Time to Learn About New Cardiac Drugs

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DISCLOSURE

- Dr. Michael White has no financial relationships with ineligible companies

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Objectives for Lecture

- At the conclusion of the lecture, the successful learner will be able to:
  - Determine the appropriate first and adjunctive therapies for LDL lowering in patients with differing risks according to guideline recommendations
  - Compare and contrast the mechanism of action and potential utility of the new LDL lowering drugs bempedoic acid and inclisirin versus traditional options
  - Describe hypertrophic cardiomyopathy and its risks
  - Identify the mechanism of action and potential utility of mavacamten versus agents currently recommended in guidelines

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New Lipid Lowering Choices

Bempedoic Acid and Inclisiran

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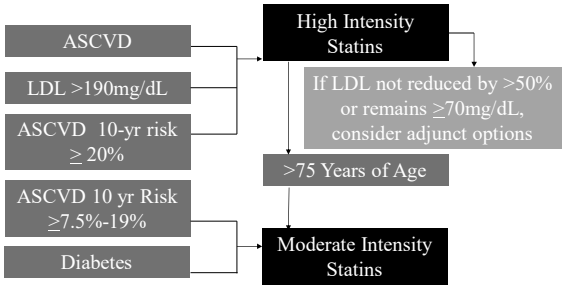
AHA/ACC 2018 Statin Guidance



Grundy S. JACC 2018; https://doi.org/10.1016/j.jacc.2018.11.003

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Guideline Approved Statins

High Intensity	Moderate Intensity
LDL Reduction >50%	**LDL Reduction 30-50%**
Atorvastatin 40-80mg	Atorvastatin 10-20mg
Rosuvastatin 20-40mg	Rosuvastatin 5-10mg
	Simvastatin 20-40mg
	Pravastatin 40-80mg
	Lovastatin 40mg
	Fluvastatin 40mg BID
	Pitavastatin 2-4mg

Grundy S. JACC 2018; https://doi.org/10.1016/j.jacc.2018.11.003

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Question 1

- Mary Maple is an 80 year old with angina pectoris, what intensity of statin therapy should she receive and how much should her LDL be reduced?

a) Moderate intensity, 30%
b) High intensity, 50%
c) Low intensity, 20%

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Guideline Approved Adjuncts

	Ezetimibe	PCSK9 Inh
20% Reduction to Goal	++++ Effective, safe, well tolerated, low cost, proof of event reductions	
35% Reduction to Goal	++ Will not get patients to goal but will go part of the way with low cost	++ Effective, safe, well tolerated, proof of event reduction BUT not cost effective
50% Reduction to Goal		+++ Effective, safe, well tolerated, proof of event reduction and reasonable cost

Lower NNTs Help with Cost-Effectiveness →

White CM. J Cardiovasc Pharmacol Ther. 2018;23:301-308.

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Adjunct Trials w/ Additional LDL Lowering

Variables	IMPROVE-IT 2014	FOURIER 2018	ODYSSEY OUTCOMES 2017
Therapy	Ezet 10mg + Simva 40mg vs. Plac + Simva 40mg	Evolocumab 140mg Q2W or 420mg QM vs. Plac	Alirocumab 75mg or 150mg Q2W vs. Plac
Inclusion Criteria		Everyone needed to be on moderate to max statins	
Population	Pts < 10 days of ACS	Pts w/ Hx of MI, Stroke, PAD	Pts <1y post ACS
Follow-up	6 y	2 y	4 y
LDLs Baseline End % Diff LDL	 94mg/dL E:53; P:70mg/dl -24%	 94mg/dL E:30; P:92mg/dL -67%	 93mg/dL A:53.3; P:101mg/dL -55%

White CM. Ann Pharmacother. 2018;52:175-184.
White CM. J Cardiovasc Pharmacol Ther. 2018;23:301-308.

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Adjunct Trials w/ Additional LDL Lowering

Variable	IMPROVE IT	ODDYSSEY Outcomes	FOURIER
MACE Events	35% vs. 33%, P=0.016	11.1% vs. 9.5%, P<0.001	11.0% vs. 9.2%, P<0.001
Death	15% vs. 15% P=0.782	4.1% vs. 3.5%, P=0.023	3.2% vs. 3.1%, P=0.99
MI	18% vs. 13%, P=0.002	7.6% vs. 6.6%, P=0.006	4.6% vs. 3.4%, P<0.01
Ischemic Stroke	4.1% vs. 3.4%; P=0.008	1.6% vs. 1.2%, P=0.01	1.9% vs. 1.5%, P=0.01
Revasc Proc	23% vs. 22% P=0.107	8.8% vs. 7.7%, P=0.009	7.0% vs. 5.5%, P<0.01

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LDL-CV Event Reduction Relationship

- Cholesterol Treatment Trialists (CTT) assessment of all major statin vs. placebo, high statin vs. low statin, and statin + adjunct ezetimibe or PCSK9 inhibitor vs. statin trial
- For every 39mg/dL reduction in LDL, the 5-year risk of cardiovascular events is reduced by 22%
  - Holds for LDL's as low as 30mg/dL

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Question 2

- According to the CTT relationship, whether the intensity of statin was increased or adjunctive therapy with ezetimibe or evolocumab was used, the relationship between LDL lowering and cardiovascular event reduction had the same relationship

a) True
b) False

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Important Unknown

- Does the CTT relationship apply to all LDL reducers or just to statins, ezetimibe, and PCSK9 inhibitors?
  - Role of bile acid sequestrants, niacin, lomitapide, and mipomerson unclear
    - Don't use the cholesterol cascade mechanism or the PCSK9 mechanism to lower LDL

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New Options for LDL Reduction: Inclisiran and Bempedoic Acid

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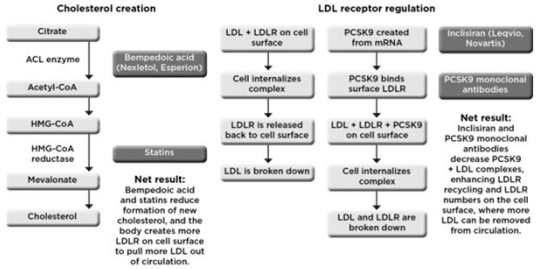
Bempedoic Acid and Inclisiran Mechanism of Action



White CM.
https://www.pharmacypracticenews.com/aimages/2022/ppn0722_016b_15202_.jpg

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Bempedoic Acid Less Likely to Cause Statin Myopathy

- Bempedoic acid requires activation by very long-chain acyl-CoA synthetase I (ACSVL1) to ETC-1002-CoA
  - ACSVL1 is present in hepatocytes but not myocytes

White CM.
https://www.pharmacypracticenews.com/aimages/2022/ppn0722_016b_15202_.jpg

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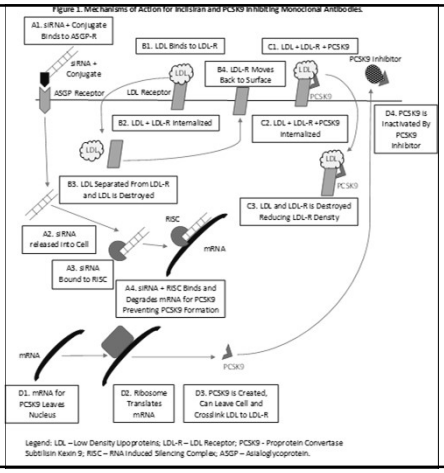

Smith K, White CM. J Clin Pharmacol 2022; DOI: 10.1002/jcph.2045

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Bempedoic Acid Administration

- The FDA-approved dose is 180mg of bempedoic acid administered orally once daily with or without 10 mg of ezetimibe
  - Can be taken at any time of day, with or without food

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Inclisiran Administration

- Dose is 284 mg (1.5mL total volume) administered as a single subcutaneous injection initially, 3 months later, and then every 6 months
- No preservatives in the pre-filled inclisiran syringe, so it is not advised to give partial doses and save the rest for later

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Bepedoic Acid LDL Impact

- Ballantyne et al randomized patients to combination product of 180 mg of bempedoic acid plus 10 mg of ezetimibe daily (36% LDL reduction) daily, 180 mg of bempedoic acid daily alone (17.2% LDL reduction), 10 mg of ezetimibe daily (23% LDL reduction), or placebo (1% LDL increase)

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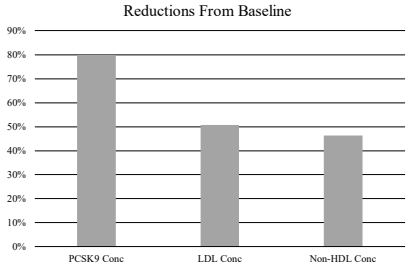
Inclisiran Lipid Lowering

Meta analysis from 3,660 participants in the ORION 9, 10, and 11 trials



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Bempedoic Acid ADEs

- Bempedoic acid can raise LFTs like statins
- Bempedoic acid may increase blood uric acid levels inducing hyperuricemia
  - Occurs early after initiation, persist throughout treatment, and lead to the development of gout
  - Clinicians should assess uric acid levels periodically as clinically indicated, especially in those with a history of hyperuricemia

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Bempedoic Acid ADEs

- Bempedoic acid rarely induced tendon rupture (0.5% of patients treated) versus placebo (0%)
  - Tendon rupture may occur more frequently in patients over 60 years of age, patients taking corticosteroid or fluoroquinolone drugs, patients with renal failure, and patients with previous tendon disorders

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Inclisiran Adverse Events

- Adverse event leading to treatment withdrawal similar with inclisiran vs. placebo
  - 2.5% vs. 1.9%; RR 1.28 (95%CI: 0.83 to 1.98)
- Inclisiran caused mild injection reactions [3.7% vs. 0.6%; RR 6.05 (95%CI: 3.21 to 11.42)], and moderate injection reactions [1.3% vs. 0.1%; RR 23.86 (95%CI: 3.23 to 176.15)]
- Injection site irritation (3.1%), pain (2.2%), redness (1.6%), and rash (0.7%)

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Inclisiran Adverse Events

- No concerning biochemical changes
  - Creatine kinase >5 times the upper limit of normal [1.3% vs. 1.2%; RR 1.08 (95%CI: 0.61 to 1.93)]
  - Alanine aminotransferase >3 times the upper limit of normal [0.5% vs. 0.4%; RR 1.28 (95%CI: 0.48 to 3.42)]

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Bepedoic Acid Place in Therapy

- LDL reductions of 18% for bempedoic acid in line with bile acid sequestrants, niacin, and ezetimibe
  - Costs $10/day or $3,650 much more than colesevelam ($2.60/day)
  - Bile acid sequrestrants have more drug interactions but fewer systemic ADEs
  - No proven event reductions like with ezetimibe
- Bempedoic acid + ezetimibe no more effective than bile acid sequestrant + ezetimibe
  - Single pill vs. two pills daily

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Inclisiran Place in Therapy

- Use in people who are on statins +/- ezetimibe and require additional LDL lowering to achieve LDL <70mg/dL or a >50% reduction from baseline who cannot use PCSK9 inhibitors
  - Q6 mo SQ injections vs. 2-4 week SQ injections like the PCSK9 inhibitors
  - Inclisiran has no proof of event reductions like PCSK9 inhibitors provide
  - More expensive ($9,500 year 1, $6,500/year afterwards) than PCSK9 inhibitors ($5,500 – $5,800/year)

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Question 3

- Which of the following describes the mechanism of action correctly?
  A. Inclisiran inhibits the formation of PCSK9 by inserting small interfering RNA into the cell
  B. Bempedoic acid blocks the binding of PCSK9 to the LDL receptor
  C. Both of the mechanisms are described correctly

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Question 4

- Which is true about inclisiran vs. bempedoic acid?
  A. Inclisirin lowers LDL more but can raise uric acid levels leading to gout
  B. Inclisiran is more expensive but requires SQ dosing
  C. All of the above are true

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Mavacamten: A New Choice for Hypertrophic Cardiomyopathy

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Hypertrophic Cardiomyopathy

- Prevalence 1:200 people
- ~2/3 of patients with hypertrophic cardiomyopathy eventually develop left ventricular outflow obstruction
- ~1/3 of patients with hypertrophic cardiomyopathy will experience severe adverse events including lethargy/shortness of breath, atrial or ventricular arrhythmias, strokes, and death

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Current Treatments for HCM

- ICDs to prevent ventricular arrhythmias
- Antiarhythmics to prevent atrial fibrillation or along with ICDs for ventricular arrhythmias
- Anticoagulants for stroke risk reduction
- Beta-blockers OR Non-DHP CCBs +/- disopyramide to enhance ventricular relaxation
- Surgical or procedural debulking of septum to reduce LVOT obstruction

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Mavacamten Indication

- Mavacamtam is a newly approved and first in class cardiac myosin modulator indicated to improve functional capacity and symptoms for adults with New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) and a left ventricular ejection fraction (LVEF) >55%

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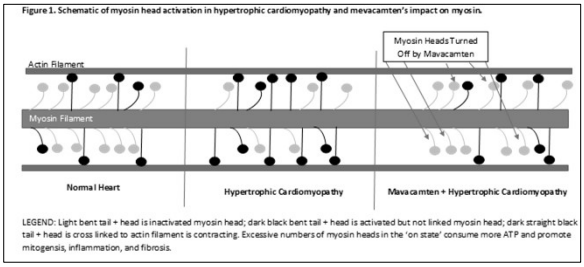
Mavacamten Mechanism of Action



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Mavacamten Drug Interactions

- Mavacemten is contraindicated with moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors due to increased risk of serious adverse events and with moderate to strong inducers of CYP2C19 or CYP3A4 due to concerns for lack of efficacy

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Mavacamten Drug Interactions

- Omeprazole (weak CYP219 inhibitor) increases mavacamten's AUC by 48%
- Ketoconazole (strong CYP3A4 inhibitor) predicted increases mavacamten's AUC 130%
- Verapamil/Diltiazem (moderate CYP3A4 inhibitor) increases mavacamten AUC by ~55%
- Rifampin (strong CYP2C19 and CYP3A4 inducer) decreases mavacamten AUC by 87%

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Mavacamten Drug Interactions

- Mavacamten is also an inducer of CYP3A4, CYP2C8, CYP2C9, and CYP2C19 substrates
  - Mavacamten decreases midazolam (CYP3A4 substrate) AUC by 13%
  - Mavacamten decreases the AUC of repaglinide (CYP2C8 and CYP3A substrate), tolbutamide (CYP2C9 substrate) and omeprazole (CYP2C19 substrate) by 12-39%, 33-65%, and 48-67%

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Mavacamten Clinical Trial

- EXPLORER-HCM (30 week R, DB, PC) trial conducted in 13 countries (n=251) around the world (43% in U.S.)
- Mostly men (54% vs. 65%), White (93% vs. 89%), NYHA Class II (72% vs 74%) or III (28% vs 26%) and had a high LVEF (74$\pm$6% vs 74$\pm$6%)
- Most patients received beta-blockers (76% vs. 76%) or non-DHP calcium channel blockers (20% vs. 13%)
- Patients needed to have a peak LVOT gradient at rest, after Valsalva maneuver, or after exercise of at least 50 mmHg

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Mavacamten Clinical Trial

- 20% of patients on mavacamten had both at least a 3.0 mL/kg per min increase in pVO2 and at least one class improvement in NYHA class as compared with 8% receiving placebo (+12·5% [95%CI 4.0% to 21.0%])
- The post exercise LVOT gradient change (-35.6 [95%CI: -43.2 to -28.1] mmHg), pVO2 improvement (1.4 [95%CI:0.6 to 2.1] mL/kg/min), >1 NYHA class improvement (34% [95%CI: 22% to 45%]), and the KCCQ-Clinical Summary Scores (9.1 [95%CI: 5.5 to 12.7]) were significantly impacted

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Mavacamten Dosing

- Therapy started at 5mg if the LVEF is >55%
- After 4 and 8 weeks, the LVOT and LVEF is assessed
  - If the LVEF is <50%, therapy will be held for 4 weeks regardless of the LVOT
  - If the LVOT is <20mmHg the dose is halved or maintained if it is >20mmHg

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Mavacamten Dosing

- Patients on a stable dose at week 12 (and every 12 weeks thereafter) need an assessment of their LVEF and LVOT
  - If the LVEF is <50%, therapy is held, if the LVEF is 50-55% or the LVEF is >55% and the Valsalva LVOT gradient is <30mmHg, the same dose is maintained for 12 additional weeks. If the LVEF is >55% and the Valsalva LVOT is >30mmHg, the dose can be increased from 2.5mg to 5mg, 5mg to 10mg, or 10mg to 15mg

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Mavacamten Cost

- The wholesale acquisition cost of mavacamten is about $245.20 per capsule, $89,500.24/year
- Mavacamten would cost $5.6 million more than myectomy and $7.0 million more than septal ablation to reduce one death from hypertrophic cardiomyopathy

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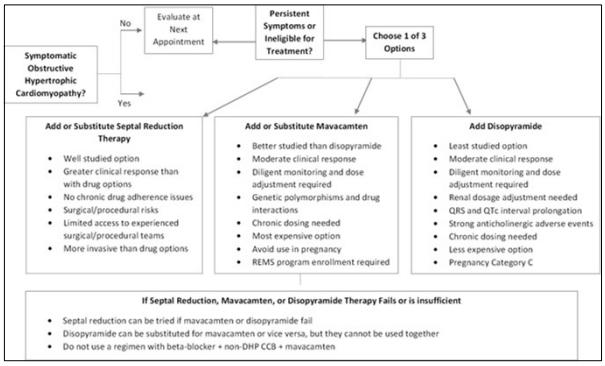
Place in Therapy



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Question 5

- Hypertrophic cardiomyopathy can lead to what adverse events?
  A. Atrial and ventricular arrhythmias
  B. Stroke
  C. Both of these issues

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Question 6

- Mavacamten might be able to replace which of the following HCM treatments?
  A. Beta-blockers of Non-DHP CCBs
  B. ICDs or anticoagulants
  C. Disopyramide or septal reduction therapies

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Conclusions

- Bempedoic acid is a new option for LDL reduction with limited utility versus other options
  - Increased uric acid and risk of tendon rupture limits utility
- Inclisirin is a new potent LDL reducer that is more expensive than PCSK9 inhibitors and does not have data for event reduction
- Mavacamten is a new drug for hypertrophic cardiomyopathy and offers important benefits in exchange for a very high price tag, drug interactions, and need for intensive ongoing monitoring

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