Don't Miss a Beat! Outpatient Cardiovascular Update

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Disclosure Statement

- Sarah Aldrich Renner and Marilee Clemons have no relevant financial relationship(s) with ineligible companies to disclose.

  and

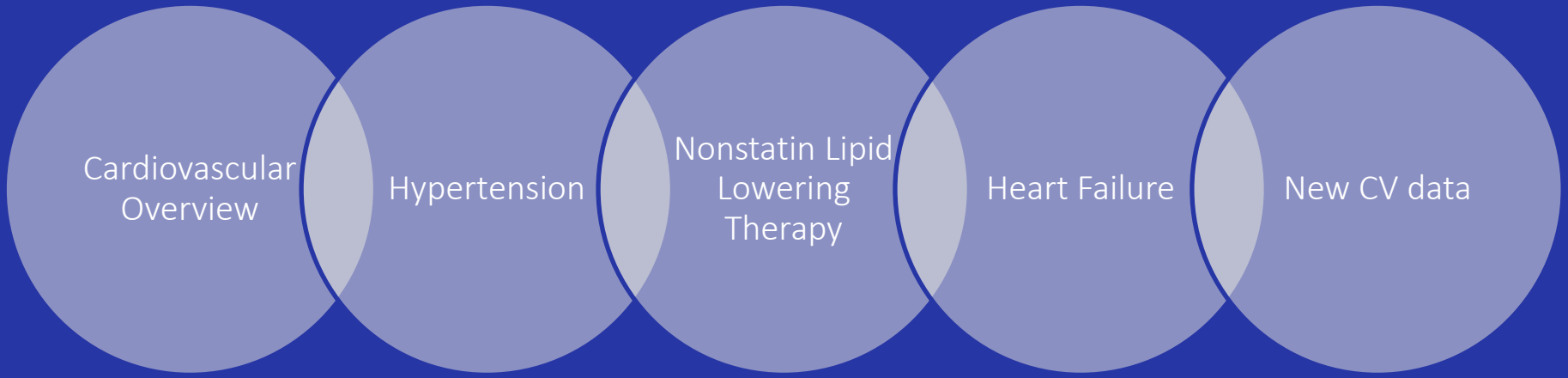
- None of the planners for this activity have relevant financial relationships with ineligible companies to disclose.

Learning Objectives

At the completion of this activity, the participant will be able to:

1. Discuss the consequences of cardiovascular disease as it relates to other comorbidities
2. Summarize pharmacotherapeutic approaches to improve morbidity and mortality in outpatients with cardiovascular disease or who are at high risk of cardiovascular disease
3. Discuss important outpatient clinical perspectives related to medications used to treat those with known cardiovascular disease or those at high risk of cardiovascular disease

Today's Topics



Abbreviations

AAFP	American Academy of Family Physicians	CKD	Chronic kidney disease
ACEi	Angiotensin-converting enzyme inhibitor	CV	Cardiovascular
ACC	American College of Cardiology	CVD	Cardiovascular disease
ACP	American College of Physicians	DKD	Diabetic kidney disease
ACS	Acute coronary syndrome	DM	Diabetes Mellitus
AHA	American Heart Association	DPP-4i	Dipeptidyl peptidase-4 inhibitor
ARB	Angiotensin II receptor blocker	EF	Ejection fraction
ARNI	Angiotensin receptor-neprilysin inhibitor	eGFR	Estimated glomerular filtration rate
ASCVD	Atherosclerotic cardiovascular disease	ESC	European Society of Cardiology
BA	Bempedoic acid	ESH	European Society of Hypertension
BID	Twice daily	GDMT	Guideline-directed medical therapy
BMP	Basic metabolic panel	HF	Heart failure
bpm	Beats per minute	HFH	Heart failure hospitalization
BUN	Blood urea nitrogen	HLD	Hyperlipidemia
BP	Blood pressure	HR	Heart rate
BPH	Benign prostatic hyperplasia	HTN	Hypertension
CCB	Calcium-channel blocker	ISA	International Society of Hypertension

Abbreviations

K+	Potassium	PDE-5i	Phosphodiesterase-5 inhibitors
KDIGO	Kidney Disease Improving Global Outcomes	PMH	Past medical history
HR	Heart rate	QID	Four times daily
HTN	Hypertension	RAASi	Renin-angiotensin-aldosterone-system
LDL	Low density lipoprotein	SCr	Serum creatinine
LVEF	Left ventricular ejection fraction	SGLT2i	Sodium-cotransporter-2 inhibitor
Mg	Magnesium	SR	Sustained release
MI	Myocardial infarction	T2DM	Type 2 diabetes mellitus
MRA	Mineralocorticoid receptor antagonist	TIA	Transient ischemic attack
NNT	Number needed to treat	TID	Three times daily
NYHA	New York Heart Association	WNL	Within normal limits
PCSK9 i	Proprotein convertase subtilisin/kexin type 9 inhibitor		

CARDIOVASCULAR DISEASE OVERVIEW

Cardiovascular Disease Overview

- Cardiovascular disease is the leading cause of death in US
- Accounted for >600,000 deaths in 2021
- General term that refers to a disease of the heart or blood vessels
- Encompasses many conditions:

Heart failure	Stroke	Myocardial infarction	Arrhythmias

National center for health statistics. 2022. Cdc.gov.
NCCDPHP. 2020. Cdc.gov.

ACC/AHA Guidelines for Primary Prevention of CV Disease 2019

Nonpharmacologic highlights:

Healthy lifestyle

Healthy diet

- Minimize trans fats, red meats, refined carbohydrates and sweetened beverages
- Weight loss recommended if overweight

Exercise

- 150 min per week of moderate-intensity physical activity

Team based care

Social determinants of health

Tobacco cessation

Arnett et al. Circulation. 2019;140(11).

ACC/AHA Guidelines for Primary Prevention of CV Disease 2019

Pharmacological Highlights:

Utilize 10-year ASCVD Risk Estimator+

Statin therapy is first-line treatment for primary prevention of ASCVD

Aspirin should be used infrequently in routine ASCVD primary prevention

Diabetes:

- Lifestyle improvements
- Metformin is first line followed by SGLT2i or GLP-1 RA
- SGLT2i may be preferred in patients with T2DM + CKD

HTN:

- Lifestyle improvements
- Target blood pressure generally <130/80

Arnett et al. Circulation. 2019;140(11).

Aspirin for Primary Prevention

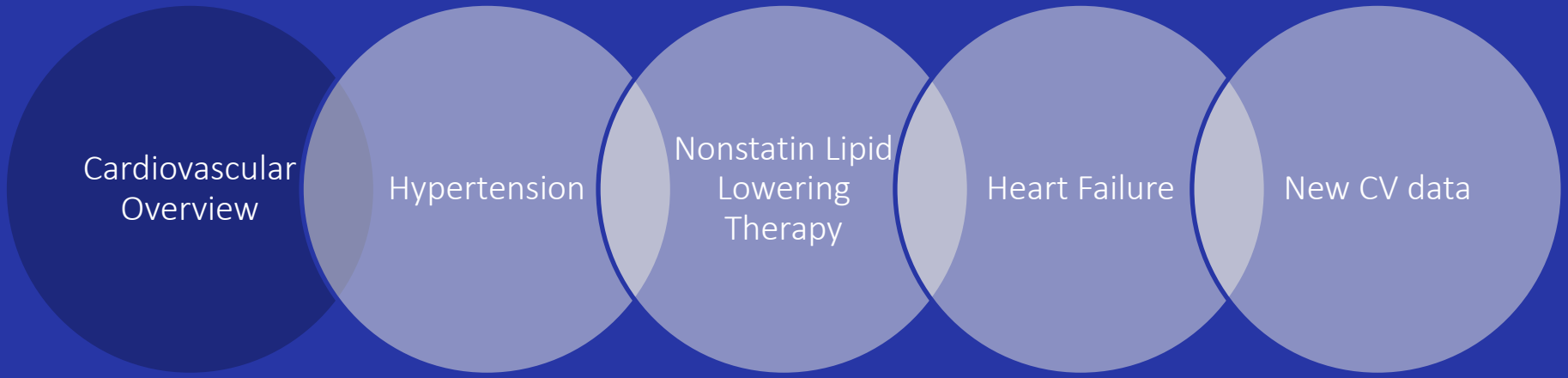
Population	Recommendation
Adults 40-59 years with ASCVD risk ≥10%	Individual review of risk vs benefit. Net benefit small. Patients not at increased risk of bleeding and are willing to take aspirin are more likely to benefit
Adults ≥60 years	Not recommended for initiation
Adults ≥75 years	Consider stopping aspirin

Aspirin use. USPSTF. 2022.

CVD Overview Takeaways

- CVD is leading cause of death in US
- Treatment of many chronic diseases prevents and reduces the risk of CVD
- Aspirin use for primary prevention benefit may not outweigh risks in patients with low ASCVD risk

Today's Topics



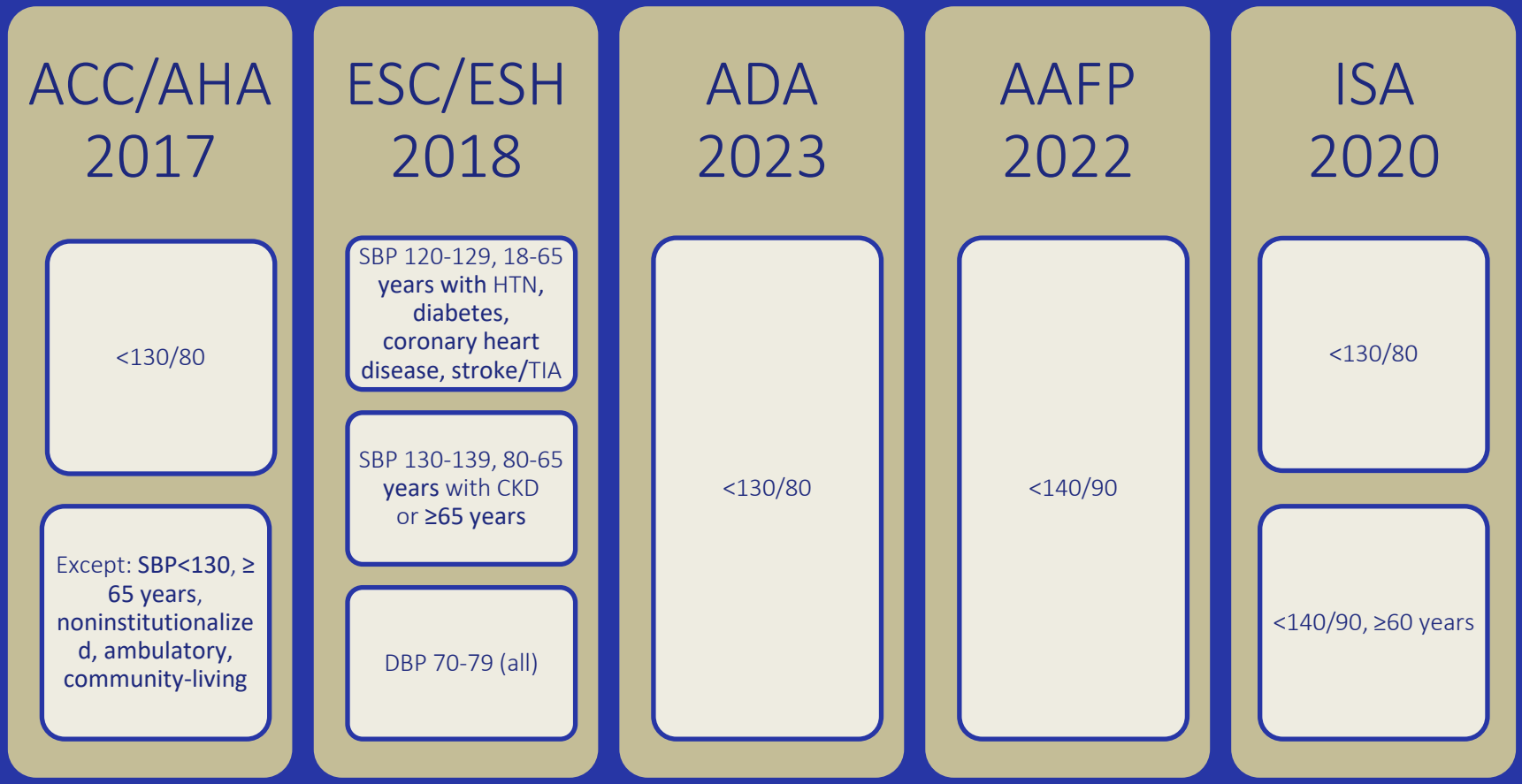
HYPERTENSION

Hypertension Background

- Elevated BP defined as SBP >120 mmHg and diastolic blood pressure >80 mmHg
- Cardiovascular morbidity and mortality are directly correlated with BP
- Goal of treatment is to reduce morbidity and mortality from CV events

MacLaughlin, et al. Pharmacotherapy. 2020.

Blood Pressure Goals



*Not an all-inclusive list of guidelines
*Units for all=mmHg

Welton, et al. ACC/AHA. 2018.
ElSayed, et al. Diabetes Care. 2022.
Coles, et al. AAFP. 2023.

Blood Pressure Goals in Older Adults

- Targeting a blood pressure <130/80 in older adults is often controversial
- Guideline recommendations vary for patients ≥ 60 years

Welton, et al. ACC/AHA. 2018.
Coles, et al. AAFP. 2023.
Chui, et al. Hypertension. 2023.

Blood Pressure Goals in Older Adults

Trial	Inclusion	Take Away
SPRINT (2015)	Patients ≥ 50 years with SBP>130 with HTN (without DM)	Reduction in CV events and death from any cause in treatment to SBP target <120 compared to <140
SPRINT-75 (subgroup analysis of SPRINT) (2016)	Patients ≥75 years with HTN (without DM)	Reductions in CV events and overall mortality with SBP target <120 compared to SBP target <140
SPRINT-80 (secondary analysis of SPRINT) (2019)	Patients ≥80 years with HTN (without DM)	Reduction in CV events with SBP target <120 compared to SBP target <140
HYVET (2008)	Patients ≥80 years with HTN	Reductions in stroke and heart failure with active treatment to target <150 compared to placebo
STEP (2021)	Patients 60-80 years	Reduction in CV events with SBP target 110 to <130 compared to SBP target 130 to <150

Chui, et al. Hypertension. 2023.
Pajewski. J Am Geriatr Soc.2020.
Juraschek, et al. Hypertension. 2020.

Hypertension Treatment

- Lifestyle changes
  - Reduce dietary sodium, alcohol and caffeine
  - Increase exercise
- 3 First-Line Classes of Medications:

ACEi or ARB	dihydropyridine CCB	thiazide diuretics

- Additional pharmacotherapy determined using compelling indications and comorbid conditions

Welton, et al. ACC/AHA. 2018.

Comparison of Chlorthalidone vs HCTZ for CV events

- 13,523 randomized VA patients, 65-years+ who were receiving HCTZ 25 mg or 50 mg/day for HTN
- Intervention
  - Group 1 continued HCTZ 25 mg or 50 mg daily
  - Group 2 switched to chlorthalidone 12.5 mg or 25 mg daily
- Results (avg follow-up 2.4 years)
  - Primary outcome: Composite of nonfatal CV disease event or non-cancer related death
    - Group 1 10.4% vs. Group 2 10.0% [HR 1.04 (0.94-1.16)]
  - Safety outcomes: Hypokalemia
    - Group 1 6.0% vs. Group 2 4.4% [HR 1.38 (1.19-1.60)]

95% pts remained on starting dose

Takeaway: Chlorthalidone (at starting doses) did not result in lower incidence of major cardiovascular outcomes or non-cancer related deaths

Ishani, et al. NEJM. 2022.

Patient Case #1

CJ is an 80-year-old white male seen for a BP check. PMH includes HTN, BPH, HLD, and stroke (2020).

Current medications include atorvastatin 40 mg daily, aspirin 81 mg daily, lisinopril 40 mg daily, amlodipine 10 mg daily, and carvedilol 25 mg BID. NKDA.

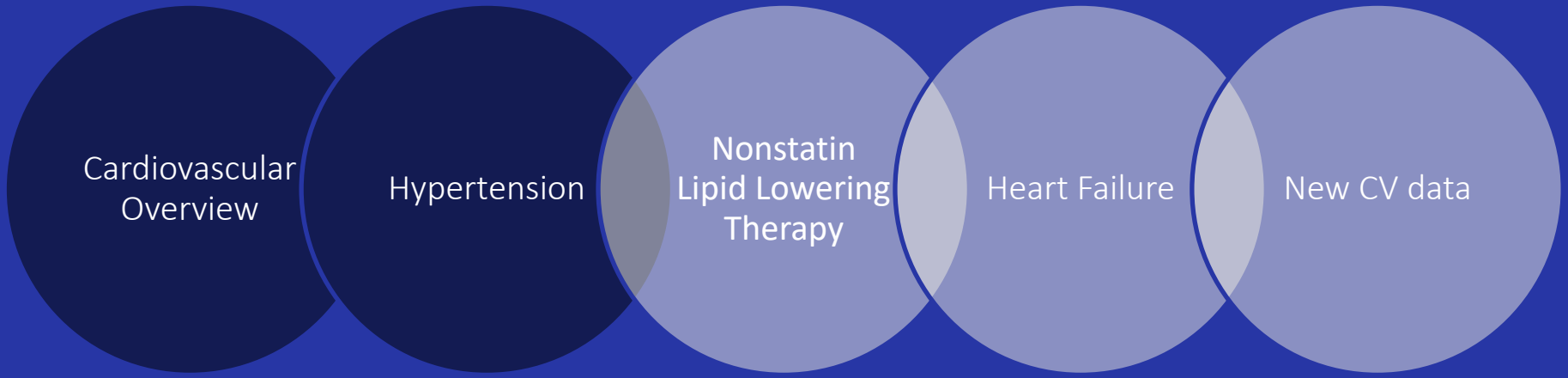
Labs + Vitals: BP 146/84, HR 60, SCr 1.1, eGFR 56, K+ 4.0

1. What is this patient's blood pressure goal?
    a) Do you need any additional information?
2. What risks are associated with uncontrolled blood pressure?
3. What medication changes are appropriate?
4. What monitoring would you recommend?

Hypertension Takeaways

- HTN guidelines remain variable but BP <130/80 is appropriate for most patients, even in older adults
  - Increasing evidence supporting lower BP goals in patients ≥ 60 years old
- Consider patient specific factors, including CV risk, life expectancy, and comorbidities when determining a BP goal

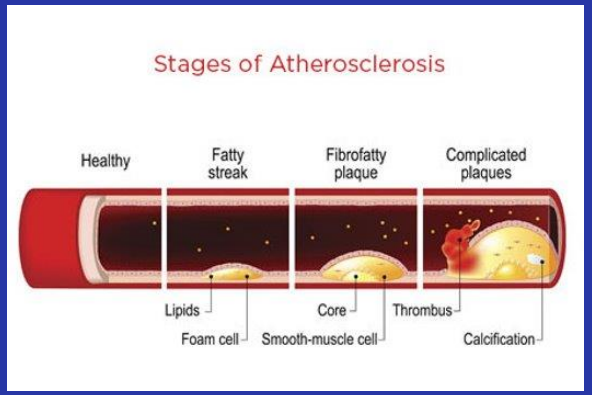
Today's Topics



NONSTATIN LIPID LOWERING THERAPY

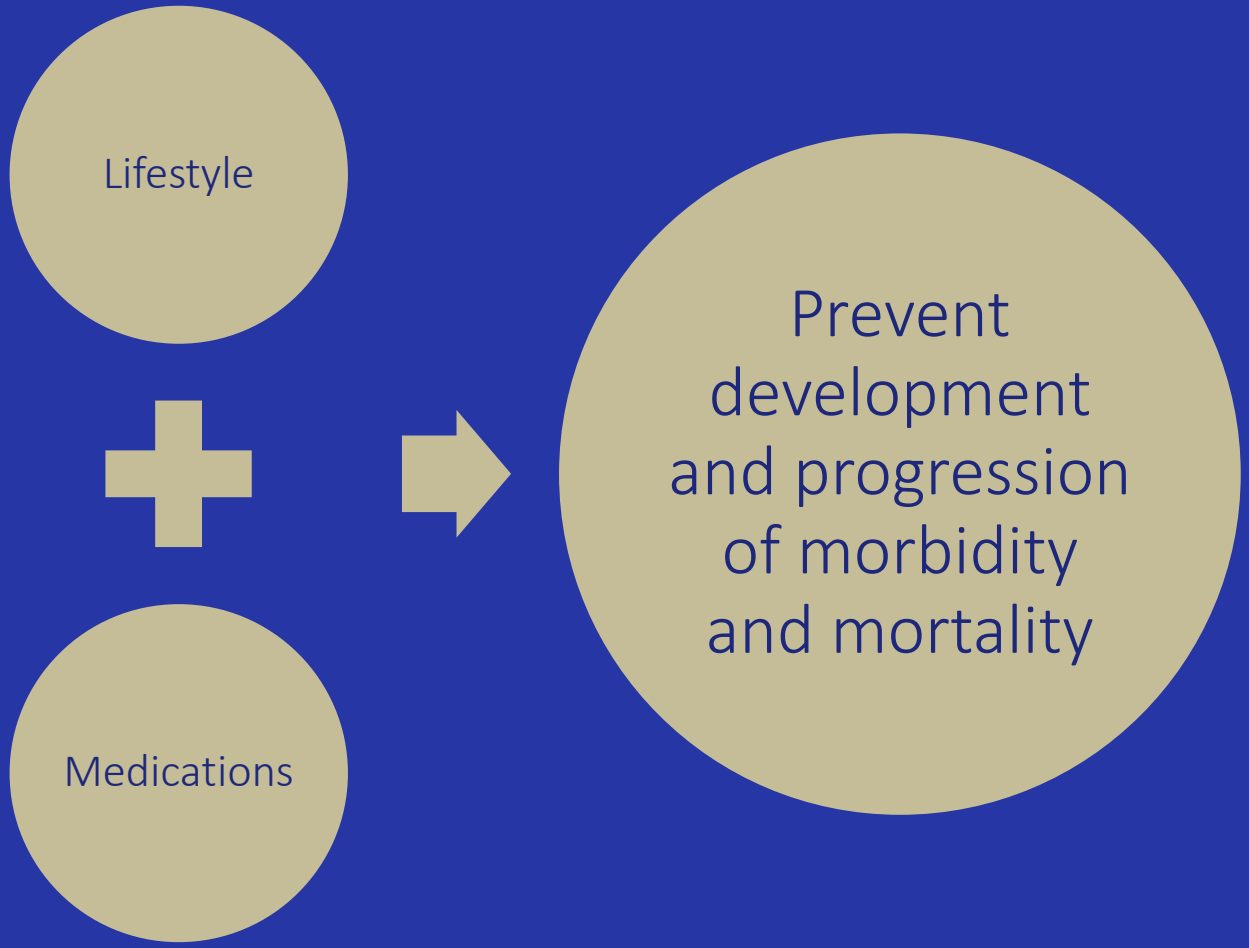
Background

- "Hyperlipidemia" refers to multiple disorders of high levels of circulating fats
- High level of low-density lipoprotein (LDL) is most extensively studied and causal risk factor in atherosclerotic disease leading to CV mortality and morbidity
- General goal is reducing LDL to minimize CV risk



Dipiro, et al. Pharmacotherapy. 2023

Lipid Management



Dipiro, et al. Pharmacotherapy. 2023

Medications

- Statins
- Ezetimibe
- PCSK9i
- Bempedoic acid
- Inclisiran

Dipiro, et al. Pharmacotherapy. 2023

HMG-CoA Reductase Inhibitors

Drug names	MOA	LDL Lowering	Clinical Impact	Cost
atorvastatin rosuvastatin pravastatin simvastatin	Blocks conversion of HMG-CoA to melavonate interrupting cholesterol biosynthesis	High intensity: >50% Moderate intensity: 30-50% Low intensity: ~30%	Reduce risk of CV event (1st and recurrent)	$

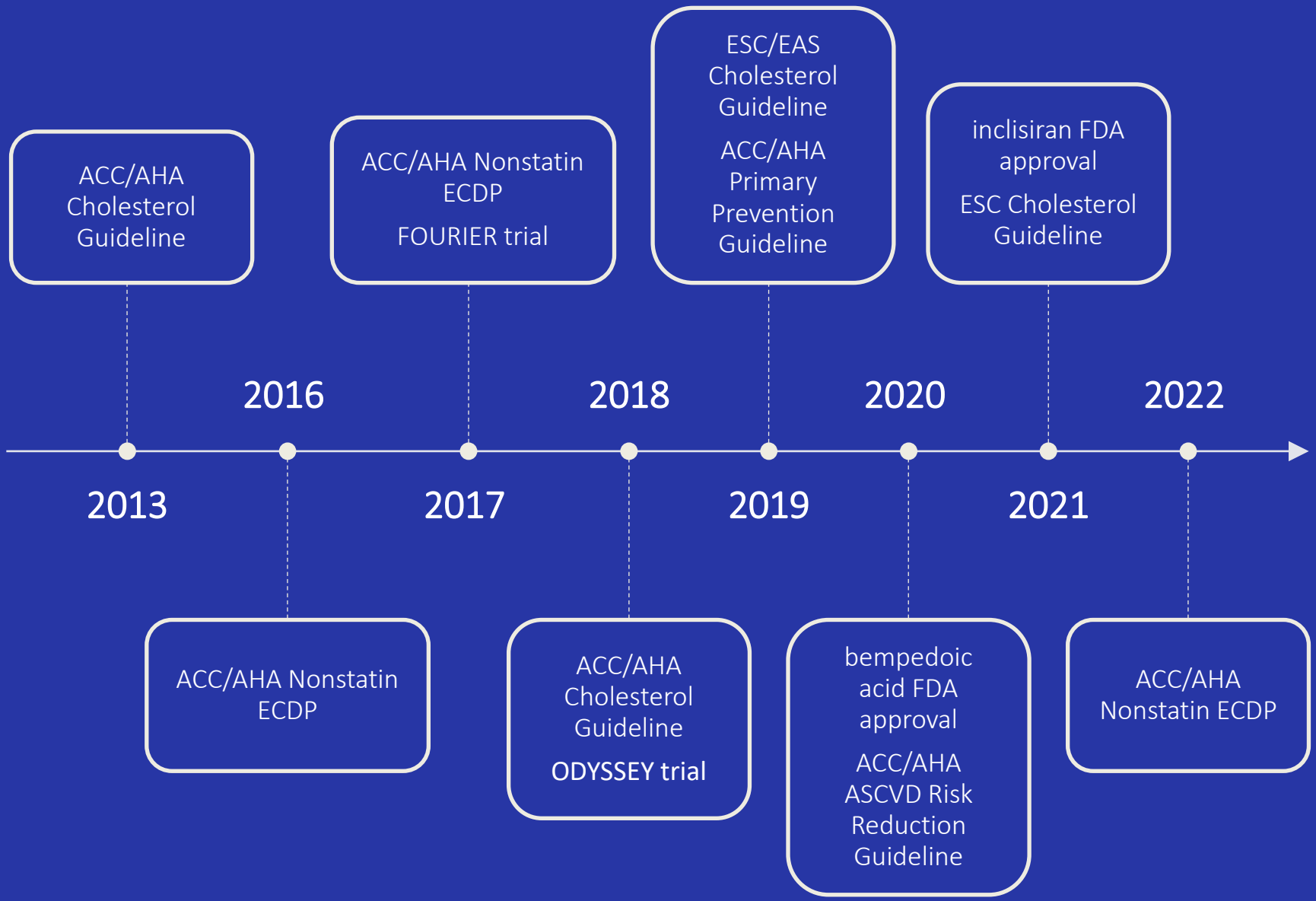
Cholesterol Absorption Inhibitor

Drug name	MOA	LDL Lowering	Clinical Impact	Cost
ezetimibe	Inhibits cholesterol absorption in small intestine & hepatocytes	15-24%	Modest CV risk reduction in secondary prevention	$

Dipiro, et al. Pharmacotherapy. 2023

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors				
Drug names	**MOA**	**LDL Lowering**	**Clinical Impact**	**Cost**
alirocumab evolocumab	Inhibits PCSK9, increasing LDL receptors on cell membrane and clearance of LDL	~70%	CV risk reduction in high risk patients and those with ASCVD	$$$$
ATP Citrate Lyase (ACL) Inhibitor)				
Drug name	**MOA**	**LDL Lowering**	**Clinical Impact**	**Cost**
bempedoic acid	ACL "upstream" of HMG-CoA reductase in cholesterol biosynthesis pathway	~20%	CV risk reduction in high risk patients and those with ASCVD	$$$
RNA Inhibitor of PCSK9				
Drug name	**MOA**	**LDL Lowering**	**Clinical Impact**	**Cost**
inclisiran	Inhibits production of PCSK9	~52%	TBD	$$$$

Dipiro, et al. Pharmacotherapy. 2023



ECDP = Expert Consensus Decision Pathway

2022 ACC ECDP Nonstatin Highlights

Reviews place in therapy for nonstatin options prior to completion of CV trials

Emphasis on specific and lower LDL targets

PCSK9 mABs are first line nonstatin therapy in some high risk groups

Lloyd-Jones, et al. J Am Coll Cardio. 2022

Four Patient Management Groups

Primary Prevention	Secondary Prevention
• Adults with LDL ≥ 190 mg/dL • Adults with diabetes • Adults without diabetes	• Adults with clinical ASCVD

Lloyd-Jones, et al. J Am Coll Cardio. 2022

LDL goals

Primary Prevention

- Reduce LDL 30 - ≥ 50%
- Goal LDL < 70 or 100 mg/dL

Secondary Prevention

- Reduce LDL ≥ 50%
- Goal LDL < 55* or 70 mg/dL

***FOURIER and ODYSSEY trial showed less CV events in lower LDL goals, specifically in "very high risk ASCVD"**

- **Multiple ASCVD events**
- **1 ASCVD event + multiple high risk conditions**

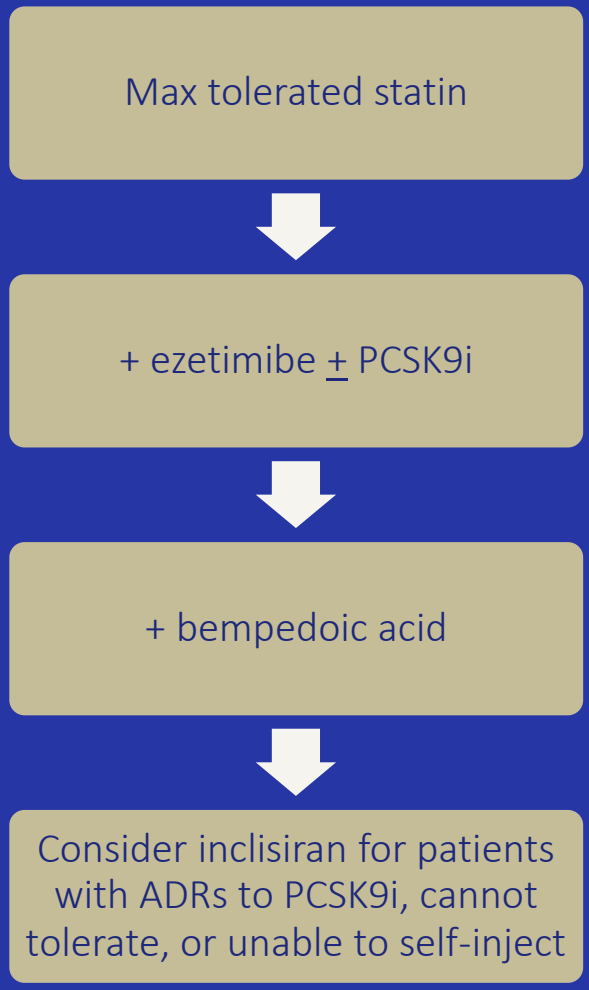
Focus on targeting LDL goal vs. % reduction of LDL

Lloyd-Jones, et al. J Am Coll Cardio. 2022

General Pathway for Nonstatin Therapies

FACTORS TO CONSIDER

- Adherence to medication
- Lifestyle changes
- Risk enhancing factors
- Magnitude of LDL lowering needed
- Cost
- Potential benefit
- Risk of harm
- Patient preference



Lloyd-Jones, et al. J Am Coll Cardio. 2022

CLEAR-outcomes Trial (2023)

- 13,970 patients; statin intolerant; high risk or established ASCVD
  - Age 18 – 85, unable to tolerate ≥ 2 statins, unwilling to try second statin, LDL ≤ 100 mg/dL
- Intervention
  - Group 1 received bempedoic acid (BA) 180mg once daily
  - Group 2 received placebo once daily
- Results (avg follow up of 40.6 months)
  - Primary endpoint (4-point MACE):
    - Group 1 11.7% vs. Group 2 13.3% (p=0.004)
  - Secondary outcomes (BA vs. Placebo)
    - 3-point MACE: 8.2 vs. 9.5% (p=0.006)
    - Change in LDL at 6 months: -21.1 mg/dL vs. -0.8mg/dL (p< 0.06)

Takeaway: BA reduces risk of major CV events and LDL in statin intolerant patients with high risk ASCVD or established ASCVD

Nissen, et al. NEJM. 2023.

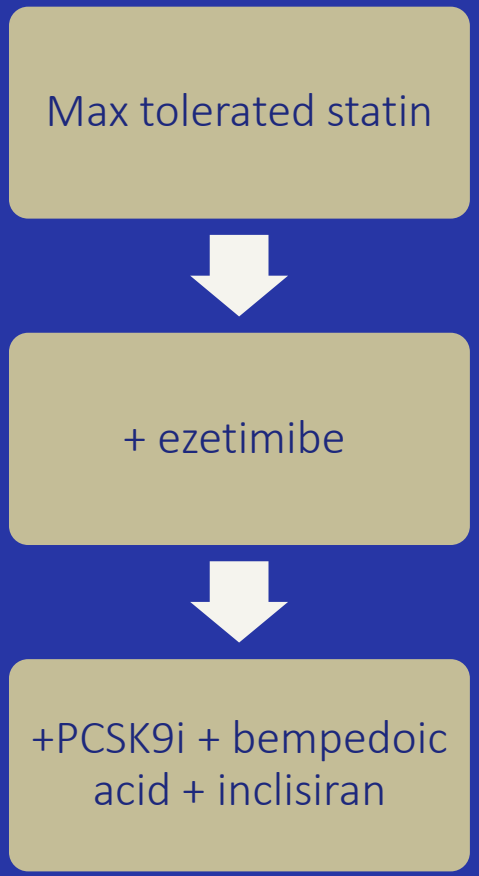
Primary Prevention Highlights

CONSIDERATIONS

- Therapy initiation and goals based on ASCVD risk, DM status, baseline LDL, coronary artery calcium score
- PCSK9, bempedoic acid, inclisiran only recommended if baseline LDL ≥ 190 mg/dL OR genetic component (HeFH or HoFH)
- Focus on achieving LDL goal vs. % reduction from baseline

LDL goal
- ≤ 70 or ≤ 100 mg/dL

LDL % reduction goal
- 30 – ≥ 50% baseline



Lloyd-Jones. J Am Coll Cardio. 2022

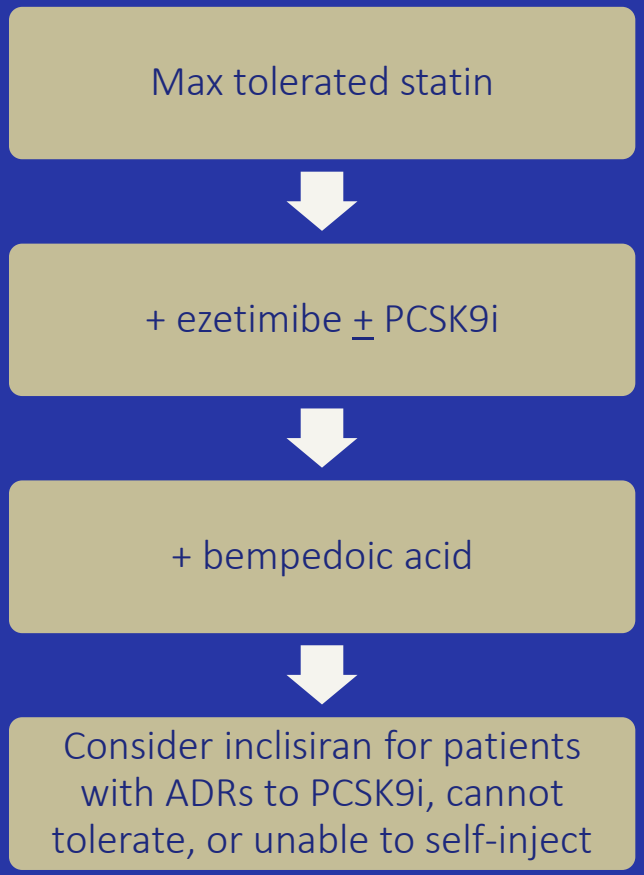
Secondary Prevention Highlights

CONSIDERATIONS

- Therapy initiation and goals based on risk* of recurrent event and baseline LDL
- Can initiate ezetimibe + PCSK9i in high-risk patients or LDL ≥ 190 mg/dL
- Focus on achieving LDL goal vs. % reduction from baseline

LDL goal
- ≤ 55** or ≤ 70 mg/dL

LDL % reduction goal
- ≥ 50% baseline



*Very high risk = Hx of multiple ASCVD events OR 1 major ASCVD event + multiple high-risk conditions
** Lower LDL goal in very high-risk patients

Lloyd-Jones, et al. J Am Coll Cardio. 2022

Special Populations

- Age 20 – 39: Risk vs. benefit
  - Primary prevention: lifestyle changes + consider statin with DM specific risk factors*
  - Secondary prevention: Statin/follow secondary prevention pathway
- Age > 75:
  - Primary prevention: Consider continuing statin if well tolerated
  - Secondary prevention: Continue statin

*Duration of DM, CKD, UACR ≥ 30, retinopathy, neuropathy, ABI < 0.9

Lloyd-Jones, et al. J Am Coll Cardio. 2022

Pharmacotherapy Considerations

- Cost/Access
  - Statins, ezetimibe are less expensive
  - PCSK9i, bempedoic acid, inclisiran are newer agents $$$$
    - Savings programs available
- Prescribers may not be well versed in updated guidelines
  - Key role of pharmacist to educate team
- 2022 ACC ECDP discuss referral to "lipid specialist"
  - Virtual visits may be available for rural areas

Lloyd-Jones, et al. J Am Coll Cardio. 2022

Nonstatin Therapy Takeaways

- Goal is to target specific and lower LDL levels
- Continue to maximize patients to highest tolerated statin
- Utilize ezetimibe ± PCSK9i as second line options depending on risk/ASCVD status

Lloyd-Jones, et al. J Am Coll Cardio. 2022

Patient Case #2

DC is a 63-year-old white male seen for lipid management. PMH includes CABGx3 (2018), MI (2018), HTN and T2DM.

Current medications include lisinopril 40 mg daily, aspirin 81 mg daily, rosuvastatin 40 mg daily, metformin 1000 mg BID, empagliflozin 25 mg daily, dulaglutide 4.5 mg weekly. NKDA.

Labs + Vitals: BP 118/72, HR 78, FLP: TC 190, HDL 40, LDL 121, TG 145, A1c 6.9%, CMP WNL

Patient confirms adherence to current medications.

1. What is this patient's LDL goal?
2. In addition to lifestyle management, what are feasible pharmacotherapy options for him?

HEART FAILURE

Heart Failure Background

- Chronic and progressive clinical syndrome resulting from changes in cardiac structure or function
  - Changes impair ventricular ability to fill or eject blood
  - Confirmed elevated natriuretic peptide levels or evidence of pulmonary or systemic congestion
- Abnormalities may be in systolic function (decreased contractility), diastolic function (restriction in ventricular filling) or both
- Leading causes of heart failure are hypertension and coronary artery disease

Schwinghammer, et al. Pharmacotherapy Handbook. 2021.

Heart Failure Symptoms

Volume Overload	Reduced Perfusion	Other
• Shortness of breath, orthopnea • Weight gain • Lower extremity edema, bloating • Anorexia	• Fatigue • Weakness	• Mood disturbances • Poor sleep

Givertz, et al. Harrison's. 2022.

Heart Failure Staging and Classification

AHA/ACC Heart Failure Stages		NYHA Functional Class	
A	At risk for HF but without current or previous sign/symptoms and without structural changes or biomarkers	n/a	
B	Pre-HF: Without current or previous signs/symptoms but 1 of the following: Structural heart disease, increased filling pressures, risk factors and abnormal biomarkers	I	No limitation of physical activity. Ordinary activity does not cause fatigue, palpitation, dyspnea.
C	With current or previous signs/symptoms	II	Slight limitation of physical activity. Comfortable at rest. Ordinary activity results in fatigue, palpitation, dyspnea.
		III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity results in fatigue, palpitation, dyspnea.
D	Marked symptoms that interfere with activities of daily living and with recurrent hospitalizations despite GDMT	IV	Unable to complete any physical activity without discomfort. Symptoms at rest. Discomfort increases with any physical activity.

Givertz, et al. Harrison's. 2022.
Heidenreich, et al. Circulation. 2022.

Heart Failure Based on Ejection Fraction

Type of HF	Criteria	Comments
HFrEF (HF with reduced EF)	LVEF ≤ 40%	Previously systolic dysfunction
HFimpEF (HF with improved EF)	Previous LVEF ≤ 40% and follow-up LVEF >40%	
HFmrEF (HF with mildly reduced EF)	LVEF 41%-49% Evidence of increased left ventricular filling pressures	
HFpEF (HF with preserved EF)	LVEF ≥ 50% Evidence of increased left ventricular filling pressures	Previously diastolic dysfunction

*Adapted from Table 4 AHA/ACC/HFSA Guideline for the Management of HF

Heidenreich, et al. Circulation. 2022.

2022 Heart Failure Guideline Updates

2022 AHA/ACC/HFSA GUIDELINE FOR THE MANAGEMENT OF HEART FAILURE: A REPORT OF THE AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION JOINT COMMITTEE ON CLINICAL PRACTICE GUIDELINES

ACC/AHA Class of Recommendations and Level of Evidence (Updated May 2019)

Class (Strength of Recommendation) (COR)		Level (Quality of Evidence) (QOL)	
Class 1 (Strong)	Benefit >>>Risk	Level A	High-quality evidence from more than 1 RCT Meta-analyses of high-quality RCTs One or more RCTs corroborated by high-quality registry studies
Class 2a (Moderate)	Benefit>>Risk	Level B-R (randomized)	Moderate-quality evidence from 1 or more RCT Meta-analyses of moderate-quality RCTs
Class 2b (Weak)	Benefit≥Risk	Level B-NR (nonrandomized)	Moderate quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies or registry studies Meta-analyses of such studies
Class 3: No Benefit (Moderate)	Benefit=Risk	Level C-LD (limited data)	Randomized or non-randomized observational or registry studies with limitations of design or execution Meta-analyses of such studies Physiological or mechanistic studies in human subjects
Class 3: Harm (Strong)	Risk>Benefit	Level C-EO (expert opinion)	Consensus of expert opinion based on clinical experience

Heidenreich, et al. Circulation. 2022.

HEART FAILURE PHARMACOTHERAPY

RAAS Inhibitors

- Reduction in **morbidity and mortality** in HFrEF
- ARNI > ACEi > ARB in patients with HFrEF and NYHA Class II-III symptoms
- Do not use with history of angioedema
- Monitoring: BP, K+, BUN, and SCr 10-14 days after initiation or dose changes
- NNT for all-cause mortality at 36 months is 26 for ACEi/ARBs, 27 for ARNI
  - NNT increases over time

Medication	Initial Daily Dose	Target Daily Dose
ACEi		
Enalapril	2.5 mg twice daily	10-20 mg twice daily
Lisinopril	2.5-5 mg once daily	20-40 mg once daily
ARB		
Candesartan	4-8 mg once daily	32 mg once daily
Losartan	25-50 mg once daily	50-150 mg once daily
Valsartan	20-40 mg once daily	160 mg twice daily
ARNI		
Sacubitril/ valsartan	24/26 mg or 49/51 mg twice daily	97-103 mg twice daily
*Do not use ARNI within 36 hours of ACEi		

Heidenreich, et al. Circulation. 2022.
Lisi. US Pharmacist. 2023.

Beta Blockers

- Reduction in risk of **morbidity and mortality**, improvement in LVEF and improvement in symptoms in HFrEF
- Monitoring: HR and BP
- NNT for all-cause mortality at 12 months is 28

Medication	Initial Daily Dose	Target Daily Dose
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	20-50 mg twice daily
Metoprolol Succinate ER	12.5-25 mg once daily	200 mg once daily

Heidenreich, et al. Circulation. 2022.
Lisi. US Pharmacist. 2023.

Mineralocorticoid Receptor Antagonists

- Reduction in **morbidity and mortality** and sudden cardiac death
- Recommended in NYHA Class II-IV symptoms with eGFR>30 and K+ <5.0
  - SCr >2.5 excluded from trials
- Monitoring: BP, volume status, K+, BUN, Mg^{2+}, and SCr within 14 days of initiation or dose changes
  - Discontinue if K+ cannot be maintained <5.5
- NNT for all-cause mortality at 18 months is 28

Medication	Initial Daily Dose	Target Daily Dose	Notes
Spironolactone	12.5-25 mg once daily	25-50 mg once daily	Non-selective
Eplerenone	25 mg once daily	50 mg once daily	Selective
*Finerenone not indicated in HFrEF			

Heidenreich, et al. Circulation. 2022.
Lisi. US Pharmacist. 2023.

SGLT2i

- Reduction of **morbidity and mortality** in all categories of heart failure
- Also indicated for T2DM, no inherent risk of hypoglycemia when used alone
- Monitoring: includes SCr after 1-3 months of use, BP and adverse effects (genital mycotic infections, volume status, euglycemic ketoacidosis)
- NNT for all-cause mortality at 63 months is 28

Medication	Initial Daily Dose	Target Daily Dose	Other
Empagliflozin	10 mg once daily	10 mg once daily	eGFR should be ≥20 for initiation Can increase to 25 mg in T2DM
Dapagliflozin	10 mg once daily	10 mg once daily	eGFR should be ≥20 for initiation
*Canagliflozin and ertugliflozin not indicated for heart failure			

Heidenreich, et al. Circulation. 2022.
Lisi. US Pharmacist. 2023.
KDIGO Diabetes WG. Kidney Int. 2022.

Hydralazine + Isosorbide Dinitrate

- Reduction in **morbidity and mortality** and **improved symptoms**
- Added in black patients with NYHA Class III-IV symptoms on optimal GDMT
- NNT for all-cause mortality at 12 months is 21

Medication	Initial Daily Dose	Target Daily Dose	Other
Fixed dose combination	20 mg isosorbide dinitrate and 37.5 mg hydralazine TID	40 mg isosorbide dinitrate and 75 mg hydralazine TID	Contraindicated with concomitant PDE-5 inhibitors or riociguat
Variable dose combination	20-30 mg isosorbide dinitrate and 25-50 mg hydralazine TID to QID	120 mg isosorbide dinitrate total daily in divided doses and 300 mg hydralazine total daily in divided doses	

Heidenreich, et al. Circulation. 2022.
Lisi. US Pharmacist. 2023.

Diuretics

- Potent diuresis resulting in **improved symptoms** (congestion, fluid retention and worsening symptoms)
  - No clear benefit on morbidity or mortality
- Loop diuretics preferred initial agents
- Can add metolazone in patients not responsive to moderate or high doses of loops
  - Thiazides can also be used in patients with comorbid hypertension
- Monitoring: BMP, daily weights, urine output

Medication	Initial Daily Dose	Maximum Total Daily Dose
Loop Diuretics		
Bumetanide	0.5-1.0 mg once or twice daily	10 mg daily
Furosemide	20-40 mg once or twice daily	600 mg daily
Torsemide	10-20 mg once daily	200 mg daily
Thiazide Diuretics		
Chlorthalidone	12.5-25 mg once daily	100 mg daily
Hydrochlorothiazide	25 mg once or twice daily	200 mg daily
Metolazone	2.5 mg once daily	20 mg daily

Heidenreich, et al. Circulation. 2022.
Lisi. US Pharmacist. 2023.

Additional Therapies Once GDMT Optimized

Criteria	Medication (LOR)	Potential Benefit
NYHA Class II-III, HFrEF, normal sinus rhythm, heart rate ≥ 70, on maximally tolerated beta blocker	Ivabradine (2a)	Reduce hospitalizations and CV death
NYHA Class II-IV, LVEF <45%, recent HF hospitalization, or intravenous diuretics, elevated natriuretic peptide levels	Vericiguat (2b)	Reduce hospitalizations and CV death
Symptomatic HFrEF	Digoxin (2b)	Decrease hospitalizations
NYHA Class II-IV	Omega-3 Polyunsaturated fatty acid (2b)	Reduce mortality and CV hospitalizations
HF with hyperkalemia while taking RAASi	Potassium binders (2b)	Reduce hyperkalemia and allow optimal doses of RAASi

Heidenreich, et al. Circulation. 2022.

DIAMOND Trial (2022)

Patiromer for the management of hyperkalemia in HFrEF

- 1642 patients with HFrEF and current or history of RAASi-related hyperkalemia on MRA
- Intervention:
  - Group 1: patiromer
  - Group 2: placebo
- Results (Followed for 27 weeks):
  - Primary endpoint: Adjusted mean change in K+
    - Group 1 +0.03 mmol/L vs. Group 2 +0.13 mmol/L ($p<0.001$)
  - Secondary endpoints (Group 1 vs. Group 2)
    - Risk of hyperkalemia >5.5 mmol/L: 13.9% vs. 19.4% ($p=0.006$)
    - Reduction in MRA dose: 13.9% vs. 18.9% ($p=0.006$)
    - Total adjusted hyperkalemia events/100 person-years: 77.7 vs. 118.2 ($p<0.001$)

Takeaway: Potassium binders could be utilized to reduce K+ in the setting of high dose MRAs to enable target doses of RAASi

Butler. European Heart Journal. 2022.

Pharmacotherapy with Unproven Value or Potential Harm

Unproven Value	NSAIDs (LOE B-R)	Vitamins/Supplements (LOE B-R)	Dihydropyridine CCB (LOE A)
HARM	Nondihydropyridine CCB (LOE A)	TZDs (LOE A)	Class IC antiarrhythmics (LOE A)
		DPP-IV Inhibitors (LOE B-R)	

Heidenreich, et al. Circulation. 2022.

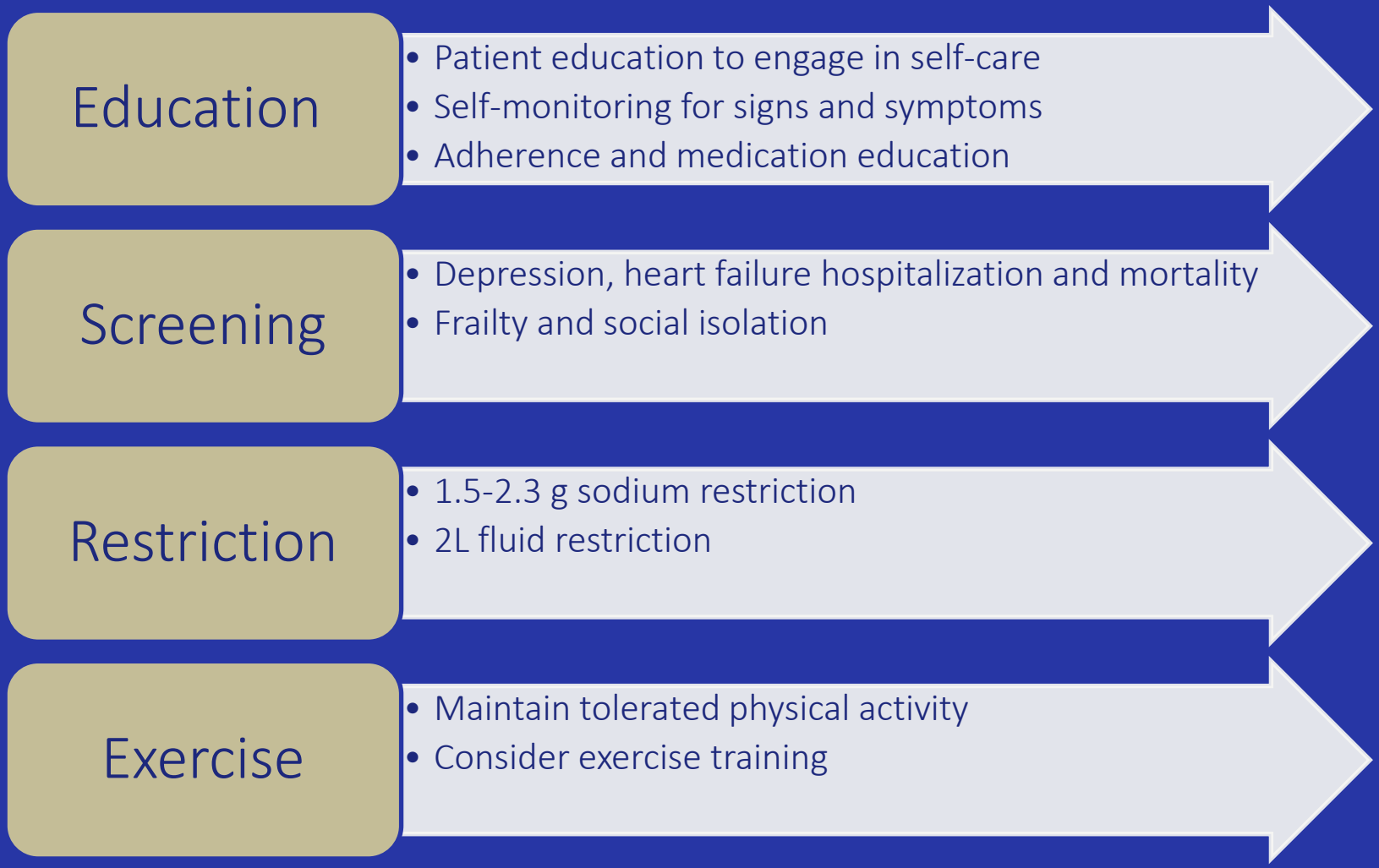
HEART FAILURE GDMT HIGHLIGHTS BY STAGE AND LVEF

Approach to Treatment

Lifestyle modifications and screen for patients at risk	Accurate diagnosis (including timely referral to HF specialist)	Identify and correct underlying cause
Eliminate or minimize precipitating factors	Identify and treat risk factors	Close monitoring and follow-up
Manage comorbid conditions	Appropriate pharmacologic and non-pharmacologic therapy	All patients with current or prior HF (irrespective of EF) should be considered for GDMT

Colvin. ACC. 2022.

Nonpharmacologic Recommendations

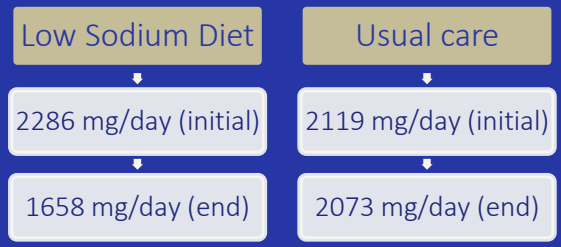


Heidenreich, et al. Circulation. 2022.

SODIUM-HF (2022)

Reduction of dietary sodium to less than 100 mmol in HF

- 806 patients randomly assigned to low-sodium diet
  - Adult patients with chronic heart failure (NYHA functional class 2-3) receiving optimally tolerated guideline directed medical treatment
- Intervention
  - Group 1: low sodium diet (<1500 mg/day)
  - Group 2: usual care
- Results
  - Primary outcome: composite of cardiovascular-related hospital admission, emergency department visits or all-cause death within 12 months of the intention to treat (ITT) population
    - Group 1 17.2 events per 100 pt years vs group 2 19.2 events per 100 patient years (HR 0.99 (0.66-1.47), p-value 0.95)



Takeaway: sodium reduction may not reduce clinical events in heart failure patients, but guidelines recommend avoidance of sodium excess

Ezekowitz. Lancet. 2022.

Stage A: Patients at Risk for Heart Failure

Primary prevention focus

BP control for hypertension (COR 1, LOE A)

Education on healthy lifestyle habits to reduce risk (COR 1, LOE B-R)

SGLT2i should be used to prevent hospitalizations from HF in patients with T2DM and either high cardiovascular risk or established CVD (COR 1, LOE A)

Heidenreich, et al. Circulation. 2022.

Stage B: Pre-Heart Failure

Focus on preventing clinical HF

Stage A recommendations still applicable

Statins for prevention in patients with history of MI or ACS (COR 1, LOE A)

ACEi should be used in patients with LVEF ≤ 40% (COR 1, LOE A)

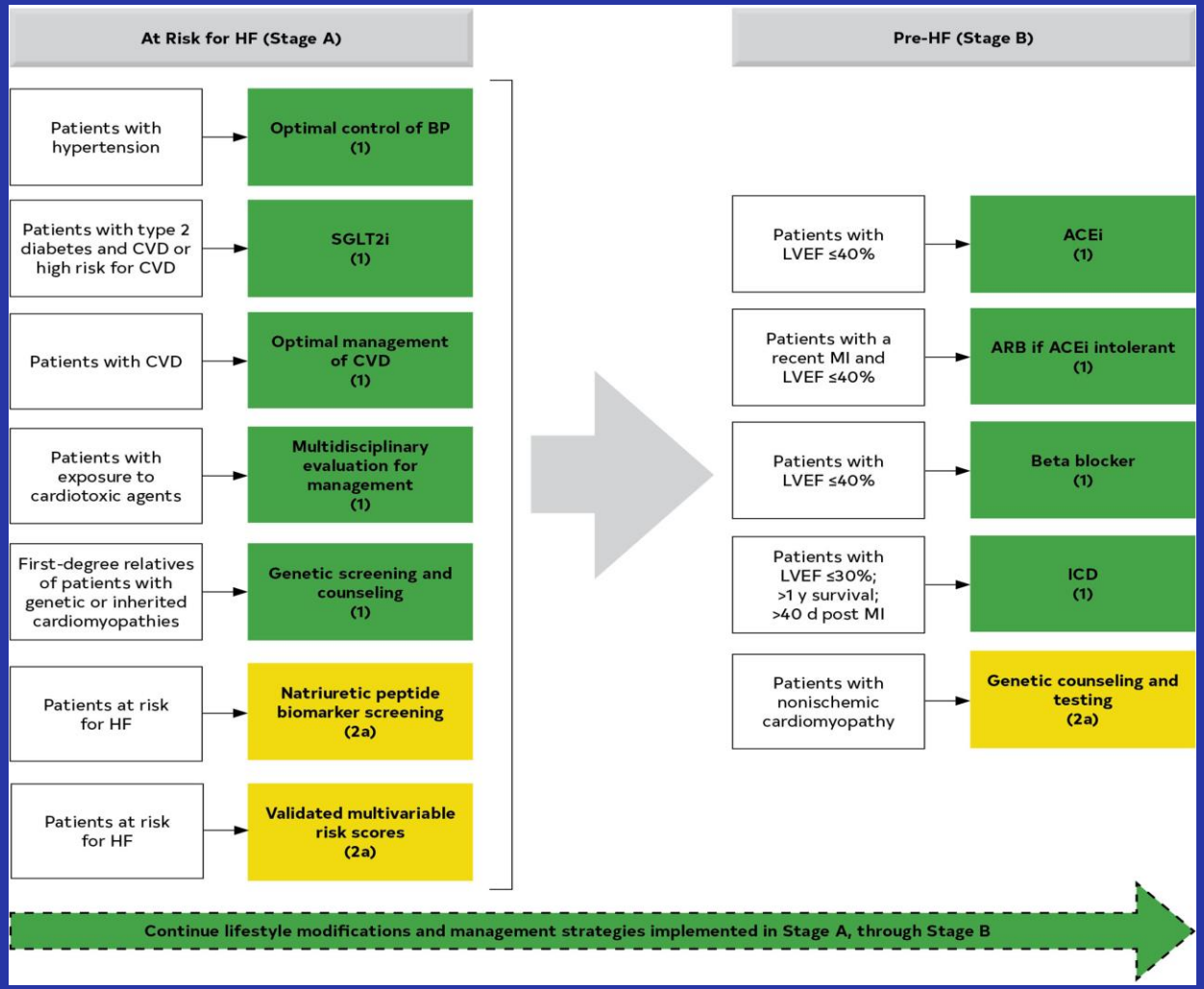
- ARB if ACEi intolerant + hx of MI (COR 1, LOE A)
- ARNI not shown to be superior to ACEi

Beta blocker should be used in patients with LVEF ≤ 40%, hx of MI or ACS (COR 1, LOE A)

AVOID TZDs (COR 3: Harm, LOE B-R) and nondihyropyridine CCBs (COR 3: Harm, LOE C-LD)

Heidenreich, et al. Circulation. 2022.

Stages A + B Treatment



Heidenreich, et al. Circulation. 2022.

Stage C: Symptomatic HF

- Four mainstays of therapy:
  1. ARNI is preferred over ACEi and ARB
  2. Beta blocker (bisoprolol, carvedilol, SR metoprolol succinate)
  3. MRA (NYHA Class II-IV symptoms)
  4. SGLT2i

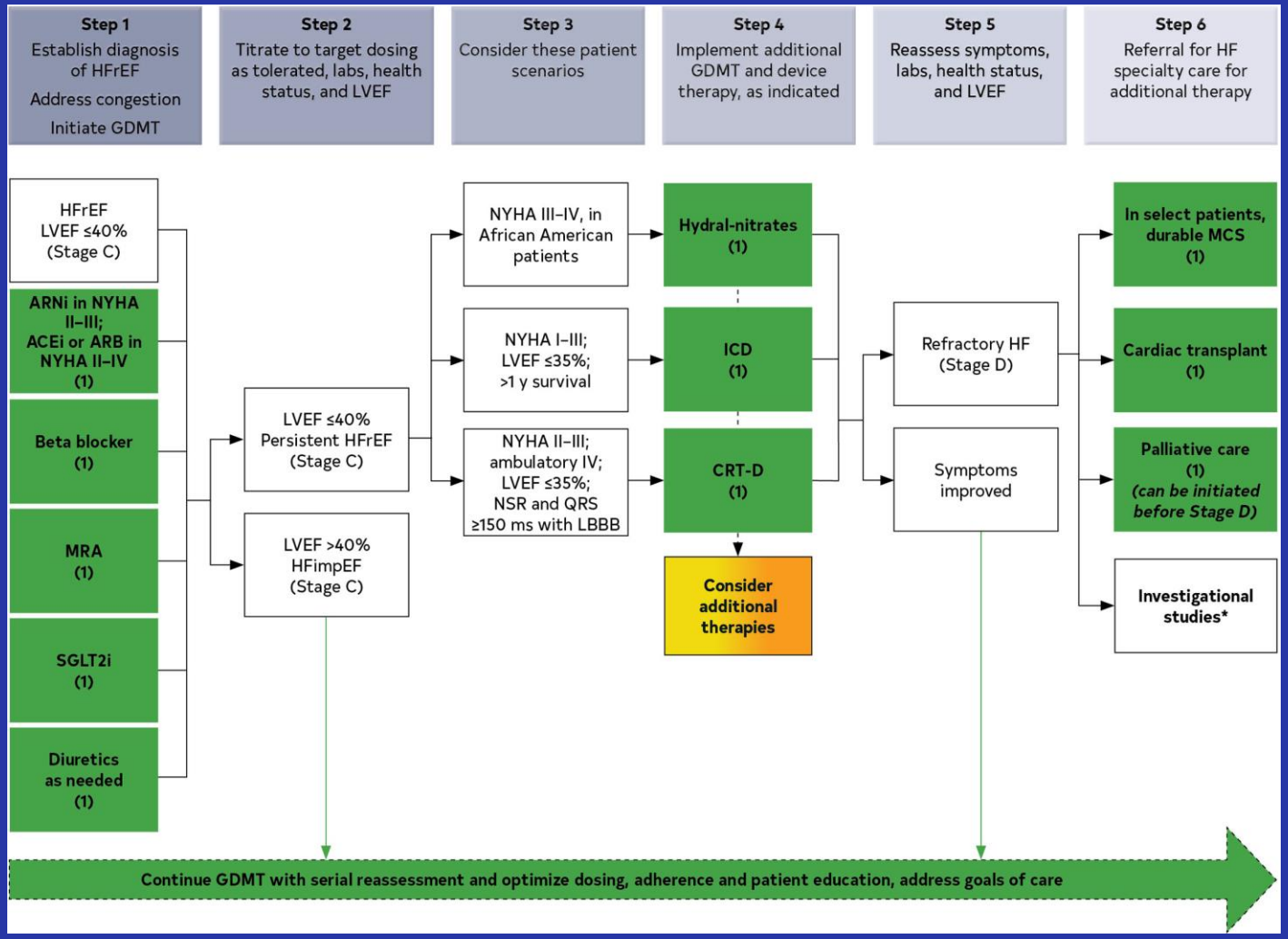
COR 1, LOE A

Additionally:

1. Self-identified black patients with HFrEF NYHA Class III to IV on optimal GDMT, indicated for combination of hydralazine and isosorbide dinitrate
2. Diuretics as needed (COR 1, LOE B-NR)

Heidenreich, et al. Circulation. 2022.

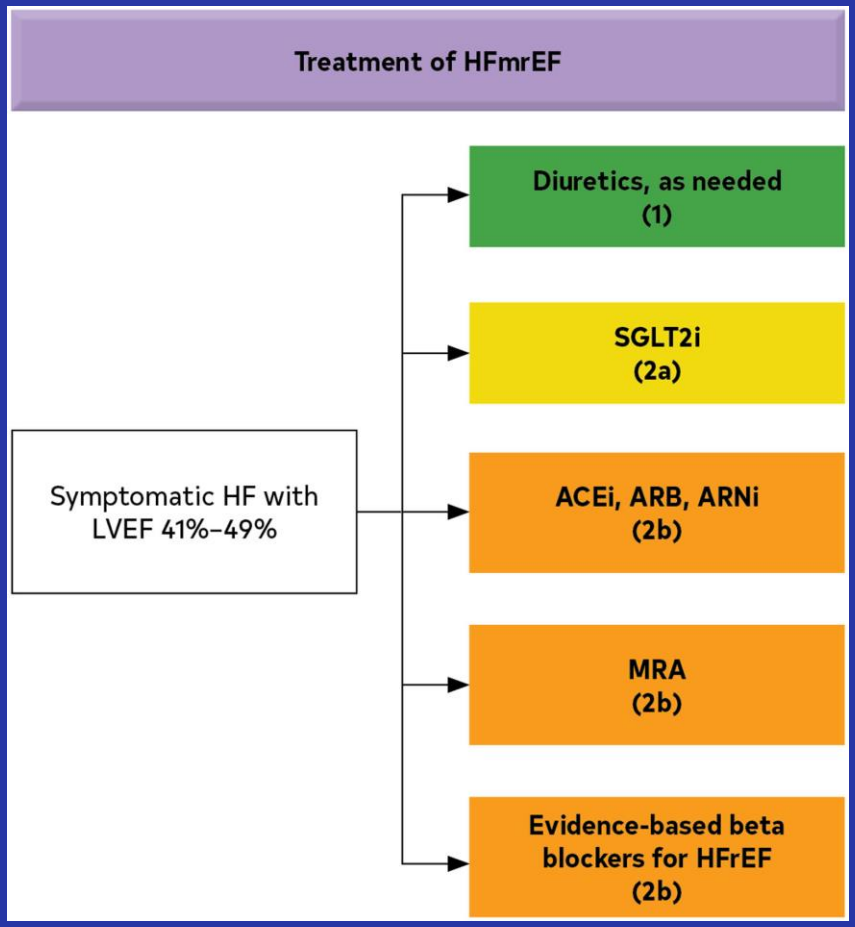
Stages C + D Treatment



Heidenreich, et al. Circulation. 2022.

HFmrEF

- SGLT2i for reduction in **morbidity and mortality** (COR 2a, LOE B-R)
- Consider beta blockers, ARNi/ACEi/ARB or MRA with current or previous symptoms (COR 2b, LOE B-NR)



Heidenreich, et al. Circulation. 2022.

HFimpEF

- Continue current GDMT (COR 1, LOE B-R)
- Functional capacity may improve but LV function never fully recovers/normalizes
- Relapse would eventually occur with withdrawal of GDMT

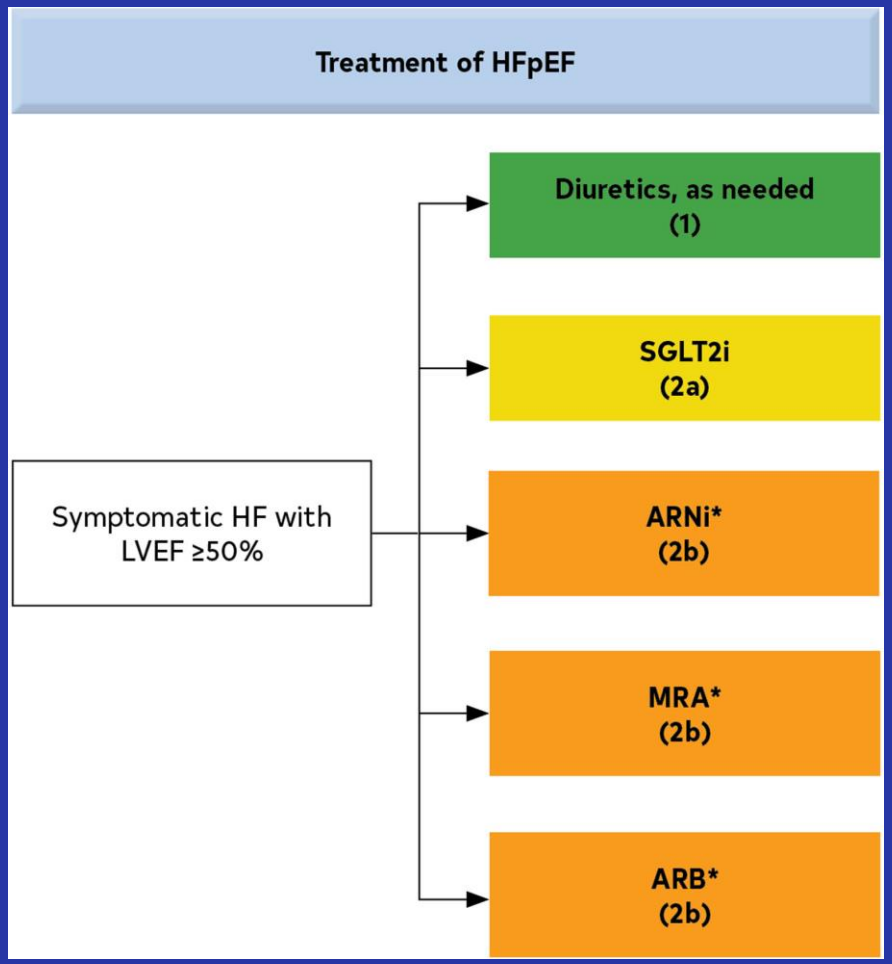
Heidenreich, et al. Circulation. 2022.

HFpEF

1. +HTN: titrate medications to achieve blood pressure goals and prevent morbidity (COR 1, LOE C-LD)
2. SGLT2i for reduction in **morbidity and mortality** (COR 2a, LOE B-R)
3. Consider MRAs, ARBs or ARNis to decrease hospitalizations (COR 2b, LOE B-R)
4. Use diuretics as needed for symptom management (COR 1, LOE A)
5. AVOID routine use of phospodiesterase-5 inhibitors or nitrates (COR 3: No benefit, LOE B-R)

Heidenreich, et al. Circulation. 2022.

HFpEF



Heidenreich, et al. Circulation. 2022.

Patient Case #3

AS is a 65-year-old black male newly diagnosed with HFpEF. PMH includes HTN x30 years, hypothyroidism and HLD.

Current medications include lisinopril 40 mg once daily, rosuvastatin 20 mg daily and levothyroxine 100 mcg daily. NKDA.

Labs + Vitals: BP is 128/78, HR 78, BMP WNL

1. Would you add any pharmacotherapy for this patient?
2. What type of benefit would this therapy offer?
3. What monitoring would you recommend?

GDMT SEQUENCING + TITRATION

Recommendations for HFrEF GDMT Dosing

- Titration of guideline-directed medication **dosing to achieve target doses** = reduction in **morbidity and mortality** (COR 1, LOE A)
- Titration can occur as frequently as every 1-2 weeks depending on symptoms, vital signs, and laboratory findings (COR 2a, LOE C-EO)

Heidenreich, et al. Circulation. 2022.

Simultaneous vs Sequential Initiation of HFrEF GDMT

American College of Cardiology Expert Analysis

Significant evidence exists regarding pharmacotherapies offering morbidity and mortality benefit in HFrEF but optimization of GDMT is lacking

Previously, GDMT agents were started individually with slow titration

New evidence supports simultaneous initiation and rapid titration of GDMT

- Safe, effective and offers maximum benefit for the patient
- ARNi, SGLT2i, beta blocker and MRA

Rapid sequence initiation can help improve CV outcomes and standardize HFrEF care

Keisuke. ACC. 2022.

Simultaneous/Rapid Sequence Initiation and Titration of GDMT

Figure 1

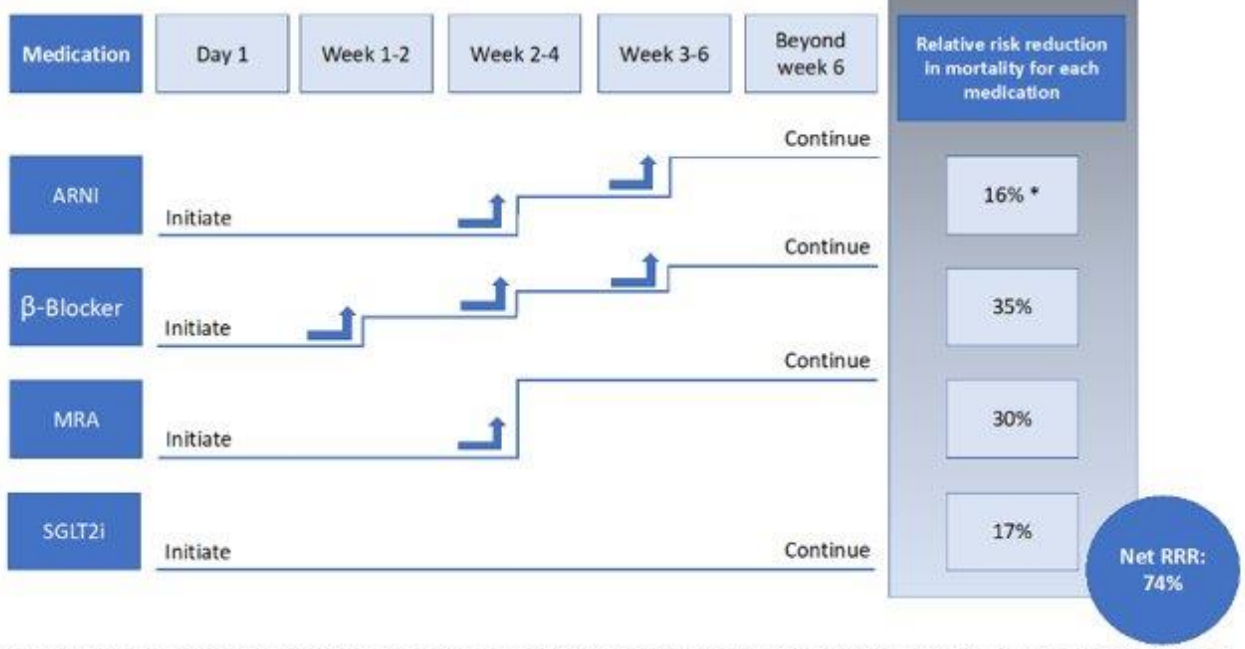


Figure 1: Simultaneous/Rapid Sequence Initiation and Titration of Comprehensive Disease Modifying Medical Therapy. Low starting doses should be used, in the absence of contraindications. Therapy should be up-titrated, as well tolerated, with beta-blocker up-titration prioritized. Clinical benefits are apparent, even at low dose, within 14-30 days of initiation. ARNI: angiotensin receptor-neprilysin inhibitor. MRA: mineralocorticoid receptor antagonist. SGLT2i: sodium glucose cotransporter 2 inhibitor. RRR: relative risk reduction. *replacing angiotensin-converting enzyme inhibitor / angiotensin receptor blocker. *Courtesy of Brownell N, Ziaelan B, Fonarow GC.*

Keisuke. ACC. 2022.

Patient Case #4

MC is a 68-year-old white female newly diagnosed with Stage C HFrEF. She reports SOB has gradually increased and is worse at night along with lower extremity edema. PMH includes HTN x18 years, MI (2010), HFrEF NHYA Class III.

Current medications include losartan 50 mg once daily, atorvastatin 40 mg daily and aspirin 81 mg daily. NKDA.

Labs + Vitals: BP is 134/76, HR 75, LVEF is 35%, BMP WNL

1. What would you do next for this patient's HFrEF in addition to adding a loop diuretic?
   a) Start metoprolol succinate 25 mg daily, start empagliflozin 10 mg daily, start spironolactone 12.5 mg daily and continue losartan 50 mg daily
   b) Start metoprolol succinate 25 mg daily, start empagliflozin 10 mg daily, start spironolactone 12.5 mg daily, stop losartan 50 mg daily, and start sacubitril/valsartan 24mg/26 mg twice daily
   c) Start metoprolol succinate 25 mg daily and continue losartan 50 mg daily. Follow-up in 2 weeks to adjust therapy.

Heart Failure Takeaways

- Heart failure guidelines now include SGLT2i as a mainstay of therapy for HFrEF and reduction of heart failure **morbidity and mortality** across all stages
- Simultaneous/rapid initiation of GDMT for heart failure may be appropriate to reduce morbidity and mortality

Today's Topics

NEW CARDIOVASCULAR DATA

SGLT2i in Heart Failure

Reduces mortality AND morbidity in HFrEF and HFpEF

HFrEF trials	**HFpEF trials**
DAPA HF (2019)	DELIVER (2022)
EMPEROR REDUCED (2020)	EMPEROR PRESERVED (2021)

CKD progression, ESRD, death from renal causes *regardless* of DM status

McMurray, et al. NEJM. 2019. Packer, at al. NEJM. 2020. Solomon, et al. NEJM. 2022. Anker, et al. NEJM. 2023

SGLT2i in CKD

Reduces mortality AND morbidity in CKD

Trials

CREDENCE (2019)*

DAPA CKD (2020)

EMPA KIDNEY (2023)

*CKD+DM pts only

CKD progression, ESRD, death from renal causes *regardless* of DM status

Perkovic, et al. NEJM. 2019. Heerspink, et al. NEJM. 2020. Herrington, et al. NEJM. 2023.

Finerenone in CKD

Reduces mortality AND morbidity in T2DM + CKD

Trials

FIDELIO DKD (2020)

FIGARO DKD (2021)

CKD progression and CV events in T2DM + CKD

Bakris, et al. NEJM. 2020. Pitt, et al. NEJM. 2021.

Nonsteroidal Mineralocorticoid Receptor (ns-MRA) Antagonist			
Drug	**Renal MOA**	**Indication**	**Clinical Impact**
Finerenone 10 – 20 mg once daily	Inhibits mineralocorticoid receptors No affinity or activity on androgen, progesterone, estrogen, or glucocorticoid receptors	T2DM + eGFR > 25, normal K+, UACR > 30 despite max tolerated RAASi	-Reduces renal and CV outcomes in patients with CKD and T2DM -Reduces UACR in patients with CKD on RAASi
Monitoring	**CI/DDI**	**ADRs**	**Cost**
SCr, K+, BP	CI: Strong CYP3A4 inhibitors, adrenal insufficiency	Hypotension Hyperkalemia	$$$

Kerendia [package insert]. 2023.

Finerenone Dosing

Do not initiate if K+ ≥ 5

Recommended Starting Dosage	
eGFR ≥ 60	20mg once daily
eGFR ≥ 25 - 59	10mg once daily
EGFR < 25	Do not initiate

Monitor K+ within 4 weeks of initiation, restart, or dose adjustment

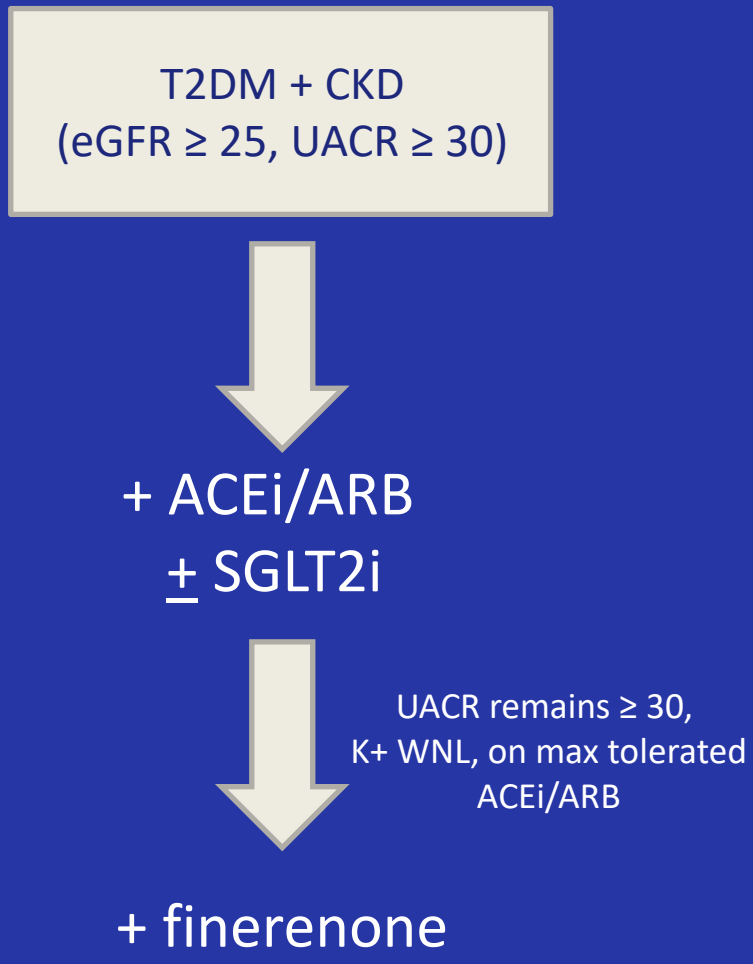
Dose Adjustment Based on Current K+ and Current Dose			
		Current Dose	
		10mg	20mg
Current K+	≤ 4.8	Increase to 20mg*	Maintain 20mg
	> 4.8 - 5.5	Maintain 10mg	Maintain 20mg
	>5.5	Hold finerenone Can restart when K+ < 5	Hold finerenone Can restart 10mg when K+ < 5

*if eGFR decreased ≥ 30% compared to previous, maintain 10mg

Kerendia [package insert]. 2023.

Finerenone Place in Therapy

2022 KDIGO Guideline for Management of Diabetes in CKD



KDIGO Diabetes WG. Kidney Int. 2022.

Bempedoic Acid

Reduces mortality in statin intolerant patients

Trial
CLEAR OUTCOMES (2023)

LDL and CV events in statin intolerant patients with ASCVD or high risk ASCVD

Nissen, et al. NEJM. 2023.

Tirzepatide

CV risk reduction unknown

Trial
SUMMIT* (Fall 2023)
SURPASS-CVOT (2024)
TREASURE-CKD (2025)
SURMOUNT-MMO** (2027)

*HFpEF

**mobidity and mortality in obesity

New Medication Access

- Many new agents reviewed today are considered high-cost medications
- Patient access and affordability may be barriers to medication use
- Methods to improve access:
  - Drug manufacturer copay assistance cards
  - Medication assistance programs
  - Review of formulary updates and mechanisms for approval

Patient Case #5

RD is a 64-year-old black male seen for follow-up. PMH includes T2DM, HTN, and CKD stage 3.

Current medications include metformin ER 2000 mg daily, semaglutide 1 mg weekly, atorvastatin 40 mg daily, lisinopril 40 mg daily and empagliflozin 25 mg daily. NKDA.

Labs + Vitals: BP 128/74, HR 72, A1c 7.1%, UACR 154, eGFR 49, K+ 4.2

1. Is this patient a candidate for finerenone?
2. If patient is started on finerenone, what dose would we initiate?
3. Once initiated, what monitoring should be completed?

CV Update Takeaways

- SGLT2i reduce mortality and morbidity in HF and CKD regardless of DM status
- Bempedoic acid demonstrates reduced CV events in primary prevention
- Finerenone reduces CKD progression in T2DM + CKD on max tolerated RAASi

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Thank you!

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