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Angiographic Disease Outcomes When Target Goals of Lipid Modifying Therapy are Not Met: Update

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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. 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. 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.*

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 CRF, 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.*

INTRODUCTION

Interventional lipidology (Harvey Hecht, MD, term used with permission) is the treatment of dyslipidemia with the goal of prevention of atherothrombotidc disease (ATD) or if ATD is extant, then the prevention of subsequent clinical events. Change in angiographic plaque is a useful marker of ATD prognosis, with stabilization/regression of plaque on serial angiography being associated with a lesser incidence of subsequent ATD events (1-5) and progression being associated with a worse prognosis (6-10). The trials studying this effect have used lipid modifying therapy (LMT). Since the only reason to treat dyslipidemia is, as previously noted, the prevention of initial or subsequent ATD events, then limitation of plaque progression is the aim of LMT. This manuscript will show that failure to achieve target lipid goals leads to plaque progression and to predicted worsening ATD outcomes.

To show that the goals of LMT must be achieved to prevent plaque progression, this paper will utilize the data bases of eight published angiographic regression studies. (11) The author will examine plaque progression when the goals of LMT are not met.

Low density lipoprotein cholesterol (LDL-c) has been the standard for achieving maximum benefit of LMT. However, the author has

proposed an alternate lipid predictor: the Cholesterol Retention Fraction (CRF), which uses both LDL and high density lipoprotein cholesterol (HDL-c). The CRF is defined as (LDL-HDL)/LDL and represents the percentage of the LDL-c remaining within the artery wall after reverse cholesterol transport has removed its portion of arterial wall cholesterol. The CRF more accurately predicts plaque dynamics than does LDL cholesterol by itself. (12-14)

An earlier report gave the results of an analysis of a large outcomes study (TexCAPS/AFCAPS) and a large angiographic regression trial. (15) This manuscript enlarges on that previous report.

MATERIALS AND METHODS

The author has in his possession the patient databases of the eight cited trials: Program on the Surgical Control of the Hyperlipidemias (POSCH) (12), St. Thomas Atherosclerosis Regression Study (STARS) (16), Familial Atherosclerosis Treatment Study (FATS) (17), National Heart, Lung, and Blood Institute Type II Coronary Interventional Study (NHLBI) (18), Lipoprotein and Coronary Atherosclerosis Study (LCAS) (19), the Heidelberg Study (20), Lopid Coronary Angiography Trial (LOCAT) (21), and Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I)(22). The author reviewed each of these databases, patient by patient, line by line, (from baseline till the end of the trial. The author utilizes a nested risk cohort scheme to analyze plaque changes in response to LMT.

Before turning to the RESULTS portion of this paper, it should be noted that the LDL-c levels noted in the eight published angiographic regression trial were based on a calculated LDL-c, which in turn was based on the precipitation method for determining HDL-c, as per the Friedewald formula. (23) In 1999, the manufacturers of the auto-analyzers switched to the enzymatic method of HDL-c measurement. These two differing methodologies do not give the same results. The precipitation method gives a value for HDL-c that is on the order of 10 mg/dl (0.25 mmols/L) lower than the one measured by the new enzymatic method. Consequently, LDL-c levels, calculated on the basis of the newer HDL-cholesterol method, will be on the order of 10 mg/dl (0.25 mmols/L) lower than when calculated by the precipitation method. 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 angiographic correlations. The differences in these two techniques is not trivial—especially when the CRF is utilized. In 2008 the author reported a case of a 53 year-old white male patient who sustained an acute myocardial infarction while in another town. The author had never measured his lipids because the patient had been seen for acute complaints and had no obvious reasons to measure a lipid profile, including family history of either dyslipidemia or ATD. His lipids were measured upon his presentation to the other hospital and were only mildly abnormal, but when the lipid values were converted from the enzymatic technique to the precipitation technique, the lipids were much more abnormal and the CRF was markedly abnormal.(24) This is important to remember when considering the data in the RESULTS section.

RESULTS

To examine the effects of LMT on dyslipidemia and subsequent changes in plaque, end-of-trial LDL-cholesterol was stratified by CRF in a 6x6 factorial for each trial. (See Figures I A-G.) When this was done, zones of decreasing risk of plaque progression were noted:

1) the red zone: this portion of the figure encompasses all CRF values $\geq$ 0.70 and all LDL-C values $\geq$ 125 mg/dl (3.2 mmoles/L)

2) the yellow zone: this portion of the figure encompasses CRF values 0.60-0.69 and LDL levels of 100-124 mg/d (2.5-3.2 mmoles/L)l.

3) the green zone: this portion of the figure encompasses CRF values < 0.59 and LDL-C $\leq$ 99 mg/dl (2.5 mmols/L).

The parameters of each of these zones were selected due to the risk of ATD in the BGS General Population and ATD Population databases. The percentage of plaque progression is displayed in Tables I-III and pictorially in Figures I A-G. These Tables and Figures 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.

In brief, the POSCH study yielded the best results. POSCH involved a partial ileal bypass. NHLBI trial, which used bile acid sequestrants (resins), comes closest to the results of the POSCH trial. Both FATS and LCAS used resins, though only in selected 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.)

DISCUSSION

Table I-III and Figures I A-G show that if the lipid goal of CRF $\leq$ 0.59 and/or the LDL-C goal of $\leq$ 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 (6-10) and plaque non-progression (stabilization/regression) is associated with a marked reduction in ATD events (1-5), such a reduction in plaque progression can act as a surrogate for ATD outcomes. Hence, LMT to achieve a position within the green zone is a reasonable goal of therapy. It should be noted that the results when the CRF goal is achieved are very similar to the results when the LDL-c goal is achieved.

Table I: *% Progression in Angiographic Regression Trials Nested Cohort*

Trial	Red	Yellow	Green
POSCH	146 313 47%	14 114 12%	3 303 1%
NHLBI	21 71 30%	0 13 0%	0 6 0%
FATS	21 45 47%	5 25 20%	12 50 24%
LCAS	37 84 44%	39 106 37%	37 143 26%
Heidelberg	26 71 37%	3 13 23%	2 5 40%
PLAC-1	66 129 51%	30 77 39%	25 76 33%
LOCAT	152 229 66%	54 95 57%	21 48 44%

POSCH Means Program on the Surgical Control of the Hyperlipidemias

NHLBI Means National Heart Lung and Blood Institute

FATS Means Familial atherosclerosis Treatment Study

LCAS Means Lipoprotein and Coronary Atherosclerosis Study

Heidelburg Means Study on The Effects of Regular Physical Exercise and Low-Fat Diet on the Progression of Coronary Artery Disease

PLAC-1 Means Pravastatin Limitation of Atherosclerosis in the Coronary Arteries

LOCAT Means Lopid Coronary Angiography Trial

Table II: *% Progression in the Green Nested Cohorts w/r to CRF and LDL-c*

Trial	LDL-c $\leq$ 99	CRF $\leq$ 0.59
POSCH	2 268 1%	3 222 1%
NHLBI	0 5 0%	0 2 0%
FATS	5 32 16%	10 45 22%

LCAS	21 76 27%	34 132 26%
Heidelberg	2 3 67%	1 3 33%
PLAC-1	11 28 39%	20 63 32%
LOCAT	17 38 45%	15 34 44%

POSCH Means Program on the Surgical Control of the Hyperlipidemias

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Table III: *Percent Progression When End-of-Trial Lipids in Green Zone*

	CRF≥ 0.60, LDL-c ≤ 99	**CRF≤ 0.59, LDL-c ≥ 100**	**CRF≤ 0.59, LDL-c ≤ 99**
POSCH	0 81 0%	1 35 3%	2 187 1%
NHLBI	0 1 0%	0 4 0%	0 1 0%
FATS	2 5 40%	7 18 39%	3 27 11%
LCAS	3 11 27%	16 67 24%	18 65 28%
Heidelberg	1 2 50%	0 2 0%	1 1 100%
PLAC-1	5 13 38%	14 48 29%	6 15 40%
LOCAT	6 14 43%	4 10 4%	11 24 46%
∑	17 127 13%	42 184 23%	41 320 13%
∑ **(Minus POSCH)**	17 46 37%	41 149 28%	39 133 29%

POSCH Means Program on the Surgical Control of the Hyperlipidemias

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Figure I-A: *CRF vs LDL-c in % Progression Angiographic Outcomes: POSCH*

CRF

LDL-c	≥ 0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤ 0.59	∑
≥ 200	21 33 64%	5 7 71%	0 1 0%				26 41 63%
175-199	29 41 71%	13 26 50%	2 4 50%	1 1 100%			45 72 63%
150-174	26 43 60%	22 59 37%	3 21 14%	0 7 0%	0 2 0%	0 1 0%	51 133 38%
125-149	10 17 59%	8 30 27%	7 31 23%	1 20 5%	0 4 0%	1 8 13%	27 110 25%
100-124	2 3 67%	3 8 38%	5 27 19%	2 27 7%	0 15 0%	0 26 0%	12 106 11%
≤ 99			0 12 0%	0 24 0%	0 45 0%	2 187 1%	2 268 1%
∑	88 137 64%	51 130 39%	17 96 18%	4 79 5%	0 66 0%	3 222 1%	163 730 22%

CRF Means Cholesterol Retention Fraction

POSCH Means Program on the Surgical Control of the Hyperlipidemias

LDL-c Means Low Density Lipoprotein Cholesterol

Figure I-B: *CRF vs LDL-c in % Progression Angiographic Outcomes: NHLBI*

CRF

LDL-c	≥ 0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤ 0.59	∑
≥ 200	14 44 32%	1 6 17%	1 3 33%				16 53 30%
175-199	0 2 0%	1 2 50%	0 3 0%	0 3 0%	0 1 0%		1 11 9%
150-174	1 3 33%	3 4 75%	0 3 0%	0 1 0%	0 2 0%		4 13 31%
125-149		0 1 0%		0 1 0%		0 2 0%	0 4 0%
100-124	0 1 0%	0 1 0%	0 1 0%	0 1 0%	0 1 0%	0 2 0%	0 7 0%
≤ 99					0 1 0%	0 1 0%	0 2 0%
∑	15 50 30%	5 14 36%	1 10 10%	0 6 0%	0 5 0%	0 5 0%	21 90 23%

CRF Means Cholesterol Retention Fraction

NHLBI Means National Heart Lung and Blood Institute

LDL-c Means Low Density Lipoprotein Cholesterol

Figure I-C: *CRF vs LDL-c in % Progression Angiographic Outcomes: FATS*

CRF

LDL-c	≥ 0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤ 0.59	∑
≥ 200	3 5 60%	1 5 17%	1 1 100%				5 12 42%
175-199	1 4 25%	2 4 50%	2 7 29%				5 15 33%
150-174	0 1 0%	4 5 80%	2 2 100%	0 4 0%	0 2 0%	1 1 100%	7 15 47%
125-149		2 4 50%	3 6 50%	1 1 100%	1 5 20%	0 3 0%	7 19 37%
100-124			1 4 25%	2 6 33%	0 3 0%	6 14 43%	9 27 33%
≤ 99			1 1 100%		1 4 25%	3 27 11%	5 32 16%
∑	4 10 40%	9 19 47%	10 21 48%	3 11 27%	2 14 14%	10 45 22%	38 120 32%

CRF Means Cholesterol Retention Fraction

FATS Means Familial atherosclerosis Treatment Study

LDL-c Means Low Density Lipoprotein Cholesterol

Figure I-D: *CRF vs LDL-c in % Progression Angiographic Outcomes: LCAS*

CRF

LDL-c	≥ 0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤ 0.59	∑
≥ 200	0 1 0%	1 2 50%					1 3 33%
175-199		3 10 30%	1 4 25%	1 3 33%	1 1 100%		6 18 33%
150-174	4 5 80%	3 11 27%	4 11 36%	1 8 13%	1 1 100%	1 3 33%	14 39 16%
125-149	1 1 100%	6 13 46%	14 26 54%	6 21 29%	4 11 36%	1 14 7%	32 86 37%
100-124		2 3 67%	5 13 38%	7 16 44%	11 29 38%	14 50 28%	39 111 35%
≤ 99				1 7 14%	2 4 50%	18 65 28%	21 76 27%
∑	5 7 71%	15 39 38%	24 54 44%	16 55 29%	19 46 41%	34 132 26%	113 333 34%

CRF Means Cholesterol Retention Fraction

LCAS Means Lipoprotein and Coronary Atherosclerosis Study

LDL-c Means Low Density Lipoprotein Cholesterol

Figure I-E: *CRF vs LDL-c in % Progression Angiographic Outcomes: Heidelberg*

CRF

LDL-c	≥ 0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤ 0.59	∑
≥ 200	4 10 40%	1 1 100%	1 1 100%				6 12 50%
175-199	2 13 15%	4 8 50%	1 2 50%				7 23 30%
150-174	2 7 29%	2 7 29%	3 9 33%	1 1 100%			8 24 33%
125-149	1 2 50%	4 7 57%	1 4 25%		0 1 0%	0 2 0%	6 16 38%
100-124		1 5 20%	1 1 100%	0 4 0%	0 1 0%		2 11 18%
≤ 99			1 1 100%		0 1 0%	1 1 100%	2 3 67%
∑	9 32 28%	12 28 43%	8 18 44%	1 5 20%	0 3 0%	1 3 33%	31 89 35%

CRF Means Cholesterol Retention Fraction

Heidelburg Means Study on The Effects of Regular Physical Exercise and Low-Fat Diet on the Progression of Coronary Artery Disease

LDL-c Means Low Density Lipoprotein Cholesterol

Figure I-F: *CRF vs LDL-c in % Progression Angiographic Outcomes: PLAC-1*

CRF

LDL-c	≥ 0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤ 0.59	∑
≥ 200	4 8 50%	1 2 50%	0 1 0%				5 11 45%
175-199	6 11 55%	6 10 60%	6 11 55%	1 1 100%			19 33 58%
150-174	7 11 64%	14 23 61%	12 23 52%	1 6 17%	1 1 100%	0 1 0%	35 65 54%
125-149	1 5 20%	3 9 33%	6 15 40%	5 11 45%	3 12 25%	5 15 33%	23 67 34%
100-124			4 12 33%	5 15 33%	10 19 53%	9 32 28%	28 78 36%
≤ 99			1 2 50%	2 4 50%	2 7 29%	6 15 40%	11 28 39%
∑	18 35 51%	24 44 55%	29 64 45%	14 37 38%	16 39 41%	20 63 32%	121 282 43%

CRF Means Cholesterol Retention Fraction

PLAC-1 Means Pravastatin Limitation of Atherosclerosis in the Coronary Arteries

LDL-c Means Low Density Lipoprotein Cholesterol

Figure I-G: *CRF vs LDL-c in % Progression Angiographic Outcomes: LOCAT*

CRF

LDL-c	≥ 0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤ 0.59	∑
≥ 200	9 10 90%	1 1 100%					10 11 91%
175-199	13 17 76%	8 12 75%	1 1 100%				22 30 73%
150-174	22 34 65%	29 37 78%	10 18 56%		1 2 50%	1 1 100%	63 92 68%
125-149	17 24 71%	19 40 48%	23 35 66%	12 18 67%	5 9 56%	1 1 100%	77 127 61%
100-124	1 3 33%	6 12 50%	11 22 50%	12 17 71%	6 11 55%	2 8 25%	38 73 52%
≤ 99	0 1 0%	1 1 100%	1 2 50%	0 2 0%	4 8 50%	11 24 46%	17 38 45%
∑	62 89 70%	64 103 62%	46 78 59%	24 37 65%	16 30 53%	15 34 44%	227 371 61%

CRF Means Cholesterol Retention Fraction

LOCAT Means Lopid Coronary Angiography Trial

LDL-c Means Low Density Lipoprotein Cholesterol

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 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. 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. Some FATS and 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 (26,27), ezetimibe (28, 29), and niacin (30,31). This proposal has been made before (32) and merits further investigation.

Conclusion

The fight to prevent ATD, or if ATD is extant, then to stabilize/regress plaque requires the achievement of target goals of lipid therapy, as

discussed above. The treatment goals offered in this paper are simple, in principal, and are comprised of a CRF-LDL-c cohort within the green zone. It also appears that the means of intervention may also be important and only dyslipidemic medication should be used that positively impact ATD putcomes.

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