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J CARDIOVASC PHARMACOL THER 2010 15: 380 originally published online 5 August 2010

DOI: 10.1177/1074248410374041

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Journal of Cardiovascular
Pharmacology and Therapeutics
15(4) 380-383
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DOI: 10.1177/1074248410374041
http://cpt.sagepub.com

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Abstract

Introduction: High-density lipoprotein (HDL) cholesterol is a well-established inverse risk factor for cardiovascular disease. The extent to which cardiovascular risk can be modified through changes in HDL, however, is less clear. We further examined the role of aggressive HDL raising therapy on cardiovascular outcomes in the 143 patients enrolled in the Armed Forces Regression Study (AFREGS). **Methods:** Reanalysis of the AFREGS population. Patients with stable coronary disease were randomized to receive gemfibrozil, niacin, and cholestyramine in combination or matching placebos, on top of aggressive dietary and exercise modification for a 30-month period. Blood work was performed at baseline and repeated after 1 year of therapy. **Results:** Patients were divided into 3 groups based on their therapeutic response: no HDL increase, mild HDL increase, and large HDL increase (% change in HDL ≤ 0 , $\leq$ the lower 2 tertiles of HDL increase, and $>$ the upper tertile of HDL increase, respectively). A progressive decrease in cardiovascular events was noted across these groups (30.4%, 19.4%, and 3.2%, respectively, $P = .01$). Kaplan-Meier analysis according to percentage change in HDL demonstrated a similar improvement in event-free survival ($P = .01$). Proportional hazards modeling also demonstrated that increasing HDL predicted a lower hazard of cardiovascular events, even after adjusting for changes in low-density lipoprotein (LDL) ($P < .01$). For every 1% increase in HDL achieved, a 2% decrease in events was recognized. **Conclusions:** These data suggest that in a population of patients with stable atherosclerosis, the greater the percentage increase in HDL achieved, the greater the cardioprotective benefit. This further supports HDL raising as a beneficial therapeutic strategy.

Introduction

It is well established that high-density lipoprotein (HDL) cholesterol is an inverse risk factor for coronary heart disease (CHD), even in patients with other lipid abnormalities.¹⁻⁶ As such, HDL screening is routinely used as a method for stratifying cardiovascular (CV) risk in adults.⁷ Although this relationship is well described, the more specific issue of how changes in HDL can modify the CV risk of an individual patient remains less clear.

Multiple studies have looked at HDL altering therapy and CV outcomes. It has been demonstrated in dyslipidemic men that targeted HDL therapy with gemfibrozil reduces CV events.^{8,9} It has also been shown that treatment with bezafibrate may provide long-term cardioprotective effects^{10,11} and that use of fenofibrate may reduce nonfatal myocardial infarction in diabetic individuals.¹² Despite the evidence that increasing HDL can favorably modify CV risk, a 2009 meta-analysis by Briel et al concluded that increasing circulating HDL does not reduce the likelihood of coronary events and that lowering low-density lipoprotein (LDL) should remain the primary goal of lipid therapy.¹³ The picture is even further complicated by the

finding that novel agents designed to modify and/or raise HDL cholesterol have disappointed in recent clinical trials.¹⁴⁻¹⁶ These events have cast even greater doubt about HDL as a therapeutic target and support a primary focus of therapeutic prevention on LDL cholesterol.¹⁷⁻¹⁹ What is most clear from these investigations is that increasing HDL with the intent of achieving favorable effects on CV outcomes remains controversial.

The Armed Forces Regression Study (AFREGS) was a randomized, double-blind, placebo-controlled trial of aggressive HDL-targeted medical therapy comprising gemfibrozil, niacin, and cholestyramine on a baseline of aggressive dietary and lifestyle intervention that was performed prior to the statin

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Table 1. Baseline Demographic Data of Patients^a

Demographic	All Patients (n = 143)	Cardiovascular Event (n = 28)	Event Free (n = 115)
Age in years, mean $\pm$ SD	63.2 $\pm$ 7.1	63.1 $\pm$ 6.5	63.2 $\pm$ 7.3
Female, %	7.7	10.7	7.0
History of MI, %	43.4	57.1	40.0
Previous smoker, %	84.6	85.7	84.3
Active smoker, %	8.4	10.7	7.8
BMI, kg/m ² , mean $\pm$ SD	26.5 $\pm$ 3.7	27.1 $\pm$ 4.6	26.3 $\pm$ 3.5
Systolic blood pressure	139 $\pm$ 17	138	139
Fasting blood glucose	82 $\pm$ 14	81 $\pm$ 13	82 $\pm$ 14
Total cholesterol	196 $\pm$ 31	189 $\pm$ 28	198 $\pm$ 31
LDL cholesterol	128 $\pm$ 27	123 $\pm$ 23	130 $\pm$ 27
HDL cholesterol	34 $\pm$ 6	33 $\pm$ 5	34 $\pm$ 6
Triglycerides	168 $\pm$ 81	163 $\pm$ 78	169 $\pm$ 82

NOTE: SD = standard deviation; MI = myocardial infarction; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

^a No statistically significant differences were observed between cardiovascular event and event-free groups.

era.²⁰ The purpose of this reanalysis was to examine whether the degree of HDL increase predicted the reduction in CV outcomes including unstable angina, myocardial infarction, transient ischemic attack, stroke, percutaneous coronary intervention, and coronary artery bypass grafting during this study.

Methods

Men and women age <76 years with stable coronary artery disease confirmed by catheterization were recruited from within a 150-mile radius of Wilford Hall Medical Center in San Antonio, Texas. Each patient was required to have a measurable stenosis between 30% and 80% of the luminal diameter within the coronary tree by quantitative coronary angiography. Patients with greater than an 80% stenosis of a single vessel were eligible only if they had a favorable prognosis based on functional testing (ability to exercise for more than 9 minutes on a full Bruce protocol exercise treadmill test). The exclusion criteria included a major vascular event (myocardial infarction, cerebrovascular accident, coronary artery bypass grafting, or other coronary catheter-based intervention) within 6 months, a history of congestive heart failure (other than in the setting of a myocardial infarction), or a left ventricular ejection fraction <40% by ventriculography. Selection criteria have previously been published in an extended fashion.²⁰

The population used in this study comprised all enrolled (143) AFREGS patients. Lipid profiles (including HDL, LDL, total cholesterol, and triglyceride levels) were measured at baseline and repeated after 1 year of therapy. Per protocol, patients were randomly assigned to either the treatment group (gemfibrozil 600 mg twice daily, niacin starting at 250 mg and titrated up to 3000 mg/d as tolerated, and cholestyramine 16 g/d), or matching placebos. All patients received aggressive exercise and dietary intervention.²⁰ Patients were thoroughly

informed of the details of the study and voluntarily enrolled between January 1993 and March 1994. No patients were lost to follow-up. Each patient initially signed an Informed Consent Statement that was reviewed and approved by the Institutional Review Board at Wilford Hall Air Force Medical Center in San Antonio, Texas.

Composite CV events during the study period were defined as having at least 1 of the following: unstable angina, myocardial infarction, transient ischemic attack, stroke, percutaneous coronary intervention, or coronary artery bypass grafting. Patients were divided into 3 groups, according to their percentage change in HDL after the first 12 months of therapy: no HDL increase ($\leq 0\%$ HDL increase, 46 patients), mild HDL increase (lower 2 tertiles of HDL increase, $\leq 42\%$ HDL increase, 62 patients), and large HDL increase (upper tertile of HDL increase, $>42\%$ HDL increase, 31 patients). Dichotomized outcomes were compared using the Pearson Chi-square test or Fisher's exact test where appropriate, and means were compared with a 2-tailed *t* test. Event-free survival curves were compared by the log-rank test, and multivariate analysis was performed using Cox proportional hazards. Inclusion in the model was determined by significance on univariate analysis as well as the external clinical judgment of the investigators. The proportional hazards assumption was tested and upheld graphically. For all tests, a *P* value $<.05$ was considered statistically significant. Data were analyzed and compiled using JMP 8.0 software (SAS Institute, Inc, Cary, North Carolina).

Results

The baseline characteristics of all patients are included in Table 1. None of these demographics were significantly different between those having an event and those that were event-free. Figure 1 shows the percentage of patients that had an in-trial CV event in each of the groups of HDL change; 30.4% of patients in the no HDL increase group had CV events, whereas 19.4% of patients in the mild HDL increase group and 3.2% of patients in the large HDL increase group had events (*P* = .01). Figure 2 shows the results of a Kaplan-Meier survival analysis that demonstrates time to event distributed among the 3 groups of HDL change. Patients who achieved the greatest HDL increase had the best chance of remaining free of CV events. Event-free survival was greater for patients in large HDL increase than for patients in mild HDL increase, and was greater for patients in mild HDL increase than for patients in no HDL increase (*P* = .01).

Table 2 shows the changes in lipid parameters dichotomized by those suffering events and those that were event-free. Event-free survivors achieved significantly larger reduction in LDL and triglycerides and had a significantly larger increase in HDL (*P* = .04, *P* = .04, *P* < .01). A Cox proportional hazard model is included in Table 3 and demonstrates that HDL increase remains a significant predictor of event-free survival even after adjustment for changes in LDL (*P* < .01).

Figure 1. Percentage of patients experiencing composite events distributed by the amount of HDL increase, $P = .01$. HDL indicates high-density lipoprotein.

Figure 2. Time-to-event analysis distributed by the amount of HDL increase, $P = .01$. HDL indicates high-density lipoprotein.

Discussion

This analysis suggests that in a population of patients with stable atherosclerotic disease, aggressive therapy targeted at raising HDL cholesterol prevents CV events. Although the original AFREGS study concluded that HDL-targeted triple therapy had a beneficial impact on CV outcomes, the primary mechanism of this benefit was less clear because of the multiple effects of the therapeutic agents. In light of our current analysis, we conclude that the percentage improvement in HDL primarily drove risk reduction, as patients appeared to have fewer events and longer event-free survival with greater HDL improvement.

As defined in our methods, patients were stratified into 3 groups: no HDL increase, mild HDL increase, and large HDL increase based on their percentage of change in HDL over the first year of treatment. Interestingly, the patients that achieved the greatest HDL benefit suffered the fewest CV events (Figure 1). This relationship appeared linear, as no HDL increase had the highest incidence of CV events (30.4%), mild HDL increase had modestly lower events (19.4%), and large HDL increase had the fewest events (3.2%). Using these same

Table 2. Changes in Lipid Parameters After 1 Year of Treatment

Demographic	Cardiovascular Event (n = 28)	Event Free (n = 115)	P Value
Total cholesterol change (%)	-8.4 ± 17.1	-1.3 ± 16.7	.06
LDL cholesterol change (%)	-0.9 ± 20.2	-10.6 ± 26.1	.04
HDL cholesterol change (%)	7.8 ± 19.1	23.0 ± 30	<.01
Triglycerides change (%)	-7.4 ± 38.1	-24.3 ± 36.5	.04

NOTE: HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 3. Proportional Hazards Model

Lipid Parameter	Odds Ratio	95% CI	P Value
% LDL change	1.01	0.99-1.02	.35
% HDL change	0.98	0.96-1.00	<.01

NOTE: HDL = high-density lipoprotein; LDL = low-density lipoprotein.

groups, a similar conclusion can be drawn from event-free survival analysis. Patients that achieved no increase in HDL had the worst event-free survival. Comparatively, patients receiving the largest HDL benefit showed a much improved event-free survival and patients receiving a mild HDL benefit showed a less dramatic improvement over the patients with no HDL benefit (Figure 2). Interestingly, in a proportional hazards model increase in HDL remained a significant predictor of improved event-free survival, even after adjustment for changes in LDL. In this model, a 1% increase in HDL resulted in a 2% reduction in CV events.

In summary, these data support the tenet that percentage of HDL increase was the primary mechanism of the CV protection in the AFREGS trial. These results have the broader implication that HDL should have a role not only as a prognostic marker but also as a therapeutic target in patients with existing atherosclerotic disease. Although the results of previous investigations into this arena have been ambiguous, it remains possible that not all mechanisms of HDL increase are equally beneficial. In a recent editorial regarding upregulation of lecithin:cholesterol acyltransferase (LCAT) as mechanism of HDL increase, Rader concluded that HDL increases achieved through this mechanism were not atheroprotective¹⁶; but proposed that HDL increases through other methods may still prove beneficial. AFREGS used the unique combination of gemfibrozil, niacin, and cholestyramine for lipid modulation, and we postulate that this particular mechanism of HDL raising is cardioprotective in patients with established coronary disease. In light of growing recognition of statin intolerance in the general population, these agents may provide an interesting therapeutic alternative and certainly warrant larger clinical studies.

Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Financial Disclosure/Funding

The authors disclosed receipt of the following financial support for the research and/or authorship of this article: This research was completed with an unrestricted grant from Pfizer Pharmaceuticals. Dr Krauski is on the speaker's bureau of Pfizer Pharmaceuticals.

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