. (LEADER) *N Engl J Med.* 2016;375:311-322.

LEADER (liraglutide): Additional Analysis

- Post-hoc analysis of CV events[1]
  - LDL groups (LDL < 50 mg/dL, LDL 50 to 70 mg/dL, LDL > 70 mg/dL)
  - HDL and non-HDL
  - Statin user vs. non-statin users
  - Liraglutide benefited all groups
- Diabetes-related foot ulcer (DFU) incidence + post-hoc analysis of DFU-related complications[2]
  - Patients reporting at least 1 DFU: similar between groups – 3.8% in liraglutide vs. 4.1% placebo (HR, 0.92; 95% CI, 0.75 to 1.13; p=0.41)
  - DFU-related complications
    - Liraglutide ↓ amputations vs. placebo (HR, 0.65; 95% CI, 0.45 to 0.95; p=0.03)
    - No significant difference between groups in incidence of foot infections, involvement of underlying structures, or peripheral revascularization

1. Verma S et al. *Circulation.* 2018; 138 doi:10.1161/CIRCULATIONAHA.118.036862.
2. Dhataryia K et al. *Diabetes Care.* 2018 doi:10.2337/dc18-1094.

SUSTAIN-6 (semaglutide)

Type 2 DM, previous CV disease or CV risk factor

Multicenter, randomized, double-blind, placebo-controlled

Primary Outcome: 3-point MACE-CV death, nonfatal MI, nonfatal stroke. Powered for noninferiority.

*not prespecified for superiority

semaglutide

The primary outcome occurred in 6.6% of the semaglutide group and in 8.9% of the placebo group

(HR in semaglutide, 0.74; 95% CI, 0.58 to 0.95; p<0.001 noninferiority).

NNT for primary outcome = 43

Marso SP et al. (SUSTAIN-6) *N Engl J Med.* 2016;375:1834-1844.

SUSTAIN-6 (semaglutide): Secondary Outcomes

- Lower rates in semaglutide vs. placebo - significant findings
  - Expanded composite (3-point MACE + coronary revascularization or hospitalization for unstable angina or heart failure) – 12.1% vs. 16.0% (HR, 0.74; 95% CI, 0.62 to 0.89; p=0.002)
  - All-cause death, nonfatal MI, or nonfatal stroke – 7.4% vs. 9.6% (HR, 0.77; 95% CI, 0.61 to 0.97; p=0.03)
  - Nonfatal stroke – 1.6% vs. 2.7% (HR, 0.61; 95% CI, 0.38 to 0.99; p=0.04)
  - Revascularization – 5.0% vs. 7.6% (HR, 0.65; 95% CI, 0.50 to 0.86; p=0.003)
  - New or worsening nephropathy – 3.8% vs. 6.1% (HR, 0.64; 95% CI, 0.46 to 0.88; p=0.005)

- Higher rate in semaglutide vs. placebo - significant finding
  - Retinopathy complications – 3.0% vs. 1.8% (HR, 1.76; 95% CI, 1.11 to 2.78; p=0.02)

- Non-statistically significant findings
  - Death from any cause, death from CV cause, nonfatal MI, hospitalization for unstable angina pectoris, hospitalization for heart failure

Marso SP et al. (SUSTAIN-6) *N Engl J Med.* 2016;375:1834-1844.

Harmony Outcomes (albiglutide)

Type 2 DM, previous CV disease or CV risk factor

Multicenter, randomized, double-blind, placebo-controlled

Primary Outcome: 3-point MACE-CV death, nonfatal MI, nonfatal stroke. Powered for noninferiority and superiority.

albiglutide

The primary outcome occurred in 7% of the albiglutide group and in 9% of the placebo group

(HR in albiglutide, 0.78; 95% CI, 0.68 to 0.90; p<0.001 noninferiority, p = 0.006 superiority).

NNT for primary outcome = 50

Hernadez AF et al. (Harmony Outcomes) *Lancet.* 2018; http://dx.doi.org/10.1016/S0140-6736(18)32261-x;
Cefalu WT et al. *Diabetes Care* 2018;41:14-31.; Green JB et al. *Am Heart J.* 2018;203:30-38.

Remember JJ

- 52-year-old African-American male, BMI 32.1 kg/m^2
- A1c 8%, SCr 0.9 mg/dL, BMP WNL
- Past Medical History:
  - Type 2 DM (x 1 yr)
  - Stroke
- JJ's BG log book reveals:

Timing of BG values	Range of BG values (mg/dL)
Fasting BG	120 – 150
2hr postprandial	210 - 250

- Current medications:
  - Metformin 1000 mg orally twice daily
  - Atorvastatin 40 mg orally nightly
  - Aspirin 81 mg orally daily

Question 5

The results of the 5 published GLP-1 RA CVOT may not apply to JJ due to which of the following?

a) A1c
b) BMI
c) Duration of diabetes
d) Previous CV disease

Answer to Question 5

The results of the 5 published GLP-1 RA CVOT may not apply to JJ due to which of the following?

c) Duration of diabetes

- JJ has had T2DM for only 2 years. The mean duration of diabetes ranges from 8.1 years in SUSTAIN-6 to 14.1 years in Harmony Outcomes.

Pfeffer M et al. (ELIXA) *N Engl J Med*. 2015;373:2247-2257.; Holman R et al. (EXSCEL) *N Engl J Med.* 2017;377:1228-1239.; Marso SP et al. (LEADER) *N Engl J Med.* 2016;375:311-322.; Marso SP et al. (SUSTAIN-6) *N Engl J Med.* 2016;375:1834-1844.; Hernadez AF et al. (Harmony Outcomes) *Lancet.* 2018; http://dx.doi.org/10.1016/S0140-6736(18)32261-x

Ongoing GLP-1 RA CVOTs

Drug	Study	Main inclusion criteria	Median follow-up	Primary outcome
Dulaglutide	REWIND[1-4]	T2DM and ≥ 50 yr with CVD or ≥ 55 yr and subclinical vascular disease OR ≥ 60 yr + ≥ 2 CV risk factors (n = 9,901)	*Anticipate ~ 8 yr*	3-point MACE *Anticipated completion 2018*
Oral semaglutide	PIONEER 6[1,5]	T2DM and ≥ 50 yr with CVD OR ≥ 60 yr + ≥ 1 CV risk factor (n = 3,176)	19 months	3-point MACE *Anticipated completion 2018*

1. Cefalu WT et al. *Diabetes Care* 2018;41:14-31.
2. REWIND. https://clinicaltrials.gov/ct2/show/NCT01394952 (accessed 2018 Sept 9).
3. Ferdinand KC, Mahata I. *Ann Transl Med*. 2017;5(23):476
4. Gerstein HC et al. *Diabetes Obes Metab.* 2018;20:42–49.
5. PIONEER. https://clinicaltrials.gov/ct2/show/study/NCT02692716 (accessed 2018 Sept 9).

Meet MP

- MP, a 60-year-old female with a history of T2DM, hypercholesterolemia, cerebrovascular accident, and migraines, presents to your diabetes clinic for medication management. She currently has 1+ edema in both lower extremities and significant abdominal obesity. Significant abdominal obesity.
- Currently BP is well controlled at 154/84 mm Hg, Pulse of 82 bpm
- Pertinent current medications:
  - Clopidogrel 75 mg orally daily
  - Rosuvastatin 40 mg orally daily
  - Alirocumab 150 mg SC every 2 weeks
  - Carvedilol 12.5 mg orally twice daily
  - Metformin 1,000 mg orally twice daily
  - Insulin glargine 130 units SC daily
  - Insulin lispro ~63 units/day SC divided 3-4 times
  - Hydrochlorothiazide 25 mg orally daily
  - Lisinopril 40 mg po daily

Meet MP

- Labs
  - A1c: 10.5%
  - Vitamin D 29 ng/mL
  - CBC WNL
  - TC 248, LDL 176, TG 145, HDL 43 (mg/dL)
  - TSH 2.35 uIU/ml, T4 6.6 mcg/dL, T3 Uptake 24%, Free Thyroxine Index 1.6, T3 123 ng/dL
- Interventions
  - Vitamin D/K2 with 3,000 IU Vitamin D_3 orally daily
  - Continue to monitor thyroid (not optimal)
  - Order Insulin Pump with a continuous glucose monitor
  - Increase carvedilol to 25 mg orally twice daily

Question 6

Your team is starting MP on a continuous infusion of insulin to reduce her insulin requirements and decrease her glucose variability.

- Starting dose before auto mode: basal 2 units/hr, bolus 4.6 g/unit, active insulin time 3 hours, Correction bolus 1 unit 18 mg/dL, Target BG 100-120 mg/dL

What additional medication class has the MOST potential for MP to further reduce insulin requirements, lose weight, and reduce cardiovascular risk?

a) SGLT-2is
b) GLP-1 RAs
c) TZDs
d) Alpha-glucosidase inhibitors

Answer to Question 6

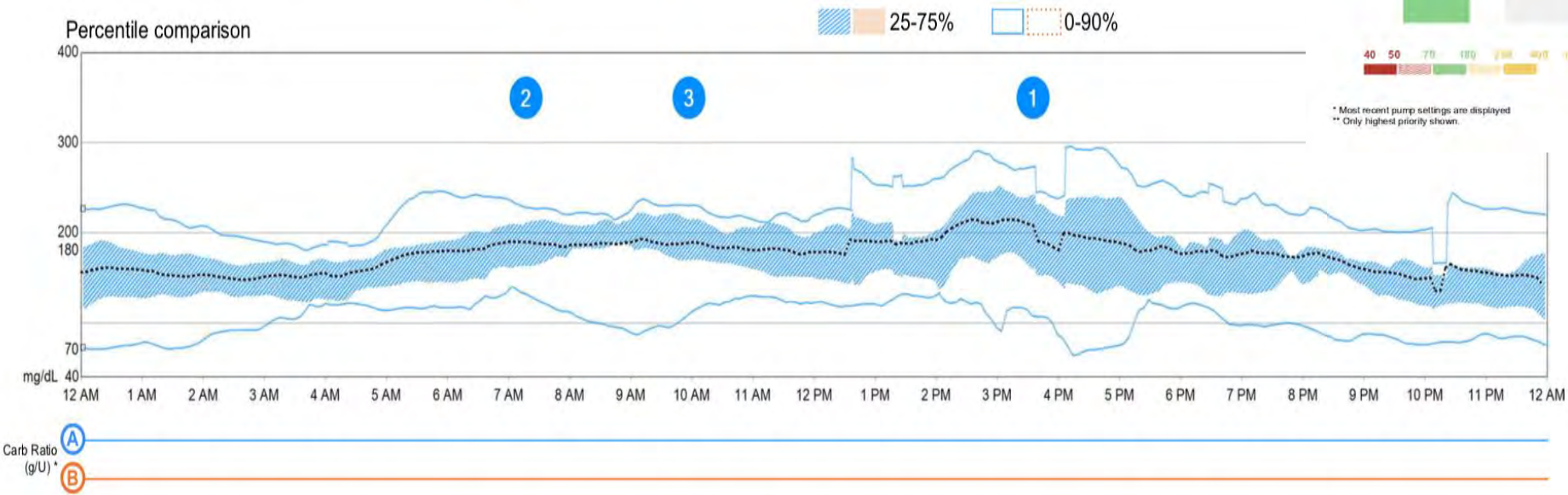
What additional medication class has the MOST potential for MP to further reduce insulin requirements, lose weight, and reduce cardiovascular risk?

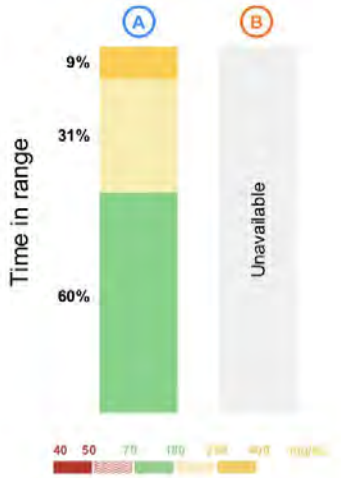
b) GLP-1 RA

- Both GLP-1 RA and SGLT-2i would be options for cardiovascular risk reduction, but the best option for lowering insulin requirements would be adding a GLP-1 RA.
- Based on available evidence, a reduction of basal insulin dose by 10% and a decrease of prandial insulin dose by 30 – 40% is recommended when GLP-1 RAs are added.

Artigas CF et al. *Expert Opin Pharmacother.* 2015; 16:1417-21.

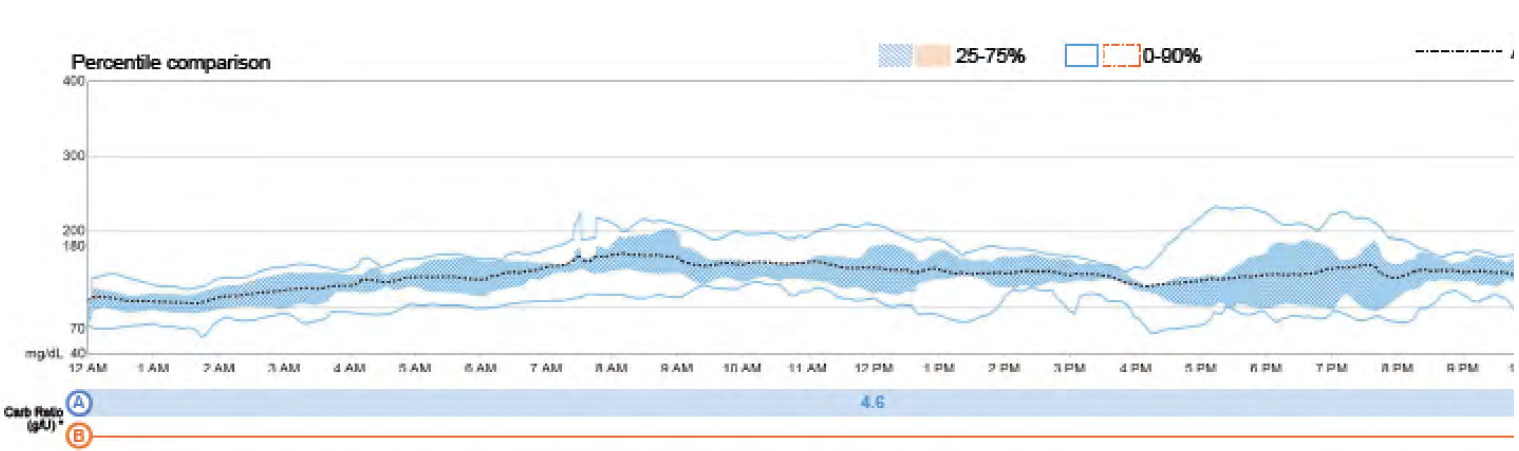
MP’s current CGM profile looks like this with her first week of semaglutide 0.5 mg SC once weekly (switched from a few weeks of long-acting exenatide).

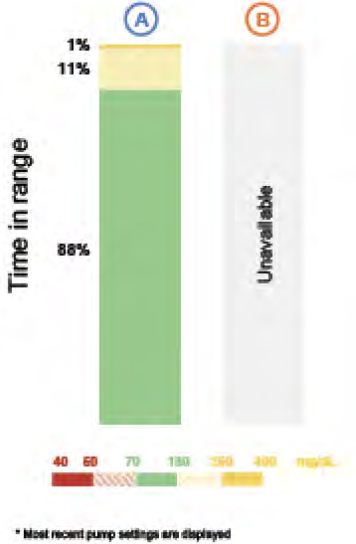




MP Case Follow-up

- MP was placed on a Medtronic 670g Insulin pump with CGM
- CGM below is 7 days after pump start. (manual mode)





MP Case Follow-up

- Patient achieved improved glucose variability
- Decreased total daily dose (TDD) of insulin from 193 units/day down to 75 units.
- Next Steps:
  - Patient now with anxiety, depression
  - Blood pressure still elevated
  - R/O hypercortisolism
    - Dexamethasone suppression test ordered
    - 4 point salivary cortisol

SGLT2i and ASCVD Risk Reduction

- Agents address other cardiovascular risk factors
  - BP (reductions in SBP up to 6 mm Hg)
  - Weight
  - Glucose control
- Along with blocking glucose reabsorption, SGLT2i cause a reduction in protein and sodium reabsorption in the nephron, which results in osmotic diuresis, milder than other diuretic agents
- This loss of fluid volume activates the renin-angiotensin-aldosterone (RAAS) system and starts a counter-regulatory response to maintain homeostasis.
- SGLT2i provide documented benefits for reducing preload and afterload work on the heart

Desouza CV et al. *Clin Ther*. 2015;37(6):1178-94.

SGLT2i and ASCVD Risk Reduction

- Despite the potential for SGLT-2i to cause a small, dose-related LDL increases sometimes accompanied by HDL increases, there are no CV outcomes trials at this time demonstrating that the LDL increases translate into increased CV events
- SGLT2i have been shown in multiple trials to provide a CVD benefit while aiding in lowering BP

Zinman B et al. (EMPA-Reg) *N Engl J Med*. 2015;373(22):2117–28.
Neal B et al. (CANVAS) *N Engl J Med.* 2017; 377:644-57.

Baseline Characteristics of SGLT2i CVOTs

	EMPA-Reg (empagliflozin)	CANVAS Program (canagliflozin)
N	7034	10142
Mean Age, yr	63.1	63
Mean BMI, kg/m^2	30.6	31.9
Previous CV Disease, %	>99	66
Mean A1c %	8.1	8.2
Mean duration of diabetes, yr	>57% with a diabetes duration >10 years	13.5
Insulin use, %	48.0	50.4

Zinman B et al. (EMPA-Reg) *N Engl J Med*. 2015;373(22):2117–28.
Neal B et al. (CANVAS) *N Engl J Med.* 2017; 377:644-57.

Other Study Design for SGLT-2i CVOTs

	EMPA-Reg (empagliflozin)	CANVAS Program (canagliflozin)
CV Risk status	CVD History	CVD history or risk factors
Median time to follow up, yr	3.2	2.4
MACE, events	772	1,011

Zinman B et al. (EMPA-Reg) *N Engl J Med*. 2015;373(22):2117–28.
Neal B et al. (CANVAS) *N Engl J Med.* 2017; 377:644-57.

EMPA-Reg (empagliflozin)

Type 2 DM, high risk for CV Events, BMI≤ 45 kg/m^2,Multicenter, randomized, double blind, placebo-controlled,

Primary Outcome: 3 point MACE- CV death, nonfatal MI, nonfatal stroke. Powered for noninferiority and superiority

empagliflozin

The primary outcome occurred in 10.5% of the empagliflozin group and in 12.1% of the placebo group (HR in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority).

NNT for primary outcome = 63

Zinman B et al. (EMPA-Reg) *N Engl J Med*. 2015;373(22):2117–28.

EMPA-Reg (empagliflozin)

- There were no significant between-group differences in the rates of MI or stroke, but in the empagliflozin group there were significantly lower rates of:
  - death from CV causes (3.7% vs. 5.9% in the placebo group; 38% relative risk reduction),
  - hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction),
  - and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction).

Zinman B et al. (EMPA-Reg) *N Engl J Med*. 2015;373(22):2117–28.

EMPA-Reg (empagliflozin)

- Incident or worsening nephropathy occurred in 12.7% of empagliflozin group and in 18.8% of placebo group (HR 0.61; 95% CI, 0.53-0.70; P<0.001).
- Doubling of SCr occurred in 1.5% of empagliflozin group and 2.6% of placebo group, a significant relative risk reduction of 44%

Zinman B et al. (EMPA-Reg) *N Engl J Med*. 2015;373(22):2117–28.

CANVAS (canagliflozin)

Type 2 DM, history or high risk CVD

Multicenter, randomized, double-blind, placebo-controlled, parallel-group

Primary outcome: 3 point MACE, CV death, nonfatal stroke, and nonfatal MI

canagliflozin

The rate of the primary outcome was lower with canagliflozin than with placebo (occurring in 26.9 vs. 31.5 participants per 1000 patient-years; hazard ratio, 0.86; 95% confidence interval [CI], 0.75 to 0.97; P<0.001 for noninferiority; P = 0.02 for superiority).

Number Needed to treat for Primary Outcome =224

Neal B et al. (CANVAS) *N Engl J Med.* 2017; 377:644-57.

CANVAS-R Program (canagliflozin)

- Although not statistically significant, the results also showed a possible benefit from canagliflozin with respect to the progression of albuminuria (hazard ratio, 0.73; 95% CI, 0.67 to 0.79) and the composite outcome of a sustained 40% reduction in the eGFR, the need for renal-replacement therapy, or death from renal causes (hazard ratio, 0.60; 95% CI, 0.47 to 0.77.)
- Credence Renal Trial stopped early in July 2018 due to positive outcomes.

Neal B et al. (CANVAS) *N Engl J Med.* 2017; 377:644-57.
https://www.jnj.com/phase-3-credence-renal-outcomes-trial-of-invokana-canagliflozin-is-being-stopped-early-for-positive-efficacy-findings

CREDENCE

- Inclusion Criteria
  - Type 2 DM
  - Age ≥30 yr
  - A1c ≥ 6.5% to ≤ 12% (≥ 6.5% to ≤ 10.5% in Germany)
  - Kidney disease in the setting of T2DM
    - Absence of alternative diagnosis to account for kidney pathology
  - Estimated GFR ≥ 30 to <90 mL/min/1.73m^2
  - Albuminuria: defined as urine albumin:creatinine ratio [UACR] 300 to 5,000 mg/g
- Goal was to enroll 60% of the patient population with stage 3 CKD with eGFR of ≥ 30 to < 60 mL/min/1.73m^2 at study entry.
- Patients were required to be on maximum labeled or tolerated dose of ACEi or ARB for ≥ 4 weeks prior to randomization.
  - Combination of ACE/ARB/direct renin inhibitor was not allowed

Jardine M et al. *Am J Nephrol.* 2017;46:462-472.

CREDENCE

- Selected exclusion criteria: past use of a SGLT-2i within 12 weeks, or randomization, current or past participation in another canagliflozin study
- Canagliflozin 100 mg orally once daily
- Primary Endpoint
  - Composite of end-stage kidney disease, doubling of SCr, and renal or CVD death
- Enrollment was 4,401
  - Mean duration of T2DM was 15.8 yr
  - Mean A1c of 8.3%
  - Mean baseline eGFR was 56.2 mL/min/1.73m^2
  - Median UACR was 927 mg/g
- No CV history inclusion requirement

Jardine M et al. *Am J Nephrol.* 2017;46:462-472.

CANVAS: Canagliflozin and Heart Failure

- CV death or hospitalized HF was reduced in those treated with canagliflozin compared with placebo (16.3 versus 20.8 per 1000 patient- years; hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.67–0.91)
- In addition, fatal or hospitalized HF (HR, 0.70; 95% CI, 0.55–0.89) and hospitalized HF alone (HR, 0.67; 95% CI, 0.52–0.87) were also reduced.
- **The benefit for CV death or hospitalized HF may be greater in patients with a prior history of HF** (HR, 0.61; 95% CI, 0.46–0.80) compared with those without HF at baseline (HR, 0.87; 95% CI, 0.72–1.06; *P* interaction =0.021).

Rådholm K et al. *Circulation.* 2018;138:458–468.

CANVAS Vs. EMPA-Reg

- Major difference was inclusion criteria.
  - CANVAS was primary and secondary prevention, patients without existing CV disease but were at risk for CV disease, accounted for 34.4% of patients.
  - This broader population in CANVAS likely influenced the higher number needed to treat than EMPA-Reg.
  - In the CANVAS trial, adverse reactions were consistent with the previously reported risks associated with canagliflozin except for an increased risk of amputation (6.3 vs. 3.4 participants per 1000 patient-years; hazard ratio, 1.97; 95% CI, 1.41 to 2.75); amputations were primarily at the level of the toe or metatarsal.

Neal B et al. (CANVAS) *N Engl J Med.* 2017; 377:644-57.

Amputations SGLT-2i vs. DPP-4i

- Active comparator study
- New user cohort
- 30,216 comparable patients in each arm
- After 0.6 years of follow-up, 60 amputations: 36 SGLT-2i, 25 DPP-4i
  - Most at the level of the partial foot (75%) and associated with diabetes-related vascular disease (66.7%)
- The incidence of amputations was higher amount SGLT-2i patients with a HR 1.38 (CI: 0.83-2.31)
- Subgroup analyses, risk differed by SGLT-2i
  - Canagliflozin HR 1.15 (CI 0.63-2.09); dapagliflozin or empagliflozin HR 2.25 (CI 0.78-6.47).
- Risk of amputations was higher with SGLT-2is than DPP-4is but difference was not significant

Adimadhyam S et al. *Diabetes Obes Metab.* 2018; doi: 10.1111/dom.13459.

OBSERVE-4D

- Large comprehensive real-world observational study of below-knee lower extremity (BKLE) amputation and hospitalization for heart failure (HHF)
- HR estimate for canagliflozin vs. non-SGLT-2i
  - 0.39 (95% CI, 0.26-0.60) for HHF
  - 0.75 (95% CI, 0.40-1.41) for BKLE amputation
- Effects in subpopulation with established CV disease were similar for both outcomes
- No consistent differences observed between canagliflozin and other SGLT-2i

Ryan PB et al. *Diabetes Obes Metab.* 2018; 20(11):2585-2597.

CVD-REAL

- The CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) study was a multinational, observational study of adults with T2DM.
- Patients prescribed an SGLT-2i or other glucose-lowering drugs (GLDs) were matched based on a propensity score for initiation of an SGLT-2i.
- Hazard ratios (HRs) for the risk of death, HF, and HF or death in patients with and without established CVD were estimated for each country and pooled

Cavender MA et al. *J Am Coll Cardiol.* 2018;71(22):2497-2506.

CVD-REAL

- After propensity score matching, 153,078 patients were included in each group. At baseline, 13% had established CVD.
- Compared with therapy using other GLDs, initiation of an SGLT-2i was associated with lower risk of death in patients with and without CVD (HR: 0.56; 95% confidence interval [CI]: 0.44 to 0.70; and HR: 0.56; 95% CI: 0.50 to 0.63, respectively).
- There were also associations between SGLT-2i and lower risk of HF (HR: 0.72; 95% CI: 0.63 to 0.82; and HR: 0.61; 95% CI: 0.48 to 0.78, respectively) and the composite of HF or death (HR: 0.63; 95% CI: 0.57 to 0.70; and HR: 0.56; 95% CI: 0.50 to 0.62, respectively) observed in patients with and without established CVD.

Cavender MA et al. *J Am Coll Cardiol.* 2018;71(22):2497-2506.

Ongoing Study

- DECLARE-TIMI58
  - Dapagliflozin
  - Type 2 DM, history of CVD or HTN
  - Multicenter, randomized, double-blind, placebo-controlled
  - 3 point MACE: CV death, stroke, and MI
  - Randomized 17,160 patients in a 1:1 fashion to dapagliflozin or placebo
  - Results expected 2019
- AstraZeneca also announced a new CVOT trial- DELIVER
  - Will look at SGLT-2i in patients with HF (reduced EF)

Wiviott SD et al. *Am Heart J.* 2018; 200:83-89.

SGLT-2i in DM + CHF Risk

- SGLT-2i drugs showed the largest reduction for heart failure risk (RR 0.56, 95% CI 0.43-0.72) versus other medications for type 2 diabetes when compared with placebo
- A pooled analysis restricted to the trials only assessing SGLT-2i showed a similar significant reduction in the risk of hospitalization for heart failure when compared with placebo (RR 0.56, 95% CI 0.41-0.77, *P*=0.067, I^2=70.2%).
  - Not seen with GLP-1 RA or DPP-4i analysis
- The researchers also found no significant association between heart failure risk in these trial participants with a lowering of A1c over time, measured with a meta-regression analysis.

Kramer C et al. JACC Heart Fai. 2018,
published online https://doi.org/10.1016/j.jchf.2018.05.021.
Devore A et al. JACC Heart Fai. 2018,
published online https://doi.org/10.1016/j.jchf.2018.07.014.

SGLT-2i for CV Benefits Outside of DM

- In a comparison of dapagliflozin vs. bumetanide in CHF[1]
  - Dapagliflozin had little impact on circulating blood volume
  - More impact on interstitial edema

- Noted effects of SGLT-2i beyond glucose lowering[2]
  - Improvement in ventricular loading conditions through a reduction in preload and afterload
  - Improvement in cardiac metabolism and bioenergetics
  - Myocardial Na+/H+ exchange inhibition- direct myocardium effects
  - Reduction of necrosis and cardiac fibrosis
  - Alteration in adipokines, cytokine production, and epicardial adipose tissue mass

- Baseline and time-dependent changes in A1c, blood pressure, and cholesterol do not seem to determine the overall benefit of SGLT-2i on cardiovascular outcomes

Hallow KM et al. *Diabetes Obes Metab*. 2018;20(3):479-487.
Verma S et al. *Diabetologia.* 2018;61(10):2108-2117.

Meet PT

- PT, a 61-year-old female with T2DM, CAD (unstable angina), and CHF reports to your clinic today for diabetes management.
- Current A1c is 8.7%, BP is 130/82 mm Hg
- Physical Exam Today: Noted 1+ Pitting Edema bilateral lower extremities
- CGM profile shows her BG often gets down to 55-60's overnight and spikes to 300's after meals
- CMP WNL
- Current Therapy
  - Metformin 1,000 mg orally twice daily
  - Insulin glargine 80 units SC daily
  - Insulin lispro 15 units SC with meals (often forgets to take)
  - ASA 325 mg orally daily
  - Metoprolol tartrate 50 mg orally BID
  - Atorvastatin 80 mg orally daily
  - Furosemide 20 mg orally daily
  - Spironolactone 25 mg orally daily

Question 7

Which of the following medications would be most appropriate to add to metformin in PT based on current treatment guidelines and recent evidence of efficacy for patients with comorbidities like hers?

a) Sitagliptin
b) Liraglutide
c) Empagliflozin
d) Acarbose

Answer to Question 7

Which of the following medications would be first priority to add to PT's therapy based on recent guidelines and evidence for her comorbidities?

c) Empagliflozin

- Patient has HF, and ADA/ESAD 2018 guidance lists SGLT-2i first based on evidence of HF reduction in a CVOT (if the patient has adequate kidney function), with a GLP-1 receptor agonist with proven CVD benefit as an alternative
- Patient may also need a GLP-1 RA to get to goal A1c and reduce insulin requirements, but adding SGLT-2i therapy should be first priority

American Diabetes Association 2018 Scientific Sessions. June 26, 2018; Orlando, Florida.
Custodio JS et al. *Heart Fail Rev.* 2018;23(3):409-418.

Question 8

Based on PT's other medications, what side effect would be most important to monitor for?

a) Volume depletion
b) Hyperkalemia
c) Hypoglycemia
d) Bradycardia

Answer to Question 8

Based on PT's other medications, what side effect would be most important to monitor for?

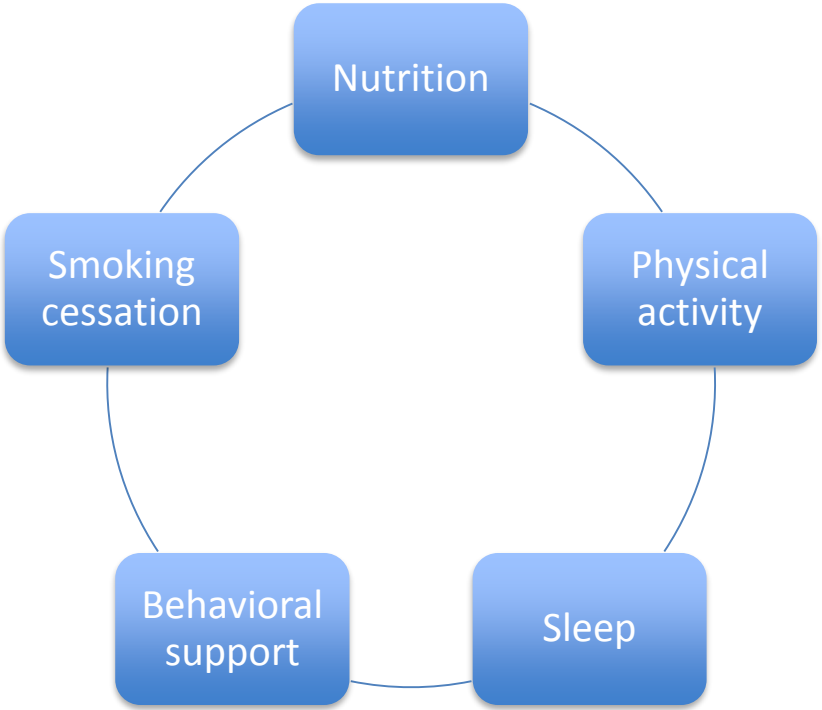
a) Volume depletion

Because volume depletion can occur during empagliflozin therapy and PT is taking other diuretics (furosemide and spironolactone), use of an empagliflozin daily dose of 10 mg with monitoring for volume depletion and upward titration as tolerated are appropriate. The furosemide dose could be decreased to allow for further titration of empagliflozin.

Jardiance (empagliflozin) prescribing information: Ridgefield, CT: Boehringer Ingelheim International;2017 Dec.

Current Guidelines for Management of T2DM

AACE/ACE Lifestyle Therapy



Garber AL et al. *Endocr Pract.* 2018; 24:91-120.

AACE/ACE Algorithm: Beyond Lifestyle

A1C < 7.5%: Monotherapy	A1C ≥ 7.5%: Metformin +	A1C > 9%

• Metformin
• GLP-1 RA
• SGLT-2i
• DPP-4i
• TZD – use with caution
• AGi
• SU/GLN – use with caution
	• Dual therapy or Triple therapy
	  • Same ordered preference list
		• Symptomatic
		  • Insulin + other agents
		• Asymptomatic
		  • Dual or triple therapy

In order of preference

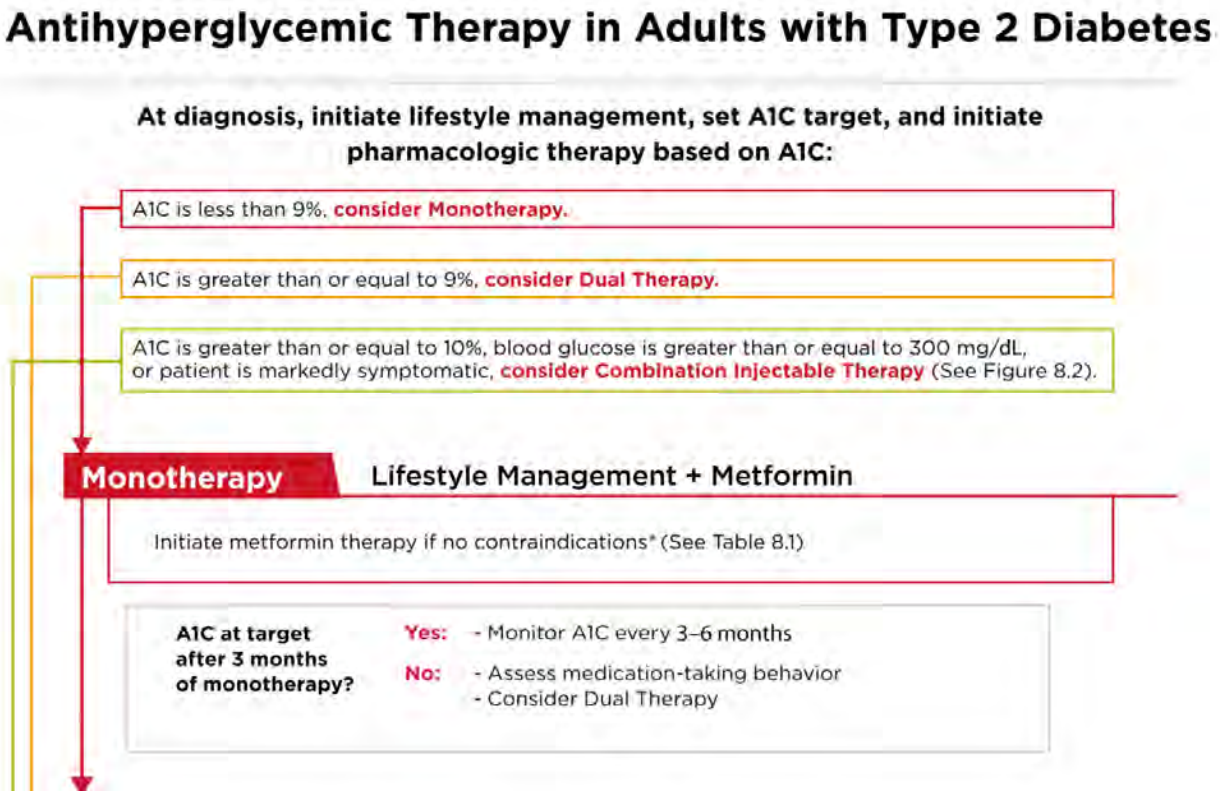
Garber AL et al. *Endocr Pract.* 2018; 24:91-120.

AACE/ACE Considerations for Therapy Selection

- Risk of hypoglycemia
- Impact on weight
- Renal/genitourinary effects
- GI symptoms
- Cardiac effects
  - ASCVD
  - CHF
- Bone impact
- Potential to cause ketoacidosis

Garber AL et al. *Endocr Pract.* 2018; 24:91-120.

ADA Guidelines



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ADA Guidelines

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ADA Guidelines- CV Guidance

Drug Class	ASCVD	CHF
SGLT-2 Inhibitors (SGLT-2i)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, empagliflozin
GLP-1 receptor agonists (GLP-1 RA)	Neutral: lixisenatide, exenatide ER, dulaglutide Benefit: liraglutide, Semaglutide, albiglutide*	Neutral
DPP-4 Inhibitors (DPP-4i)	Neutral	Potential Risk: saxagliptin, alogliptin
TZD	Potential Benefit: Pioglitazone	Increased Risk

*off market in US

Modified from Table 8.1 American Diabetes Association.
Diabetes Care. 2018;41(Suppl. 1):S1–S159.

ADA Guidelines- CV Guidance (cont.)

Drug	ASCVD	CHF
Sulfonylureas (SU)	Neutral	Neutral
Metformin	Potential Benefit	Neutral
Insulin	Neutral	Neutral

Modified from Table 8.1 American Diabetes Association.
Diabetes Care. 2018;41(Suppl. 1):S1–S159.

ADA Guidelines

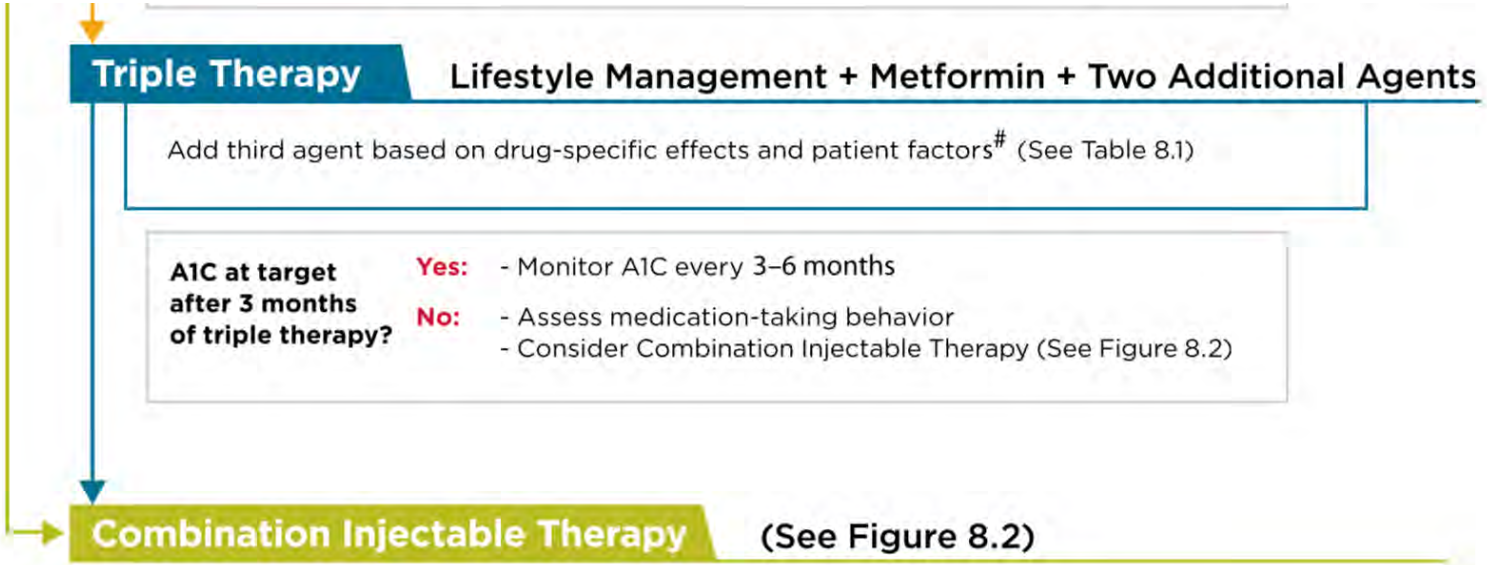

Figure 8.1—Antihyperglycemic therapy in type 2 diabetes: general recommendations. *If patient does not tolerate or has contraindications to metformin, consider agents from another class in Table 8.1. #GLP-1 receptor agonists and DPP-4 inhibitors should not be prescribed in combination. If a patient with ASCVD is not yet on an agent with evidence of cardiovascular risk reduction, consider adding.

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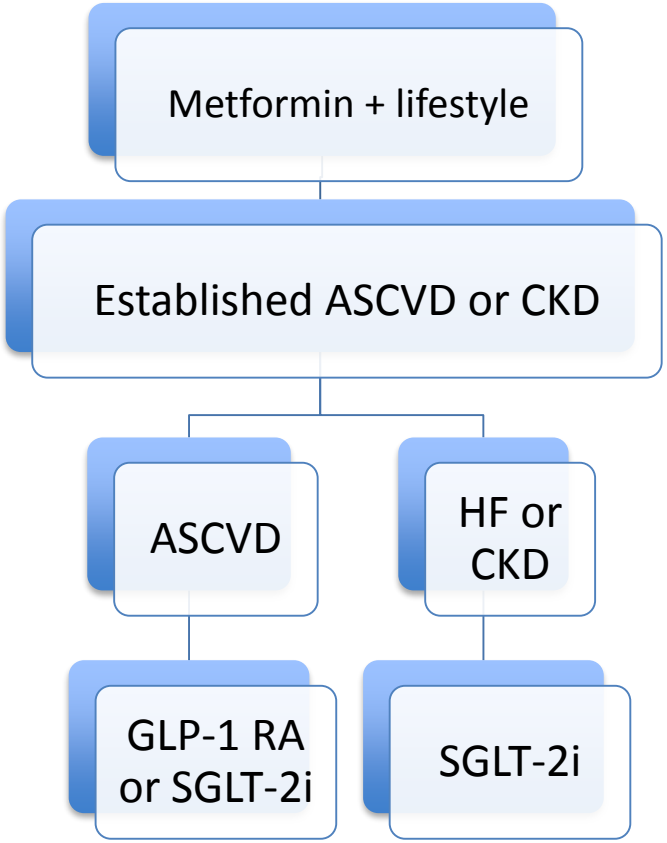
American Diabetes Association (ADA) & European Association for the Study of Diabetes (EASD) 2018 Consensus Report

- Assess ASCVD status first!
- Lifestyle modification and metformin are still considered the cornerstones of treatment
- ASCVD predominates
  - **GLP-1 RA** with proven CVD benefit or **SGLT-2i** with proven CVD benefit
- Heart failure or CKD predominates:
  - Listed first is a **SGLT-2i** with evidence of reducing heart failure or CKD progression in a cardiovascular outcomes trial (if the patient has adequate kidney function), with a **GLP-1 RA** with proven CVD benefit as an alternative option.

Davies MJ, et al. Diabetes Care. 2018, Oct 4. [Epub ahead of print]. doi: 10.2337/dci18-0033.

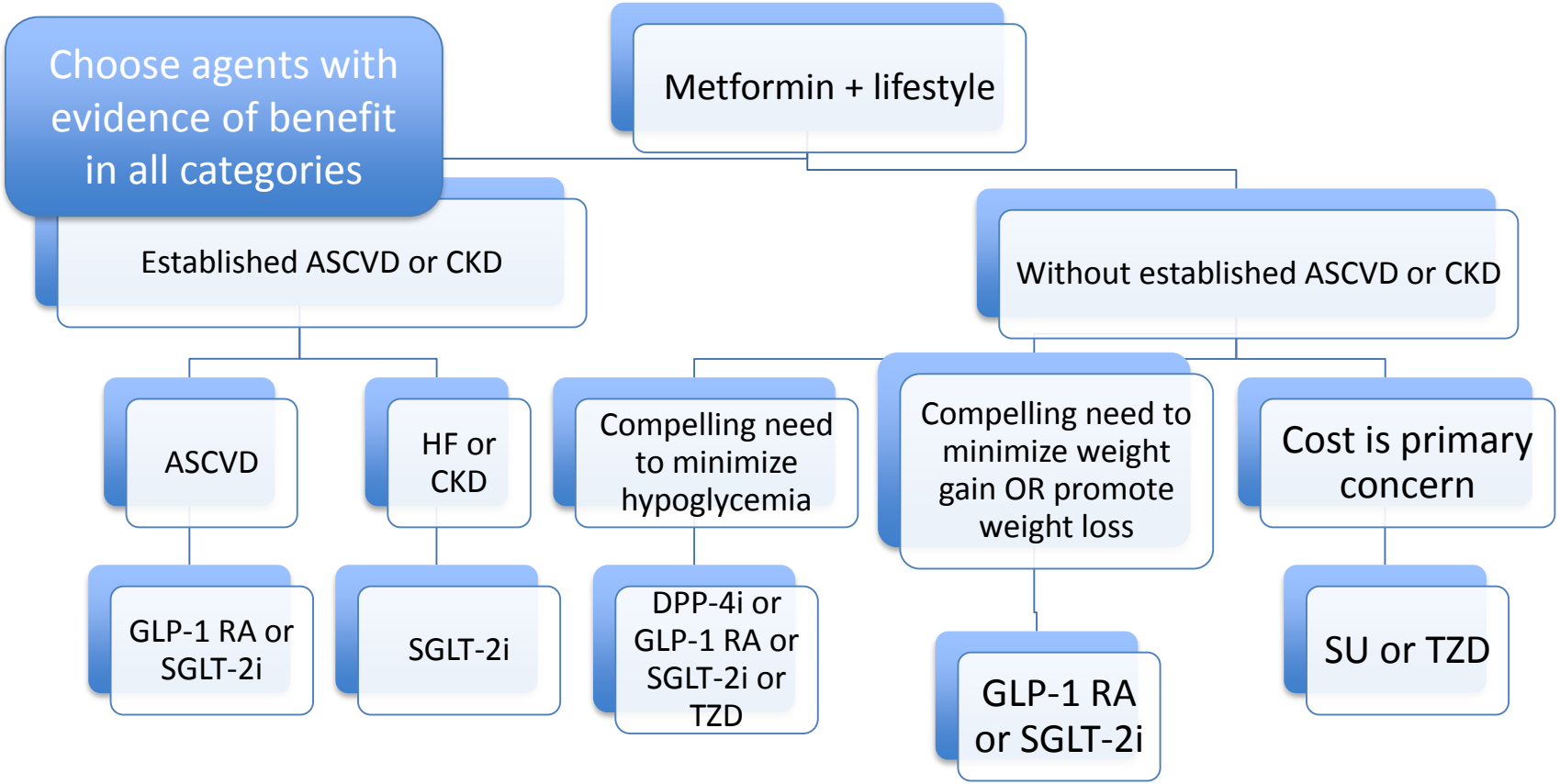
ADA & EASD 2018 Consensus Report: Dual-Therapy



Choose agents with evidence of benefit in all categories

Davies MJ, et al. *Diabetes Care.* 2018, Oct 4. [Epub ahead of print]. doi: 10.2337/dci18-0033.

ADA & EASD 2018 Consensus Report: Dual-Therapy



Davies MJ, et al. *Diabetes Care*. 2018, Oct 4. [Epub ahead of print]. doi: 10.2337/dci18-0033.

Other Consensus Guideline Notes

- If A1c 1.5% above individualized goal, early combination therapy is warranted
- Patients without ASCVD
  - Focus on agents that promote weight loss in overweight patients
  - First line still metformin then SGLT-2i or GLP-1
- Minimize hypoglycemia
  - Metformin first, then GLP-1 or SGLT-2i or TZD or DPP-4i
- If cost is a MAJOR issue
  - SU or TZD, then consider lowest cost basal insulin or DPP-4i or SGLT-2i

Davies MJ, et al. Diabetes Care. 2018, Oct 4. [Epub ahead of print]. doi: 10.2337/dci18-0033.

Revisit CJ

- 55-year-old African American male with a history of CABG x 3
- Type 2 DM x 15 years
- HTN
- Hyperlipidemia (high TG and LDL)

- Current medications include:
  - Clopidogrel 75 mg orally daily
  - ASA 325 mg orally daily
  - Metformin 1,000 mg orally twice daily
  - Glipizide 5 mg orally twice daily
  - Lisinopril/HCTZ 20-12.5, two tablets orally daily
  - Metoprolol 25 mg ER orally daily
  - Atorvastatin 40 mg orally daily

Revisit CJ

- Height 5 ‘ 9”
- Weight 260 lb
- BMI: 38.4 kg/m^2

- BP today is 145/87 mm Hg, Pulse of 62 bpm

- Today CJ is here for follow-up for his diabetes. A1c is 9.5%, other labs are WNL, including renal function.

- During your initial review of systems with CJ you learn that his blood glucose levels are fluctuating anywhere from 55 to 400 mg/dL in a given day.

- He also reports that he stopped metformin due to daily diarrhea even with the extended release version.

Question 9

Based on the current treatment guidelines what type of treatment would be recommended for CJ?

a) Dual Therapy (SGLT-2i & GLP-1 RA)
b) Dual Therapy (GLP-1 RA & Insulin)
c) GLP-1 RA Monotherapy
d) Basal Insulin Monotherapy

Answer to Question 9

Based on the current treatment guidelines what type of treatment would be recommended for CJ

a) Dual Therapy (SGLT-2i & GLP-1 RA)

- This patient would be a good candidate for both SGLT-2i and GLP-1 RA medications to not only lower glucose, but also provide CV benefits; these agents would be a better choice than adding insulin.
- Also, the effects of both agents are glucose-dependent, and they improve GV.
- Patient has A1c over 9%, thus a good candidate for dual therapy
- Also likely would remove glipizide from current treatment to reduce risk of hypoglycemia.
  - Severe hypoglycemia = Increased risk for mortality. (ADVANCE)

Garber AL et al. *Endocr Pract. 2018; 24:91-120.*; American Diabetes Association. *Diabetes Care.* 2018;41(Suppl. 1):S1–S159.
Patel A et al. *N Engl J Med.* 2008; 358:2560–2572.

Question 10

Which of the following medications would you recommend to reduce CJ's A1c to less than 6.5% based on current treatment guidelines?

a) Dapagliflozin 10 mg daily + liraglutide 1.8 mg daily
b) Empagliflozin 25 mg daily + exenatide 2 mg once weekly
c) Empagliflozin 25 mg daily + liraglutide 1.8 mg daily
d) Dapagliflozin 10 mg daily + dulaglutide 1.5 mg once weekly

Answer to Question 10

Which of the following medications would you recommend to reduce CJ's A1c to less than 6.5% based on current treatment guidelines?

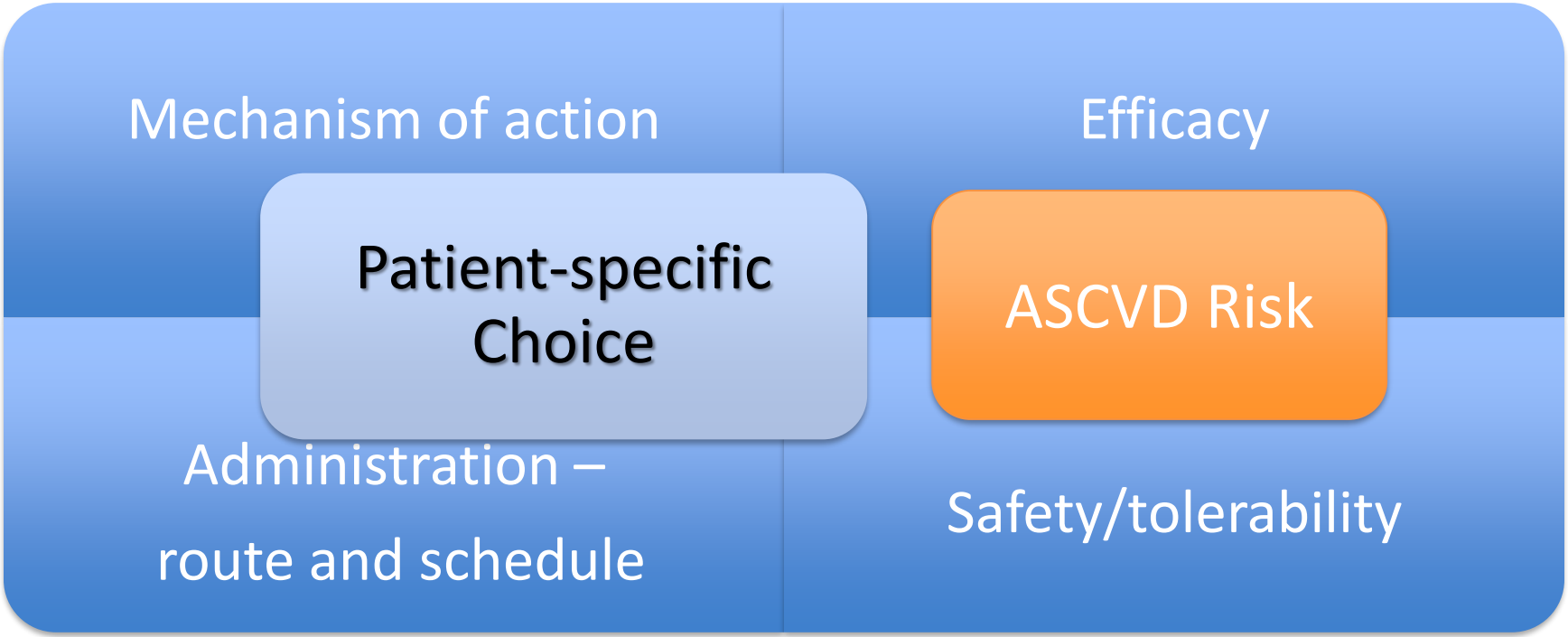
c) Empagliflozin 25 mg daily + liraglutide 1.8 mg daily

- Both of these agents have published data demonstrating favorable cardiovascular risk reduction profiles
- Empagliflozin (and probably other SGLT-2i) also have the potential to lower systolic BP (SBP) by ~5-6 mm Hg
- Both empagliflozin and liraglutide have data demonstrating reductions in glucose variability
- Both empagliflozin and liraglutide are associated with weight loss

Garber AL et al. Endocr Pract. 2018; 24:91-120.
American Diabetes Association. *Diabetes Care.* 2018;41(Suppl. 1):S1–S159.

Strategies for Identifying and Integrating New CVOT Literature Into Practice

Overall Comparison of Medications



T2DM Pharmacotherapy Approach in 2018

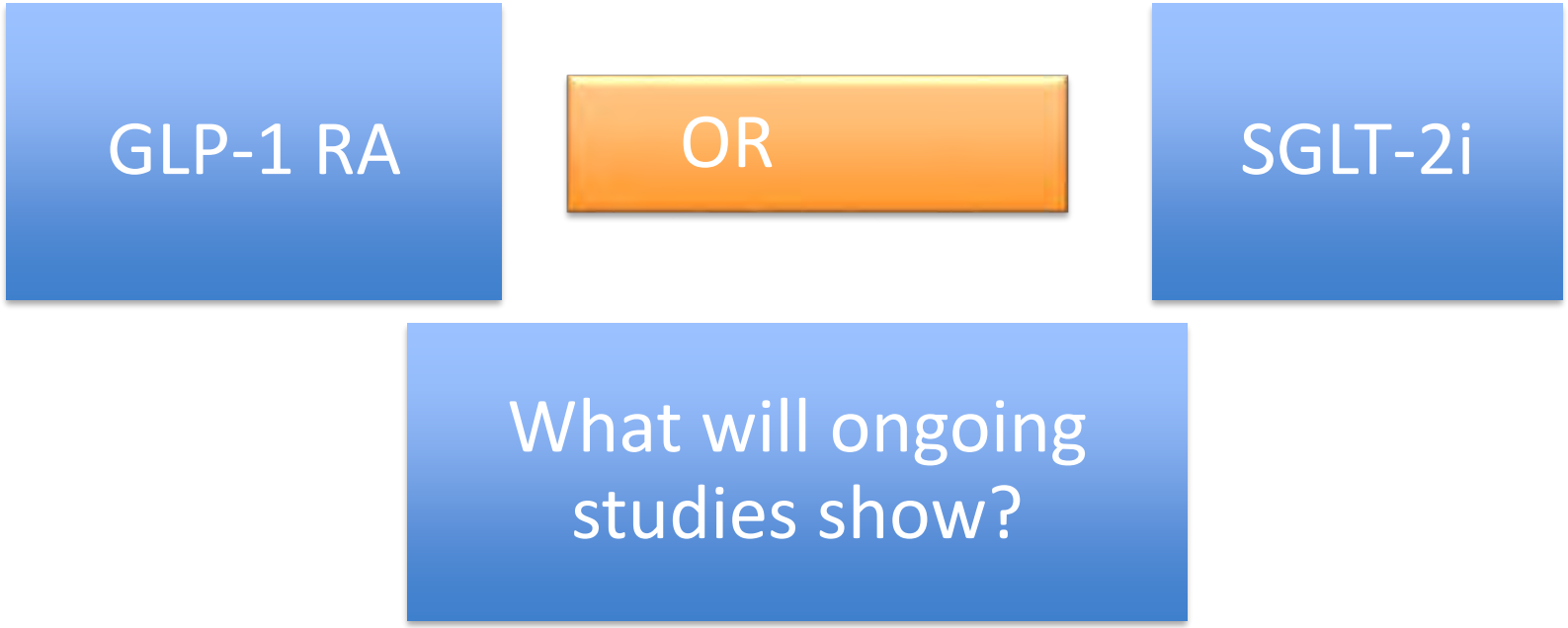
1st – Assess CVD risk

Metformin + lifestyle modifications

Determine addition of dual or triple therapy based on ASCVD risk

Davies MJ, et al. Diabetes Care. 2018, Oct 4. [Epub ahead of print]. doi: 10.2337/dci18-0033.
American Diabetes Association. *Diabetes Care.* 2018;41(Suppl. 1):S1–S159.
Garber AL et al. Endocr Pract. 2018; 24:91-120.

T2DM Pharmacotherapy Approach in 2018: ASCVD Risk



Davies MJ, et al. *Diabetes Care.* 2018, Oct 4. [Epub ahead of print]. doi: 10.2337/dci18-0033.
American Diabetes Association. *Diabetes Care.* 2018;41(Suppl. 1):S1–S159.
Garber AL et al. *Endocr Pract.* 2018; 24:91-120

Question 11

According to the 2018 American Association of Clinical Endocrinologist (AACE) and ADA/EASD recommendations for managing patients with T2DM, what factor is the FIRST consideration for which therapy should be added after lifestyle modifications and metformin?

a) Route of administration
b) ASCVD risk status
c) Mechanism of action
d) Safety

Answer to Question 11

According to the 2018 AACE and ADA/EASD recommendations for managing patients with T2DM, what factor is the FIRST consideration for which therapy should be added after lifestyle modifications and metformin?

b) ASCVD risk status

- Current recommendations and anticipated recommendations for managing patients with T2DM emphasize the importance of assessing the patient's ASCVD risk first before selecting an option for dual therapy.
- Although patient-specific considerations for the route of administration, the use of agents with complementary mechanisms of action, and safety are important, these can be addressed after the patient's ASCVD status has been determined.

American Diabetes Association 2018 Scientific Sessions. June 26, 2018; Orlando, Florida.
American Diabetes Association. *Diabetes Care.* 2018;41(Suppl. 1):S1–S159.
Garber AL et al. Endocr Pract. 2018; 24:91-120.

KEY TAKEAWAYS

1) **KEY TAKEAWAY**
   The benefits of antidiabetic therapy beyond A1c lowering effects allow for individualized selection of therapy.
2) **KEY TAKEAWAY**
   Based on guidelines and cardiovascular outcome clinical trials (CVOT), patients with established ASCVD or at high risk of CVD should receive GLP-1 RA or SGLT-2i with proven benefit in these patient populations.
3) **KEY TAKEAWAY**
   Being aware of CVOT that are recently completed or scheduled for completion in the near future will help you stay up-to-date with primary literature.
4) **KEY TAKEAWAY**
   Guidelines for management of T2DM are updated as new clinical trial results become available, so monitoring for new evidence-based guidelines and study reports on a routine basis can optimize patient care.

Questions?