THE HEART OF THE MATTER: GLP-1RA'S & SGLT-2I'S *A BRIEF OVERVIEW*

Robb Selfe, DO

Diabetology

CHW Diabetes & Endocrinology Center

October 25, 2024

GO GREEN

GO WHITE

DISCLOSURES

I am a speaker for Novo Nordisk & Dexcom Speaker Bureaus and receive honorariums for my time.

OBJECTIVES

- Review Major Medical Societies Guidelines for Use
- Mechanisms of Action & Side Effect Profiles
- Provide Brief Review of ASCVD Outcomes Trial Data
- Best Practice Recommendations – Outpatient vs Inpatient

MAJOR MEDICAL SOCIETIES

- American Association of Clinical Endocrinology 2022
- American Heart Association 2022
- American College of Cardiology 2020
- American Stroke Association 2021 Guidelines
- American Diabetes Association 2024 Standards of Care:

'In adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease, heart failure (HF), and/or chronic kidney disease (CKD), the treatment plan should include agent(s) that reduce cardiovascular and kidney disease risk: SGLT-2i and/or GLP-1 RA for glycemic management and comprehensive cardiovascular risk reduction, ***Independent of A1C*** *and in consideration of person-specific factors'*

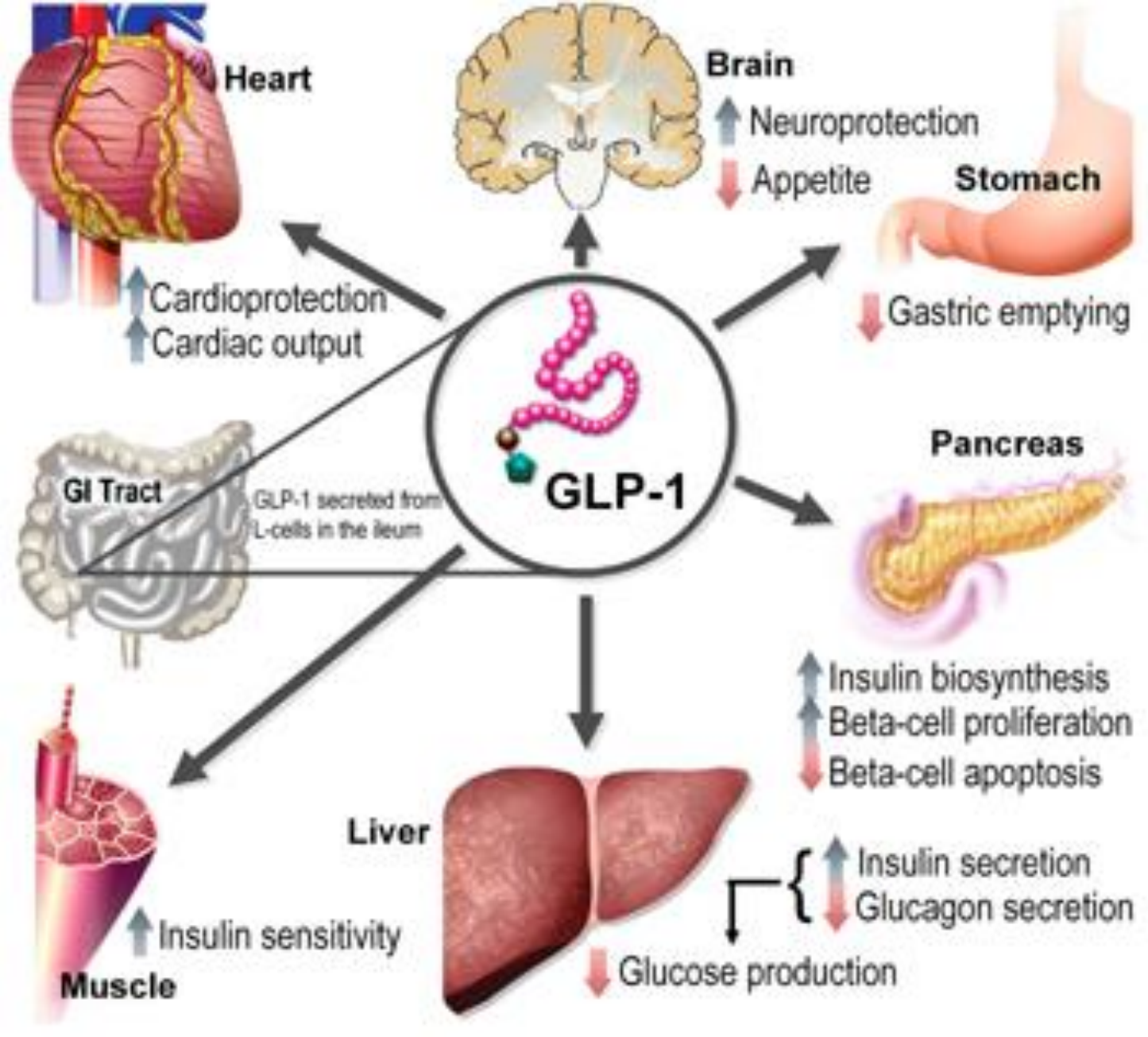
GLP-1RA'S

Mechanism of Action & ASCVD Outcomes Trial Data Review

GLP-1RA MECHANISM OF ACTION & ADVERSE EVENT REVIEW

- Glucagon-Like Peptide-1 (GLP-1) receptor agonist
  - Incretin Hormones – GLP-1 & GIP (glucose-dependent insulinotropic polypeptide) were discovered & isolated in the 1970s
- Increase glucose-dependent insulin secretion in the Pancreatic Islet (beta cells)
- Suppress glucagon secretion in a glucose-dependent manner (alpha cells). Reduced gluconeogenesis.
- Slowed gastric & gut motility
- CNS regulation of appetite and satiety

- Adverse Events:
  - Nausea (10-20%)
  - Vomiting (5-9%)
  - Diarrhea (6-9%)
  - Constipation (3-5%)
  - Bloating (5-7%)
  - Flatus/Belching (3-5%)
- Rare Incidence – pancreatitis, AKI, Acute Gall Bladder disease
- Hypoglycemic occurrence with concomitant use of SU's &/or insulin Tx
- Black Box Warnings:
  - Risk of Thyroid C-cell tumors in rodents
  - Contra-indicated in patient's w/ h/o Medullary Thyroid CA, MEN-2 Syndrome



Motivation for Use:

- Multi-prong approach to 'normalizing physiology'
- Powerful A1c lowering - > 1.5%
- Minimal risk for hypoglycemia
- Convenience of dosing /MASH
- Marked weight loss promotion
- Systemic Complication risk reduction:
  - ASCVD, CKD/Nephropathy
  - ? OSA, HF, MAFLD/MASH

GLP-1 ASCVD OUTCOMES TRIAL DATA

Table 10.38—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: GLP-1 receptor agonists

	ELIXA (260) (n = 6,068)	LEADER (255) (n = 9,340)	SUSTAIN-6 (256)* (n = 3,297)	EXSCEL (261) (n = 14,752)	REWIND (259) (n = 9,901)	PIONEER-6 (257) (n = 3,183)
Intervention	Lixisenatide/placebo	Liraglutide/placebo	Semaglutide s.c. injection/placebo	Exenatide QW/ placebo	Dulaglutide/placebo	Semaglutide oral/placebo
Main inclusion criteria	Type 2 diabetes and history of ACS (<180 days)	Type 2 diabetes and preexisting CVD, CKD, or HF at ≥50 years of age or CV risk at ≥60 years of age	Type 2 diabetes and preexisting CVD, HF, or CKD at ≥50 years of age or CV risk at ≥60 years of age	Type 2 diabetes with or without preexisting CVD	Type 2 diabetes and prior ASCVD event or risk factors for ASCVD	Type 2 diabetes and high CV risk (age of ≥50 years with established CVD or CKD, or age of ≥60 years with CV risk factors only)
A1C inclusion criteria (%)	5.5–11.0	≥7.0	≥7.0	6.5–10.0	≤9.5	None
Age (years)†	60.3	64.3	64.6	62	66.2	66
Race (% White)	75.2	77.5	83.0	75.8	75.7	72.3
Sex (% male)	69.3	64.3	60.7	62	53.7	68.4
Diabetes duration (years)†	9.3	12.8	13.9	12	10.5	14.9
Median follow-up (years)	2.1	3.8	2.1	3.2	5.4	1.3
Statin use (%)	93	72	73	74	66	85.2 (all lipid-lowering)
Metformin use (%)	66	76	73	77	81	77.4
Prior CVD/CHF (%)	100/22	81/18	60/24	73.1/16.2	32/9	84.7/12.2
Mean baseline A1C (%)	7.7	8.7	8.7	8.0	7.4	8.2
Mean difference in A1C between groups at end of treatment (%)	−0.3‡^	−0.4‡	−0.7 or −1.0^	−0.53‡^	−0.61‡	−0.7
Year started/reported	2010/2015	2010/2016	2013/2016	2010/2017	2011/2019	2017/2019
Primary outcome§	4-point MACE 1.02 (0.89–1.17)	3-point MACE 0.87 (0.78–0.97)	3-point MACE 0.74 (0.58–0.95)	3-point MACE 0.91 (0.83–1.00)	3-point MACE 0.88 (0.79–0.99)	3-point MACE 0.79 (0.57–1.11)

Continued on p. S199

Table 10.3B—Continued

	ELIXA (260) (n = 6,068)	LEADER (255) (n = 9,340)	SUSTAIN-6 (256)* (n = 3,297)	EXSCEL (261) (n = 14,752)	REWIND (259) (n = 9,901)	PIONEER-6 (257) (n = 3,183)
Key secondary outcome§	Expanded MACE 1.02 (0.90–1.11)	Expanded MACE 0.88 (0.81–0.96)	Expanded MACE 0.74 (0.62–0.89)	Individual components of MACE (see below)	Composite microvascular outcome (eye or renal outcome) 0.87 (0.79–0.95)	Expanded MACE or HF hospitalization 0.82 (0.61–1.10)
Cardiovascular death§	0.98 (0.78–1.22)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.91 (0.78–1.06)	0.49 (0.27–0.92)
MI§	1.03 (0.87–1.22)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	0.96 (0.79–1.15)	1.18 (0.73–1.90)
Stroke§	1.12 (0.79–1.58)	0.86 (0.71–1.06)	0.61 (0.38–0.99)	0.85 (0.70–1.03)	0.76 (0.61–0.95)	0.74 (0.35–1.57)
HF hospitalization§	0.96 (0.75–1.23)	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	0.93 (0.77–1.12)	0.86 (0.48–1.55)
Unstable angina hospitalization§	1.11 (0.47–2.62)	0.98 (0.76–1.26)	0.82 (0.47–1.44)	1.05 (0.94–1.18)	1.14 (0.84–1.54)	1.56 (0.60–4.01)
All-cause mortality§	0.94 (0.78–1.13)	0.85 (0.74–0.97)	1.05 (0.74–1.50)	0.86 (0.77–0.97)	0.90 (0.80–1.01)	0.51 (0.31–0.84)
Worsening nephropathy§‖	—	0.78 (0.67–0.92)	0.64 (0.46–0.88)	—	0.85 (0.77–0.93)	—

—, not assessed/reported; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; GLP-1, glucagon-like peptide 1; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction. Data in this table were adapted from Cefalu et al. (313). *Powered to rule out a hazard ratio of 1.8; superiority hypothesis not prespecified. †Age was reported as means in all trials; diabetes duration was reported as means in all trials except EXSCEL, which reported medians. ‡Significant difference in A1C between groups ($P < 0.05$). ^A1C change of 0.66% with 0.5 mg and 1.05% with 1-mg dose of semaglutide. §Outcomes reported as hazard ratio (95% CI). ‖Worsening nephropathy is defined as the new onset of urine albumin-to-creatinine ratio >300 mg/g creatinine or a doubling of the serum creatinine level and an estimated glomerular filtration rate of <45 mL/min/1.73 m^2, the need for continuous renal replacement therapy, or death from renal disease in LEADER and SUSTAIN-6 and as new macroalbuminuria, a sustained decline in estimated glomerular filtration rate of 30% or more from baseline, or chronic renal replacement therapy in REWIND. Worsening nephropathy was a prespecified exploratory adjudicated outcome in LEADER, SUSTAIN-6, and REWIND.

OUTCOMES TAKE AWAYS

- MACE (CV Death, MI, Stroke) Reduction
  - Favorability – LEADER, SUSTAIN-6 & REWIND
    - SUSTAIN 6 – Stroke Incidence Reduction was the driver (39% RRR)
    - REWIND – 12% RRR for Primary & Secondary CVD (5 yrs f/u)
- CKD/DKD/Nephropathy Reduction
  - Favorability – LEADER, SUSTAIN 6, & REWIND
- WEGOVY Data – semaglutide for weight loss
  - SELECT – 20% RRR in MACE for patients with Obesity or Overweight
  - Independent of DM-2
- FLOW Data – Favorability for Heart Failure

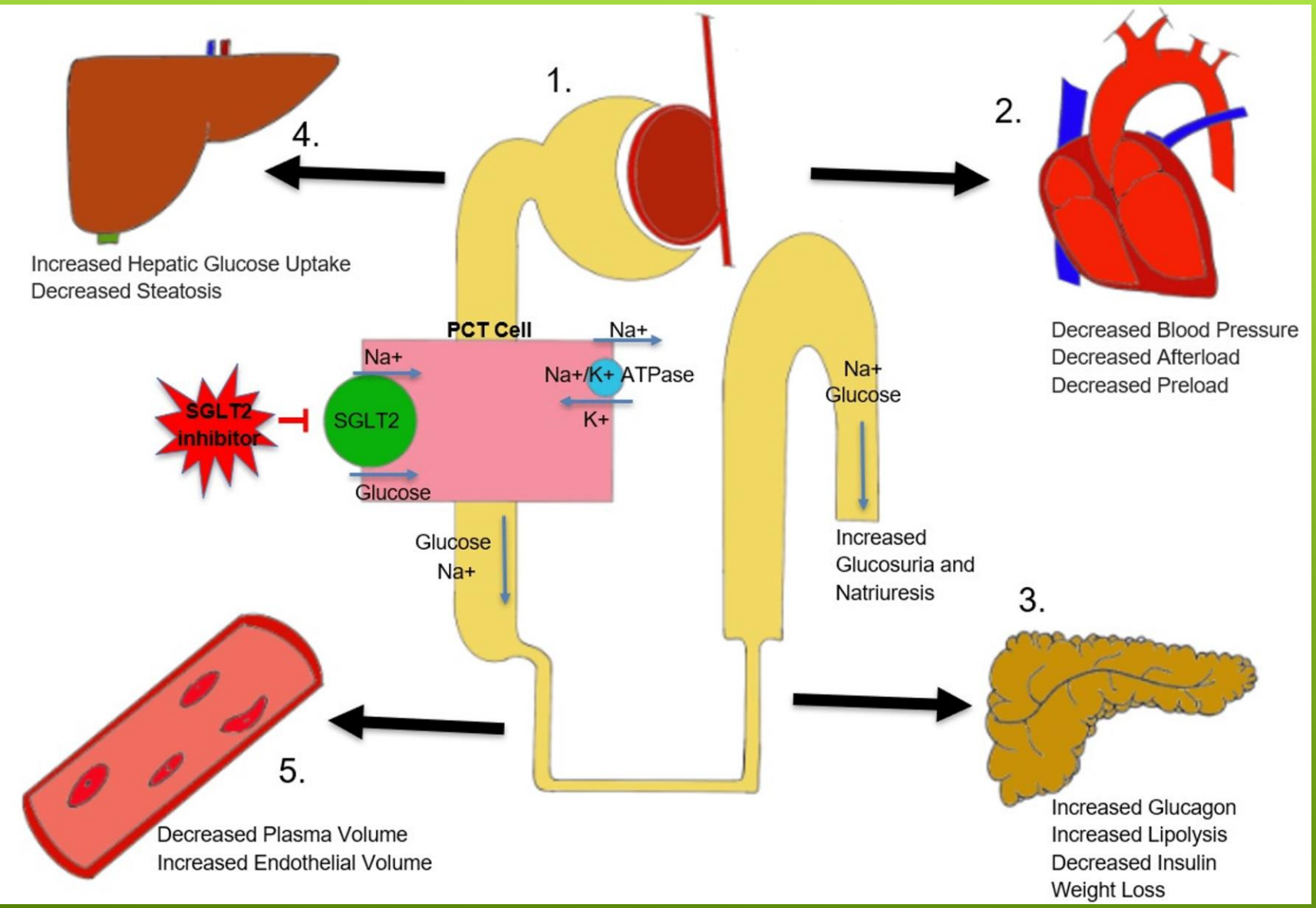
SGLT-2I'S

Mechanism of Action & ASCVD Outcomes Trial Data Review

SGLT-2i MECHANISM OF ACTION & ADVERSE EVENT REVIEW

- Sodium Glucose CoTransporter 2 is expressed in the Proximal tubules
  - Mediates 90% of glucose reabsorption
- Current SGLT-2i's inhibit < 50% glucose excretion thru urine. (UA – glucosuria)
- Glucose excretion is mitigated by Plasma glucose levels
  - Minimal Hypoglycemic occurrence
- Modest Weight loss & BP lowering
  - Volume loss
- Glucose excretion is dependent on Kidney Function
  - Ineffective – GFR < 30 mL/min/1.73 m2

- **<u>Contraindicated in Type 1 DM</u>**
  - High likelihood of DKA
  - Complicated by euglycemic labs
  - Dehydration increases incidence
- Genitourinary Tract/Yeast Infections
- Fournier's Gangrene
- Bone loss & Fracture Risk
  - Unclear mechanism of action vs secondary side effects – Falls(?)
- Volume Loss & diuresis
  - Mindful of HF management
- Increased DKA incidence
  - Ketosis-Prone DM-2, Pancreatic Insufficiency, EtOH abuse, Ketogenic diets, Acute stressors (surg/hosp/inf)
- *Slight increase LE Amputations*



Motivation For Use:

- Once Daily PO Dosing (AM)
- Minimal Risk for Hypoglycemia
- A1c Lowering – 0.5-1%
- Modest Weight Loss – 5-8 lbs
- Optimize Diuretic Use
- Systemic Complication Risk Reduction:
  - ASCVD, HF, CKD/DKD

SGLT-2 ASCVD OUTCOMES TRIAL DATA

Table 10.3C—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: SGLT2 inhibitors

	EMPA-REG OUTCOME (11) (*n* = 7,020)	CANVAS Program (12) (*n* = 10,142)	DECLARE-TIMI 58 (248) (*n* = 17,160)	CREDENCE (247) (*n* = 4,401)	DAPA-CKD (250,314) (*n* = 4,304; 2,906 with diabetes)	VERTIS CV (254,315) (*n* = 8,246)	DAPA-HF (14) (*n* = 4,744; 1,983 with diabetes)	EMPEROR-Reduced (253) (*n* = 3,730; 1,856 with diabetes)	EMPEROR-Preserved (242,316) (*n* = 5,988; 2,938 with diabetes)	DELIVER (252) (*n* = 6,263; 2,807 with diabetes)
Intervention	Empagliflozin/placebo	Canagliflozin/placebo	Dapagliflozin/placebo	Canagliflozin/placebo	Dapagliflozin/placebo	Ertugliflozin/placebo	Dapagliflozin/placebo	Empagliflozin/placebo*	Empagliflozin/placebo	Dapagliflozin/placebo
Main inclusion criteria	Type 2 diabetes and preexisting CVD	Type 2 diabetes and preexisting CVD at ≥30 years of age or ≥2 CV risk factors at ≥50 years of age	Type 2 diabetes and established ASCVD or multiple risk factors for ASCVD	Type 2 diabetes and albuminuric kidney disease	Albuminuric kidney disease, with or without diabetes	Type 2 diabetes and ASCVD	NYHA class II, III, or IV heart failure and an ejection fraction ≤40%, with or without diabetes	NYHA class II, III, or IV heart failure and an ejection fraction ≤40%, with or without diabetes	NYHA class II, III, or IV heart failure and an ejection fraction >40%	NYHA class II, III, or IV heart failure and an ejection fraction >40% with or without diabetes
A1C inclusion criteria (%)	7.0–10.0	7.0–10.5	≥6.5	6.5–12	—	7.0–10.5	—	—	—	—
Age (years)†	63.1	63.3	64.0	63	61.8	64.4	66	67.2, 66.5	71.8, 71.9	71.7
Race (% White)	72.4	78.3	79.6	66.6	53.2	87.8	70.3	71.1, 69.8	76.3, 75.4	71.2
Sex (% male)	71.5	64.2	62.6	66.1	66.9	70	76.6	76.5, 75.6	55.4, 55.3	56.1
Diabetes duration (years)†	57% >10	13.5	11.0	15.8	—	12.9	—	—	—	—
Median follow-up (years)	3.1	3.6	4.2	2.6	2.4	3.5	1.5	1.3	2.2	2.3
Statin use (%)	77	75	75 (statin or ezetimibe use)	69	64.9	—	—	—	68.1, 68.8	—
Metformin use (%)	74	77	82	57.8	29	—	51.2% (of people with diabetes)	—	—	—
Prior CVD/CHF (%)	99/10	65.6/14.4	40/10	50.4/14.8	37.4/10.9	99.9/23.1	100% with CHF	100% with CHF	100% with CHF	100% with CHF
Mean baseline A1C (%)	8.1	8.2	8.3	8.3	7.1% (7.8% in those with diabetes)	8.2	—	—	—	6.6
Mean difference in A1C between groups at end of treatment (%)	−0.3^	−0.58‡	−0.43‡	−0.31	—	−0.48 to −0.5	—	—	—	—
Year started/reported	2010/2015	2009/2017	2013/2018	2017/2019	2017/2020	2013/2020	2017/2019	2017/2020	2017/2020	2018/2022

Continued on p. S201

Table 10.3C—Continued

	EMPA-REG OUTCOME (11) (*n* = 7,020)	CANVAS Program (12) (*n* = 10,142)	DECLARE-TIMI 58 (249) (*n* = 17,160)	CREDENCE (247) (*n* = 4,401)	DAPA-CKD (250,314) (*n* = 4,304; 2,906 with diabetes)	VERTIS CV (254,315) (*n* = 8,246)	DAPA-HF (14) (*n* = 4,744; 1,983 with diabetes)	EMPEROR-Reduced (253) (*n* = 3,730; 1,856 with diabetes)	EMPEROR-Preserved (242,316) (*n* = 5,988; 2,938 with diabetes)	DELIVER (252) (*n* = 6,263; 2,807 with diabetes)
Primary outcome§	3-point MACE 0.86 (0.74–0.99)	3-point MACE 0.86 (0.75–0.97)	3-point MACE 0.93 (0.84–1.03) CV death or HF hospitalization 0.83 (0.73–0.95)	ESRD, doubling of creatinine, or death from renal or CV cause 0.70 (0.59–0.82)	≥50% decline in eGFR, ESKD, or death from renal or CV cause 0.61 (0.51–0.72)	3-point MACE 0.97 (0.85–1.11)	Worsening heart failure or death from CV causes 0.74 (0.65–0.85) Results did not differ by diabetes status	CV death or HF hospitalization 0.75 (0.65–0.86)	CV death or HF hospitalization 0.79 (0.69–0.90)	Worsening HF or CV death 0.82 (0.73–0.92)
Key secondary outcome§	4-point MACE 0.89 (0.78–1.01)	All-cause and CV mortality (see below)	Death from any cause 0.93 (0.82–1.04) Renal composite (≥40% decrease in eGFR rate to <60 mL/min/1.73 m^2, new ESRD, or death from renal or CV causes 0.76 (0.67–0.87)	CV death or HF hospitalization 0.69 (0.57–0.83) 3-point MACE 0.80 (0.67–0.95)	≥50% decline in eGFR, ESKD, or death from renal cause 0.56 (0.45–0.68) CV death or HF hospitalization 0.71 (0.55–0.92) Death from any cause 0.69 (0.53–0.88)	CV death or HF hospitalization 0.88 (0.75–1.03) CV death 0.92 (0.77–1.11) Renal death, renal replacement therapy, or doubling of creatinine 0.81 (0.63–1.04)	CV death or HF hospitalization 0.75 (0.65–0.85)	Total HF hospitalizations 0.70 (0.58–0.85) Mean slope of change in eGFR 1.73 (1.10–2.37)	All HF hospitalizations (first and recurrent) 0.73 (0.61–0.88) Rate of decline in eGFR (−1.25 vs. −2.62 mL/min/1.73 m^2; *P* < 0.001)	Total number worsening HF and CV deaths 0.77 (0.67–0.89) Change in KCCQ TSS at month 8 1.11 (1.03–1.21) Mean change in KCCQ TSS 2.4 (1.5–3.4) All-cause mortality 0.94 (0.83–1.07)
Cardiovascular death§	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.82–1.17)	0.78 (0.61–1.00)	0.81 (0.58–1.12)	0.92 (0.77–1.11)	0.82 (0.69–0.98)	0.92 (0.75–1.12)	0.91 (0.76–1.09)	0.88 (0.74–1.05)
MI§	0.87 (0.70–1.09)	0.89 (0.73–1.09)	0.89 (0.77–1.01)	—	—	1.04 (0.86–1.26)	—	—	—	—
Stroke§	1.18 (0.89–1.56)	0.87 (0.68–1.09)	1.01 (0.84–1.21)	—	—	1.06 (0.82–1.37)	—	—	—	—
HF hospitalization§	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.73 (0.61–0.88)	0.61 (0.47–0.80)	—	0.70 (0.54–0.90)	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.73 (0.61–0.88)	0.77 (0.67–0.89)
Unstable angina hospitalization§	0.99 (0.74–1.34)	—	—	—	—	—	—	—	—	—
All-cause mortality§	0.68 (0.57–0.82)	0.87 (0.74–1.01)	0.93 (0.82–1.04)	0.83 (0.68–1.02)	0.69 (0.53–0.88)	0.93 (0.80–1.08)	0.83 (0.71–0.97)	0.92 (0.77–1.10)	1.00 (0.87–1.15)	0.94 (0.83–1.07)
Worsening nephropathy§‖	0.61 (0.53–0.70)	0.60 (0.47–0.77)	0.53 (0.43–0.66)	(See primary outcome)	(See primary outcome)	(See secondary outcomes)	0.71 (0.44–1.16)	Composite renal outcome 0.50 (0.32–0.77)	Composite renal outcome** 0.95 (0.73–1.24)	—

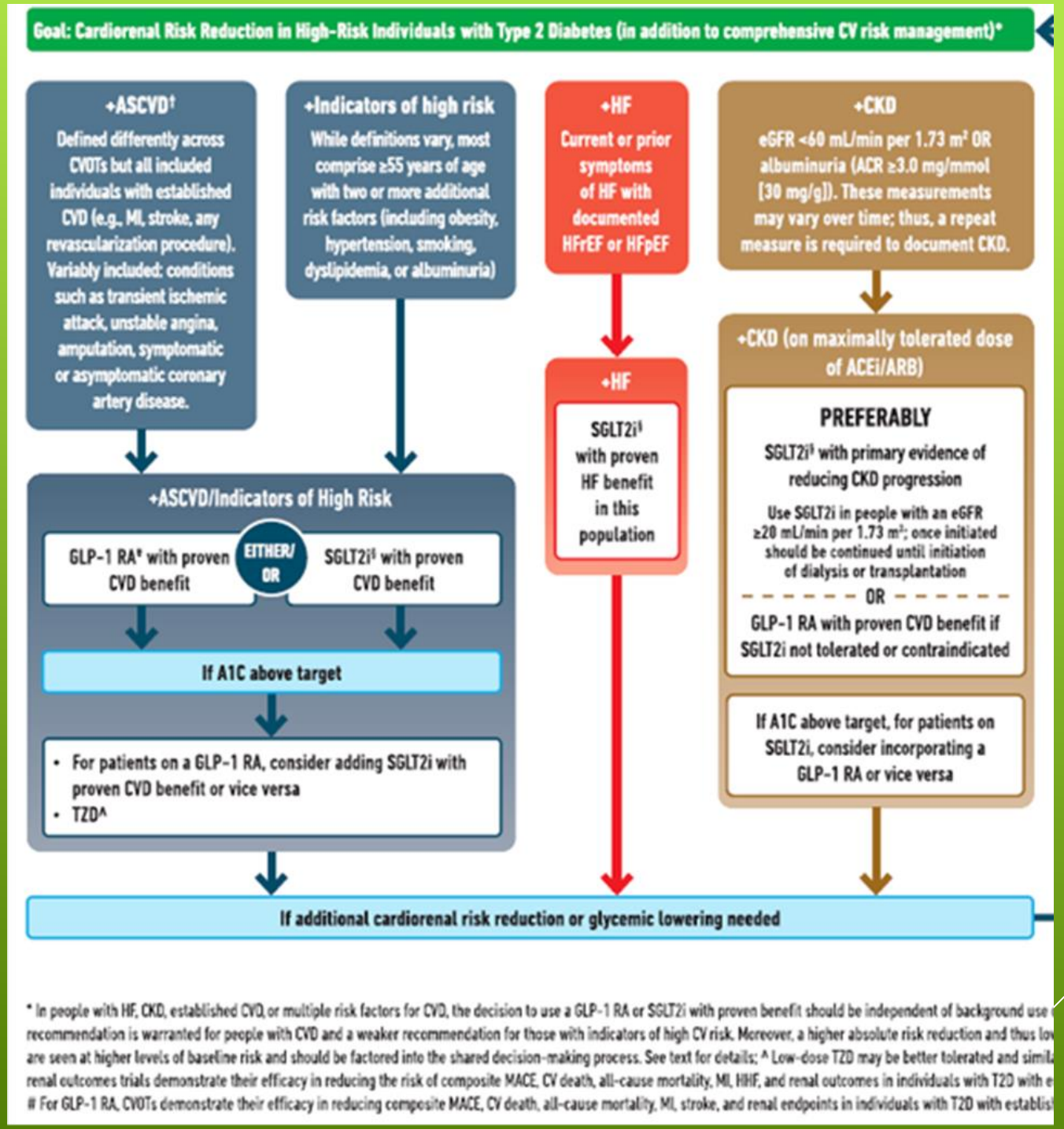
—, not assessed/reported; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; KCCQ TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; MACE, major adverse cardiovascular event; MI, myocardial infarction; SGLT2, sodium–glucose cotransporter 2; NYHA, New York Heart Association. Data in this table were adapted from Cefalu et al. (313). *Baseline characteristics for EMPEROR-Reduced displayed as empagliflozin, placebo. †Age was reported as means in all trials; diabetes duration was reported as means in all trials except EMPA-REG OUTCOME, which reported as percentage of population with diabetes duration >10 years, and DECLARE-TIMI 58, which reported median. ‡Significant difference in A1C between groups ($P < 0.05$). ^A1C change of 0.30 in EMPA-REG OUTCOME is based on pooled results for both doses (i.e., 0.24% for 10 mg and 0.36% for 25 mg of empagliflozin). §Outcomes reported as hazard ratio (95% CI). ‖Definitions of worsening nephropathy differed between trials. **Composite outcome in EMPEROR-Preserved: time to first occurrence of chronic dialysis, renal transplantation; sustained reduction of ≥40% in eGFR, sustained eGFR <15 mL/min/1.73 m^2 for individuals with baseline eGFR ≥30 mL/min/1.73 m^2.

OUTCOMES TAKE AWAYS

- MACE Reduction in DM-2 & Known CVD
  - Favorability – CANVAS & EMPA-REG
  - Meta-analysis – suggestive of EMPA, CANA & DAPA
- Heart Failure Reduction
  - Favorability – Class Effect
- CKD/DKD Reduction
  - Favorability – CANVAS, EMPA-REG, & DAPA-CKD

BEST PRACTICE USE

Outpatient & Inpatient Management



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use
recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lo
are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and simil
renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with e
For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with establis

GLP-1 BEST PRACTICE

- Lifestyle, Lifestyle, Lifestyle (DM ED)
- GI Side Effect Counseling
  - Patient expectations
  - Dietary tips/tricks
- Concomitant Med Adjustments
- Supply Access Concerns resolving!
- Insurance constraints
  - Documentation/Strict Criteria (A1c 7-9%)
  - Prescribing scrutiny & legal action
- Cost of Meds!
  - PAP/Copay programs
  - CM & Clinical Pharmacist as resource
- Avoid Compounded Formulations!

SGLT-2I BEST PRACTICE

- Do Not prescribe for Type 1 DM
- Do not initiate therapy w/ A1c > 10%
- Dose in AM for increased diuresis
- Hydration improves tolerability
- Avoid/Counsel those at risk for UTI/Yeast inf
  - Aggressive treatment early typically resolves concerns
  - Stop med use if recurrent
- Coordinate with Cardio/AHF Team/Nephro regarding concomitant RAASi/diuretic use
- Suggest avoidance with active LE wounds/PAD care – Use after resolution (?)

REFERENCES

- American Diabetes Association - www.diabetes.org
- American Heart Association – www.aha.org
- American College of Cardiology – www.acc.org
- American Stroke Association – www.stroke.org
- New England Journal of Medicine - www.nejm.org
- Up To Date – www.uptodate.com