

# Objectives

- Describe the elements of a successful clinical management strategy
- Examine outcome data for aggressive vs. moderate LDL-C lowering
- Analyze the recommendations by the PBM-MAP regarding the combination of statins and fibrates

# National Dyslipidemia Data

- **26 percent of American adults have dyslipidemia**
- **105 million Americans have cholesterol of more than 200 mg/dl**

# VA Dyslipidemia Data

- **More than 1 in 5 veterans are being treated for dyslipidemia**
- **Between 1999 and 2001, the number of veterans receiving treatment for dyslipidemia tripled – from 614,000 to 1.7 million**
- **In 2003, VA spent \$221 million on lipid lowering agents**

# VHA/DoD Clinical Practice Guidelines for the Management of Dyslipidemia in Primary Care

[www.oqp.med.va.gov/  
cpg/cpg.htm](http://www.oqp.med.va.gov/cpg/cpg.htm)

[www.cs.amedd.army.mil/  
qmo/](http://www.cs.amedd.army.mil/qmo/)

# High Risk Patients

- **Dyslipidemia**
- **Hypertension**
- **Diabetes**
- **Tobacco use**
- **Family history of premature CAD**
- **Presence of ASCVD**
- **Increasing age**

# Risk Calculators on the Web

[www.nhlbi.nih.gov/  
guidelines/cholesterol/  
index/htm](http://www.nhlbi.nih.gov/guidelines/cholesterol/index/htm)

# "Joe"

## Initial Presentation



- 64 year old male
- Retired steel worker
- PMH: HTN, No CAD
- 2ppd smoker
- BP 142/88 mmHg
- 280 pounds,  
truncal obesity

# "Joe" Initial Presentation



- **Cholesterol: 198mg/dL**
- **LDL-C: 151mg/dL**
- **HDL-C: 29mg/dL**
- **Triglycerides: 88mg/dL**

# **"Joe"**

## **Initial Treatment**

- **Consider secondary causes**
  - **Diabetes (routine labs)**
  - **Hypothyroidism (TSH)**
  - **Nephrotic syndrome (U/A)**
  - **Obstructive liver disease (LFT)**
  - **Concurrent medications**

# **"Joe"**

## **Initial Treatment**

- **Address lifestyle**
  - **Increase physical activity**
  - **Lose weight**
  - **Adopt low-fat, low-cholesterol diet**
  - **Stop smoking**
- **Follow-up appointment in 6-8 weeks**

# "Joe"

## Follow-up Presentation

- **Marginal compliance with lifestyle modifications**
- **Total cholesterol: 188mg/dL**
- **LDL-C: 144mg/dL**
- **HDL-C: 26mg/dL**
- **Triglycerides: 92mg/dL**

# "Joe" 10-Year Risk

- **37%**
- **CAD equivalent**

# **"Joe"**

## **Medication Options**

- **Statins (high-potency)**
  - Well studied
  - Well tolerated
- **Fibrates**
  - VA-HIT trial
- **Niacin/Resins**

# Statin Choice

- **Desired percent LDL-C reduction**
- **Safety tolerability/  
Clinical outcome data**
- **Consider drug-drug interaction**
- **Formulary agent availability**

# Statin Metabolism

- **CYP 450 statin metabolism**
  - **lovastatin, simvastatin, atorvastatin**
    - CYP 3A4
  - **fluvastatin and rosuvastatin**
    - CYP 2C9
  - **rosuvastatin**
    - CYP 2C19
  - **pravastatin**
    - No CYP metabolism

# Potent CYP 3A4 Inhibitors

- **macrolides**
- **azole antifungals**
- **cyclosporine**
- **protease inhibitors**
- **delavirdine**
- **amiodarone**
- **calcium channel blockers (e.g. verapamil and diltiazem)**
- **grapefruit juice**

# Potent CYP 2C9 Inhibitors

- **amiodarone**
- **azole antifungals**
- **cimetidine**
- **omeprazole**
- **TMP/SMX**
- **zafirlukast**
- **fluvoxamine**
- **metronidazole**

# Scenario 1

- **No Potent CYP 3A4 inhibitor:**
  - **High-potency statin**  
**lovastatin, simvastatin or**  
**atorvastatin (non-formulary)**

[www.vapbm.org/criteria/  
Fluva-prava-atorva-r.pdf](http://www.vapbm.org/criteria/Fluva-prava-atorva-r.pdf)

# Scenario 2

- **Potent CYP 3A4 inhibitor:**
  - **Short-Term**  
**(e.g. macrolide antibiotic)**
  - **Withhold statin therapy until course completed**

# Scenario 3a

- **Potent CYP 3A4 Inhibitor:**
  - **Long-Term**  
(e.g. protease inhibitor, cyclosporine)
  - **Avoid 3A4 metabolized statin:**
    - **Select fluvastatin or pravastatin (non-formulary)**
    - **If further LDL-C needed, switch to rosuvastatin (non-formulary)**

# Scenario 3b

- **Potent CYP 3A4 Inhibitor:**
  - Long-Term  
(e.g. protease inhibitor, cyclosporine)
  - 3A4 metabolized statin selected:
    - lowest dose possible
    - Educate “Joe” to recognize signs of muscle toxicity

# Recommendations for LDL-C, HDL-C & TGs

- **VA/DoD Guidelines**
  - LDL-C <120 mg/dL
- **2002 NCEP ATP III**
  - LDL-C <100 mg/dL
- **2004 Circulation update**
  - LDL-C <70 mg/dL (very high risk)

# **Trials of Aggressive LDL-C Lowering**

- **Post CABG Trial**
- **HPS Trial**
- **Reversal Trial**
- **PROVE-IT Trial**
- **A-Z trial**

# PROVE-IT

- **ACS patients, N=4162**
- **Prava 40mg vs Atorva 80mg**
- **Significant reduction in composite primary endpoint**

# PROVE-IT

- **Drop outs**  
30-33% at 2 years
- **LFT > 3x ULN**  
Prava 1.1%    Atorva 3.3%
- **Muscle symptoms**  
Prava 2.7%    Atorva 3.3%

# A-Z Trial

- **ACS patients N=4497**
- **Simva 40-80mg vs Placebo – Simva 20mg**
- **NS reduction in composite primary endpoint**
  - **CV death reduced**
  - **4 to 24 months significant reduction**

# A-Z Trial

- **Drop outs**  
32 to 34% at 2 years
- **LFT > 3x ULN**  
Simva only 0.9%  
Placebo/Simva 0.4%
- **Myopathy (CK > 10x ULN w/ Sx)**  
Simva 80mg 0.4%-9 cases

# High Dose Statin

- **Simva 80mg vs Atorva 80mg**
- **Likelihood of achieving LDL goal**
- **CK, LFT**
- **Educate patients –  
muscle symptoms, compliance**

# Future Studies

- **SEARCH**
  - Simva 20mg vs Simva 80mg
- **TNT**
  - Atorva 10mg vs Atorva 80mg
- **Ideal**
  - Atorva 80mg vs Simva 20-40mg

# PBM-MAP Recommendations

- **Identify appropriate candidates**
- **Continue with LDL goal < 100mg/dL**
- **Consider the harms with high dose statin therapy and educate patients to recognize symptoms of myopathy**
- **Medication adherence**

# "Joe" 1-Year Checkup

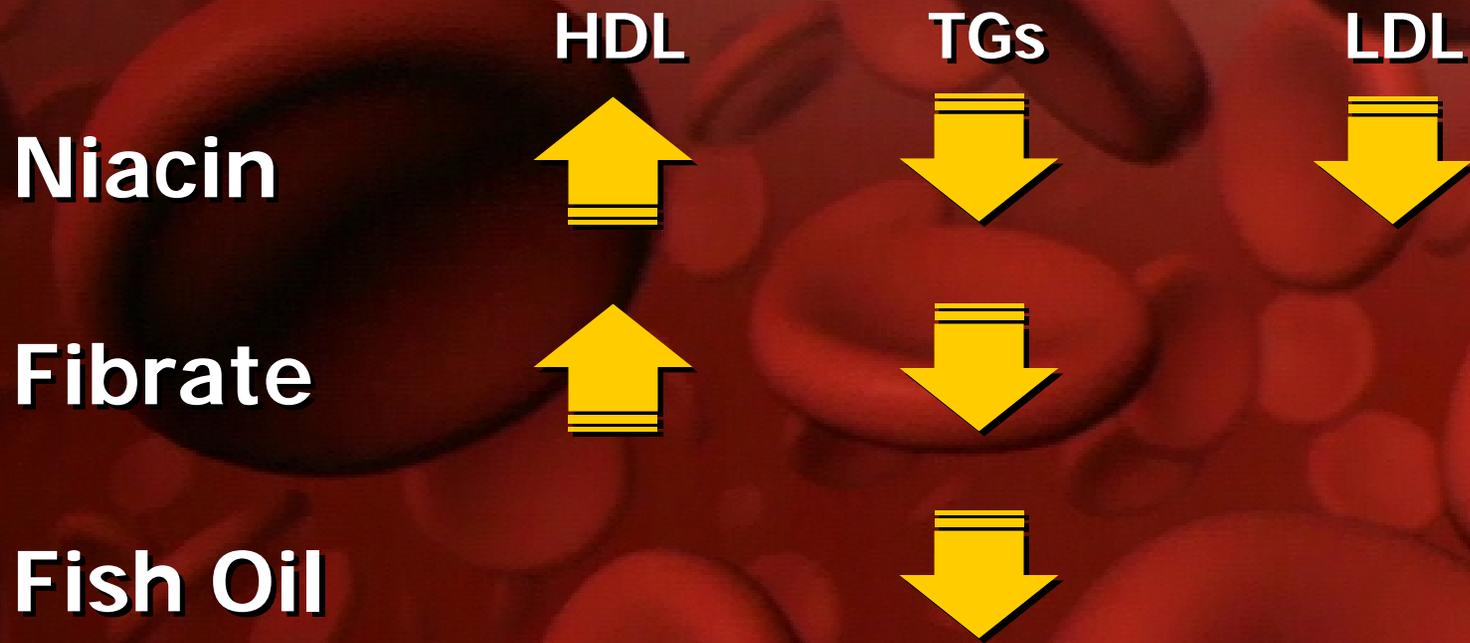
- **Elevated blood glucose**
- **Diabetes Dx made**
- **Total cholesterol: 206mg/dL**
- **LDL-C: 108mg/dL**
- **HDL-C: 26mg/dL**
- **Triglycerides: 359mg/dL**

# Metabolic Syndrome

**Any 3 of the following:**

- Abdominal obesity**
- Elevated triglycerides**
- Low HDL**
- HTN**
- Glucose intolerance**

# Additional Lipid Lowering Therapies



# PBM-MAP Statin-Fibrate Safety Report: General Goals

- **Is there evidence for reduced CV events with combination therapy vs. either agent alone?**
  - **Lack of Outcome Data for Combination**
  - **ACCORD (Action to Control Cardiovascular Risk in Diabetes)**
    - **N=5000 Type 2 diabetics**
    - **Fenofibrate + Simvastatin vs. Simvastatin**
    - **Anticipated results in 2008 or 2009**

# PBM-MAP Statin-Fibrate Safety Report: General Goals

- **Is there a safety advantage of a particular fibrate when combined with statins?**
  - **Theories for increased risk of combination:**
    - **Additive effect on skeletal muscle**
    - **Displacement of statins from proteins**
    - **Alteration in statin pharmacokinetics (glucuronidation)**
  - **Lack of outcome data on safety between fibrates**

# PBM-MAP Statin-Fibrate Safety Report: General Goals

- **Appropriate candidates for statin-fibrate combination?**
  - **Not routinely recommended**
  - **Consider in mixed dyslipidemia (LDL-C >100 mg/dL, HDL-C <40 mg/dL and/or TG >500 mg/dL)**
  - **Normal renal, liver and thyroid function**

# PBM-MAP Statin-Fibrate Safety Report: General Goals

- **Appropriate candidates for statin-fibrate combination?**
  - **Avoid if concomitant 3A4 inhibitors or other meds known to alter statin metabolism**
  - **Consider fish oils or niacin prior to fibrates**
  - **Lowest effective statin dose**
  - **EDUCATE and DOCUMENT risks and benefits in medical record.**

# **"Joe" Follow-up**

- Continue to monitor lipid panel**
- Review symptoms of myopathy**
- Stress diet and medication adherence and follow-up appointments**

# VANTS Call

**1-800-767-1750  
x32837#**

**September 28, 2004**

**2PM ET**

