Newer therapies for Type 2 Diabetes: brief review for PCPs

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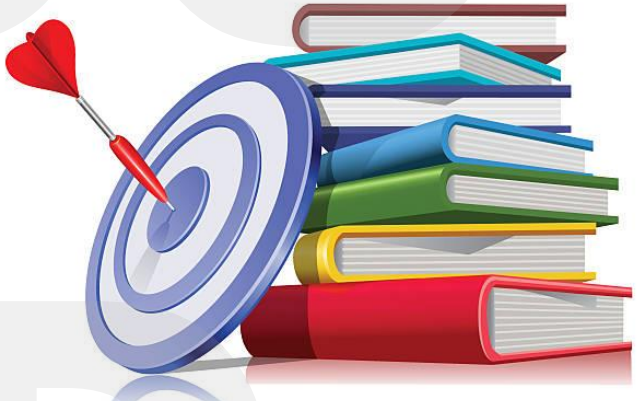
Learning Objectives

- Understand the goals for pharmacotherapy for DM2
- Recognize indications for “newer” therapies for DM2
- Review briefly the evidence behind these therapies



Pharmacotherapy for DM2

Glucose centric targets

Complications based model

Lifestyle modification underlies all therapy

Person centric management of DM2

Goal

* Prevent complications
* Optimize QoL

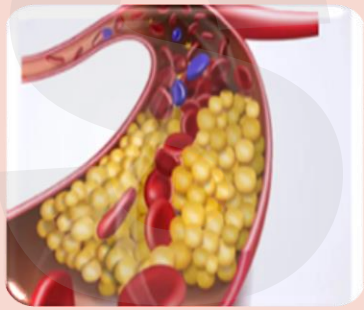
Assess

* Comorbidities
* Access
* Cost/Financial barriers
* Preferences
* Tolerability/Side effects

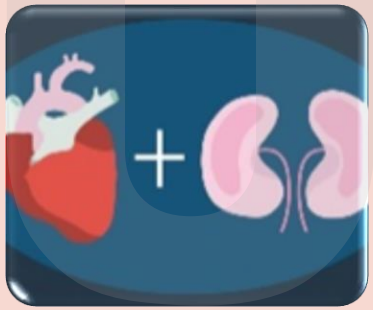
Reduction in DM Complications

Glycemic Management

BP Management



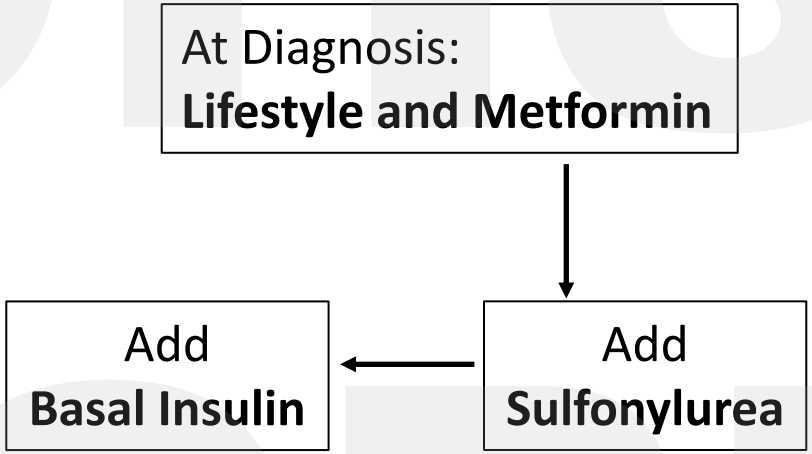
Lipid Management



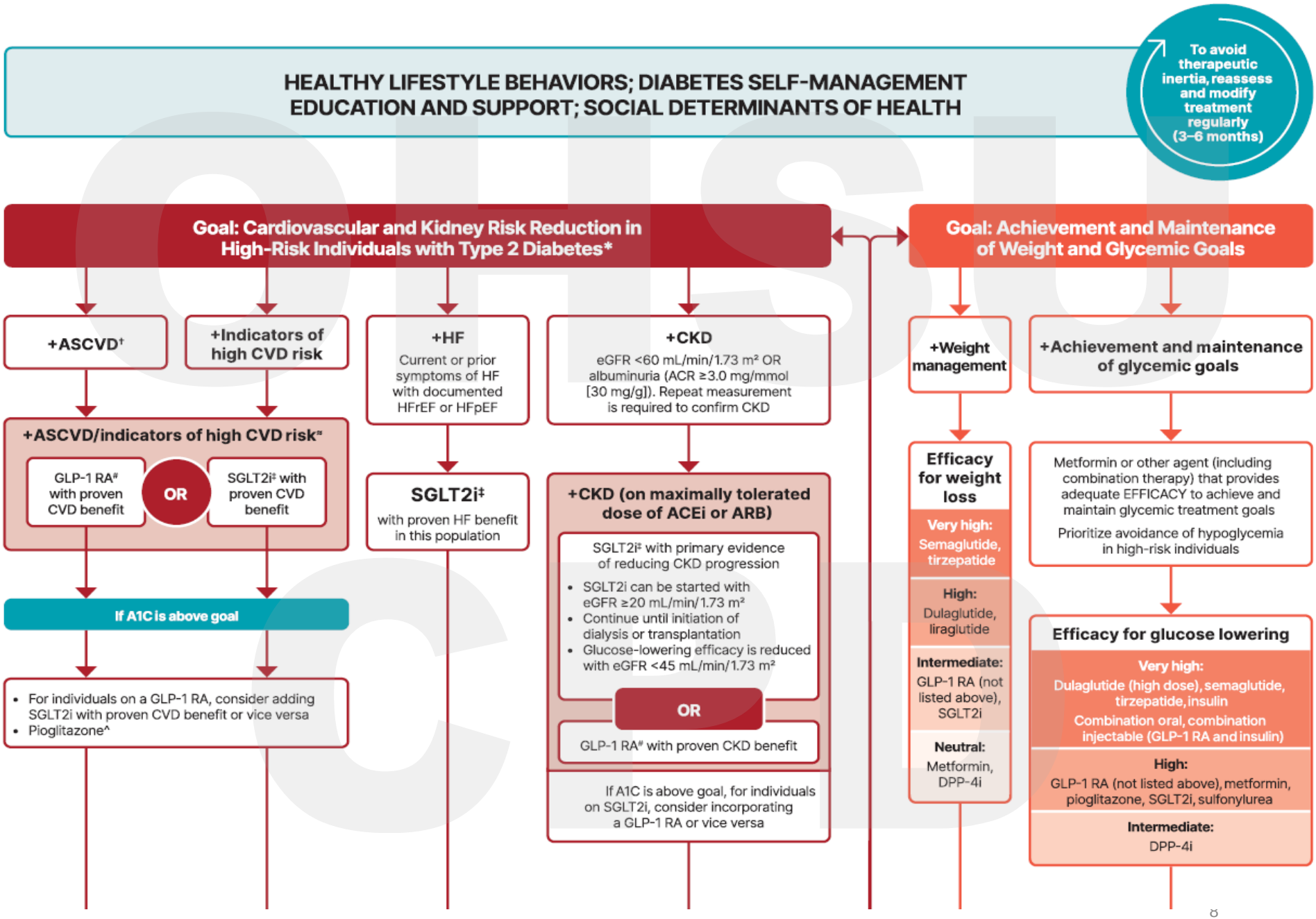
Agents with CV and Renal benefit

Lifestyle modification underlies all therapy

Pharmacotherapy for DM2 (2009)

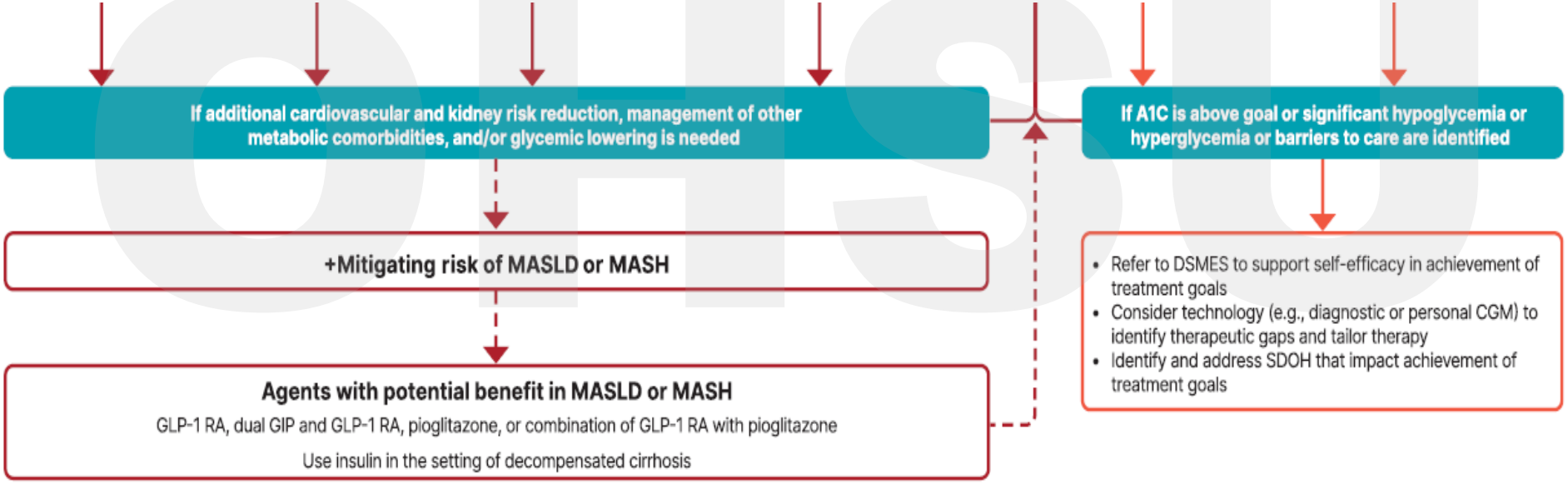


Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



Pharmacologic Approaches to Glycemic Treatment:
Standards of Care in Diabetes - 2025 Diabetes Care 2025;48(Suppl. 1):S181-S206

Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



* 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 made irrespective of background use of metformin or A1C.

† ASCVD: Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, and arterial revascularization procedure) and variably included conditions such as transient ischemic attack, unstable angina, amputation, and symptomatic or asymptomatic coronary artery disease. Indicators of high risk: While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

≈ A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high-risk CVD. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.

For GLP-1 RAs, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and kidney end points in individuals with T2D with established or high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1 RA in individuals with CKD and T2D.

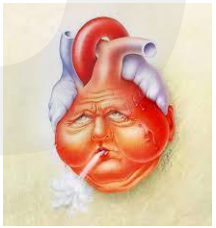
‡ For SGLT2is, CV and kidney outcomes trials demonstrate their efficacy in reducing the risks of composite MACE, CV death, all-cause mortality, MI, HHF, and kidney outcomes in individuals with T2D and established or high risk of CVD.

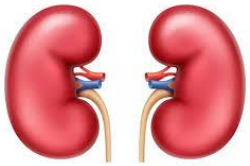
^ Low-dose pioglitazone may be better tolerated and similarly effective as higher doses.

Pharmacologic Approaches to Glycemic Treatment:
Standards of Care in Diabetes - 2025 Diabetes Care 2025;48(Suppl. 1):S181-S206

Pharmacotherapy for DM2

- Risk factors to consider treatment selection:





Goal:

- ✓ CardioRenal risk reduction
- ✓ Weight management
- ✓ Achievement and maintenance of glycemic goals
- ✓ Mitigation of MASLD (metabolic dysfunction associated liver disease) or MASH (metabolic dysfunction associated steatohepatitis)

Person centric management of DM2

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* Access
* Cost/Financial barriers
* Preferences
* Tolerability/Side effects

Pharmacotherapy for DM2

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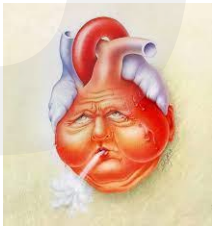

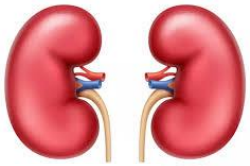

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Goal: CardioRenal Risk Reduction

ASCVD *or* Indicators of high risk

GLP1RA with proven CV benefit

or

SGLT2i with proven CV benefit

Liraglutide
(LEADER Trial)

Semaglutide
(SUSTAIN-6 Trial)

Dulaglutide
(REWIND Trial)

Empagliflozin
(EMPA-REG OUTCOME Trial)

Canagliflozin
(CANVAS Trial)

A1C above goal

- Add GLP1RA or SGLT2i depending on initial choice
- Low dose Pioglitazone

SGLT2i and CVOTs
ASCVD

EMPA-REG OUTCOME Trial

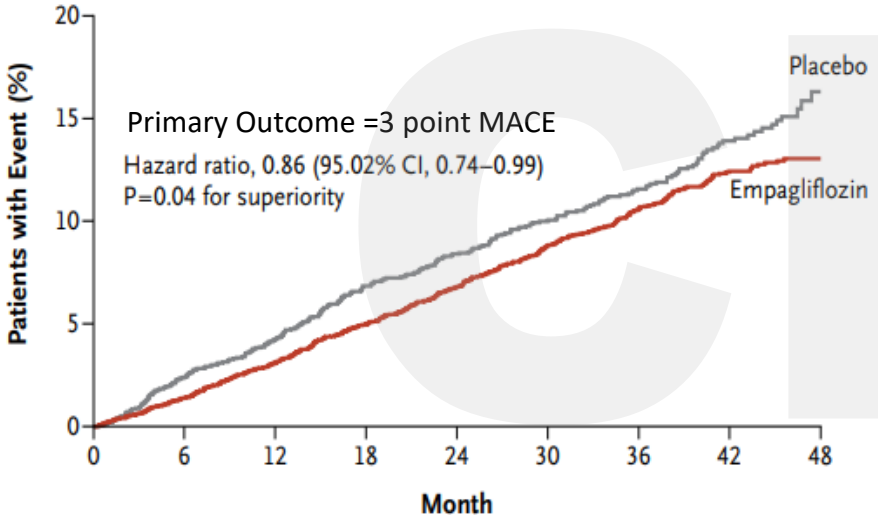
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Inclusion Criteria
- Established ASCVD
- DM2
- GFR ≥50

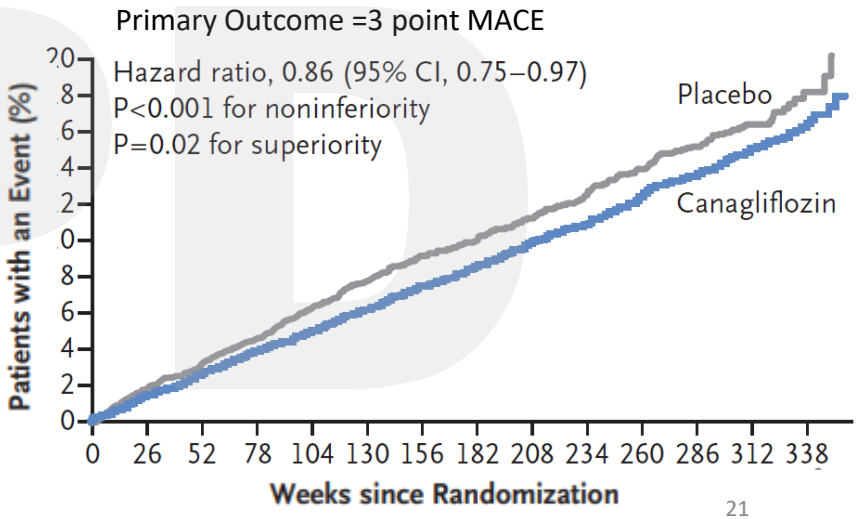
CANVAS Trial

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Inclusion Criteria
- ≥30y/o with established ASCVD or ≥50y/o with ≥2 risk factors for CV disease
- DM2
- GFR ≥ 30



N Engl J Med 2015;373:2117-28.



N Engl J Med 2017;377:644–657

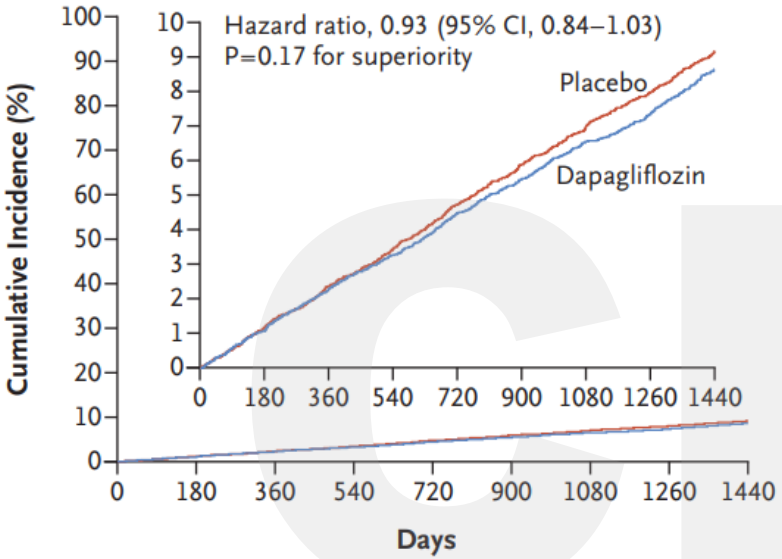
Dapagliflozin (Farxiga)

DECLARE-TIMI 58 Trial

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

N Engl J Med 2019;380:347-57

MACE



DM2 + ASCVD or increased risk → did not lower rate of MACE but resulted in a lower rate of HF hospitalization (HR, 0.73; 95% CI, 0.61 to 0.88)

GLP1 and CVOTs ASCVD

LEADER Trial

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Inclusion Criteria
- DM2
- Age ≥50 yrs with at least 1 ASCVD or Age ≥60yrs with at least 1 risk factor.

SUSTAIN-6 Trial

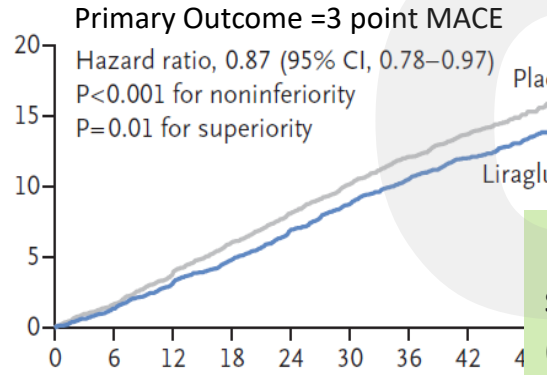
Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

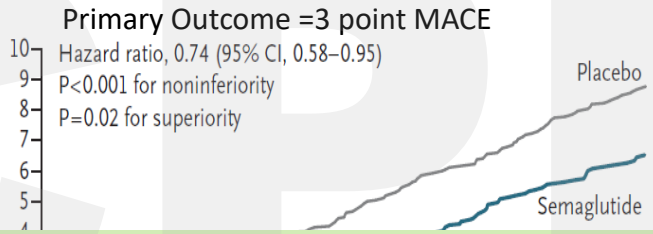
Inclusion Criteria
- DM2
- Age ≥50 yrs with at least 1 ASCVD or Age ≥60yrs with at least 1 risk factor.

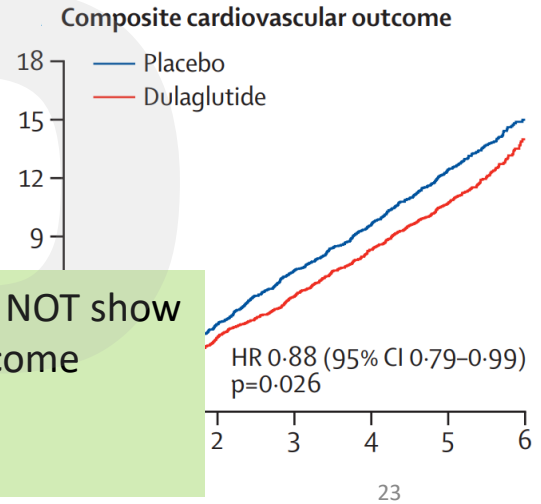
REWIND Trial

Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes

Inclusion Criteria
- Age ≥50 y/o
- DM2
- ASCVD or risk factor of ASCVD







PIONEER -6 Trial (in 2019): oral semaglutide did NOT show statistically significant reduction in primary outcome (3-point MACE)
(HR, 0.79; 95% CI, 0.57 to 1.11)

N Engl J Med 2016;375:311-22.

N Engl J Med 2016;375:1834–1844

Lancet 2019; 394: 121–30

Circulation
Volume 139, Issue 17, 23 April 2019; Pages 2022-2031
https://doi.org/10.1161/CIRCULATIONAHA.118.038868

ORIGINAL RESEARCH ARTICLE

Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus

Systematic Review and Meta-Analysis of Cardiovascular Outcomes Trials

GLP1RA and SGLT2i reduce atherosclerotic MACE to a similar degree in patients with established ASCVD, whereas SGLT2i have more marked effect on preventing hospitalization for heart failure and progression of kidney disease.

Goal: CardioRenal Risk Reduction

ASCVD *or* Indicators of high risk

GLP1RA *or* **SGLT2i**

- **Liraglutide**
- **Semaglutide**
- **Dulaglutide**

- **Empagliflozin**
- **Canagliflozin**

A1C above goal

- Add GLP1RA or SGLT2i depending on initial choice
- Low dose Pioglitazone

Goal: CardioRenal Risk Reduction

HF

SGLT2i with proven HF benefit

Empagliflozin
(EMPEROR-REDUCED Trial)
(EMPEROR-PRESERVED Trial)

Dapagliflozin
(DAPA-HF Trial)
(DELIVER Trial)

A1C above goal

Add GLP1RA

SGLT2i and CVOTs
HFrEF

DAPA-HF Trial

Dapagliflozin in patients with Heart Failure and Reduced Ejection Fraction

Inclusion Criteria
- HFrEF NYHA II-IV

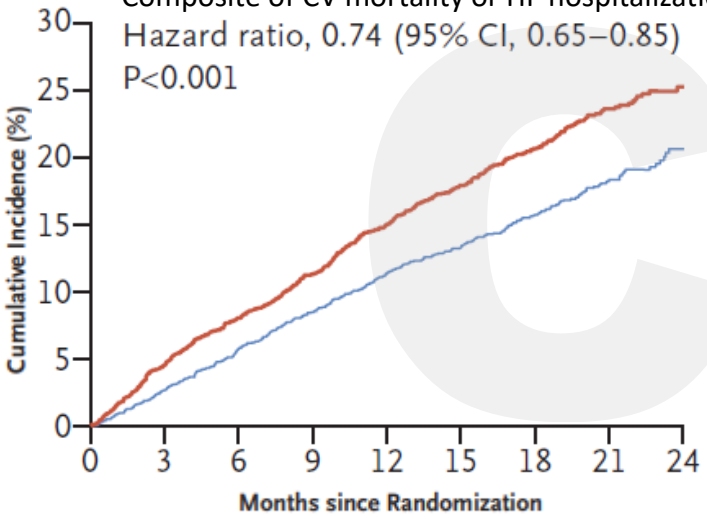
GDMT+ **Dapagliflozin or Empagliflozin** → benefit regardless of presence or absence of DM

EMPEROR-REDUCED Trial

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

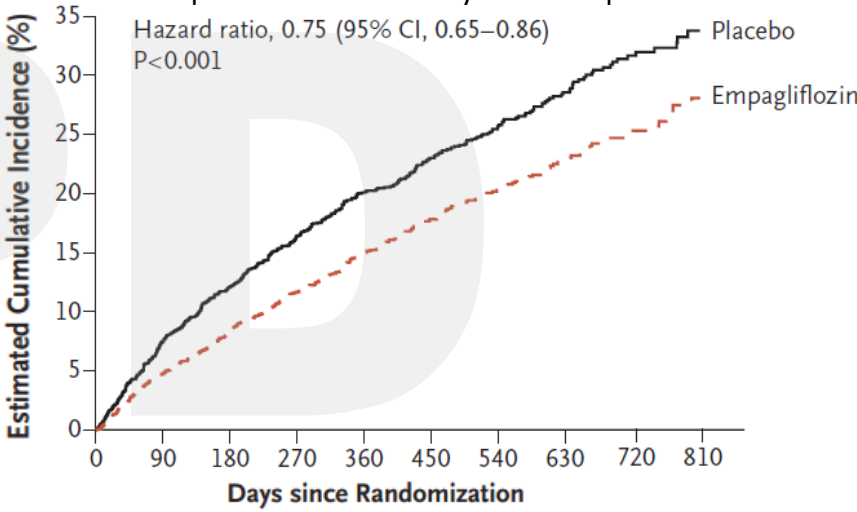
Inclusion Criteria
- HFrEF NYHA II-IV

Primary Outcome=
Composite of CV mortality or HF hospitalization



N Engl J Med. 2019;381(21):1995–2008

Primary Outcome =
Composite of CV mortality or HF hospitalization



N Engl J Med 2020;383:1413-24

SGLT2i and CVOTs
HFpEF

EMPEROR-PRESERVED Trial

Empagliflozin in Heart Failure with Preserved Ejection Fraction

Inclusion Criteria
- HF, EF> 40% NYHA II-IV

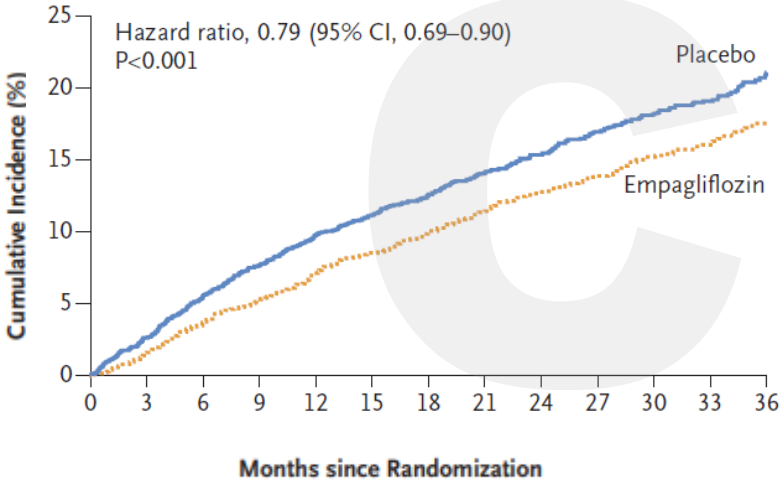
Dapagliflozin or Empagliflozin → benefit regardless of presence or absence of DM

DELIVER Trial

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

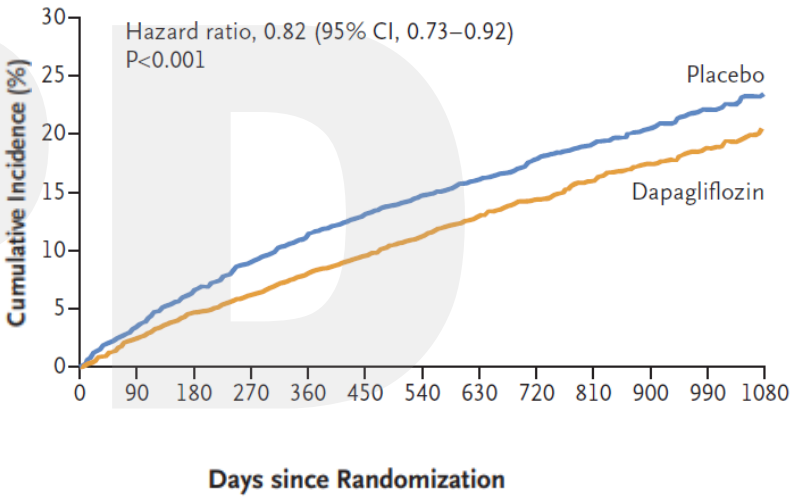
Inclusion Criteria
- HF, EF> 40%

Primary Outcome=
Composite of CV mortality or HF hospitalization



N Engl J Med 2021;385:1451-61

Primary Outcome =
Composite of CV mortality or HF hospitalization



N Engl J Med 2022;387:1089-98.

SGLT2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials

Muthiah Vaduganathan, Kieran F Docherty*, Brian L Claggett, Pardeep S Jhund, Rudolf A de Boer, Adrian F Hernandez, Silvio E Inzucchi, Mikhail N Kosiborod, Carolyn S P Lam, Felipe Martinez, Sanjiv J Shah, Akshay S Desai, John J V McMurray†, Scott D Solomon†*

Lancet 2022; 400: 757–67

SGLT2i reduced the risk of CV death and hospitalizations for HF in a broad range of patients with HF, supporting their role as foundational therapy for HF**, irrespective of ejection fraction or presence of absence of DM**

Goal: CardioRenal Risk Reduction

ASCVD *or* Indicators of high risk

GLP1RA *or* **SGLT2i**

- **Liraglutide**
- **Semaglutide**
- **Dulaglutide**

- **Empagliflozin**
- **Canagliflozin**

A1C above goal

- Add GLP1RA or SGLT2i depending on initial choice
- Low dose Pioglitazone

HF

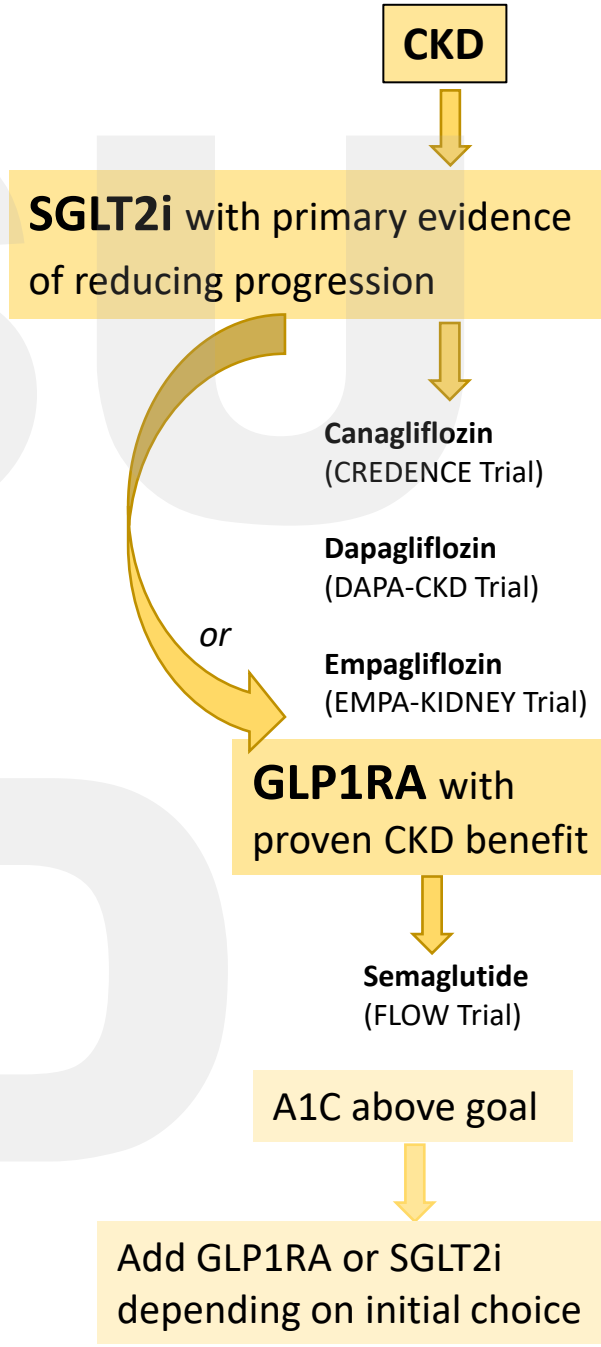
SGLT2i

- **Empagliflozin**
- **Dapagliflozin**

A1C above goal

Add GLP1RA

Goal: CardioRenal Risk Reduction



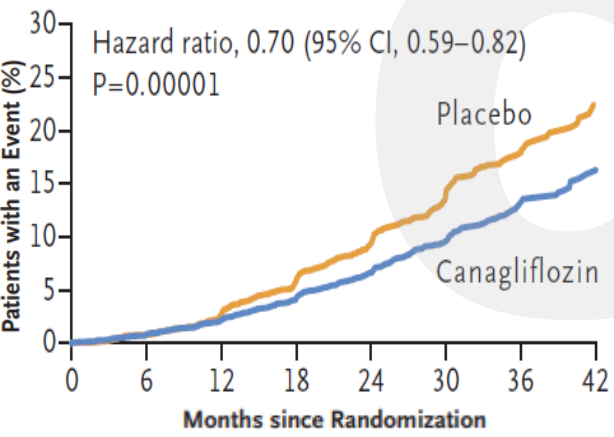
SGLT2i and Renal Outcomes

CREDENCE Trial

Canagliflozin and Renal Events Diabetes and Established Nephropathy Clinical Evaluation

Inclusion Criteria
- DM2
- CKD and UACR> 300
- On ACE

Primary Outcome= ESRD+ doubling of serum Cr+ renal or CV mortality



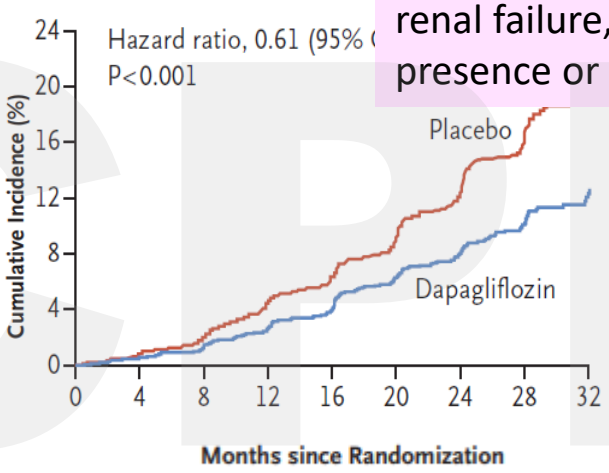
N Engl J Med 2019;380:2295– 2306

DAPA-CKD Trial

Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease

Inclusion Criteria
- CKD with albuminuria

Primary Outcome= composi
of at least 50%, ESKD, or ren



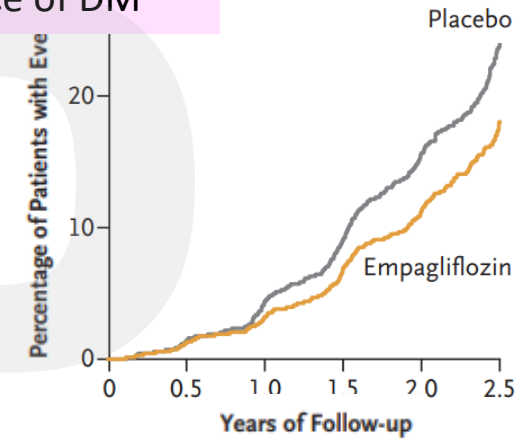
N Engl J Med 2020;383:1436-46

EMPA-KIDNEY Trial

Empagliflozin in patients with Chronic Kidney Disease

Inclusion Criteria
- CKD with
  - GFR 20-35
  - GFR 40-90 with UACR >200

: composite of progression
or CV mortality



N Engl J Med 2023;388:117-27.

Dapagliflozin and Empagliflozin → lower risk of renal failure, regardless of presence or absence of DM

GLP1-RA and Renal Outcomes

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 11, 2024 VOL. 391 NO. 2

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators*

Semaglutide reduced the risk of clinically important kidney outcomes and death from CV causes in patients with DM2 and CKD

Goal: CardioRenal Risk Reduction

ASCVD *or* Indicators of high risk

GLP1RA *or* **SGLT2i**

Liraglutide
Semaglutide
Dulaglutide

Empagliflozin
Canagliflozin

A1C above goal

- Add GLP1RA or SGLT2i depending on initial choice
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HF

SGLT2i

Empagliflozin
Dapagliflozin

A1C above goal

Add GLP1RA

CKD

GLP1RA *or* **SGLT2i**

Semaglutide

Canagliflozin
Dapagliflozin
Empagliflozin

A1C above goal

Add GLP1RA or SGLT2i depending on initial choice

SGLT2i

- Glycemic efficacy: Intermediate to High
- Weight reduction: Intermediate

- GFR< 45 --> glucose lowering effect blunted but renal and CV benefits continue at GFR of 20
  - Can initiate with GFR ≥ 20; continue until dialysis or transplant
  - Do not initiate when GFR < 20
- DKA risk (rare in DM2): should be d/ced before surgery (3-4 days), prolonged fasting or critical illness to avoid potential risk
- GU infections
- Dehydration, Hypotension
- Fournier's gangrene (rare)

GLP1RA

- Glycemic efficacy: High to very high
- Weight reduction: Intermediate to very high

Semaglutide (Ozempic) 0.25-2 mg weekly

Dulaglutide (Trulicity) 0.75-4.5 mg weekly

Liraglutide (Victoza) 0.6-1.8 mg daily

- GI s/e (N/V/D): Careful with initiating and increasing dose due to risk of AKI with vomiting/diarrhea
- Acute pancreatitis risk
- Ileus: risk is not well established, should be d/ced prior to planned surgery
- Biliary disease
- Diabetic retinopathy (close monitoring of high risk patients needed)
- Risk of thyroid C cell tumors (human relevance unknown)

CVOTs: DPP4i and other SGLT2i, GLP1RA

DPP4i	Trial
Saxagliptin (Onglyza)	SAVOR-TIMI 53
Alogliptin (Nesina)	EXAMINE
Sitagliptin (Januvia)	TECOS
Linagliptin (Tradjenta)	CARMELINA

No significant difference in rates of MACE or renal outcomes as compared to placebo

SGLT2i	Trial
Ertugliflozin (Steglatro)	VERTIS CV

Showed no significant difference in rates of MACE as compared to placebo

GLP1RA	Trial
Semaglutide, oral (Rybelsus)	PIONEER-6
Exenatide, q weekly (Bydureon)	EXSCEL

Showed no significant difference in rates of MACE or renal outcomes as compared to placebo

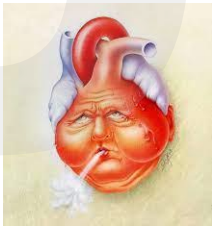
Saxagliptin: patients were more likely to be hospitalized for HF vs placebo

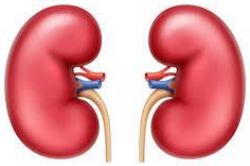
Question #4

38 y/o F presents for ongoing management of DM2 (A1C=9), obesity, and chronic abdominal pain related to her h/o recurrent pancreatitis. SMBG range: 200–300. Not on any meds, has tried metformin including XR unsuccessfully (due to severe GI s/e). Does not want insulin.

Pharmacotherapy for DM2

- Risk factors to consider treatment selection:





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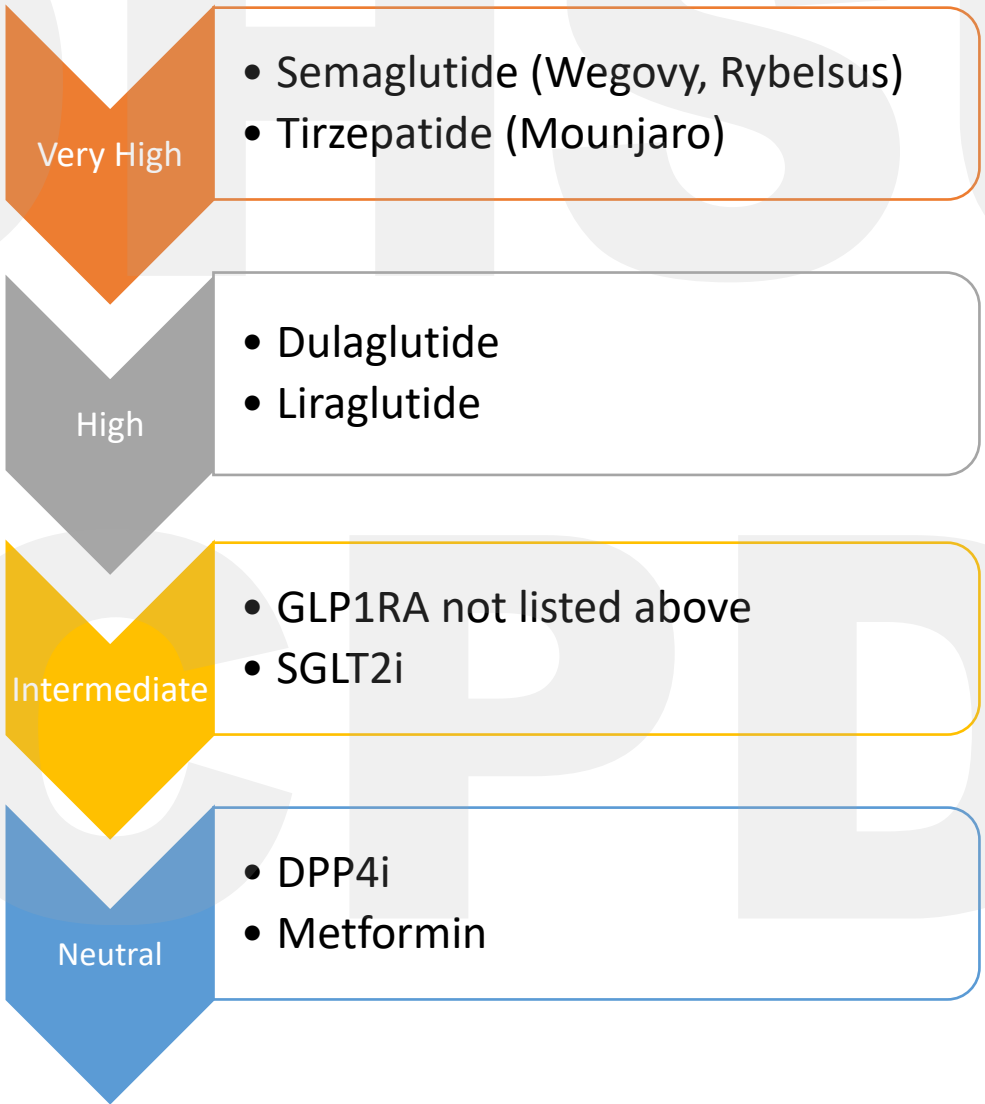
Weight management

Pharmacotherapy for DM2: Efficacy for weight loss



Dual GLP1RA+ GIP: Tirzepatide (Mounjaro)

- Dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist
- Very high efficacy in glucose lowering and weight loss with no hypoglycemia risk
- CV effects, benefits in HF and renal effects – under investigation***
- FDA approved for weight management as of Nov 2023 (Zepbound)

Weight management

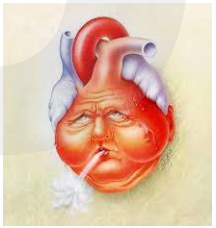
- Meds to avoid if possible: associated with weight gain
  - Insulin
  - Sulfonylureas
  - Thiazolidinediones

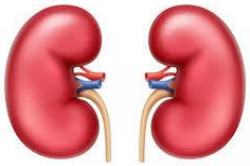
- FDA approved pharmacotherapy for weight loss
  - Glucose lowering meds: Semaglutide, Tirzepatide, Liraglutide
  - Phentermine and Topiramate
  - Naltrexone and Bupropion

- Bariatric surgery for weight loss (when indicated)

Pharmacotherapy for DM2

- Risk factors to consider treatment selection:





Goal:

- ✓ CardioRenal risk reduction
- ✓ Weight management
- ✓ Achievement and maintenance of glycemic goals
- ✓ Mitigation of MASLD (metabolic dysfunction associated liver disease) or MASH (metabolic dysfunction associated steatohepatitis)

Person centric management of DM2

Goal

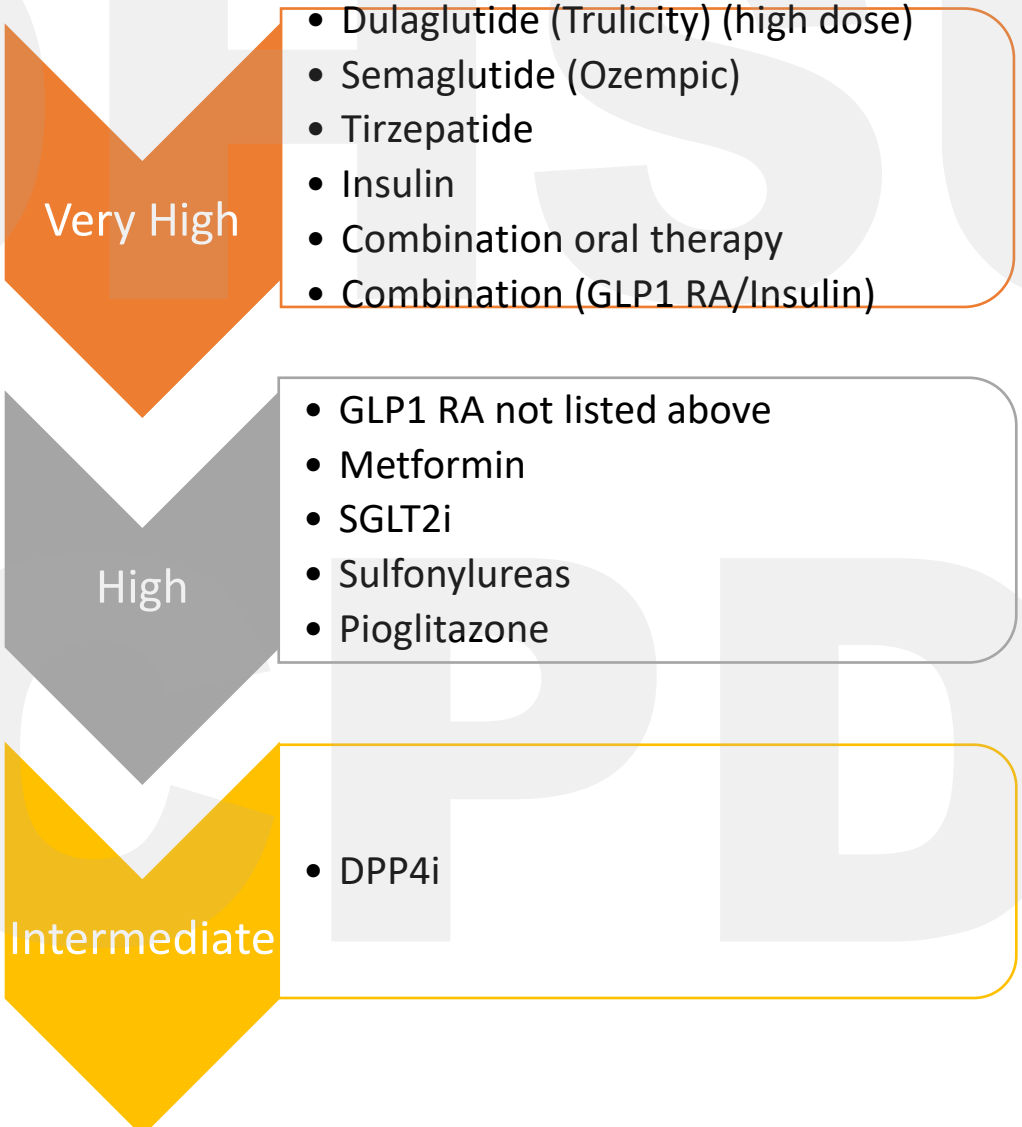
* Prevent complications
* Optimize QoL

Assess

* Comorbidities
* Access
* Cost/Financial barriers
* Preferences
* Tolerability/Side effects

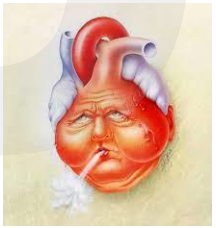
Glycemic goals

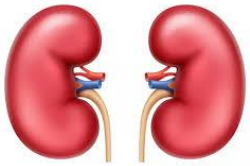
Pharmacotherapy for DM2: Efficacy for glucose lowering



Pharmacotherapy for DM2

- Risk factors to consider treatment selection:





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Person centric management of DM2

Goal

* Prevent complications
* Optimize QoL

Assess

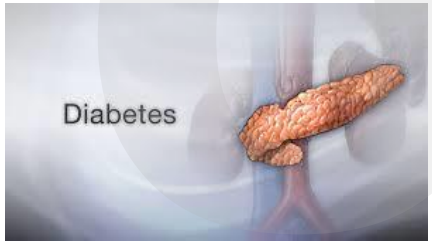
* Comorbidities
* Access
* Cost/Financial barriers
* Preferences
* Tolerability/Side effects

DM2 and MASLD

- Major risk factor for developing MASLD
- Progression of fibrosis is more in MASLD + DM2 as compared to MASLD without DM2

- Bidirectional relationship between MASLD and DM2 → presence of one increases the risk and severity of the other.

Pharmacotherapy in DM2 and MASLD



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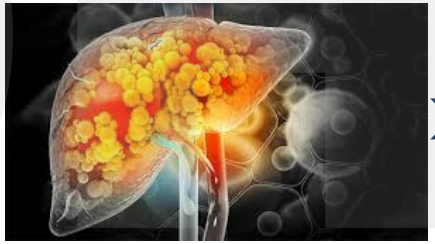
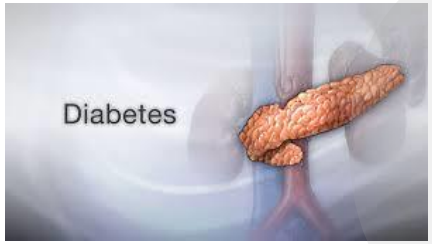


- Pioglitazone
- GLP1RA ± Pioglitazone
- Dual GLP1RA+ GIP



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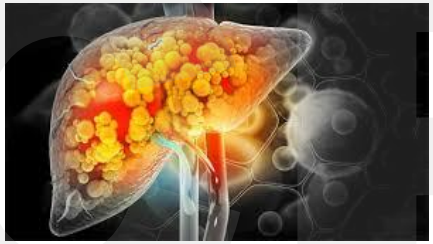

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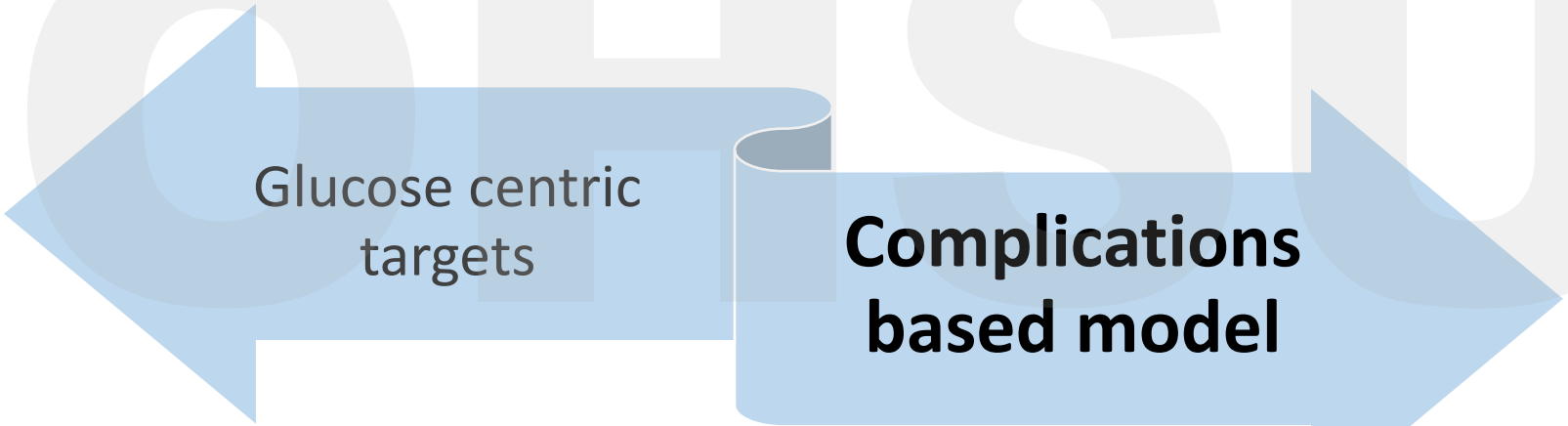
- GLP1RA
- Dual GLP1RA+ GIP

Pharmacotherapy for DM2



Lifestyle modification underlies all therapy

Glucose centric management

No complication to target

A1C >7.5%

- Start 2 agents

A1C> 9.0% *or*
>1.5% above goal

- Start 2-3 agents

A1C> 10% *and/or*
Glu> 300 with sx

- Basal insulin +/- GLP1RA

Metformin

Used to be first line treatment

DM2 with no additional considerations

- Effective and safe
- Inexpensive and widely available
- Reduces risk of microvascular complications, CV events
- Weight neutral
- No hypoglycemia risk
- GI s/e can be mitigated with slow dose titration, using XL and administration with food
- Check Vitamin B12 with long term use or symptoms of neuropathy

Metformin dosing in CKD

≥ 60	• No contraindications; monitor renal function annually
≥45-60	• Continue use; monitor renal function every 3-6 months
≥30-45	• Use with caution, consider dosage reducton (eg 50% reduction or 50% of maximal dose, monitor renal function every 3 months • Do not initiate metformin when <45
<30	• Discontinue

- Long term use: associated with Vit B12 deficiency and worsening symptoms of neuropathy → suggest periodic testing of

Insulin

Need Injectable therapy to reduce A1C

GLP1RA or dual GIP+GLP1RA prior to insulin

- *Already on GLP1RA or dual GLP1RA+ GIP or*
- *Unable to take either or*
- *A1C still above target*

Basal insulin

Starting dose: 10 units *or* 0.1- 0.2U/kg/day followed by titration based on BS numbers
(2 units every 3 days to reach FPG target)

Except

Insulin: first line if evidence of:

- Catabolism (weight loss)
- Symptoms of hyperglycemia (polyuria, polydipsia)
- HbA1C >10 or BG≥ 300
- Possibility of diagnosis of DM1

Practical tips on basal insulin

- Hypoglycemia Risk

- When converting one basal insulin to another: generally unit for unit but can consider reduction of 10-20% and close monitoring and titration

- Avoid **overbasalization:**
  - High bedtime-to-morning glucose differential
  - High preprandial-to-postprandial glucose differential
  - Hypoglycemia

Insulin

Basal insulin

- *A1C still above target*
- *Post prandial hyperglycemia*
- *Overbasalization*

Already on or considered GLP1RA or dual GLP1RA+ GIP

Prandial insulin

1 dose to the largest meal or meal with greatest BS level

Starting dose: 4 units or 10% of basal insulin

Additional prandial and finally full basal-bolus regimen

Goal: CardioRenal Risk Reduction

ASCVD *or* Indicators of high risk

GLP1RA *or* **SGLT2i**

Liraglutide
Semaglutide
Dulaglutide

Empagliflozin
Canagliflozin

A1C above goal

- Add GLP1RA or SGLT2i depending on initial choice
- Low dose Pioglitazone

HF

SGLT2i

Empagliflozin
Dapagliflozin

A1C above goal

Add GLP1RA

CKD

GLP1RA *or* **SGLT2i**

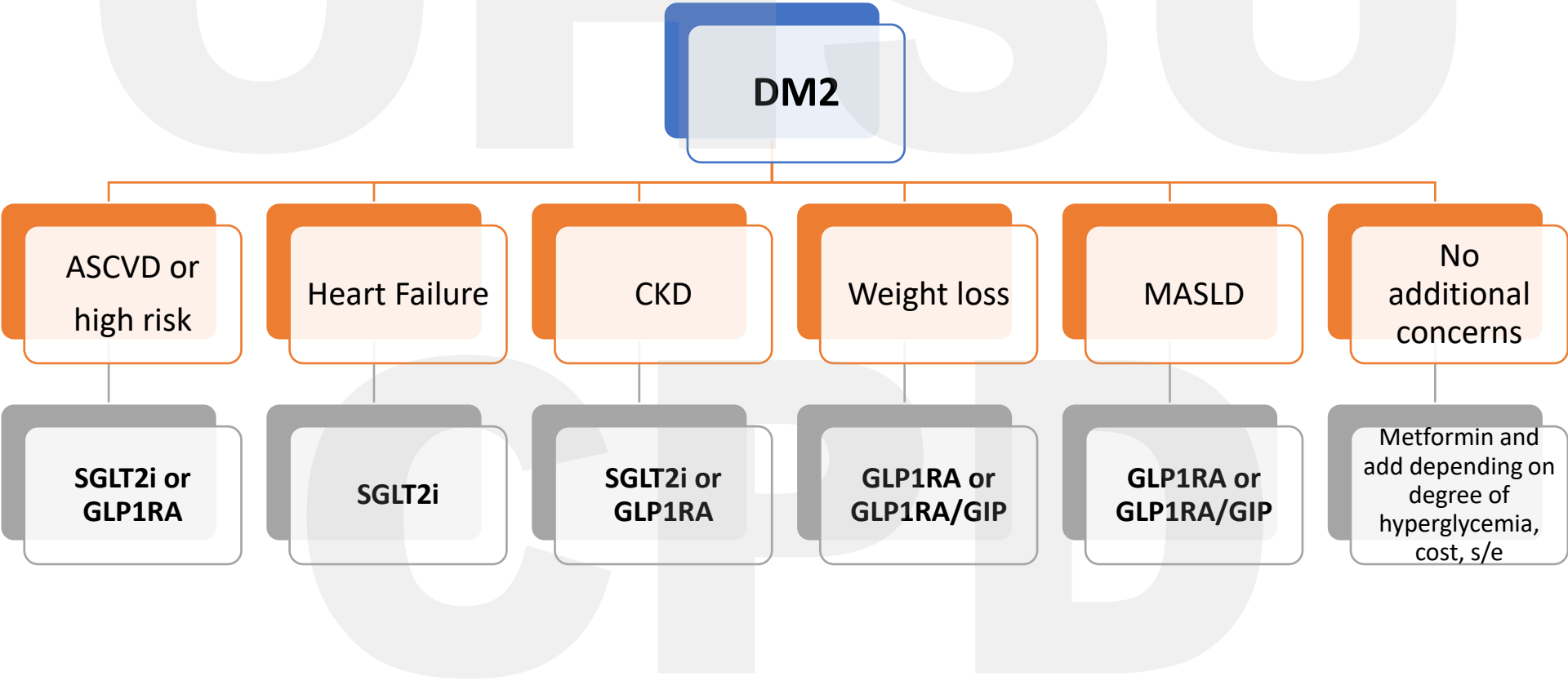
Semaglutide

Canagliflozin
Dapagliflozin
Empagliflozin

A1C above goal

Add GLP1RA or SGLT2i depending on initial choice

Pharmacotherapy for DM2 (2025)



Adapted from UCSF Grandrounds: Management of Diabetes: Updates and Future Directions

References

- American Diabetes Association: Standards of Medical Care in Diabetes, 2025

- In The Clinic: Type 2 Diabetes

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- 2023 AACE Consensus Statement: Comprehensive Type 2 Diabetes Management