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LDL Lowering: Evidence for a Plaque Non-Progression Threshold

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Introduction

The holy grail of Interventional Lipidology* is the prevention of the cholesterol-rich plaque, which is the basis, along with thrombosis, of atherothrombotic disease (ATD), or if the cholesterol-rich plaque is extant, then stabilization/regression of that plaque, in the hope of preventing subsequent ATD events. The prediction of the population at risk of ATD is the bedrock upon which the prevention of ATD is based. Fortunately, the population at risk of ATD is readily and accurately predictable, so that the prevention of ATD is possible [1]. However, the population at risk of ATD is not always found early enough to permit prevention of the cholesterol-rich plaque, and often not early enough to prevent the clinical ATD event. In such cases, the goal behind the term interventional lipidology is the stabilization/regression of the cholesterol–rich plaque.

This paper will attempt to answer the fundamental question: What is the low-density lipoprotein (LDL) cholesterol treatment goal that maximizes plaque stabilization/regression? To provide an answer to this question, angiographic data published in 2000 will be employed [2]. This publication analyzed eight published angiographic regression trials: St. Thomas Angiographic Regression Trial (STARS) [3], the Heidelberg Study [4], the Program on the Surgical Control of Hyperlipidemia (POSCH) [5], the National Heart, Lung, and Blood Institute Type II Secondary Prevention Trial (NHLBI) [6], Lopid Angiography Trial (LOCAT) [7], Familial Atherosclerosis Treatment Study (FATS) [8], the Lipoprotein and Coronary Atherosclerosis Study (LCAS) [9], and the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) [10]. Pre- and post-treatment lipid and blood pressure data, as well as angiographic outcomes data, were sent to the author by the trials' principal investigators. The data sent were on an individual patient basis.

This paper will examine LDL, high-density lipoprotein (HDL) cholesterol, and a measure of the LDL-HDL balance, the Cholesterol Retention Fraction (CRF, defined as [LDL-HDL]/LDL). The usefulness of the CRF in predicting the population at risk of ATD was previously established [1] and its usefulness in predicting plaque stabilization/regression has been published as well [2]. This paper will demonstrate and compare the treatment levels of LDL, HDL, and CRF that must be achieved to maximize plaque stabilization/regression (or non-progression). Additionally, this paper will examine systolic blood pressure (SBP) control as a factor in maximizing plaque non-progression.

*Harvey Hecht, MD, used with permission

Materials and Methods

The angiographic data are taken from the cited publication [2]. The pre- and post treatment lipid/blood pressure data and angiographic outcomes data were requested in writing, and sometimes in person, by the author from the principal investigators of the various angiographic regression trials. The principal investigators on the eight trials listed above responded positively. The principal investigators of the eight trials noted above sent, collectively, 2089 data sets: pre- and post-treatment lipid/blood pressure data with the associated pre- and post-treatment serial angiogram outcomes. (A few data sets were missing some data, and so could not be utilized in some of the analyses, but could be utilized in other analyses.) Treatment modalities involved diet, exercise, statins, resins, fibrates, niacin, and a surgical procedure, the partial ileal bypass procedure (POSCH).

Of the 2089 patients with full end-of-trial data, 448/2014 (22%) had end-of-trial LDL levels of 99 mg/dl (2.5 mmoles/L) or less. Since the National Cholesterol Education Program (NCEP) goal for the treatment of ATD patients, in 2001, specified this level [11], and since the long-awaited update of NCEP guidelines (NCEP IV) have not yet been released, this paper will focus on those 448 patients with end-of-trial LDL levels of 99 mg/dl (2.5 mmoles/L) or less.

Results

Table 1 gives the angiographic outcomes for seven of the eight angiographic regression trials, focusing on those patients who achieved end-of-trial LDL levels of 99 mg/dl (2.5 mmoles/L) or less. The eighth study, STARS, did not provide this data.

Table 1 reveals that when end-of-trial LDL levels of 99 mg/dl (2.5 mmoles/L) or less is achieved, then angiographic regression occurs in 302/448 (67%) of cases, angiographic stabilization occurs in 88/448

Table 1: Angiographic Outcomes When End-of Trial LDL ≤ 99 mg/d Mean values of the Various Parameters Angiographic Outcome.

Parameter	Non-Progression	Progression
	390	58
LDL	31031	4967
	80	86
	380	57
CRF	187.28	30.45
	0.49	0.53
	390	58
HDL	15675	2343
	40	40
	387	62
SBP	64022	8106
	166	130

Abbreviations: LDL: Low-Density Lipoprotein (cholesterol); HDL: High-Density Lipoprotein (cholesterol); CRF: Cholesterol Retention Fraction [(LDL-HDL)/LDL]; SBP: Systolic Blood Pressure LDL and HDL values given in mg/dl. SBP values given in mmHg. All negative CRF values excluded

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(20%) of cases, and angiographic progression occurs in 58/448 (13%) of cases. The table also shows the average LDL, HDL, CRF, and SBP values associated with each angiographic outcome category. It will be noted that the number of patients in the CRF row is less than in the other rows. This is because therapy in the trials was sometimes so effective that it lowered LDL to levels below the associated HDL levels, thus engendering a negative CRF. To avoid confusion, those patients were excluded from analysis in this table. (This would include eight patients in POSCH, two patients in LCAS, and one patient in LOCAT.) This exclusion does not significantly change the percentages of the various angiographic outcomes: regression occurs in 293/437 (67%), stabilization in 87/437 (20%), and progression in 57/437 (13%).

Table 1 reveals that when angiographic regression and stabilization are combined into a non-progression category, their LDL and CRF values are lower than those for the progression category. HDL levels are identical in the two categories, and SBP values are higher in the non-progression category versus the progression category. This is because, as will be shown in Table 3, plaque non-progression is driven by the POSCH trial and POSCH was not structured to control SBP*. Table 2 compares the plaque non-progression rates of LDL, CRF, and HDL, when these lipid predictors are divided into sextiles, ranging from highest to lowest. Evaluation of Table 2 reveals that there is a steady increase in the percentage of plaque non-progression for LDL from the 99 mg/dl (2.5 mmoles/L) sextile to the 80-89 mg/dl sextile (2.0-2.5 mmoles/L), but thereafter the percentage of plaque non-progression is unchanged, remaining constant at 93% for all LDL levels below 79 mg/dl (2.0 mmoles/L). This plateauing effect does not occur for CRF until levels of 0.49 or lower. No such plateauing effect is seen for HDL. Indeed, the percentage of plaque non-progression is essentially the same at all levels of HDL.

It should be noted that 204/448 (46%) patients achieved CRF goals, for plaque non-progression, of 0.49 or less, whereas 173/448 (39%) achieved the LDL goal, for plaque non-progression, of 79 mg/dl (2.0 mmoles/L) or less. This means that the CRF goal is easier to achieve than is the LDL goal.

Table 3 lists each trial for which LDL, CRF, and HDL data are available, listing the lipid predictors in terms of averages in each of the angiographic outcomes categories. Inspection of Table 3 reveals that the results in the plaque non-progression category are overwhelmingly driven by POSCH whereas the plaque progression category tends to be driven by LCAS and LOCAT. Further inspection reveals that in general, allowing for categories in which there are relatively few patients, CRF and LDL tend to be lower and HDL levels higher in the plaque non-progression categories than in the plaque progression category. (This is also evident in Table 1).

Tables 4 and 5 examine LDL sextiles, stratified by HDL and CRF sextiles respectively. At any level of LDL, neither HDL nor CRF appear to provide a clear-cut advantage with respect to plaque progression rate. Conversely, at any level of CRF or HDL, a lower LDL offers a lesser risk of plaque progression.

As noted previously, POSCH was not structured to control blood pressure. Table 6 reveals the end-of-trial SBP data for all patients except for LCAS, which did not provide this data. It is clear that SBP levels in POSCH are much higher than in the other trials, and yet POSCH has the highest numbers of patients with plaque non-progression.

*Henry Buchwald, MD, personal communication

Table 2: Percentage of Non-Progression Rates in Various Risk Factor Profiles When End-of-Trial LDL ≤ 99 mg/dl.

Parameter	Sextile Value	Non-Progression Cases	Progression Cases	%Non-Progression
LDL	90-99	120	27	82%
	80-89	109	19	85%
	70-79	80	6	93%
	60-69	41	3	93%
	50-59	22	2	92%
	≤49	18	1	95%
HDL	≥60	23	3	88%
	50-59	49	6	89%
	40-49	91	19	83%
	30-39	169	22	88%
	20-29	57	8	88%
	≤19	1	0	100%
CRF	≥0.70	15	5	75%
	0.65-0.69	34	3	92%
	0.60-0.64	61	9	87%
	0.50-0.59	94	23	80%
	0.40-0.49	98	10	91%
	≤0.39	88	8	92%

Abbreviations: LDL: Low-Density Lipoprotein (cholesterol); HDL: High-Density Lipoprotein (cholesterol); CRF: Cholesterol Retention Fraction [(LDL-HDL)/LDL]; SBP: Systolic Blood Pressure LDL and HDL values given in mg/dl. SBP values given in mmHg. All negative CRF values excluded

Table 3: Comparison of Lipid Predictor Averages in Angiographic Outcomes When End-of-Trial LDL ≤ 99 mg/dl.

		Non Progression			Progression	
	CRF	LDL	HDL	CRF	LDL	HDL
	1	1	1	2	2	2
Heidelburg	0.62	94	36	0.85	192	112
	0.62	94	36	0.43	96	56
	2	2	2	-	-	-
NHLBI	1.03	155	71	-	-	-
	0.52	78	36	-	-	-
	17	17	17	11	11	11
Plac-1	9.4	1516	671	6.40	945	392
	0.55	89	39	0.58	86	36
	27	27	27	5	5	5
FATS	12.69	2204	1163	3.01	433	171
	0.47	82	43	0.60	87	34
	54*	55	55	20*	21	21
LCAS	21.91	4673	2765	9.61	1805	970
	0.41	85	50	0.48	86	46
	20*	21	21	17	17	17
LOCAT	10.27	1716	835	9.72	1501	647
	0.51	82	40	0.57	88	38
	259*	267	267	2	2	2
POSCH	131.36	20673	10107	0.86	91	49
	0.51	77	38	0.43	46	25
	380*	390	390	57*	58	58
SUM	187.28	31025	15648	30.45	4967	2341
	0.49	80	40	0.53	86	40

*Means negative values not included

Abbreviations: LDL: Low-Density Lipoprotein (cholesterol); HDL: High-Density Lipoprotein (cholesterol); CRF: Cholesterol Retention Fraction [(LDL-HDL)/LDL]; SBP: Systolic Blood Pressure LDL and HDL values given in mg/dl. SBP values given in mmHg. All negative CRF values excluded

Table 4: % Progression When End-of Trial LDL ≤ 99 mg/dl, Stratified by HDL.

	LDL	≥ 60	50-59	40-49	30-39	20-29	≤ 19
HDL		2	3	10	9	3	0
90-99		7	30	33	61	15	1
		29%	10%	30%	15%	20%	0%
		1	2	8	7	1	-
80-89		12	13	38	56	9	-
		8%	15%	21%	13%	11%	-
		0	1	0	5	0	-
70-79		3	8	25	39	11	-
		0%	13%	0%	13%	0%	-
		0	0	1	1	1	-
60-69		3	2	11	17	11	-
		0%	0%	9%	6%	9%	-
		0	0	0	0	2	-
50-59		1	2	3	11	7	-
		0%	0%	0%	0%	33%	-
		-	-	-	0	1	-
≤ 49		-	-	-	7	12	-
		-	-	-	0%	8%	-

For each fraction, the numerator represents the number of progression cases, while the denominator represents the total number of cases.
Abbreviations: LDL: Low-Density Lipoprotein (cholesterol); HDL: High-Density Lipoprotein (cholesterol); CRF: Cholesterol Retention Fraction [(LDL-HDL)/LDL]; SBP: Systolic Blood Pressure LDL and HDL values given in mg/dl. SBP values given in mmHg. All negative CRF values excluded

Table 5: % Progression When LDL ≤ 99 mg/dl Stratified by CRF.

	LDL	>0.70	0.65-0.69	0.60-0.64	0.50-0.59	0.40-0.49	≤ 0.39
CRF		3	3	4	12	3	2
90-99		12	19	38	40	27	11
		25%	16%	11%	30%	11%	18%
		1	0	3	6	6	3
80-89		5	12	17	41	32	21
		20%	0%	18%	15%	19%	14%
		0	0	2	3	0	1
70-79		2	5	10	26	25	18
		0%	0%	20%	12%	0%	6%
		1	0	0	0	1	1
60-69		1	1	6	8	10	18
		100%	0%	0%	0%	9%	6%
		-	-	-	2	0	0
50-59		-	-	-	4	9	11
		-	-	-	50%	0%	0 %
		-	-	-	-	0	1
≤ 49		-	-	-	-	2	17
		-	-	-	-	0%	6%

For each fraction, the numerator represents the number of progression cases, while the denominator represents the total number of cases.
Abbreviations: LDL: Low-Density Lipoprotein (cholesterol); HDL: High-Density Lipoprotein (cholesterol); CRF: Cholesterol Retention Fraction [(LDL-HDL)/LDL]; SBP: Systolic Blood Pressure LDL and HDL values given in mg/dl. SBP values given in mmHg. All negative CRF values excluded

Discussion

The goals of LDL therapy have been widely discussed in the medical literature. Trials using various endpoints have been done to assess the effectiveness of lowering LDL to various levels. Eight angiographic regression trials are used in this meta-analysis. Clinical outcomes trials have been promoted as "gold standard," since they monitor the ATD events that physicians are trying to prevent*. However, cigarette smoking and blood pressure, depending on the ATD events serving as trial endpoints, can induce clinical ATD events, even when lipid levels are optimal. This effect can mask the beneficial effect of dyslipidemia therapy [12]. Cigarette smoking has been reported not to influence plaque progression [13]. Studies of plaque progression vs. non-progression may be surrogates but the atheromatous plaque is critical lesion in ATD, and these studies reflect changes occurring at plaque level in the arterial wall and provide a direct view of the fundamental ATD process. Moreover, while outcomes studies may take many years to yield results, plaque progression studies can give results in only two years, and it has been established that when plaques stabilize or regress angiographically, the rate of subsequent clinical ATD events fall off dramatically [14,15].

IVUS studies have been touted as giving a better view of the atherosclerotic process since they examine arterial wall plaque at an earlier stage than can be detected by angiography [16,17]. These studies include ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) [18], which resulted in the greatest degree of plaque regression ever seen in a statin trial as LDL levels plunged to an average level of about 61 mg/dl (1.5 mmoles/L). Nissen has created a graph that clearly demonstrates that, based on various IVUS trials, the change in percent atheroma volume is directly proportional to the change in LDL level post-treatment: the lower the end-of-trial LDL, the greater the decline in LDL, the greater the decline in percent atheroma volume [19]. Nissen's graph, however, does not rule out a plateau effect.

Angiographic and IVUS plaque regression trials do in fact translate into clinical event reduction. The TNT (Treat to New Targets) trial used low dose (10 mg) versus high dose (80 mg) atorvastatin and found that the higher dose of atorvastatin led to an average end-of-trial LDL of 77 mg/dl (1.9 mmoles/L), whereas the lower dose led to

Table 6: Average SBP Levels in Non Progression vs. Progression Outcomes (End of Trial SBP Outcomes)*.

	Non Progression	Progression
Trial		
	565	163
POSCH	103062	30449
	182	187
	161	121
PLAC-1	21114	15896
	131	131
	82	38
FATS	10144	4790
	124	126
	69	21
NHLBI	8790	2680
	127	128
	56	18
STARS	7114	2382
	127	132
	144	227
LOCAT	19862	31842
	138	140
	57	30
Heidelburg	7333	4005
	129	134

*LCAS did not provide SBP end of trial data

an average LDL of 101 mg/dl (2.5 mmoles/L). The high-dose cohort had a 22% decrease (relative risk) in major cardiovascular events compared to the low-dose cohort [20]. Moreover, the JUPITER (Justification for the Use of Statins in Prevention: An Interventional Trial Evaluating Rosuvastatin) compared rosuvastatin 20 mg daily versus placebo. The cohort receiving rosuvastatin lowered its median LDL level at the end of trial to 55 mg/dl (1.4 mmoles/L) whereas the placebo cohort's median LDL remained stable at 109 mg/dl (2.7 mmoles/L). The rosuvastatin cohort had a 44% decrease (relative risk) in major cardiovascular events compared to the placebo cohort [21].

Thus, angiographic, IVUS, and outcomes trials all support the concept that treatments that bring the end-of-trial LDL level s to 79 mg/dl (2.0 mmoles/L) or less lead to lower rates of plaque progression as well as lower rates of major cardiovascular events. The obvious next question to be asked is whether or not there is a threshold level of LDL below which further lowering of LDL does not lead to further end-point reduction. The current mantra ("Lower is better.") suggests that there is no lower threshold. However, the data presented in this paper suggest that there is in fact just such a lower threshold. This concept is borne out by the SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin) [22]. In SATURN one cohort was treated with 40 mg of rosuvastatin while the other cohort was treated with 80 mg of atorvastatin on a daily basis. The former cohort achieved end-of-trial average LDL levels of 62 mg/dl (1.6 mmoles/L) while the latter cohort achieved average end-of-trial LDL levels of 70 mg/dl (1.8 mmoles/L). Serial IVUS studies revealed no significant difference in decrease in percent atheroma volume between the two cohorts, although the secondary endpoint of normalized total atheroma volume did favor the rosuvastatin cohort.

The AIM-HIGH (Atherosclerosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) [23] is also pertinent here. This study used statin (simvastatin 40-80 mg daily) therapy with/without ezetimibe add-on therapy (10 mg daily) to bring LDL levels down to levels of 40-80 mg/dl (1.0-2.0 mmoles/L). When this goal was achieved, extended-release niacin was given in the amount of 1500-2000 mg daily to raise HDL levels to determine if raising HDL in the face of optimal LDL levels led to improved cardiovascular outcomes; this was the active-treatment group. The control group received a low dose of immediate-release niacin to induce a mild flushing reaction and thus conceal the "placebo" cohort from the active-treatment group (extended-release niacin). The active-treatment group further lowered its average LDL to 65 mg/dl (1.6 mmoles/L) and raised its HDL to 44 mg/dl (1.1 mmoles/L), while the control group achieved an average LDL of 68 mg/dl (1.7 mmoles/L) and an average HDL of 39 mg/dl (1.0 mmoles/L). There was no difference between the two cohorts in the incidence of major cardiovascular events, except that there were more ischemic strokes in the active-treatment group, for which reason the trial was terminated early. The inevitable conclusion of AIM-HIGH is that when LDL levels are brought to optimal levels, additional lipid therapy does not improve clinical cardiovascular outcomes. It may, however, be true that the initial treatment phase of AIM-HIGH resulted in lipid-poor plaques that were "resistant" to the cholesterol-effluxing properties of HDL and that had the trial been carried out to its planned duration, then a beneficial effect of extended-release niacin may have been noted. (Personal communications, Philip Barter, MD, 17 November 2011, and John Chapman, MD, 17 December 2011).

In summary, the available evidence from data presented and a brief literature review strongly suggest that there is indeed a threshold below which LDL need not be lowered in order to maximize plaque stabilization/regression, and by extension ATD events, and that the threshold exists at an LDL level of 79 mg/dl (2.0 mmoles/L). Two caveats, however, need to be noted. First, it must be noted that the lipid parameters used in virtually all clinical trials done prior to the year 2000 used the indirect measurement (precipitation technique) of HDL, and that the trials done after the year 2000 used the direct measurement (enzymatic technique) of HDL. The two measurement techniques do not give equivalent results. In general the direct method of HDL measurement gives a result about 10 mg/dl (0.25 mmoles/L) higher than the equivalent HDL result obtained using the indirect method. Since LDL is usually calculated by the Friedewald formula, the LDL value based on the direct measurement of HDL will of necessity be about 10 mg/dl (0.25 mmoles/L) lower than the LDL value based on the indirect measurement of HLD. This point is not trivial. The author has reported a case of a 55 year old Caucasian male who suffered an acute myocardial infarction with a relatively normal lipid profile based on the direct measurement of HDL, and no other ATD risk factors, but whose lipid profile, when converted to the equivalent profile based on the indirect measurement of HDL was significantly worse and characteristic of males with ATD events in the sixth decade of life [24]. Hence the threshold goal for LDL lowering in 79 mg/dl (2.0 mmoles/L) if the indirect method of HDL measurement is utilized and 69 mg/dl (1.7 mmoles/L) if the direct method of HDL measurement is utilized. In essence, "the old 80 mg/dl is the new 70 mg/dl."

The second caveat is that no clinical trial (angiographic, IVUS, or outcomes) has a "zero" progression rate. While this has been termed "Residual Risk," it may be that plaques have lives of their own and may progress despite optimal medical therapy. Borrisoff [25] has discussed the role of the hemostatic system, and especially the role of platelets, in the progression of the atheromatous plaque. He points out that platelets exert a number of pro-thrombotic effects on the arterial wall, especially at the site of plaques where a "persistent inflammatory state" is promoted and sustained , leading to deposition of fibrin over the fibrous cap and stimulation of migration of smooth muscle cells and mononuclear cells into the plaque area. Within and about the atheromatous plaque, the smooth muscle cells secrete a matrix which enlarges the plaque volume. These effects offer a possible explanation of why "lipid-poor" plaques may unexpectedly "progress" despite optimal therapy. Such a non-atherosclerotic mechanism could support the view that it is not necessary to lower LDL below the threshold level.

Finally, one additional observation needs to be made. The bulk of the angiographic non-progression cases in the cited meta-analysis [2] were composed of patients in POSCH. POSCH was not structured to control blood pressure, as noted earlier, though this aspect of POSCH has now been rectified, and hence, the plaque regression reported occurred in the face of uncontrolled hypertension (Table 6). This finding supports the primacy of optimal treatment of dyslipidemia for the regression/stabilization of coronary plaque.

This paper has a number of strengths and weaknesses. Its strengths lie in the multiplicity of trials on which this paper is based and on the uniformity of their findings. However, serial angiograms may be misleading due to increases in plaque volume due to intra-plaque hemorrhage or the adherence of thrombi to the fibrous plaque or to "progression" of the plaque due to deposition of fibrin and/or

infiltration of smooth muscle cells, with their attendant secretion of matrix. Similarly, plaques may "regress" due to resolution of these phenomena. In addition, different laboratories may differ in their ability to accurately measure lipids and different radiologists may differ in their ability to read angiograms or IVUS studies. Finally, plaques that stabilize/regress at LDL levels well above the LDL threshold may well progress over longer periods of time. It is a necessity of clinical trials that the patients selected to participate in those trials must be at high risk to have an ATD event within the timeframe of the trial, and it is not a at all clear that the drastic lowering of LDL necessary to modify plaque or outcomes in the short term is necessary in the pre-clinical phase of ATD, where treatment of dyslipidemia to lesser LDL goals over a much longer period of time may be equally efficacious. Indeed, this consideration is well recognized by the NCEP in its last set of guidelines, with its different LDL goals depending on the likelihood of the presence of ATD [11]. What is needed is a long-term angiographic trial to determine what level of lipids needs to be attained to achieve long-term plaque stabilization/regression.

The author's current practice, in ATD patients, is to lower LDL levels to below 80 mg/dl (based on the precipitation method of HDL measurement) for at least two years, and to maintain them there if HDL levels are very low—i.e., less than 30 mg/dl (0.8 mmoles/L). However, this goal can be difficult to achieve and maintain, so that after two years, if HDL is high enough, then the author treats the patient's lipids to maintain a CRF of 0.49 or less, since this goal is easier to achieve than the LDL goal of 79 mg/dl (2.0 mmoles/L). However, even a CRF goal of 0.49 or less can be hard to achieve and so an optional CRF goal of 0.59 or less is acceptable since, in the absence of cigarette smoking, ATD events are rare when the CRF is 0.59 or less [1].

*William Bolden, MD, personal communication

Conclusions

This paper offers an answer to the question of whether or not there is a lower threshold for LDL lowering, beneath which there is no further cardiovascular benefit for additional LDL lowering and/or HDL raising. This paper provides evidence that the threshold for LDL lowering, at least for the first several years beyond the initiation of therapy, is 79 mg/dl (1.8 mmoles/L) based on the indirect method of HDL measurement or 69 mg/dl (1.7 mmoles/L) based on the direct method of HDL measurement. LDL lowering below this threshold does not result in additional cardiovascular benefit, at least as evidenced by plaque non-progression. This paper also shows that when this LDL threshold is reached, further modification of the atherogenic potential of LDL, whether by additional LDL lowering or by HDL raising, does not provide additional cardiovascular benefit. Hence, lipid predictors that include both LDL and HDL, such as the CRF, offer no improved prediction of plaque non-progression, although the target goal of CRF is easier to achieve than that of LDL. These findings are specific to the ATD population and should not be generalized to the general dyslipidemic populations who have not yet developed clinical ATD.

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