Adult/Geriatric Drug Therapy 2020

Pharmacologic Management of Difficult Lipid Cases

Savitha Subramanian. MD

Objectives for Learning Outcomes:

1. To identify and treat individuals with high cardiovascular risk.
2. To appropriately use non-statin cholesterol lowering medications.
3. To identify the role of triglycerides in cardiovascular risk.

PHARMACOLOGIC MANAGEMENT OF DIFFICULT LIPID CASES

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Nothing to disclose

Cases

1. To identify and treat individuals with high cardiovascular risk
2. To appropriately use non-statin cholesterol lowering medications
3. To identify the role of triglycerides in cardiovascular risk

Some common lipid terminology

- TG = triglycerides
- LDL = low density lipoprotein
- HDL = high density lipoprotein
- ASCVD = atherosclerotic cardiovascular disease
- FH = familial hypercholesterolemia

Case 1: Hypercholesterolemia: LDL-C > 190 mg/dL

- 67 year old woman presents for a routine visit
- She has had elevated LDL-C ranging between 170-220mg/dL known since age 45
- Resistant to taking statin- took a statin ~15 years ago and developed unclear side effects
- Takes no medication
- Very active lifestyle (running, pilates) and very clean eating
- Family history:
  - father died of MI at age 50, paternal uncle had MI at age 41 (alive and s/p CABG); paternal cousin – MI at 49, alive
  - 1 sister age 65, healthy without ASCVD, 3 adult children are reportedly healthy
- Physical exam: BP 128/76; BMI 21.6 kg/m^2, anxious appearing woman, otherwise unremarkable

Case 1: Hypercholesterolemia: LDL-C > 190 mg/dL

Labs- (9 months prior)
- Total cholesterol 289; TG 75; HDL 78; LDL 196 mg/dL
- Previous LDL-C values have ranged 174-210 mg/dL

On day of visit (fasting)
- Total cholesterol 295; TG 90; HDL 72; LDL 205 mg/dL
- ALT 20; creatinine 0.8; TSH 3.2; A1C 5.5%

Does she need therapy?

Case 5: Hypercholesterolemia : LDL-C > 190 mg/dL

- In addition to counseling her on her cardiovascular risk, the next best step in management of her lipids?

1. A moderate intensity statin should be prescribed
2. A high intensity statin should be prescribed
3. Try bempedoic acid – what?
4. Refer to lipid specialist
5. Agree with her choice of no treatment and document discussion in chart

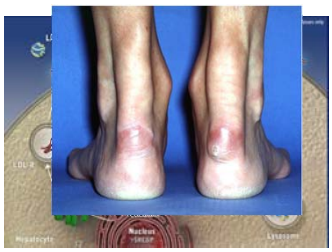
Case 1: Hypercholesterolemia : LDL-C > 190 mg/dL

- What does she have?

Familial hypercholesterolemia (FH)

- Autosomal dominant inheritance
- 1 in 250-500 heterozygous form
- Defects in LDL receptor

- Premature heart disease
- Tendon xanthomas – in 65-70%
- Total cholesterol >300 mg/dL , LDL >200mg/dL
- Aggressive cholesterol lowering
- More than one cholesterol lowering drug necessary



2018 ACC/AHA Multisociety guidelines for cholesterol lowering

- Statins are first line therapy for LDL-C lowering to decrease ASCVD risk
  - Statins inhibit the rate limiting enzyme within the liver cell
  - One of the most widely utilized and most potent of drugs

- In all individuals, emphasize a heart-healthy lifestyle across the life course

- Statins can be used in varying intensities – low, moderate or high

2018 Guideline on the Management of Blood Cholesterol

GUIDELINES MADE SIMPLE

Grundy SM, Stone N. Ann Intern Med 2019 June

Statin intolerance and/or aversion

- Definition: inability to use statins for lipid lowering due to significant symptoms that can be temporally associated to the initiation and/or dose escalation of statins

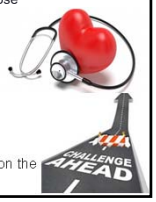
- Limits many patients from achieving LDL-C goals
- 10-25% patients in clinical practice report statin intolerance (in clinical trials <5%!)

- Muscle side effects are the most commonly reported symptom

1. Bays H Am J Cardiol 2006;
2. Stroes ES 2015 Eur Heart J

Statin associated muscle symptoms: evaluation and management

- Myalgias occur within 4 weeks of initiation, but sometimes much later
  - Symmetric – bilateral thighs, calves, upper proximal muscles
  - Improves upon withdrawal
- Same symptoms will recur after rechallenge
  - 40-60% can tolerate the same or another statin at the same or different dose
  - Washout period is mandatory
  - Can use alternative statin regimens
- Re-challenge can be a challenge
  1. Cardiovascular benefits well established
  2. Statins are safe medicines in use for over 30 years
  3. Serious muscle injury is very rare
  4. Aches and pains are very common in middle aged and older individuals
  5. Statins as a common cause of muscle symptom is a myth perpetuated on the internet and other media



Case : Hypercholesterolemia : LDL-C > 190 mg/dL

- She agrees to take low dose rosuvastatin 2.5mg 3x a week

Date	TC	TG	HDL	LDL	treatment
	289	75	78	196	
First visit	295	89	72	205	Rosuvastatin 2.5mg every other day
3 months later	240	72	78	148	2.5mg daily attempted but could not tolerate

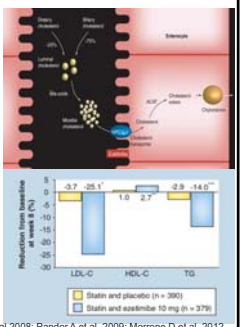
Is this enough LDL-C lowering?

When LDL lowering is not low enough or inadequate

- Residual cardiovascular risk despite intensive therapy
  - Inherited/genetic disorders
  - Resistance/aversion to therapy
  - Nonadherence
  - Adverse effects from statins – intolerance

Additional and/or new drug therapies are necessary

Don't forget - ezetimibe



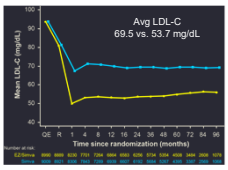
- A small molecule drug, taken orally
- Inhibits cholesterol absorption in the small intestine
- It is well tolerated with very few side effects

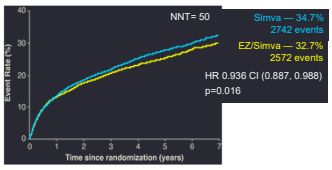
- LDL-C lowering:
  - 18% as monotherapy
  - Additive effect with statins - 20-25% LDL-C lowering

Bays H et al 2008; Pandor A et al, 2009; Morrone D et al, 2012
Stitzeil NO et al. 2014 NEJM

Cardiovascular outcome with ezetimibe: IMPROVE-IT study

- Patients after an acute coronary syndrome
- Randomized to simvastatin 40mg vs simvastatin + ezetimibe 10mg
- Cardiovascular benefit after 7 years of study





Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

Ezetimibe use is infrequent

- Modest LDL-C-lowering efficacy versus statins (but some patients have large response)
- IMPROVE-IT showed only modest CV reduction (6%)
- FDA did NOT give ezetimibe indication for CV reduction

- Remained branded after most statins were generic (until 10/16)
- Remained expensive ~1 ½ years after going generic (now ~$15-20 /month)

- Ezetimibe use only ~5% in recent trials of PCSK9 inhibitors

When to use ezetimibe?

- In patients who have unacceptable side effects on statins
- Severe primary hypercholesterolemia- familial hypercholesterolemia (FH)
- Those who have insufficient reduction in LDL-C on maximum tolerated statin dose

- (There are no CV outcomes trials of ezetimibe alone)

Case : Hypercholesterolemia : LDL-C > 190 mg/dL

Date	TC	TG	HDL	LDL	treatment
First visit	295	89	72	205	Rosuvastatin 2.5mg three times a week (tolerated well but could not take 2.5mg daily)
3 months later	240	72	78	148	Add ezetimibe 10mg daily
4 months later	170	80	72	84	

Alternative scenarios

- If this was a 68 y/o with on-treatment LDL-C 84 mg/dL and known ASCVD (CAD s/p PTCA and stenting), hypertension
- What about an 80 y/o on treatment, with LDL-C of 84mg/dL?

Very High-Risk for Future ASCVD Events*

Table 4

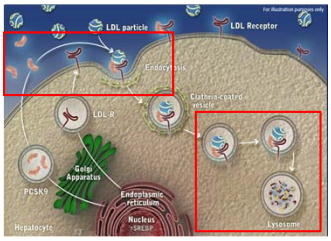
Major ASCVD Events
Recent acute coronary syndrome (within the past 12 months)
History of myocardial infarction (other than recent acute coronary syndrome event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ankle brachial index <0.85, or previous revascularization or amputation)
High-Risk Conditions
Age ≥65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s)
Diabetes Mellitus
Hypertension
Chronic kidney disease (eGFR 15-59 mL/min/1.73 m²)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL (≥2.6 mmol/L)) despite maximally tolerated statin therapy and ezetimibe
History of congestive heart failure

*Very High Risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.

Newer agents

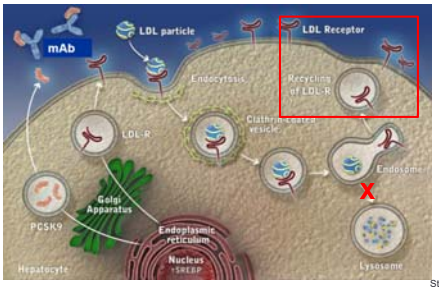
How does LDL and the LDL Receptor work?

- LDL receptors on the hepatocyte surface bind to LDL
  - Complex is endocytosed
  - LDL receptor is recycled
- PCSK9 binds with LDL receptor and prevents its recycling
- Gain-of-function mutations → severe hypercholesterolemia



Stein EA. PCSK9 Forum.

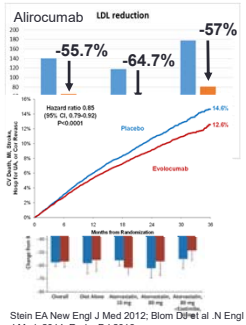
How PCSK9 Monoclonal Antibodies Lower Cholesterol



Stein EA. PCSK9 Forum.

PCSK9i – what do we know?

1. Lower LDL-C up to 60% from baseline
2. Given subcutaneously q2w
3. Maintain a consistent reduction in LDL-C
4. Effective as monotherapy and in addition to statin therapy
5. Safe and well tolerated
6. Cardiovascular benefit- 15% relative risk reduction



Stein EA New Engl J Med 2012; Blom DJ et al .N Engl J Med. 2014, Rader DJ 2016.

Who will benefit from PCSK9i therapy?

- Along with diet and maximally tolerated statin therapy
  - Genetic hypercholesterolemia (FH)
  - ASCVD who require additional LDL lowering (patients with highest risk)
    - Individuals with diabetes and ASCVD
    - Recurrent ASCVD events
    - Symptomatic peripheral artery disease
    - (Statin associated muscle symptoms)

PCSK9 inhibitors: more things we know

- Cost and cumbersome insurance prior authorizations (improving as now available in pharmacies)
- No new onset diabetes
- Ultra low LDL-C levels (single digit values)

New oral therapies for LDL-C lowering

Additional oral options that complement maximally tolerated lipid-lowering therapies are needed for patients unable to achieve adequate LDL-C lowering

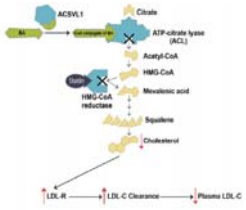
– Insufficient response to high-intensity statins

– Inability to take effective doses of statins due to tolerability issues

-- Cost of injectables

Bempedoic acid (approved Feb 2020 as Nexletol)

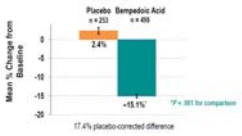
- A once-daily oral, first-in-class, small-molecule drug developed for treatment of high cholesterol
- A prodrug - activated in liver
- Activated drug acts in the same cholesterol synthesis pathway as statins
- **Inhibits ATP-citrate lyase**, upstream of HMG-CoA reductase
  - This decreases hepatic sterol synthesis, upregulates the LDL receptor, and reduces plasma LDL-C levels
- Activated bempedoic acid is not present in skeletal muscle



Thompson et al, J Clin Lipidol. 2015;9:295-304
Goldberg AC et al CLEAR, JAMA 2019

Bempedoic acid: efficacy and safety

EFFICACY



- Patients with ASCVD on statin, LDL-C >70 mg/dL
- 15-25% LDL-C reduction
- Effective in 4-6 weeks, maintained up to 52w in clinical trials
- Overall good tolerance

SAFETY

- AE profile of bempedoic acid was generally similar to that of placebo
- Nasopharyngitis, UTIs
- No new onset diabetes or worsening of diabetes
- No muscle side effects
- Gout and uric acid elevation (esp in those with pre-existing gout)

Goldberg A et al JAMA 2019 Dec

Bempedoic acid: current status

- Bempedoic acid 180mg once a day approved on 2-21-2020; bempedoic acid/ezetimibe combination approved 2-26-2020

Potential uses:

- Patients on maximally tolerated statin dose above LDL-C thresholds
- Statin intolerant patients
- Patients averse/intolerant to injectable therapies

"NO, HDL and LDL were not the robots in Star Wars."

Case 2: Type 2 diabetes and moderate hypertriglyceridemia

- A 64 year old male with T2D for 7 years; also has HTN and dyslipidemia; microalbuminuria
- Takes metformin 1g twice daily, glargine 35 units qhs, Lisinopril 40mg, atorvastatin 40mg
- Last A1C 6.9%
- Lipids – Total cholesterol 170 mg/dL, Triglycerides 280 mg/dL; LDL 90mg/dL; HDL 34 mg/dL, non-HDL-C 146 mg/dL

Case 2

- The next best step in management of his triglyerides is:

1. Increase atorvastatin to 80mg
2. Start ezetimibe 10mg
3. Start fenofibrate 160mg
4. Start purified icosapent ethyl 4g
5. No change in therapy

- Would your choice for management of his lipids be different if he has known ASCVD?

Questions regarding moderate TG elevations

1. Should we be concerned about moderately elevated triglycerides?
   - Do elevated triglycerides increase ASCVD risk?
2. If so, how do we treat moderate hypertriglyceridemia?
3. Do triglyceride lowering medications decrease cardiovascular risk?

Questions

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   - Do elevated triglycerides increase ASCVD risk?
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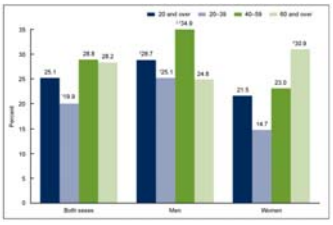
3. Do triglyceride lowering medications decrease cardiovascular risk?

Moderate hypertriglyceridemia is very common

- 16% of US adults have TG >200mg/dl (2006)
- In 2015- 25.1% US adults have TG >150mg/dL

Higher in certain populations

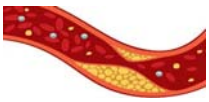
- Mexicans
- South Asians

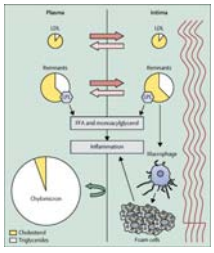


Cohen JD et al 2010
https://www.cdc.gov/nchs/products/databriefs/db198.htm

How might TGs cause vascular disease?

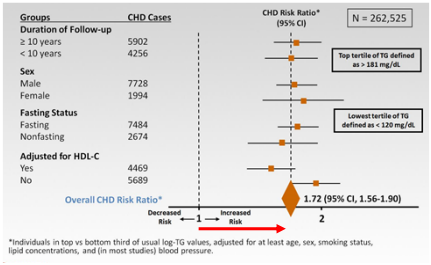
- Chylomicrons are too large to enter the artery wall
- Arterial plaques do not contain triglycerides (TG)
- Remnant lipoproteins from breakdown of larger chylomicrons can enter the intima
  - Local injury, inflammation
- Enable retention of small dense LDL particles





Nordestgaard and Varbo et al Lancet 2014

Triglycerides and CVD risk: meta-analysis



>10,000 cases with coronary heart disease (CHD) in 29 Western prospective studies

Positive association between TG and CHD

Impact similar in men and women

Fasting or non-fasting – no difference

Sarwar N et al Lancet 2007 and 2010

Questions

1. Should we be concerned about moderately elevated triglycerides?
   - Do elevated triglycerides increase ASCVD risk?
2. If so, how do we treat moderate hypertriglyceridemia?
3. Do triglyceride lowering medications decrease cardiovascular risk?

1. First identify and treat secondary causes

- Diabetes (untreated or chronic suboptimal glycemia)
- Hypothyroidism
- Renal disease
- Drugs - beta-blockers, thiazides, oral estrogen, glucocorticoids, atypical antipsychotics etc
- Excessive alcohol consumption
- Weight gain

Chait & Subramanian Endotext 2019

2. Lifestyle intervention and triglycerides

- Weight loss (5-10% ↓ body weight) → TG ↓ 25%, HDL-C ↑ 8%
- Dietary modification → TG ↓ 15% (Mediterranean diet)
- Healthy eating habits – reduced caloric intake, avoidance processed carbohydrates, reduction of alcohol intake
- Avoidance of certain fad diets
- Referral to a trained registered dietitian

3. What drugs lower triglycerides?

- Fibrates – gemfibrozil, fenofibrate 30-50% ↓ TG
- Fish oil – requires >2g for 30-50% ↓ TG
- ~~Niacin – crystalline, slow release; 30-45% ↓ TG~~
- Statins – not first line for TG lowering; dose dependent modest TG lowering (25-40%)

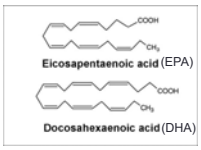
Fibrate trials data are unrevealing so far for cardiovascular protection (gemfibrozil, fenofibrate)

- Fraught with inconsistencies due to patient selection (mostly male), lipid levels, treatment regimens
- 2 fibrate monotherapy trials showed cardiovascular benefit (gemfibrozil – pre-statin era)
- Fibrate studies in patients with T2D showed no benefit
  - Patients with TG >200 and HDL<34mg/dL derived most cardiovascular benefit
  - Reduction in retinopathy and albuminuria in patients with diabetes
- Can be used for lowering pancreatitis risk for TG >1000mg/dL

What about marine or omega-3 fatty acids and cardiovascular disease?

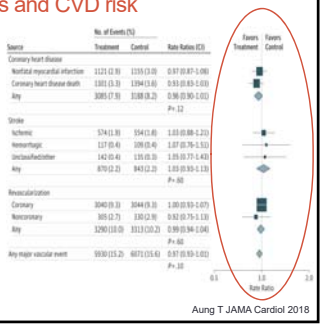
- Lower TGs by 15-50%
- Observational studies - fish oil consumption 1-2x a week associated with reduced risk of heart disease
- 40-60g oily fish/day = 0.2-1.0g/d of n-3 fatty acids
- However RCT results – conflicting!
- Persistent interest because of certain types of vascular benefit: Arrhythmias, heart failure, death from CHD
- Huge global market; widely variable purity and content of supplements and environmental concerns

Omega-3 fish oils



Metanalysis of omega-3 fatty acids and CVD risk

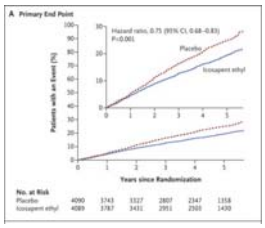
- 10 trials with >77,000 individuals
  - At least 500 individuals each (61% men)
  - Varying doses of EPA and DHA
- No significant effect on of coronary death, nonfatal MI, stroke, revascularization events, or any major vascular events.
- No association of omega-3 FA with all-cause mortality or cancer.



Aung T JAMA Cardiol 2018

REDUCE-IT 2019 – study of EPA in high risk individuals

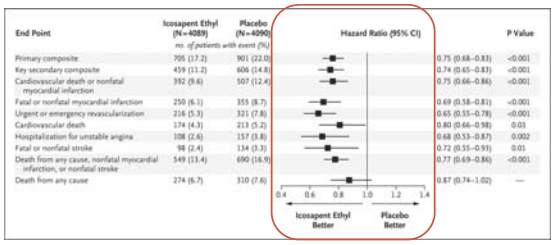
- Cardiovascular efficacy of purified EPA (icosapent ethyl, IPA); N=8179 followed for 4.9y
- Treated with statin
- Had ASCVD or diabetes +1 other risk factor
- Given 4g/d EPA or placebo (mineral oil)
- Fasting TG 135-499mg/dL; LDL 75mg/dL
- Endpoint – 5 point MACE (cardiovascular death, MI, stroke, coronary revascularization, or hospitalization for unstable angina)



•Primary CV endpoint - 17.2% vs 22.0% (HR- 0.75, 95% CI 0.68–0.83; *P* = 0.00000001).
•NNT= 21

DL Bhatt et al. N Engl J Med 2019;380:11-22.

REDUCE-IT: results



DL Bhatt et al. N Engl J Med 2019;380:11-22.

REDUCE-IT: summary of purified EPA study

1. Decreased cardiovascular endpoints by 25%
   - 20% CV death reduction
2. Decreased CV risk attained irrespective of TG levels (not related to attainment of normal TG levels)
3. Mechanism likely explained by metabolic effects beyond TG lowering
   - ? membrane stabilization effects, plaque stability or regression; decrease in inflammation
4. Appropriate patient selection (consider bleeding risk, atrial fibrillation)
   - Secondary prevention in select high risk individuals
5. Possibly highly cost effective

Case 2: Type 2 diabetes and moderate hypertriglyceridemia

- A 64 year old male with T2D for 7 years; also has HTN and dyslipidemia; microalbuminuria
- Takes metformin 1g twice daily, glargine 35 units qhs, Lisinopril 40mg, atorvastatin 40mg
- Last A1C 6.9%
- Lipids – Total cholesterol 170 mg/dL, Triglycerides 280 mg/dL; LDL 90mg/dL; HDL 34 mg/dL, non-HDL-C 146 mg/dL

What next?

- Fibrate?
- Marine fish oil?

- Purified eicosapent ethyl (Vascepa) was prescribed

- Too expensive for patient

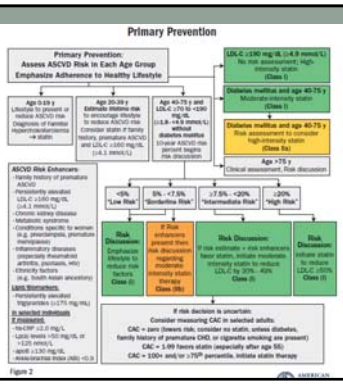
Conclusions

1. LDL-C is primary target for ASCVD risk reduction
2. Statins are the mainstay of lipid lowering
   - High risk people – genetic, diabetes and ASCVD should be treated with intensive regimens
3. Non-statin drugs may be used when ASCVD risk is very high
4. Treatment choices should be based on clinician-patient risk discussions with shared decision-making, particularly for primary prevention treatment choices
5. Elevated triglycerides are now considered a cardiovascular risk
   - Data for fibrate therapy is unclear except in certain subgroups with high TG and low HDL-C
   - Recent data on icosapent ethyl holds great promise for select HTG patients for secondary ASCVD prevention

- THANK YOU!

- UW Medicine Lipid Clinic at South Lake Union
- Email: ssubrama@uw.edu

ACC/AHA Multisociety Blood Cholesterol Guidelines: Primary prevention



ACC/AHA Multisociety Blood Cholesterol Guidelines: Secondary prevention