Journal of Clinical Epidemiology and Toxicology

SCIENTIFIC Research and Community

Research Article

Open Access

Atherothrombotic Disease Outcomes When Target Goals of Lipid Modifying Therapy Are Not Met

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ABSTRACT

Introduction: Once a lipid disorder has been identified, therapy should be initiated. The goal of therapy, however, may not be clear. Some physicians treat dyslipidemia using the "fire and forget" concept. The purpose of this article is to demonstrate that when target goals of dyslipidemia therapy are not achieved, then the atherothrombotic disease process continues. To define the target goal of dyslipidemia therapy, the author has analyzed the end of trial lipid values in eight published angiopgraphic regression trials and one large primary prevention trial. Angiographic plaque progression is a hallmark for future atherothrombotic disease events.

Materials and Methods: The author has in his personal possession the databases of eight angiographic regression trials and one large primary prevention trial. The end-of-trial lipid values were graphed in a 6x6 factorial using low-density lipoprotein cholesterol (LDL-c) and the Cholesterol Retention Fraction (CRF, defined as [LDL-c minus HDL-c]/LDL-c). The results are determined for each of the angiographic trial and color-coded for abnormal values, borderline abnormal values, and ideal values. The percentage of plaque progression on the last angiogram is the determined for each of the three zones. In the primary prevention trial, atherothrombotic disease events are examined.

Results: Abnormal LDL-c is defined as a value of 125 mg/dl (3.2 mmoles/L) and higher; borderline abnormal, at 100-124 mg/dl (2.6-3.2 mmoles/L); ideal at 99 mg/dl (2.5 mmoles/L) and lower. Abnormal CRF is defined as 0.70 or higher; borderline abnormal at 0.60-0.69; and ideal at 0.59 and lower. When both predictors are abnormal, there is a higher percentage of plaque progression. The percentage of plaque progression decreases markedly when both predictors are borderline abnormal, and is minimal when both predictors are ideal.

Conclusions: In the angiographic regression trials, failure to achieve target (ideal) lipid goals, whether LDL-c or CR, is associated with plaque progression in a graded manner. In the primary prevention trial, failure to achieve target (ideal) lipid goals is associated with more atherothrombotic disease events, again in a graded manner. These findings support the view that to prevent atherothrombotic disease, or if extant, then to prevent subsequent atherothrombotic disease events (as predicted by the percentage of plaque progression), one must achieve the target (ideal) lipid therapy goals. The "fire and forget" concept should be discarded.

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Received: January 15, 2021; **Accepted:** January 22, 2021; **Published:** January 29, 2021

Introduction

The recently published guidelines from the American Heart Association/American College of Cardiology (AHA/ACC) concerning the management of dyslipidemia have abandoned the traditional target goals for lipid modifying therapy (LMT) [1]. Since the only reason to treat dyslipidemia is the prevention of atherothrombotic disease (ATD), or if ATD is extant, then the stabilization/regression of ATD plaque in order to prevent future clinical ATD events, this abandonment of target goals for lipid therapy could, in theory, lead to ATD events. The purpose of this paper is to demonstrate failure to achieve target goals of LMT will fail to prevent ATD in a primary prevention scenario and fail to stabilize/regress plaque in a secondary prevention scenario.

Cholesterol bound to low-density lipoprotein cholesterol (LDL-C) is well known to enter the artery wall and initiate the ATD process. Equally well known, but virtually ignored by the National Cholesterol Education Panel (NCEP) in its initial publications and allowed only status as a goal of treatment after LDL-C goals had been met in its last publication is that cholesterol bound to high-density-lipoprotein (HDL-C) exits the artery wall via reverse cholesterol transport [2-4].

A logical extension of cholesterol's two-way traffic is the combination of LDL-C and HDL-C into a single lipid predictor. This has been accomplished in the form of the Cholesterol Retention Fraction (CRF, or [LDL-HDL]/LDL). The CRF has been shown to accurately predict the population at risk of ATD and to be superior to LDL-C in that prediction [5,6]. The derivation of the CRF has been published previously [7,8]. Additionally, the CRF, when combined with systolic blood pressure (SBP), has been shown to accurately guide therapy of dyslipidemia to stabilize/regress angiographically-demonstrated plaque [9].

The combination of the CRF and SBP into a predictive (of the population at risk of ATD) graph is demonstrated in Figure I. The CRF is on the ordinate and SBP on the abscissa. The

Bowling Green Study (BGS), based on the CRF-SBP plots of its ATD patients, has generated a threshold line with CRF-SBP loci (0.74,100) and (0.49,140), above which lie the CRF-SBP plots of the vast majority of its ATD patients [5]. (These loci are based on the precipitation method of HDL-C measurement; if the enzymatic method of HDL-C is utilized, the loci plots are [0.62,100] and [0.40,140].)

Above this threshold line lie the CRF-SBP plots of 85% (600/710) BGS ATD patients who developed some form of clinical ATD during the BGS timeframe of 4 November 1974 and 4 November 2013. Of the 110 patients with CRF-SBP plots below the threshold line, most (61%, or 67/109) are cigarette smokers, current or past. (The cigarette smoking status of one of these patients is unknown to the BGS.) That leaves only 6% (42/709) of patients whose ATD events could not have been predicted by CRF-SBP plot above the threshold line and/or cigarette smoking status. The average age of ATD onset in these latter patients is 78 years for males and 75 years for females. Death, on average, does notoccur for an additional 10-15 years [5]. (See Figure I.)

Non-HDL cholesterol has been proposed as a likely lipid predictor. However, in a study of drug-naïve diabetic patients, analyzing inflammatory markers, the CRF and non-HDL cholesterol were found to be highly correlated (0.0001), while LDL-C was not [10].

To show that goals of LMT should not be abandoned, this paper will utilize the database of a large ATD outcomes study, Tex/AFCAPS, and the database of a large angiograqphic regression study (the Program on the Surgical Control of the Hyperlipidemias, or POSCH), which was published as part of a meta-analysis of several angiographic regression studies in 2000 [9,11]. In the former case, this paper will show that failure to bring the patients'CRF-SBP plots below the threshold line resulted in no advantage for those patients receiving lovastatin therapy. In the latter case, this paper will show that failure to achieve lipid target goals resulted in increased rates of plaque progression.

Materials and Methods

The author has in his possession the patient databases of the nine cited trials: TexCAPS/AFCAPS (11), Program on the Surgical Control of the Hyperlipidemias (POSCH), St. Thomas Atherosclerosis Regression Study (STARS), Familial Atherosclerosis Treatment Study (FATS), National Heart, Lung, and Blood Institute Type II Coronary Interventional Study (NHLBI), Lipoprotein and Coronary Atherosclerosis Study (LCAS), the Heidelberg Study, Lopid Coronary Angiography Trial (LOCAT), and Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) [12-19]. The author reviewed each of these databases, patient by patient, line by line, year by year (from baseline till the end of the trial). Since TexCAPS/AFCAPS was an outcomes trial, the BGS graph (See Figure I) was used as the outcomes measure, but since plaque changes in response to therapy was the endpoint in the 2000 meta-analysis, a different approach was utilized. Since POSCH was not structured to control hypertension (Henry Buchwald, MD, personal communication), and since plaque non-progression (stabilization/regression) was enhanced in POSCH, the author decided to utilize a nested risk cohort scheme to analyze plaque changes in response to LMT.

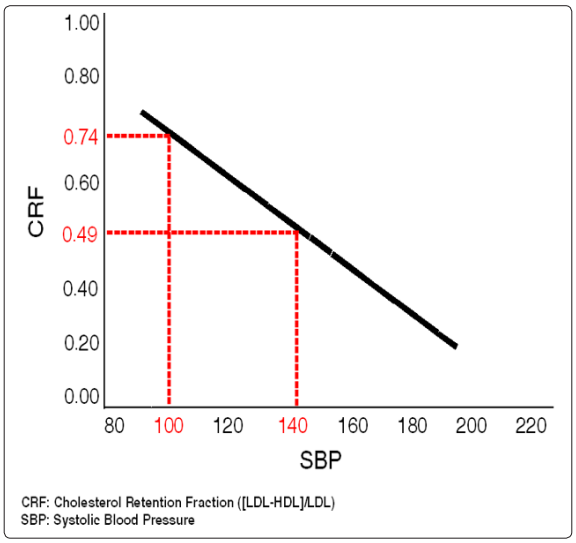

Figure 1

Results

In TexCAPS/AFCAPS, only 5499 patients had paired baseline and one-year CRF and SBP data. At baseline, 98% (2741/2794) of patients in the lovastatin cohort and 98 2664/2705) in the placebo cohort had CRF-SBP plots above the threshold line. Of the 53 lovastatin-cohort patients with baseline CRF-SBP plots below the threshold line, 1 (1.9%) sustained an ATD event. Of the 41 patients in the placebo cohort with baseline CRF-SBP plots below the threshold line, 1 (2.4%) sustained an ATD event.

Of the 5405 patients with baseline CRF-SBP plots above the threshold line, 2741 were treated with lovastatin and 2664 were treated with placebo. All patients received dietary therapy. In the lovastatin cohort, only 17% (463/2741) had their CRF-SBP plots brought below the threshold line, compared with but 2.7% (71/2664) in the placebo cohort. The overall ATD event rate in the lovastatin cohort was 3.0% (82/2741) and 4.6% (122/2664) in the placebo cohort. In lovastatin-treated patients whose CRF-SBP plots were brought below the threshold line, the ATD event rate was 1.7% (8/463), whereas if the CRF-SBP plot was not brought below the threshold line, the ATD event rate was 3.2% (78/2408). Similarly, in the placebo cohort, if the CRF-SBP plot was brought below the threshold line, the ATD event rate was 4.2% (3/71), but if not, the ATD event rate remained at 4.6% (127/2736). (SBP data is missing in a large number of patients, with the result that the above numbers in the baseline and end groups do not add to the same totals.) (See Table I.)

Table 1: TexCAPS/AFSCAPS Outcomes When Starting CRF-SBP Plot above the Threshold Line

			Lovastatin	Placebo
		Baseline CRF-SBP plot above threshold line		
Baseline		ATD Patients	82	122
		NATD Patients	2659	2542
		∑	2741	2664
		% ATD	3.0%	4.6%
End		**End CRF-SBP Plot Above Threshold Line**	78	127
	1	ATD Patients	2330	2609
		NATD Patients	2408	2736
		∑	3.2%	4.6%
		% ATD		
		End CRF-SBP Plot Above Threshold Line		
	2	ATD Patients	8	3
		NATD Patients	455	68
		∑	463	71
		% ATD	1.7%	4.2%

ATD means Atherothrombotic Disease
NATD means no Atherothrombotic Disease
SBP means Systolic Blood Pressure
CRF means Cholesterol Retention Fraction
Note: 102 placebo cohort and 80 lovastatin cohort patients are missing SBP data; hence base and end groups are not equal in numbers of patients.

In the angiographic regression trials, a different approach was taken [9]. Since POSCH was not structured to control hypertension (Henry Buchwald, MD, personal communication), and hence hypertension was not a focus of therapy, the marked degree of plaque stabilization/regression that was seen occurred in the face of hypertension, which was often severe. The profound changes in lipids noted in POSCH accounted for the marked stabilization/regression of plaque. To examine the effects of LMT on dyslipidemia and subsequent changes in plaque, LDL-C was stratified by CRF in a 6x6 factorial. (See Figure II.) When this was done, zones of decreasing risk of plaque progression were noted:

Figure II
Predictor III A
% Progression in POSCH
End Lipids
CRF

LDL	**> 0.80**	**0.75-0.79**	**0.70-.074**	**0.65-.69**	**0.60-0.64**	**≤ 0.59**
	21	5	0			
> 200	33	7	1			
	64%	71%	0%			
	29	13	2	1		
175-199	41	26	3	1		
	71%	50%	50%	100%		
	26	22	3	0	0	0
150-174	43	59	21	7	2	1
	60%	37%	14%	0%	0%	0%
	10	8	7	1	0	1

125-149	17	30	31	20	4	8
	59%	27%	23%	5%	0%	13%
	2	3	5	2	0	0
100-124	3	8	27	27	15	26
	67%	38%	19%	7%	0%	0%
			0	0	0	2
≤ 99			12	24	45	188
			0%	0%	0%	1%

Red Zone 146/313 = 47%
Yellow Zone 14/114 = 12%
Green Zone 3/304 = 1%
a. The red zone: this portion of the figure encompasses all CRF values > 0.70 and all LDL-C values > 125 mg/dl.
b. The yellow zone: this portion of the figure encompasses CRF values 0.60-0.69 and LDL levels of 100-124 mg/dl.
c. The green zone: this portion of the figure encompasses CRF values < 0.59 and LDL-C < 99 mg/dl.

The parameters of each of these zones were selected due to the decreasing risk of ATD in the BGS General Population and ATD Population databases. The percentage of plaque progression is displayed in Table II and pictorially in Figure II. Table II and Figure II reveal that there is a decreasing risk of plaque progression when the CRF-LDL-C cohort is located in the red zone or the yellow zone or the green zone. Indeed in the green zone, plaque progression is virtually nil.

Table 2: Nested Risk Factor Cohorts CRF vs. LDL-C % Plaque Progression in POSCH

	Red	Yellow	Green
Patients With Progression	146	14	3
Total Patients	313	114	304
% Progression	47%	12%	1%

CRF means Cholesterol Retention Fraction
LDL-C means Low Density Lipoprotein Cholesterol
POSCH means Program on the Surgical Control of the Hyperlipidemias

Other angiographic regression trials have been displayed on this 6x6 factorial: NHLBI, FATS, LCAS, Heidelberg study, LOCAT, and PLAC-I. These figures are presented in the Appendix. In brief, the NHLBI trial, which used bile acid sequestrants (resins), comes closest to the results of the POSCH trial. Both FATS and LCAS used resins, though not in every patient in LCAS, and their results are intermediate between POSCH and NHLBI, as compared to PLAC-I, Heidelberg study, and LOCAT, none of which used resins. (LDL-C data is not available from STARS, and so STARS data is not included here.)

The nested risk cohort approach can be utilized in TexCAPS/AFCAPS as well. (See Figure III.) Though not as clearly seen as in Figure II with the POSCH data, there is still a decline in ATD events from the red zone to the yellow zone to the green zone.

Figure III
ATD Incidence in TexCAPS/AFSCAPS
Lovastatin Cohort
End of Trial Lipids
CRF

LDL	> 0.80	0.75-0.79	0.70-.074	0.65-.69	0.60-0.64	≤ 0.59
> 200	0	0				
	4	2				
175-199	1	0	0	0		
	8	8	3	1		
150-174	3	0	2	0	0	
	19	50	36	9	1	
125-149	0	6	7	2	2	1

	19	120	247	169	60	19
100-124	0	5	12	15	10	5
	13	98	284	453	339	254
≤ 99	0	0	0	2	3	10
	4	4	22	91	123	379

Red Zone 19/516 = 3.7%
Yellow Zone 46/1427 = 3.2%
Green Zone 21/896 = 2.3%

Discussion

This paper demonstrates the fallacy of abandoning lipid treatment goals in the new AHA/ACC guidelines. In TexCAPS/AFCAPS failure to achieve the goal of bringing the patient's CRF-SBP plot below the threshold line in the cohort receiving lovastatin therapy resulted in no benefit with respect to ATD events. (See Table I.) Overall, ATD event rates are low, perhaps because of the low cigarette smoking rates seen in TexCAPS/AFCAPS (11%). It has been shown that current cigarette smoking accelerates the rate at which the underlying ATD process is expressed clinically [20].

Similarly, Table II and Figure I I show that if the lipid goal of CRF < 0.59 and/or the LDL-C goal of < 99 mg/dl is achieved then in POSCH there is minimal progression of plaque. Indeed, there is a progressive decrease in the incidence of plaque progression, from the red zone to the yellow zone to the green zone. Since plaque progression is associated with future ATD events and plaque non-progression (stabilization/regression) is associated with a marked reduction in ATD events, such a reduction in plaque progression can act as a surrogate for ATD outcomes [21-24]. Additionally, Figure III shows that similar results can be obtained, though not as distinct as in POSCH, in an ATD outcomes study such as TexCAPS/AFCAPS. Hence, LMT to achieve a position within the green zone is a reasonable goal of therapy.

The question arises as to why plaques progress or ATD events occur when the target goals described in this paper are met. In POSCH and NHLBI (see appendix for NHLBI) such events are infrequent and could relate to plaque hemorrhage or thrombosis overlying a plaque, with either event leading to plaque swelling (former scenario) or apparent plaque swelling (latter scenario), with apparent shrinkage of plaque as the intra-plaque hemorrhage resolves or the thrombosis lyses. In any event, the occurrence of such infrequent events should not interfere with the setting of target goals of LMT, as described in this paper.

The other six trials in the nested risk cohort analysis did not show the same marked reduction in plaque progression as did POSCH and NHLBI. (See appendix) This may be due to the types of intervention in these trials. There is an additional consideration when considering this question. POSCH involved a partial ileal bypass, which shunts dietary cholesterol away from gut bacteria. NHLBI used resins (cholestyramine) which can bind gut cholesterol and bile acids, thus preventing the gut bacteria from metabolizing dietary cholesterol and bile acids. FATS and some LCAS patients also received resins. The first two trials (POSCH, NHLBI) had results that were considerably better than the second two (FATS, LCAS), which in turn had results that were considerably better than the other three (PLAC-I, Heidelberg study, and LOCAT), none of which used resins. These findings should be considered in light of the recent publication by Tang that revealed the contribution of gut bacteria to the ATD process by metabolizing dietary cholesterol and phosphatidylcholine into trimethylamine-N-oxide, a substance that inhibits reverse cholesterol transport [25].

The differences in the outcomes of the various angiographic regression trials could suggest an important finding. It may well be that the method by which LMT is accomplished may be an important aspect of interventional lipidology. This is supported by various trials, whose therapeutic modalities have had favorable effects on lipids but no effect on plaque: Cholesterol ester transport protein inhibitors, ezetimibe, and niacin [26-31]. This proposal has been made before and merits further investigation [32].

Caveat

The POSCH trial and the other studies described in the 2000 meta-analysis were all performed prior to a change in the laboratory determination of the HDL-cholesterol level from a precipitation method to an enzymatic method [9,33].These different methodologies do not give the same results for HDL-cholesterol. The older precipitation method gives a value for the HDL-cholesterol fraction that is on the order of 10 mg/dl lower than one measured by the new enzymatic method. Consequently, since LDL-cholesterol is usually calculated by the Freidewald equation, LDL-cholesterol levels, calculated on the basis of the newer HDL-cholesterol method, will be on the order of 10 mg/dl lower than when calculated by the older method [34]. All the LDL- and HDL-cholesterol values involved in this effort were based on analyses by the older precipitation method and are, therefore, uniform with regard to their arteriography correlations.

Conclusion

The abandonment of target goals for LMT may well be detrimental to the fight to prevent ATD, or if ATD is extant, then to stabilize/regress plaque. The treatment goals offered in this paper augment those offered by the NCEP in their last revision and should include a CRF-SBP plot position below the threshold line and/or a CRF--LDL-C cohort within the green zone in a secondary prevention scenario [4]. It also appears that the means of intervention may also be important.

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