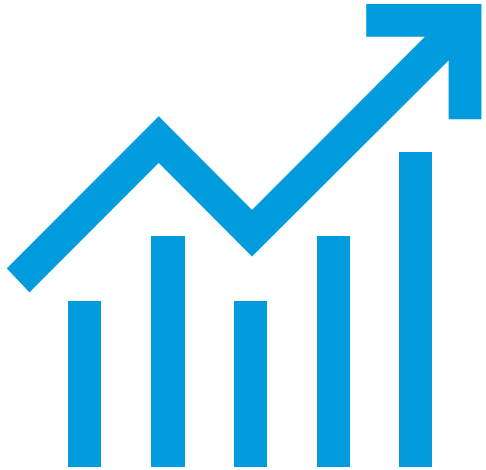
MAYO CLINIC

To A1C and Beyond: Exploring Renal and Cardiovascular Benefits of Antidiabetic Agents



Laurel Lake, PharmD
PGY2 Ambulatory Care Pharmacy Resident

Mayo Clinic Pharmacy Grand Rounds
September 8, 2020

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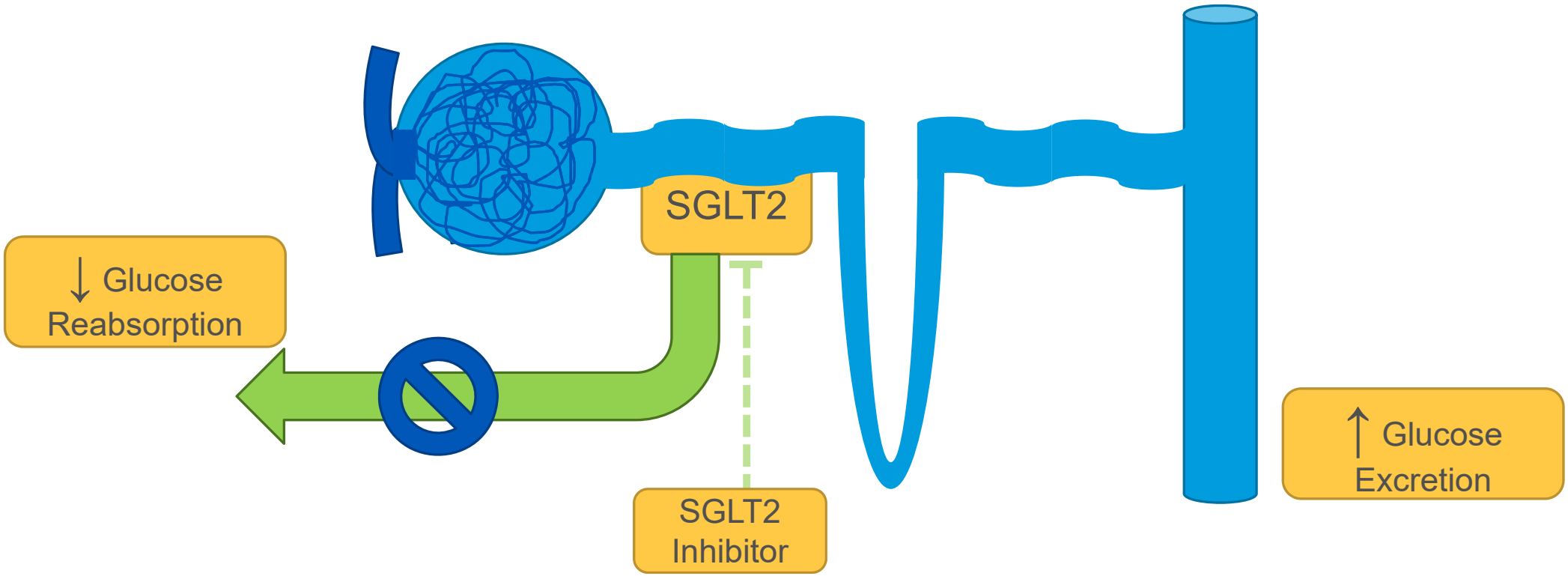
Objectives

#1 Describe the recent literature examining cardiovascular benefits of GLP-1 receptor agonists and SGLT2 inhibitors

#2 Discuss the body of evidence for renal outcomes with GLP-1 receptor agonists and SGLT2 inhibitors

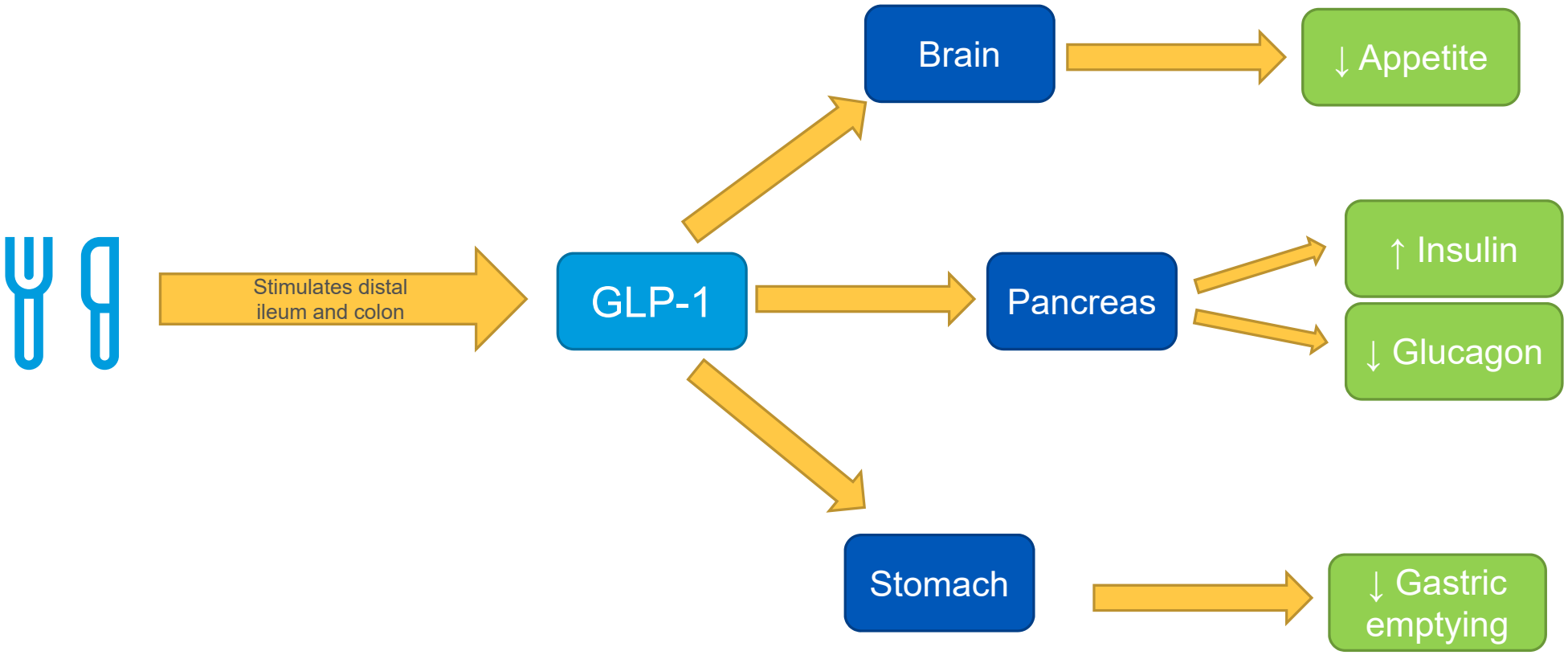
#3 Recognize situations to implement and optimize these therapies in patient care plans

Background: Mechanism of Action of SGLT-2 Inhibitors



Moses. *Australas Med J*. 2014; 7(10): 405–415.

Background: Mechanism of Action of GLP-1 Receptor Agonists



Cohen. *Med J Aust.* 2013;199(4):246-9.

Objective #1

Describe the recent literature examining cardiovascular benefits of GLP-1 receptor agonists and SGLT2 inhibitors

Agents With FDA Approval for CV Benefit

Medication	Indication	Date of FDA Approval
SGLT2 Inhibitors		
Empagliflozin	-Risk reduction of cardiovascular death in adult patients with T2DM and *established* ASCVD	Dec. 2016
Canagliflozin	-Risk reduction of MACE in adults with T2DM and *established* ASCVD	Oct. 2018
Dapagliflozin	-Risk reduction of hospitalization for heart failure in patients with T2DM and *established* ASCVD or multiple ASCVD *risk factors* **-Risk reduction of cardiovascular death and hospitalization for heart failure in adults with HFrEF**	Oct. 2019 **May 2020**

Das. *JACC*. 2020: 76(9):1117-1145.

Evidence of SGLT2 Inhibitors for CV Benefit

	CANVAS	CREDENCE	DECLARE-TIMI 58	DAPA-HF	EMPA-REG	EMPEROR-Reduced
Medication	**Canagliflozin**	**Canagliflozin**	**Dapagliflozin**	**Dapagliflozin**	**Empagliflozin**	**Empagliflozin**
Baseline prevalence of CV disease/HF (%)	72	50	41	---	99	---
Baseline prevalence of HF (%)	14	15	10	100	10	100
MACE outcomes (HR)	**0.86**	**0.80**	0.93	---	**0.86**	---
Hospitalization for HF or CV death (HR)	**0.66**	**0.69**	**0.83**	**0.75**	**0.66**	**0.75**
CV death (HR)	**0.62**	0.78	0.98	**0.82**	**0.62**	0.92
MI (HR)	0.87	---	0.89	---	0.87	---
Stroke (HR)	1.18	---	1.01	---	1.18	---
All-cause mortality (HR)	**0.68**	0.83	0.94	**0.83**	**0.68**	0.92
HF hospitalization (HR)	**0.65**	**0.61**	**0.73**	**0.70**	**0.65**	**0.69**

HR = Hazard Ratio
BOLD = confidence interval does not cross 1

Das. *JACC*. 2020: 76(9):1117-1145.
Packer, *NEJM*. 2020,

Agents with FDA approval for CV benefit

Medication	Indication	Date of FDA Approval
GLP-1RA		
Liraglutide	-Risk reduction of MACE in adults with T2D and established ASCVD	Aug. 2017
Semaglutide	**-Risk reduction of MACE in adults with T2D and established ASCVD**	**Jan. 2020**
Dulaglutide	**-Risk reduction of MACE in adults with T2D and established ASCVD OR at high risk for ASCVD**	**Feb. 2020**

Das. JACC. 2020: 76(9):1117-1145.

Evidence of GLP1-RA for CV Benefit

	LEADER	EXSCEL	REWIND	SUSTAIN-6	PIONEER-6
Medication	**Liraglutide**	**Exenatide**	**Dulaglutide**	**Semaglutide SQ**	**Semaglutide PO**
Baseline prevalence of ASCVD/HF(%)	81	73	31	72	85
Baseline prevalence of HF (%)	18	16	9	24	---
MACE outcomes (HR)	**0.87**	0.91	**0.88**	**0.74**	0.79
CV death (HR)	**0.78**	0.88	0.91	0.98	**0.49**
MI (HR)	0.86	0.97	0.96	0.74	1.18
Stroke (HR)	0.86	0.85	**0.76**	**0.61**	0.74
All-cause mortality (HR)	**0.85**	**0.86**	0.90	1.05	**0.51**
HF hospitalization (HR)	0.87	0.94	0.93	0.86	1.11

*HR (95% CI)
BOLD = confidence interval does not cross 1

Das. *JACC*. 2020: 76(9):1117-1145.
Packer, *NEJM*. 2020,

A Closer Look: Dapagliflozin

Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction

DAPA-HF

DAPA-HF Population

4,744 participants

Important inclusion criteria:

- Age ≥18 years old
- EF ≤40% and NYHA class II-IV
- NT-proBNP of ≥600 pg/mL or ≥400 if hospitalized for HF in past 12 months
- Receipt of standard HF drug therapy/devices

Important exclusion criteria:

- Type 1 diabetes mellitus
- Hypotension or SBP < 95 mmHg
- eGFR <30 mL/min

Important!

- 58.2% of participants did NOT have diabetes

McMurray. *NEJM*. 2019: 381:1995-2008

DAPA-HF Methods

Intervention: Randomized to dapagliflozin 10 mg PO daily or placebo

McMurray. *NEJM*. 2019: 381:1995-2008

DAPA-HF Methods

Primary Outcome

- Composite of worsening heart failure or cardiovascular death

Secondary Outcomes

- Composite of hospitalization for HF or cardiovascular death
- Total number of hospitalizations for HF and cardiovascular deaths
- Change in baseline symptoms scoring
- Composite of worsening renal function
- Death from any cause

McMurray. *NEJM*. 2019: 381:1995-2008

DAPA-HF Methods

Primary Outcome

- **Composite of worsening heart failure or cardiovascular death**

Secondary Outcomes

- Composite of hospitalization for HF or cardiovascular death
- Total number of hospitalizations for HF and cardiovascular deaths
- Change in baseline symptoms scoring
- Composite of worsening renal function
- Death from any cause

McMurray. *NEJM*. 2019: 381:1995-2008

DAPA-HF Results

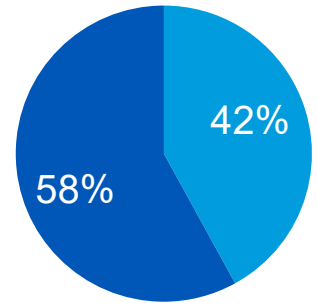
	Dapagliflozin 10 mg daily	Placebo	Hazards Ratio	CI
Primary Outcome (Composite of worsening HF or CV death)	386 patients (16.3%)	502 patients (21.2%)	**0.74**	**0.65-0.85**
Hospitalization/ urgent visit for HF	237 (10%)	326 (13.7%)	**0.70**	**0.59-0.83**
Hospitalization for HF	231 (9.7%)	318 (13.4%)	**0.70**	**0.59-0.83**
Death from CV causes	227 (9.6%)	273 (11.5%)	**0.82**	**0.69-0.98**
Death from any cause	276 (11.6%)	329 (13.9%)	**0.83**	**0.71-0.97**

BOLD = confidence interval does not cross 1

McMurray. *NEJM*. 2019: 381:1995-2008

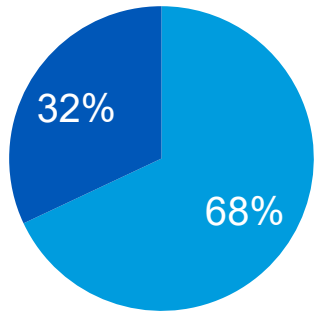
Subgroup Variations of Primary Outcome

Diabetes



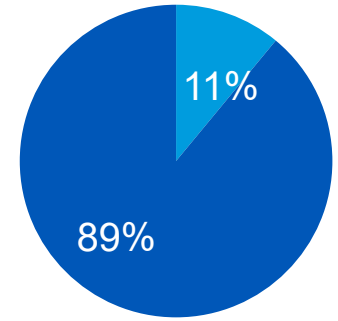
HR 0.75 (0.63-0.87)
HR 0.73 (0.60-0.88)

HF Severity



HR 0.63 (0.52-0.75)
HR 0.90 (0.74-1.09)

Sacubitril-Valsartan



HR 0.75 (0.50-1.13)
HR 0.74 (0.65-0.86)

McMurray. *NEJM*. 2019: 381:1995-2008

Impacts of DAPA-HF

Conclusion

- In patients with HFrEF with or without diabetes, dapagliflozin may be considered to decrease the risk of hospitalizations for HF and cardiovascular death

FDA approvals

- **Led to May 2020 approval: Risk reduction of cardiovascular death and hospitalization for heart failure in adults with HFrEF**

McMurray. *NEJM*. 2019: 381:1995-2008

A Closer Look: Semaglutide

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

SUSTAIN-6

SUSTAIN-6 Population

3,297 participants

Important inclusion criteria:

- T2DM and A1C ≥7%
- ≥50 years old with at least 1 of the following:
  - Established cardiovascular disease
  - Chronic heart failure (NYHA class II or III)
  - Chronic kidney disease of stage 3 or higher
- ≥60 years old with at least one cardiovascular risk factor

Important exclusion criteria:

- History of acute coronary or cerebrovascular event in last 90 days
- Planned revascularization
- Long-term dialysis

Marso. *NEJM*. 2016; 375:1834-1844

SUSTAIN-6 Methods

Intervention: Randomized to receive either 0.5 mg or 1.0 mg of once-weekly subcutaneous semaglutide or placebo

Marso. *NEJM*. 2016; 375:1834-1844

SUSTAIN-6 Methods

Primary Outcome

- Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

Secondary Outcomes

- Expanded composite: death from CV causes, nonfatal MI, nonfatal stroke, revascularization, or hospitalization for HF or unstable angina
- Composite of death from all causes, non-fatal MI, or nonfatal stroke
- Retinopathy complications
- New/worsening nephropathy

Marso. *NEJM*. 2016; 375:1834-1844

SUSTAIN-6 Methods

Primary Outcome

- **Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke**

Secondary Outcomes

- Expanded composite: death from CV causes, nonfatal MI, nonfatal stroke, revascularization, or hospitalization for HF or unstable angina
- Composite of death from all causes, non-fatal MI, or nonfatal stroke
- Retinopathy complications
- New/worsening nephropathy

Marso. *NEJM*. 2016; 375:1834-1844

SUSTAIN-6 Results

	Semaglutide	Placebo	Hazards Ratio	CI
Primary Outcome (Composite of death from CV causes, nonfatal MI, or nonfatal stroke)	108 patients (6.6%)	146 patients (8.9%)	**0.74**	**0.58-0.95**
Expanded composite	199 (12.1%)	264 (16.0%)	**0.74**	**0.62-0.89**
All-cause death, nonfatal MI, or nonfatal stroke	122 (7.4%)	158 (9.6%)	**0.77**	**0.61-0.97**
Nonfatal stroke	27 (1.6%)	44 (2.7%)	**0.61**	**0.38-0.99**

BOLD = confidence interval does not cross 1

Marso. *NEJM*. 2016; 375:1834-1844

SUSTAIN-6 Impacts

Conclusion:

- Semaglutide contributed to a 26% lower risk of the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke compared to placebo
- Non-inferior to placebo

FDA Approvals:

- **Led to 2020 approval for risk reduction of MACE in adults with T2D and established ASCVD**

Marso. *NEJM*. 2016; 375:1834-1844

A Closer Look: Dulaglutide

Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes

REWIND

REWIND Population

9,901 participants

Important inclusion criteria:

- T2DM and A1C ≤ 9.5%
- Up to 2 oral glucose-lowering drugs with or without insulin
- BMI ≥ 23 kg/m2

Important Exclusion Criteria

- eGFR <15 mL/min
- Cancer in past 5 years
- Coronary or cerebrovascular event in past 2 months
- Plans for revascularization

Important!

- Only 31.5% of participants had previously established cardiovascular disease
  - Majority withOUT

Age ≥ 50 years old and :
Vascular disease

Age ≥ 55 years old and:
Myocardial ischemia, artery stenosis, left ventricular hypertophy, eGFR <60 mL/min, **or** albuminuria

Age ≥ 55 years old include if 2+ of:
Tobacco use, dyslipidemia, HTN, or abdominal obesity

Gerstein. *Lancet.* 2019:394(10193):121-130.

REWIND Methods

Intervention: Randomized to receive either 1.5 mg once-weekly subcutaneous dulaglutide or placebo

Gerstein. *Lancet.* 2019:394(10193):121-130.

REWIND Methods

Primary

- Composite of non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular causes or unknown causes

Secondary

- Myocardial infarction (fatal or non-fatal)
- Stroke (fatal or non-fatal)
- Death
- Hospital admission for unstable angina
- Heart failure requiring hospital admission/urgent therapy

Gerstein. *Lancet.* 2019:394(10193):121-130.

REWIND Methods

Primary Outcome

- **Composite of non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular causes or unknown causes**

Secondary Outcomes

- Myocardial infarction (fatal or non-fatal)
- Stroke (fatal or non-fatal)
- Death
- Hospital admission for unstable angina
- Heart failure requiring hospital admission/urgent therapy

Gerstein. *Lancet.* 2019:394(10193):121-130.

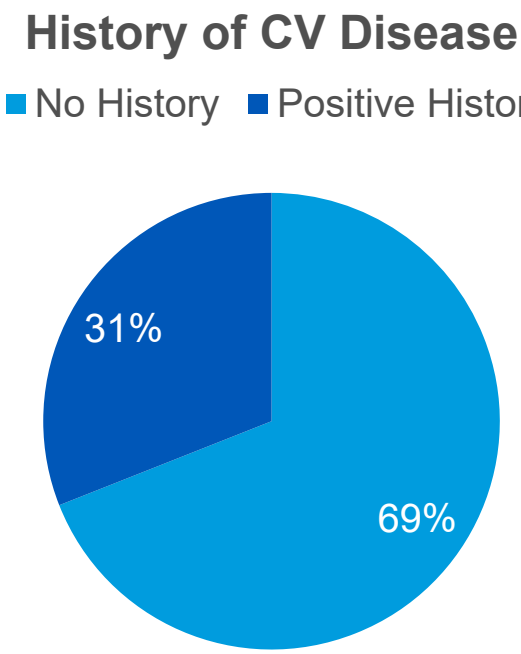
REWIND Results

	Dulaglutide 1.5 mg weekly	Placebo	Hazards Ratio	95% CI
Primary Outcome (Composite of non-fatal MI, non-fatal stroke, and death from CV causes or unknown causes)	594 patients (12.0%)	663 patients (13.4%)	**0.88**	**0.79-0.99**
Myocardial infarction	223 (4.5%)	231 (4.7%)	0.96	0.79-1.15
Stroke	158 (3.2%)	205 (4.1%)	**0.76**	**0.62-0.94**
Cardiovascular death	317 (6.4%)	346 (7.0%)	0.91	0.87-1.06
Non-Cardiovascular death	219 (4.4%)	246 (5.0%)	0.88	0.73-1.06
All-cause death	536 (10.8%)	592 (12.0%)	0.90	0.80-1.01
Hospital admission for HF	213 (4.3%)	226 (4.6%)	0.93	0.77-1.12

BOLD = confidence interval does not cross 1

Gerstein. *Lancet.* 2019:394(10193):121-130.

Subgroup Variations of Primary Outcomes



HR 0.87 (0.74-1.02)
HR 0.87 (0.74-1.02)

Gerstein. *Lancet.* 2019:394(10193):121-130.

REWIND Impact

Conclusion:

- Dulaglutide improved cardiovascular outcomes in participants both with or without previous cardiovascular disease

FDA Approvals:

- **Led to 2020 approval for CV disease reduction in patients with established ASCVD or at high risk for ASCVD**

Gerstein. *Lancet.* 2019:394(10193):121-130.

At a Glance: Empagliflozin

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

EMPEROR-Reduced

EMPEROR-Reduced Methods

- Enrolled 3,730 adults with heart failure (functional class II-IV) with LVEF ≤40%
- Primary outcome:
  - Composite of cardiovascular death or hospitalization for HF
- Secondary outcomes:
  - Hospitalizations for HF (first event and recurrent events)
  - Rate of decline in eGFR
- Intervention: randomized to empagliflozin 10 mg daily or placebo

Packer, *NEJM*. 2020.

EMPEROR-Reduced Results

	Empagliflozin 10 mg	Placebo	Hazards Ratio	95% CI
Primary Outcome (Composite of CV death or hospitalization for HF)	361 (19.4%)	462 (24.7%)	**0.75**	**0.65-0.86**
Hospitalization for HF	246 (13.2%)	342 (18.3%)	**0.69**	**0.59-0.81**
Cardiovascular death	187 (10.0%)	202 (10.8%)	0.92	0.75-1.12
Total number of hospitalizations for HF	388	553	**0.70**	**0.58-0.85**
Mean slope of change in eGFR	-0.55±0.23	-0.2.28±0.23	**1.73**	**1.10-2.37**
Composite renal outcome	30 (1.6%)	58 (3.1%)	**0.50**	**0.32-0.77**
Death from any cause	249 (13.4%)	266 (14.2%)	0.92	0.77-1.10

BOLD = confidence interval does not cross 1

Packer, *NEJM*. 2020.

Knowledge Check #1

GLP-1RA have been FDA approved for which of the following indications?

A. Risk reduction of cardiovascular death and hospitalization for HFrEF

B. Risk reduction of cardiovascular death and hospitalization for HFpEF

C. CV disease risk reduction in type 2 diabetics without established ASCVD

D. Improvement of glycemic control in adults with type 1 diabetes mellitus

Knowledge Check #1

GLP-1RA have been FDA approved for which of the following indications?

A. Risk reduction of cardiovascular death and hospitalization for HFrEF

B. Risk reduction of cardiovascular death and hospitalization for HFpEF

C. CV disease reduction in type 2 diabetics without established ASCVD

D. Improvement of glycemic control in adults with type 1 diabetes mellitus

Objective #2

Discuss the body of evidence for renal outcomes with GLP-1 receptor agonists and SGLT2 inhibitors

Agents with FDA approval for RENAL benefit

Medication	Indication	Date of FDA Approval
SGLT2 Inhibitor		
Canagliflozin	-Reduce the risk of ESKD, doubling of SCr, CV death, and hospitalization for HF in patients with T2DM and diabetic nephropathy	Sept. 2019

Das. *JACC*. 2020: 76(9):1117-1145.

Agents with evidence for renal benefit

SGLT2 Inhibitors	CANVAS-R	CREDENCE	DECLARE-TIMI 58	DAPA-HF	EMPA-REG	EMPEROR-Reduced
Medication	Canagliflozin	Canagliflozin	Dapagliflozin	Dapagliflozin	Empagliflozin	Empagliflozin
Renal Composite (HR)	**0.60**	**0.70**	**0.53**	0.71	**0.54**	**0.50**

GLP1 Receptor Agonists	LEADER	EXSCEL	REWIND	SUSTAIN-6	PIONEER-6
Medication	Liraglutide	Exenatide	Dulaglutide	Semaglutide SQ	Semaglutide PO
Renal Composite (HR)	**0.78**	0.88	**0.85**	**0.64**	**0.64**

HR = Hazard Ratio
BOLD = confidence interval does not cross 1

Das. *JACC*. 2020: 76(9):1117-1145.
Packer, *NEJM*. 2020.

A Closer Look: Canagliflozin

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

CREDENCE

CREDENCE Population

4,401 participants

Important inclusion criteria:

- T2DM and CKD
- ≥30 years old
- A1C 6.5-12.0%
- eGFR of 30-90 mL/min
- Macroalbuminuria
- Treatment with ACEI/ARB

Important exclusion criteria:

- Non-diabetic kidney disease
- Type 1 diabetes
- History of dialysis or kidney transplant

Percovik. *NEJM*. 2019; 380:2295-2306.

CREDENCE Methods

Intervention: Randomized to canagliflozin 100 mg by mouth daily or placebo

Percovik. *NEJM*. 2019; 380:2295-2306.

CREDENCE Methods

Primary Outcome

- Composite of ESRD, doubling of serum creatinine level, or death from renal of cardiovascular causes

Secondary Outcomes

- Composite of CV death or hospitalization for HF
- Composite of CV death, MI, or stroke
- Hospitalization for HF
- Composite of ESRD, doubling of serum creatinine level, or renal death

Percovik. *NEJM*. 2019; 380:2295-2306.

CREDENCE Methods

Primary Outcome

- **Composite of ESRD, doubling of serum creatinine level, or death from renal of cardiovascular causes**

Secondary Outcomes

- Composite of CV death or hospitalization for HF
- Composite of CV death, MI, or stroke
- Hospitalization for HF
- Composite of ESRD, doubling of serum creatinine level, or renal death

Percovik. *NEJM*. 2019; 380:2295-2306.

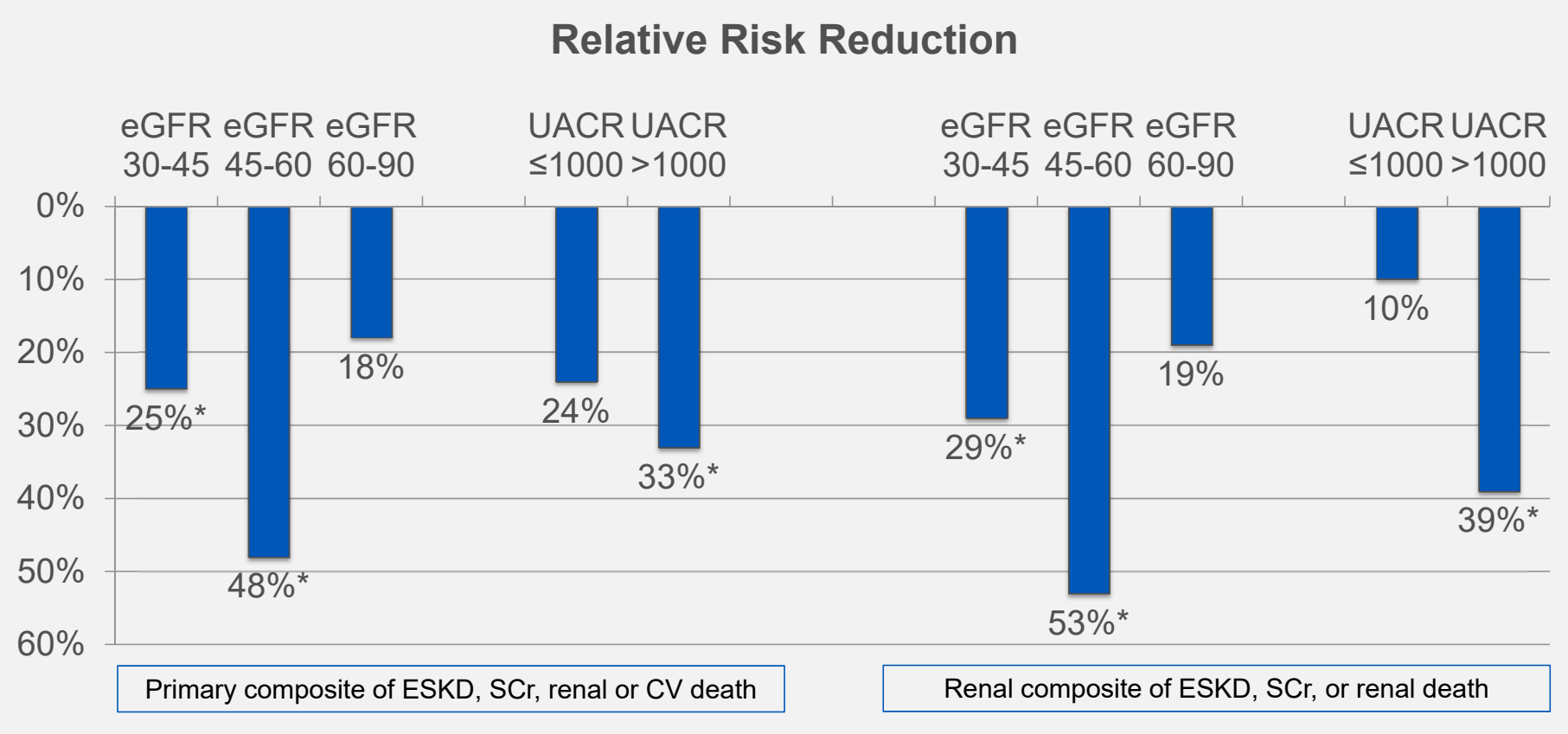
CREDENCE Results

	Canagliflozin 100 mg weekly	Placebo	Hazards Ratio	CI
Primary Outcome (Composite of ESRD, doubling of Scr, or renal or CV death)	245 patients (11.1%)	340 patients (15.5%)	**0.70**	**0.59-0.82**
Doubling of SCr	118 (5.4%)	188 (8.5%)	**0.60**	**0.48-0.76**
ESRD	116 (5.3%)	165 (7.5%)	**0.68**	**0.54-0.86**
CV death	110 (5.0%)	140 (6.4%)	0.78	0.61-1.00
Renal Death	2 (<0.1%)	5 (0.2%)	NA	NA
Hospitalization for HF	89 (4.0%)	141 (6.4%)	**0.61**	**0.47-0.80**

BOLD = confidence interval does not cross 1

Percovik. *NEJM*. 2019; 380:2295-2306.

Subgroup Variations



* 95% confidence interval does not cross 1

Percovik. *NEJM*. 2019; 380:2295-2306.

CREDENCE Impact

Conclusion:

- Among patients with T2DM and CKD, canagliflozin resulted a lower risk of end-stage kidney disease, doubling of the serum creatinine level, or death from renal or cardiovascular causes compared to placebo

FDA Approvals:

- Led to 2019 approval for risk reduction of ESKD, doubling of SCr, CV death, and hospitalization for HF in patients with T2DM and diabetic nephropathy

Percovik. *NEJM*. 2019; 380:2295-2306.

Knowledge Check #2

- The CREDENCE trial is the only trial showing favorable *evidence* for the use of an SGLT2 inhibitor in renal disease.
  - TRUE
  - FALSE

Knowledge Check #2

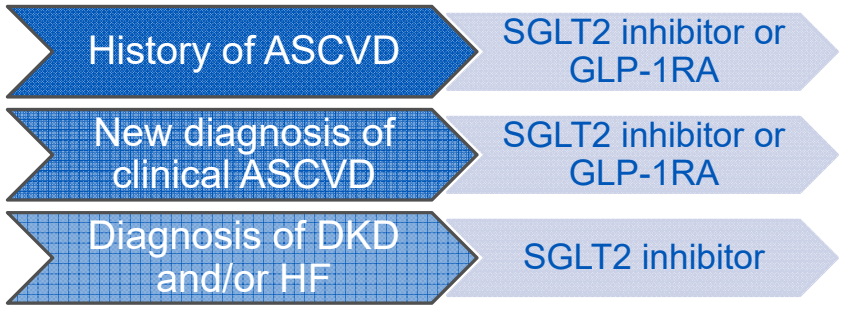
- The CREDENCE trial is the only trial showing favorable *evidence* for the use of an SGLT2 inhibitor in renal disease.
  - TRUE
  - **FALSE**

Objective #3

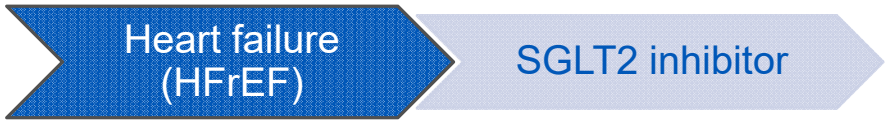
Recognize situations to implement and optimize these therapies in patient care plans

Starting an agent?

- **Patients with T2D and:**



- **Patients without T2D but with:**



Das. *JACC*. 2020: 76(9):1117-1145.

Additional Factors to Consider

- Many patient-specific factors weigh into decision to select an SGLT2 inhibitor or GLP-1RA
- Reasons to ***select*** a class:

	SGLT2 Inhibitor	GLP-1RA
MACE prevention	+++	+++
HF treatment	+++	
Weight loss	+	+++
Renal disease prevention	+++	+
Administration	Oral	Subcutaneous

Das. *JACC*. 2020: 76(9):1117-1145.

Additional Factors to Consider

- Many patient-specific factors weigh into decision to select an SGLT2 inhibitor or GLP-1RA
- Reasons to ***avoid*** a class:

SGLT2 Inhibitor	GLP-1RA
Significantly decreased renal function	Intolerable nausea
Recurrent genital candidiasis/UTI	History of gastroparesis
History of DKA	Active gallbladder disease
If canagliflozin, consider fracture history	History of MEN2 or medullary thyroid cancer
Pregnant or breast feeding	

Das. *JACC*. 2020: 76(9):1117-1145.

Knowledge Check #3

- A 63 year old male presents with a new diagnosis of T2DM and an A1C of 8.9%
- He is currently on no medications to treat his diabetes
- PMH significant for:
  - Obesity (BMI of 34 kg/m^2)
  - HF with an ejection fraction of 38%
  - CrCl is 52 mL/min

Knowledge Check #3

Which agent(s) would be the MOST appropriate to initiate?

A. Metformin 1000 mg BID monotherapy

B. Metformin 1000 mg BID plus dapagliflozin 10 mg daily

C. Metformin 1000 mg BID plus dulaglutide 1.5 mg SubQ weekly

D. Metformin 1000 mg BID plus basal insulin regimen

Knowledge Check #3

Which agent(s) would be the MOST appropriate to initiate?

A. Metformin 1000 mg BID monotherapy

B. Metformin 1000 mg BID plus dapagliflozin 10 mg daily

C. Metformin 1000 mg BID plus dulaglutide 1.5 mg SubQ weekly

D. Metformin 1000 mg BID plus basal insulin regimen

To A1C… And Beyond

- Ongoing studies:
  - EMPEROR-Preserved trial ongoing
    - Empagliflozin and CV death or hospitalization in **HFpEF**
    - Anticipated results 2021
  - Dapagliflozin in PRESERVED Ejection Fraction Heart Failure (PRESERVED-HF)
    - Anticipated completion 2021
  - DAPA-CKD
    - Resulted presented August 2020; publication expected next month
    - 39% decline in the risk of declining kidney function, the onset of end-stage kidney disease, or kidney failure death
    - Distinguish factor: ~1/3 of patients did NOT have diabetes
  - EMPA-KIDNEY is ongoing and data expected in 2022

Conclusions

There is robust data supporting the use of SGLT2 inhibitors and GLP-1RA for cardiovascular risk reduction.

Canagliflozin has shown benefit in diabetic kidney disease. Stayed tuned for additional data with other agents.

In addition to metformin, an SGLT2 inhibitor or GLP-1RA may be considered “first line” in patients with CVD or CVD risk factors.

Please direct further questions or comments to Lake.Laurel@mayo.edu

