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Original Article

Lipid Risk Factors in Atherothrombotic Disease: Is the Cholesterol Retention Fraction Better than Low-density Lipoprotein Cholesterol?

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ABSTRACT

Introduction: *In order to protect patients against atherothrombotic disease (ATD) one must be able to predict the population at risk of ATD. Cigarette smoking, dyslipidemia, and hypertension are the chief causal ATD risk factors. The chief causative factors in the lipid portion of ATD risk are low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol. The former has atherogenic properties, while the latter has anti-atherogenic properties. The Cholesterol Retention Fraction (CRF) is defined as (LDL-HDL)/LDL. This article compares the CRF with LDL-cholesterol (LDL-c) in its ability to predict the population at risk of ATD and to guide dyslipidemic therapy.*

Results*: If the CRF and LDL-c data from the General Population are divided into sextiles, then in the highest CRF and LDL-c sextiles, wherein are located the characteristics of most ATD patients, the CRF has more patients than does LDL-c, and the patients in those CRF sextiles in the ATD Population are younger than those in the comparable LDL-c sextiles. In the lowest CRF and LDL-c sextiles the CRF has more patients in the General Population than does LDL-c, and in the ATD Population, those patients characterized by the CRF are older than the comparable LDL-c patients.*

If the various lipid sextiles in the General Population are graphed against octiles of systolic blood pressure (SBP), and if the prevalence of ATD in each of those CRF-SBP cohorts is determined, then in the case of the CRF, the lowest prevalence of ATD is located in the cohorts where the CRF and SBP are lowest and the prevalence of ATD increases as the CRF-SBP cohorts radiate out from this area of low ATD prevalence. This phenomenon is not seen with LDL-c

Kaplan-Meier curves can be drawn for the CRF and LDL-c sextiles in the General Population in terms of the cumulative ATD cases per sextile with respect to age. In the four highest sextiles, the Kaplan-Meier curves for LDL-c lie to the left of the comparable sextiles for the CRF, a finding interpreted to mean that the CRF is more protective against an earlier age on ATD onset.

In a previously published analysis of eight published angioographic regression studies, angiographic outcomes were equivalent when the lowest CRF or LDL-c goals were achieved. However, in POSCH (the Program on the Surgical Control of the Hyperlipidemias) changes in the CRF predicted angiographic plaque outcome with 100% accuracy. This was not true for LDL-c.

Conclusions: *CRF has been compared to LDL-c in the prediction of the population at risk of ATD and found to be superior. In predicting angiographic outcome in POSCH the CRF was also shown to be superior to LDL-c. In eight angiographic regression trials, when the lipid goal of achieving the lowest sextile is reached, angiographic outcomes are equivocal for the CRF and LDL-c.. The CRF is therefore deserving of further evaluation as the lipid predictor of choice,*

Keywords:

1. INTRODUCTION

The lipid underpinning of atherothrombotic Disease (ATD) around the world has rested upon low-density lipoprotein cholesterol (LDL-c). This emphasis was high-lighted by the National Cholesterol Education Panel in 1991 (1) and by others in the years since then (2-7). This emphasis on LDL-c has pushed high-density lipoprotein cholesterol (HDL-c) into the background—indeed, in its original publication in 1988, the National Cholesterol Education Panel only mentioned HDL-c once. (8) It is clear that LDL-c represents the cholesterol entering the artery wall (9) while HDL-c represents the cholesterol being removed from the artery wall by reverse cholesterol transport. (10) It is logical to expect that a ratio between LDL-c and HDL-c would be a superior predictor than either LDL-c or HDL-c individually. This is why W.B, Kannel, MD, of the Framingham Heart Study used a ratio between total cholesterol (CT) and HDL-c as his favored lipid predictor. (11) Kannel was forced to use the CT:HDL-c ratio because the

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Framingham Heart Study for its first quarter century used non-fasting blood for analysis, thus invalidating any calculation of LDL-c. (12)

The Bowling Green Study of the Primary and Secondary Prevention of Atherothrombotic Disease was established by the author on 4 November 1974 and continued until 1 January 2019. During the course of this investigation, the author evolved a slightly different lipid predictor. This new lipid predictor is termed the Cholesterol Retention Fraction (CRF, defined as [LDL-HDL]/LDL). The evolution of the CRF has been described in multiple publications (13-17) and in brief estimates the amount of cholesterol, in theory, that accumulates within the artery wall. It is the purpose of this paper to compare the CRF with LDL-c in the pathogenesis of ATD.

2. MATERIALS AND METHODS

The details of the Bowling Green Study have been discussed elsewhere. (13-14) Very briefly, the Bowling Green Study was begun on 4 November 1974 when the author set up his practice of family medicine in Bowling green, the county seat of Wood County, in northwest Ohio. As a family physician the author cared for people of all ages, from birth to very old age, and both sexes. The author had—and still has-- a special interest in the prediction of the population at risk of ATD and he knew that to make such predictions, he would need to establish an age-sex database of the known ATD risk factors, with as much data as possible obtained earlier in life, before his patients developed clinical ATD events. Hence, the author began measuring blood pressures and heights, and weights on all patients, each and every time they presented to his office. Whenever practical he obtained fasting blood for lipid analysis and a two hour postprandial blood glucose level. Prior to 1 January 1978, the lipid panel was limited to CT and triglycerides, but after that date, HDL-c became available, and with it the ability to calculate LDL-c on the basis of the Friedewald formula. (18) In 1983, when the paramount importance of cigarette smoking in the pathogenesis of ATD became apparent to the author, the author began collecting tobacco use data on all patients aged 15 years and older—and in the early 1990's, on all patients aged 10 years and older. All of this data was incorporated into an age-sex database for the General Population.

In the 1980's and 1990's the risk factors for ATD were not well understood—even by the other physicians in Wood County, many of whom resisted the author's research—despite the publications of the Framingham Heart Study. (19-20) Additionally, much of Wood County is rural and populace did not understand the importance of preventive medicine. Indeed, when the author broached the topic of therapy for dyslipidemia –or for that matter cessation of cigarette smoking—patients sometimes left the author's practice. Leaving the author's practice, however, did not ameliorate those ATD risk factors and hence former patients did develop clinical ATD events, at least according to reports by relatives who remained within the author's practice. Moreover, the pharmaceutical armamentarium available to treat dyslipidemia was suboptimal, at least until the late 1980's when statins became available. (In general, the same limitations were present for anti-hypertensive medication.) As a result, even when treated, the various ATD risk factors were often not able to be treated well enough to regress plaque and the patients developed clinical ATD events.

In 1981, enough of the author's patients have developed clinical ATD events to permit the formation of an ATD Population database, separate from the General Population database. These two databases form the basis for the data presented in this manuscript.

3. CAVEAT

Before proceeding, it is necessary to make a very important point. Prior to 1999, the method used to determine HDL-c levels was the precipitation method. In early 1999, in the author's local hospital laboratory, the manufacturers of the auto-analyzers that measure lipids decided to change the methodology of HDL-c measurement from the precipitation method to the enzymatic method—without telling the medical profession in general. The problem with this change is that the two different methodologies do not give the same results. Indeed, the enzymzatic method gives an HDL-c value on the order of 10 mg/dl (0.25 mmoles/L) higher than does the precipitation method. Since LDL-c is usually calculated on the basis of HDL-c (by the Freidewald formula), the resultant LDL-c calculation will be on the order of 10 mg/dl (0.25 mmoles/L) lower for the enzymatic method than for the precipitation method. When one uses ratios to determine ATD risk the difference in results is much greater. This is not a trivial point. In 2008 the author reported the case of a 53 year old man, with no obvious ATD risk factors and no reason to measure his lipids, who sustained an acute myocardial infarction while working in another town. The local hospital measured his lipids on admission and sent the results to the author. That hospital utilized the enzymatic method of HDL-c measurement. The lipid panel obtained at the other hospital was mildly abnormal, but when converted to the precipitation-method equivalent was significantly more abnormal and the myocardial infarction occurred precisely when it was predicted to occur. (21) The author's database is constructed on the basis of lipid panels obtained using the precipitation method or its equivalent conversion from the enzymatic method, and this will need to be taken into account when the author's findings are applied to patients of other physicians.

4. RESULTS

The General Population database contains data on lipids, systolic blood pressure (SBP), and cigarette smoking status, as well as the patients who were known/not known to have developed clinical ATD events. It is thus possible to place CRF

values versus SBP values on a graph and then to determine the prevalence of ATD in each cohort. A similar graph can be made for LDL-c versus SBP cohorts. These graphs are presented in Figure I-A (CRF-SBP cohorts) and Figure I-B (LDL-c-SBP cohorts). Green coloration is given to all cohorts with ATD prevalence of 14% or less; yellow coloration, to cohorts with an ATD prevalence of 15-24%; and red coloration to cohorts with an ATD prevalence of 25% or greater. Figure I-A shows a pattern similar to a sunset, with the green cohorts in the southwest corner, with the yellow cohorts radiating out like the sunlight from the setting sun, and with the red cohorts covering the rest of the graph, much as the darkness of the night covers the rest of the sky. A similar pattern is not seen in Figure I-B.

Kaplan-Meier curves can also be generated for the General Population, utilizing the cumulative ATD incidence for each CRF sextile and for each LDL-c sextile. (See Table I A-B) These curves are seen in Figure II A-F. Definitions for each LDL-c or CRF sextile are given in Table II. Table I-A gives the actual data points for the Kaplan-Meier curves for CRF, while Table I-B gives the similar data points for LDL-c. These curves represent the cumulative prevalence of ATD with respect to age group for each CRF and LDL-c sextile. In general, the curves for each sextile (III-VI) demonstrate that the LDL-c curves lie to the left of the corresponding curves for CRF, whereas the curves for CRF lie to the left of the curves for LDL-c in sextiles I-II. It will be noted that the distance between the curves decreases progressively as the sextiles decrease from VI to I, though in sextile I, the curves essentially intertwine until very old age.

Table III-A gives the distribution of CRF sextiles in terms of LDL-c sextiles in the General Population. The general pattern the emerges is that higher levels of LDL-c sextiles are associated with higher CRFsextiles, and conversely, the lower LDL-c sextiles are associated with lower CRF sextiles. Similarly, Table IIIB gives the distribution of LDL-c sextiles in terms of CRF sextiles and the results are similar. Taken together, sextiles IV-VI of the CRF database encompass 38% of the population and sextiles III-VI of the LDL-c database encompass 50% of the population. (The reason for using sextile III in the high risk LDL-c group is that this sextile contains the most patients in the ATD Population.)

Table IV gives the average age of ATD onset in terms of CRF and LDL-c sextiles. In general, at any level of LDL-c, a higher CRF portends an earlier average age of ATD onset and a lower CRF portends an older average age of ATD onset. Furthermore, examining the average age of ATD onset for each of the CRF sextiles and LDL-c sextiles gives a linear decrease in average age of ATD onset with increasing sextile number. However, the slope for the CRF is greater than that for LDL-c. This is illustrated in Figure III.

This data can be illustrated by stratifying LDL-c sextiles by CRF sextiles. This is seen in Figure IV. Here the LDL-c sextiles are stratified by CRF sextiles, and the data in each cohort is given in terms of the average age of ATD onset. The average age of ATD onset is color coded as follows: the red cohorts are those in which the average age of ATD onset is 64 years or less; the yellow zone, 65-74 years of age; and the green zone, 75 years of age or higher. This figure represents all comers with respect to cigarette smoking status. It will be apparent that at any level of LDL-c, in general, younger average ages of ATD onset (red zone) are found in the highest CRF ranges and the older average ages of ATD (green zone) are found in the lowest CRF ages.

Another approach is to determine the incidence of each CRF or LDL-c sextile in the General Population and to compare that with the ATD incidence per individual sextile. These data are presented in Tables III A-B (numbers in blue coloration) for the General Population and in the "$\sum$" rows in Tables I A-B for the ATD incidence per sextile, and in Figures V-A for the CRF and V-B for LDL-c. These data reveal that the lower sextiles contain more General Population patients than do the higher sextiles, but the lower sextiles have fewer ATD patients than do the higher sextiles. Conversely, the higher sextiles have fewer General Population patients, but more ATD patients. The difference is that the higher CRF sextiles in the General Population have more patients than do the higher sextiles of LDL-c and that the lowest sextile for CRF has many more patients than the comparable sextile for LDL-c.

Finally, the emphasis on LDL-c has been bolstered by the failure of HDL-c raising therapies to impact plaque regression. (22-23) However, this emphasis has ignored the findings from the Program on the Surgical Control of the Hyperlipidemias (POSCH). (24) In this study (effect of partial ileal bypass), the CRF predicted plaque outcome with 100% accuracy. If the CRF at one year fell, even minutely, taken the angiogram at three years always revealed plaque stabilization/regression. Conversely, if the CRF rose, even minutely, at one year, the angiogram at three years always revealed plaque progression. This finding is not seen when LDL-c is used instead of CRF. (See Table VA and VB.)

This finding is compatible with another POSCH finding. If one graphs the changes in LDL-c against HDL-c in a 6x6 factorial, as portrayed in Figure VI, and color-codes the plaque changes in terms of pure stabilization/regression in green, mixed plaque response in yellow, and pure plaque progression in red, then it is clear that plaque progression can occur if LDL-c levels fall, so long as HDL-c fall even more. It is also clear that plaque stabilization/regression can occur even if LDL-c levels rise, so long as HDL-c levels rise even more. See Figure VI.

In the year 2000, the author reported a meta-analysis of eight published angiographic regression trials (14), discussing the treatment of CRF and systolic blood pressure (SBP) on the angiographic outcome of extant plaque. However seven of the eight trials had associated LDL-c data and so can be analyzed in terms of CRF versus LDL-c. Figures VII A-G show the nested cohorts for the end-of-trial CRF and LDL-c in terms of plaque

progression. Figure VII-A shows the outcomes for the Program on the Surgical Control of the Hyperlipidemias (POSCH) (24); Figure VII-B, for the National Heart Lung and Blood Institute's Type II Coronary Intervention Trial (NHLBI (25)); Figure VII-C, for the Familial Atherosclerosis Treatment Study (FATS) (26); Figure VII-D, for the Lipoprotein and Coronary Atherosclerosis Study (LCAS) (27); Figure VII-E, for Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-1) (28); Figure VII-F, for the Lopid Coronary Angiography Trial (LOCAT) (29); and Figure VII-G for The Effects of regular Exercise and Low Fat Diet on the Progression of Coronary Artery Disease (the Heidelberg Study) (30). The nested cohorts show elevated risk for end-of-trial CRF values > 0.70 and end-of-trial LDL-c values > 125 mg/dl (3.1 mmoles/L), show borderline risk for CRF values of 0.60-0.69 and LDL-c values of 100-124 mg/dl (2.5-3.0 mmoles/L), and show minimum risk for CRF values < 0.59 and LDL-c values < 99 mg/dl (2.4 mmoles/L). The color code for elevated risk is red; for borderline risk is yellow; and for minimum risk is green. Data from the Saint Thomas Atherosclerosis Regression Trial (STARS) is excluded due to lack of LDL-c data—CRF data was requested and that was what was sent. (31)

The percentage of patients showing plaque progression in the minimum risk zones for POSCH and NHLBI is identical and virtually identical for LCAS and LOCAT. In the minimum risk zone for FATS, there is more progression for the CRF than for the LDL-c cohorts whereas in PLAC-1 the opposite is true. The numbers in the Heidelberg Study are too small to be considered.

5. DISCUSSION

"If one can't predict, one can't protect," and "The better one can predict, the better one can protect." These two common sense axioms are at the heart of this manuscript. In a prior publication the author presented data to accurately predict the population at risk of ATD (16) and in a subsequent publication he presented evidence to support contention that cigarette smoking was the chief risk factor for early onset ATD, followed closely by dyslipidemia, and more distantly by hypertension. (17) The usual measure of dyslipidemia is LDL-c. This manuscript presents evidence that the CRF is equivalent to or superior to LDL-c as a measure of the lipid component of ATD risk. This makes sense since the CRF contains two risk factors, whereas LDL-c per force consists of only one risk factor, and two risk factors should predict better than just one.

Assuming that the goal of dyslipidemic therapy is not to "put statins in the drinking water," then it is important to be able to accurately predict the population at risk of ATD. This is initially done by determining the at risk population. In Figure I-A, the low risk population (risk of ATD of 14% or less) is clearly indicated in the green cohorts; the medium risk population (15-24% risk) is clearly indicated in the yellow zone; and the high risk population (25% or greater) is clearly indicated in the red zone. Such a clear demarcation is not seen with LDL-c. (See Figure I-B.)

Examining the Kaplan-Meier curves in Fi8gures II A-F, one notes that the curves for LDL-c lie to the left of the curves for CRF in sextiles III-VI. The author interprets this to show that the anti-atherogenic properties of apolipoprotein A-I (as manifested by HDL-c) delay the onset of ATD. The finding that the CRF curve for sextile II lies to the left of the curve for LDL-c is interpreted to show equivalency of CRF and LDL-c since the curves do not really separate until later in life. The author considers the curves for CRF and LDL-c in sextile I to be virtually super-imposable, at least until very late in life.

Figures V-A and B show the incidence of each CRF and LDL-c sextile in the General Population database, as contrasted with the ATD incidence per sextile. It is clear that while the lower LDL-c sextiles contain the most patients and the higher LDL-c sextiles contain the least patients, the lowest incidence of ATD patients is in the lower LDL-c sextiles and the highest incidence of ATD patients is in the higher LDL-c sextiles. A somewhat similar pattern is seen for CRF, but there are many more patients in sextile I of the General Population and population incidence of the higher CRF sextiles in the General Population database does not fall off as much for the CRF as compared to LDL-c. Thus CRF predicts more ATD patients in the higher sextiles than does LDL-c and the CRF and it predicts more people in the lowest sextile, people who are older at age of ATD onset (See Figures II A-F.)—or who are cigarette smokers (data not shown).

Another way to determine the superiority of CRF over LDL-c is to determine the average ages of ATD onset per sextile. Table IV shows that the average age of ATD onset is younger for its higher sextiles and older for its lower sextiles than for the comparative LDL-c sextiles. (See Figure III.) This would appear to provide support for the superiority of CRF over LDL-c. Additionally, Figure IV shows that in general at any level of LDL-c, the patients with the youngest average age of ATD onset are in the highest CRF sextiles, whereas those with the oldest average age of ATD onset are in the lowest CRF sextiles.

Finally, the findings from POSCH show that whereas the CRF perfectly predicts plaque outcome angiographically, LDL-c does not. (See Tables V A-B.) The main difference in the prediction of plaque outcome appears to be that plaques can progress even if LDL-c levels fall as long as HDL-c levels fall even more, and this can occur in 40% of cases. This is important since it could explain the residual risk after statin therapy. As noted, this is not a problem when the CRF is used as the lipid predictor. Other studies have not shown this finding, however, and this discrepancy may be due to the trial intervention. By using the partial ileal bypass, POSCH has done the only angiographic regression trial that does not involve medications, thus avoiding any possible interference of adverse and/or pleomorphic effects of medications. (See Figure VI.)

The author interprets the angiographic regression data to show that when the minimum risk zone is achieved by the trial's intervention, then the results using the CRF are equivalent to those using LDL-c. This finding is important when LDL-c treatment strategies can not achieve a treatment goal of < 99 mg/dl.

The strength of this manuscript is that, for that data related to the author's medical practice, it represents the findings of a single medical practitioner who has been in place for a very long period of time, who has evaluated patients of all ages and both sexes, and who is dedicated to the primary and secondary prevention of ATD. The weakness of the trial is that full follow-up is not available on all of his patients. However, the finding that the author's data are supported by published international research is reassuring as to the validity of his findings.

6. CONCLUSIONS

The author has presented evidence that a lipid predictor such as the CRF that encompasses both LDL-c and HDL-c is the equivalent of or superior to a predictor that uses LDL-c as a stand-alone predictor. This contention should be evaluated in studies with larger databases and more complete follow-up.

Figure I-A: CRF vs SBP in BGS Gen Pop, Σ Cigarettes SBP: Σ, Σ Male & Female:

	≤ 118	120	130	140	150	160	170	≥ 180
≥ 0.80	19 73 26%	35 103 34%	32 81 40%	22 63 35%	10 20 50%	6 15 40%	4 0%	4 5 80%
0.75	25 113 22%	32 107 30%	26 82 32%	16 60 27%	10 25 40%	9 22 41%	6 9 67%	4 8 50%
0.70	22 137 16%	28 116 24%	24 78 31%	23 74 31%	7 20 35%	12 28 43%	2 5 40%	5 8 63%
0.65	18 170 11%	25 118 21%	20 75 27%	13 47 28%	7 22 32%	7 14 50%	2 4 50%	4 5 80%
0.60	14 138 10%	17 90 19%	12 43 28%	15 41 37%	4 10 40%	3 5 60%	1 3 33%	4 7 57%
≤ 0.59	52 655 8%	36 284 13%	25 118 21%	27 81 33%	17 44 39%	10 25 40%	3 9 33%	2 11 18%

SBP

CRF means Cholesterol Retention Fraction

SBP means Systolic Blood Pressure

BGS means Bowling Green Study

Figure I-B: LDL vs SBP: Original Logs, ΣMale & Female: Σ Cigarettes, BGS ATD pop : Σ

LDL	≤ 118	120	130	140	150	160	170	≥ 180
≥200	14 826 59	18 1,057 59	20 1,213 61	12 760 63	8 487 61	8 519 65	2 160 80	10 717 72
175	13 783 60	24 1,478 62	25 1,626 65	16 1,056 66	7 433 62	8 511 64	4 269 67	13 866 67
150	30 1,993 66	35 2,003 57	24 1,469 61	25 1,716 69	16 988 62	19 1,318 69	11 826 75	13 847 65
125	31 1,805 58	50 3,264 65	44 2,903 66	38 2,427 64	17 1,110 65	18 1,252 70	9 614 68	13 839 65
100	36 2,460 68	32 2,033 64	30 1,879 63	19 1,145 60	18 1,196 66	13 873 67	5 315 63	10 731 73
≤ 99	27 1,728 64	21 1,384 66	19 1,335 70	19 1,231 65	9 634 70	4 308 77	4 318 80	7 465 66

SBP

LDL means Low Density Lipoprotein

SBP means Systolic Blood Pressure

BGS means Bowling Green Study

ATD means Atherothrombotic Disease

Figure II-A: Cumulative ATD Incidence per Sextile BGS Gen Pop ∑∑ Cigarettes Sextile VI

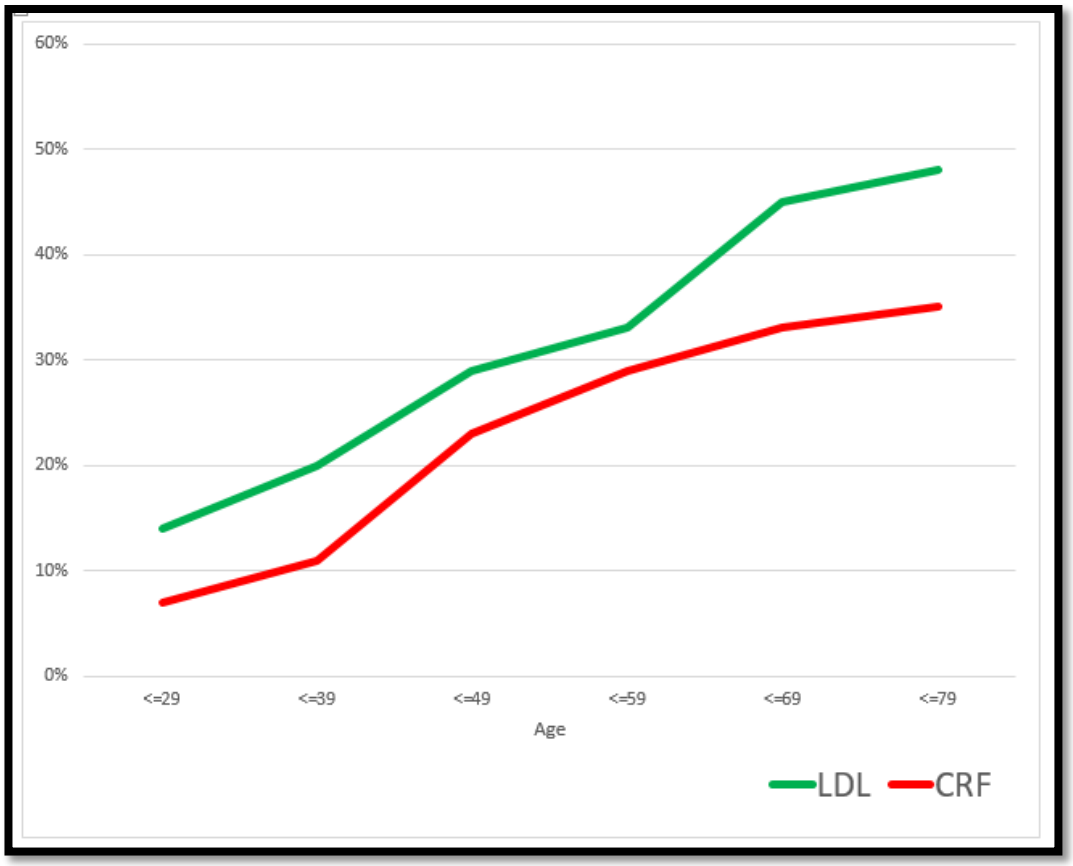


Figure II-B: Cumulative ATD Incidence per Sextile BGS Gen Pop ∑∑ Cigarettes Sextile V

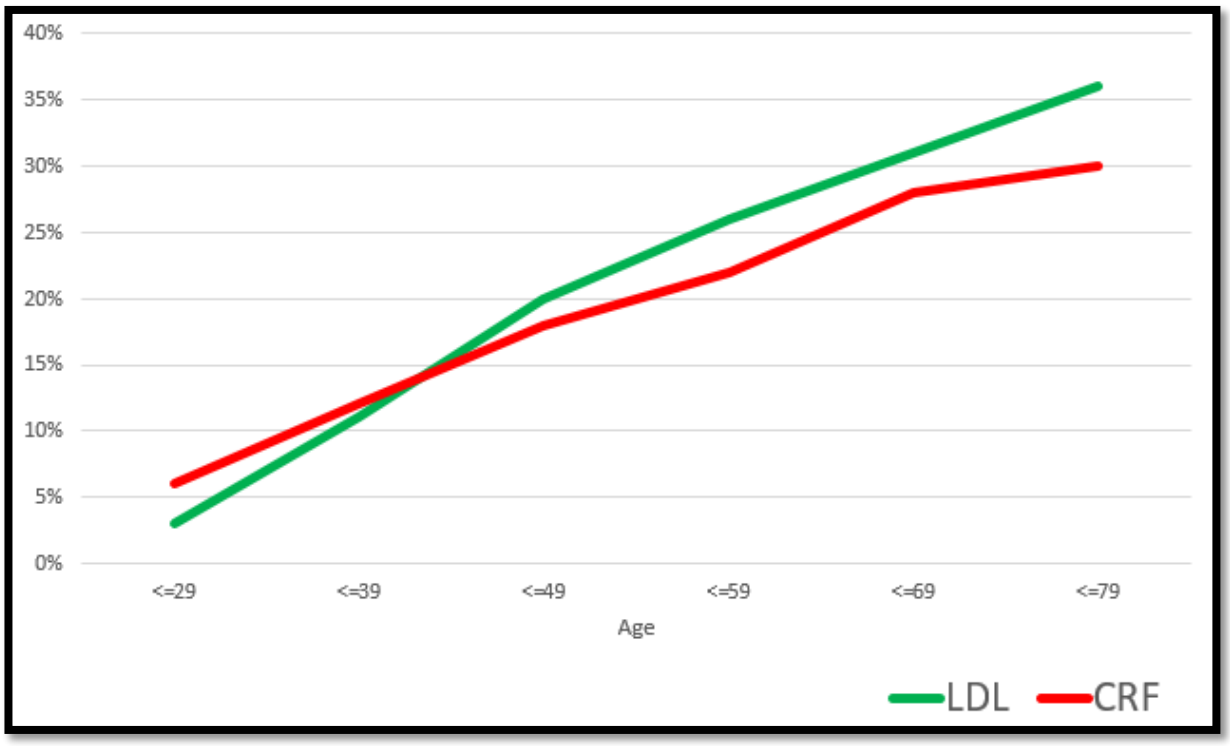


Figure II-C: Cumulative ATD Incidence per Sextile BGS Gen Pop ∑∑ Cigarettes Sextile IV

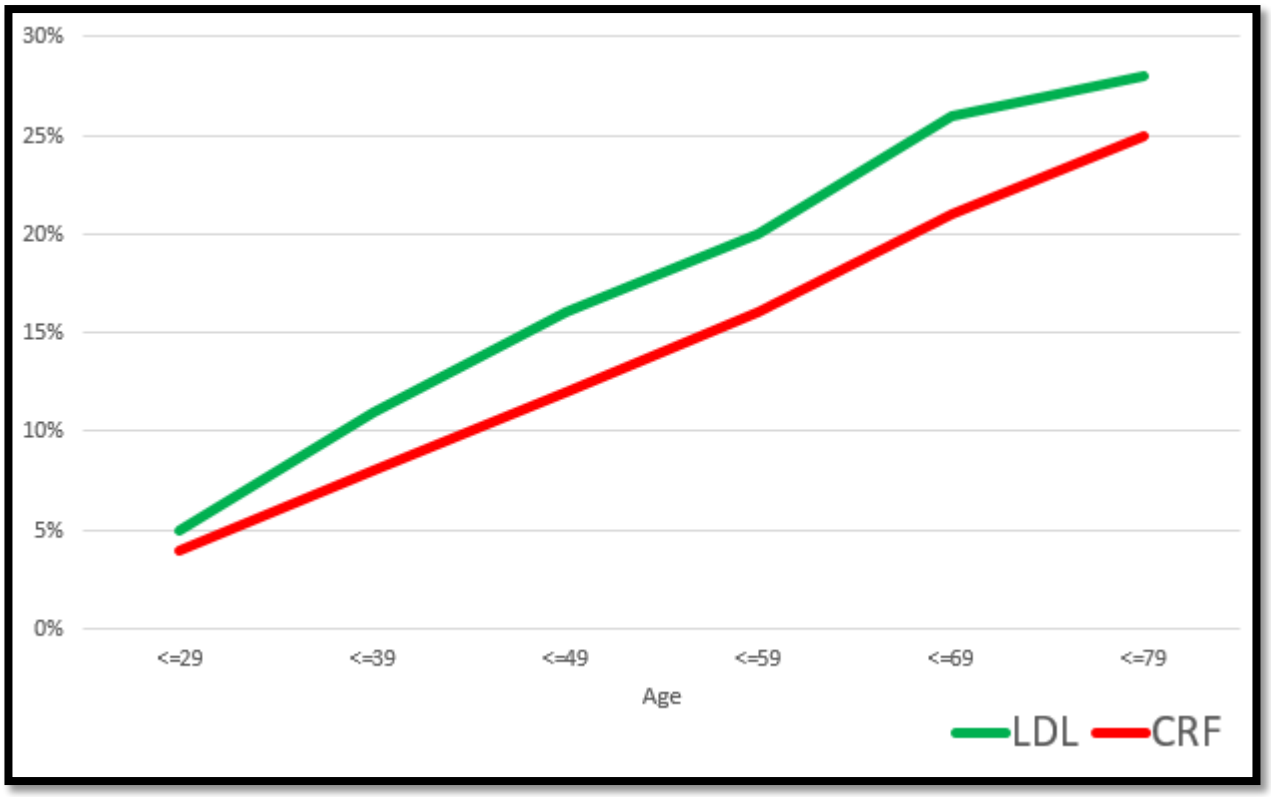


Figure II-D: Cumulative ATD Incidence per Sextile BGS Gen Pop ∑∑ Cigarettes Sextile III

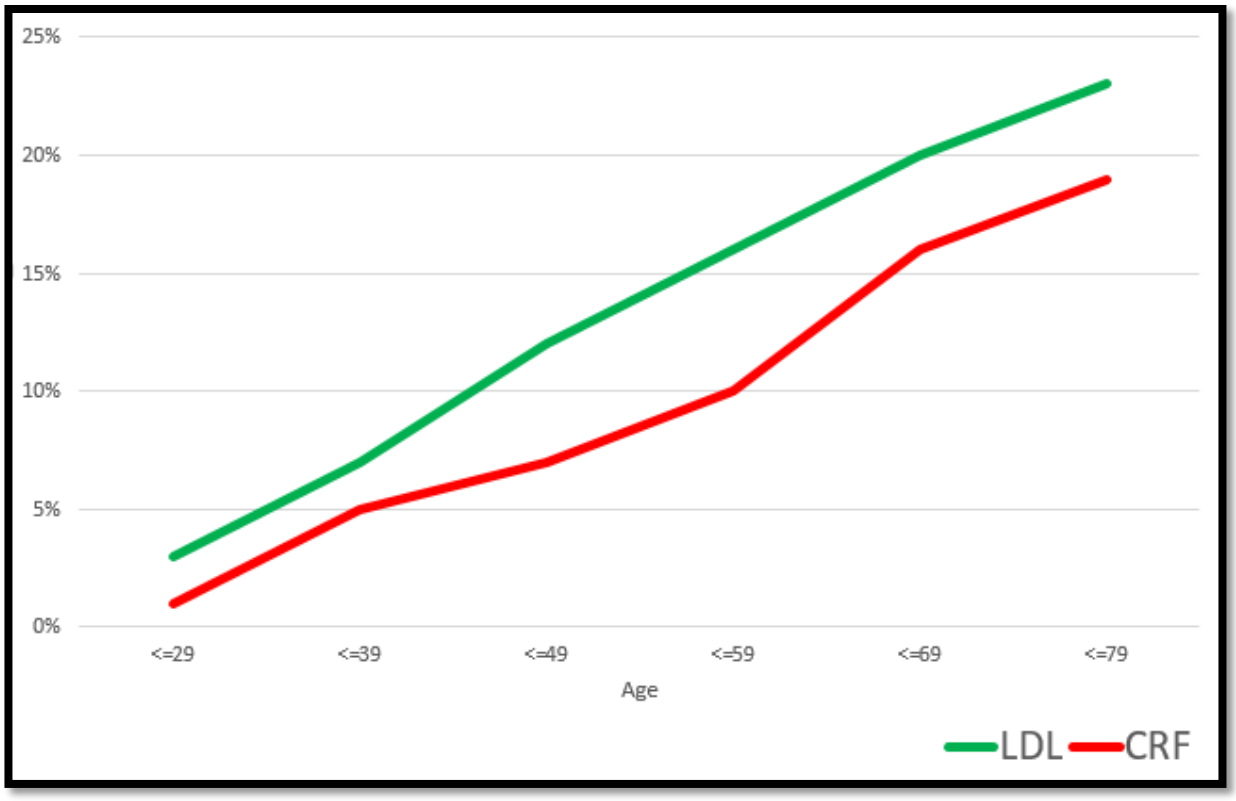


Figure II-E: Cumulative ATD Incidence per Sextile BGS Gen Pop ∑∑ Cigarettes Sextile II

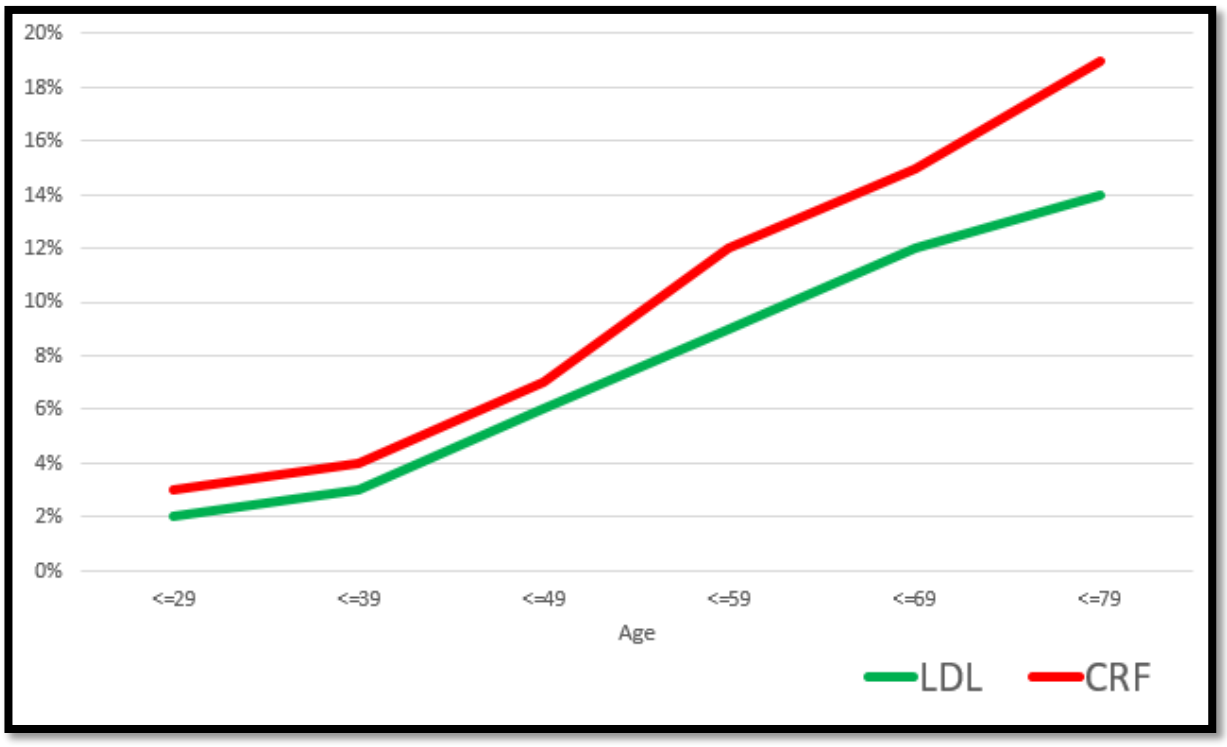


Figure II-F: Cumulative ATD Incidence per Sextile BGS Gen Pop ∑∑ Cigarettes Sextile I

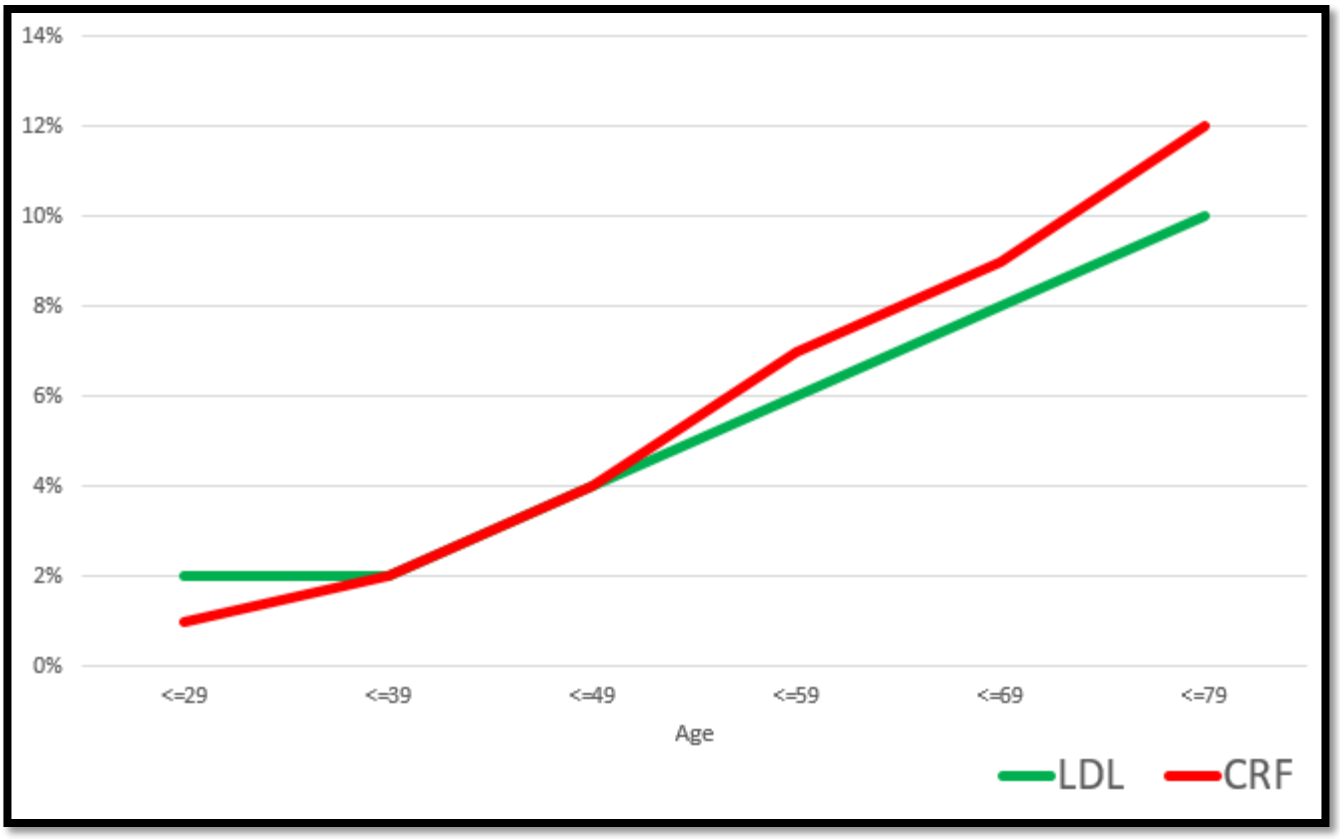


Figure III: Ave Age of ATD Onset w/ CRF and ∑∑ ATD Pop ∑∑ Cigarettes

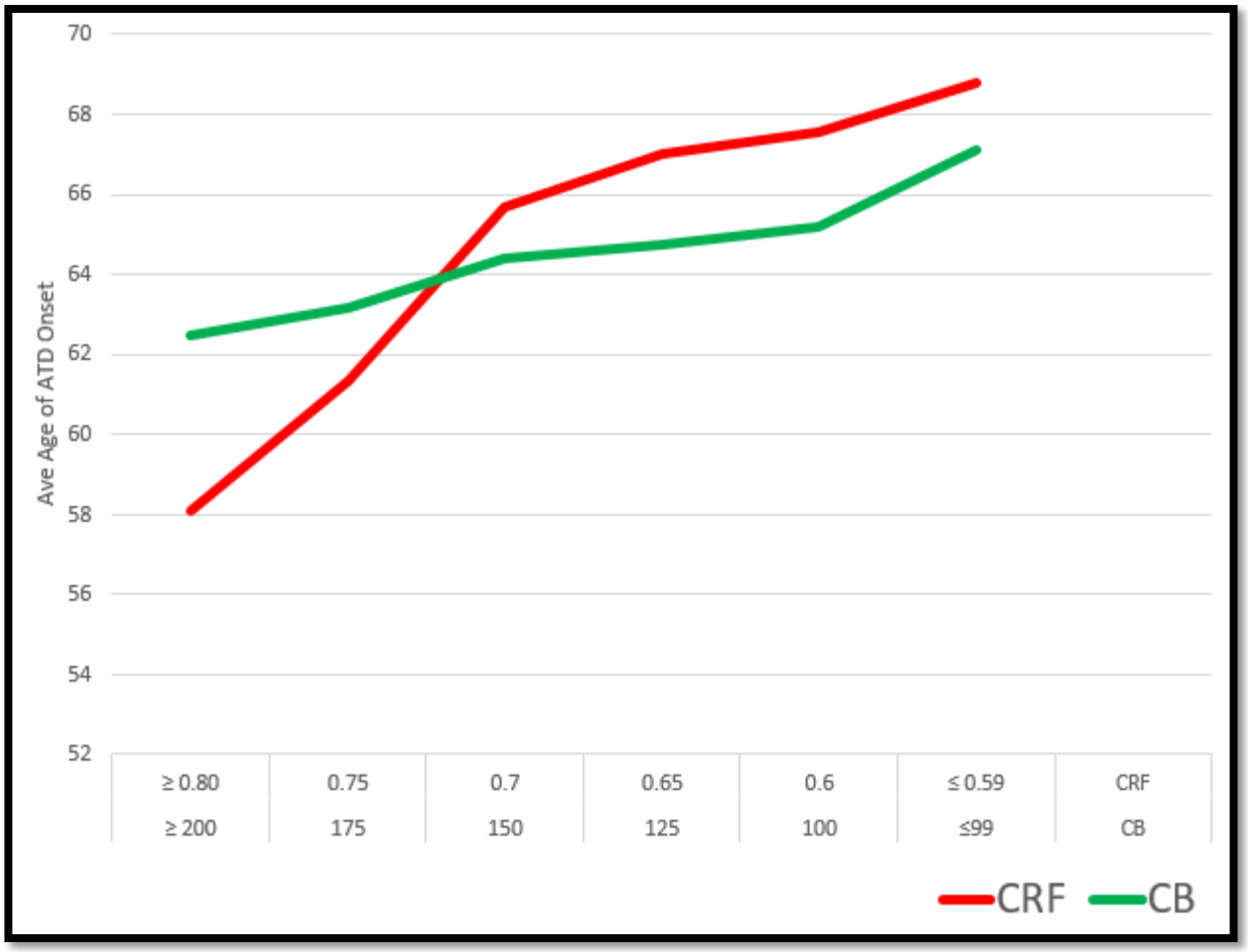


Figure IV: LDL vs CRF: Original Logs, ΣMale & Female : Σ Cigarettes, BGS ATD pop : Σ

LDL	≥ 0.80	0.75	0.70	0.65	0.60	≤ 0.59
≥ 200	50 2,923 58	20 1,308 65	15 1042 69	5 323 65	1 58 58	2 154 77
175	38 2,133 56	27 1,718 64	19 1,327 70	14 903 65	7 511 73	4 292 73
150	45 2,662 59	47 2,886 60	43 2,783 65	17 1,139 67	8 657 82	14 1,077 77
125	19 1,033 54	43 2,567 60	51 3,337 65	39 2,556 66	29 1,924 66	41 2,954 72
100	9 586 65	11 629 57	21 1,285 61	27 1,880 70	28 1,813 65	65 4,300 66
≤99	2 132 66	1 35 35	5 343 69	11 770 70	14 914 65	79 5,324 67

CRF

Figure V-A: ATD incidence per sextile vs Sextile Incidence for Gen Pop CRF ∑∑ Cigarettes

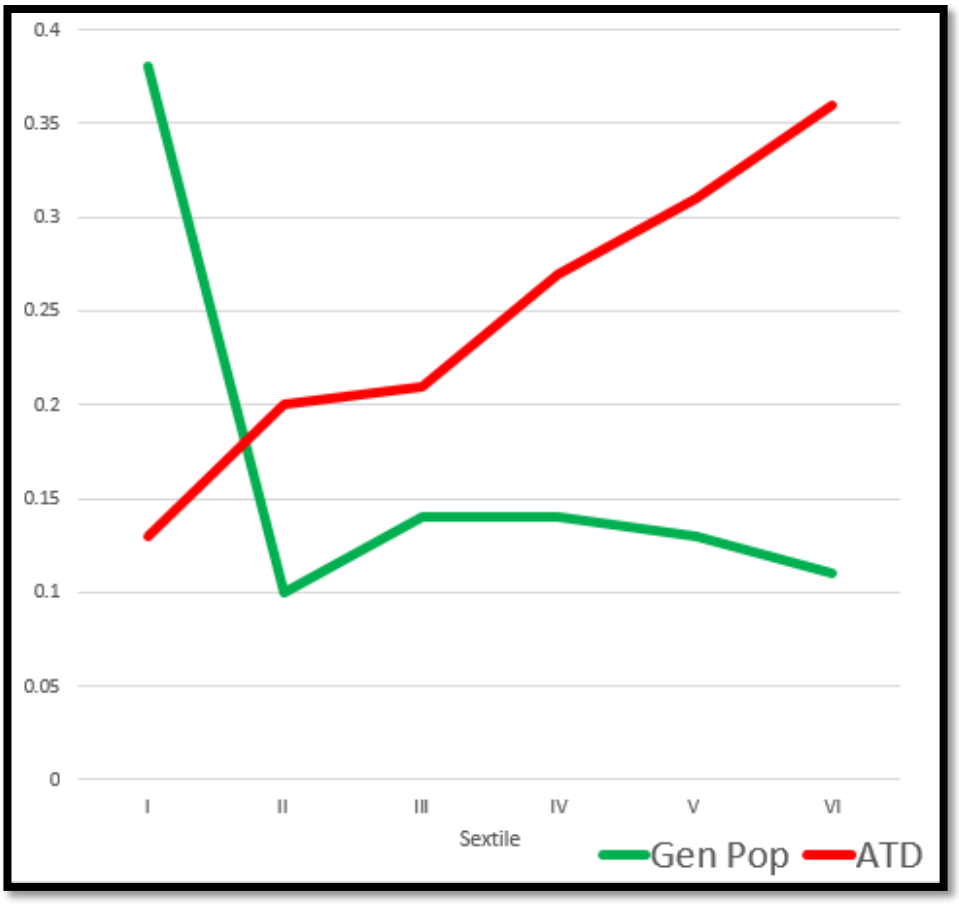


Figure V-B: ATD incidence per sextile vs Sextile Incidence for Gen Pop LDL-c ∑∑ Cigarettes

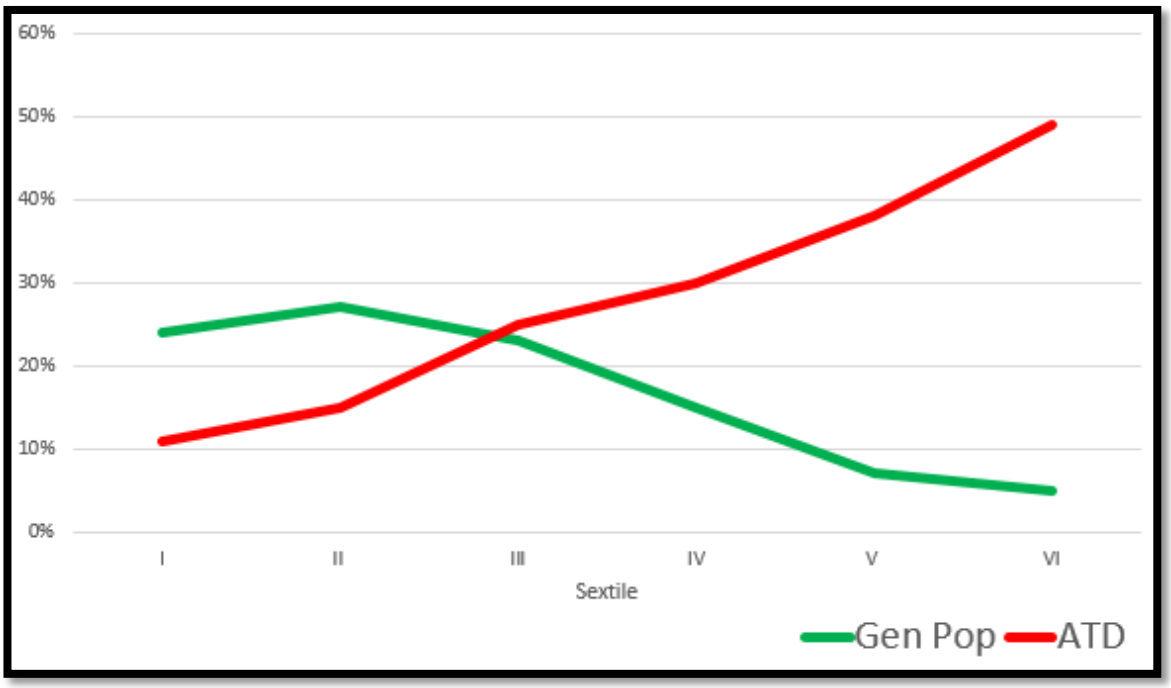
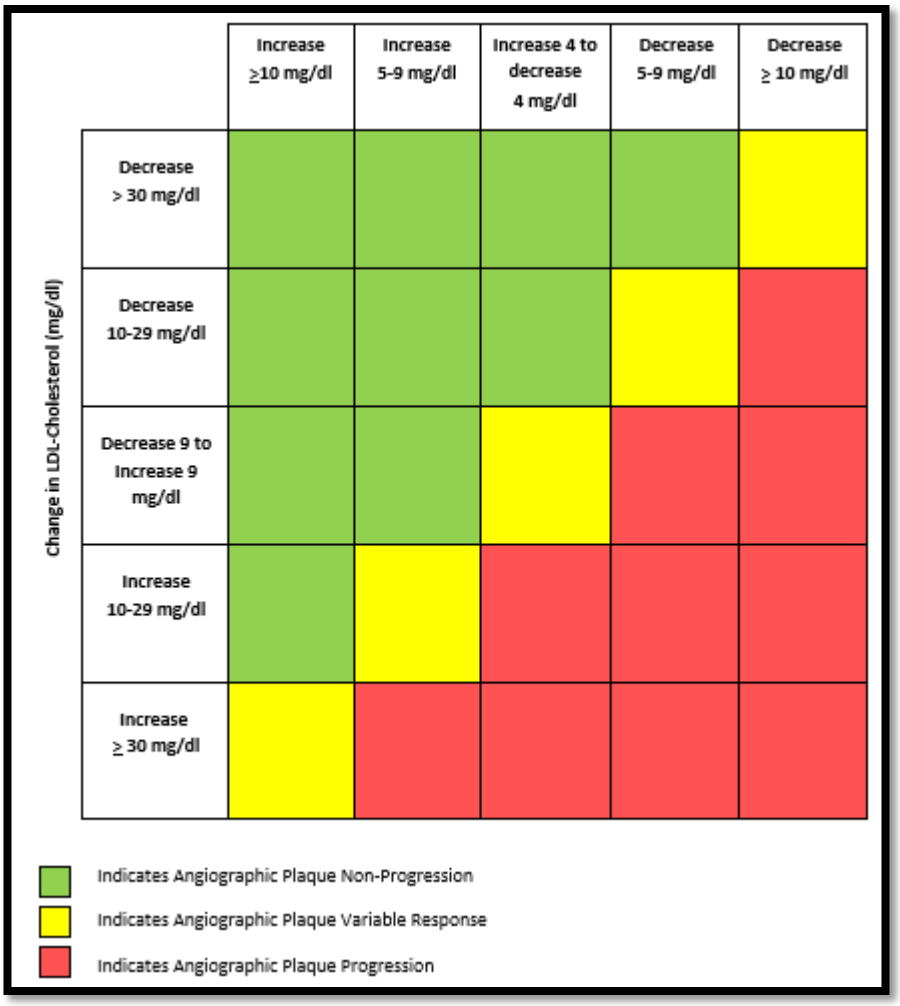


Figure VI: Change in HDL-Cholesterol (mg/dl)



HDL=high density lipoprotein

LDL= low density lipoprotein

Figure VII-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 VII-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 VII-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 VII-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 VII-E: 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 VII-F: CRF vs LDL-c in % Progression Angiographic Outcomes: LOCAT CRF

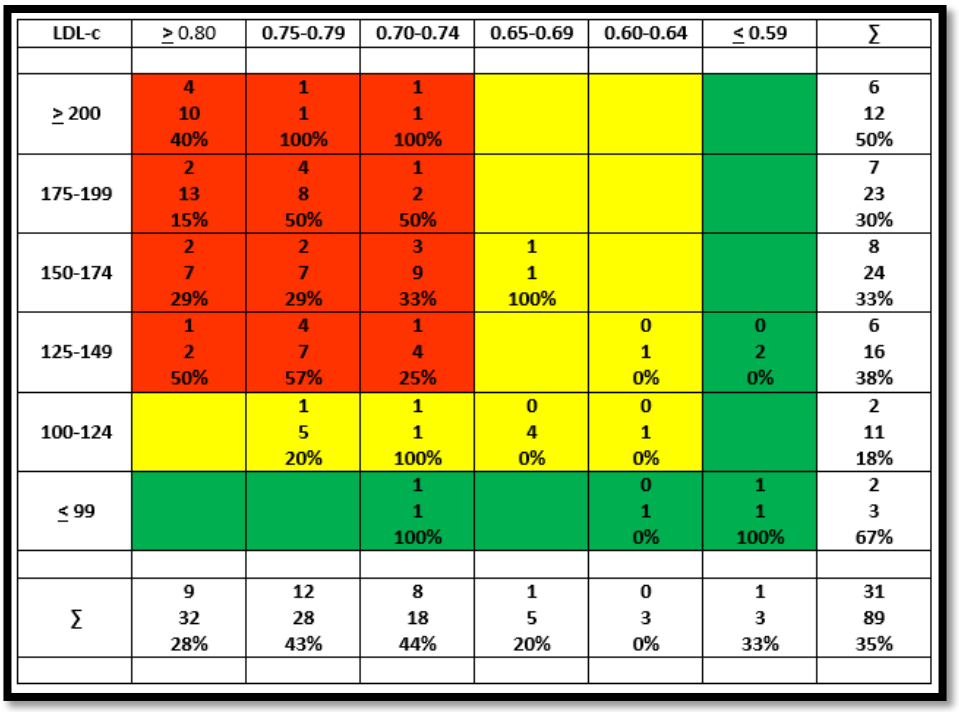
LDL-c	≥ 0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤ 0.59	∑
≥ 200	9 10 90%	1 1 100%					10 11 91%
175-199	13 17 76%	8 12 75%	1 1 100%				22 30 73%
150-174	22 34 65%	29 37 78%	10 18 56%		1 2 50%	1 1 100%	63 92 68%
125-149	17 24 71%	19 40 48%	23 35 66%	12 18 67%	5 9 56%	1 1 100%	77 127 61%
100-124	1 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

Figure VII-G: 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

Table I-A: Cumulative ATD Incidence per CRF Sextile in ∑ Gen Pop ∑∑ Cigarettes CRF

Age Group	≥ 0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤ 0.59	∑
	4	6	6	2	5	9	32
≤ 29	61	94	137	188	156	709	1345
	7%	6%	4%	1%	3%	1%	2%
	16	23	18	13	9	19	98
≤ 39	143	195	234	275	217	928	1992
	11%	12%	8%	5%	4%	2%	5%
	58	54	40	23	19	44	238
≤ 49	251	304	327	339	273	1080	2574
	23%	18%	12%	7%	7%	4%	9%
	95	81	64	38	38	87	403
≤ 59	331	367	401	388	313	1203	3003
	29%	22%	16%	10%	12%	7%	13%
	123	119	96	70	53	119	580
≤ 69	371	428	449	446	343	1268	3305
	33%	28%	21%	16%	15%	9%	18%
	136	136	119	92	67	153	703
≤ 79	387	451	478	476	361	1317	3470
	35%	30%	25%	19%	19%	12%	20%

	140	141	132	103	76	182	774
∑	392	458	493	490	372	1353	3558
	36%	31%	27%	21%	20%	13%	22%

LDL means Low Density Lipoprotein

ATD means Atherothrombotic Disease

CRF means Cholesterol Retention Fraction

Table I-B: Cumulative ATD Incidence Per LDL-c Sextile in ∑ Gen Pop ∑∑ Cigarettes LDL-c

Age Group	≥ 200	175-199	150-174	125-149	100-124	≤ 99	∑
	2	1	5	8	7	9	32
≤ 29	14	33	92	245	436	525	1345
	14%	3%	5%	3%	2%	2%	2%
	7	9	23	27	19	13	98
≤ 39	35	79	209	409	601	659	1992
	20%	11%	11%	7%	3%	2%	5%
	24	26	50	66	44	28	238
≤ 49	83	132	311	569	752	727	2574
	29%	20%	16%	12%	6%	4%	9%
	40	47	83	111	79	43	403
≤ 59	121	182	406	676	844	774	3003
	33%	26%	20%	16%	9%	6%	13%
	74	70	121	148	103	64	580
≤ 69	163	224	467	750	894	807	3305
	45%	31%	26%	20%	12%	8%	18%
	87	88	138	185	125	80	703
≤ 79	180	247	494	796	925	828	3470
	48%	36%	28%	23%	14%	10%	20%
	89	94	157	205	140	89	774
∑	182	250	517	818	948	839	3558
	49%	38%	30%	25%	15%	11%	22%

LDL means Low Density Lipoprotein

ATD means Atherothrombotic Disease

Table- II

Sextile	LDL Cholesterol	CRF
I	≤ 99 mg/dl	≤ 0.59
II	100-124 mg/dl	0.60-0.64
III	125-149 mg/dl	0.65-0.69
IV	150-174 mg/dl	0.70-0.74
V	175-199 mg/dl	0.75-0.79
VI	≥ 200 mg/dl	≥ 0.80

LDL means Low Density Lipoprotein

CRF means Cholesterol Retention Fraction

Table III-A: LDL-c Sextiles Stratified by CRF in ∑ Gen Pop ∑∑ Cigarettes CRF

LDL-c	≥ 0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤ 0.59	∑
≥ 200	102	42	20	12	2	4	182
	56%	23%	11%	7%	1%	2%	5%
175-199	75	72	50	38	11	8	254
	30%	28%	20%	15%	4%	3%	7%
150-174	104	144	125	62	37	45	517
	20%	28%	24%	12%	7%	9%	15%
125-149	73	129	169	174	110	163	818
	9%	16%	21%	21%	13%	20%	23%
100-124	30	58	105	156	157	442	948
	3%	6%	11%	16%	17%	47%	27%
≤ 99	7	13	25	49	54	691	839
	1%	2%	3%	6%	6%	82%	24%
∑	391	458	494	491	371	1353	3558
	11%	13%	14%	14%	10%	38%	

LDL-c means Low Density Lipoprotein Cholesterol

CRF means Cholesterol Retention Fraction

Table III-B: CRF Sextiles Stratified by LDL-c in ∑ Gen Pop ∑∑ Cigarettes CRF

LDL-c	≥ 0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤ 0.59	∑
≥ 200	102	42	20	12	2	4	182
	26%	9%	4%	2%	1%	~ 0%	5%
175-199	75	72	50	38	11	8	254
	19%	16%	10%	8%	3%	1%	7%
150-174	104	144	125	62	37	45	517
	27%	31%	25%	13%	10%	3%	15%
125-149	73	129	169	174	110	163	818
	19%	28%	34%	35%	30%	12%	23%
100-124	30	58	105	156	157	442	948
	8%	13%	21%	32%	42%	33%	27%
≤ 99	7	13	25	49	54	691	839
	2%	3%	5%	10%	15%	51%	24%
	391	458	494	491	371	1353	3558
∑	11%	13%	14%	14%	10%	38%	

LDL-c means Low Density Lipoprotein Cholesterol

CRF means Cholesterol Retention Fraction

Table IV: CRF vs LDL-c in ∑∑ ATD Pop ∑∑ Cigarettes CRF

LDL-c	≥ 0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤ 0.59	∑
	50	20	15	5	1	2	93
≥ 200	2923	1308	1042	323	58	154	5808
	58	65	69	65	58	77	62
	38	27	19	14	7	4	109
175-199	2132	1718	1327	903	511	292	6883
	56	64	70	65	73	73	63
	45	47	43	17	8	14	174
150-174	2662	2886	2783	1139	657	1077	11204
	59	60	65	67	82	77	64
	19	43	51	39	29	41	222
125-149	1033	2567	3337	2556	1924	2954	14371
	54	60	65	66	66	72	65
	9	11	21	27	28	65	161
100-124	586	629	1285	1880	1813	4300	10493
	65	57	61	70	65	66	65
	2	1	5	11	14	79	112

≤ 99	132	35	343	770	914	5324	7518
	66	35	69	70	65	67	67
	163	149	154	113	81	205	871
∑	9468	9143	10117	7571	5877	14101	56277
	58	61	66	67	68	69	65

CRF means Cholesterol Retention Fraction

LDL means Low Density Lipoprotein

ATD means Atherothrombotic Disease

Table V-A: Plaque Outcomes in POSCH w/r CRF CRF

Plaque Outcome	Increase	No Change	Decrease
Non Progression	0 564 0%	0 564 0%	564 564 100%
Progression	163 163 0%	0 163 0%	0 163 0%
Σ	163 727 22%	0 727 0%	564 727 78%

Table V-B: Plaque Outcomes in POSCH w/r LDL-c LDL

Plaque Outcome	Increase	No Change	Decrease
Non Progression	37 564 7%	0 564 0%	527 564 93%
Progression	96 163 59%	1 163 1%	66 163 40%
Σ	133 727 18%	1 727 ~0%	593 727 82%

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