



CLINICAL LIPIDOLOGY Bibliography & Resource Guide

BOOKS

- Therapeutic Lipidology. Michael H. Davidson & Peter Toth, Humana Press 2007.
- Primary Hyperlipidemias. J. Davignon. Clinical Publishing 2007

ORGANIZATIONS

- National Lipid Association www.lipid.org
Publications, online reviews, slides
- NLA CardioMetabolic Risk Reduction www.cardiometrisk.com
References, case studies
- Lipids Online www.lipidsonline.org
Tutorials, reviews, slides
- The SHAPE Society www.shapesociety.org
SHAPE guidelines, resources
- Metabolic Syndrome Institute www.metabolicsyndromeinstitute.com
Newsletter, studies, slides
- The Obesity Society www.obesityonline.com
Resources, reviews, slides

WEB SITES

- Framingham Risk Calculator www.nhlbi.nih.gov/guidelines/cholesterol/index.htm
- BMI Calculator www.nhlbisupport.com/bmi/
- Calories in Food <http://nal.usda.gov/fnic/foodcomp/search/>
- Pedometers <http://accusplit.com>
- Diet and Dieticians www.eatright.org
www.susanshealthycourmet.com
www.northstarportions.com
- Fish Oil www.carlsonlabs.com
- Office Equipment for Larger Patients
Chairs www.carstone.com/bariatric
Gowns, BP cuffs www.amplestuff.com
- NMR LipoProfile www.lipoprofile.com
LDL and HDL particle counts
- Atherotech VAP test www.VAPtest.com
LDL particle size
- Berkeley Heart Lab www.bhinc.com
LDL particle size

IMPORTANT PUBLICATIONS

- NCEP ATP III GUIDELINE www.nhlbi.nih.gov/guidelines/cholesterol/index.htm
- Screening for Obesity
U.S.Preventive Services Task Force 2003
<http://www.ahrq.gov/clinic/3rduspstf/obesity.obesrr.htm>

- Metabolic Syndrome
Diagnosis and Management of the Metabolic Syndrome.
AHA and NHLBI Scientific Statement
Circulation 2005; 112:000
- Statin Safety
Safety of Statins: Focus on Clinical Pharmacokinetics and Drug Interactions
Circulation 2004; 109:50-57

IMPORTANT TRIALS

- FATS. Brown, NEJM 1990; 323: 1289
Familial Atherosclerosis Treatment Study. Men with CAD, meticulous coronary angio study documenting progression/regression of disease with treatment: diet, lovastatin, colestipol. 70% risk reduction with niacin&colestipol
- HATS. Brown NEJM 2001; 345:1583
HDL Atherosclerosis Treatment Study
Secondary prevention, Coronary angio study
Niacin, Simvastatin, Niacin+Simva, AntiOx Vitamins. No benefit of vitamins, and they counteracted benefit of Niacin&Simva. Surprising 89% reduction in hard cardiac endpoints with only trivial regression of obstruction by angio
- STELLAR Trial AmJCardiol 2003; 92:152
Dose comparison Rosuva, Atorva, Prava, Simva
for LDL reduction. Doubling dose only results in 6% further LDL reduction
- HEART PROTECTION STUDY Lancet 2002;360:7
Secondary prevention study of Simva in 20,000 patients. Same % reduction in hard CHD events whether LDL less than 100, 100-130, over 130. Same benefit in 953 patients with LDL less than 80. Does the LDL-C matter? Is it your risk level that matters? Or just the pleotropic effects of statins? See ASTEROID
- PROVE-IT/TIMI-22 Cannon, NEJM 2004;350:1495
Atorva 80 vs Prava 40mg in 4000 ACS hosp pts.
2 yr major adverse cardiac event rates 22 vs 26%
LDL reduced to 62 proved safe
- TNT Study. LaRosa NEJM 2005; 352: 1425
Treat to New Targets. Atorva 80mg vs 10. Myalgias same with both. When LDL at goal, risk is still elevated if HDL less than 37
- BARI-2D Brooks, AmJCardiol 2006;97:96
And AmJCardiol 2009; 104:52
1800 T2 diabetics with CAD treated with TZDs for 6 months. 17% fewer stenotic lesions, lower hs-CRP. Independent of diabetes control and other risk factors
- COURAGE Boden, NEJM 2007; 356:1503
PCI vs medical therapy for patients cathed and having at least one 70% stenosis. 35,000 screened, only 2287 qualified, randomized. Follow up almost 5 yrs, 33% medical treatment group crossed over to PCI in follow up. Controversial. This was a coronary angio trial, not a medical therapy trial in a very small segment of population cathed. Nonetheless, med Rx works

- ENHANCE Kastelein NEJM 2008; 358:1431
Simva/Ezet(Vytorin) vs Simva to reduce carotid IMT in patients with familial hypercholesterolemia.
Controversy over Ezetamide. LDLC and hs-CRP reduced but CIMT got worse. ?markers of risk reduced but no anatomic benefit. A poor study. Patients had been previously treated with other statins, had severe genetic disorder, a secondary endpoint used not hard endpoint. Wait for IMPROVE-IT
- JUPITER Ridker, NEJM 2008; 359:2195
Primary prevention in a population similar to our community: white 75%, few hypertensives, smokers, 50% had Met Syndrome, Men 50, Women 60. At entry LDL 108, HS-CRP 4. Rosuva lowered LDL to 55 & proved safe. Hard end points. Stopped early due to benefit in Rx group.
A Rosuva trial, not an hs-CRP trial. Is hs-CRP a useful target for therapy or only a marker of MetSyn?
- MESA (MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS):
200 Publications so far. Recent examples:
Association between A1C and subclinical CAD (in MESA) McNeely, DiabetesCare 2009;32:1727-33,
Relationship between coronary artery and thoracic aortic calcification as detected by computed tomography in MESA. Takasu, Atherosclerosis 2009; 204:440-46
Prevalence and progress of subclinical atherosclerosis in younger adults with low short term and high lifetime risk for CAD (CARDS and MESA) Chan, Circulation 2009; 119:382-89
- ASTEROID Wiviott, AmJCardiol 2009; 104:29
Rosuva and coronary IVUS. LDL under 40 safe and effective, HDL increased 14%. High dose rosuva reduced plaque burden.
- AIM-HIGH Ongoing trial
Met syndrome and low HDL. Simva vs Simva/Niacin like HATS but longer
- ACCORD Ongoing trial T2 diabetes
Glucose lowering arm stopped early due to adverse outcomes if A1C target too low. Lipid arm compares statin alone to statin plus fenofibrate

JOURNAL ARTICLES

CORONARY HEART DISEASE RISK ASSESSMENT

- Reynolds Risk Score for Men
Ridker, Circulation 2008; 118:2243-51
- Reynolds Risk Score for Women
Ridker, JAMA 2007; 297:611-19
- Framingham risk score and prediction of lifetime risk
Lloyd-Jones, AmJ Cardiol 2004; 94:20-24
- Prediction of Lifetime risk for CVD at age 50
Lloyd-Jones, Circulation 2006; 113:791-98
- The changing face of cardiovascular risk
Grundy, AmJCardiol 2005; 46:173-75
Framingham less relevant today. Risk factors have changed
- Prevention of CHD and the NCEP
Kuller, Circulation 2006; 113: 598-600
A disconnect now exists between traditional lipid levels like LDL-C and ApoB

- From Vulnerable Plaque to Vulnerable Patient, SHAPE Task Force. Naghavi, AmJCardiol 2006; 98 Supplement 2
The SHAPE guidelines. Also look at SHAPE Society website
- Things to come of SHAPE
Diamond, AmJCardiol 2007; 99:1013-15
Is SHAPE approach cost effective?
- Screening for CHD: Has the time for universal imaging arrived?
Lauer, ClevClin Jounal 2007; 74: 645-54
Argues against screening
- Prevalence and Progression of Subclinical Atherosclerosis in younger adults with low short-term but high lifetime estimated risk for cardiovascular disease. MESA
Berry, Circulation 2009; 119:382-89
CACs and CIMT in MESA and CARDIA cohorts.
Greater progression
- Insights into atherosclerosis from invasive and non-invasive imaging studies: should we treat subclinical atherosclerosis?
Santos, Atherosclerosis 2009; 205:349-56
Patients with evidence of significant subclin disease should be aggressively treated

METABOLIC SYNDROME AND DIABETES

- Metabolic syndrome and risk of incident CV events
Gami, JACC 2007; 49: 403-14
Meta-analysis of studies. Documents increased risk
- Global risk management in patients with T2 diabetes
Davidson, AmJCardiol 2007;99suppl: 41b
Cardiologists should be more aggressive with lipid Rx in diabetic patients
- Usefulness of fasting plasma glucose to predict mortality or CHD in persons over 60 without diabetes or with undiagnosed diabetes(Dubbo Study)
Simons, AJCardiol 2008; 102:831-34
FPG more predictive in women than men.
Does risk begin for FPG as low as 83?
In Framingham, risk for CHD began at FPG 110
- Metabolic syndrome and CIMT in the Health 2000 survey
Sipila, Atherosclerosis 2009; 204: 276-81
MetSyn an independent determinant of CIMT
- Why screen for heart disease in diabetes
Fadini, Atherosclerosis 2009; 204:11-15
Are screening tests cost effective?
- Detection of occult CAD in asymptomatic individuals with diabetes using non-invasive cardiac angiography
Rivera, Atherosclerosis 2009; 203; 442-48
Korean population. Framingham risk 13%.
66% had occult angiographic CAD, half non-calcified

CORONARY ARTERY CALCIUM SCORING

- Coronary artery calcium score combined with Framingham score
Greenland, JAMA 2004; 291:210
CACs predicted risk in moderate FRS group 10-20%
- Prevalence of emerging cardiovascular risk factors in younger individuals with a family history of premature CHD and a low Framingham risk score
Sallam, Clin.Cardiol 2008; 31: 542-45
FRS poorly predicts risk in this group. CACS

- Arterial age as a function of CACS in MESA
McClelland, AmJCardiol 2009; 103:59-63
Using arterial age from coronary ca score in Framingham risk scoring system proved more predictive
- Diagnostic and prognostic value of absence of coronary artery calcification
Sarwar, JACC Cardiovasc Imaging 2009;2:675
CACS of 0 in 85,000 patients reviewed associated with very low risk
- Absence of coronary artery calcification and all cause mortality
Blaha, JACC Cardiovasc Imaging 2009; 2; 692
Score of 0 implies a 1% 10yr mortality
- Eligibility for individuals with subclinical coronary artery calcium and intermediate coronary heart disease risk for reclassification from Framingham Heart Study
Preis, AmJCardiol 2009; 103:1710-15
25% had high CAC scores and reclassified to high risk
- Coronary Artery Calcification Screening. Estimated radiation dose and cancer risk
Kim, ArchInt Med 2009; 169: 1188-94
Doses varied 10 fold but can be as low as 0.8 mSv
- Calcium scoring with computed tomography. What is the radiation risk?
Gibbons, ArchIntMed2009; 169: 1185-87
General discussion of radiation risks in general
- Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles
Budoff, JACC 2009; 53:345
Documents predictive value of 0, 100,400 cut points
- Are you as old as your arteries or as old as your coronary calcium score?
Schiele, JACC 2009; 53: 353
Perspective on using CACS

CAROTID INTIMA-MEDIA THICKNESS

- Measurement of CIMT in dyslipidemic patients increases the power of traditional risk factors to predict cv events
Baldassarre, Atherosclerosis 2007; 191:403-08
Intermediate FRS patients with high CIMT had outcomes equal to high risk FRS
- A negative carotid plaque area is superior to other noninvasive studies for reducing likelihood or having significant underlying CAD.
Brook, Arterio Thromb Vasc Biol 2006;26:656-62
Carotid plaque is superior to CIMT, hs-CRP and even CACS in predicting 50% coronary obstruction by coronary CTAngio
- Association of CIMT, plaques and CRP with future cardiovascular disease. The Cardiovascular Health Study
Cao, Circulation 2007; 116: 32-38
Elevated hs-CRP associated with increased CVD risk in 5000 patients over age 65 only in those with carotid plaque
- CIMT and CACS as indications of subclinical atherosclerosis
Lester, MayoClinProc 2009; 84:229-33
Young 36-59yo patients with low risk FRS. 89 with CACS of 0, carotid plaque found in 34%. 40 with low risk CIMT, 10% and CACS above 50%ile.
These tests detect subclinical disease in young, low risk FRS patients.

LDL AND HDL PARTICLE COUNTS

- LDL particle number and risk for CVD
Cromwell, Current AtheroReports 2004; 6:381-87
The basic pathophysiology

- Increased small LDL particle number: a prominent feature of the metabolic syndrome in the Framingham Heart Study
Kathiresan, *Circulation* 2006; 113:20-9
- LDL particle subclasses, LDL size and carotid atherosclerosis in MESA
Mora, *Atherosclerosis* 2006;
- LDL and HDL particle subclasses predict coronary events and are favorably changed by gemfibrozil in VA-HIT
Otvos, *Circulation* 2006; 113:1556-63
NMR measured particle counts explain benefit of gemfibrozil better than LDL-C and HDL-C
- Comparability of methods for LDL subfraction determination: a systematic review
Chung, *Atherosclerosis* 2009; 205: 342-48
Long established reliable methods still give differing results. NMR particle methods, Berkeley, VAP and other methods compared. Best to stick with one

NON-HDL CHOLESTEROL AND APO B

- Non-high-density lipoprotein cholesterol and apolipoprotein b in prediction of CHD in men
Pischon, *Circulation* 2005; 112: 3375-83
Both better than LDL-C, Apo B best
- ApoB vs nonHDL-C. And the winner is
Sniderman, *Circulation* 2005; 112:3366
Broad review. Both can be done non fasting.
Studies show ApoB more closely associated with all features of Metabolic Syndrome than non-HDL-C
- Potential effect of an Apo-B based algorithm on management of new patients with hypertriglyceridemia
Brook, *ClinCardiol* 2009; 32:251-55
50% patients at non-HDL goal (per ATP III) but not at Apo B goal. Using ApoB results in more aggressive Rx

BIOMARKERS

- Markers of inflammation and CAC. A systematic review
Hamirani, *Atherosclerosis* 2008; 201:1-7
Association is very weak. Not useful to predict presence of coronary calcium.
- Novel and conventional biomarkers for prediction of incident cardiovascular events
Melander, *JAMA* 2009; 302: 49-57
Gains over conventional risk factors minimal
- Genetic loci associated with CRP levels and risk of CHD
Elliott, *JAMA* 2009;302: 37-48
28,000 cases found no association with CRP genetic variants and CHD. Argues against any causative role for CRP in pathogenesis of CHD
- Apo E genotype, lipids and CHD risk
Ward, *Ach Int Med* 2009; 169: 1424-29
CHD risk not associated with any genotype

STATINS

- Primary prevention of cardiovascular mortality with statin treatment.
Mills, *JACC* 2008; 52: 1769-81
19 pooled trials. Benefit with all statins

- The benefits of statins in people without established CAD but with CV risk factors: meta-analysis\
Brugts, BMJ 2009; 338: b2376
70,000 people. 4 year follow up
Risk ratios 0.70 for major CHD events, 0.81 for cerebrovascular events, 0.88 all cause mortality. No risk of cancer found.
- Association between statin myopathy and skeletal muscle damage
Mohaupt, CMAJ2009; 181:E11-18
Biopsies of 83 patients. Muscle injury in 25 of 44 with dx myopathy. CPK elevation did not correlate with evidence of myopathy. Statin doses were moderate
- Red Yeast Rice for dyslipidemia in statin-intolerant patients. A randomized trial.
Becker, Ann Int Med 2009; 150: 830-39
62 patients successfully treated. No muscle symptoms

COMBINATION DRUG THERAPY

- Simultaneous LDL-C lowering and HDL-C elevation for optimal cardiovascular disease prevention with various drug classes, and their combinations: a meta-analysis of 23 randomized lipid trials
Brown, Curr Opin Lipidol 2006; 17:631-36
Greg Brown M.D. continues to point out the extraordinary risk reduction from combination therapy. 1% reduction in event rate for each 1% reduction in LDL-C, and 1% reduction for each 1% increase in HDL-C. These effects are independent and additive. A 40% reduction in LDL-C and a 30% increase in HDL-C results in a 70% CHD risk reduction, something not equaled in any trial of statin therapy alone
- Effects of adding prescription OM-3 esters to Simva 20mg on lipids and lipoprotein particles in men and women with mixed dyslipidemia
Maki, AmJCardiol 2008; 102: 429-33
4 Lovaza capsules plus Simva 20mg. Non-HDL-C dropped by 40% compared to Simva alone. LDL particle size increased. BP dropped 5mmHg.

DIET

- Consuming fructose-sweetened, not glucose-sweetened beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans
Stanhope, JCI 2009; 10: 1-13
Evidence that high fructose corn syrup specifically increases hepatic lipogenesis and promotes visceral adiposity, decreases insulin sensitivity, promotes dyslipidemia
- The “Sunshine Deficit” and cardiovascular disease
Wallis, Circulation 2008; 118:1476-1485
Vitamin D deficiency associated with 30-50% higher CV mortality and morbidity. ?Vit D improves insulin sensitivity.