

Reducing Cardiovascular Risk Using Advanced Testing

Bradley Bale, MD

September 8th and 9th, 2004



Berkeley HeartLab Distance Learning Symposium

“Reducing Cardiovascular Risk Using Advanced Testing”

Bradley F Bale, MD September 2004

Advanced tests to discuss

- LDL GGE
- HDL GGE
- ApoB
- Lipo (a)
- Fibrinogen
- Homocysteine
- Insulin
- ApoE genotype
- hs-CRP

Abnormal LDL & HDL sub-particles

- Frequently associated with insulin resistance
Therefore all of these patients should have the following evaluation:
 - 1) FBS– red flag if > 90; abn. if > 100
 - 2) A1c– red flag if > 5.0
 - 3) 2 hr. PPBS-- red flag if >120; abn. if > 140
 - 4) fasting insulin– abn. if > 9
 - 5) metabolic syndrome?– if yes, positive for IR
 - 6) TG/HDL – usually IR if > 3.5
- May be hereditary without IR

3

Efficacy of ATP III MS criteria in identifying IR

- 74 caucasians without DM & FG < 110
- Used euglycemic – hyperinsulinemia glucose clamp technique
- 12.2% (9) had MS
- 39.2% (29) had IR
- Specificity of MS for IR > 90%
- Sensitivity of MS to identify IR < 50%
- Suggest more sensitive criteria needed to dx IR such as sub-particle profile

Diabetes Care 2004; 27: 978 -983

Berkeley HeartLab database

HDL 2b deficiency is found in a significant number of pts. that do not have an LDL sub-particle problem

49% of pts. with low HDL 2b have normal LDL sub-particle distribution

It is necessary to measure both LDL and HDL sub-particles

5

Treatment choices for sub-particles

- Weight loss
- Exercise– according to STRRIDE has to be intense
- Niacin
- Fibrates
- TZDs--- especially if IR

6

Mean changes from baseline in plasma lipoproteins according to exercise type

| Lipoprotein measurement | Low amount, moderate intensity | Low amount, high intensity | High amount, high intensity | p* |
|----------------------------|--------------------------------|----------------------------|-----------------------------|------|
| Size of HDL particles (nm) | 0 | 0 | +2 | 0.02 |
| Size of LDL particles (nm) | +0.1 | +0.1 | +0.3 | 0.05 |

* p for intention-to-treat analysis, comparing changes in high-amount, high-intensity group with changes in control patients.

Kraus WE et al. *N Engl J Med* 2002; 347:1483-92.

7

Lipoprotein effects of lipid modifying therapy

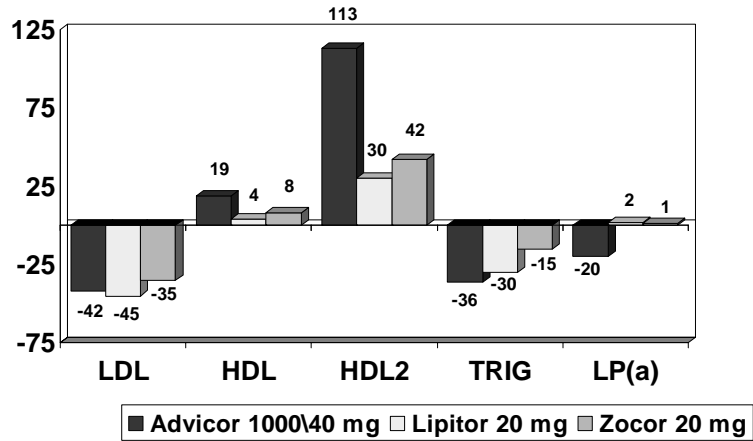
| | Statins | Nicotinic Acid | Fibrates |
|-------------------------------|------------|----------------|--------------|
| LDL | ↓ 18 – 55% | ↓ 5 – 25% | ↓ 5 – 20% |
| HDL | ↑ 5 – 15% | ↑ 15 – 35% | ↑ 10 – 20% |
| Triglycerides | ↓ 7 – 30% | ↓ 20 – 50% | ↓ 20 – 50% |
| Small,Dense LDL | No effect | Decrease | Decrease |
| Effects on Insulin Resistance | None | May Increase | May Decrease |

Third Report of the National Cholesterol Education Program Expert Panel. Executive Summary. NIH Publication No. 01-3670. May 2001.

Guerre-Millo M, et al. *J Biol Chem*. 2000;275:16638-16642.

8

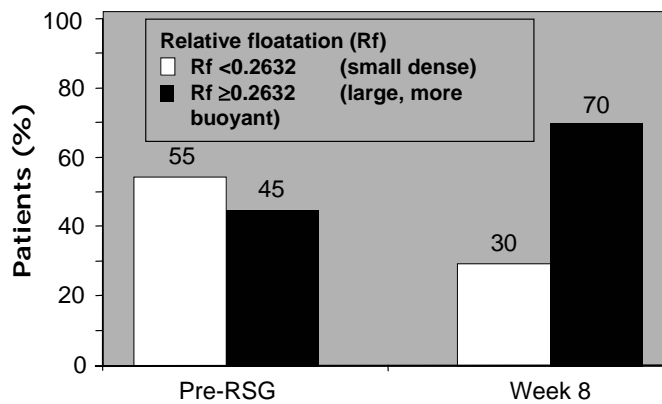
Advocate study



American Journal of Cardiology Vol. 91, March 15, 2003.

9

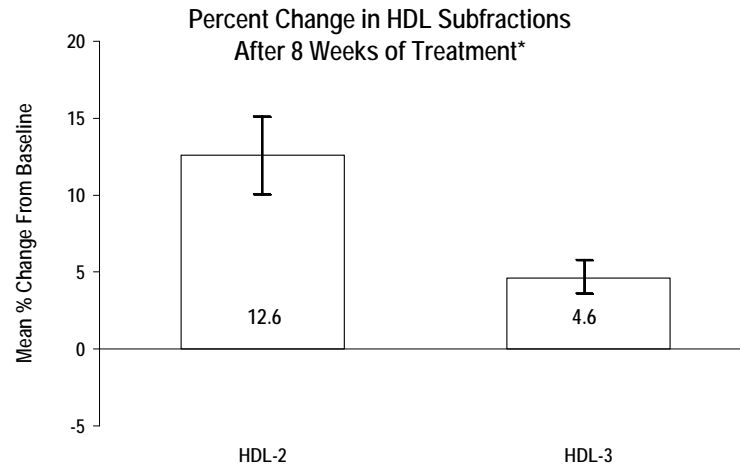
Rosiglitazone treatment improves LDL particle density phenotype



Study 108. Data on file.
GlaxoSmithKline.

10

Rosiglitazone increases HDL₂



*Results using rosiglitazone 8 mg/day given in divided doses. Prospective cardiovascular clinical outcome trials are ongoing. Geometric mean (Intent to treat, LOCF). Error bars represent \pm standard error. Freed MI et al. *Am J Cardiol.* 2002;90:947-952.

11

Observations regarding sub-particle treatment

- Niacin works well on LDL 3a & 3b
- Niacin may not effect or may even increase LDL4b
- Niacin works well on HDL2b
- Fenofibrate works moderately well on LDL sub-particles
- Fenofibrate may help HDL2b
- TZDs improve sub-particles but usually cannot totally correct

12

Treatment of ApoB

- Exercise
- Weight loss
- Statins
- Niacin
- Fibrates
- Ezetimibe
- Bile acids

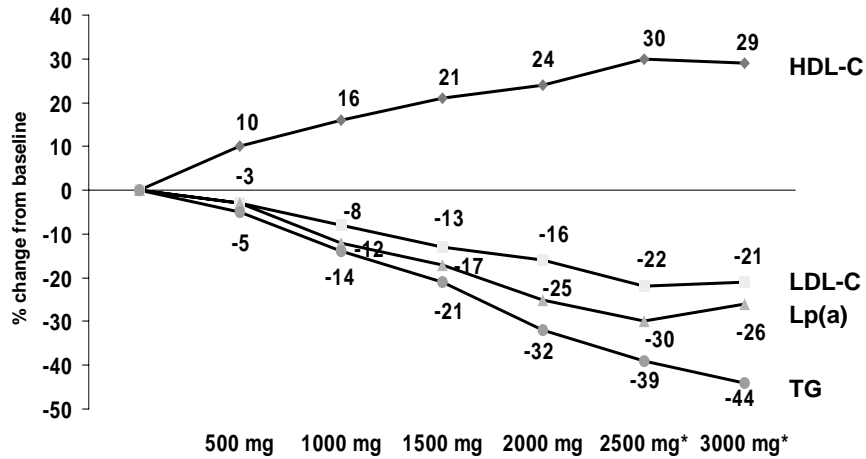
13

Treatment for Lipo (a)

- Niacin
- Almonds
- ? Fenofibrate?

14

Niaspan[®] efficacy Combined data from pivotal studies



*Greater than recommended daily doses.

15

Almonds lower lipo(a)

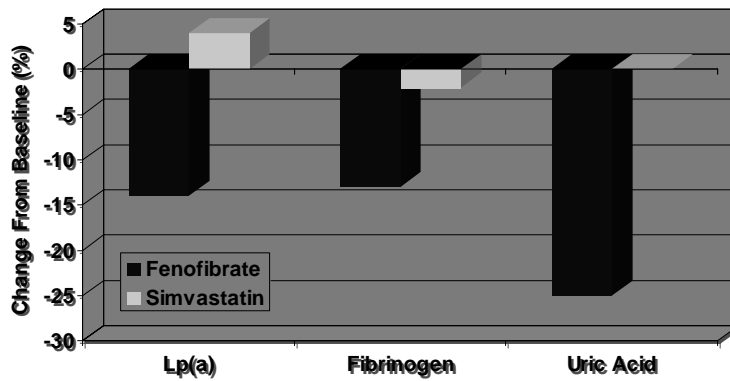
| Reduction area | Full-dose almonds | p value |
|------------------------|-------------------|--------------|
| Lipoprotein (a) | 7.8 ± 3.5% | 0.034 |

27 men and women
73 g/day; 22% of total caloric intake
One month

Jenkins DJA et al. *Circulation*
[DOI: 10.1161/01.CIR.0000028421.91733.20]. 2002.

16

Fenofibrate and Lp(a)



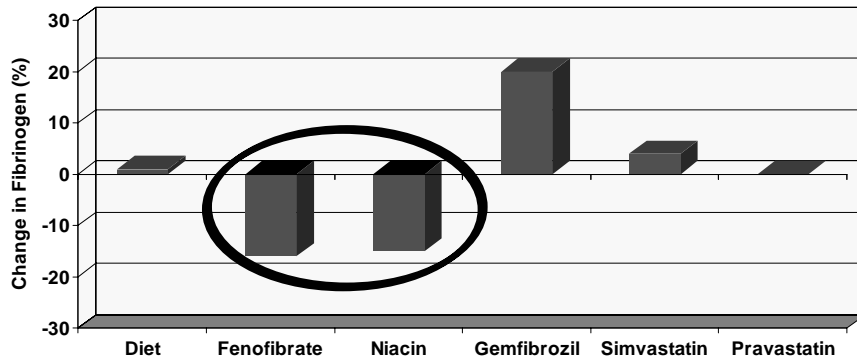
17

Treatment for fibrinogen

- Niacin
- Fenofibrate
- TZDs
- Pravastatin neutral; other statins make it worse

18

Lipid lowering agents and fibrinogen



Branchi A, et al. *Thromb Haemost.* 1993;70:241-243

TZD's
lower fibrinogen 19

Fibrinogen and treatment

TZD's have been shown to decrease PAI-1 & fibrinogen

Current Therapeutic Research Vol. 59, NO. 8,
August 1998

Journal of Diabetes and Its Complications 1998;
12:181-186



20

Treatment for homocysteine

- Diet -- foods rich in vit. B
- Folic acid 1 to 5mg
- Vit. B-6 50 – 250 mg/day
- Vit. B-12 1 mg/day
- ?? Foltx
 - a) folic acid- 2.5mg
 - b) vit. B-6 - 25mg
 - c) vit. B-12 – 1mg
- May not want to treat in a recently stented pt.
FACIT study

21

Folate rx increases in-stent restenosis in pts. post PCI (FACIT)

626 pts.; six-month follow-up

Placebo or folic acid 1.2mg, B6 4.8mg, B12 .06mg

Results:

Restenosis rate— 35% for treatment group
27% for placebo group

Surprise !!!!

Opposite of one year Swiss Heart Study-JAMA 2003

Why?????

Stent rate Swiss—50%; FACIT—100%

More diabetics in Swiss

Bottom line:

Pts. with increased homocysteine who just had a stent; do not start folate

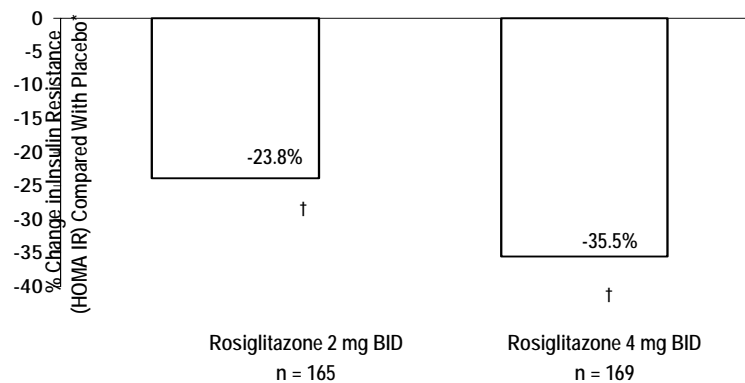
ACC Scientific Sessions 2003

Treatment of IR

- Weight loss – every 10lbs. = 50% decreased risk going on to DM
- Exercise – as important as weight loss
- TZD – off label unless diabetic

23

Rosiglitazone monotherapy improves insulin resistance



* Adjusted geometric mean values.

† $P < .0001$.

Comparison with placebo and rosiglitazone over 26 weeks in a randomized, placebo-controlled study. Study 011. Data on file, GlaxoSmithKline.

24

Practical advice from Apo E

- E 2
exercise !! extremely important
no refined carbohydrates
alcohol may be helpful
- E 3
diet and exercise help moderately
bran is good
more likely to need medications
- E 4
low fat diet!! extremely important
No alcohol !!!!
exercise modest help
increased risk CAD; rx co-morbidities aggressively

Arterioscler. Thromb. Vasc. Biol. 1995 Jan.; 15 (1): 105 -111
Am. J. Epidemiol. 2002; 155: 487 -495

25

Treatment for hs-CRP

- Must determine if really due to endothelial inflammation
 - a) repeat measures
 - b) acute inflammation in previous two weeks ??
 - c) ? due to medication like estrogen
- If is apparently real, other tests should tell you why
for example, IR

- Observation: it is far from a perfect test and if lipo (a) is involved, HsCRP may not mark the risk

26

The patient is in the heart attack zone!!

How should we treat them??

Normal foundation

Lifestyle advice -- depends on ApoE genotype

Anti-platelet therapy

Statin

ACEI or ARB

If post MI, beta-blocker & Plavix

27

Outcomes in aspirin responders and nonresponders

| Outcome | Aspirin nonresponders (%) | Aspirin responders (%) | p |
|----------------|---------------------------|------------------------|------|
| Death, MI, CVA | 24 | 10 | 0.03 |
| Death | 12 | 5 | 0.13 |
| MI | 7 | 4 | 0.54 |
| CVA | 12 | 1 | 0.09 |

Gum PA et al. *J Am Coll Cardiol* 2003; 41:961-5.

28

The effect of statin treatment on coronary events as a function of baseline lipid levels:
Pravastatin Pooling Project

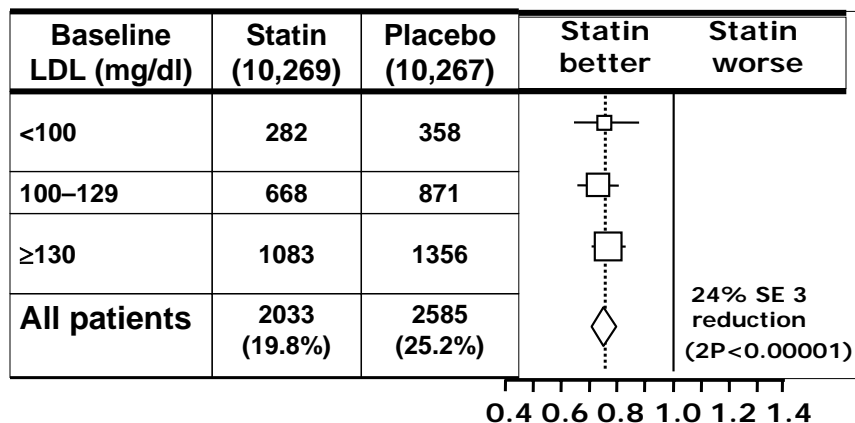
| Baseline LDL (mg/dl) | Patients | CV Events (death, MI) | RRR (95% CI) | P Value |
|----------------------|----------|-----------------------|--------------|---------|
| 70-134 | 4,414 | 537 | 22 (34-7) | 0.005 |
| 135-174 | 8,035 | 987 | 23 (32-13) | <0.001 |
| 175-232 | 7,318 | 670 | 32 (42-21) | <0.001 |

(3 trials, 19,768 patients, 102,559 pt-yr of f/u, 2194 end points)
 Pravastatin 40 mg/d vs Placebo (LDL reduction 27%, HDL increase 5%)
 Sacks FM et al. *Circulation* 2000;102:1893-1900.

29

HPS: statin benefit is entirely Independent of baseline LDL

Risk ratio and 95% CI



www.hpsinfo.org

30

ASCOT summary and conclusions

- Risk reductions in CHD events were unrelated to baseline cholesterol levels and were consistent across the whole range of cholesterol
- Were the trial to have continue to its planned duration of 5 years, it is estimated that atorvastatin would have reduced CHD incidence by approximately 50%
- Benefits occurred in the absence of any increased risk of non-cardiovascular disease, including fatal cancer
- These findings have implications for future lipid-lowering guidelines, particularly with reference to hypertensive patients

Sever PS, Dahlöf B, Poulter N, Wedel H, et al, for the ASCOT Investigators. Lancet. 2003;361:1149-58

31

Final word: Cannon

The inhibition of the renin-angiotensin-aldosterone system is extremely important

"I think that has become now a mandatory component of heart failure and coronary disease management."

**Christopher Cannon Professor of M.
Harvard Med School CV Division**



Cannon
32

Final word: The right track

These studies show we are on the right track

- **Antithrombotic therapy in coronary disease**
- **Treating cardiac failure with the ACE pathway**
- **ACE inhibition for CAD patients regardless of risk**



Valentin Fuster Dir. CV Institute
Mt. Sinai School of Med. NY

33

Building on the foundation

Problems not adequately addressed with cornerstones

- Sub-particles
 - Niacin
 - Fibrates
 - TZD's
- Lipo (a)
 - Niacin
 - ? fenofibrate
- Fibrinogen
 - Niacin
 - Fenofibrate
 - TZD's
- Homocysteine
 - Vits. B6, B12 & folic acid
- IR
 - TZD's
 - Niacin &/or fenofibrate frequently needed for associated lipids & fibrinogen

34

Cases for discussion and illustration

35

38 yo Caucasian female
Wt. - 107 lbs. ; BMI – 23; Waist – 28 ins.
Excellent health habits
BP 120/80
No meds
FRS - < 1% ten year risk
IMT of carotid – 17 years >; three soft plaque all > 1.4 mm

36

TC – 279 ; TG – 70 ; LDL – 198 ; HDL – 67
FBS – 83 ; 2 hr. PPBS – 79 ; A1c – 5.0 ; insulin – 2
LDL 3a & 3b – 10.9% ; LDL 4b – 1.9%
HDL 2b – 25%
Fibrinogen – 423
Lipo(a) – 54
ApoB – 147
Homocysteine – 6.1
HsCRP - .8 mg/L
ApoE – 3/3

37

- Dx
 - ASVD / IMT
 - Hyperlipidemia
 - Hyperfibrinogenemia

How would you treat this patient??????

38

Foundation

- Lifestyle based on apoE 3/3
- Antiplatelet therapy – ASA 81 mg
- Statin
- ACEI or ARB

Does this cover everything?????

39

Issues beyond the foundation

- Lipo(a)
- HDL 2b
- Fibrinogen
- ?? ApoB

How can we deal with these??????

40

- Lipo (a) – niacin; ? fenofibrate
- HDL 2b -- niacin; fibrate
- Fibrinogen – niacin; fenofibrate
- ApoB – niacin; fibrate; bile acid; ezetimibe

Logical choice is niacin

41

What really happened?

- Lifestyle – did follow BHL advice
- ASA 81mg
- Pravastatin 40mg
- ACEI or ARB declined
- ER niacin to 1000mg

What has transpired with this treatment ??

42

| | 9/26/03 | 12/22/03 1 mo. Prav. 40mg | 3/19/04 2 mo. Niacin 1000mg | 7/26/04 Same meds | Comments BHL diet: flax; soy; tofu | |
|------------|---------|---------------------------------|-----------------------------------|----------------------|--|----|
| Wt. | 107 | 106 | 107 | 105 | Exercise 6X/wk; 45-60 | |
| BP | 120/80 | 118/80 | 118/76 | 116/78 | | |
| ASAck | | okay | | | | |
| TC | 279 | 182 | 159 | 162 | | |
| TG | 70 | 67 | 59 | 60 | | |
| LDL | 198 | 105 | 91 | 84 | | |
| HDL | 67 | 64 | 56 | 66 | | |
| TC/HDL | 4.2 | 2.8 | 2.8 | 2.5 | | |
| HDL2b | 25% | | | 32% | | |
| ApoB | 147 | | | 79 | | |
| Fibrinogen | 423 | | | 397 | | |
| Lipo(a) | 54 | | | 54 | | 43 |

59yo Caucasian male
Wt. -- 201 lbs. ; BMI – 28; waist – 40 ins.
BP 120/80
Chest pain & exertional palpitations
Meds: atorvastatin 80mg
FRS – 10% ten year risk
Treadmill – positive
Holter monitor – negative
Angiogram – negative
IMT of carotid – 16 yrs. > ; four large soft plaques

TC – 191 ; TG – 751 ; LDL – N/A ; HDL – 32
FBS – 115 ; 2hr. PPBS – 228 ; A1c – 5.7 ; insulin – 8
LDL 3a & 3b – 35.9% ; LDL 4b – 11.2%
HDL 2b – 6%
Fibrinogen – 407
Lipo(a) – 8
ApoB – 59
Homocysteine – 5.4
HsCRP -- .3 mg/L
Apo E – 3/2

45

Dx:
ASVD / IMT
Metabolic syndrome – IFG, diabetic 2 hr. PPBS = IR
Dyslipidemia – IR
Hyperfibrinogenemia

How would you treat this?????

46

Foundation treatment

- Lifestyle
- Antiplatelet therapy
- Statin
- ACEI or ARB

Does this cover everything????

47

Issues beyond the foundation

- LDL & HDL sub-particles
- Fibrinogen
- Insulin resistance

How can we deal with these??

48

- LDL & HDL sub-particles – niacin, fibrate, TZD
- Fibrinogen -- niacin, fenofibrate, TZD
- Insulin resistance -- TZD
- TG -- niacin, fibrate

Logical choices -- TZD and fenofibrate (high TG)

49

What really happened?

- Lifestyle – diet, lots exercise, daily alcohol, fish oil
- ASA 81mg
- Pravastatin 40mg ; d/c'ed atorvastatin
- Ramipril 10mg
- Rosiglitazone 4mg
- Fenofibrate 160mg

50

| | | | |
|-------------|----------------------------|---|--|
| | 10/03 Atorvastatin 80mg | 4/04 BHL lifestyle Prava. 40mg; ramipril Rosiglitazone 4mg Fenofibrate 160mg ASA 81mg; fish oil | At last visit said chest pains stopped; palpi. stopped Added niacin |
| TC | 191 | 127 | |
| TG | 751 | 252 | |
| LDL | N/A | 43 | |
| HDL | 32 | 34 | |
| TC / HDL | 6.0 | 3.7 | |
| LDL 3a & 3b | 35.9% | 30.3% | |
| LDL 4b | 11.2% | 6.9% | |
| HDL 2b | 6% | 7% | |
| Fibrinogen | 407 | 286 | |
| FBS | 115 | 88 | |
| 2 hr. PPBS | 228 | 121 | |
| A1c | 5.7 | 4.7 | |
| Waist | 40 ins. | 37.5 ins. | |
| Wt. | 201 | 184 | 51 |

3/04 HAPC
59yo Asian male came in for third opinion
Known CAD:
9/01 had multiple stents in RCA at Arizona HI for total occlusion; no sustained patency but had good collaterals; CABG offered- declined
40% narrowing of Cx and LAD
EF normal
Other known problems:
gout for years
high TG and low HDL for years
ED for several years
Habits:
Past marathon runner; still moderate exercise 5X/wk
Occas. alcohol; good diet
Famhx:
Father died CAD @ 69yo; known CAD in 50's
Paternal grandfather with CAD
Numerous fam members with elevated TG's
Son with type 1 DM

Meds:

Fluvastatin XL 80mg

Niacin ER 2000mg

ASA 325mg

Fish oil 3000mg

Folate 1mg

Allopurinol 300mg

Anything missing???

Exam: quesses???

wt. 150 lbs.; ht. 67 inches; waist 33 inches

BP – 114/80

FBS - ???

95

2hr. PPBS - ???

168

Rx changes ??????

53

Rx:

Add pioglitazone 30mg and in one week ramipril

Tests ordered:

What would you want ???????

54

IMT – 13 yrs. older and one soft plaque 1.4mm
 ASack- responder
 A1c – 5.1 ; insulin – 17 (FBS-95 ; 2hr. PPBS-168)
 TC – 183
 TG – 216
 LDL – 90
 HDL – 50
 TG / HDL = 4.3
 LDL 3a & 3b – 30.2% (<15%)
 LDL 4b - 13.5% (<5%)
 HDL 2b - 11.0% (>20%)
 Fibrinogen - 578 (<350)
 Lipo(a) - 8 (<20)
 Homocyst. - 6.7
 HsCRP - .3 mg/L
 Microalb. - 30 (<30)
 Creat. - 1.1
 TSH - normal
 BNP - 15
 Alt/Ast - 48/29
 Apo E - 3/3

What would you do now?????

55

Rx: 4/04
 Continue meds: (fluva.; niacin; ramipril; pio.; ASA; fish oil; folate)
 Add:
 Fenofibrate 160mg - TG; subs; fibrinogen

Labs: 5/04
 TG
 90
 HDL
 65
 TC
 202
 LDL
 119
 Fibrinogen
 280
 Microalb.
 7.8
 HsCRP - .2mg/L
 Creat. - 1.0
 Alt/Ast - 40/25

What would you do now?????????

56

Rx: 5/04

Continue meds: fluva.; niacin; fenofibrate; ramipril; pio.; ASA; fish oil; folate

Add: ezetimibe 10mg

What was the result three months later????

57

| | 3/04; F,N,A | 5/04;F,N,A, P,R,F | 8/04;F,N,A P,R,F,Z | | | |
|-----------|-------------|----------------------|-----------------------|--|--|----|
| BP | 114/80 | 120/70 | 90/60 | | | |
| TC | 183 | 202 | 129 | | | |
| TG | 216 | 90 | 64 | | | |
| LDL | 90 | 119 | 57 | | | |
| HDL | 50 | 65 | 59 | | | |
| TG/HDL | 4.3 | 1.4 | 1.1 | | | |
| TC/HDL | 3.7 | 3.1 | 2.2 | | | |
| 3a & 3b | 30.2 | | 18.0 | | | |
| 4b | 13.5 | | 12.0 | | | |
| H 2b | 11.0 | | 17.0 | | | |
| ApoB | 89 | | 55 | | | |
| Fibrin. | 578 | 280 | | | | |
| HsCRP | 0.3 | 0.2 | 0.2 | | | |
| Microalb. | 30 | 7.8 | 5.2 | | | |
| FBS | 95 | | 84 | | | |
| 2hr. PPBS | 168 | | 76 | | | |
| A1c | 5.1 | | | | | |
| Creat. | 1.1 | 1.0 | | | | |
| Alt/Ast | 48/29 | 40/25 | 38/21 | | | 58 |