AU InforMed

Volume 14 Number 6 (Issue 285) *Friday, September 2, 2016*

Guest Editors: Jonathan Le, Frank Smith, Matt Cole, Pharm.D. Candidates 2017
Bernie R. Olin, Pharm.D., Editor

Key Inforbits

- Cholesterol Overview
- Lifestyle Changes - Diet
- Lifestyle Changes - Exercise
- Drugs Contributing to Abnormal Lipid Panels
- Pharmacotherapy Overview
- New Lipid-Lowering Therapy

The month of September is…

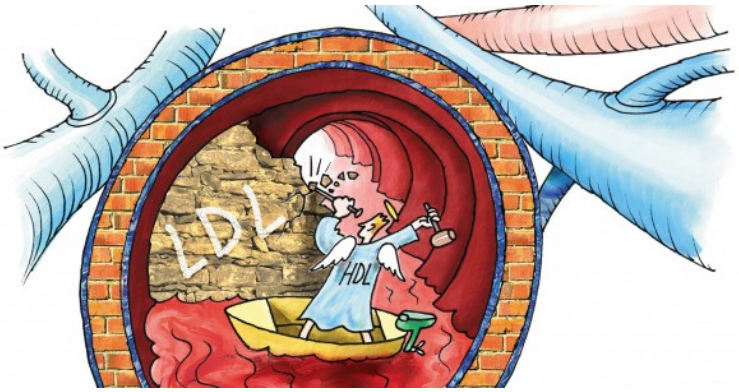
Available from: http://kisbyto.blogspot.com/2012/09/national-cholesterol-education-month.html

Cholesterol Overview

Why is cholesterol important?

Prevention of Coronary Heart Disease (CHD)

"Evidence over the past decades have linked elevated total and LDL cholesterol and reduced HDL to the development of CHD".[1]



Available from: https://www.smartlivingnetwork.com/cholesterol/b/good-cholesterol-vs-bad-cholesterol/

Cholesterol is essential for cell membrane formation, bile acid formation, and hormone production.[2] Triglycerides are the most common type of fat in the body and are an important source of stored energy.[2] Phospholipids provide structure and protection for cellular function and lipid transportation.[2] Together, they form lipoproteins.[2]

The three major lipoproteins in the blood are high-density lipoproteins (HDL), very-low-density lipoproteins (VLDL), and low-density lipoproteins (LDL).[1] Total cholesterol is composed of approximately 20-30% HDL, 10-15% VLDL, and 60-70% LDL.[1] Tagged as the

"good cholesterol", HDL is desirable due to its function of transporting cholesterol from vascular tissue back to the liver.[2] VLDL and LDL are considered the "bad cholesterol" because they contribute to the development of atherosclerosis.[2] LDL encompasses the majority of total cholesterol, thus making it the primary target of therapy.

What are normal lipid panel values?[1]

- Total cholesterol: <200 mg/dL
- LDL cholesterol: <100 mg/dL
- HDL cholesterol: >40 mg/dL
- Triglycerides: <150 mg/dL

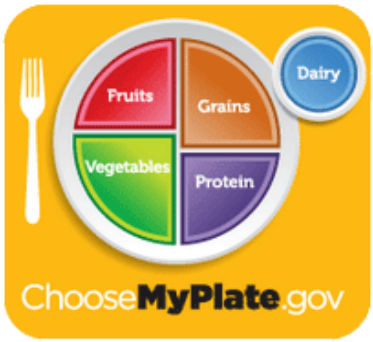
What are risk factors for dyslipidemia?[1]

- Age
  - Male: ≥45 years
  - Female: ≥55 years
- Family history of premature CHD or diabetes
- HTN (≥140/90 mmHg or on anti-HTN medication)
- Cigarette smoking
- Low HDL (below 40 mg/dL)

References:
1. Talbert RL. Hyperlipidemia. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Well BG, Posey LM, editors. Pharmacotherapy: A Pathophysiologic Approach. 9th ed. New York: McGraw-Hill Medical; c2014. Chapter 11.
2. Ito MK. Dyslipidemias, Artherosclerosis, and Coronary Heart Disease. In: Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BR, editors. Koda-Kimble & Youngs Applied Therapeutics: The Clinical Use of Drugs. 10th ed. Philadelphia: Wolters Kluwer, Lippincott Williams & Wilkins; c2013. p. 271

Diet

- 2013 AHA/ACC Lifestyle Management Guideline Recommendations[1]:
  - Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils, and nuts



- The DASH dietary pattern[1]
  - High in vegetables, fruits, low-fat dairy products, whole grains, poultry, fish, and nuts
  - Low in sweets, sugar-sweetened beverages, and red meats
  - Low in saturated fat, total fat, and cholesterol
  - Rich in potassium, magnesium and calcium, as well as protein and fiber
- My Plate[2]
  - MyPlate is a reminder to find your healthy eating style and build it throughout your lifetime. Everything you eat and drink matters. The right mix can help you be healthier now and in the future.
- Sodium Intake[1]
  - Total salt intake for any patient is less than 2,400mg (~1 teaspoon)/day
  - If patient also has high BP, further sodium restriction (<1500 mg/day) is desirable

References:
1. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Miller NH, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Nonas CA, Sacks FM, Smith SC, Svetkey LP, Wadden TA, Yanovski SZ. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association. J Am Coll Cardiol [Internet]. 2013 [cited 2016 Aug 2];63:2960-2984. Available from: http://circ.ahajournals.org/content/129/25_suppl_2/S76
2. ChooseMyPlate. Alexandria, VA: U.S. Dept. Agriculture Center for Nutrition Policy and Promotion . Updated 2016 May 9 [accessed 2016 Aug 31]. Available at: https://www.choosemyplate.gov/MyPlate

Physical Activity

- Exercise reduces LDL-C and non-HDL-C[1]
  - Moderate to vigorous aerobic physical activity
  - 40 minutes per session, 3-4 times a week
    - Small incremental steps to build to overall goal
    - Recommend overweight patients to lose 10% of body weight[2]

Guide to Common Physical Activities[2]	
Activity	**Calories Burned per 30 minutes**
Walking causally (2 mph)	85
Walking quickly (4 mph)	170
Jogging (5 mph)	275
Gardening	135
Bicycling (10 mph)	205
Swimming	240
*miles per hour (mph)	

References:

1. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Miller NH, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Nonas CA, Sacks FM, Smith SC, Svetkey LP, Wadden TA, Yanovski SZ. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association. J Am Coll Cardiol [Internet]. 2013 [cited 2016 Aug 2];63:2960-2984. Available from: http://circ.ahajournals.org/content/129/25_suppl_2/S76
2. U.S. Department of Health and Human Services: National Institutes of Health, National Heart, Lung, and Blood Institute. Your guide to lowering your cholesterol with TLC [Internet]. Bethesda (MD):U.S. Department of Health and Human Services: National Institutes of Health, National Heart, Lung, and Blood Institute; 2005 Dec [cited 2016 Aug 15]. Box 26, A Handy Guide to Calories Burned in Common Activities; p. 45. Available from: https://www.nhlbi.nih.gov/files/docs/public/heart/chol_tlc.pdf

Drugs Contributing to Abnormal Lipid Panels

There are a number of drugs that are able to adversely affect lipid panels. Several of these drugs/drug classes are widely used and may often be used alongside lipid-lowering medications to reduce cardiovascular risk (i.e. diuretics, beta-blockers, etc.). Included in the table below are drugs/drug classes and their adverse effects on total cholesterol (TC), LDL-C, HDL-C, and triglycerides (TG).[1,2,3]

[3]

Drug Class	TC	LDL	HDL	TG
Loop/Thiazide-type Diuretics	↑5-10%	↑5-10%	-	↑5-15%
Beta-Blockers	-	-	↓5-20%	↑10-40%
Alpha-Blockers	↓5%	↓5%	↑2-5%	↓4-14%
Estrogen Monotherapy	↓2-10%	↓7-20%	↑5-20%	↑40%
Selective Estrogen Receptor Modulators (SERMs)	↓5-15%	↓10-20%	-	↑0-30% (tamoxifen)
Retinoids (isotretinoin)	↑15%	↑15%	-	↑35-144%
Immunosuppresants	↑10-40%	↑0-50%	↑0-90%	↑0-70%
Protease Inhibitors (Ritonavir)	↑30-40%	n/a	-	↑200-300%
Antipsychotics	-	-	-	↑0-50%
Anticonvulsants	↑0-20%	n/a	↑ or ↓	-
No change (-); Not available (n/a)				

References:

1. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. Circulation [Internet]. 2014 [cited 2016 Aug 2];129(suppl 2):S1–S45.
2. Ito MK. Dyslipidemias, Artherosclerosis, and Coronary Heart Disease. In: Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BR, editors. Koda-Kimble & Youngs Applied Therapeutics: The Clinical Use of Drugs. 10th ed. Philadelphia: Wolters Kluwer, Lippincott Williams & Wilkins; c2013. p. 271
3. Adapted from: Mantel-Teeuwisse AK, Kloosterman JM, Maitland-van der Zee AH, Klungel OH, Porsius AJ, de Boer A. Drug-Induced lipid changes: a review of the unintended effects of some commonly used drugs on serum lipid levels. Drug Saf [Internet]. 2001 [cited 2016 Aug 15];24(6):443-56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11368251

Pharmacotherapy Overview

Drug Class	Brand Name	Generic Name	Generic Available*	Effects on Lipids
HMG-CoA Reductase Inhibitors	Lipitor® Lescol® XL Mevacor®/Altoprev® Livalo® Pravachol® Crestor® Zocor®	atorvastatin fluvastatin lovastatin pitavastatin pravastatin rosuvastatin simvastatin	Yes Yes Yes No Yes Yes Yes	High intensity LDL: ↓≥50% Mod. Intensity LDL: ↓30-50% Low Intensity LDL: ↓<30%
Fibric Acid Derivatives	Trilipix® Lopid® Atromid-S®	fenofibrate gemfibrozil clofibrate	Yes Yes No	LDL: ↓15-27% HDL: ↑10-30% TG: ↓30-60%
Bile Acid Sequestrants	Prevalite® Welchol® Colestid®	cholestyramine colesevelam colestipol	Yes No No	LDL: ↓15-30% HDL: ↑3% TG: ↓3-10%
Nicotinic Acid	Niacor®	niacin niacin ER	Yes Yes	LDL: ↓15-30% HDL: ↑20-35% TG: ↓30-60%
Cholesterol Absorption Inhibitor	Zetia®	ezetimibe	No	LDL: ↓18-22% HDL: ↑0-2% TG: ↓0-5%
Omega-3 Ethyl Esters	Lovaza® Vascepa®	omega-3 fatty acids	Yes No	LDL: ↑35-45% TG: ↓30-60%
PCSK9 Inhibitors	Praluent® Repatha®	alirocumab evolocumab	No No	LDL: ↓50-52%
Microsomal Triglyceride Transfer Protein (MTP) Inhibitor	Juxtapid®	lomitapide	No	LDL: ↓40-50% HDL: ↑0-1%
Oligonucleotide Inhibitor	Kynamro®	mipomersen	No	LDL: ↓~47% HDL: ↑8% TG: ↓27%
Combination Products	Caduet® Vytorin®	atorvastatin + amlodipine simvastatin + ezetimibe	No No	LDL: ↓30-50%

References:

1. Ito MK. Dyslipidemias, Artherosclerosis, and Coronary Heart Disease. In: Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BR, editors. Koda-Kimble & Youngs Applied Therapeutics: The Clinical Use of Drugs. 10th ed. Philadelphia: Wolters Kluwer, Lippincott Williams & Wilkins; c2013. p. 271
2. Talbert RL. Hyperlipidemia. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Well BG, Posey LM, editors. Pharmacotherapy: A Pathophysiologic approach. 9th ed. New York: McGraw-Hill Medical; c2014. Chapter 11.
3. Atorvastatin [2016 Aug], Fluvastatin [2016 Aug], Lovastatin [2016 Aug], Pitavastatin [2016 Aug], Pravastatin [2016 Aug], Rosuvastatin [2016 Aug], Simvastatin [2016 Aug], Fenofibrate [2016 Aug], Gemfibrozil [2016 Aug], Clofibrate [2016 Aug], Cholestyramine [2016 Jul], Colesevelam [2016 Jun], Colestipol [2016 Aug], Niacin [2016 Aug], Ezetimibe [2016 Aug], Omega-3-Acid Ethyl Esters [2016 Jun], Alirocumab [2016 Apr], Evolocumab [2016 Jul], Lomitapide Mesylate [2016 Aug], Mipomersen [2016 May], Amlodipine Besylate/Atorvastatin Calcium [2016 Aug], Ezetimibe/Simvastatin [2016 Aug]. In: *DRUGDEX® System (electronic version)* [AUHSOP intranet database]. Greenwood Village, CO: Truven Health Analytics Inc. [updated 2016, cited 2016 Aug 10]. Available from http://www.micromedexsolutions.com/micromedex2/librarian/

Update - (Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors

Praluent® (alirocumab)

Praluent®, a monoclonal antibody approved in July of 2015, exhibits its pharmacological effects by inhibition of PCSK9 binding to LDL-receptors.[1,2] This mechanism of action is theorized to reduce degradation of the LDL receptor; therefore, more LDL receptors will be available to extract LDL from circulation.[1,2]

A study conducted by Cannon P, et al., compared alirocumab versus ezetimibe as add-on therapy to patients currently receiving statin therapy.[1,3] Cannon P, et al., found that there was an approximately 50.6% reduction in LDL from baseline at 24 weeks when compared to ezetimibe add-on therapy, which achieved approximately 20.7% reduction from baseline.[1,3] Based on these findings, it seems that Praluent® may be a reasonable option for patients who are on maximized doses of statins or who are unable to tolerate maximally indicated doses and unable to achieve LDL-C reduction goal based on ASCVD risk. Praluent®'s effects on reduction of cardiovascular risk have yet to be determined.[1,2]

Available from: http://www.cbsnews.com/news/praluent-cholesterol-lowering-drug-high-cost-statin-alternative/

Current data indicates that Praluent® seems to be well tolerated in patients with most common ADRs including: allergic reaction and injection site reaction.[1,2] Praluent® is administered every two weeks subcutaneously, which may be appealing to patients with suspected adherence limitations.[1,2] The limiting factor for use in most patients will be related to cost. Medication cost per month is approximately $1300.[4]

Repatha® (evolocumab)

Similar to Praluent®, Repatha® is a monoclonal antibody approved in August of 2015. Repatha® also exhibits pharmacological action due to inhibition of PCSK9 binding to LDL-receptors.[1,2] Current indications of Repatha® are add-on pharmacotherapy to LDL-lowering medications for patients who require additional lipid lowering.[1,2]

Stroes, et al., conducted a study targeting patients who were intolerant to multiple statins and only able to receive low-dose statins or none at all. Their study found that Repatha® demonstrated reductions in LDL of approximately 55% as compared to ezetimibe, which demonstrated LDL lowering effects of approximately 17%.[1,5] Available studies have not determined Repatha®'s effects on cardiovascular risk reduction; therefore, Repatha® is indicated as adjunct to statin therapy or monotherapy for patients unable to tolerate statin therapy.[1,2]

Available from: http://www.multivu.com/players/English/7414054-amgen-repatha-fda-approval/

Most common ADRs associated with Repatha® use are similar to that of Praluent®, presenting in allergic-type reactions and increased incidence of upper

respiratory tract infections.[1,2] Repatha® in comparison to Praluent® is dosed subcutaneously every two weeks or once monthly.[1,2] Similar to Praluent, cost will be a major factor limiting utilization of Repatha® with monthly cost of approximately $1400.[4]

A recent study published by Kazi DS, et al. found that the PCSK9 inhibitors are not cost-effective as compared with current therapy.[6] Their study determined, based on 2015 wholesale price, that both PCSK9 inhibitors are approximately $14,000/year in cost and that the medication cost would have to decrease by over two-thirds to $4536 to become cost-effective.[6] For now it seems that PCSK9 inhibitors may continue to play a secondary role in therapy; at least, for the foreseeable future.

References:

1. Alirocumab [2016 Apr], Evolocumab [2016 Jul]. In: *DRUGDEX® System (electronic version)* [AUHSOP intranet database]. Greenwood Village, CO: Truven Health Analytics Inc. [updated 2016, cited 2016 Aug 10]. [about 17 p.]. Available from http://www.micromedexsolutions.com/micromedex2/librarian/
2. Alirocumab [2015 Oct], Evolocumab [2016 Jul]. In: Drug Facts and Comparisons (Facts and Comparisons eAnswers) [AUHSOP Intranet]. St. Louis: Wolters Kluwer Health/Facts and Comparisons [updated 2016, cited 2016 Aug 10]. [about 11 p.]. Available from http://online.factsandcomparisons.com/index.aspx?
3. Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. Eur Heart J [Internet]. 2015 May 14 [cited 2016 Aug 10];36(19):1186-94. Available from: http://eurheartj.oxfordjournals.org/content/ehj/36/19/1186.full.pdf
4. Praluent, Repatha. In: Red Book Online (electronic version) [AUHSOP intranet database]. Greenwood Village, CO: Truven Health Analytics Inc. [accessed 2016 Aug 10]. Available from http://www.micromedexsolutions.com/micromedex2/librarian/CS/17A746/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/DB2BF4/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/redbook.FindRedBook?navitem=topRedBook&isToolPage=true
5. Stroes E, Colquhoun D, Sullivan D, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol [Internet]. 2014 Jun 17 [cited 2016 Aug 10];63(23):2541-8. Available from: http://www.sciencedirect.com/science/article/pii/S0735109714017288
6. Kazi DS, Moran AE, Coxson PG, Penko J, Ollendorf DA, Pearson SD, Tice JA, Guzman D, Bibbins-Domingo K. Cost-Effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. JAMA [Internet]. 2016 Aug 16 [cited Aug 17];316(7):743-53. Available from: http://jama.jamanetwork.com/article.aspx?articleid=2544639

The last "dose" …

"I drive way too fast to worry about cholesterol."
– Steven Wright [American comedian, 1955 -]

An electronic bulletin of drug and health-related news highlights, a service of …
Auburn University, Harrison School of Pharmacy, Drug Information Center
• Phone 334-844-4400 • Fax 334-844-8366 • http://www.pharmacy.auburn.edu/dilrc/dilrc.htm
Bernie R. Olin, Pharm.D., Director
Archived issues are available at: http://pharmacy.auburn.edu/dilrc/au_informed.htm