Case 1

- 48 year old caucasian male with T2DM x 6 years
- BP readings 110-125/80-85; BMI 25.5; lifelong non-smoker
- 2 months ago, had an episode of chest pain, was investigated using a cardiac catheterization which revealed minor coronary artery abnormalities not requiring intervention
- Meds: EC-ASA 81 mg, Prandin 1 mg TID, Metformin ER 500 mg BID and Lisinopril 10 mg daily. He does not tolerate Niacin-ER [Niaspan®].
- HbA1c three days ago 6.2; annual microalbumin/creat ratio 56 ug/mg creat [Normal: 0-30 μg/mg creat]. No urinary symptoms, inactive urine sediment with negative nitrite test
- A fasting lipid profile was obtained

Case 1: Lipid Profile

- Total cholesterol 170 mg/dl
- Triglycerides 178 mg/dl
- HDL-c 30 mg/dl
- LDL-c 96 mg/dl
- Non-HDL-c 140 mg/dl

MCQ

TRUE OR FALSE?
1. His Lisinopril dosage needs be increased
2. Macrovascular complications can be more favorably impacted by good glycemic control as opposed to microvascular complications
3. He may benefit by a statin prescription
4. His LDL and non-HDL levels are on target.
### TRUE OR FALSE?

1. His Lisinopril dosage needs be increased
2. Macrovascular complications can be more favorably impacted by good glycemic control as opposed to microvascular complications
3. He may benefit by a statin prescription
4. His LDL and non-HDL levels are on target.

### Diabetes And Cardiovascular Disease

- NCEP-ATP III states that diabetes mellitus is a coronary artery disease equivalent.
- Lipid targets: LDL-c < 100 mg%; HDL-c < 130 mg%; HDL > 40 mg%
- His LDL is ‘at target’; his non-HDL [140 mg%] and HDL [30 mg%] are not.
- He has microalbuminuria, which is an independent CV risk factor.

- He will likely benefit by a statin-although his LDL-c is at target. Statins are very effective in lowering non-HDL-c
- Most diabetics with elevated non-HDL have increased sd-LDL-P, which is more atherogenic.
Steno-2 Supports Aggressive Multifactorial Intervention in Type 2 Diabetes

- Target-driven, long-term, intensified intervention aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria
  - Blood pressure < 130/80 mm Hg
  - A1C < 6.5%
  - Total cholesterol < 175 mg/dL
  - Triglycerides < 150 mg/dL
- Produced risk reductions in CV and microvascular outcomes
  - Primary outcome (combined CV disease) 53% decrease
  - Nephropathy 61% decrease
  - Retinopathy 58% decrease
  - Autonomic neuropathy 63% decrease

Schmittdiel JA et al. [J Gen Intern Med. 2008 May;23(5):588-94.]

- OBJECTIVE: Rank non-adherence Vs. lack of intensification in explaining above-target CVD risk factor levels.
- In 2005, 161,697 Kaiser Permanente N. California adult DM patients included in the study.
- "Above target" = >7% A1c; >100 mg% LDL-c; >130 mmHg SBP
- "poor adherence" = medication gaps for >/=20% of days covered for all medications for each condition separately

NEPTUNE SURVEY
[The NCEP Evaluation Project Utilizing Novel E-Technology]

- 4885 patients; 67% achieved LDL target goals
- 89% in those with 0-1 RF; 76% in 2+ risk factors; 62% in those with CAD!!
- 55% in those with DM and 40% with other CAD risk equivalents
- In all 1447/4885 had CVD.75% "very high risk" according to NCEP 2004 update-only 17.8% were at target LDL < 70 mg%.

Schmittdiel JA et al.-contd

- Poor adherence - 20-23% of patients across the 3 conditions. [PATIENT INERTIA]
- No evidence of poor adherence with no treatment intensification was found in 30% of hyperglycemia patients, 47% of hyperlipidemia patients, and 36% of hypertension patients. [PHYSICIAN INERTIA]
- Poor adherence or lack of therapy intensification was evident in 53-68% of patients above target levels across conditions.

CONCLUSIONS: Both non-adherence and lack of treatment intensification occur frequently in patients above target for CVD risk factor levels; however, lack of therapy intensification was somewhat more common.
CASE 1 - Treatment Pointers

- Comprehensive risk reduction strategy is a must in all diabetics
- Statins are helpful in reducing ldl and non-hdl
- In those with low hdl, treating ldl to below target [10-15%] has cvd outcome benefits
- Therapy strategy must address patient and physician inertia.

Case #2 JD

- Primary prevention but very high risk with very high LDL in African American male smoker with controlled hypertension
- Smaller than average results with statins alone
- Cholesterol hyperabsorption on statins and significant response to ezetimibe
- Benign CK elevations that can be followed safely

Case Study: JD, a 59 year old African-American male with multiple risk factors

- Smoker
- HTN
- Mild Glucose Intolerance
- Low HDL-C
- Metabolic Syndrome
- No known CVD
- No Family History
- Lp(a) 13
- CRP-HS 5.91
- Framingham score 30% 10 yr. risk
- TC 309, trig 130, LDL 244, HDL 39
- BMI- 27.66
- Exercise: Weather inhibited. Alot in summer with gardening.
- Meds:
  - Lisinopril 10
  - Atorvastatin 80
  - Fish Oil 2000 BID
Case Study: JD
Goals LDL<70, non-HDL<100

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<thead>
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Variability of Cholesterol Absorption
- Most patients are at around 60%
- Varies from 30-90%
- Statins increase cholesterol absorption
- Scandinavian Simvastatin Survival Study (4S) - 1998
  - Direct correlation between absorption and events
  - Highest quartile of cholesterol absorbers had a higher coronary event rate with 20-40 mg of Simvastatin as compared to a lower event rate with placebo
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<td><strong>Ezetimibe</strong></td>
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<tr>
<td>✓ Blocks absorption of dietary/biliary cholesterol and phytosterols by intestinal enterocytes</td>
<td>✓ Repeated delivery to the intestinal brush border</td>
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<tr>
<td>✓ Inhibits absorption through a mechanism dependent on NPC 1L1 protein (Niemann-Pick)</td>
<td>✓ Minimal systemic exposure</td>
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<tr>
<td>✓ Reduces cholesterol content of chylomicrons</td>
<td>✓ Half-life 22 hours – once daily dosing</td>
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<td>✓ Does not reduce absorption of lipid-soluble vitamins or steroid hormones</td>
<td>✓ Reduces GI cholesterol delivery to the liver</td>
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<td>✓ Glucuronidated in the intestine</td>
<td>• Hepatocytes compensate by upregulating LDL receptor uptake</td>
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<td>✓ Parent compound and metabolite excreted in bile and circulate enterohepatically</td>
<td>✓ Efficacy</td>
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<td>• Decreases LDL-C by about 18%</td>
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<td>– Higher percentage decrease combined with statins when statin dose is lower</td>
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<td>• Increase HDL-C by about 1-3%</td>
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<td>• Decreases triglycerides by about 2%</td>
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**Case Study: JD**

**Goals LDL<70, non-HDL<100**

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**Statin Intolerance**

- Myalgias - pain, soreness, cramps, weakness, without ↑ CK
- Around 5% on statins?
- Dose related, regardless of hydrophilicity of drug
- Myositis/Myopathy - symptoms with ↑ CK
- .1%-.5% on statin monotherapy
- Myopathic risk factors (age, renal dz, DM, small body frame, infection, untreated hypothyroidism, perioperative periods, substance/ETOH abuse)
Statin Safety Assessment Conference

- Sponsored by the National Lipid Association and published in two phases - Spring 2006 and Spring 2007 in The American Journal of Cardiology
- Review and independent research of
  - NLA information
  - FDA Adverse Event Reporting System
  - Cohort and clinical trial results
  - Analysis of administrative claims database information
  - Assessment of its 4 Expert Panels

Muscle and Statin Safety

- Pts with tolerable muscle complaints and CK <10 X UL
  ✓ continue statin therapy
- Intolerable muscle symptoms with or without CK elevation
  ✓ D/C statin until symptoms resolved. Restart same or different statin at same or lower dose to test for reproducibility

Muscle and Statin Safety

- Baseline CK only for high risk patients
  ✓ Controversial and frequently performed by experts
- Counsel to report any muscle symptoms
- Do not measure CK if asymptomatic
- Check CK in symptomatic patients
- Evaluate muscle symptoms or ↑ CK level for other causes

Rhabdomyolysis

CK >10,000 U/L or CK >10 x ULN
With ↑ Serum Creatinine
Or requiring IV hydration
- D/C statin.
- Once recovered, evaluate the risk vs. benefit
Case Study: JD
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46 Yr old caucasian male

- BMI 30
- Suffers with hypertension and is recovering from an acute attack of podagra [gouty arthritis]
- Drugs: Lisinopril/HCTZ 10/12.5 and EC-ASA 81 mg
- No family h/o dyslipidemia or premature CV disease
- Poor dietary habits and no exercise
- BP 130/80 mmHg; central adiposity-otherwise normal exam

Laboratory Tests

- T.Chol 208 mg%
- HDL-c 25 mg%
- Trig 256 mg%
- LDL-c 115 mg% [target:130 mg%]
- Non-HDL-c 183 mg% [target 160 mg%]
- 75 gm GTT: impaired fasting glucose only
- Uric acid 6.9mg% [3-7 mg%]; normal liver, renal function; no microalbuminuria
- Calculated Framingham Risk Score 7% [low]; Metabolic syndrome-Yes

CASE 3

46 Yr old caucasian male

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Besides lifestyle measures...

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<tr>
<td>- Start Fish oil, fenofibrate;</td>
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<tr>
<td>- Start Fish oil, Niaspan; continue</td>
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<tr>
<td>Lisinopril/HCTZ</td>
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<td>- Start Metformin, Niaspan; replace</td>
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And the answer is...

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Case-3 Contd...

- Fish oil [EPA+DHA 3 gm daily], Micronized fenofibrate and Niacin-ER [Niaspan®] all reduce triglyceride effectively
- But Niaspan does increase serum uric acid levels and would not be a wise choice for someone recovering from acute gout and high normal serum uric acid levels
- In contrast, fenofibrate in most clinical trials produce significant decreases in serum uric acid levels and will be a good choice here.
- Fish oil is neutral with respect to uric acid and can be combined with a fibrate.

Case-3 Contd...

- HCTZ raises serum uric acid levels as well. So it is best that the combination therapy be stopped and may be substituted with Lisinopril alone, at a higher dose.
- Beta blockers are not indicated in this patient with mixed dyslipidemia with no overt evidence of CAD.will likely worsen dyslipidemia and dysglycemia.
- Metformin is inferior to therapeutic lifestyle measures in preventing/postponing diabetes-not indicated in combination with Niaspan.
- YOU WILL NEVER BE WRONG IN REFERRING ANY PATIENT TO THE ROSS LIPID CLINIC!
**Case 3 Treatment Pointers**

- Beware of hidden dangers of coprescribing lipid lowering drugs in a patient with the metabolic syndrome risk cluster.
- Niaspan can still be prescribed—but after the patient loses weight, is on a low purine diet +/- Allopurinol.

**Case Study: Walter, a 50 year old white male with CAD**

- Previous MI, angioplasty
- HTN
- Obesity
- Gout
- Dyslipidemia
- Low HDL
- +FH
- Former smoker
- Metabolic Syndrome
- Myalgias with Lipitor 80
- CRP-HS – 8.24
- Lp(a) – 66
- TC-216, Trig-173, HDL-C-34, LDL-C-147, Non-HDL-C-182
- Eating: poor
- Exercise: poor due to ortho issues
- BMI – 40.09
- Meds: Fenofibrate 145 d
  - Niaspan 1000 d
  - Ezetimibe 10 d
  - Cholestyramine 2 sc. BID
  - Fish oil 1000 BID
  - Allopurinol 100 d
  - Atenolol 100 d
  - ASA 325 d

**Case #4 Walter**

- Secondary prevention in an obese caucasian male with CAD and a mixed dyslipidemia
- Demonstrates myalgias on Atorvastatin and primary care chose not to try other statins
- Efficacy of low dose Rosuvastatin
- Effect of weight loss

**Case Study: Walter, 50 year old white male with CAD**

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| +6 wks  | 277 | 120 | 54   | 52  | 57  | 68     | 33  |     | same        |
# Case Study: Walter

**Goals:** LDL-C <50 due to high Lp(a), non-HDL-C < 80

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While taking CkAltnon-HDL LDLLDLTrigTCWt.Date

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CASE 5

54 Year Old Caucasian Woman

- Referred for dyslipidemia and abnormal liver tests.
- BMI 30; BP 138/86 [on Lisinopril 20+HCTZ 25]; Non-smoker, no ETOH
- T.Chol 280 mg%; TG 255 mg%; HDL-c 33 mg%; LDL-c 195 mg%; ALT 66 U/L; AST 56 U/L [< 40]; Glucose 108 mg%; electrolytes/urinalysis/TSH-normal; Hepatitis serology negative
- Calculated Framingham risk score is 7%

US Abdomen

Fatty Infiltration Minimally Enlarged Tender Liver

True Statements Include

- Her CV risk is at least twice that of a like aged individual who is lean and normolipidemic.
- Any sort of lipid lowering agent is contraindicated in this patient
- Metformin and TZD drugs may lower transaminases in this patient.
- Hs-CRP may lend additional prognostic information
### True Statements Include

- Her CV risk is at least twice that of a like aged individual who is lean and normolipidemic.
- Lipid lowering agents are contraindicated in this patient.
- Metformin and TZD drugs may lower transaminases in this patient.
- Hs-CRP may lend additional prognostic information.

### NASH can be improved by

- 10% weight loss
- Metformin therapy
- TZD drugs
- Lipid lowering therapy [Niacin SR contraindicated]
- Ursodeoxycholic acid [open labeled studies]

### NASH

- This patient has all five components of metabolic syndrome.
- CVD risk is increased about two times in those with MetS as opposed to those without.
- Hs-CRP if elevated > 3 ng/ml does portend higher risk in those with MetS in all FRS categories.
- Statins are not absolutely contraindicated, but caution is advised.
- Niacin-ER in doses < 2 GM may be appropriate with careful surveillance.
- Fish oil and fibrates can be prescribed as well.
- ‘Start low-go slow’ policy with dosing; frequent biochemical surveillance mandatory.
- Transaminases may go up before coming down.
- Can be co-managed in consultation with a Lipidologist and a Hepatologist.
CASE 5-Treatment Pointers

- Hyperlipidemia is a risk factor for NASH
- Treating the dyslipidemia may improve NASH and prevent progression to cirrhosis
- Niacin-sustained release form is best avoided in those with altered liver function.
- Statins are not contraindicated in NASH, and can be used judiciously and with specialist consultation.

Case study: Reese, a 54 yo female with CAD

- Previous angina, no MI
- CAD on cath
- HTN
- Diabetes M. dx 2001
- Metabolic Syndrome
- Low HDL-C
- +FH
- Fatty Liver
- Previous statin SE with Liver enzymes up and myalgias (simva,atorva,rosuva)
- Niaspan SE-flushing + aches
- TC 156, Trig 164, LDL 84, HDL 39, HgA1c 7.3
- Overweight – BMI-28.49
- Exercise- consistent long term 5d/wk walk treadmill, wts 2d/wk
- Eating-lots of f + v but skips lunch and nighttime sweets problem
- CRP-HS 1.35
- Waist-40 inches
- Wants help with lifestyle mod. to lose weight
- Meds:ziac10,diovan320,ezet10chole1s,glip15

Case #6 Reese

- Secondary prevention with a mixed dyslipidemia
- Effect of exenatide in a patient with DM, metabolic syndrome, and CAD who is overweight, wants to lose weight, is having trouble doing it on current meds, and wants to get her lipids and HgA1c to goal
- Effect of low dose rosuvastatin in a case where patient has had multiple med intolerances including myalgias and refused to consider another statin during our initial visits

| Case study: Reese, a 54 yo female with CAD, Goals LDL<70 and non-HDL<100 |
|------------------------------------------------|----------------|
| date   | wt | TC | trig | HDL | LDL | Non-HDL | HgA1c | Alt CK | While taking                     |
| initial| 156 | 164| 39   | 84  | 117 | 7.3     | 38    | 215   | Exen10,chole1s, glip15          |
| +3wks  | 184 | 164| 39   | 84  | 117 | 7.3     | 38    | 215   | Same plus exenatide5BID         |
| +4wks  | 181 | 102| 40   | 54  | 84  | 6.1     | 32    |       | Same plus exen10BID             |
| +6wks  | 178 | 124| 40   | 54  | 84  | 6.1     | 32    |       | exen10BID, rosvu a5000,glip10, ez 10, chol1s |
| +5wks  | 177 | 137| 245- not fasting | 39  | 49  | 98      | 6.2   | 25    | Same except rosvu SO3d- mild myalgias |
Case study: Reese, a 54 yo female with CAD. Goals LDL<70 and non-HDL<100

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Case study: Reese, a 54 yo female with CAD. Goals LDL<70 and non-HDL<100

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Exenatide – Synthetic Glucagon-Like Peptide-1 (GLP-1)

- Incretin hormone naturally produced by endocrine cells of small intestine
- Exenatide augments pancreas response (i.e. increases insulin secretion) in response to eating meals; the result is the release of a more appropriate amount of insulin that helps lower the rise in blood sugar from eating.
- Suppresses pancreatic release of glucagon in response to eating
- Slows gastric emptying decreasing the rate of glucose appearance in the blood stream
- Variably suppresses appetite via hypothalamic receptors
- Studies have shown a steady suppression of appetite and continued weight loss over more than 2 years in the high responders

Exenatide – Synthetic Glucagon-Like Peptide-1 (GLP-1)

- Most patients tolerate it quite well after initial nausea which usually resolves within weeks
- Hypoglycemia may occur if patient is on sulfonylurea and dose of the latter may need reduction
- Also approved for concurrent use with metformin and TZDs

Exenatide – Synthetic Glucagon-Like Peptide-1 (GLP-1)

- Off label use as monotherapy in Diabetes in patients who need and want weight loss, and in metabolic syndrome patients
- Only other diabetes drugs that do not promote weight gain: metformin, acarbose, pramlintide
- Results in lower HgA1c, reduced triglycerides, increased HDL, especially in patients who lose weight
  - Happy patients
Pilot Study on Effects of Changing Statin in Patients unable to Tolerate other Statins due to Adverse Effects

- Subjects:
  - n=61
  - Mean LDL-C 177
  - Previously discontinued statin therapy due to intolerable AE.
  - Failed to attain LDL-C goals with nonstatin treatment
  - Intervention: Rosuvastatin 5 and 10 mg/day
  - Median 16 weeks

- Outcomes:
  - Acceptability, Efficacy and Safety

- Results:
  - One patient discontinued treatment due to myalgias (10 mg dose)
  - No ALT, AST elevations>3xULN
  - No CK levels>10xULN
  - Mean reduction in LDL-C 75 mg/dl for 5 mg dose; 79 mg/dl for 10 mg dose

Rosuvastatin Safety

- FDA petition response to Public Citizen March 2005 – denied need to remove from market
  - Rate of proteinuria was within the range observed with several other statins and placebo at 40 mg daily and under
  - No patients developed significant deterioration in renal function -
    - On average, patients showed a decrease in serum creatinine
  - Muscle toxicity data revealed no compelling evidence to distinguish Rosuvastatin from other statins
  - Low dose Rosuvastatin on a MWF schedule frequently tolerated and effective without myalgias when no other statin at any effective dose can be tolerated

**CASE 7**

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<th>Motivational Interviewing in Health Care: Helping Patients Change Behavior (Applications of Motivational Interviewing)</th>
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<td>by Stephen Rollnick, William R. Miller, and Christopher C. Butler 2007</td>
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**50 Year Old African American Male**

- Pharmaceutical company executive HTn X 6 years well controlled on Candesartan/HCTZ. He also takes ASA 81 mg. Describes himself as a ‘health freak’.
- Excellent diet with plenty of exercise [45 mt-1 hr daily and 1 hr weekends] in the local gym; lifelong non-smoker. not on any supplements /anabolic steroids.
- No family h/o premature CAD / DM; Muscular individual; BMI 24.6; BP 125/75; no central obesity. T.Chol 194 mg%; HDL-c 52 mg%; LDL-c 128 mg%; TG 133 mg%; FBG 88 mg%; normal liver, kidney function tests.
- Gets hs-CRP and the PLAC® tests done at a Pharma fair, and is concerned about the results.
**CV Risk Profile**

- 2 RFs that modify LDL-c goal--male age > 45 years and HTn.
- Calculated FRS 5% risk of CVD over next 10 years.
- Hs-CRP = 3 mg/L
- Lp-PLA2 = 345 ng/ml [after abstaining from physical exercise for 48 hours]

**Hs-CRP**

- Is a marker for systemic inflammation.
- Is a risk predictor; low risk < 1 mg/l; moderate risk 1-3 mg/l; high risk > 3 ng/l
- Values above 10 mg/l-consider acute phase response; repeat after 3 weeks/resolution of acute event

---

**In addition to continuing lifestyle measures and maintaining good BP control, you will...**

- Recommend no medications now, as he is at lipid and BP targets already.
- Recommend a statin drug to lower LDL to 100 mg%
- Recommend a statin drug to lower LDL to 70 mg%
- Recommend Yoga or meditation three times daily. No medications at present.

---

**hsCRP Adds Prognostic Information Beyond the Framingham Risk Score in ALL Major Cohorts Evaluated**
PLAC® Test

Measures Lp-PLA₂ produced in large quantities within an unstable atherosclerotic plaque

- LOW RISK: Lp-PLA₂ < 200 ng/mL
- BORDERLINE RISK: Lp-PLA₂ = 200-235 ng/mL
- HIGH RISK: Lp-PLA₂ > 235 ng/mL

---

PLAC® Test

- CPT Code: 83698. Medicare reimbursable
- Indicated in those with intermediate or high risk for MI/stroke
- High specificity for plaque inflammation; less variable as compared to other markers.
- Useful marker for “hidden” CV disease
Recommend no medications now, as he is at lipid and BP targets already.

Recommend a statin drug to lower LDL to 100 mg% [2RF=target 130]

Recommend a statin drug to lower LDL to 70 mg% [not indicated]

Recommend Yoga or meditation. No medications at present.