Anti-inflammatory properties of lipid-lowering agents

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A. Introduction

Reduction of elevated levels of LDL has) been shown to improve mortality in patients with coronary artery disease (CAD). In addition to altering lipid profiles, lipid-lowering agents may have other properties that contribute to their improvement in mortality. In the VA-HIT study, the mortality benefit of gemfibrozil was in excess of that expected from increases in HDL and decreases in LDL and triglycerides [1]. Alterations in lipid profile could account for only 23% of the reduction in coronary events in the study.

CAD is thought to be in part a disease of chronic inflammation. C-reactive protein (CRP), fibrinogen, and t-plasminogen activator inhibitor (PAI) are markers of systemic inflammation. CRP has been shown to be strongly predictive of cardiovascular events, even in patients that do not have elevated LDL [2,3]. Pravastatin and lovastatin have been shown to reduce CRP [3,4]. The effect does not correlate with LDL-reduction.

There is less data on the anti-inflammatory effects of other lipid lowering agents. A significant reduction in fibrinogen levels was shown in patients with CAD and mixed hypedipidemia who were treated with bezafibrate, but not in those patients treated with fluvastatin [5]. No significant reduction in CRP or PAI was seen with either agent. A small study comparing niacin to gernfibrozil showed that niacin reduced fibrinogen levels and gemfibrozil raised them [6]. Niacin's effect on CRP has not been studied.

1. Robins SJ et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA. 285(12):1585-91, 2001 Mar 28.

2. Ridker, PM et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. NEW 342 (12) 83643 2000

3. Ridker, PM et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. NEJIVI 244 (26) 195"5 2001

4. Albert, MA et al. Effect of statin therapy on c-reactive protein levels (PRINCE) JAMA 286 (1) 64-70 2001

5. Cortellaro, M et al. Effects of fluvastatin and bezafibrate combination on plasma fibrinogen, Effects on plasma fibrinogen, t-plasminogen activator inhibitor, and c reactive protein levels in coronary artery disease patients with mixed hyperlipidernia (FACT study) Thrombosis and Haemostasis 2000 (80) 549-53

6. Guyton JR et al, Extended-release niacin vs, gemfibrozil for the treatment of low levels of high-density lipoprotein cholesterol. Niaspan-Gemfibrozil Study Group. Archives of Internal Medicine. 160(8):1177-84,2000 Apr 24.

B. Review of the Literature

Robins SJ et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA. 285(12):1585-91, 2001 Mar 28.

2531 men with CHD and low HDL and low LDL (mean LDL 111) five-year placebo controlled trial of secondary prevention with gernfibrozil. Relative risk reduction of 22% (95% CI 7-35%). Multivariable Cox proportional hazards analysis showed that alterations in lipid profile could account for only 23% of the reduction in coronary events in the study.

Ridker, PM et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. NEJM 244 (26) 195965 2001 [Air Force/Texas CAPS database]

5742 participants with normal total cholesterol and low HDL in a five-year placebo controlled trial of primary prevention with lovastatin. On average, there was a 15% reduction in CRP. Subgroup analysis: lovastafin was effective in preventing events in participants with a high total cholesterol to HDL ratio, and also in patients with a low ratio and high CRP.

Cortellaro M et al. Effects of fluvastatin and bezafibrate combination on plasma fibrinogen, t-plasminogen activator inhibitor and C reactive protein levels in coronary artery disease patients with mixed hyperlipidaemia (FACT study). Fluvastatin Alone and in Combination Treatment. Thrombosis & Haemostasis. 83(4): 549-53, 2000

Randomized, double blind, multicenter trial 333 patients with CAD and mixed hyperlipidemia (LDL-cholesterol 135-250 mg/dI and triglycerides (TG) 180-400 mg/dl) were randomized to one of four regimens (fluvastatin 40 mg, bezafibrate 400 mg, fluvastatin 20 mg + bezafibrate 400 mg or fluvastatin 40 mg + bezafibrate 400 mg treatments) for 24 weeks. Plasma fibrinogen significantly decreased after treatment with the combinations fluvastatin+bezafibrate (- 14 and -16%) and with bezafibrate monotherapy (-9%). No significant reduction was observed after fluvastatin monotherapy (-4%). No significant changes were observed in PAI-1 or CRP plasma levels.

C. Hypothesis

Statins decrease markers of inflammation more than gemfibrozil.

D. Definitions

CAD defined as MI, stenosis on angiography >50% in a major vessel, anginal chest pain with EKG evidence of ischemia, or positive stress test.

E. Drug choice

Bezafibrate versus Pravastatin Gemfibrozil and Fluvastabn have not been shown to reduce markers of inflammation.

F. Study Design

a. Secondary Prevention:

Enroll patients with newly diagnosed CAD not previously on lipid lowering agents. Also enroll patients with known CAD not on lipid lowering meds for six months or more.

b. Exclusion criteria:

1. Solitary elevated LDL with normal HDL and triglycerides as fibric acids are not thought to be as effective as statins for these patients
2. Significant liver disease

Measure baseline CHD/dyslipidemia risk factors: diet, EtOH use, smoking, BMI, and DM. Measure again at end of study. All patients recommended to comply with a step one diet.

Pill counts to estimate compliance.

Measure baseline fasting lipid panel twice and average results Measure lipid panel, CRP, and fibrinogen at 12 and 24 weeks. PRINCE showed an effect on CRP at 12 weeks.

c. Power calculation: $n = 1+ 16(\text{std.dev/effect})^2$

Assume 10% effect difference, 80% power, and alpha=0.05

68% of normal distribution lies within +/- I SD
34125 = 1.36

i. CRP:

median = 0.42, interquartile range = 0.21 - 0.83 [ref 2]
$n = 1 + 16(.42/.04)^2 = 1 + 16(110.25) = 1777$

median = 0.27, interquartile range = 0. 12-0.53 [PRINCE secndry prevention]
$n = 1 = 16(.21/.027)^2 = 1706$

ii. Fibrinogen:

321 +/-50.7 [FACT)
$n = 1 +16(69/32.1)^2$ 75

Assuming the biological effect is short lived, the study could be performed as a cross-over with 12 weeks on each medication. This would require half as many patients.

d. Statistical Analysis

ANOVA