CURRENT ISSUES AND CONTROVERSIES IN LIPID MANAGEMENT IN WOMEN

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(no conflicts to disclose)
Objectives:

1. Summarize basic data supporting the benefit of cholesterol reduction.
2. Discuss the latest concepts in the treatment of cholesterol, LDL, triglycerides and HDL plus emphasize the cholesterol treatment gap.
3. Identify problems with certain pharmaceuticals including what is innovative and of value versus what is marketing.
4. Interrelate the importance of inflammatory risk factors in coronary heart disease management.
5. Discuss future directions in coronary heart disease prevention.
6. Consider the nature and prevalence of the metabolic syndrome in the spectrum of coronary heart disease.
7. Consider specific characteristics of CHD in women.
Mortality rates in US women

- Heart disease
- Stroke
- Colon cancer
- Endometrial cancer
- Breast cancer
- Lung cancer

ETHNIC DIFFERENCES

In the Heart and Estrogen/progestin Replacement Study (HERS) over 4.1 years†, events from CHD occurred approximately twofold in African American women compared with Caucasian women.

METABOLIC SYNDROME, SYNDROME X or CV DYSMETABOLIC SYNDROME

HAVE AT LEAST 3 OF 5 MAJOR COMPONENTS†:

- TG $\geq 150$ mg/dl.
- HDL < 40 mg/dl in men and < 50 mg/dl in women.
- BP $\geq 130/85$ mm/Hg.
- Waist girth $> 102$ cm (men) and $> 88$ cm (women).
- Fasting glucose $\geq 100$ mg/dl.

OTHER COMPONENTS:

- ↑ dense LDL, Insulin resistance, Hyperuricemia,
- ↑ PAI-1, ↑ hsCRP, ↑ Tissue necrosis factor-α
- ↑ Interleukin-6, ↑ Resistin, and ↓ Adiponectin.

MUST TREAT EACH INDIVIDUAL MAJOR COMPONENT.

Latest Overweight and Obesity Rates

Metabolic Syndrome: Prevalence Increases with Age

47 million or 23% of US adults have the metabolic syndrome

The Metabolic Syndrome (MS) Associates with CHD/Myocardial Infarction more than any Individual Component† but still not as much as Diabetes Mellitus. MS also markedly associated with PVD.†

†Similar occurrence with stroke

ASPIRIN AND PRIMARY PREVENTION IN WOMEN

Women’s Health Study* (WHS-39,876 women):

477 MACE with ASA over 10 years vs. 522 events with placebo (a nonsignificant 9% ↓ MACE).
Stroke rate 19% lower with ASA (p=0.04).
Small but insignificant increment in MI risk with ASA, not seen with placebo.

Meta-analysis of ASA# in women and men:

Composite of MACE decreased due to effect of ASA in decreasing ischemic stroke in women and MI in men.

ACE INHIBITOR IN PREGNANCY

MAJOR CONGENITAL MALFORMATIONS HAVE NOW BEEN ASSOCIATED WITH EXPOSURE TO ACE INHIBITORS IN ALL THREE TRIMESTERS WHEREAS, PREVIOUSLY, IT WAS CONSIDERED ONLY A CONCERN AFTER THE 1st TRIMESTER†. Rx acceptable during pregnancy: Alphamethyldopa, Metoprolol tartrate and Labetalol.

First Coronary Event

Women’s Survival Rates

Probability of Event-Free Survival

Years of Follow-up

Low hsCRP, Low LDL-C
Low hsCRP, High LDL-C
High hsCRP, Low LDL-C
High hsCRP, High LDL-C

* Cushman M, Novel Risk Factors: C-Reactive Protein, p. 125. Women’s Health Study Data.
Asymptomatic Women’s Survival Rates by Calcium Score

- **Ca\(^{2+}\) score <10**
- **Ca\(^{2+}\) score 11-100**
- **Ca\(^{2+}\) score 101-400**
- **Ca\(^{2+}\) score 401-1000**
- **Ca\(^{2+}\) score >1000**

**Cumulative Unadjusted All-Cause Survival**

**Follow-up (years)**

- **N=4191**

LJ Shaw and P Raggi, Diagnostic Procedures, p. 188. EBT Research Foundation Study Data.
Cardiac Syndrome X

ST-Segment Depression during Treadmill Exercise Stress Testing

Baseline

Peak exercise

4 minute recovery

BP 130/80

BP 180/90
Chest Pain

BP 138/90

JC Kaski, Cardiac Syndrome X, p. 206.
LOW GRADE CHRONIC INFLAMMATION IN POLYCYSTIC OVARIAN SYNDROME (PCOS)

• PCOS ASSOCIATIONS: OLIGOMENORRHEA AND ↑TESTOSTERONE.
• WOMEN WITH PCOS: INSULIN RESISTANT, ↑RISK FOR CHD AND ↑RISK FOR TYPE 2 DIABETES.
• WOMEN WITH PCOS: SIGNIFICANTLY ↑C-REACTIVE PROTEIN LEVELS COMPARED TO WOMEN WITH NORMAL MENSES AND NORMAL ANDROGEN LEVELS

ESTROGEN REPLACEMENT

• ↑HDL, ↓LDL, endothelial stabilization (good).
• Increase in CRP; occasional marked increase in triglycerides; thrombogenesis [oral estrogens and not transdermal estrogens] (bad).
• Heart Estrog/Prog Replacement Study (HERS)*.
  – Mean age 67. No CV benefit and in 1st year: ↑CHD, ↑MI.
• Trend toward ↓CHD risk when estrogen started closer to menopause# and < age 60 as compared to ↑CHD risk in women more distant from menopause.
• Decreased coronary calcified-plaque burden in a trial in women with estrogen†.

WOMEN’S HEALTH INITIATIVE IN 2002 (WHI)

• Large randomized trial.
• PremPro: 0.625 mg conjugated estrogens with 2.5 mg medroxyprogesterone acetate, did not prevent CV disease and may have increased MI and stroke.
• No increased MI if less than 10 years postmenopausal but stroke risk still increased in this subgroup.

Estrogen Therapy and Coronary Artery Calcification

• Substudy of WHI†.
• Estrogen only – Premarin 0.625 mg/d.
• Ages 50-59.
• Duration - over 7.4 yr of Estrogen, 8.7 yr later.
• Coronary calcium score - significantly less in women on Estrogen.

CHD CHARACTERISTICS OF WOMEN

• Women present older with first MI (68.6 vs 60.1 years).*
  – 28 day mortality higher for women (18.5 vs 8.3%).
• CHD still occurs primarily after menopause when LDL increases and HDL decreases.
• Women overall are less likely to die of CHD.
  – Female to male ratio is 1/(2.5-4.5).
  – Protection is less in diabetic women.
• CHD is the major health problem in women.
  – 1 in 2 deaths due to CVD vs 1 in 29 deaths due to breast cancer.

CHD CHARACTERISTICS OF WOMEN*

- Once MI occurs, women do worse. In hospital mortality of women < 50 is twice that of men (6.1 vs 2.9%).
- CHD in the young woman appears to be in an especially malignant form.
- Aggressive statin use and LDL lowering appear essential in the young woman with CHD.

CHD CHARACTERISTICS OF WOMEN

- **Arterial inflammation probably different.**
  - High levels of TNF-alpha receptors significant only in women in Nurses’ Health Study vs men in Health Professionals Follow-up Study.†

- **Procedure problems in women.**

- **Care delays in women.** *
  - One third with no chest pain.
  - Family caregivers.
  - Can lead to less aggressive treatments.
  - Have ↑ cardiac complications/mortality as a result.

- **Aggressive statin use and LDL lowering:**
  - Essential in the young woman with CHD.

 PCI IN WOMEN†

• Benefit from an early invasive strategy is similar in women and men with further increased benefit in women with markers of increased CV risk.

• This benefit occurs despite some unavoidable disadvantages such as anatomically smaller coronary arteries.

Operative Mortality from CABG

Gender Differences in Mortality Trends

Characteristics of Plaques Prone to Rupture From Inflammation and LDL

HIGH SENSENSITIVITY C–REACTIVE PROTEIN (hs-CRP)

• A MARKER OF INFLAMMATION: CRP AND hsCRP ARE SAME PROTEIN.
• MAY BE ANOTHER RISK FACTOR AND PLAY A ROLE IN PLAQUE FORMATION.
• MAY PREDICT HIGH RISK ACUTE CORONARY SYNDROME.
• MAY INDICATE PATIENTS MOST LIKELY TO RESPOND TO STATINS.
• ASSOC. WITH ↑ELEMENTS OF METAB. SYNDR.
• STATINS SHOWN TO REDUCE CRP.
  – EZETIMIBE ACCENTUATES THIS EFFECT.*
• NEED STATIN DOSE RESPONSE CURVE.

CURRENT CLINICALLY USEFUL MARKERS OF INFLAMMATION

• LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2*.  
  – PLAC® TEST.

• HIGH SENSITIVITY C-REACTIVE PROTEIN (hsCRP)#.

• NEVERTHELESS, LDL REMAINS THE STANDARD MAJOR RISK FACTOR (GOLD STANDARD OF TREATMENT).

OVER 7.4 YEARS, MAJOR CORONARY EVENTS REDUCED BY 19% WITH P = 0.05.*

LDL-APHERESIS ATHEROSCLEROSIS REGRESSION STUDY (LAARS)*

- For 2 years, 42 men treated with biweekly LDL-apheresis plus simvastatin 40 mg/d vs. simvastatin 40 mg/d alone.
- LDL reduced 63% in apheresis group vs. reduced 47% with simvastatin alone.
- Quantitative coronary angio endpoints.
  - On basis of coronary segment, mean percent stenosis of all lesions showed tendency to decrease.
  - Only in the apheresis group, more minor lesions disappeared in comparison to the medication group.
- On bicycle exercise test, time to 0.1 mV increased significantly by 39% and the maximum level of ST depression decreased significantly by 0.07 mV in the apheresis group vs. no changes in the medication group.

PROGRAM ON THE SURGICAL CONTROL OF THE HYPERLIPIDEMIAS (POSCH)*

• Between 1975 and 1983, 838 survivors of single MI entered into study which ended in 1990.*
  – 417 patients to Rx/diet/control group.
  – 421 patients to diet/partial ileal bypass intervention group.
    • Apparent zero surgical mortality in the first 57 patients.†

• All POSCH post 5 yr. mort./ath. endpts. favorable.*
  – Mort. from CHD/nonfatal MI: 157 vs. 105 (P<0.001).
  – Nonfatal MI: 109 vs. 68 (P<0.001).
  – CABG or PTCA: 201 vs. 106 (P<0.001).
  – Onset of PVD: 93 vs. 68 (P=0.02).

• POSCH: LDL 37.7% lower and HDL 4.3% higher.*

Key Statin Pleiotropic Effects*

- Improved endothelial motor dysfunction.
- Increased fibrinolysis (via ↓ PAI-1).
- Favorable modulation of immune function.
- Antithrombotic properties-decreased platelet aggregation.
- Decreased metalloproteinase activity with decreased macrophage activity
- Anti-inflammatory effects.
- Increased nitric oxide.

Trial design: Apparently healthy patients with LDL cholesterol <130 mg/dl and hs-CRP ≥2 mg/dl were randomized to rosuvastatin 20 mg daily or placebo. Clinical outcomes were compared at a median of 1.9 years.

Results

- Rosuvastatin associated with a significant ↓ in the primary outcome of MI, stroke, unstable angina, revascularization, or cardiovascular death (HR 0.56, 95% CI 0.46-0.69, p < 0.00001)
- All-cause mortality ↓ with rosuvastatin (p = 0.02)
- Serious adverse effects were similar (p = 0.60)

Conclusions

- Rosuvastatin was associated with a significant reduction in major cardiovascular events, including death, in patients with LDL <130 mg/dl, but high hs-CRP (≥2.0 mg/dl)
- May require revision of current guidelines

Ridker PM, et al. NEJM 2008;359:2195-207
Presented by Dr. Paul Ridker at AHA 2008
JUPITER: ASTRONOMICAL SCIENCE OR ASTRONOMICAL MARKETING*

• Critical reappraisal of JUPITER:†
  – Primary end point a soft potpourri of MI, stroke arterial revasc. (a decision), hospitalization for unstable angina (a decision) or CV death.
  – Stopped too soon (fewer than 2 years) with only 240 total hard endpoints (MI, stroke, confirmed CV death) out of total of 17,802 patients (8,901 each group) even though 83 for rosuvastatin and 157 for placebo seems impressive.
  – After dissecting the data by subtracting “nonfatal MI” from “any MI”:
    • Rosuvastatin: 9 fatal MI’s
    • Placebo: 6 fatal MI’s

• Troubling concerns about this and other commercially sponsored trials.†
  – In JUPITER, per the methods, the sponsor collected the trial data and monitored the study sites.
  – Risk of poor quality.
  – Bias.

• hsCRP is not recommended by guidelines as a target of Rx based on lack of clinical trial evidence to support clinical benefit.#

†deLorgeril M. Arch Intern Med 2010;170:1032-1036.
#Kaul S. Arch Intern Med 1010;170:1073-1077.
OTHER IMPORTANT POINTS WITH STATINS

• SUDDEN STATIN WITHDRAWAL MAY INCREASE EVENT RATES IN ACUTE CORONARY SYNDROME (ACS).*

• EARLY STATIN USE MAY ↓ EVENT RATES IN ACS (BENEFIT QUESTIONED AT LOW CHOLESTEROL LEVELS).

• ADHERENCE IMPROVED BY STARTING STATINS DURING HOSPITALIZATION AND MAY HELP STABILIZE PLAQUES.†

*Spencer F. Arch Intern Med 2004; 164:2162-2168.
†Fonarow G. Am J Cardiol 2001;87:819-822.
Baseline IVUS Exam

Follow-up IVUS 24 months rosuvastatin

ASTEROID STUDY, 2006

Atheroma Area 10.16 mm²

Lumen Area 6.16 mm²

Atheroma Area 5.81 mm²

Lumen Area 5.96 mm²
CHD Risk Is Increased With Very High TG Levels\(^\#\) (≥500 mg/dL)

TGs are independently associated with premature familial CHD*.

*Triglyceride odds ratio adjusted for HDL-C; n=653 (FHx early CHD), n=1029 (control)

Sites of Action of ACEIs and AT₁-Receptor Blockade

Angiotensinogen → Renin → Angiotensin I → ACEI

ACE-Kininase II → Bradykinin → Inactive degradation products

Chymase → Trypsin Peptidase

Angiotensin II

AT₁-receptor blocker

AT₁-receptor

Vasoconstriction
Salt/water retention
Remodeling

AT₂-receptor

Anti-proliferation
Cell differentiation
Tissue repair

Natriuretic/diuresis
Anti-remodeling

NO

Statins: ↓ reg.

Log-Linear Relationship Between LDL Levels and Relative Risk for CHD

- This relationship is consistent with a large body of epidemiologic data and data available from clinical trials of LDL-C-lowering therapy. Goal for high CV risk is LDL < 70 mg/dl.
- These data suggest that for every 30 mg/dL change in LDL, the relative risk for CHD is changed in proportion by about 30%.
- The relative risk is set at 1.0 for LDL = 40 mg/dL.

LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease.

FURTHER SUPPORT OF LOWER IS BETTER

SUBSTUDY OF PROVE-IT SHOWED THAT SUBGROUPS OF LDL < 40 MG/DL AND LDL 40-60 MG/DL HAD FEWER MAJOR CARDIAC EVENTS†.

HIGH DOSE STATINS IN ACS

PROVE-IT STUDY (2004)+:
Decreased ACS problems with Atorvastatin (A) 80 mg vs Pravastatin (P) 40 mg; hsCRP ↓ almost the same: from 12.3 to 1.3 (A) vs. 2.1(P). [Mean lowest LDL 62].

MIRACL STUDY (ACS)*:
Atorvastatin 80 mg/d ↓ ischemic events and rehospitalizations in the first 16wks

## Statins and Fatal Rhabdomyolysis*

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<th>FATALITIES</th>
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</tr>
<tr>
<td>Fluvastatin</td>
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<td>0.00</td>
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</tbody>
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Data for rosuvastatin and pitavastatin not available in 2002.

Occasionally, can see histopathologic changes of myopathy with statins despite normal CPK (Ann Intern Med. 2002;137:581-585).
AORTIC STENOSIS (AS)

EXACERBATION BY ↑ LDL.
EXACERBATION BY ↑ Lp(a).
STATINS (2002) MAY ↓ DEVEL.* OF AS.
A SMALL RANDOMIZED 2005 STUDY SHOWED FAILURE OF ATORVASTATIN TO DECREASE PROGRESSION# OF AS.
A 2005 STUDY WITH ROSUVASTATIN+ MARKEDLY SLOWED PROGRESSION OF AS.
NO ↓ IN AS IN SEAS TRIAL WITH EZETIMIBE/SIMVASTATIN^.

STROKE ALSO REDUCED BY STATINS

- **Heart Protection Study (HPS)** showed decreased strokes with simvastatin 40 mg, except with pre-existing cerebrovascular disease.*
- **CARDS** Study showed decreased strokes with atorvastatin 10 mg in Type 2 Diabetes patients.#
- **SPARCL** Study showed decreased strokes with atorvastatin 80 mg in patients with recent stroke or TIA and no known CHD. There was a slight increase in hemorrhagic stroke.+

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Residual Cardiovascular Risk Despite LDL-C Lowering

Therapies based on LDL-C lowering reduce the risks of CAD despite LDL-C lowering, 60-70% residual risk remains.

4S=Scandinavian Simvastatin Survival Study; CARE=Cholesterol and Recurrent Events; WOSCOPS=West of Scotland Coronary Prevention Study; LIPID=Long-term Intervention with Pravastatin in Ischemic Disease; AFCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; HPS=Heart-Protection Study; PROSPER=Prospective Study of Pravastatin in Elderly at RISK; CARDS=Collaborative Atorvastatin Diabetes Study; ASCOT-LLA=Anglo-Scand. Cardiac Outcomes Trial.
USE OF STATINS WITH OTHER MEDS. AND IN SPECIAL SITUATIONS

- **FIBRATES:**
  - **Gemfibrozil:** Never use with a statin due to inhib. of glucuronidase essen. for statin metab.
  - **Fenofibrate:** Can use with a statin with care.

- **NICOTINIC ACID** (Niaspan® or other new sustained release form® preferred): Can be used with a statin with care.

- **STATINS OVER THE COUNTER?**

- **DECREASED DOSING FREQUENCY OF STATINS?**
  - Atorvastatin and Rosuvastatin. #^

*Whayne TF. Am J Cardiol 2008;101:745.*  
^Gadarla M. Am J Cardiol 2008;101:1747-1748.
THE ENHANCE STUDY: RESULTS*

- Group-1 (eze/sim): Significant decrease in LDL (58% vs. 41% in Group-2 (sim); p < 0.01).
- Group-1: Slightly more progression in carotid intima-media thickness but very insignificant.
- Group-1 vs. Group-2: No significant differences in CV outcomes (the study was designed as an imaging only).
- Next step: an outcomes study: Improve-It+.
- Lipid Research Clinics#: Men with upper 5% CV risk using cholestyramine required 7.4 years with only LDL lowering to show decreased cardiovascular events and this can be expected to apply to ezetimibe alone.

ENHANCE STUDY: RELEVANT CLINICAL ISSUES AND VALUE OF EZETIMIBE

• LDL is most specific lipoprotein associated with CHD (the gold standard of CV risk factors)* with goal < 70 and no special claim for high dose statin except in ACS.

• Each doubling of the statin dose only decreases LDL another 6%+ and the same with hsCRP.

• The higher the statin dose, the higher the incidence of liver inflammation/myalgia. Myalgia described as 1-5% in labeling information# and reported in clinical studies up to 10.5%† (clin. trials run in eliminates many pts.). Do not need CPK increase to have significant myopathy.¶

• Ezetimibe is valuable in attaining LDL gold standard by adding approximately another 25% LDL reduction to statin Rx.

CONCERN REGARDING EZETIMIBE, LOW LDL AND CANCER

• SEAS Trial: New onset cancer in 101 patients in active-Rx vs. 65 in control group†.

• SEAS + ONGOING SHARP AND IMPROVE-IT: NO CREDIBLE EVIDENCE FOR ADVERSE EFFECT OF EZETIMIBE ON CANCER RATE†.

• NO ASSOCIATION OF CANCER AND LDL LOWERING EVER ESTABLISHED.

The Majority of Statin Monotherapy LDL Reduction Is Seen With the Initial Dose

-20\% \quad -28\% \quad -37\% \quad -46\%$

P<0.001 vs atorvastatin 10 mg; simvastatin 20 mg and 40 mg; and pravastatin 10 mg, 20 mg, and 40 mg.

P=0.026 vs atorvastatin 20 mg

Addition of ZETIA™ (ezetimibe) to Ongoing Stable Statin Therapy: Significant Improvements in LDL-C, TG, and HDL-C

Mean % Change From Treated Baseline

- LDL-C: -4% (Statin + Placebo), -25%* (Statin + ZETIA 10 mg)
- TG (median): -3%, -14%*
- HDL-C: 1%, 3%†

TG = triglyceride.
*P<0.001 vs statin + placebo.
†P<0.05 vs statin + placebo.

Adapted from Gagné C et al. Efficacy and Safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol. 2002;90:1084–1091, with permission from Excerpta Medica Inc.
EZETIMIBE AND OXIDIZED LDL*

- Ezetimibe decreased ox-LDL in association with reductions in total LDL and in large buoyant LDL.
- This change in ox-LDL by ezetimibe was not associated with any significant change in small dense LDL, HDL or VLDL.
- Increasing statin dose did not decrease ox-LDL further.
- Further investigation warranted due to strong association between ox-LDL and atherosclerosis.

Low HDL-C and High LDL-C Increase Coronary Artery Disease Risk; Elevated HDL Appears Protective

Framingham Heart Study

Relative Risk of CHD After 4 Years

CHD=coronary heart disease.
This information was adapted from The Canadian Journal of Cardiology 1988;4(Suppl A):5A–10A.
Short- and Long-Term HDL-C Effects

Change From Baseline (%)

- ROS 5 mg
- ROS 10 mg
- ATV 10 mg

Week 12 (Fixed Dose)
Week 52 (Titration)

*P < 0.05 versus atorvastatin

Multiple Actions of HDL-C as a Potential Basis for Antiatherosclerotic Activity

- Antioxidant
- Antithrombotic
  - Antiplatelet
  - Protein C activation
- Enhanced reverse cholesterol transport (RCT)
- Antiatherothrombotic effect
- Anti-inflammatory
- Profibrinolytic

Niaspan Efficacy
Combined Data from Pivotal Studies

Mechanism of Niacin-Induced Flushing by Prostaglandin D2

Adapted from Pike NB. J Clin Invest. 2005;115:3400-3403.

Dermal macrophages → Undesirable effects → Arachidonic acid → COX-1 → PGE$_2$, PGD$_2$ → EP$_2$ or EP$_4$ → Smooth muscle cell or other cell type

Nicotinic Acid–Induced Flush

Selectively DP1 Receptor Antagonist Laropiprant Markedly reduces Niacin Flush in mice and humans

Cutaneous vasodilation and burning sensation on face and upper body
CETP Inhibitors:

1. Cholesterol Ester Transferase Protein Inhibitor.
2. New investigational pharmaceutical class that will be most effective medication yet for elevating the HDL.
3. Unfortunately, Torcetrapib testing and marketing was planned only in combination with Atorvastatin instead of also being available alone to be combined as indicated with other statins and with other medications.* Extensive clinician protest then forced individual availability. However, CV complications (BP↑, MI’s, Deaths) later forced withdrawal.
4. Other CETP inhibitors are on the horizon (Anacetrapib-Merck, Dalcetrapib-Roche/Japan Tobacco), reportedly without BP/CV problems.

Percent Change from Baseline in Apo A-I (similar to HDL; DALM 2007)

Monotherapy

- Placebo
- Anacetrapib 10 mg
- Anacetrapib 40 mg
- Anacetrapib 150 mg
- Anacetrapib 300 mg

Co-administration

- Atorva 20 mg
- Anacetrapib 10 mg + Atorva 20 mg
- Anacetrapib 40 mg + Atorva 20 mg
- Anacetrapib 150 mg + Atorva 20 mg
- Anacetrapib 300 mg + Atorva 20 mg

Daniel Bloomfield,1; Gary L. Carlson,1; Aditi Sapre,1; Diane Tribble,2; James M. Mckenney,3; Thomas W. Littlejohn III,4; Christine McCrary Sisk,1; Yale Mitchel,1; Richard C. Pasternak,1.

1. Merck Research Laboratories, Rahway, NJ.
2. Isis Pharmaceuticals, Carlsbad, CA.
4. Piedmont Medical Research Associates, Winston-Salem, NC.
LIPOPROTEIN (a); [from DALM 2007]

Monotherapy

Co-administration

Median % Change from Baseline (95% CI)

Placebo
Anacetrapib 10 mg
Anacetrapib 40 mg
Anacetrapib 150 mg
Anacetrapib 300 mg
Alorva 20 mg
Anacetrapib 10 mg + Alorva 20 mg
Anacetrapib 40 mg + Alorva 20 mg
Anacetrapib 150 mg + Alorva 20 mg
Anacetrapib 300 mg + Alorva 20 mg

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NEGATIVE META-ANALYSIS OF STATIN BENEFIT*

• Meta-analysis of 11 trials (total participants 65,229) including JUPITER, ALLHAT, ASCOT, MEGA, AFCAPS/TexCAPS, WOSCOPS, PROSPER, CARDS, ASPEN, PREVEND IT, HYRIM.

• No evidence for benefit of statin therapy on all-cause mortality over average of 3.7 years was found in what was considered a high-risk primary prevention population.

• More research, free of incentives, is essential.†

†Green L. Arch Intern Med 2010;170:1007-1008.
ALTERNATIVE MEDICATIONS

• Some are of definite value.
• Unfortunately, due to the lack of financial incentive, there is no pharmaceutical company support for large placebo controlled trials to guide the clinician and bring effective alternative medications into clinical practice while incenting physicians/patients not to use ineffective/dangerous Rx. Also, the NIH has not supported trials.
• Dangerous and of no value: Chelation therapy.
• Questionable value: Folic acid/B-12/B-6 combination for elevated serum homocysteine.
• Alternative Rx with apparent value:
  Aspirin, Coenzyme Q, Nuts, Olive Oil, Omega Fatty Acids, Plant Sterols (Stanols), Policosanol, Red Wine, Red Yeast Rice, Soluble Dietary Fiber, Soy.
COENZYME Q-10
(uncertain benefit/risk)*

- MITOCHONDRIAL ENERGY TRANSDUCTION
- FUNCTIONAL ELEMENT IN ALL CELL MEMBRANES
  - ANTIOXIDANT ACTION
  - REGENERATION OF REDOX CAPACITY
- CONTROL OF MEMBRANE CHANNELS
- BIOSYNTHESIS IN MITOCHONDRIA AND ENDOPLASMIC RETICULUM
- BIOSYNTHESIS INHIBITED BY STATINS
- DOSE: 200 mg once daily (to ↓ risk of statin myositis)†

† Kelly P. Amer Col Cardiol Sci Sessions 2005 (used 100 mg once daily).
RED WINE

• BENEFIT FROM ALCOHOL
  – ALCOHOL MAY DECREASE INSULIN RESISTANCE*
  – ALCOHOL HAS AN ANTI-PLATELET EFFECT#

• BENEFIT FROM POLYPHENOLS#

• BENEFIT FROM ↑ NITRIC OXIDE (ONE SUGGESTED POLYPHENOL EFFECT)#

• BENEFIT FROM FLAVONOIDS WHICH INHIBIT LDL OXIDATION+

  RED WINE, DARK CHOCOLATE, GREEN TEA ARE MAIN SOURCES OF FLAVONOIDS

#Wallerath T. J Am Col Cardiol. 2003;41:471-478
+Maron D. Curr Ath Reports. 2004;6:7378
CONCLUSION

- hsCRP appears to be the most clinically used marker of inflammation but Phospholipase A2 avoids nonarterial inflammatory etiologies.
- LDL is still the gold standard of CV risk factors and it should be targeted aggressively.
- Ezetimibe has been subjected to ENHANCEd hype.
- Treatment of HDL may be the next basic focus to decrease CV risk.
- Failure to treat LDL in a patient with high CV risk, without specific reasons, is malpractice.
- Women have significant risk from CHD, especially if developed less than age 50.