THE PROGRAM ON THE SURGICAL CONTROL OF THE HYPERLIPIDEMIAS (POSCH) AND THE LIPID REGULATORY HYPOTHESIS

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ABSTRACT

Background: The Lipid Regulatory Hypothesis (LRH) states that the best way to regress atherosclerotic plaque is to simultaneously decrease the cholesterol being transported into the arterial wall by low-density lipoprotein (LDL) and increase the cholesterol being removed from the arterial wall, via reverse cholesterol transport, by high-density lipoprotein (HDL). The cholesterol retention fraction (CRF) is defined as (LDL cholesterol minus HDL cholesterol) divided by LDL cholesterol. The Program on the Surgical Control of the Hyperlipidemias (POSCH), which employed partial ileal bypass as the intervention modality, was selected for verification of the LRH and the validity of the CRF.

Methods: POSCH coronary arteriographic plaque progression or non-progression (stabilisation/regression) from baseline to 3 years was stratified on a five-by-five factorial grid with 25 cohort cells combining LDL cholesterol and HDL cholesterol changes from baseline to 1 year following intervention. Predictive capacity for arteriography changes of LDL cholesterol and CRF were compared. Statistics used were logistic regressions.

Results: There were 731 paired arteriographic assessments of individual POSCH patients: 163 progression (22%) and 568 non-progression (stabilisation/regression) (78%). A reciprocal LDL cholesterol and HDL cholesterol relationship represented as a five-by-five factorial showed non-progression above and progression below the dividing diagonal. 100% (163/163) of patients with plaque progression had a rise in their CRF; and 100% (568/568) of patients with plaque non-progression had a fall in their CRF. LDL cholesterol, HDL cholesterol, and CRF were all highly significant predictors of plaque progression and non-progression ($p<0.0001$).

Conclusion: In POSCH, the partial ileal bypass-induced changes in the LDL cholesterol, HDL cholesterol, and the CRF are highly correlated with the sequential coronary arteriography changes of plaque progression and non-progression. This study affirms that individual patient prognosis can be predicted by the magnitude of response to lipid intervention.

Keywords: Atherothrombotic disease, dyslipidaemia, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, plaque stabilisation/regression, plaque progression, the Lipid Regulatory Hypothesis.

INTRODUCTION

The holy grail of interventional lipidology (Harvey Hecht, M.D., used with permission) and preventive cardiology is the prevention of atherothrombotic disease (ATD), defined as atherosclerotic disease with emphasis on the associated thrombosis that produces the acute clinical ATD event (e.g. acute myocardial infarction [MI] and acute cerebral infarction). The basis of ATD is the atheromatous plaque. The efficacy of various therapies for preventing ATD relies on their ability to stabilise or regress that plaque.[1-3] Lipids comprise a significant portion of the ATD plaque. It is well established

that cholesterol is transported to the arterial wall by low-density lipoprotein (LDL) and is removed from the arterial wall by reverse cholesterol transport mediated by high-density lipoprotein (HDL). These two processes have been combined in The Lipid Regulatory Hypothesis (LRH), advanced by Dr. Esko Nikkila in the 1970's[4] and supported angiographically.[5] The LRH states that maximal regression of ATD plaque occurs when therapy to simultaneously lower LDL cholesterol and raise HDL cholesterol is utilised.

In 2000, a meta-analysis of eight published angiographic studies, comprising 2,089 paired serial angiograms, to assess the capability of various forms of dyslipidaemia therapy to stabilise and regress ATD plaque was published.[6] The outcomes of one of these trials, the Program on the Surgical Control of the Hyperlipidemias (POSCH),[1,7-9] will be analysed in relationship to the balance between LDL cholesterol and HDL cholesterol, specifically the cholesterol retention fraction (CRF): (LDL cholesterol minus HDL cholesterol), divided by LDL cholesterol ([LDL-HDL]/LDL). The derivation of the CRF has been reported.[10,11] The CRF has been shown to be an accurate predictor of the population at risk of ATD,[12] and when combined with systolic blood pressure, to accurately guide therapeutic measures to stabilise/regress coronary plaque angiographically.[6] Because the CRF represents the balance between the cholesterol entering the artery wall (LDL) and the cholesterol being removed from the arterial wall by reverse cholesterol transport (HDL), the CRF provides a superior means of monitoring plaque progression versus plaque non-progression (PNP), as is evident from the findings of the National Heart, Lung, and Blood Institute (NHLBI) study[5] and the 2000 meta-analysis.[6] In POSCH[1,7-9] there were marked changes in both LDL (lowering) and HDL (raising), as well as the greatest degree of PNP. Therefore, the CRF would appear to be the ideal tool with which to analyse POSCH results.

METHODS

Study Design

The POSCH trial was selected for verification of the LRH and the validity of the CRF because it had numerically and statistically significant LDL cholesterol reductions and HDL cholesterol elevations,[7] it was a combined clinical and arteriographic study with highly significant outcomes,[1,7] and it showed a reduction in overall mortality[8] that has persisted for 25 years.[9] POSCH was a secondary intervention trial, utilising the partial ileal bypass operation as the intervention modality; both the control and the intervention groups were placed on an American Heart Association diet protocol. POSCH was funded by the NHLBI, in four geographically separate centres, with a study population of 838 (421 surgeries, 417 controls). No patients in this trial dropped out. A single electrocardiogram and enzyme documented MI, and a total plasma cholesterol of at least 5.69 mmol/l or a LDL cholesterol of at least 3.62 mmol/l if the total cholesterol was between 5.17 mmol/l and 5.66 mmol/l were the inclusion criteria; obesity, diabetes, and a left main stem coronary artery (or equivalent) lesion >75% on coronary angiography were the main exclusion criteria. POSCH showed highly statistically significant reductions in mortality and recurrent MIs, angina pectoris, peripheral vascular disease, and the need for coronary artery surgery or angioplasty, as well as coronary arteriography (CA) demonstration of significant reductions in atherosclerotic plaque progression and actual plaque regression. POSCH was the first and only lipid/atherosclerosis trial to use a metabolic surgery procedure as the intervention modality.

Coronary Arteriography

Sequential coronary arteriograms in POSCH were obtained in all patients at baseline and in all available patients at 3, 5, 7, and 10 years postoperatively. Paired arteriograms were read by two-member panels blinded to the temporal sequence of the arteriograms, which were labeled A and B. In addition to reading the percentage of stenosis of individual coronary arterial segments, the readers gave an overall disease comparison score. The POSCH Coordinating Center, using the scores of the arteriography panels and with knowledge of the temporal sequence of a paired set of patient arteriograms, graded the paired arteriograms as demonstrating progression of atherosclerotic plaque disease or non-progression, which included plaque stabilisation and regression. For the current analysis, baseline arteriograms were compared with the first available post-randomisation study (follow-up 3 years up to 5 years). Due to patient attrition, arteriographic follow-up after 3 years diminished and these studies were not available for this assessment of the CRF.

Table 1: Change in low-density lipoprotein (LDL) versus change in high-density lipoprotein (HDL) in angiographic outcomes in POSCH.

Change in LDL cholesterol (mmol/l)	Change in HDL cholesterol (mmol/l)				
	Increase ≥0.26 mmol/l	Increase 0.13-0.23 mmol/l	Increase 0.10 to decrease 0.10 mmol/l	Decrease 0.13-0.23 mmol/l	Decrease ≥0.26 mmol/l
Decrease ≥0.78 mmol/l	70	79	193	56 2	26 9
Decrease 0.26-0.75 mmol/l	11	14	47 2	2 16	10
Decrease 0.23-Increase 0.23 mmol/l	13	19	24 27	11	12
Increase 0.26-0.75 mmol/l	3	5 3	3 35	11	4
Increase ≥0.78 mmol/l	3	2	12	2	5

POSCH: Program on the Surgical Control of the Hyperlipidemias.

Table 2: Comparison of cholesterol retention fraction (CRF) and low-density lipoprotein (LDL) sextiles in predicting percentage of angiographic progression in POSCH.

CRF		LDL (mmol/l)	
Sextile	**% Progression**	**Sextile**	**% Progression**
VI (CRF ≥0.80) n progression n total % progression	 88 137 64%	**VI (LDL ≥5.17)** n progression n total % progression	 26 41 63%
V (CRF = 0.75-0.79) n progression n total % progression	 51 130 39%	**V (LDL = 4.53-5.15)** n progression n total % progression	 44 71 62%
IV (CRF = 0.70-0.74) n progression n total % progression	 16 94 17%	**IV (LDL = 3.88-4.50)** n progression n total % progression	 51 133 38%
III (CRF = 0.65-0.69) n progression n total % progression	 4 79 5%	**III (LDL = 3.23-3.85)** n progression n total % progression	 27 109 25%
II (CRF = 0.60-0.64) n progression n total % progression	 0 66 0%	**II (LDL = 2.59-3.21)** n progression n total % progression	 12 106 11%
I (CRF ≤0.59) n progression n total % progression	 2 223 1%	**I (LDL ≤0.56)** n progression n total % progression	 2 269 1%

POSCH: Program on the Surgical Control Hyperlipidemias.

Table 3: Change in cholesterol retention fraction (CRF) in POSCH.

	Progression versus non-progression			
Change in CRF	**NP**	**P**	**Σ**	**%NP**
Decreased				
≥0.15	277	0	277	100%
0.10-0.14	77	0	77	100%
0.05-0.09	92	0	92	100%
0.01-0.04	112	0	112	100%
No Change				
0.00	10	13	23	43%
Increased				
0.01-0.04	0	93	93	0%
0.05-0.09	0	42	42	0%
0.10-0.14	0	8	8	0%
≥0.15	0	7	7	0%

POSCH: Program on the Surgical Control of the Hyperlipidemias; P: progression; NP: non-progression.

LDL cholesterol and HDL cholesterol values, comparing baseline values to the 1-year post-intervention values, were stratified as follows: LDL cholesterol (mmol/l): decrease ≥0.78, decrease 0.26-0.75, decrease 0.23 to increase 0.23, increase 0.26-0.75, and increase ≥0.78; HDL cholesterol (mmol/l): increase ≥0.26, increase 0.13-0.23, increase 0.10 to decrease 0.10, decrease 0.13-0.23, and decrease ≥0.26. This classification schema allowed for the construction of a five-by-five factorial comparison table containing 25 cohort cells. The numerical content of each of the 25 cohort cells were stratified by angiographic outcomes: progression versus non-progression (stabilisation/regression). For example, a patient whose LDL cholesterol went down by 1.29 mmol/l and whose HDL cholesterol went up by 0.31 mmol/l would be placed in the left uppermost cohort of the table; whereas a patient whose LDL cholesterol went up by 0.13 mmol/l and whose HDL cholesterol went down by 0.5 mmol/l would be placed in the centre cohort. The boxed table was constructed so that for each cohort a number in the right lower most corner represented progression and a number in the left uppermost corner represented non-progression. If a corner contains no number, then there were no patients in that category (Table 1).

The predictive capacity of the CRF ([LDL – HDL]/LDL) was tested against the POSCH arteriography data. This was done by construction of a table of sextiles for the 1-year interval CRF and LDL cholesterol levels stratified as a function of plaque progression (Table 2). Further, the change in the CRF from baseline to the 1-year interval value - from decreased, to no change, to increased - was categorised for progression, non-progression, and percent non-progression (Table 3).

Laboratory Methods

HDL cholesterol was measured by the precipitation technique, using dextran sulfate (50,000 Mw) and magnesium in the reagent. LDL cholesterol and very low density lipoprotein cholesterol are removed by centrifugation, leaving HDL cholesterol in the supernatant. The HDL cholesterol in the supernatant is then measured by a timed endpoint method. In the reaction, cholesterol esterase hydrolyses cholesterol esters into free cholesterol and fatty acids. The free cholesterol is oxidised into cholestene-3-one and hydrogen peroxide by cholesterol oxidase. Peroxidase then catalyses the reaction of hydrogen peroxide with 4-aminoantipyrine and phenol to produce a coloured quinoneimine product, which is then

measured colourimetrically. Once HDL cholesterol is known, then LDL cholesterol is calculated by the Friedewald equation.[13]

Statistics

The data were examined by independent and multiple logistic regression analyses.

RESULTS

At the first post-randomisation comparison of available arteriograms for individual POSCH patients there were 731 paired assessments: 163 cases of angiographic plaque progression (22%), and 568 cases of PNP, consisting of plaque stabilisation and plaque regression (78%). Considering changes in the LDL cholesterol independently, 47% (267/568) of those patients with PNP achieved 1-year post intervention LDL cholesterol lowering ≤2.56 mmol/l; whereas only 1% (2/162) of those patients with plaque progression had 1-year post intervention LDL cholesterol level reductions ≤2.56 mmol/l. Table 1 represents comparison of the changes in the LDL cholesterol and the HDL cholesterol stratified according to arteriographic progression (ArP) or non-progression. Of the 25 cohort cells, those in a diagonal line between the left lower most corner and the right upper most corner contained a population mixture of patients with angiographic progression (AnP) and non-progression. Essentially all cohorts above this diagonal represent patients with pure angiographic non-progression, and virtually all cohorts below this diagonal represent patients with pure AnP. This relationship is pictorially represented in Figure 1.

Certain inferences can be made from these data: plaque progression and non-progression, including actual plaque regression, are a function of a reciprocal LDL cholesterol and HDL cholesterol relationship. Most cases of PNP occur when the LDL cholesterol is lowered by at least 0.78 mmol/l; however, if the HDL cholesterol falls by as little as 0.13 mmol/l cases of plaque progression are seen, and the more the HDL cholesterol falls the more cases of progression occur. Conversely, even if LDL cholesterol levels rise, but the HDL cholesterol rises simultaneously by at least 0.26 mmol/l, PNP is the rule. The predictive capacity of the CRF was tested against POSCH arteriographic findings. This was done by constructing a table of sextiles for the 1-year interval CRF and LDL cholesterol levels, stratified as a function of plaque progression. Table 2, illustrating ArP stratified by sextiles of the 1-year interval CRF and LDL cholesterol levels, shows that the CRF sextiles proceeding from highest risk (sextile VI) to lowest risk (sextile I) sequentially predict less plaque progression than do the corresponding LDL sextiles. (Figure 2) Sextile VI for CRF contains all CRF values ≥0.80; Sextile V, CRF values 0.75-0.79; Sextile IV, CRF values 0.70-0.74; Sextile III, CRF values 0.65-0.69; Sextile II, CRF values 0.60-0.64; Sextile I, CRF values ≤59.0. For LDL, Sextile VI contains all LDL values ≥5.17 mmol/l; Sextile V, LDL values 4.53-5.15 mmol/l; Sextile IV, LDL values 3.88-4.50 mmol/l; Sextile III, LDL values 3.23-3.85 mmol/l; Sextile II, LDL values 2.59-3.21 mmol/l; Sextile I, all LDL values ≤2.56 mmol/l.

Table 3 demonstrates that 92% (150/163) of patients with plaque progression had a rise in their CRF; whereas 98% (558/568) of patients with PNP had a fall in their CRF. No-one whose CRF declined had plaque progression, and no-one whose CRF had risen had angiographic evidence of non-progression. 3% (23/731) had no change in their CRF values at 1 year. In an attempt to refine angiographic outcomes in those 23 patients whose CRF (when calculated to two decimal places) did not change, it was decided to calculate the CRF to four decimal places. When this was done, the 10 patients whose angiograms had shown regression all had declines, albeit minute, in their CRF values, and the 13 patients whose angiograms had shown progression all had rises, albeit minute, in their CRF values. Thus when the CRF is calculated to four decimal places, then all patients with a decline in their CRF values showed plaque stabilisation/regression and all patients with a rise in their CRF values sustained plaque progression. Independent regression analyses for LDL cholesterol, HDL cholesterol, and CRF are all highly significant for predicting ArP or regression/stabilisation ($p<0.0001$). The LDL cholesterol is the strongest predictor, followed by the CRF, and then HDL cholesterol.

DISCUSSION

The LRH of Nikkila[4,5] is strongly supported by the arteriography data of the POSCH trial.[1,7-9] The hypothesis, in brief, states that therapy to lower LDL cholesterol and simultaneously raise HDL cholesterol will halt the process of atherogenesis or ATD. The current analysis clearly confirms the reciprocal and complimentary relationship of the

two cholesterol transport fractions in predicting arteriographic changes over time. In a POSCH paper in preparation (not yet published) it is demonstrated that the arteriographic changes will in turn predict clinical events and overall mortality during 25 years of follow-up. Thus, life expectancy, at least in patients who have sustained a single MI (a POSCH inclusion criterion) may be predictable by coronary plaque progression or non-progression on arteriography, and these arteriography changes are predictable by therapy-engendered LDL cholesterol lowering in concert with HDL cholesterol elevation, as reflected by the CRF. Though the lipid-atherosclerosis hypothesis has long been considered a theory or even fact, the current study adds undeniable substantiation to its proof.

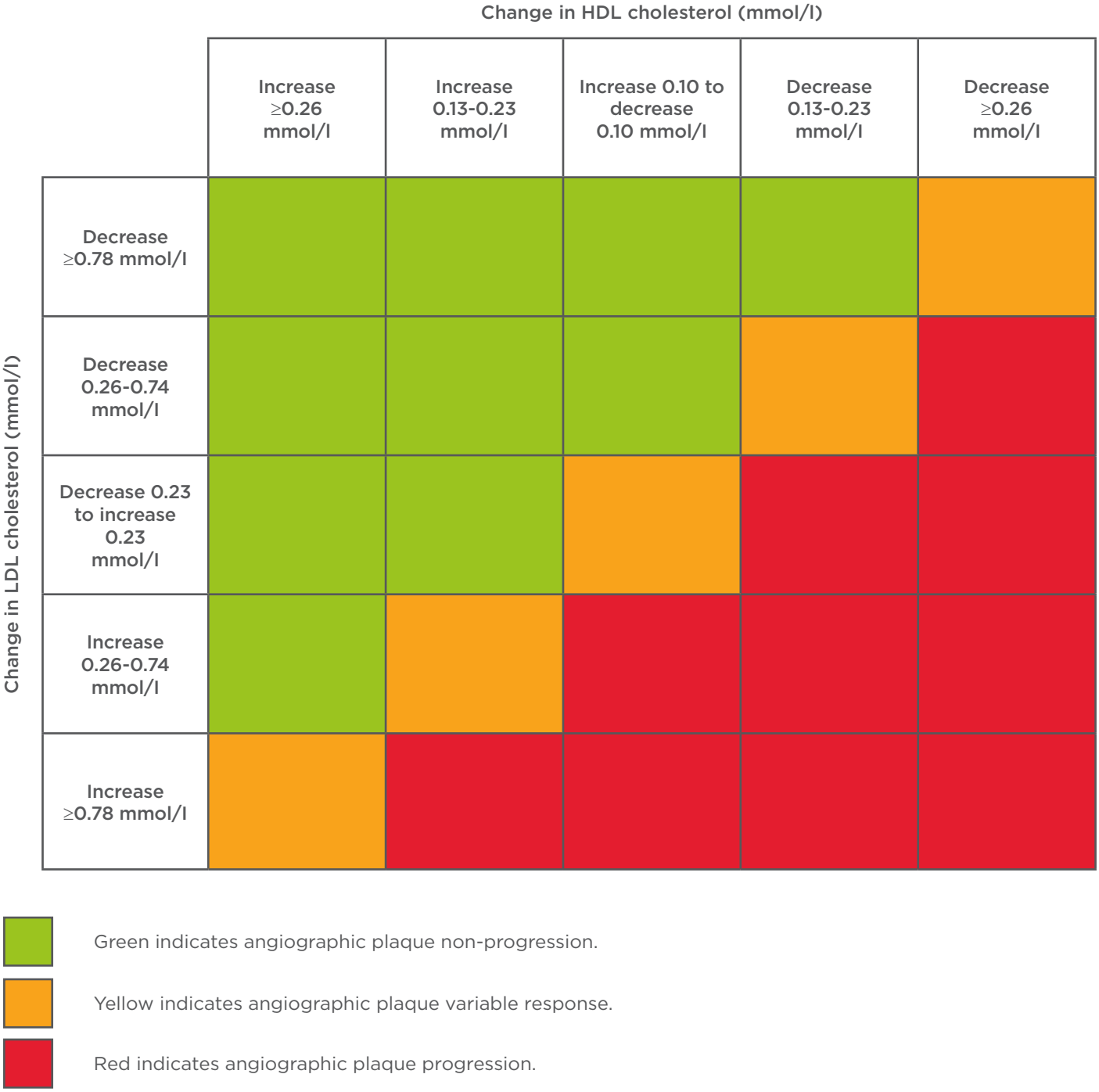

Figure 1: Change in low-density lipoprotein (LDL) versus change in high-density lipoprotein (HDL) in angiographic outcomes in POSCH.

POSCH: Program on the Surgical Control Hyperlipidemias.

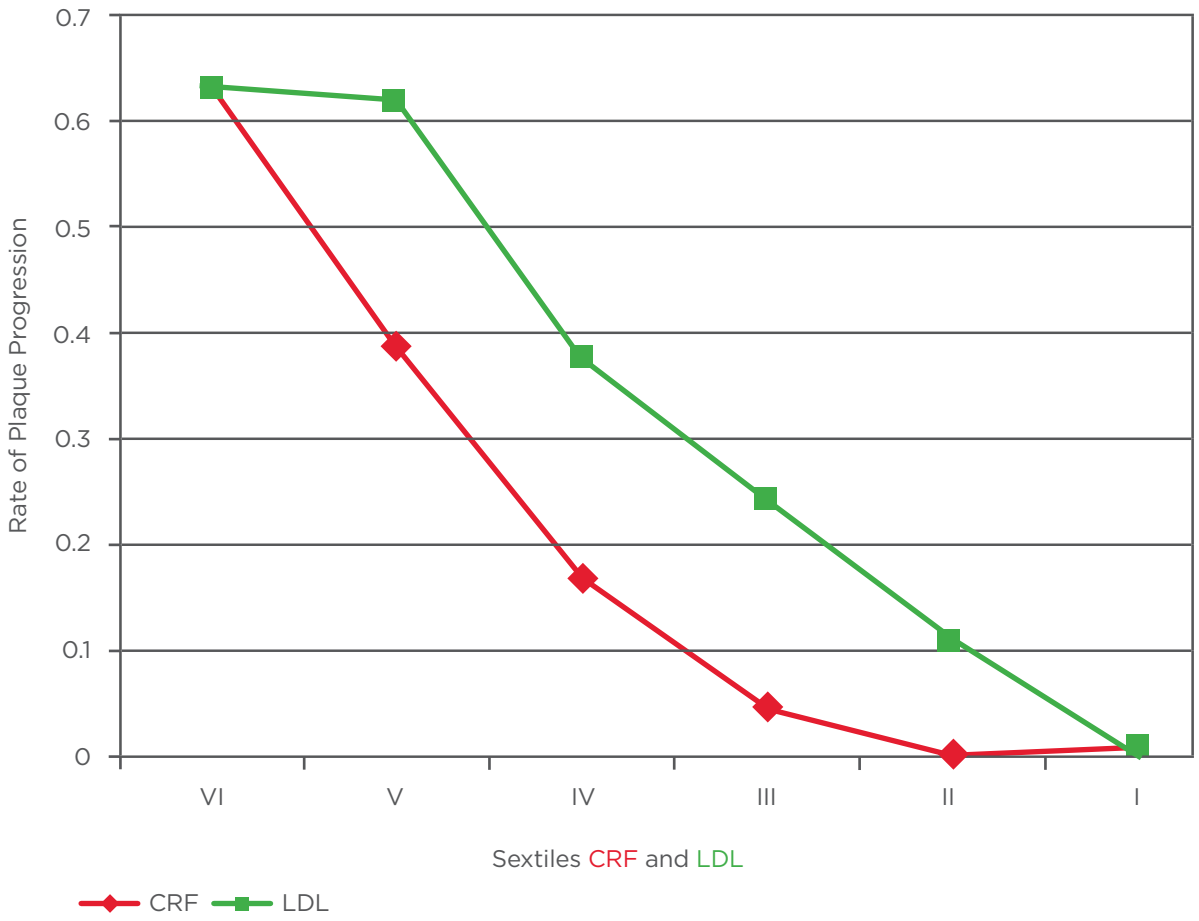

Figure 2: The incidence of plaque progression in sextiles of CRF versus sextiles of LDL cholesterol.
CRF: Cholesterol retention fraction; LDL: Low-density lipoprotein.

The efficacy of favourable lipid modulation exhibited in the POSCH trial was responsible for the selection of this study in relationship to the CRF. The overall correlation of arteriographic prognosis with the CRF is independent of whether the POSCH patients were in the intervention or control groups. Of course, the favourable changes in the cholesterol fractions were dominant in the partial ileal bypass intervention group and, therefore, the favourable changes in arteriographic progression/non-progression occurred in that group as well. The CRF incorporates the key cholesterol fractions of LDL cholesterol and HDL cholesterol, and expresses them in an equation that is predictive of the progression or non-progression of ATD. Table 1 and Figure 1 demonstrate this concept and reveal that for PNP, lowering LDL and raising HDL play complementary roles. Clearly lowering LDL is associated with PNP, though less so when HDL levels fall sufficiently. It is also clear that raising HDL is associated with PNP, though less so when LDL levels rise sufficiently. This is interpreted to mean that it is the balance between LDL and HDL that is critical to plaque progression versus non-progression, and that this balance would be best expressed by the CRF, rather than by LDL or HDL individually, since the CRF will define the extremes of lipid disorders, as well as intermediate imbalances in LDL and HDL as well. Further, in a study of drug-naïve diabetic patients, the CRF was compared to the non-HDL cholesterol component for correlation with inflammation, a key factor in ATD. The two were highly correlated (p=0.0001) as inflammatory markers, whereas the LDL cholesterol fraction was not.[14]

Figure 2 confirms the superior ability of the CRF to predict plaque stabilization/regression with respect to LDL cholesterol. While the sixth and first sextiles of both predictors show the same rates of plaque progression, plaque progression rates are lower in the intermediate CRF sextiles than in the intermediate LD cholesterol sextiles. In the intermediate sextile range, the CRF predicts less plaque progression than does LDL cholesterol, and

thus is superior to LDL cholesterol in predicting plaque non-progression.

The 2000 meta-analysis of published lipid/arteriographic studies included, in addition to POSCH, the St. Thomas Angiographic Regression Study (STARS),[15] the Heidelberg Study,[16] the NHLBI Type II Secondary Prevention Trial,[5] the Lipid Angiography Trial (LOCAT),[17] the Lipoprotein and Coronary Atherosclerosis Study (LCAS),[18] the Familial Atherosclerosis Lipid Study (FATS),[19] and the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-1) study.[20] There are several other reports of the benefits of LDL cholesterol and HDL cholesterol modification as well.[21-25] However, the end-of-trial LDL cholesterol reduction demonstrated in POSCH was achieved in only a few of these studies (e.g. FATS[19] and NHLBI[5]). The end-of-trial reciprocal blend of LDL cholesterol and HDL cholesterol values was unique to the POSCH study. Interestingly, in the six trials[5,15-20] in which we were able to perform comparable plaque evolution comparisons with the LDL cholesterol, HDL cholesterol, and the CRF, we found no relationship as compelling as the POSCH findings. Further, there are a number of trials in which large lipid modifications have been achieved, but no effect on the atherosclerotic plaque has been evident. These studies include two trials using cholesterol ester transfer inhibitors,[26,27] two trials employing the addition of ezetimibe,[28,29] and two trials where niacin was added to patients pretreated with statins.[30,31]

POSCH adds support to the role of HDL raising as a protective mechanism to stabilise/regress plaque as part of dyslipidaemic therapy. This role has been challenged in the above cited studies.[25,26,29,30] However, POSCH powerfully supports the LRH as regards HDL raising. The reason for the difference between POSCH and the other studies may be that some lipid-modifying medications may interfere with HDL functionality or fail to reduce the role of gut bacteria, leading to reduced reverse cholesterol transport.[32] This in turn proposes that dyslipidaemic medications must be shown to stabilise/regress plaque or reduce adverse ATD outcomes before they can be recommended for use.

Human metabolic studies have clearly demonstrated the mechanisms of action and causative effects of the partial ileal bypass operation: marked reduced cholesterol and bile acids (an end-product of cholesterol metabolism) absorption and reabsorption by their respective enterohepatic cycles, reciprocally marked faecal increased cholesterol and bile acid excretion, increased cholesterol synthesis, increased cholesterol turnover, and reduction in the freely miscible (including plasma), and the less freely miscible (including the arterial wall) cholesterol pools.[7] This being said, the pleiotropic effects often attributed to the statins[32,33] would not be present when the intervention modality is the partial ileal bypass operation. On the other hand, is the partial ileal bypass effect purely that of lipid modification? Can the bypass of the ileum elicit some change in the gut flora that mitigates the atherosclerotic plaque? A recent paper by Tang et al.[34] found a deleterious effect of gut organisms by their metabolising of phosphatidylcholine into trimethylamine-N-oxide, which is associated with an increase in ATD events. There is also evidence to support that gut bacteria play a role in the aetiology of other diseases, notably obesity.[35,36] Can partial ileal bypass have an opposite or beneficial effect on intestinal bacteria and the substances they elaborate? This suggestion warrants further investigation.

The POSCH study is pertinent in clinical practice today, since it is the cornerstone for the lipid/atherosclerosis theory. In essence, all of the POSCH outcomes regarding prediction of risk and prognosis have been verified and therefore serve as tested metrics now and most likely in the future. Further, POSCH is the precedent randomised controlled clinical trial utilising metabolic surgery, an emerging discipline that will contribute to our knowledge of mechanisms and therapeutics. The limitations of this study include that the validity analysis of the CRF is based on the historical and therefore immutable POSCH trial. POSCH is, however, a landmark study and the most definitive of the lipid/atherosclerosis trial evaluations. The POSCH subject population was predominantly male and Caucasian and, therefore, the comparative findings may or may not be applicable to women or non-Caucasians.

Caveat: The POSCH trial and the other studies described in the 2000 meta-analysis[6] were all performed prior to a change in the laboratory determination of the HDL cholesterol level from a precipitation method to an enzymatic method.[37] 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 of the order of

0.25 mmol/l lower than one calculated by the new enzymatic method. Consequently, since LDL cholesterol is usually calculated by the Freidewald equation,[13] LDL cholesterol levels, determined on the basis of the newer HDL cholesterol method, will be of the order of 0.25 mmol/l lower than when calculated by the older 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 and accurate with regard to their arteriography correlations.

CONCLUSION

In summary, in POSCH the partial ileal bypass-induced alterations of the LDL cholesterol, HDL cholesterol, and CRF support the LRH and are highly correlated with the sequential CA changes of atheromatous plaque progression and non-progression (stabilisation/regression). Since the POSCH sequential arteriograms have been documented to be accurate surrogates for clinical ATD events and overall mortality, this study affirms that individual patient prognosis can be predicted by the magnitude of response to lipid interventional therapy, especially as reflected by the CRF.

REFERENCES

1. Buchwald H et al. Changes in sequential coronary arteriograms and subsequent coronary events. Surgical Control of the Hyperlipidemias (POSCH) Group. JAMA. 1992;268:1429-33.

2. Brown BG et al. Lipid lowering and plaque regression. New insights into prevention of plaque disruption and clinical events in coronary disease. Circulation. 1993;87:1781-91.

3. Gotto AM. Lipid lowering, regression, and coronary events. A review of the Interdisciplinary Council on Lipids and Cardiovascular Risk Intervention, Seventh Council meeting. Circulation. 1995;92:646-56.

4. Frick MH et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med. 1987;317:1237-45.

5. Brensike JF et al. Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI Type II Coronary Intervention Study. Circulation. 1984;69:313-24.

6. Feeman WE Jr, Niebauer J. Prediction of angiographic stabilization/regression of coronary atherosclerosis by a risk factor graph. J Cardiovasc Risk. 2000;7:415-23.

7. Buchwald H et al. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. Report of the Program on the Surgical Control of the Hyperlipidemias (POSCH). N Engl J Med. 1990;323:946-55.

8. Buchwald H et al. Effective lipid modification by partial ileal bypass reduced long-term coronary heart disease mortality and morbidity: five-year posttrial follow-up report from the POSCH. Arch Intern Med. 1998;158: 1253-61.

9. Buchwald H et al. Overall mortality, incremental life expectancy, and cause of death at 25-years in the Program on the Surgical Control of the Hyperlipidemias (POSCH). Ann Surg. 2010;251:1034-40.

10. Feeman WE Jr. The Bowling Green Study of the primary and secondary prevention of atherosclerosis: descriptive analysis, findings, applications and conclusions. Ohio J Sci. 1992:153-81.

11. Feeman WE Jr. The Bowling Green Study of the primary and secondary prevention of atherosclerotic disease: update 1991-1993. Ohio J Sci. 1994:105-12.

12. Feeman WE Jr. Prediction of the population at risk of atherothrombotic disease. Exp Clin Cardiol. 2004;9:235-41.

13. Friedewald WT et al. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499-502.

14. Wang-CY, Chang TC. Non-HDL cholesterol level is reliable to be an early predictor for vascular inflammation in Type 2 diabetes mellitus. J Clin Endocrinol Metab. 2004;89:4762-7.

15. Watts GF et al. Effects on coronary artery disease of lipid lowering diet, or diet plus cholestyramine in the St. Thomas Atherosclerosis Regression Study (STARS). Lancet. 1992;339:563-9.

16. Schuler G et al. Regular physical exercise and low-fat diet. Effects on progression of coronary artery disease. Circulation. 1992;86:1-11.

17. Frick MH et al. Prevention of the angiographic progression of coronary and vein-graft atherosclerosis by gemfibrozil after coronary bypass surgery in men with low levels of HDL cholesterol. Circulation. 1997;96:2137-43.

18. Herd JA et al. Effects of fluvastatin on coronary atherosclerosis in patients with mid to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study (LCAS)). Am J Cardiol. 1997;80:278-86.

19. Brown G et al. Regression of coronary artery disease as a result of intensive lipid lowering therapy in men with high levels of apolipoprotein B. N Engl J Med. 1990;323:1289-98.

20. Pitt B et al. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. PLAC I investigation. J Am Coll Cardiol. 1995;26:1133-9.

21. Nissen SE et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006;295:1556-65.

22. Blankenhorn DH et al. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA. 1987;257:3233-40.

23. Brown BG et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med. 2001;345:1583-92.

24. Blankenhorn DH et al. Coronary angiographic changes with lovastatin therapy: the Monitored Atherosclerosis Regression Study (MARS). Ann Intern Med. 1993;119:969-76.

25. Waters D et al. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. Circulation. 1994;89:959-68.

26. Nissen SE et al. Effect of torcetrapib

on the progression of coronary atherosclerosis. N Engl J Med. 2007;356:1304-16.

27. Schwartz GG et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med. 2012;367:2089-99.

28. Kastelein JJP et al. Simvastatin with or without ezetimibe in familial hypercholesteremia. N Engl J Med. 2008;358:1431-43.

29. West AM et al. The effect of ezetimibe on peripheral arterial atherosclerosis depends upon statin use at baseline. Atherosclerosis. 2011;218:156-62.

30. Boden WE et al; AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365:2255-67.

31. Armitage J et al. Heart Protection Study 2 – treatment of HDL to reduce the incidence of vascular events (HPS2-THRIVE). Presented at: American College of Cardiology Scientific Sessions, San Francisco, California, USA, 9 March, 2013.

32. Yildirir A, Muderrisoglu H. Non-lipid effects of statins: emerging new indications. Curr Vasc Pharmacol. 2004;2:309-18.

33. Hillyard DZ et al. Inhibition of proliferation and signaling mechanisms in human lymphocytes by fluvastatin. Clin Exp Pharmacol Physiol. 2002;29:673-8.

34. Tang WH et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med. 2013;368:1575-84.

35. Das UN. Obesity: genes, brain, gut, and environment. Nutrition. 2010;26: 459-73.

36. Possemiers S et al. The intestinal environment in health and disease – recent insights on the potential of intestinal bacteria to influence human health. Curr Pharm Design. 2009;15:2051-65.

37. Feeman WE Jr. Letter to the Editor. J Clin Lipidol. 2008;2:401-2.