Preventive Cardiology

Beyond Statins for Cardiovascular Risk Reduction

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Introduction

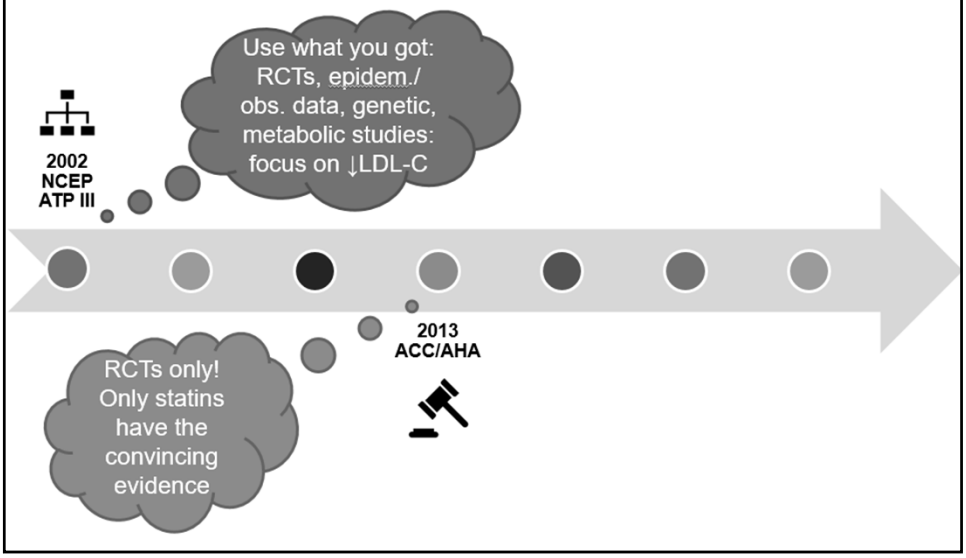
- **Objectives**
  1. **Identify clinical scenarios in which statins and/or non-statin lipid lowering treatments are indicated**
  2. **Describe the mechanism of action of and indications for PCSK9 inhibitors, SGLT2 inhibitors, and high dose omega-3-polyunsaturated fatty acids**

- **No competing interests /financial relationships to disclose**
- **I will discuss what is currently off-label use of icosapent ethyl (Vascepa®)**
- **Branded Rx/OTC products shown: not an endorsement**

Outline

- **Recent history of and important concepts in clinical lipidology**
- **New ACC/AHA Blood Cholesterol guidelines: goals are back**
- **PCSK9 inhibition: when and how?**
- **SGLT2 inhibition: inducing glycosuria improves outcomes**
- **Marine omega-3 polyunsaturated fatty acids: fishy or not?**
- **Other "nutraceuticals": is there a role?**

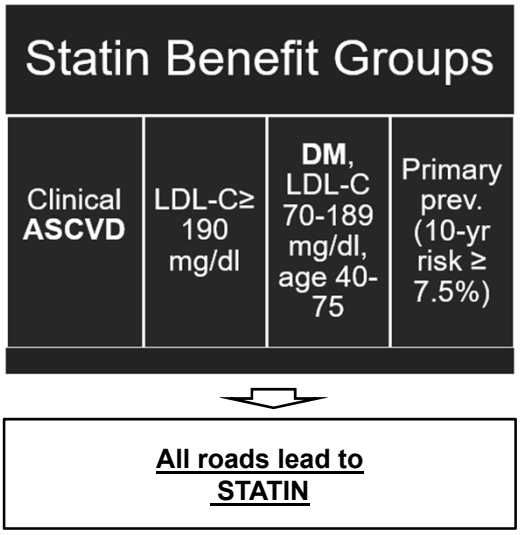
Recent History of Preventive Cardiology



2013 ACC/AHA Guidelines

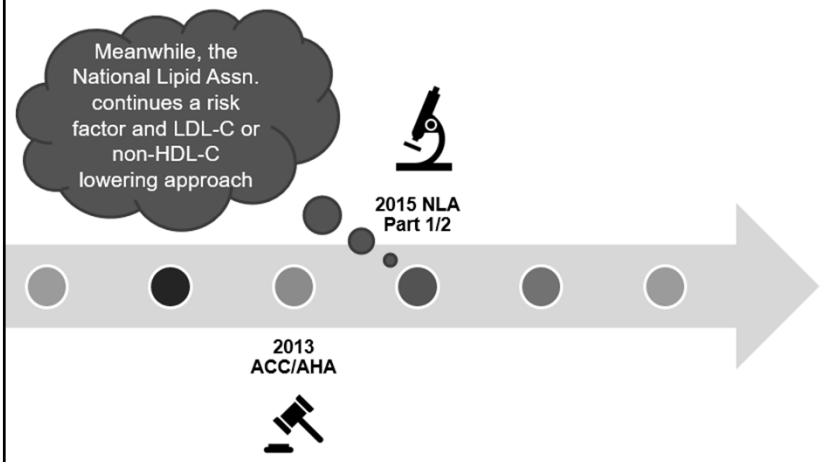
Step 1: Decide whether there is an indication for a statin
Next steps: unclear

- **Is there a goal LDL-C to achieve?**
- **What is the role of non-statins?**
- **The LDL "hypothesis": to what extent does non-statin LDL-C lowering reduce risk?**

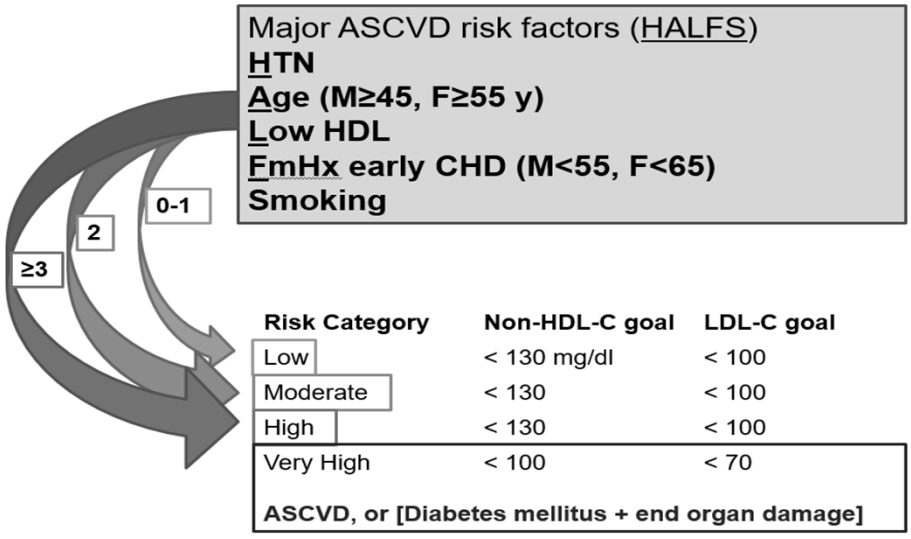


Stone NJ, et al. 2013 ACC/AHA Blood Cholesterol Guideline. *JACC* 2014;63(25):2889-934.

Recent History of Preventive Cardiology

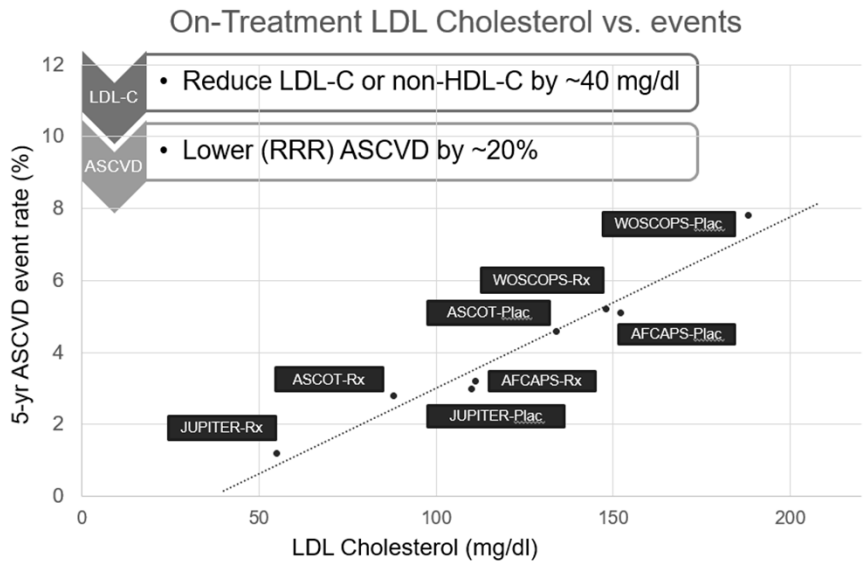


Treatment algorithm: NLA Part 1 / Part 2 (2015)



Jacobson TA, Ito MK, Maki KC, et al. *J Clin Lipidology* 2015;9:129-169.

NLA Part 1 / Part 2 (2015)



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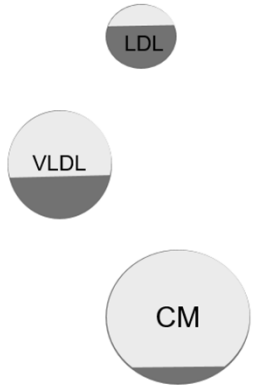
LDL-C vs. Non-HDL-C



C TG

Lipoprotein	Cholesterol (approx. % of lipid content)	Triglyceride (approx. % of lipid content)
LDL	70	30
VLDL or Chylomicron remnant	20	80
Chylomicron	5	95

Walker HK, Hall WD, Hurst JW, eds. Chapter 31, Cholesterol, Triglycerides, and Associated Lipoproteins. Butterworths 1990.

LDL-C vs. Non-HDL-C

- **We live in an LDL-C paradigm. Why?** C TG

Diagnosis → ↓ Lipids (mg/dl)	Normal	Familial Hyperchol.	Metabolic Syndrome / DM
Total-C	158	342	318
HDL-C	59	49	23
LDL-C	88	**280**	?
Triglycerides	53	67	**1,621**
Non-HDL-C	99	293	295
Depiction LDL VLDL / CM remn.			

Walker HK, Hall WD, Hurst JW, eds. Chapter 31, Cholesterol, Triglycerides, and Associated Lipoproteins. Butterworths 1990.

LDL-C vs. Non-HDL-C

- **We live in an LDL-C paradigm. Why?**

LDL-C	Non-HDL-C	N (MACE)	N (Total)	HR (95% CI)
≥ 100 mg/dl	≥ 130 mg/dl	1,877	10,419	1.21 (1.13-1.29)
≥ 100 mg/dl	< 130 mg/dl	467	2,873	1.02 (0.92-1.12)
< 100 mg/dl	≥ 130 mg/dl	283	1,435	1.32 (1.17-1.50)
< 100 mg/dl	< 130 mg/dl	2,760	23,426	1.00 (Reference)

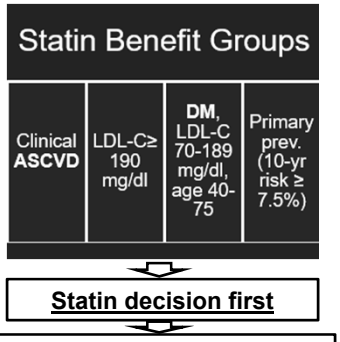
- **Statin-treated patients who reached goals of LDL-C, non-HDL-C, both, or neither**
- **When discordant, non-HDL-C predicts major CV events better than LDL-C**
- **HRs adjusted for sex, age, smoking, DM, SBP, and trial**

Boekholdt SM, Arsenault BJ, Mora S, et al. *JAMA*. 2012;307:1302–1309
Cited in Jacobson TA, Ito MK, Maki KC, et al. *J Clin Lipidology* 2015;9:129-169.

2016-2017 ACC Expert Consensus

- **Role of non-statin therapies for LDL-C lowering in management of ASCVD risk**

Step 1: Decide whether there is an indication for a statin
Step 2: Consider non-statin therapies
Step 3: Recognize non-statin indications



- **Consider adherence, statin tolerance, control of risk factors**
- **Consider percentage LDL-C & non-HDL-C reduction and level achieved**
- **Consider ezetimibe, bile acid sequestrants, PCSK9i**

Lloyd-Jones DM, et al. *J Am Coll Cardiol.* 2017 Oct 3;70(14):1785-1822.

Preventive Cardiology

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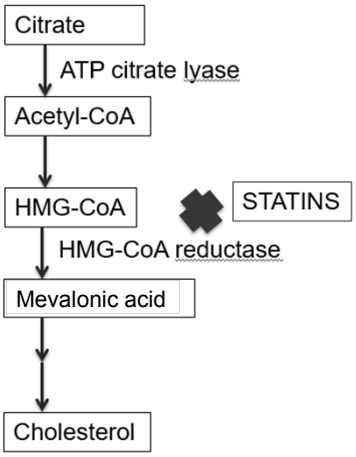
Statins



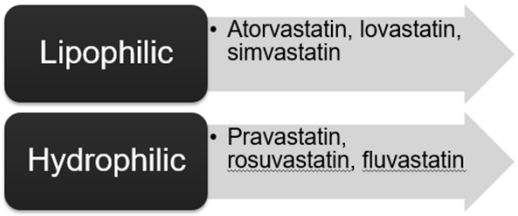
- **Dosing + Effects:**
  - **Potency varies by statin and dose**
    - **High intensity: >50% ↓LDL-C**
    - **May also decrease TRG and HDL**
  - **PO formulations**
  - **Once daily administration***
  - **Newer agents can be taken at any time of day**
- **Pleiotropic effects**
- **Adverse Effects:**
  - **Myalgias, GI upset**
- **Drug interactions**

***exception: fluvastatin**

Rosuvastatin [package insert]/ AstraZeneca. Wilmington, DE. 11/2018. Graphic original.

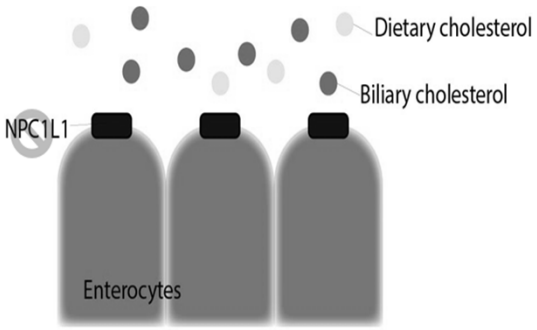
Statins – Potency + Lipophilicity

Intensity:	Lova-	Prava-	Simva-	Fluva-	Pitava-	Atorva-	Rosuvastatin
Low	20mg	20mg	10mg	40mg	1mg		
Mod.	40mg	40mg	20mg	80mg	2mg	10mg	5mg
	80mg	80mg	40mg		4mg	20mg	10mg
High			(80mg)			40mg	20mg
						80mg	40mg



Ezetimibe

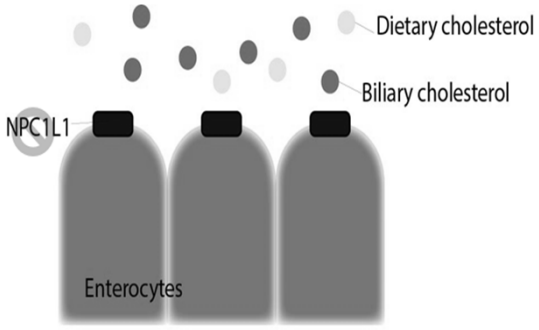
- **Mechanism**
  - **Blocks NPC1L1**
  - **Inhibits enteric cholesterol absorption**
  - **(Statins increase chol. absorption)**
- **Dosing & effect**
  - **10 mg PO daily**
  - **Expect 15-25% ↓LDL-C**



Drug information: "Ezetimibe." Drug Monograph. Gold Standard. Published August 1, 2017. Graphic original.

Ezetimibe

- **Adverse effects**
  - **Respiratory tract symptoms (4% vs. 2% placebo)**
  - **Transaminase elevations with statins (1-2%)**
  - **GI symptoms comparable to placebo Dosing & effect**



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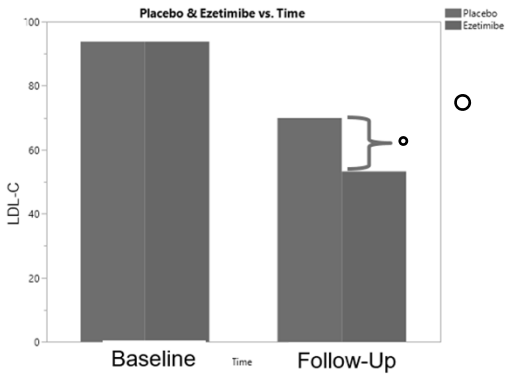
IMPROVE-IT

- **Outcomes from non-statin driven LDL-C reduction**



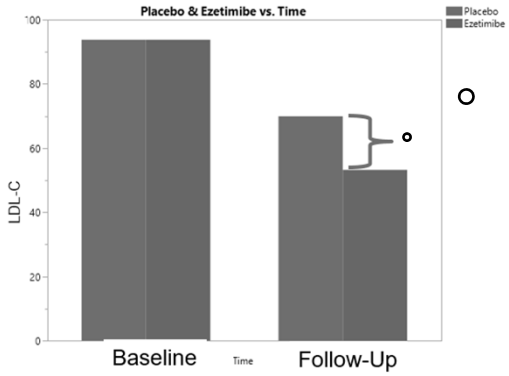
24% additional LDL-C reduction

- **18,144 patients with acute coronary syndrome**
- **LDL-C at baseline: 50 to 125 mg/dl**
- **Randomization: simvastatin 40 mg + [ezetimibe 10 mg OR placebo]**

Cannon CP, et al. *New Engl J Med* 2015;372(25).

IMPROVE-IT

- **Outcomes from non-statin driven LDL-C reduction**



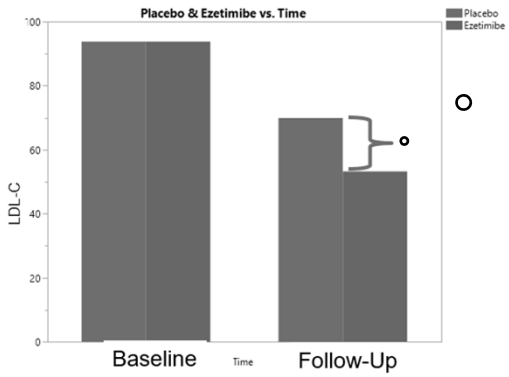
24% additional LDL-C reduction

- **Primary end point composite: cardiovascular death, nonfatal MI, UA requiring hospitalization, coronary revascularization (≥ 30 d after randomization), nonfatal CVA**

Cannon CP, et al. *New Engl J Med* 2015;372(25).

IMPROVE-IT

- **Outcomes from non-statin driven LDL-C reduction**



24% additional LDL-C reduction

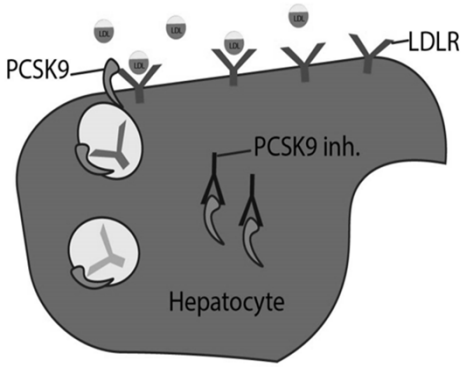
- **Median follow up 6 years**
- **Outcome: HR 0.936 (95% CI 0.89-0.99)**

Cannon CP, et al. *New Engl J Med* 2015;372(25).

PCSK9 inhibitors

***Mechanism**, dosing, and adverse effects*

- **Mechanism**
  - **Human IgG1/2 mAb that inhibits proprotein convertase subtilisin/kexin type 9 binding to LDLR**
  - **$T_{1/2}$ 17-20 days (alirocumab) or 11-17 (evolocumab) days**

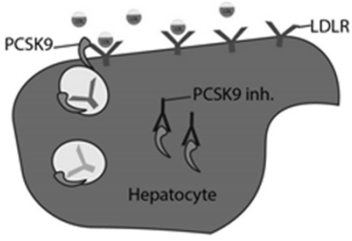


Drug information: "Alirocumb." Drug Monograph. Gold Standard. Published November 14, 2018.
Drug information: "Evolocumab. " Drug Monograph. Gold Standard. Published October 23, 2018.
Graphic original

PCSK9 inhibitors

***Mechanism**, dosing, and adverse effects*

- **Dosing & effect**
  - **Alirocumab: 75-150 mg SQ q2wk, OR 300 mg SQ q4wk**
  - **Evolocumab: 140 mg SQ q2wk or 420 mg SQ q4wk**
  - **Expect 50-70% additional ↓LDL-C**



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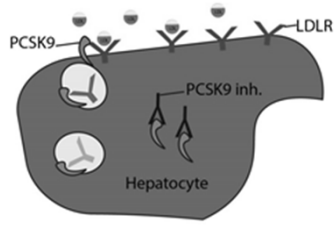
Graphic original

PCSK9 inhibitors

***Mechanism**, dosing, and adverse effects*

- **Adverse effects**
  - **Injection site reactions (7% vs. 5% placebo)**
  - **Nasopharyngitis, flu-like reaction, myalgias, new onset DM similar to placebo**
  - **Antibody formation**
  - **Rare serious allergic reactions**



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Graphic original

PCSK9 inhibitors

FOURIER: Outcomes from non-statin driven LDL-C reduction

- **Enrollment: 27,564 patients with ASCVD, LDL-C ≥ 70 mg/dl receiving statin therapy**
- **Treatment: evolocumab 140 mg q2wk or 420 mg q4wk vs. placebo**
- **Outcome: [CV death, MI, CVA, hospitalization for UA, coronary revascularization]**
- **Follow up: median 2.2 years**

Sabatine MS, Giugliano RP, Keech AC, et al. *New Engl J Med* 2017 May 4;376(18):1713-1722.

PCSK9 inhibitors

FOURIER: Outcomes from non-statin driven LDL-C reduction

- **Outcome: [CV death, MI, CVA, hospitalization for UA, cor. revasc.]**
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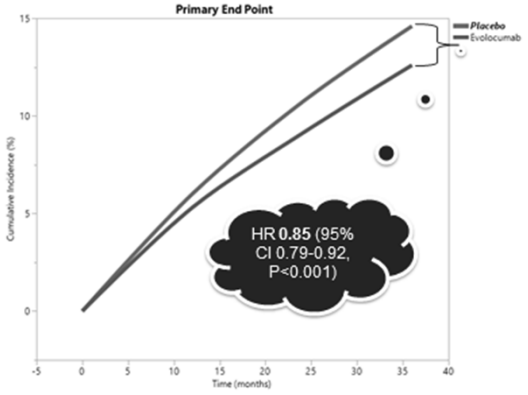

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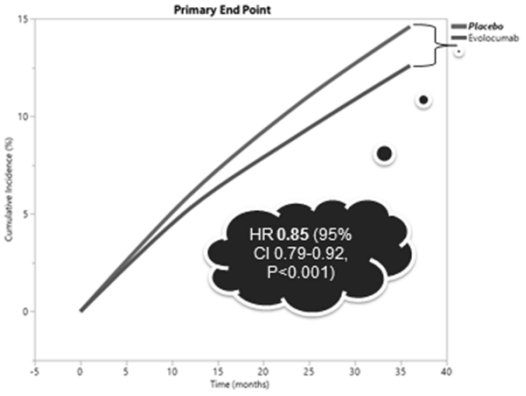
PCSK9 inhibitors

FOURIER: Outcomes from non-statin driven LDL-C reduction

- **Adverse events: no significant difference (incl. new DM, neurocognitive events) except injection site reactions (2.1% vs. 1.6% placebo)**



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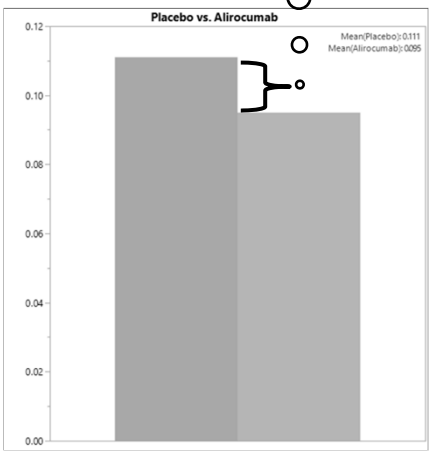
PCSK9 inhibitors

HR 0.85 (95% CI 0.78-0.93, P<0.001)

ODYSSEY OUTCOMES: Outcomes from non-statin driven LDL-C reduction

- **Enrollment: 18,924 patients with acute coronary syndrome**
- **Uncontrolled cholesterol: LDL-C ≥ 70 or non-HDL-C ≥ 100 mg/dl on high-intensity or maximum-tolerated statin**



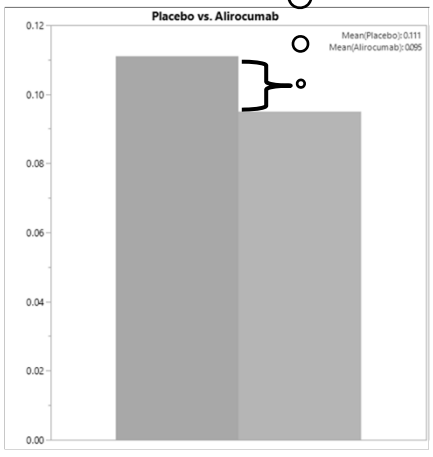
Schwartz GG, et al. *N Engl J Med.* 2018 Nov 29;379(22):2097-2107.

PCSK9 inhibitors

HR 0.85 (95% CI 0.78-0.93, P<0.001)

ODYSSEY OUTCOMES: Outcomes from non-statin driven LDL-C reduction

- **Treatment: alirocumab vs. placebo (targeted LDL-C 25 to 50 mg/dl)**
- **Outcome: [CHD death, nonfatal MI, ischemic CVA, UA req. hospitalization]**
- **Follow-up median 2.8 years**



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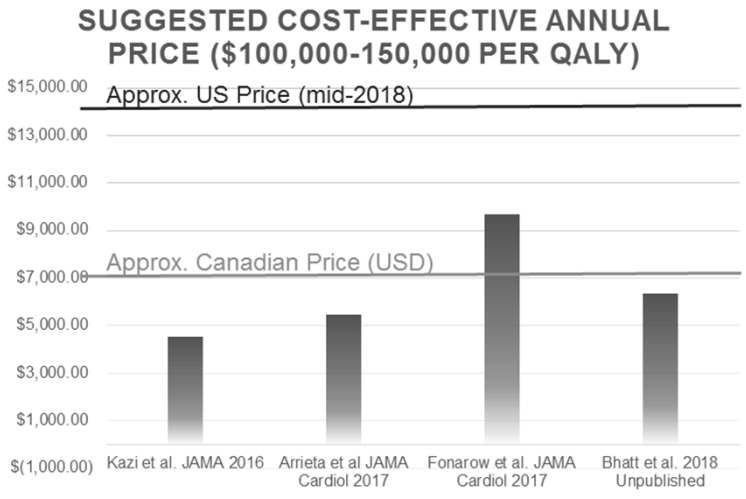
PCSK9 inhibitors

Outcomes from non-statin driven LDL-C reduction

	FOURIER	ODYSSEY OUTCOMES
Primary endpoint (composite)	CV death, MI, stroke, hospitalization for unstable angina, or cor. revascularization	CHD death, non-fatal MI, fatal or non-fatal ischemic stroke, or UA requiring hospitalization
Treatment vs. placebo	9.8% vs. 11.3%	9.5% vs. 11.1%
Median follow up	2.2 years	2.8 years
HR	0.85	0.85
NNT	67	64

PCSK9 inhibitors: what about cost?



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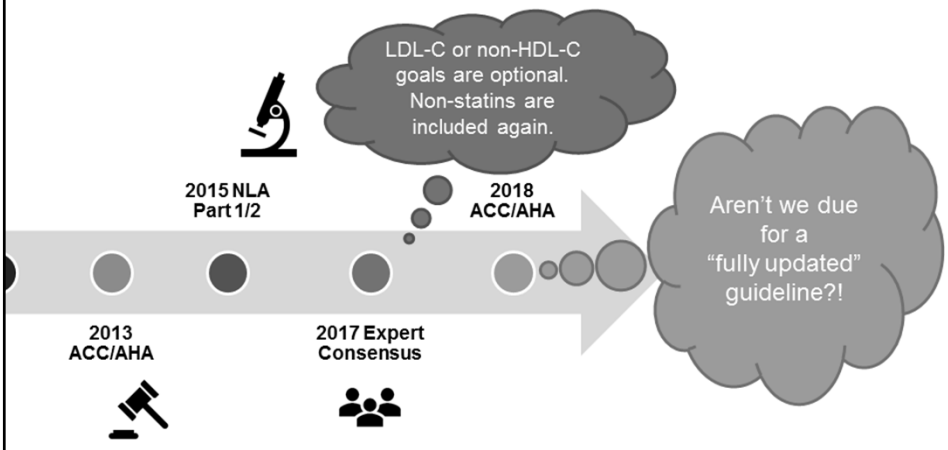
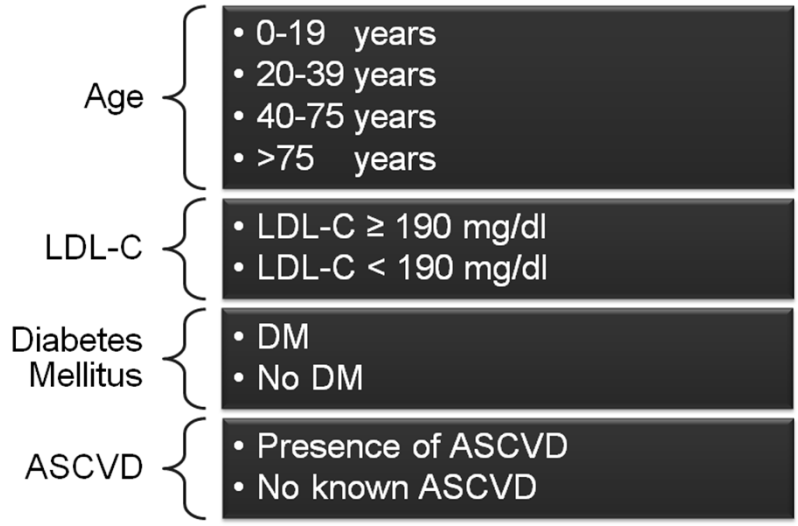
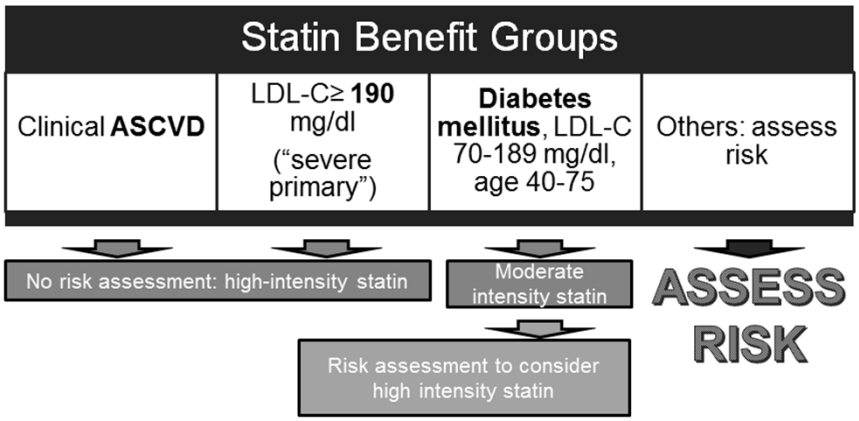


2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/ AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol



Grundy et al. *J Am Coll Cardiol.* 2018 Nov 8. pii: S0735-1097(18)39034-X.

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/ AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol



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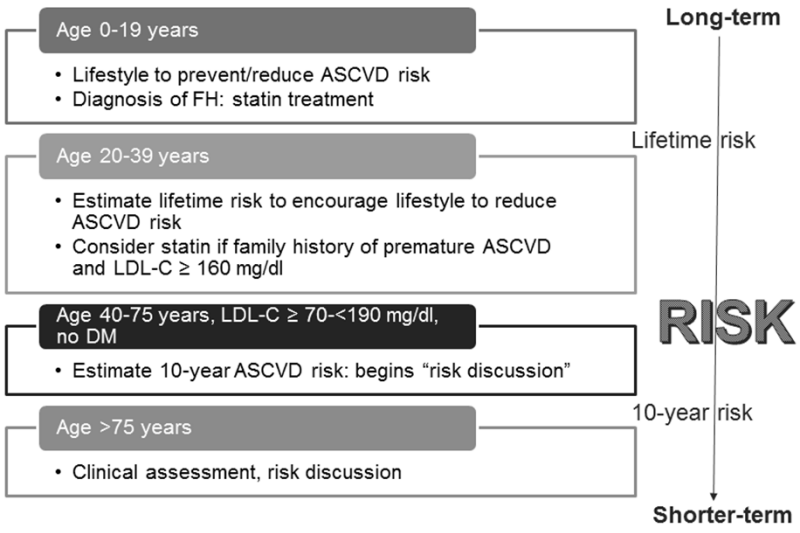

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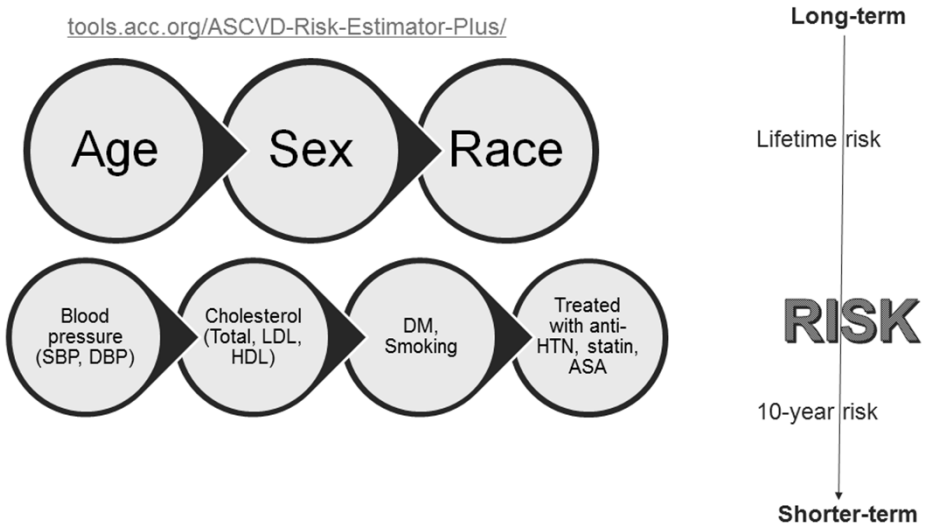

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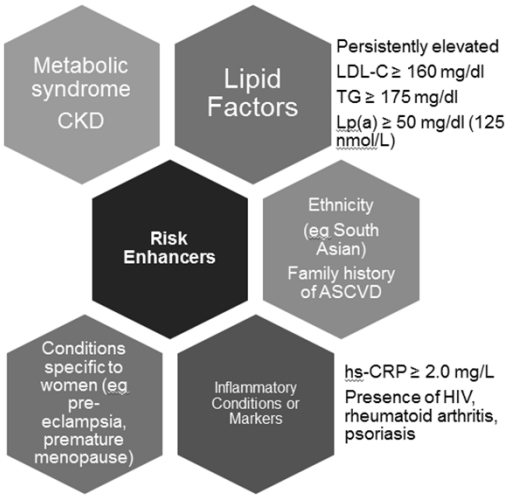
2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/ AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

- **Principles of the guideline**
  - **Assess ASCVD risk in each age group**
  - **Emphasize adherence to healthy lifestyle**



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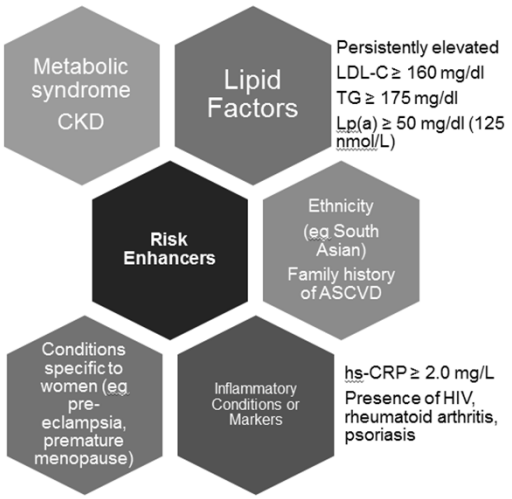
2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/ AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

- **Principles of the guideline**
  - **Consider ASCVD risk "enhancers" when making treatment decisions**



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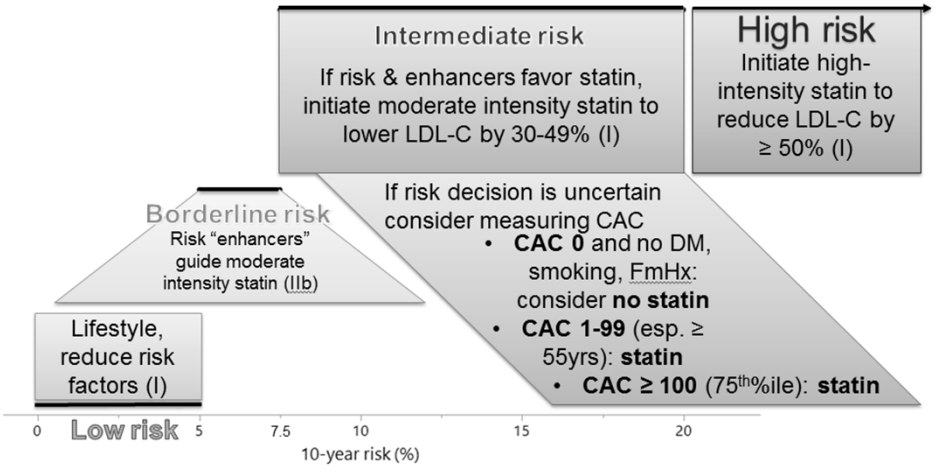
2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/ AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

At all levels:
provide a "risk discussion" as it relates to the management plan



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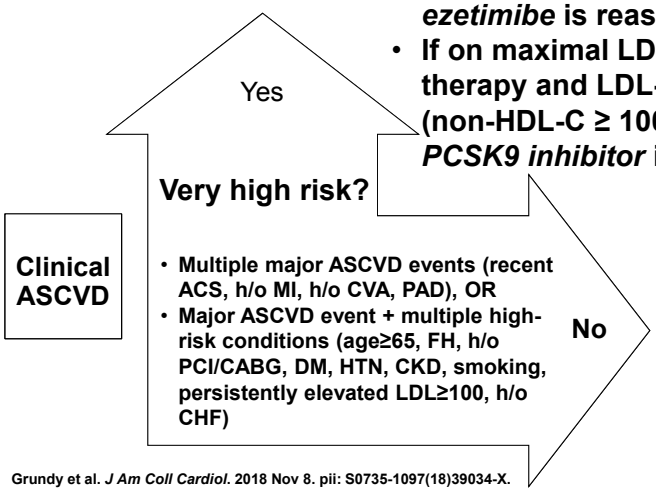
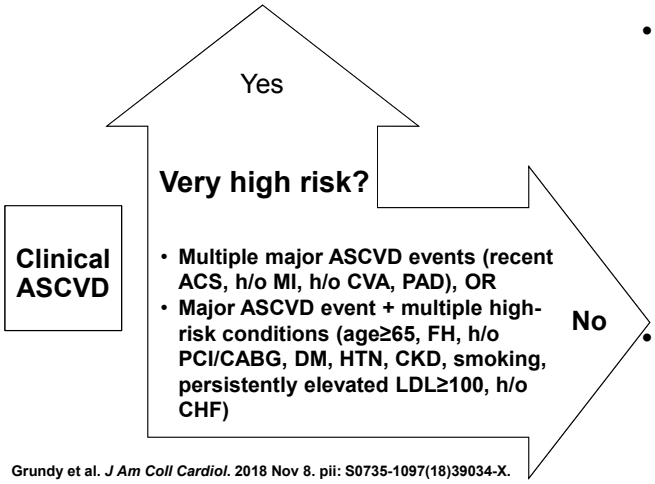
2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/ AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

- **High-intensity/maximal statin (I)**
- **If LDL-C ≥ 70 mg/dl, adding *ezetimibe* is reasonable (IIa)**
- **If on maximal LDL-C lowering therapy and LDL-C remains ≥ 70 (non-HDL-C ≥ 100) mg/dl, adding *PCSK9 inhibitor* is reasonable (IIa)**



Grundy et al. *J Am Coll Cardiol.* 2018 Nov 8. pii: S0735-1097(18)39034-X.

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/ AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol



- **High (or if >75 yrs, moderate or high [IIa]) intensity statin (I), or if not tolerated, moderate intensity statin**
- **If LDL-C ≥ 70 mg/dl, *ezetimibe* is reasonable**

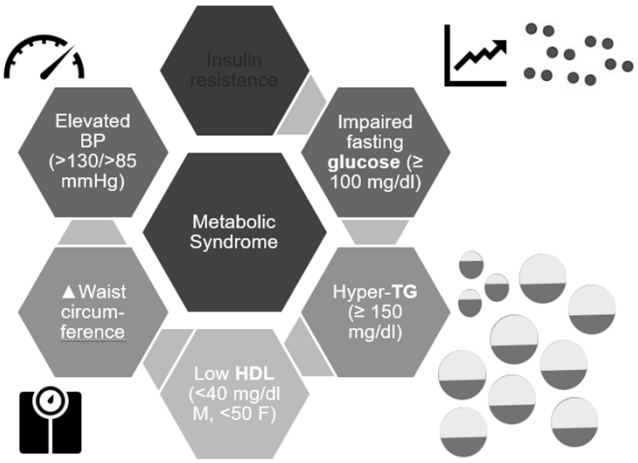
Grundy et al. *J Am Coll Cardiol.* 2018 Nov 8. pii: S0735-1097(18)39034-X.

Outline

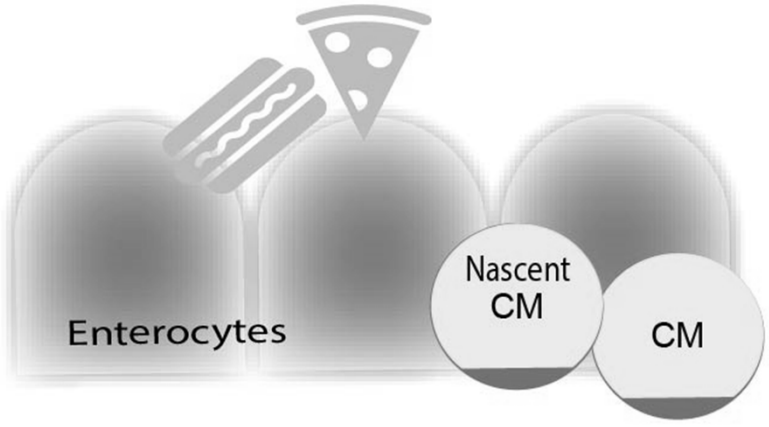
- **Recent history of and important concepts in clinical lipidology**
- **New ACC/AHA Blood Cholesterol guidelines: goals are back**
- **PCSK9 inhibition: when and how?**
- **SGLT2 inhibition: inducing glycosuria improves outcomes**
- **Marine omega-3 polyunsaturated fatty acids: fishy or not?**
- **Other "nutraceuticals": is there a role?**

Metabolic syndrome and diabetes mellitus

- **Metabolic syndrome: co-occurrence of cardiovascular risk factors**
- **Share mechanisms of type 2 diabetes mellitus**

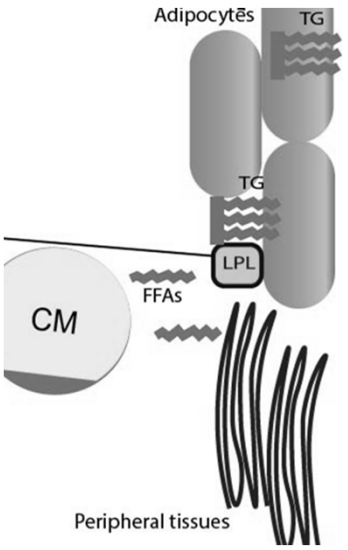


Huang PL. *Dis Model Mech* 2009. Graphics original.



- Chapter 35: Special Patient Populations: Diabetes and Metabolic Syndrome. Clinical Lipidology. Ballantyne, ed. Elsevier.
- Filippas-Ntekouan. *Exp Op Drug Metab & Tox* 2018;14(11):1113-1121.
- Graphic original.

- **Hormone sensitive lipase (HSL) mobilizes stored fat, breaking down TGs, freeing FAs**
- **More energy in bloodstream**
- **HSL is inhibited by insulin**
  - **Lipoprotein lipase (LPL) cleaves TGs into free fatty acids (FFAs)**
  - **"Clears" TG-rich particles from the circulation**
  - **Less energy in bloodstream**
  - **LPL is activated by insulin**



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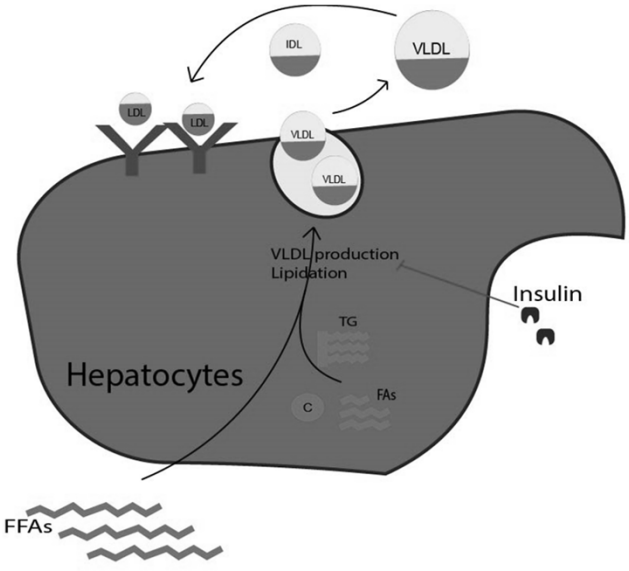
- Graphic original.



- **Hepatic VLDL production also occurs when increased circulating energy stores are needed**
- **VLDL production is inhibited by insulin**

- Chapter 35: Special Patient Populations: Diabetes and Metabolic Syndrome. Clinical Lipidology. Ballantyne, ed. Elsevier.
- Filippas-Ntekouan. *Exp Op Drug Metab & Tox* 2018;14(11):1113-1121.
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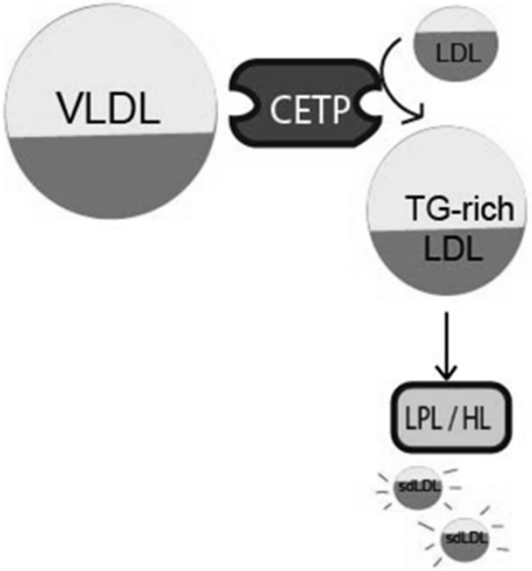
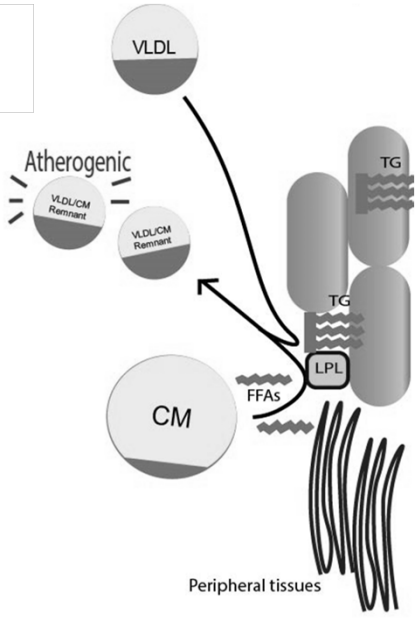


- **VLDL can transfer its TG content to LDL**
- **TG-rich LDL is preferentially converted to small, dense LDL which is particularly atherogenic**

- Chapter 35: Special Patient Populations: Diabetes and Metabolic Syndrome. Clinical Lipidology. Ballantyne, ed. Elsevier.
- Filippas-Ntekouan. *Exp Op Drug Metab & Tox* 2018;14(11):1113-1121.
- Graphic original.

- **After VLDL and chylomicrons (CM) donate their lipid contents to end-tissues, they become VLDL or CM remnants**
- **Remnants are particularly atherogenic**



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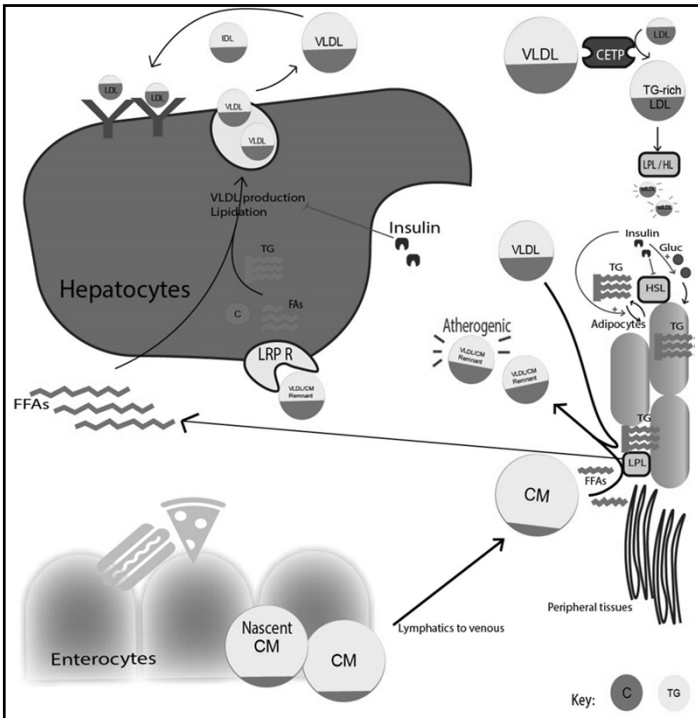

Normal state

- Circulating VLDLs and CMs are kept to a minimum
- Energy is "cleared appropriately" from the bloodstream for utilization or storage

- Chapter 35: Special Patient Populations: Diabetes and Metabolic Syndrome. Clinical Lipidology. Ballantyne, ed. Elsevier.
- Filippas-Ntekouan. *Exp Op Drug Metab & Tox* 2018;14(11):1113-1121.
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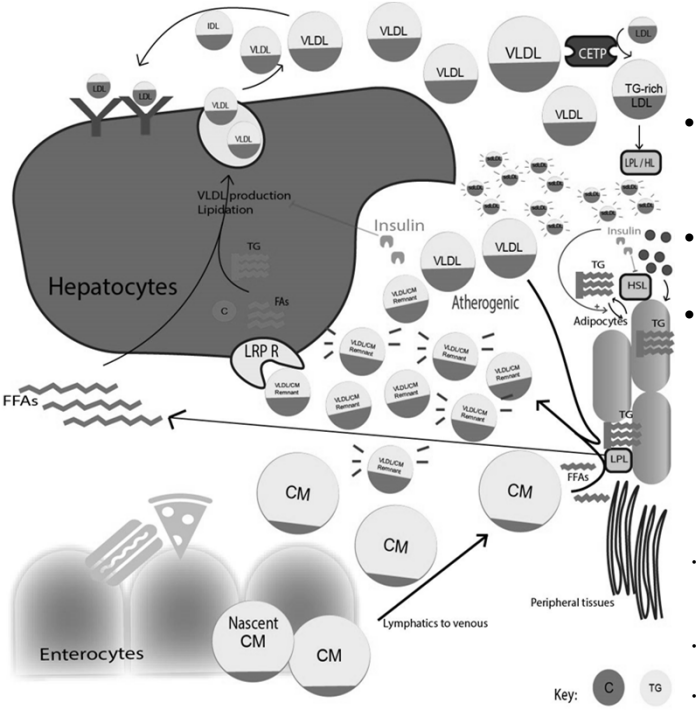


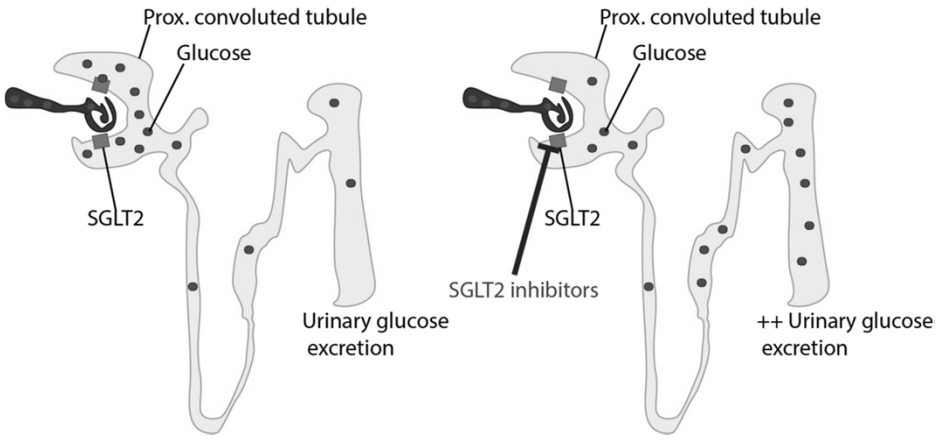
Diabetic dyslipidemia

- Increased serum triglycerides
- Decreased HDL-C
- Predominance of small dense LDL particles and VLDL/CM remnants

- Chapter 35: Special Patient Populations: Diabetes and Metabolic Syndrome. Clinical Lipidology. Ballantyne, ed. Elsevier.
- Filippas-Ntekouan. *Exp Op Drug Metab & Tox* 2018;14(11):1113-1121.
- Graphic original.

SGLT2 inhibitors

- **Therapeutic glycosuria**



SGLT2 inhibitors

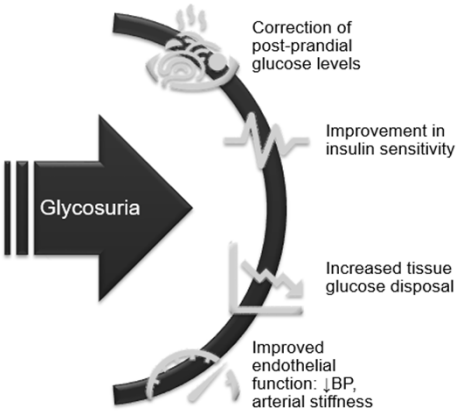
- **Class currently includes canagliflozin, dapagliflozin, and empagliflozin**
- **Mechanism**
  - **Prevent reabsorption of glucose by the kidneys**
  - **Net decrease in blood sugar**
- **Dosing & effect**
  - **Oral agents with daily dosing**
  - **A1c lowering of 0.5-0.8%**
- **Adverse effects**
  - **Hypotension**
  - **Urinary tract infections**
  - **Ketoacidosis**
  - **AKI**

Canagliflozin [package insert]. Janssen Pharmaceuticals, Inc. Titusville, NJ. 2013.

SGLT2 inhibitors

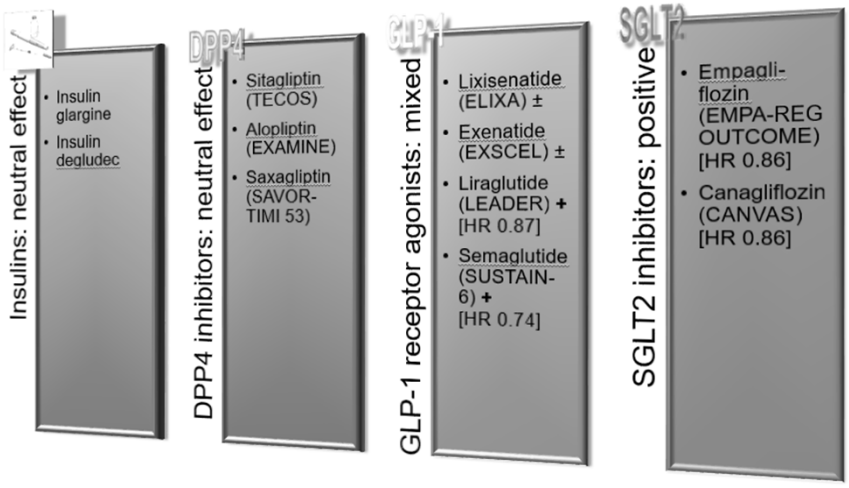
- **Therapeutic glycosuria**

Parameter	Approximate effect of SGLT2 inhibitor treatment
Body weight	↓ 4 kg
Visceral adipose tissue mass	↓ 8%
Triglycerides	↓ 4%
HDL-C	↑ 6%
LDL-C	↑ 2%



Inzucchi SE et al. *Diab & Vasc Dis Res* 2015;12(2):90-100.

Summary of CV benefit/harm of diabetic drugs



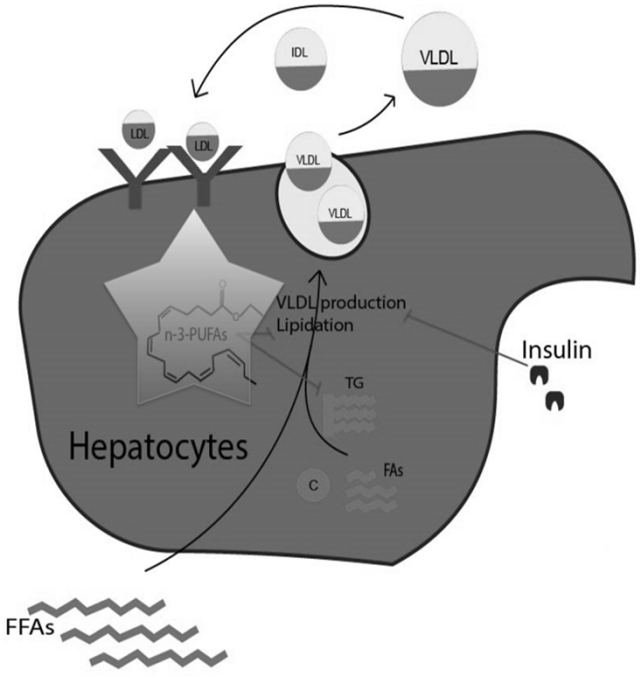
- Agent (STUDY example) [HR for generally primary endpoint of MACE, p<0.05]

Cefalu WT et al. *Diab Care* 2018;41:14-31.

See Dr. Joshua Joseph's MedNet21 webcast for more information

Outline

- Recent history of and important concepts in clinical lipidology
- New ACC/AHA Blood Cholesterol guidelines: goals are back
- PCSK9 inhibition: when and how?
- SGLT2 inhibition: inducing glycosuria improves outcomes
- Marine omega-3 polyunsaturated fatty acids: fishy or not?
- Other “nutraceuticals”: is there a role?

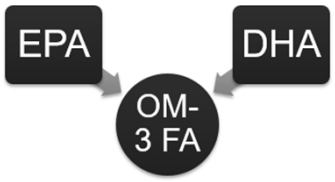


- Recall: regulation of VLDL synthesis is under the control of insulin
- Also: ω-3-poly-unsaturated fatty acids (ω-3-PUFAs) inhibit VLDL lipidation and TG production

- Chapter 35: Special Patient Populations: Diabetes and Metabolic Syndrome. Clinical Lipidology. Ballantyne, ed. Elsevier.
- Filippas-Ntekouan. *Exp Op Drug Metab & Tox* 2018;14(11):1113-1121.
- Graphic original.

Omega-3 Fatty Acids

- Mechanism of action – not well elucidated
  - Proposed: increased beta oxidation, inhibition of acyl-CoA, decreased hepatic production of VLDL, increased LPL activity
- Dosing & effect
  - For TG >500: dosed at 2g twice daily
  - Primary effect is to lower TG
    - DHA component can increase LDL
- Adverse effects
  - Prolongation of bleeding time
  - Fishy aftertaste or belching
  - Nausea

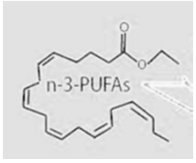


Vascepa [package insert]. Amarin Pharma Inc. Bedminster, NJ. 2012.

ω-3-poly-unsaturated fatty acids

- Do they reduce serum triglycerides?
  - Yes
- Do they change outcomes?

DHA 22:6
EPA 20:5



Parameter	Approximate effect of ω-3-PUFA treatment
Non-HDL-C	↓ 5-14%
Triglycerides	↓ 19-44%
HDL-C	±
LDL-C	↓6%-↑25%

Jacobson TA, Ito MK, Maki KC, et al. *J Clin Lipidology* 2015;9:129-169.

ω-3-poly-unsaturated fatty acids

Does treatment change outcomes?

Trial	Endpoints / Mean Follow-up	Daily dose	Outcome
Meta-analysis of 10 trials Aung et al. *JAMA Cardiol* 2018 (n=77,917) prior CHD, CVA, or high ASCVD risk	Any CHD (fatal/nonfatal) or major vascular events 4.4 years	Generally **1 g** EPA/DHA	**No effect**
GISSI-Prevenzione investigators *Lancet* 1999; (n=11,324) with recent MI (2x2 design also with vit. E)	Death, non-fatal MI, CVA 3.5 years	**1 g** EPA/DHA vs. Placebo	**Benefit** Composite RRR 10% Death RRR 14%
JELIS Yokogama et al. *Lancet* 2007 (n=18,645) unselected hypercholesterolemic (Total-C > 252 mg/dl) Japanese patients	Any CHD event (CHD death, SCD, fatal/nonfatal MI, UA, PCI, CABG) 4.6 years	Statin + [**1.8 g EPA-only** or placebo]	**Benefit** Composite RRR 19% No difference in LDL

REDUCE-IT

- **Enrollment: 8,179 patients with hypertriglyceridemia (135-499 mg/dl) and "controlled" LDL (41-100 mg/dl).**
- **Patients were (mean) 64 yrs, 71% male, BMI 30.8, most on statins**
- **Endpoint: [CV death, nonfatal MI, nonfatal CVA, coronary revascularization or UA]**
- **Treatment: icosapent ethyl (EPA only) 4 g/day (2 g bid with food) vs. placebo (mineral oil)**
- **Follow-up: 4.9 yrs.**

Parameter	Treatment (EPA)	Placebo
Triglycerides	↓18.3% (-39 mg/dl)	↑2.2% (+4.5 mg/dl)
LDL-C	↑3.1% (+2.0 mg/dl)	↑10.2% (+7.0 mg/dl)

HR 0.75 NNT 21 (RRR 20% for CV death)

Bhatt DL, et al. *N Engl J Med.* 2019 Jan 3;380(1):11-22

REDUCE-IT

What's the catch?

- **Any adverse effects?**
  - **No difference in bleeding, including hemorrhagic stroke**
  - **Hospitalization for atrial fibrillation or flutter was 3.1% in EPA group vs. 2.1% placebo (p=0.0004).**
- **Is it just the triglyceride lowering?**
  - **ACCORD-Lipid: fenofibrate lowers TG but no change in outcome**
  - **AIM-HIGH, HPS2-THRIVE: niacin lowers TG but no change in outcome**
- **Will REDUCE-IT change practice?**

Bhatt DL, et al. *N Engl J Med.* 2019 Jan 3;380(1):11-22

ω-3-poly-unsaturated fatty acids

- **Antiarrhythmic or not?**

Trial	Dose	Outcomes
REDUCE-IT 2019	4 g/d **EPA only**	↑47% excess atrial fib/flutter
Cochrane Review 2018 79 RCTs, (n=112,059)	Varies (0.5 to >5 g/d)	Marine: No difference arrhythmia Plant-based (ALA): ↓21% arrhythmias
GISSI-HF (n=6,975) with HF	1 g/d mixed	No difference in atrial fibrillation ↓9% mortality; ↓8% HF admissions

- **Animal studies suggest DHA may have antiarrhythmic properties in AF**

Bhatt et al. *New Engl J Med* 2019;380(1):11-22.
Abdelhamid et al. *Cochrane Database Syst Rev* 2018;11:CD003177.
Aleksova et al. *Eur J Heart Fail* 2013;15(11):1289-95.
Tavazzi et al. *Lancet* 2008;372(9645):1223-30.
Ninio et al. *J Cardiovasc Electrophysiol* 2005 16:1189-1194.

ω-3-poly-unsaturated fatty acids

- **Current Rx products and labeling**

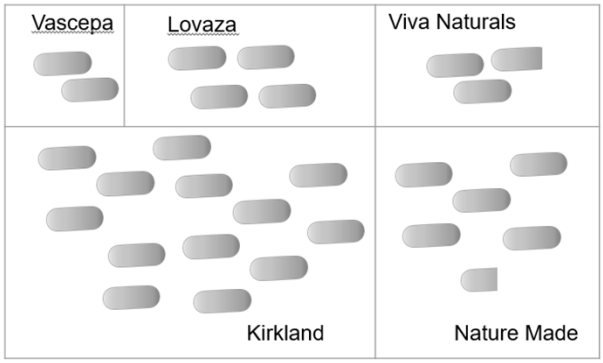
Agent	Trade Name Composition	Dose	Labeled Indication
Icosapent ethyl	Vascepa®	2 g bid **with food**	• Significant hypertriglyceridemia (>500 mg/dl) as adjunct to diet and exercise
ω-3 acid ethyl esters	Lovaza® 55% EPA / 45% DHA	4 g qd or 2 g bid +/- food	• Significant hypertriglyceridemia (>500 mg/dl) as adjunct to diet and exercise • For use as adjunct to simvastatin for hyper-TG
ω-3 carboxylic acids	Epanova® Mostly EPA	2-4 g qd +/- food	• Significant hypertriglyceridemia (>500 mg/dl) as adjunct to diet and exercise

Source: Drug Monographs. Gold Standard. Accessed 20 Jan 2019.

ω-3-poly-unsaturated fatty acids

- **Should I just buy OTC fish oil at the drug store?**

How to get 2 g EPA



700 mg EPA
240 mg DHA

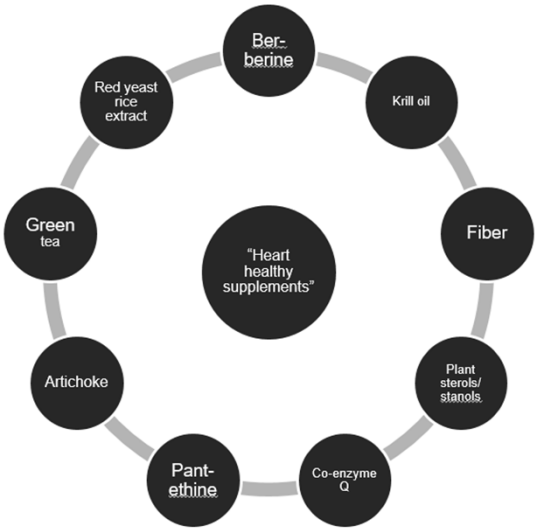
250 "omega-3"
?150 mg EPA
?100 mg DHA

360 mg EPA
300 mg DHA

"Nutraceuticals"

"Doc, is it OK if I take…?"

- ***"Certain nutraceuticals…alone or in combination with each other, as well as ezetimibe, might be considered as an alternative or add-on therapy to statins, although there is still insufficient evidence available with respect to long-term safety and effectiveness …."***



Banach et al. *J Am Coll Cardiol* 2018;72:96-118.

"Nutraceuticals" and lifestyle changes

Highlights

Intervention	Mechanism of action	Dose	Expected Δ LDL-C (relative)
Increased physical activity	Multifactorial	200-300 min/week	↓~5%
Loss of body weight	Multifactorial	↓5% body weight	↓3-5%
Diet low in saturated and trans fats	↓LDL-C production		↓5-10%
Viscous fiber	Bile acid sequestration, ↑satiety	5-10 g/day	↓5-20%
Plant sterols/stanols	Competitive inhibition of cholesterol absorption	2 g/day	↓~10%

Kraus et al. *N Engl J Med.* 2002;347(19):1483-92.
Jacobson et al. *J Clin Lipidol.* 2015;9(6 Suppl):S1-122.
Banach et al. *J Am Coll Cardiol* 2018;72:96-118.

"Nutraceuticals" and lifestyle changes

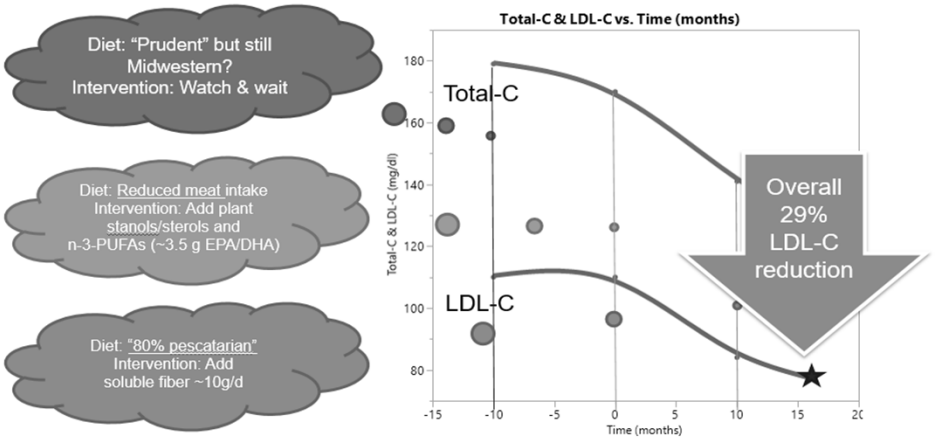
Highlights

Agent	Mechanism of action	Dose	Δ LDL-C (absolute)
Berberine	Has PCSK9 inhibitory properties, increases LDLR expression and decreases intestinal chol. absorption	300 mg/day	↓25 mg/dl
Artichoke	Luteolin interacts with HMG-CoA reductase, SREBPs, ACAT	500-2,700 mg/d	↓15 mg/dl
Garlic	Inhibition of HMG-CoA reductase	5-6 g/d	↓9 mg/d
Green tea	Inhibition of inducible NO synthase, inhibition of HMG-CoA reductase	170-1,200 mg/d	↓7 mg/dl

Summarized in Banach et al. *J Am Coll Cardiol* 2018;72:96-118.
Li et al. *J Biol Chem* 2009;284:28885-95.

A Case Study

34 year-old man with family history of heart disease is interested in lowering his cholesterol "naturally" (despite low 10-year est. ASCVD risk).



Take Home Points

- Recent history of and important concepts in clinical lipidology
  - Please consider non-HDL-C as well as LDL-C lowering, especially in hypertriglyceridemics
- New ACC/AHA Blood Cholesterol guidelines
  - Goal atherogenic cholesterol levels are both motivating and evidence based
- PCSK9 inhibition: when and how?
  - FH or ASCVD and LDL-C > 70 or non-HDL-C > 100 mg/dl

Take Home Points

- SGLT2 inhibition: inducing glycosuria improves outcomes
  - Discuss ASCVD benefits of DM drugs with PCP, endocrine
- Marine omega-3 polyunsaturated fatty acids and other “nutraceuticals”
  - May have a role, consider in statin intolerance/refusal