Matters of the Heart: Updates in Heart Failure, Co-management of Cardiac and Metabolic Disorders, and Lipid Management

GMCCP Spring Meeting

April 25, 2023

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Greater Milwaukee College of Clinical Pharmacy

Disclosures

- None of the planners for this activity have relevant financial relationships with ineligible companies to disclose

Cardiology Update: Heart Failure

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Jake Dyer, PharmD – Assistant Professor, MCW School of Pharmacy

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Objectives

1. Review pathways to optimizing guideline-directed medical therapy (GDMT) in various clinical settings.
2. Summarize relevant literature supporting the use of SGLT2 inhibitors in the management of heart failure.

Introducing!

HFpEF
EF > 40%

HFrEF
EF≤40%

COPERNICUS

COMET

CIBIS

MERIT HF

PARADIGM

Val-HEFT

SOLVD

CHARM

PARAGON

EPHESUS

RALES

TOPCAT

EMPEROR

DAPA HF

SOLOIST WHF

EMPEROR PRESERVED

DELIVER

Introducing!

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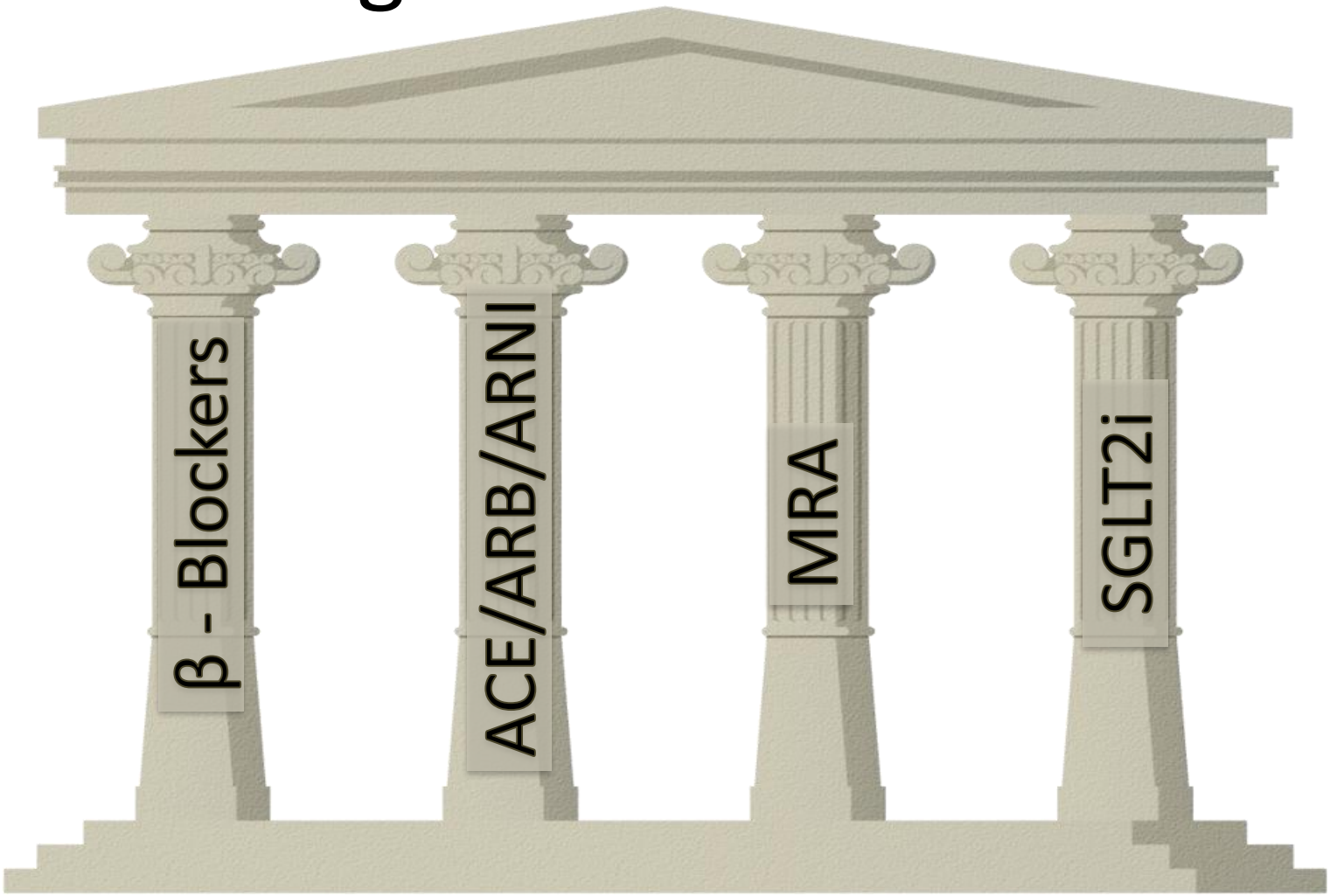
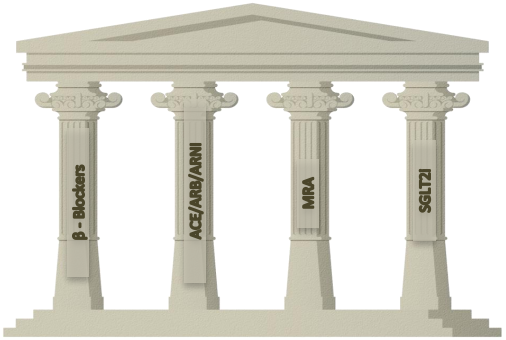
Introducing!



While Rome wasn't built in a day…

- Evidence-based therapies
- Expert opinion-based approach



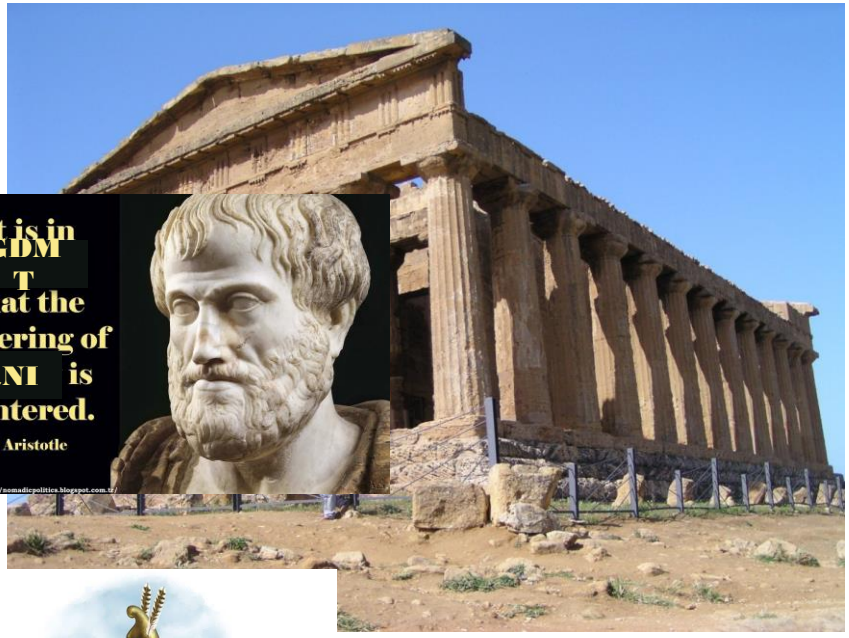
COR	LOE	Recommendations
1	A	1. In patients with HFrEF, titration of guideline-directed medication dosing to achieve target doses showed to be efficacious in RCTs is recommended, to reduce cardiovascular mortality and HF hospitalizations, unless not well tolerated.[1–10]
2a	C-EO	2. In patients with HFrEF, titration and optimization of guideline-directed medications as frequently as every 1 to 2 weeks depending on the patient's symptoms, vital signs, and laboratory findings can be useful to optimize management.

Circulation. 145(18):e895-e1032

Think! (1 minute)

- First
  - Think about which agent(s) you would start first in a HFrEF patient
- Second
  - When would you follow-up?
- Third
  - What would you do at that follow-up appointment?
- Fourth:
  - How long until your patient is on 4 pillars at optimal doses

Think! Pair… DEFEND!



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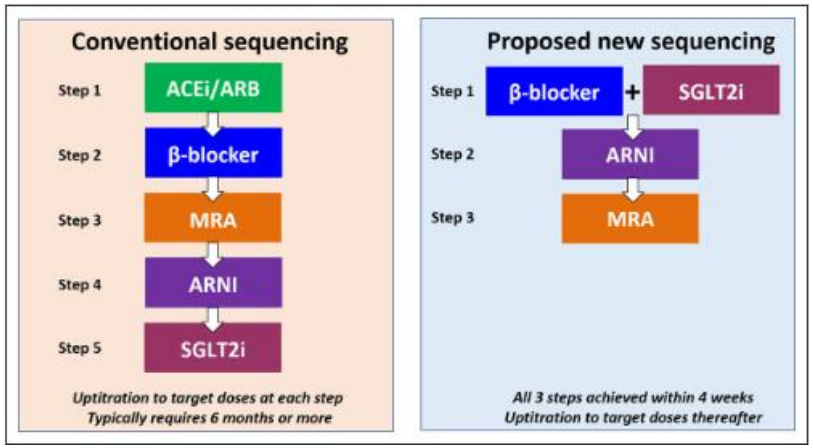
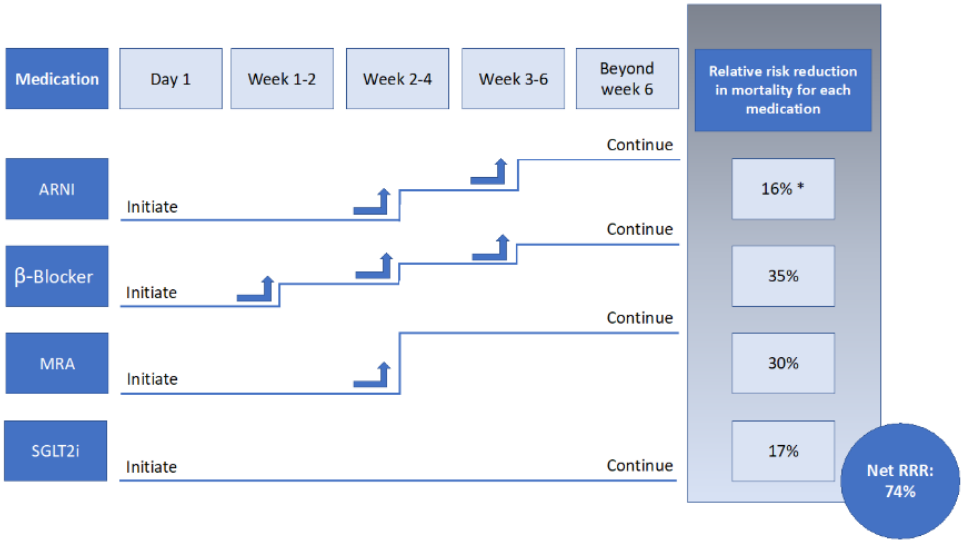
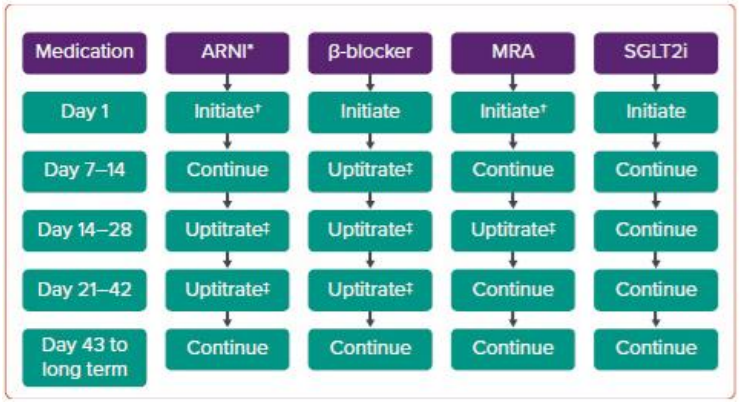
Various algorithms and pathways







Early relative risk reduction			Initiation and optimization of medication dosing				
Outcomes	Change, %	CDMMT	Day 1	Days 7-14	Days 14-28	Days 21-42	After day 42
CV death or HF hospitalization	-42	ARNI	Initiate at low dose	Continue	Titrate, as tolerated	Titrate, as tolerated	Maintenance or additional titration of the 4 foundational therapies
Death	-25	β-Blocker	Initiate at low dose	Titrate, as tolerated	Titrate, as tolerated	Titrate, as tolerated	Consideration of EP device therapies or transcatheter mitral valve repair
CV death or HF hospitalization	-37	MRA	Initiate at low dose	Continue	Titrate, as tolerated	Continue	Consideration of add-on medications or advanced therapies, if refractory
Death, HF hospitalization,or emergency/ urgent visit for worsening HF	-58	SGLT2i	Initiate	Continue	Continue	Continue	Manage comorbidities

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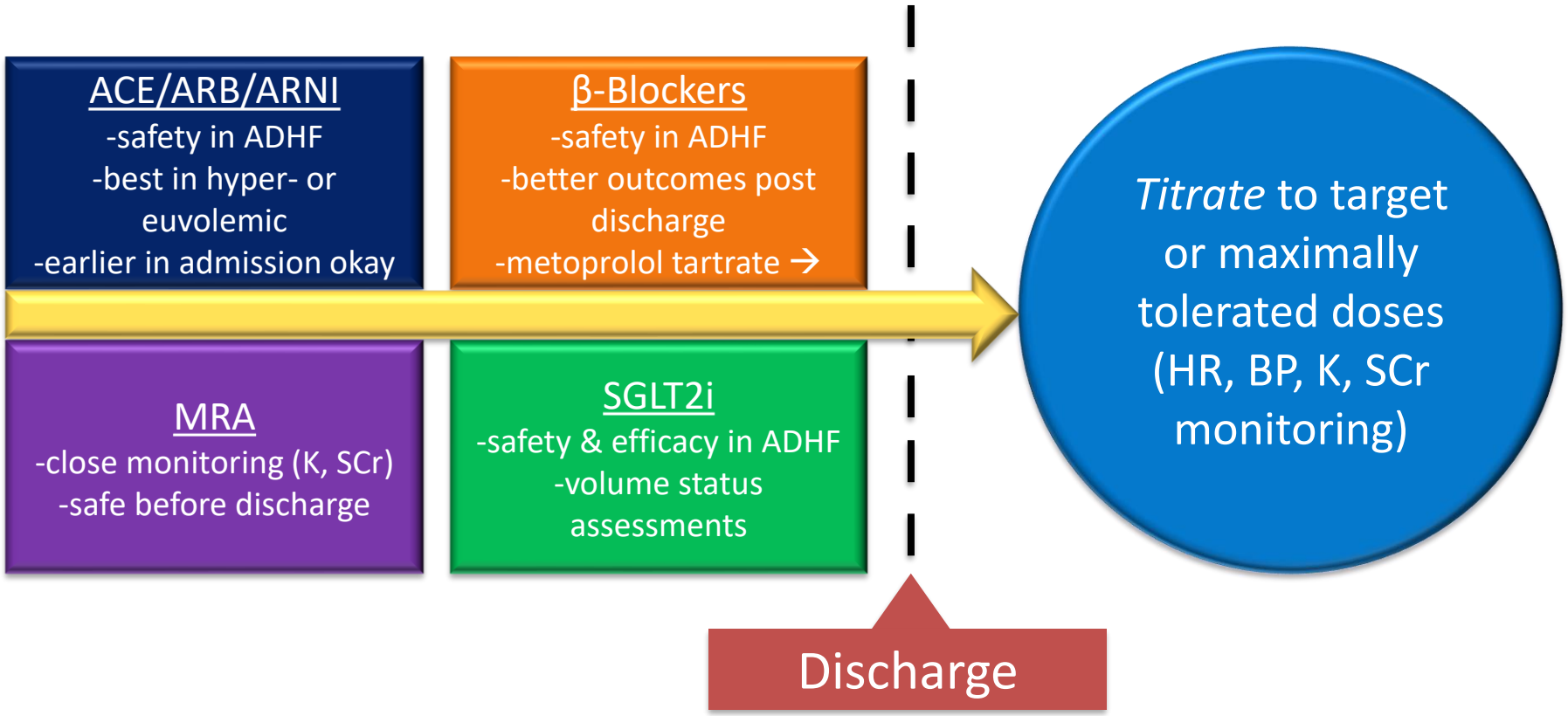
Circulation. 2021 143(9):875-877
Card Fail Rev. 2021 Mar; 7: e18
JAMA Cardiol. 2021;6(7):743-744
ACC Expert Opinion. Mar 2022. Available at:
Simultaneous Versus Sequential Initiation of HFrEF Therapies - American College of Cardiology (acc.org). [Accessed] 3/1/2023

“How?” is difficult, but so is “when?”



J Am Coll Cardiol 2004;43:1534–41.
N Engl J Med 2019;380:539-48.
J Am Coll Cardiol 2005;46:425-31
Nat Med 2022;28:568-74
American College of Cardiology Expert Opinion. June 1 2022. Available at: Inpatient Initiation of HFrEF Therapies - American College of Cardiology (acc.org). Accessed: 3/1/23

STRONG-HF

Safety, tolerability, and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial

- **Objective**: To compare a high-intensity intervention involving up-titration of heart failure treatments versus usual care among participants with admission to hospital for acute HF
- **Study Design**: Multinational, open-label, randomized, parallel-group trial across 14 countries and 87 hospitals
- **1° Outcome:** All-cause death or heart failure readmission by day 180

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Lancet. 2022 400(10367):1938-52.

STRONG HF: Intervention post-discharge

High-intensity Care

- Visits at 1, 2, 3, and 6 weeks after discharge
  - NTproBNP, electrolytes, kidney function, and Hgb
- 2 weeks post discharge: full optimal doses achieved*
- Day 90: Follow-up assessment
- Day 180: Contact patient to assess outcomes

Usual Care and Screen Failures

- Patients were followed up with as per usual care (average of 1 visit in first 90 days post-discharge)
- Day 90: Follow-up assessment
- Day 180: Contact patient to assess outcomes

*SGLT2i not included, was not standard of care at start of trial

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Lancet. 2022 400(10367):1938-52.

Patient population

- ~63 yo
- 77% white
- SBP ~123 mmHg
- Mostly NYHA II and III
- Mean LVEF 36%
  - 84% had LVEF < 50%
- 65% in Russia*; 23% in Africa
- 46% with atrial arrhythmia

Characteristic	High-Intensity Up-Titration (n = 542)	Usual Care (n = 536)
Demographics		
Age - years	62.9 (13.5)	63.0 (13.7)
Male Sex	326 (60%)	336 (63%)
White or Caucasian Race	418 (77%)	414 (77%)
Mean Systolic Blood Pressure at Baseline – mmHg	123.4 (13.30)	122.2 (12.56)
NT-proBNP at Baseline – ng/dL	4120.8 (3676.59)	3929.2 (3213.36)
Clinical History		
History of HF	465 (86%)	451 (84%)
NYHA Class Before Admission: Class I Class II Class III Class IV	 29/508 (6%) 147/508 (29%) 216/508 (43%) 116/508 (23%)	 34/492 (7%) 160/492 (33%) 199/492 (40%) 99/492 (20%)
Primary Cause of HF: Ischemic Non-Ischemic	 260/541 (48%) 281/541 (52%)	 254/534 (48%) 280/534 (52%)
LVEF at Baseline	36.7 (12.57)	35.9 (12.47)
History of Atrial Fibrillation or Atrial Flutter	238 (44%)	258 (48%)

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Lancet. 2022 400(10367):1938-52.

	High-Intensity Care (n = 542)	Usual Care (n = 536)	Adjusted Treatment Effect (95% CI)	Adjusted Risk Ratio (95% CI)	P-Value NNT
Primary Outcome					
All-cause death or heart failure readmission by day 180	74/506 (15.2%)	109/502 (23.3%)	8.1% (2.9 to 13.2)	0.66 (0.50 to 0.86)	0.0021 NNT: 12
Secondary Outcomes					
Change in quality of life from baseline to day 90 in EQ-5D (VAS)	10.72 (0.88)	7.22 (0.90)	3.49 (1.74 to 5.24)	NA	<0.0001
All-cause death by day 180	39/506 (8.5%)	48/52 (10.0%)	1.6% (-2.3 to 5.4)	0.84 (0.56 to 1.26)	0.42
All-cause death or heart failure re-admission by day 90	55 (10.4%)	72 (13.8%)	3.4% (-0.4 to 7.3)	0.73 (0.53 to 1.02)	0.081

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Lancet. 2022 400(10367):1938-52.

Trial stopped early due to benefit

Due to stopping early, trial lost power

8.1% ARR in HF hospitalization and CV death at 180d (NNT 12)

Patients felt better

Lancet. 2022 400(10367):1938-52.

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STRONG-HF: Deep Dive into Data

- Patients who benefitted:
  - Higher baseline SBP (>120 mmHg)
  - Did not have a baseline atrial arrhythmia
  - LVEF 40-50%
  - Higher baseline NT-proBNP
  - eGFR < 59.4 mL/min/1.73m^2
- High-intensity had more
  - Hypotension (5% vs 0.4%)
  - Bradycardia (5% vs 0.4%)
  - Renal impairment (2.6% vs 0.2%)
  - Hyperkalemia (3.3% vs 0%)
- Additional benefits
  - Weight loss
  - NYHA Class improvement
  - SBP, DBP, HR reduction

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Lancet. 2022 400(10367):1938-52.

Bullseye! - Patients titrated to target dose

- The majority of patients in the high-intensity care group achieved target doses
  - ACE/ARB/ARNI - 278 [55%] *vs* 11 [2%]
  - β blockers - 249 [49%] *vs* 20 [4%]
  - MRA - 423 [84%] *vs* 231 [46%])

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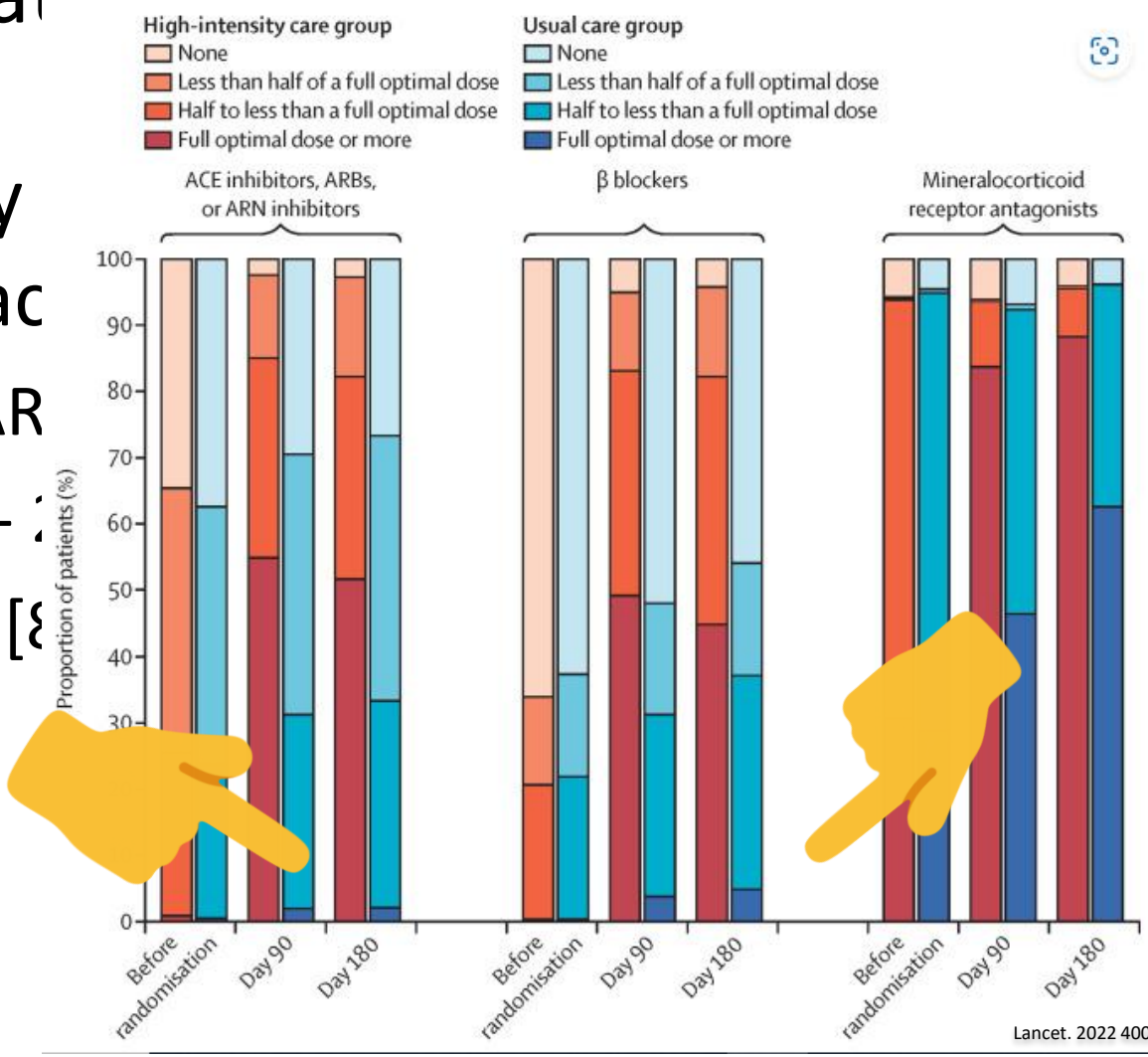
Lancet. 2022 400(10367):1938-52.

Bullseye! - Pat

- The majority care group ac
  - ACE/ARB/AR
  - β blockers - 2
  - MRA - 423 [8



Lancet. 2022 400(10367):1938-52.

GDMT Titration Take-Homes

- Initiation and titration can occur across care continuum
  - GDMT opportunities abound
- With speed comes monitoring
  - BMP, BP, HR, weight, fluid status, symptoms
- Variety of algorithms, but no “cookbook”
  - Treat the patient in front of you

STRONG-HF did not include SGLT2i… but we did

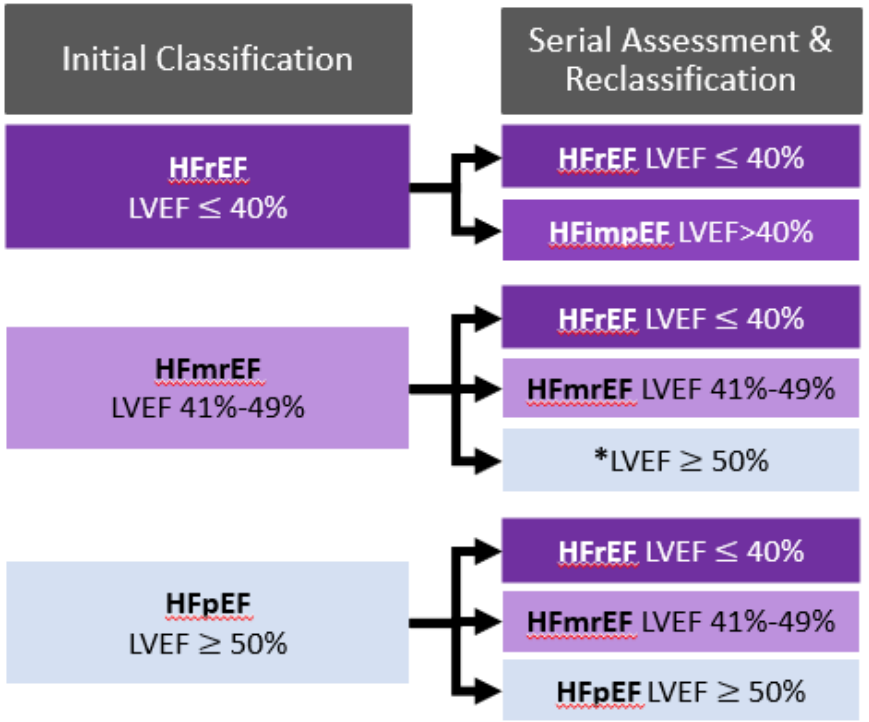
Objectives

1. Review pathways to optimizing guideline-directed medical therapy (GDMT) in various clinical settings.
2. Summarize relevant literature supporting the use of SGLT2 inhibitors in the management of heart failure.

AHA/ACC/HFSA 2022 Definitions

Newer definition changes

- HFmrEF
- HFimpEF
- Defined diagnosis definitions effect treatment approaches



Circulation. 145(18):e895-e1032

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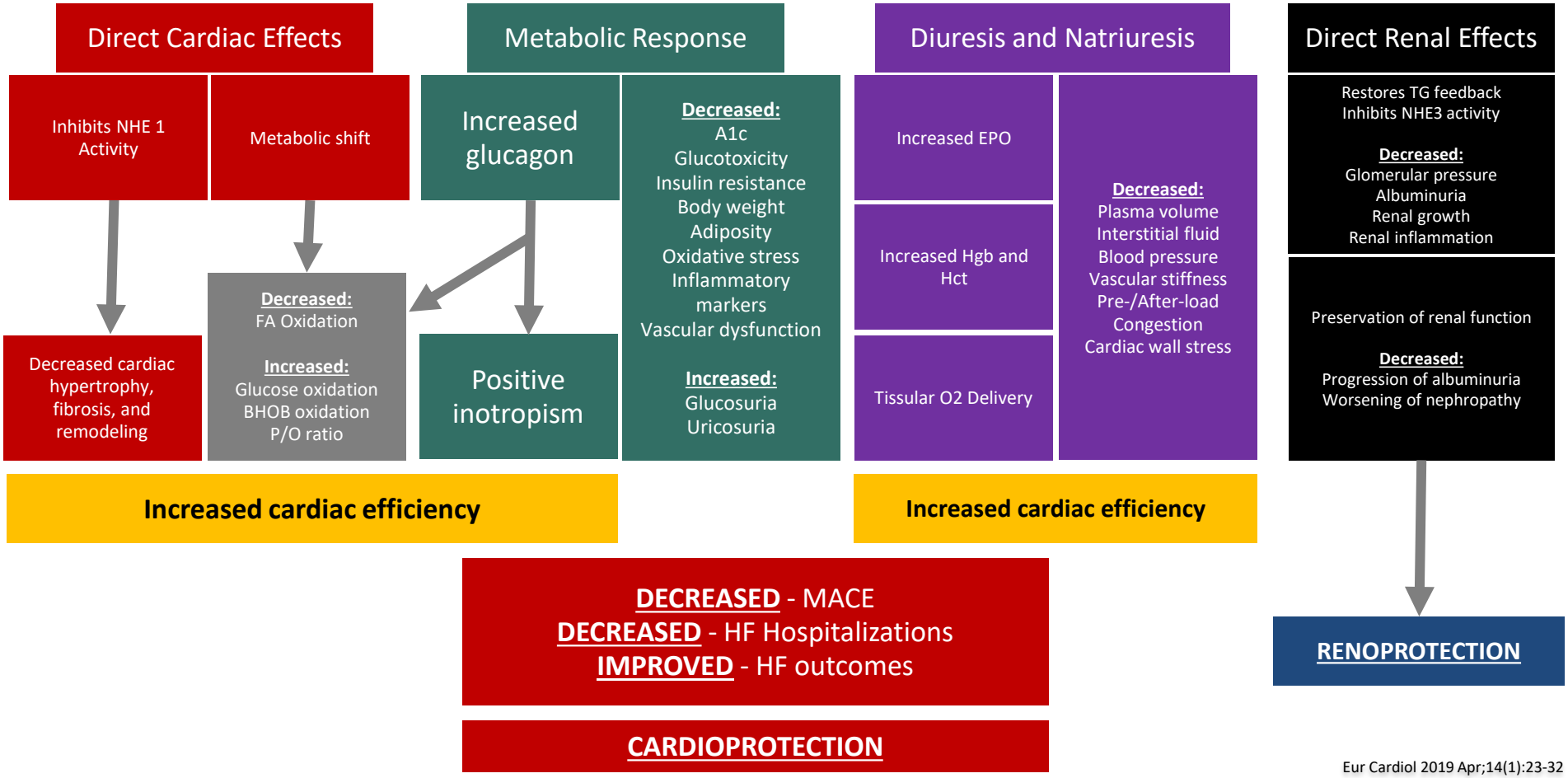
SGLT2i Mechanisms



Eur Cardiol 2019 Apr;14(1):23-32

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Evidence Overview

HFrEF

- DAPA-HF (2019)
- EMPEROR-Reduced (2020)

HFmrEF & HFpEF

- DELIVER (2022)
- EMPEROR-Preserved (2021)

HFrEF Trials – DAPA-HF

- N=2373 dapagliflozin vs 2371 placebo
- Primary endpoint 386(16.3%) vs 502(21.2%) [NNT=21]
- HF Hospitalization 231(9.7%) vs 318(13.4%)
- CV Death 227(9.6%) vs 273(11.5%)
- Minor safety concerns – uncomplicated UTI
- No statistical significance vs placebo for adverse events

N Engl J Med 2019; 381:1995-2008

HFrEF Trials – EMPEROR-Reduced

- N=1863 empagliflozin vs 1867 placebo
- Primary endpoint 361(19.4%) vs (462)24.7% [NNT=19]
- HF Hospitalization 246(13.2%) vs 342(18.3%)
- CV Death 187(10%) vs 202(10.8%)
- Minor safety concerns – uncomplicated UTI
- No statistical significance vs placebo for adverse events

N Engl J Med 2020; 383:1413-1424

BONUS HFrEF Trial – CREDENCE

- N=2202 canagliflozin vs 2199 placebo *(with and without HF)*
- CV Death/HFH 7.9% vs 15.1% [NNT=29]
- HF Hospitalization 4% vs 6.4%
- CV Death 5% vs 6.4%
- Higher side-effect rates than other SGLT2s (significant for amputation)
- *Not approved for HFrEF*

Am Heart J. 2021 Mar;233:141-148

HFmrEF & HFpEF Trials – Eligibility Criteria

- Symptomatic HF – NYHA Class II-IV
- Evidence of structural HF or HF hospitalization in prior year
- Elevated NT-proBNP [>300 (without AF; >600/900 with AF)
- ADHF excluded; no IV HF therapies
- Intermittent or stable diuretics
- EGFR >25/20 mL/min respectively

No data for asymptomatic HFpEF

EMPEROR-Preserved – [HFimpEF excluded]

- N=2997 empagliflozin vs 2991 placebo
- CV Death/HFH 415(13.8%) vs 511(17.1%)
- HF Hospitalization 407(13.5%) vs 544(18.1%)
- CV Death 219(7.3%) vs 244(8.2%)
- Hypotension and uncomplicated UTI more common in empagliflozin groups

N Engl J Med 2021; 385:1451-1461

EMPEROR-Preserved

LVEF at baseline				
<50%	145/995	193/988		0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030		0.80 (0.64–0.99)
≥60%	132/974	145/973		0.87 (0.69–1.10)

N Engl J Med 2021; 385:1451-1461

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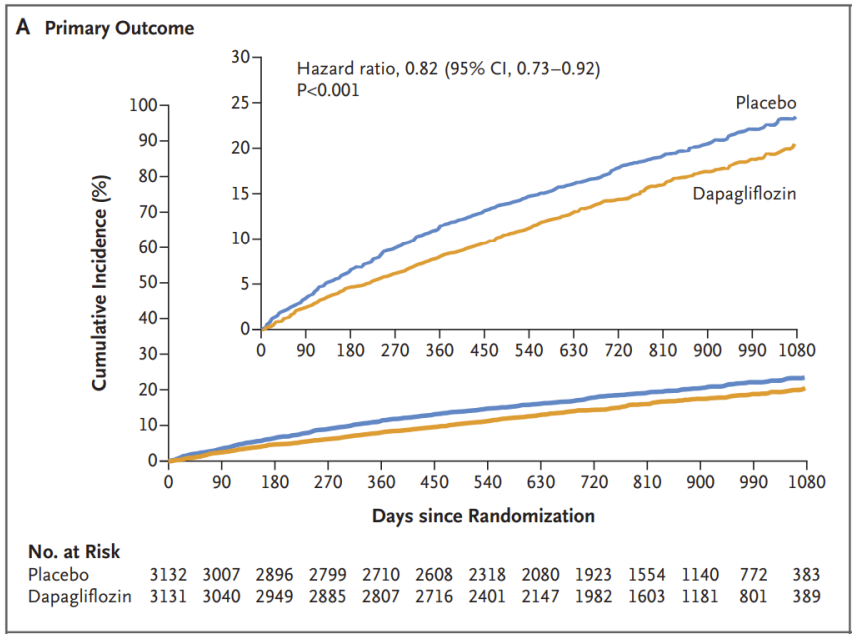
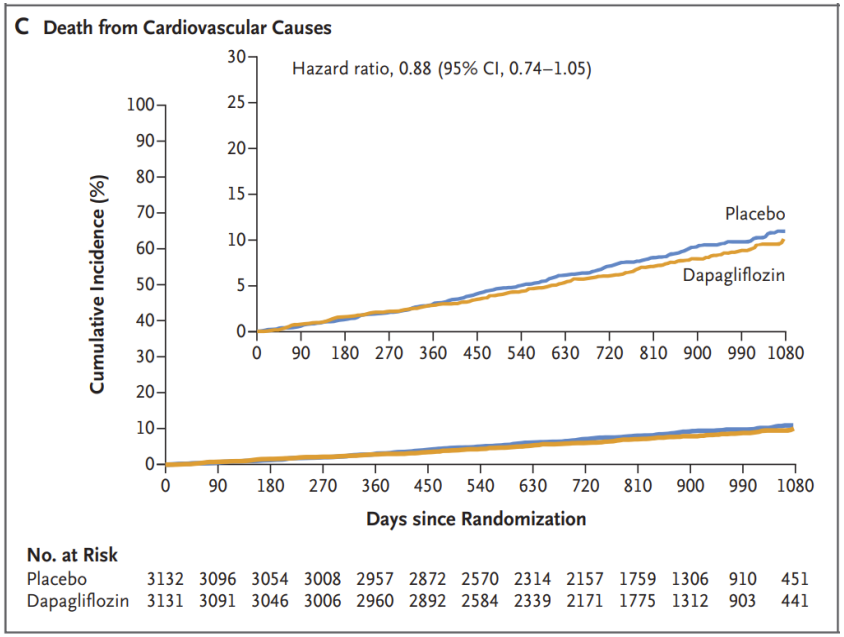
DELIVER – HFpEF & HFimpEF

- N=3131 dapagliflozin vs 3132 placebo
- CV Death/HFH/Urgent visit 512(16.4%) vs 610(19.5%)
- HF Hospitalization 329(11.8%) vs 418(13.3%)
- CV Death 231(7.4%) vs 261(8.3%)
- Similar overall effects between LVEF <60% and >60%
- No statistical significance vs placebo for adverse events

N Engl J Med 2022; 387:1089-1098

DELIVER





N Engl J Med 2022; 387:1089-1098

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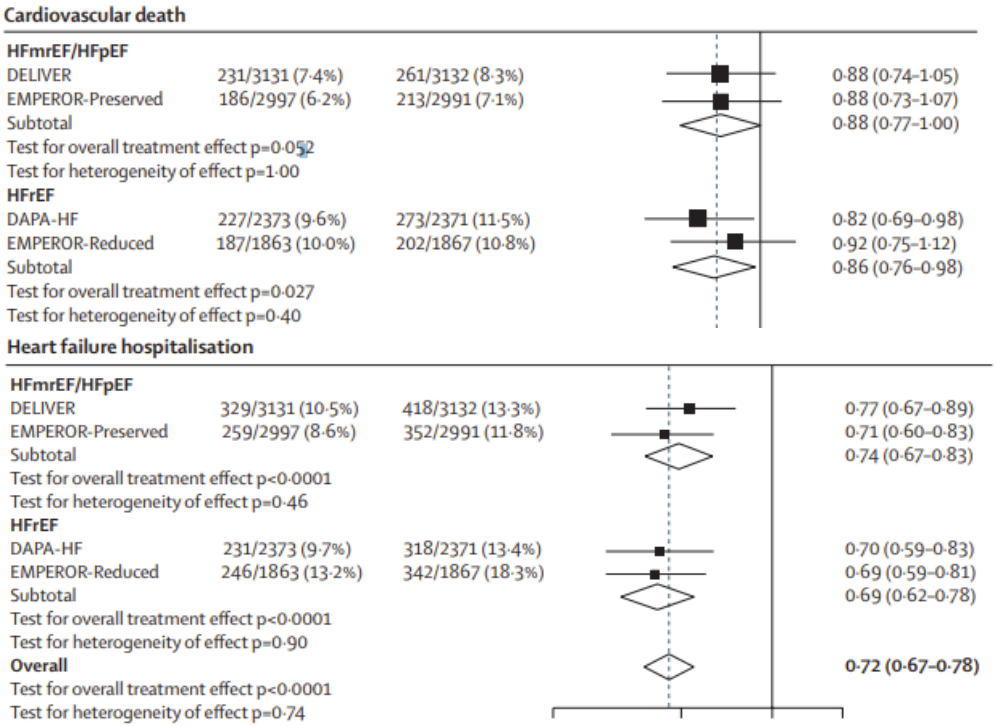
Summary of SGLT2i Evidence



Lancet. 2022 Aug 22;400(10354):757-767

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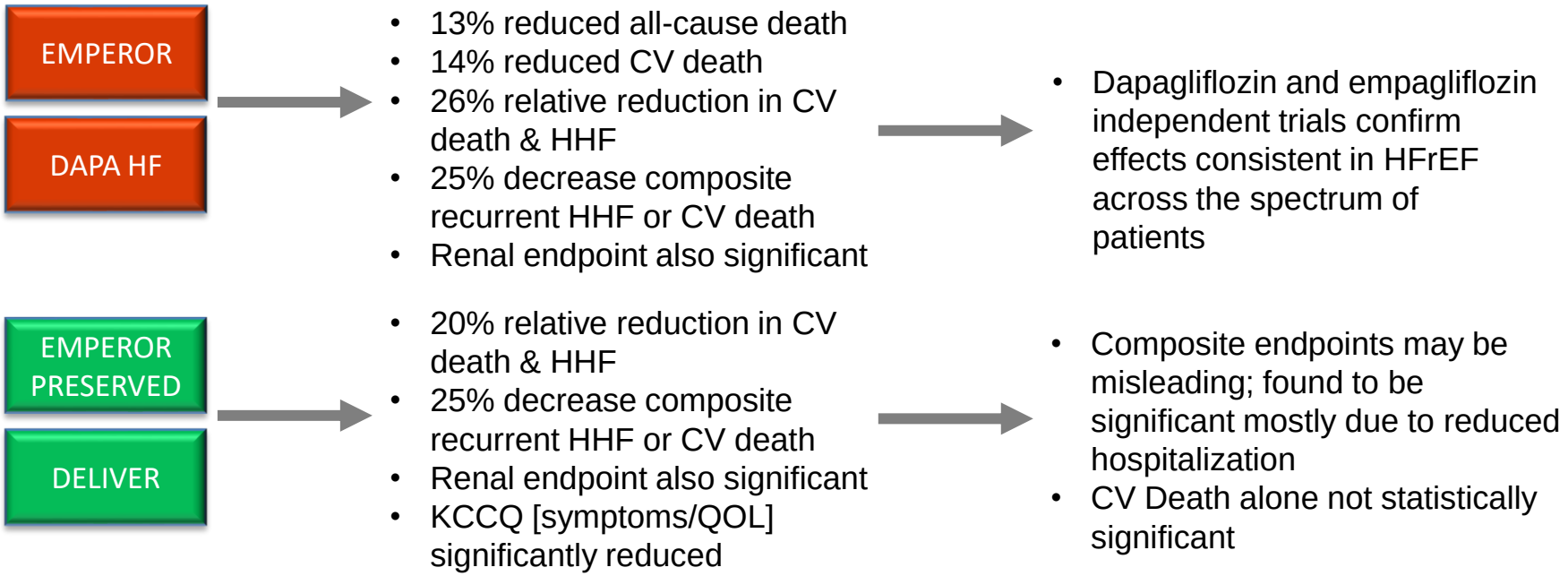
Summary of SGLT2i Evidence



JAMA Cardiol. 2022 Dec 1;7(12):1259-1263
Lancet. 2020 Sep 19;396(10254):819-829

HFimpEF

From the 2022 AHA HF Guidelines:

"EF can decrease after withdrawal of pharmacological treatment in many patients who had improved EF to normal range with GDMT."

- No consensus if HFimpEF guidance is needed separately from HFpEF or treatment strategies can be applied uniformly to both groups

Circulation. 145(18):e895-e1032

HFpEF – Research Inequities

DELIVER

Race — no. (%)†

White

Black

Black

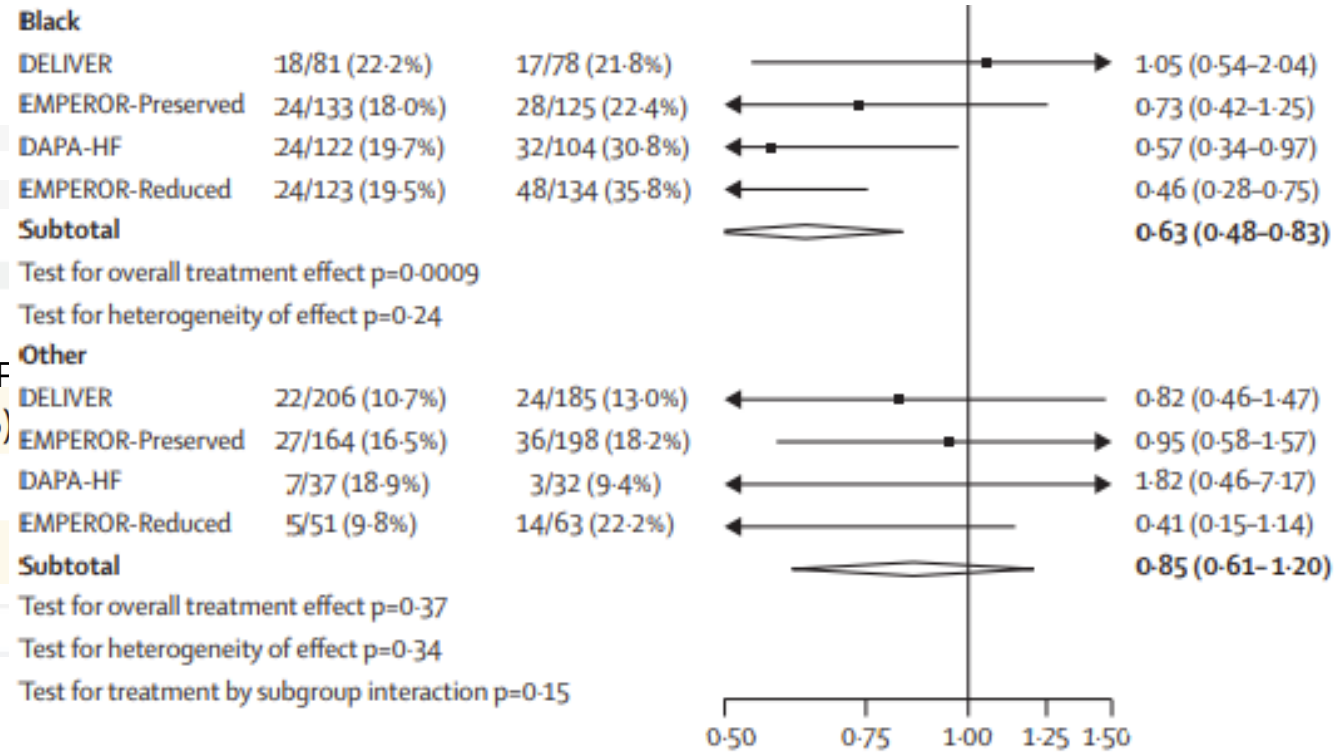
EMPEROR-F

Race — no. (%)

Asian

Black

Black



644 (20.6)

78 (2.5)

1.08 (0.58–2.01)

Lancet. 2022 Aug 22;400(10354):757-767

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Future Thoughts and Implications

- SGLT1/2 dual inhibitors may provide new outcomes (sotagliflozin, others)
- HFimpEF data lacking
- Follow-up for SGLT2i initiation unspecified
- Cost effectiveness data conflicting for HFpEF

JAMA Cardiology | Original Investigation

Cost-effectiveness of Sodium-Glucose Cotransporter-2 Inhibitors for the Treatment of Heart Failure With Preserved Ejection Fraction

CONCLUSIONS AND RELEVANCE Results of this economic evaluation suggest that at 2022 drug prices, adding an SGLT2-I to standard of care was of intermediate or low economic value compared with standard of care in US adults with HFpEF. Efforts to expand access to SGLT2-I for individuals with HFpEF should be coupled with efforts to lower the cost of SGLT2-I therapy.

JAMA Cardiol. doi:10.1001/jamacardio.2023.0077
Accessed: 3/3/2023

Summary

- Dapagliflozin and empagliflozin should be be used in all patients with HFrEF when possible to reduce CV death, HHF, and symptoms
- For HFpEF, it is reasonable to use in symptomatic patients to improve symptoms and reduce HHF; larger impact <LVEF
- Trials show that dapagliflozin and empagliflozin safe relative to placebo; caution with BP limitations or recurrent UTIs
- No evidence to deescalate therapy for those who with LVEF improvement >40%

Co-Management of Patients with Cardiac and Metabolic Conditions

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Medical College of Wisconsin

Ascension

MCW PHARMACY SCHOOL

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Learning Objectives

1. Discuss pharmacological therapies with proven cardiovascular benefits in patients with cardiac and metabolic conditions.

2. Outline the benefits of lifestyle modifications in patients with cardiac and metabolic conditions.

Abbreviations

- Glucagon-like peptide 1 receptor agonist (GLP-1 RA)
- Sodium-glucose co-transporter 2 inhibitor (SGLT2i)
- Cardiovascular disease (CVD)
- Diabetes mellitus (DM)
- Hypertension (HTN)
- Hyperlipidemia (HLD)
- Congestive Heart Failure (CHF)
- Continuous Glucose Monitoring (CGM)
- Basal Metabolic Rate (BMR)

Patient Case

- GM, a 60 yo Caucasian male presents to your clinic for a medication management visit.
- **PMH:** DMII, HLD, CKD, obesity, and CHF Stage B
- **Current Medications:**
  - Insulin glargine 75 units SQ once daily
  - Insulin lispro 12 units SQ TID AC
  - Glipizide ER 20 mg PO once daily
  - Atorvastatin 80 mg PO once daily
  - Metformin 500 mg PO BID
  - Entresto 97/103 mg PO BID
  - Metoprolol succinate 100 mg PO daily
- **SH:** Sedentary lifestyle, eats fast food 5 days per week, desk job
- **Vitals:** BP: 135/82 mmHg, HR: 76 BPM, 5' 8", 240lbs, BMI: 36.5
- **Labs:** EGFR: 42 ml/min, A1C: 9.5%, TC: 177 mg/dL, HDL: 30 mg/dL, LDL: 70 mg/dL, TG: 385 mmol/L, microalbumin: 210 mcg/mL

Engagement Question

After reviewing the patient case, what are your initial thoughts on GM's medication regimen?

**Please focus more on the metabolic aspects*

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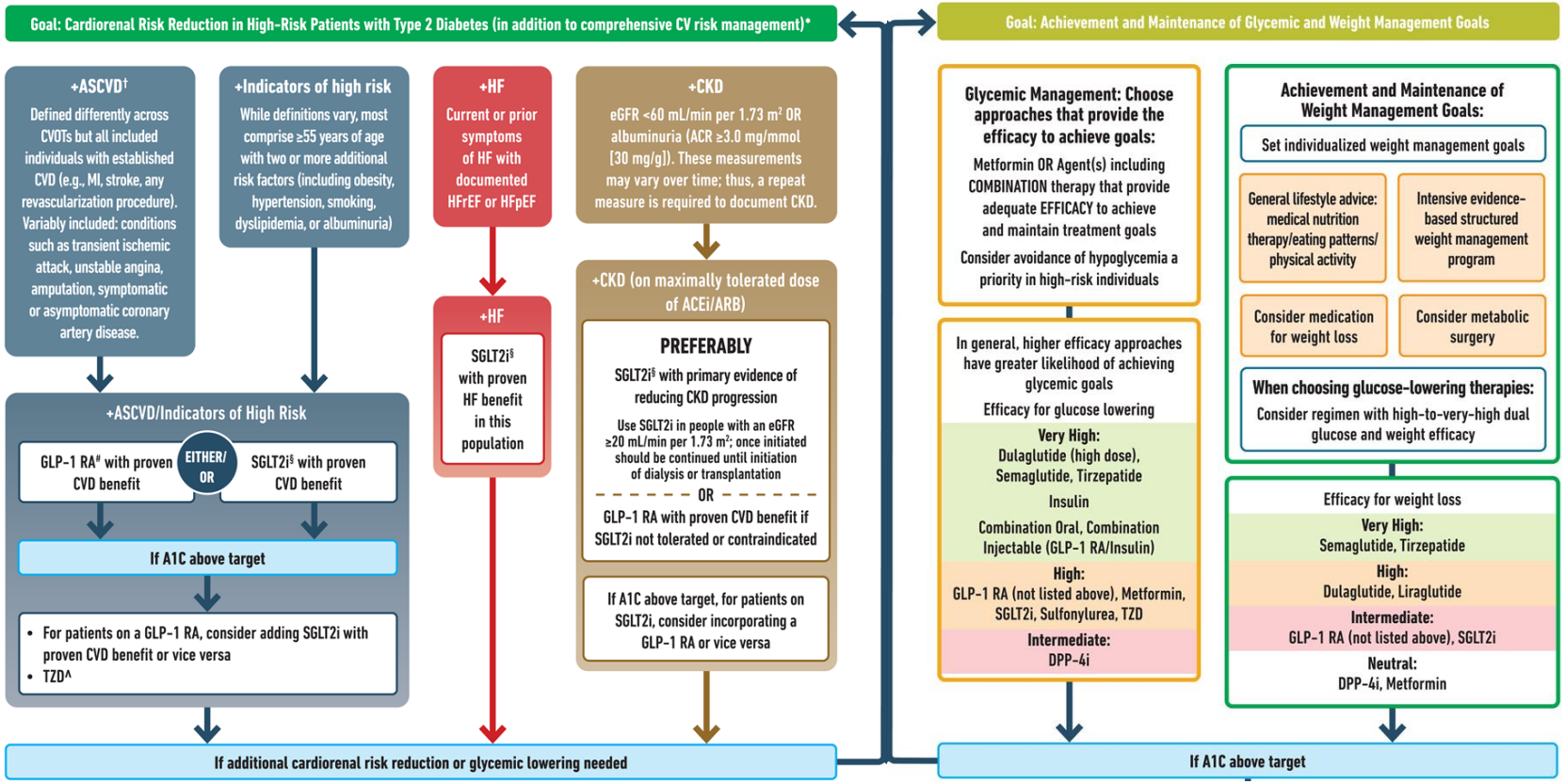
American Diabetes Association.

From: **9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023**



Diabetes Care. 2022;46(Supplement_1):S140-S157. doi:10.2337/dc23-S009

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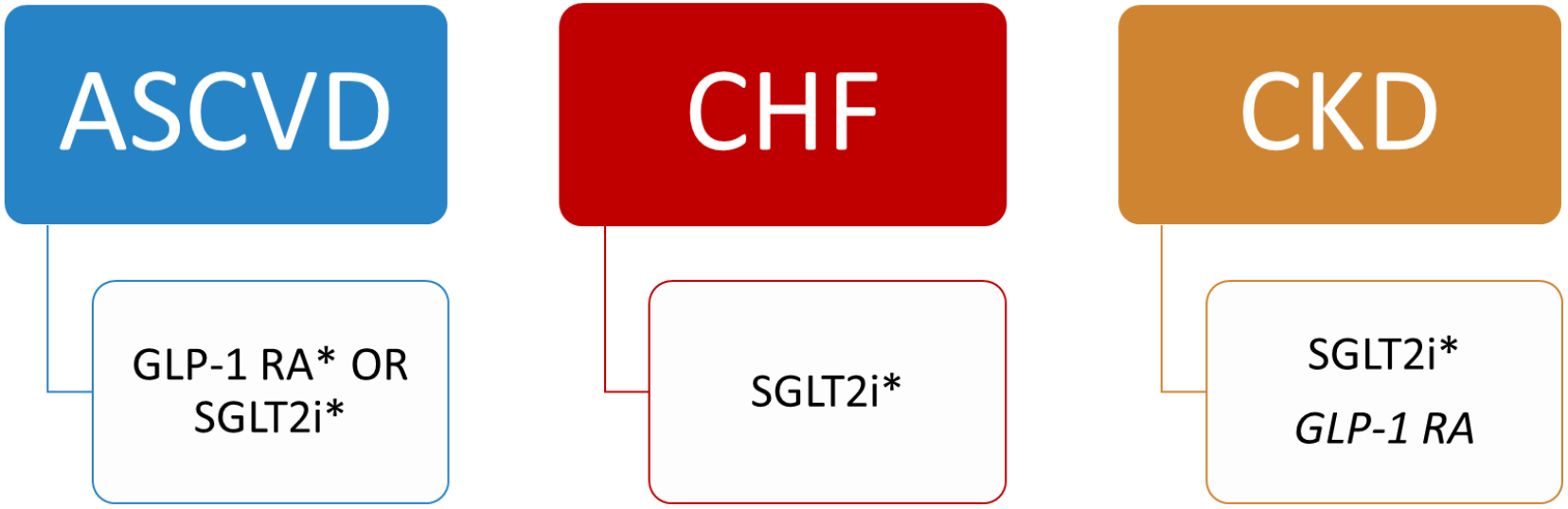
ADA Evidence Based Updates



* Therapy with proven benefit

American Diabetes Association. "Standards of Medical Care in Diabetes - 2023." *Diabetes Care* 45, no. January (2023)

ADA Evidence Based Updates

Weight Management considered just as important as glucose management

Recommended approaches:

1. Lifestyle changes
2. Evidence-based weight management programs
3. Medications
4. Metabolic surgery

Emphasis on supporting higher weight loss (up to 15%)

Efficacy for weight loss

Very High:

Semaglutide, Tirzepatide

High:

Dulaglutide, Liraglutide

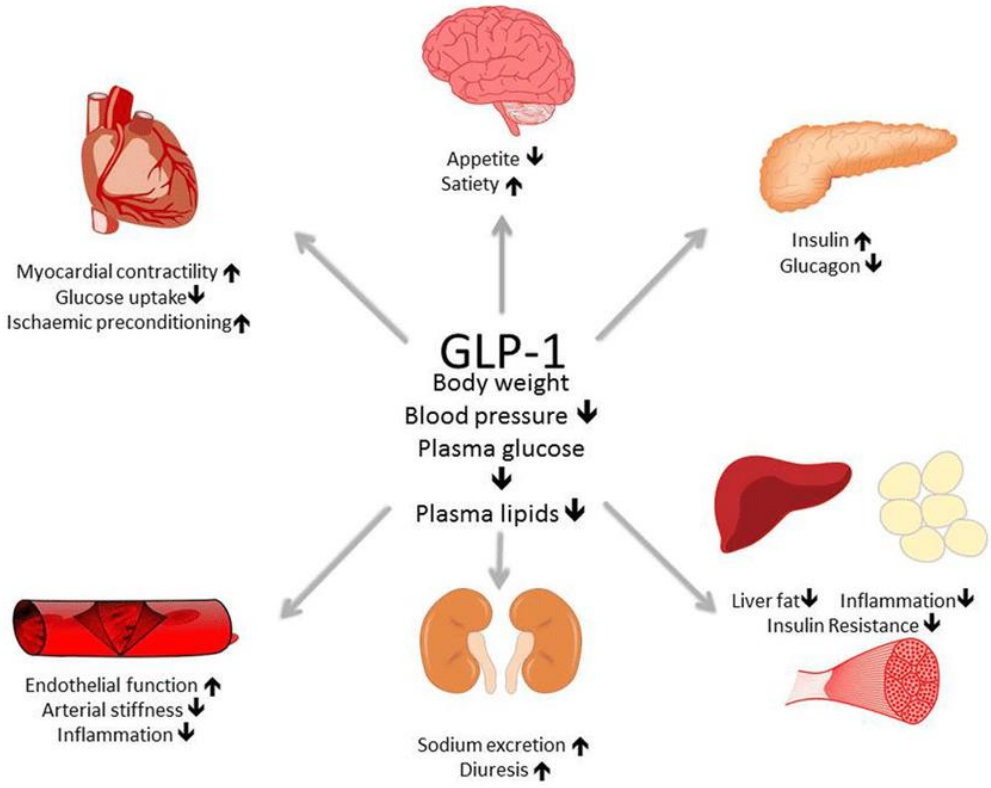
Intermediate:

Exenatide, Lixisenatide, Albiglutide, SGLT2i

American Diabetes Association. "Standards of Medical Care in Diabetes - 2023." *Diabetes Care* 45, no. January (2023)

GLP-1 RA

- Meta analysis - reduction in MACE outcomes
- FREEDOM Cardiovascular Outcomes trial



GLP-1 RA

Medication	Average weight loss (%)
Semaglutide 2.4 mg once weekly	15% (STEP 1), 9.6% (STEP 2)
Liraglutide 1.8 mg, 3 mg once daily	4.7%, 6.0%
Dulaglutide 4.5 mg once weekly	5%

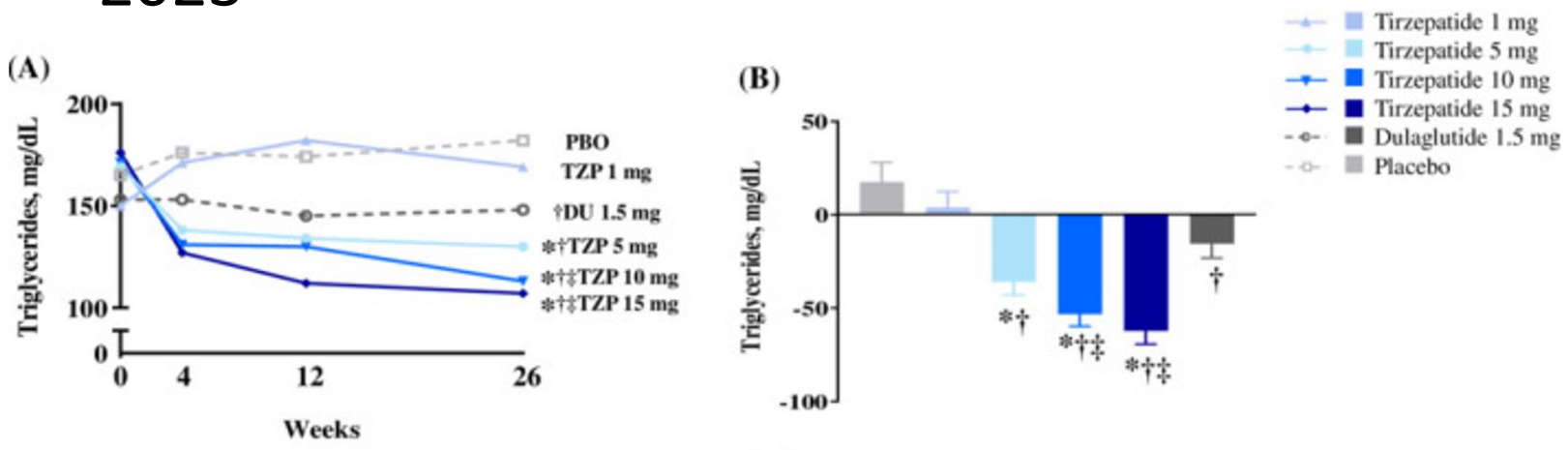
GLP/GIP Receptor Agonist

GIP Effects
• Decrease caloric intake • Increase insulin and glucagon secretion • Increase glucose uptake • Increase triglyceride uptake and storage

Tirzepatide average weight loss
• 5 mg: 15% • 10 mg: 19.5% • 15 mg: 20.9%

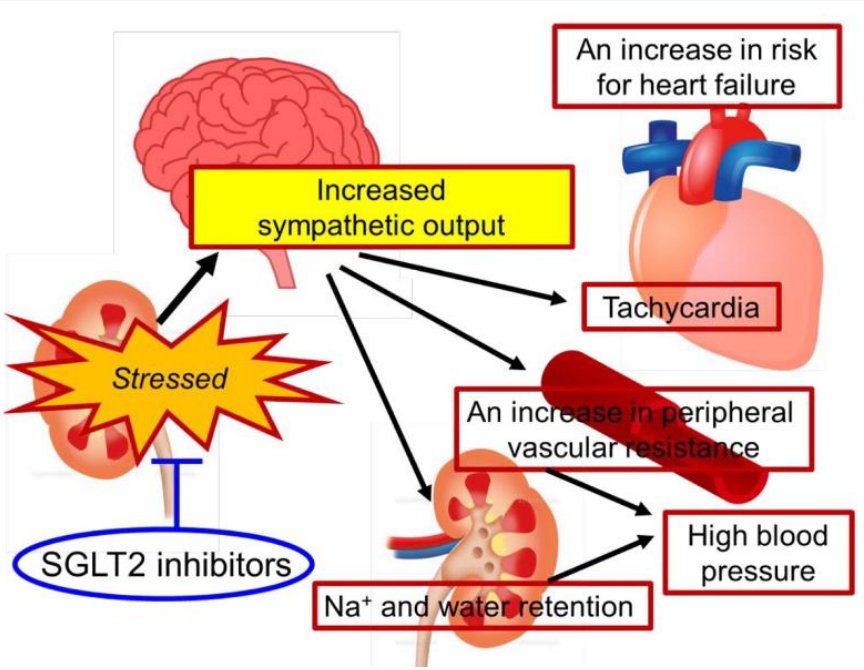
GLP/GIP Receptor Agonist

- Ongoing research with cardio protection
  - SURPASS-CVOT: Estimated completion October 2024
  - SUMMIT: Estimated completion in November 2023



SGLT2i

- 2-3 kg of weight loss
- Anti-hyperglycemic effects decreased in patients with reduced eGFR
- Sympathetic nervous system inhibition



Assessment Question #1

Which of the following medication classes have proven cardiovascular benefits?

A. DPP-4

B. SGLT2 inhibitors

C. GLP-1/GIP receptor agonists

D. Sulfonylureas

Lifestyle Modification

- **Physical Activity Benefits**
  - Improved blood glucose control
  - Reduction in cardiovascular risk factors
  - Weight loss
  - Heightened sense of well-being

Lifestyle Modification

Aerobic Physical Activity: 150 minutes/week of moderate to vigorous intensity aerobic exercise spread over at least **3 days per week** with no more than 2 consecutive rest days

Screen for CVD prior to starting in patients with the following:

Long-standing DM (> 10 years)	History of ASCVD	Multiple risk factors (HTN, HLD, CHF, etc)

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Lifestyle Modification

Get UP & MOVE !

- Resistance/Strength Training: 2–3 sessions/week on nonconsecutive days per week
- Prolonged sitting should be interrupted every 30 min for blood glucose benefits
- Flexibility training and balance training: 2–3 times/week for older adults with diabetes

Lifestyle Modification

- Who is your patient?
- Calorie deficit/restriction
  - Stress adherence to daily calorie goal
- Increasing protein and fiber intake
  - Lean meats and nuts for protein
  - Avoid foods with high saturated fats
- What is the best diet to follow?

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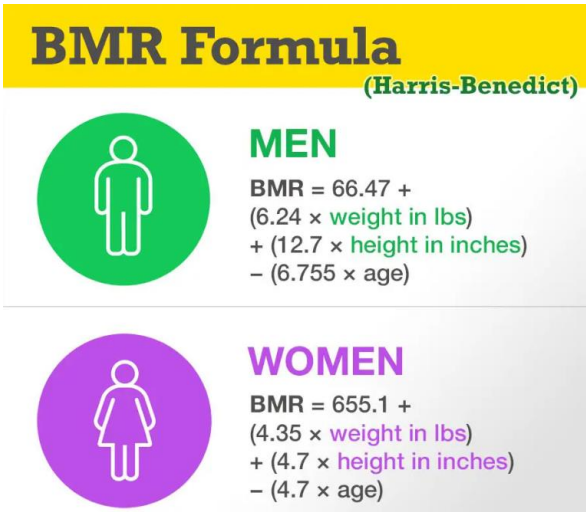
Lifestyle Modification

- Basal metabolic rate (BMR) – Energy expenditure at complete bodily rest in a thermoneutral environment.
  - Harris-Benedict
  - Mifflin St. Jeor
  - Katch-McArdle



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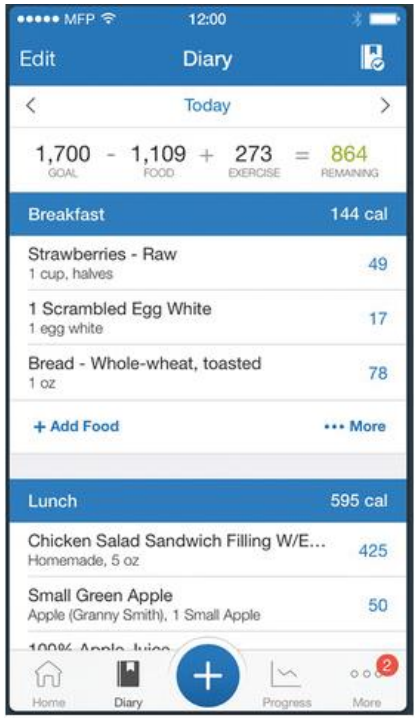
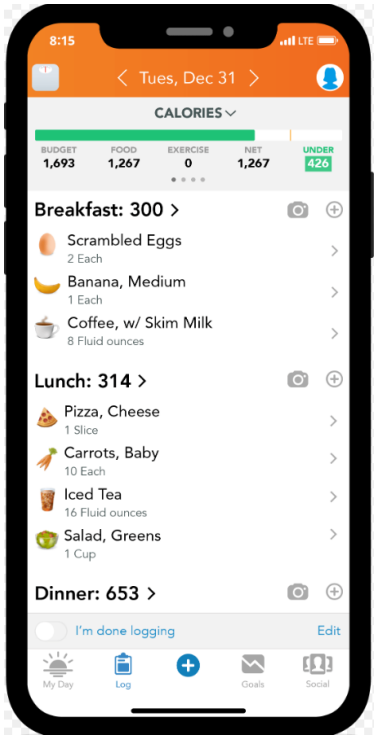
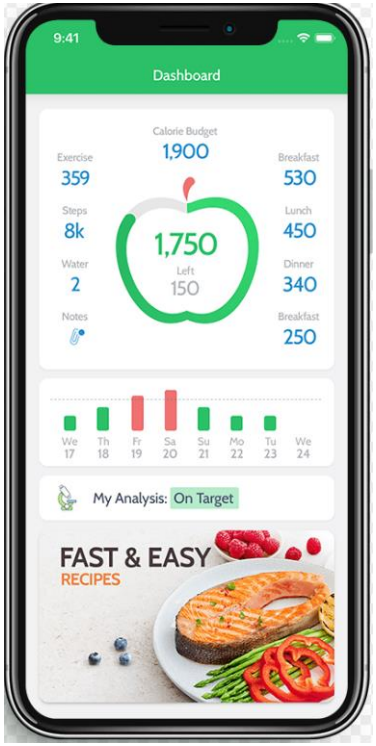
Lifestyle Modification







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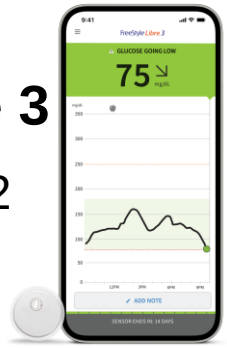
New Diabetes Technology

FreeStyle Libre 3

Released late 2022



Sensor + App®

Real-time glucose readings every 60 seconds

Sensor size: 21 x 2.9mm

One piece applicator

FreeStyle Libre 2

Sensor + Reader

Must scan to see glucose readings

Sensor size: 30 x 5 mm

Two-piece applicator

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New Diabetes Technology

Dexcom G7

Released
March 2023

Combined sensor-transmitter design

60% smaller than G6

30-minute warm-up time

Dexcom G6

Sensor + separate transmitter

Transmitter used for 3 months with new sensor every 10 days

120-minute warm-up time

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Assessment Question #2

Which of the following are benefits associated with physical activity?

A. Improved blood glucose control

B. Reduction in cardiovascular risk factors

C. Weight loss

D. Heightened sense of well-being

E. All of the above

Patient Case

- GM, a 60 yo Caucasian male presents to your clinic for a medication management visit.
- **PMH:** DMII, HLD, CKD, obesity, and CHF Stage B
- **Current Medications:**
  - Insulin glargine 75 units SQ once daily
  - Insulin lispro 12 units SQ TID AC
  - Glipizide ER 20 mg PO once daily
  - Atorvastatin 80 mg PO once daily
  - Metformin 500 mg PO BID
  - Entresto 97/103 mg PO BID
  - Metoprolol succinate 100 mg PO daily
- **SH:** Sedentary lifestyle, eats fast food 5 days per week, desk job
- **Vitals:** BP: 135/82 mmHg, HR: 76 BPM, 5' 8", 240lbs, BMI: 36.5
- **Labs:** EGFR: 42 ml/min, A1C: 9.5%, TC: 177 mg/dL, HDL: 30 mg/dL, LDL: 70 mg/dL, TG: 385 mmol/L, microalbumin: 210 mcg/mL

Engagement Question

Considering the information just presented, what changes would you recommend to GM's medication regimen?

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Summary

Utilize medications with proven cardiovascular benefits or medications that can improve metabolic syndrome

Recommend realistic and patient-specific diet and physical activity goals

Encourage technology use to empower patients

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Questions?

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Matters of the Heart: Updates in Lipid Management

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Objectives

1. Describe the mechanism of action of siRNA, PCSK9 inhibitors, and ATC Lyase inhibitors.

2. Discuss potential cost, coverage, and access barriers when prescribing dyslipidemia pharmacologic therapies

OVERVIEW OF NOVEL LIPID LOWERING AGENTS

ATC LYASE INHIBITORS

https://link.springer.com/chapter/10.1007/164_2020_361

Bempedoic Acid (Nexletol®)

MOA: Competitively inhibits Adenosine Triphosphate-Citrate Lyase (ATC-L) which is an enzyme involved in cholesterol synthesis in the liver.

FDA Approval: For patients on maximally tolerated statin therapy.

1. Established ASCVD
2. Familial Hypercholesterolemia

Bempedoic acid. Lexicomp. Feb 2023.

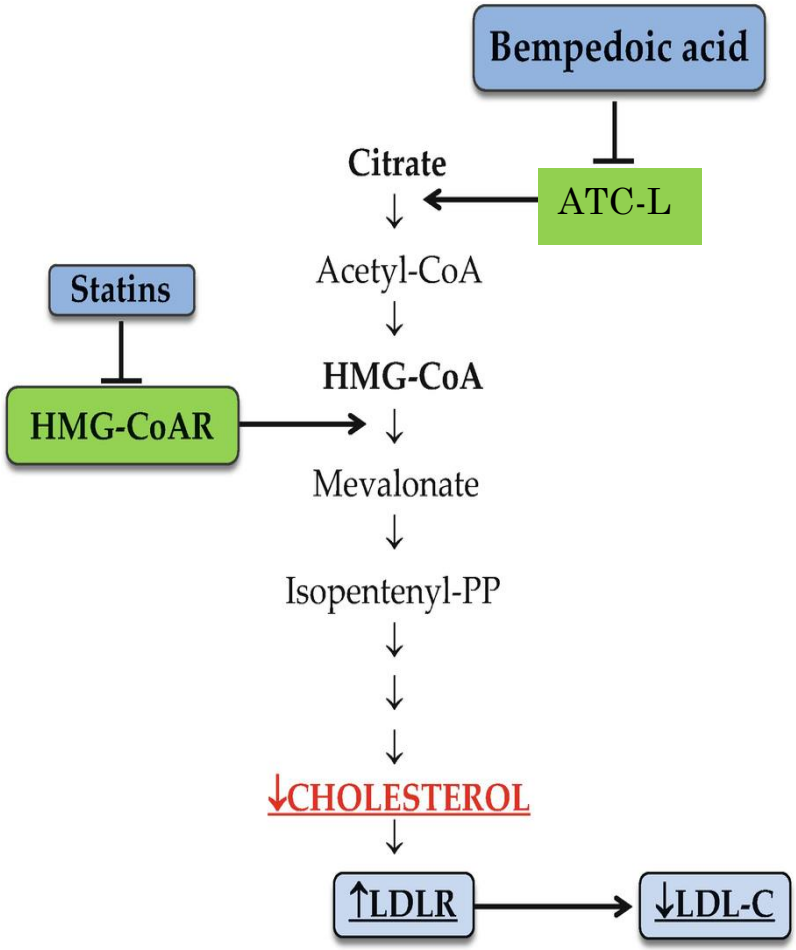
Bempedoic Acid (Nexletol®)

Prodrug: Converted to active metabolite via acyl-CoA synthetase-1, which is an enzyme not present in skeletal muscle

- **Less likely to cause myopathy as compared to statins**

CLEAR RCTs: Showed significant reduction in LDL-C of 15-24% compared to placebo at 24 weeks.

CLEAR OUTCOMES – CVD data remains unpublished



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Bempedoic acid. Lexicomp. Feb 2023.
Goldberg AC et al. JAMA. 2019;322(18):1780.

Bempedoic Acid (Nexletol®)

Dose: 180 mg/day

- ***Combination w/ ezetimibe (Nexlizet®):*** *180/10 mg*

Warnings/CIs: pregnancy or uncontrolled gout

Adverse Reactions: hyperuricemia, tendon rupture, increased LFTs, thrombocytopenia, increased BUN/SCr

Interactions (increased statin concentrations):

- Pravastatin: Do not exceed 40 mg
- Simvastatin: Do not exceed 20 mg

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Bempedoic acid. Lexicomp. Feb 2023.
Goldberg AC et al. JAMA. 2019;322(18):1780.

PCSK9 INHIBITOR MONOCLONAL ANTIBODIES (PCSK9I MABS)

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https://www.webmd.com/drugs/2/drug-169420/praluent-pen-subcutaneous/details
https://www.repatha.com/how-to-start-repatha-injection

PCSK9 Inhibitor Monoclonal Antibodies (PCSK9i mAbs)

MOA: Human monoclonal antibody that inhibits PCSK9 enzyme and decreases LDL-C by increasing expression of LDL receptors

FDA Approval: For patients on maximally tolerated statin therapy.

1. Established ASCVD
2. Familial Hypercholesterolemia

FOURIER and ODYSSEY RCTs: Significant reduction in LDL-C of ~43-64% decrease from baseline and a lowering risk of cardiovascular event(s)

Clinical Pearl: Circulating levels of PCSK9 are upregulated in the presence of statins d/t upregulation of LDL-receptors

Alirocumab. Lexicomp. Accessed Feb 2023.
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Gencer B, et al. JAMA Cardiol. 2020;5(8):952.
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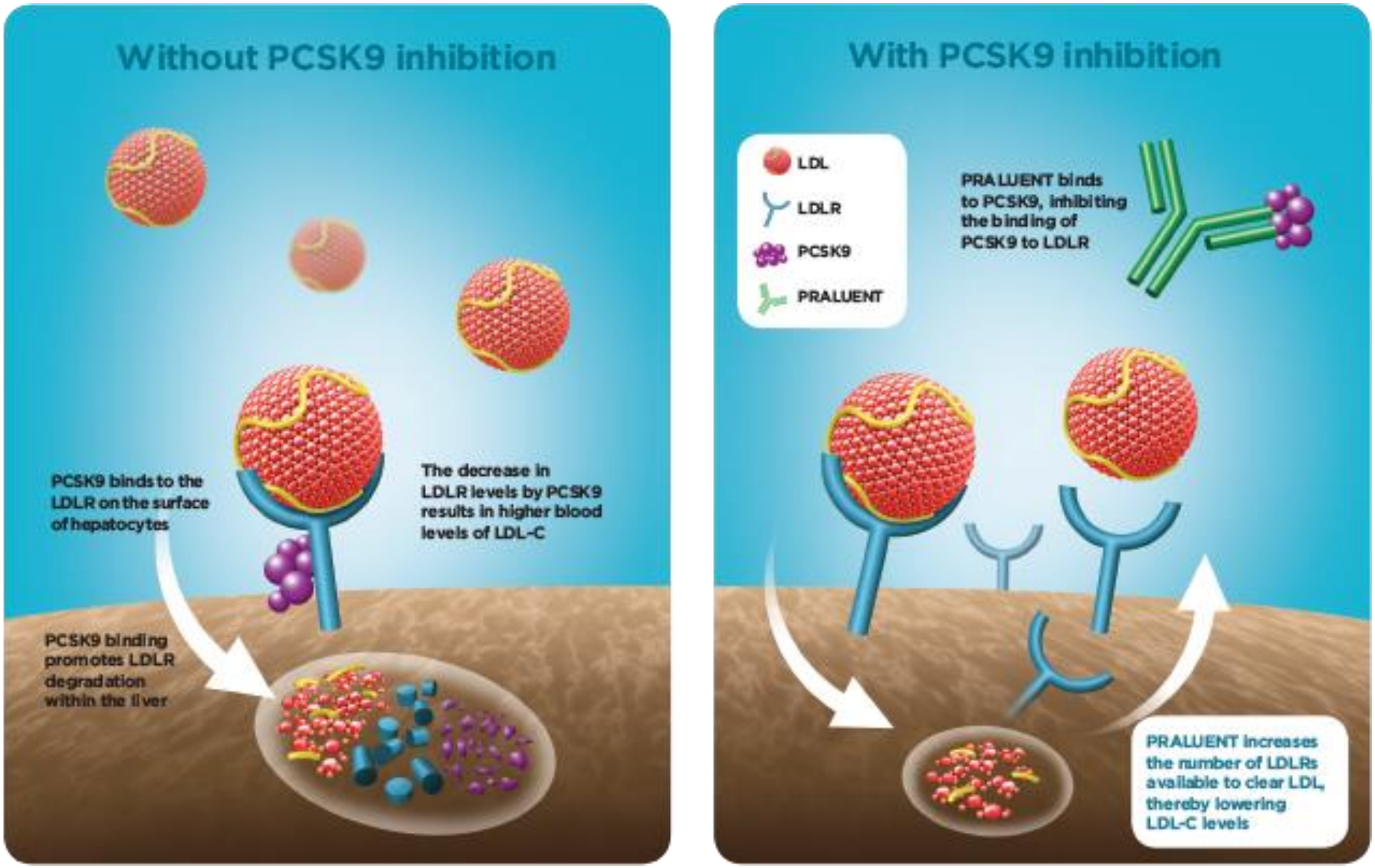
Schwartz GG, et al. N Engl J Med. 2018;379(22):2097-2107.



LDL-C = LDL Cholesterol
LDL-R = LDL Receptor

https://www.campus.sanofi/uk/science/dyslipidemia/curated-science/mechanism-of-action

PCSK9 Inhibitor Monoclonal Antibodies (PCSK9i mAbs)

Alirocumab (Praluent®):

- **Dose:** 75-150 mg SubQ injection every 2 weeks OR 300 mg SubQ injection every 4 weeks
- **Admin:** Available as pre-filled pen autoinjector

Evolocumab (Repatha®):

- **Dose:** 140 mg SubQ injection every 2 weeks OR 420 mg SubQ injection every 4 weeks
- **Admin:** Available as pre-filled pen autoinjector (140 mg dose), or body infuser (420 mg dose only)

Alirocumab. Lexicomp. Accessed Feb 2023.
Evolocumab. Lexicomp. Accessed Feb 2023.

PCSK9 Inhibitor Monoclonal Antibodies (PCSK9i mAbs)

Warnings/CIs: hypersensitivity to either agent, severe latex allergy (specific to evolocumab product).

- *Note that cross-reactivity data is limited between agents*

Adverse Reactions: injection site reaction(s), nasopharyngitis, cold/flu-like symptoms, upper-respiratory infection (URI), antibody development

Interactions: no clinically significant interactions reported

Long-Term Use: Per data FOURIER open-label extension trial (FOURIER-OLE, 2022) persistently low rates of ADEs were observed with >8 years of use of evolocumab.

Alirocumab. Lexicomp. Accessed Feb 2023.
Evolocumab. Lexicomp. Accessed Feb 2023.
O'Donoghue ML, et al. Circulation. 2022;146(15):1109-1119.

ANTILIPEMIC SMALL INTERFERING RNA (SIRNA) THERAPY

https://urldefense.com/v3/__https://www.pharmacytimes.com/view/daily-medication-pearl-inclisiran-leqvio-injection__;!!H8mHWRdzp34!5sbev5EaQjA1a9QCHhHJ3JH611BVqhmqJBklhK7LZojX5a4xsJEgs0k2k2J3ijrW6cYF3rZQIQS-K4oXQVD8ByCHumA$

siRNA Therapy – inclisiran (Leqvio®)

MOA: Small interfering Ribonucleic Acid (siRNA) that directs the breakdown of mRNA for Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)

FDA Approval: For patients on maximally tolerated statin therapy.

1. Established ASCVD
2. Familial Hypercholesterolemia

ORION-10 and ORION-11 RCTs: At Day 510, LDL-C reduced by 52.3 and 49.9% in their respective trials

CV Outcomes data not yet established.

Inclisiran. Lexicomp. Accessed Feb 2023. .
Ray KK et al. N Engl J Med. 2020;382(16):1507-1519.

siRNA Therapy – inclisiran (Leqvio®)

Dose: 284 mg SubQ injections at baseline and 3 months, then every 6 months thereafter.

- ***Note: in-clinic/alternate injection center administration by healthcare provider ONLY***

Warnings/CIs: pregnancy

Adverse Reactions: injection site reaction(s), antibody development, arthralgias, and bronchitis

Interactions: No known interactions

Inclisiran. Lexicomp. Accessed Feb 2023. .

COST, COVERAGE, & EMERGING USES FOR NOVEL LIPID LOWERING THERAPIES

Novel Lipid Lowering Therapy Cost

ATC Lyase Inhibitors

- Bempedoic acid = ~$475/month (AWP)

PCSK9 Inhibitors

- Alirocumab = ~$590/month (AWP)
- Evolocumab = ~$661/month (AWP)

siRNA Therapy

- Inclisiran = ~$7,898 (Year 1), then ~$5,265/year (AWP)

Alirocumab. Lexicomp. Accessed Feb 2023.
Bempedoic acid. Lexicomp. Feb 2023.
Evolocumab. Lexicomp. Accessed Feb 2023.
Inclisiran. Lexicomp. Accessed Feb 2023. .

ATC Lyase Inhibitor Coverage/Access

Commercial Insurance	Medicare	WI Medicaid
• Range of coverage from a "preferred" agent to "non-reimbursable" depending on plan • Manufacturer assistance available to obtain for $10/month*	• If covered by Medicare plan, likely requires a prior authorization to be completed • No manufacturer assistance available	• PA required for coverage • No manufacturer assistance available

**Terms and conditions apply for manufacturer assistance eligibility*

NEXSTEP Patient Support offers tools and resources. Accessed Feb 2023.

PCSK9 Inhibitor Coverage/Access

Commercial Insurance	Medicare	WI Medicaid
• More widely covered (with or without PA) depending on plan/coverage • Manufacturer assistance available to obtain for $25/month (alirocumab) or ~$5/month (evolocumab)*	• If covered by Medicare plan, likely requires a prior authorization to be completed • No manufacturer assistance available • Medicare plans likely preference either alirocumab OR evolocumab specifically	• PA required for coverage • No manufacturer assistance available

**Terms and conditions apply for manufacturer assistance eligibility*

Paying for Repatha. Last accessed Feb 28, 2023.
Starting & Paying for PRALUENT. Last accessed Feb 28, 2023.

siRNA Therapy Coverage/Access

1. Determine whether patient's prescription AND/OR medical benefits will cover in-clinic administered injectable.
    1. Commercial = variable among plans, possible manufacturer assistance available for $0/injection*
    2. Medicare = typically billed as Part B medical benefit (may vary by plan/coverage)
    3. WI Medicaid = must have tried PCSK9i therapy + maximal statin for ≥3 consecutive months without reaching LDL <70 mg/dL

2. Work with office/institution for accessibility to injection either as non-formulary order request OR administration via "buy-and-bill" supply

**Terms and conditions apply for manufacturer assistance eligibility*

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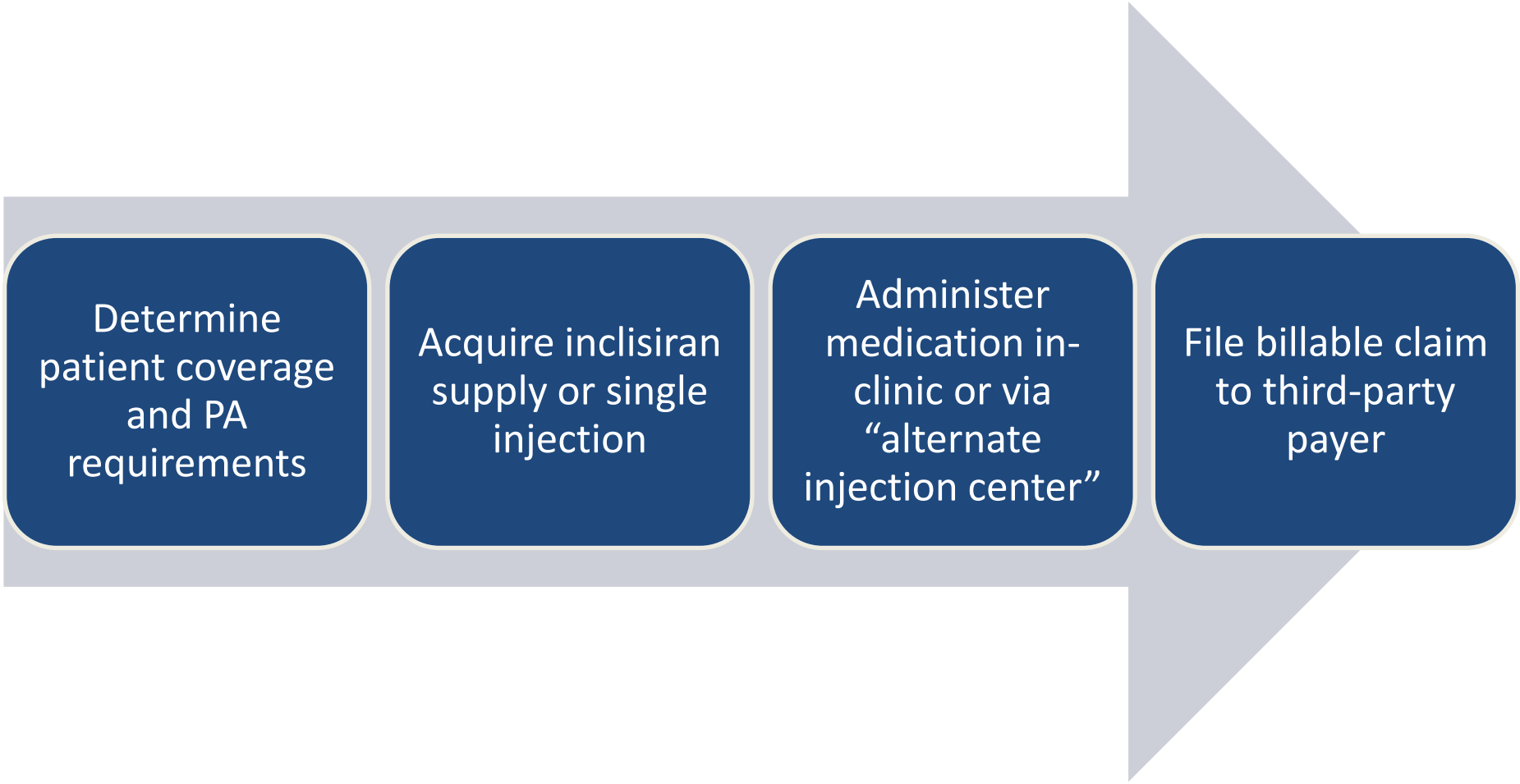
Leqvio (inclisiran) Patient Access Resources. Accessed Feb 2023.

siRNA Therapy Coverage/Access



Leqvio (inclisiran) Patient Access Resources. Accessed Feb 2023.

Novel Lipid Agents – Emerging Use

FOURIER Trial – Secondary Analysis (2020):

- Subgroup analysis based on MI occurrence (within 1-12 months vs >12 months)
  - Evaluate risk of the major adverse cardiovascular events (MACE) as a function of time from the date of the qualifying MI
  - Determine the effect of evolocumab on cardiovascular outcomes in patients with an MI within 12 months

HUYGENS – Coronary Plaque Changes & Evolocumab (2022):

- Determine the effect of evolocumab + high-intensity statin therapy on optical coherence tomography (OCT) measures of plaque composition
- Expansion of IBIS-4 findings (2019)

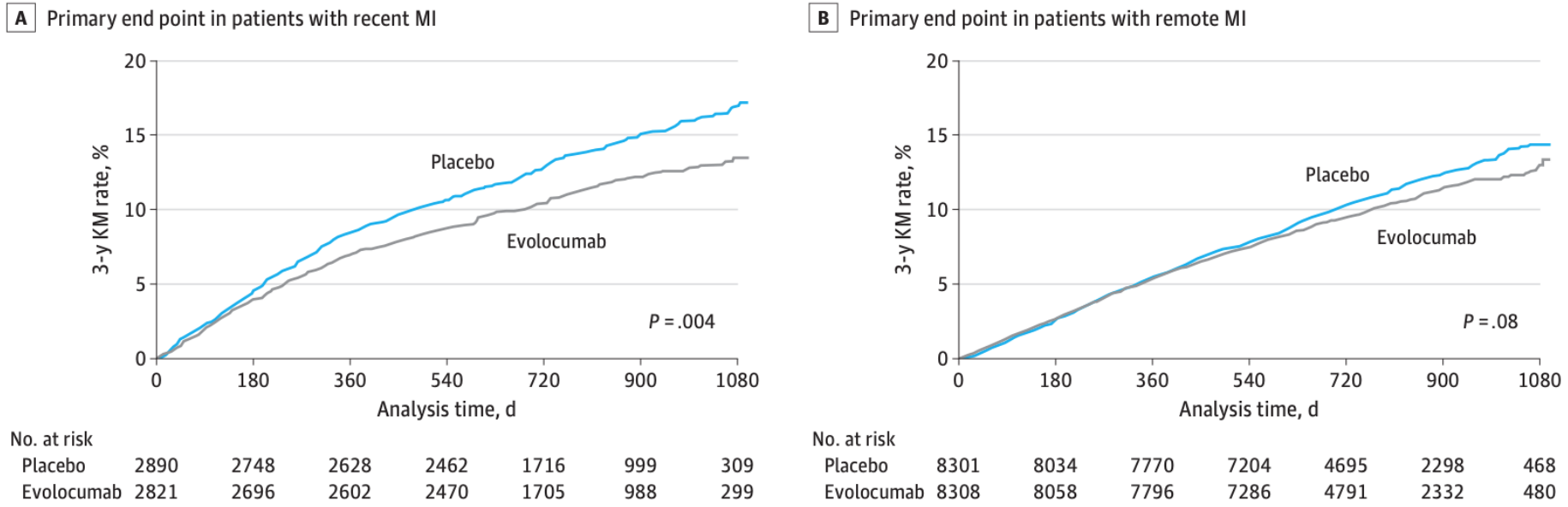
PERFECT II – Alirocumab Following post-PCI and STEMI:

- Phase 4, Open-label, on whether the early application of PCSK9 inhibitor can increase the myocardial salvage index (MSI) and improve ventricular remodeling in patients with STEMI
- Estimated completion in December 2024

Gencer B, et al. *JAMA Cardiol*. 2020;5(8):952.
Koskinas KC, et al. *JACC*. 2019;74(20):2452-2462.
Räber L, et al. *JACC: Cardiovascular Imaging*. 2019;12(8):1518-1528.
Xia J, et al. *Front Cardiovasc Med*. 2022;9:1009674.

FOURIER Trial – Secondary Analysis (2020):

Figure 2. Risks of the Primary and Key Secondary End Points in Patients With Recent and Remote Myocardial Infarction (MI) Randomized to Placebo vs Evolocumab



Participants with a recent MI (within 1-12 months of randomization):

- Higher risk of MACE
- Tended to experience greater risk reduction with evolocumab than those with more remote MIs.

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Gencer B, et al. *JAMA Cardiol*. 2020;5(8):952.

HUYGENS – Effect of Evolocumab on Coronary Plaque Phenotype and Burden in Statin-Treated Patients Following Myocardial Infarction (2022)

Goal: Assess whether PCSK9 inhibition + high-intensity statin therapy favorably modifies coronary plaque phenotype.

Findings:

- Vulnerable plaques can be stabilized in patients following an ACS at ~12 months
- Early implementation of the most effective lipid-lowering regimens following an ACS may be

TABLE 7 Intravascular Ultrasound Assessment of Plaque Burden

	Placebo (n = 39)[a]	Evolocumab (n = 40)[a]	*P* Value
Percent atheroma volume, %			
Baseline	45.1 ± 0.9	45.8 ± 0.9	0.56
Follow-up	43.9 ± 0.9	43.1 ± 1.1	0.009
LS mean change	−0.61 ± 0.46	−2.29 ± 0.47	0.009
Percent regressors	56.4	77.5	0.04
Total atheroma volume, mm^3			
Baseline	244.7 ± 10.6	244.3 ± 12.1	0.97
Follow-up	240.0 ± 11.4	204.1 ± 13.1	0.04
LS mean change	−8.9 ± 3.5	−19.0 ± 3.7	0.04
Percent regressors	66.7	80.0	0.18

Values are mean ± SE. Measures of plaque burden measured by intravascular ultrasound. [a]Number of subjects with observed data at both baseline and follow-up.

Koskinas KC, et al. *JACC*. 2019;74(20):2452-2462.

Summary Slide

- Novel agent mechanisms which indirectly increase LDL-receptor expression on hepatocytes via effects on PCSK9 have been a significant development in lipid lowering therapeutics and reduction of MACE's based on available data
- There is a place for use of novel lipid lowering therapies for patients with established clinical ASCVD and/or familial hypercholesterolemia (FH)
- Significant cost, coverage, and access barriers exist for novel lipid lowering agents but can be navigated with assistance from healthcare professionals

Assessment Question #1

Which of the following medication(s) acts to lower LDL by impacting the activity of the PCSK9 enzyme? (Select All That Apply)

a) Bempedoic acid
b) Evolocumab
c) Alirocumab
d) Inclisiran

Assessment Question #2

Which of the following is a common limitation to starting inclisiran therapy for patients with high cholesterol and a history of clinical ASCVD?

a) High out-of-pocket costs for the patient
b) Low efficacy of inclisiran in the management lipid disorders
c) Limited supply and availability for providers to administer
d) Lack of patient education regarding potential benefits of inclisiran therapy

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QUESTIONS?

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