

## Elevated HDL is a risk factor for recurrent coronary events in a subgroup of non-diabetic postinfarction patients with hypercholesterolemia and inflammation

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### Abstract

Recent studies demonstrate important roles for inflammation in development of atherosclerosis with current attention focusing on interactions of inflammation with traditional lipoprotein risk factors. Since the nature of such relationships is largely unknown, we sought to investigate interactions of inflammation with hyperlipidemia in generating cardiovascular risk in a way that would allow recognition of such interactions whether anticipated or not. Thus, we searched for subgroups at high risk for recurrent coronary events in 767 non-diabetic postinfarction patients using an exploratory three-dimensional graphical screening technique with previously established factor analysis-derived inflammatory and lipoprotein-related factors. Results indicated a high-risk patient subgroup defined by factor interaction that was best characterized clinically by high levels of C-reactive protein (CRP) and total cholesterol. Kaplan–Meier and Cox multivariate analysis confirmed high-risk. Additionally, within-subgroup risk related to metabolic, inflammatory, and thrombogenic blood markers was assessed using Cox analysis with results showing only elevated HDL as a significant and independent predictor of risk with hazard ratio, 2.24 (95% CI: 1.12, 4.49;  $p=0.023$ ). We conclude that in non-diabetic postinfarction patients, elevated HDL is predictive of risk of recurrent coronary events within a subgroup of patients characterized by simultaneous elevations in serum CRP and total cholesterol.

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That inflammation is a significant factor in development of atherosclerosis is becoming increasingly clear. Accordingly, two recent studies report beneficial effects on cardiovascular disease (CVD) risk of statin-induced reductions in C-reactive protein (CRP) levels that were independent of concomitant reductions in levels of atherogenic lipoproteins [1,2]. This is part of an evolving literature demonstrating importance of inflammatory processes in atherogenesis, an area where

lipoprotein-associated CVD risk has already been well established. Thus, considerable attention is now being focused on studies of interactions of inflammation with traditional lipoprotein risk factors since the nature of such relationships is largely unknown but potentially important regarding development of CVD risk.

We recently demonstrated for non-diabetic patients of the postinfarction thrombogenic factors and recurrent coronary events (THROMBO) study [3], CRP as a marker of inflammation [4]. This result derived from factor analysis of multiple metabolic, inflammatory, and thrombogenic blood markers that generated five factors one of which was inflammation-related. CRP was the most influential of four putative inflammatory markers making up this factor. Another factor was

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lipoprotein-related with total cholesterol as the most influential component.

In view of the potentially important role of interactions of inflammation with lipoproteins in the development of atherosclerosis, we assessed manifestations of such by searching for patient subgroups at high risk for recurrent coronary events simultaneously dependent on measures of inflammation and atherogenic lipoproteins together. As measures of inflammation and atherogenic lipoproteins, we used the inflammatory factor and the cholesterol–lipoprotein factor derived in our previous factor analysis studies [4,5] and extended this approach in a clinically more meaningful way by using CRP and total cholesterol as best representatives of the factors. Thus, CRP and total cholesterol were used in non-diabetic postinfarction patients of the THROMBO study together with an exploratory three-dimensional graphical screening procedure [6] to produce maps of prevalence of recurrent coronary events over the entire terrain defined by CRP and total cholesterol from which high-risk subgroups could be identified.

## 1. Methods

### 1.1. Study population

The study population comprised the 767 patients of the THROMBO study who were non-diabetic and had complete laboratory data. Details of the THROMBO study have been reported previously [3], and as noted, the study was carried out with approval of and according to guidelines of the Research Subjects Review Boards. Recurrent coronary outcome events for this study were cardiac death, myocardial infarction (MI), or unstable angina, whichever occurred first, and average length of follow-up was 26 months.

### 1.2. Independent variables

Blood markers on fasting sera were determined 2 months after index MI. Concentrations of apolipoprotein-B (apoB), total cholesterol (Chol), apolipoprotein-A1 (apoA1), high density lipoprotein cholesterol (HDL), triglyceride (Trig), LDL peak particle diameter (PPD), glucose (Glu), insulin (Ins), BMI, plasminogen activator inhibitor-1 (PAI-1), lipoprotein(a) (Lp(a)), C-reactive protein (CRP), von Willebrand factor antigen (vWF), fibrinogen (Fibr), d-dimer (d-dim), factor VII (FVII), and factor VIIa (FVIIa) were determined as described previously [3,4]. Median HDL particle diameter was determined using gradient gel electrophoresis as described previously [7].

### 1.3. Statistical analyses

All statistical and graphical procedures were performed with Statistica 7.0 (StatSoft Inc., Tulsa, OK 74104). Variables were age-adjusted using linear regression. Significant

differences ( $p < 0.05$ ) in laboratory values between groups were assessed using the Mann–Whitney *U*-test; and significant variables contributing to time to outcome event were determined using Kaplan–Meier analysis (log-rank statistic,  $p < 0.05$ ) and the Cox multivariate proportional hazards regression model.

### 1.4. Factor analysis

Our approach to factor analysis has been described previously [4,5]. Briefly, we used factor analysis to reduce results of multiple blood markers to fewer composite variables (factors) that represent more fundamental physiologic relationships among subsets of variables based upon correlations of variables within factors. Each factor is identified with a basic physiologic process based upon the variables making up the factor with the measure of the contribution of a variable being its loading on the factor. Factors account for most of the variance in the original data. Factor analysis results were used in subsequent statistical analyses using factor scores, the actual values of each factor for each patient [5].

### 1.5. Graphical analysis

A graphical screening technique for identification of high-risk subgroups has been described previously [6]. Briefly, three-dimensional scatter plots of patients, without and with outcome events, coded as 0 or 1, respectively, are generated as a function of two blood marker risk variables. To facilitate recognition of high-risk subgroups, concentrations are transformed to rankings (smallest concentration is assigned the value, 1) to more evenly distribute patient points over the  $x$ – $y$  bivariate domain. Then, resulting points are smoothed to produce a three-dimensional surface map with height over the  $x$ – $y$  plane becoming a measure of outcome prevalence over the bivariate blood marker domain. Potentially high-risk subgroups are identified as peaks and confirmed as such by subsequent statistical analyses. Demarcation of peaks is carried out by estimation from surface and contour plots of the isoprevalence contour line corresponding to increasing slope in comparison to surrounding relatively flat areas.

### 1.6. High-risk subgroup validation

Confirmation of high-risk in patients contained in peaks relative to remaining patients was performed using Kaplan–Meier plots and Cox analysis with adjustment of clinical covariates performed by single entry ( $p < 0.1$ ) of sex, race, smoking, prior MI, index infarct type by ECG (Q-wave versus non-Q-wave), pulmonary congestion, ejection fraction during index MI, and claudication. Significant clinical covariates were retained in a subsequent model that included addition of the binary variable denoting subgroup membership ( $p < 0.05$ ) to confirm high-risk in the subgroup relative to remaining patients.

1.7. Within-subgroup risk factors

To assess additional risk within a subgroup, Cox regression was applied to the subgroup using the 17 laboratory markers as independent variables with adjustment of clinical covariates within the subgroup performed as described above. Blood markers were dichotomized in three ways: quartile with highest concentration versus combined three quartiles with lower concentrations, combined two quartiles with highest concentrations versus combined two quartiles with lower concentrations, and combined three quartiles with highest concentrations versus quartile with lowest concentration. Separate univariate models were run for each laboratory variable dichotomized in the three ways described above. Then, a multivariate model adjusted for clinical covariates was run with simultaneous entry of all univariate significant laboratory values ( $p < 0.05$ ). Lastly, assessment of medication effects was performed by single entry into the resulting model of the following medications: statins, beta blockers, aspirin, calcium channel blockers, nitrates, ACE-inhibitors, and oral anticoagulants ( $p < 0.05$ ).

2. Results

2.1. High-risk subgroup identification

Clinical and laboratory characterization of the study population ( $N = 767$ ) have been given previously [6] as well as factor analysis results [4,5]. Summarizing factor analysis results, there were five factors that together with factor identification and blood marker contributions were in decreasing order: cholesterol–lipoprotein (cholesterol, apoB, apoAI, HDL), inflammatory (CRP, fibrinogen, d-dimer, vWF), coagulation (FVII, FVIIa), dyslipidemia (PPD, triglycerides, HDL), and glycemia (glucose, insulin).

Of the two lipoprotein factors (cholesterol–lipoprotein and dyslipidemia), the cholesterol–lipoprotein factor accounted for the higher proportion of original laboratory data variance. Thus, to assess inflammation–lipoprotein interactions, a surface map of estimated prevalence of recurrent coronary events as a function of factor score ranks of the inflammation and cholesterol–lipoprotein factors was generated and is shown in Fig. 1. The plot shows a well-defined single peak at simultaneously high values of lipoprotein–cholesterol and inflammation and relatively little risk for either high values of lipoprotein–cholesterol or inflammation alone. We also wanted to assess whether there might be similar results with single blood markers representing the two factors for more direct clinical relevance. Thus, a surface plot of estimated prevalence versus total cholesterol and CRP, the highest loading markers of the cholesterol–lipoprotein and inflammation factors, respectively, is given in Fig. 2. The plot shows a somewhat less well-defined peak, but nevertheless, a peak of high prevalence at simultaneously high values of total cholesterol and CRP and less

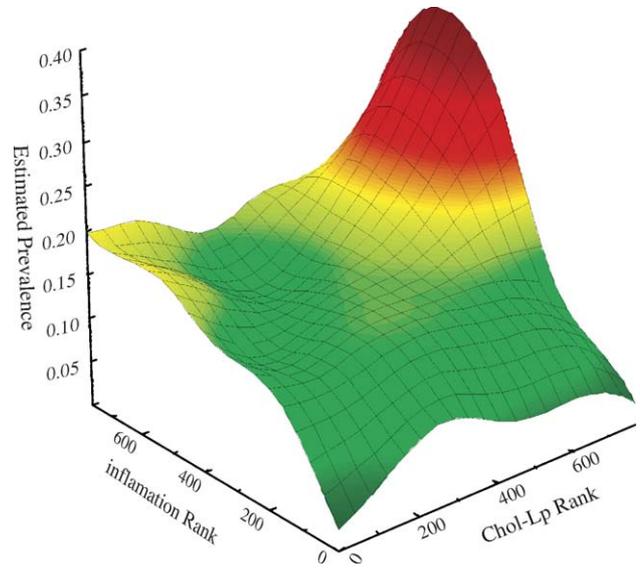


Fig. 1. Surface map of estimated prevalence of recurrent coronary event outcome as a function of cholesterol–lipoprotein (total cholesterol, apoB, apoAI, and HDL) and inflammation (CRP, fibrinogen, d-dimer, and vWF) factor score ranks in the study population of 767 non-diabetic postinfarction patients.

risk for either high values of total cholesterol or CRP alone.

2.2. High-risk subgroup validation

Inspection of the peak in the plot of Fig. 2 and at various additional orientations demonstrated the base of the peak to arise at an estimated prevalence of approximately 0.19. Thus, this value was chosen as the isoprevalence contour above which a high-risk subgroup was defined. Fig. 3 gives the

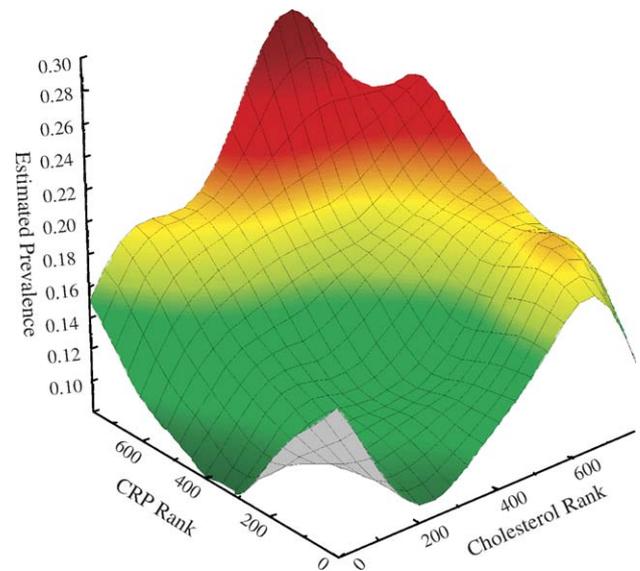


Fig. 2. Surface map of estimated prevalence of recurrent coronary events as a function of cholesterol and CRP ranks in the study population of 767 non-diabetic postinfarction patients.

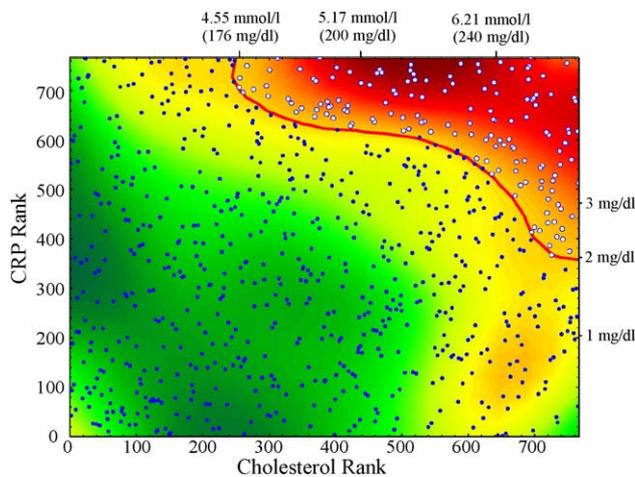


Fig. 3. Contour map of estimated prevalence of recurrent coronary events as a function of cholesterol rank and CRP rank in the study population of 767 non-diabetic postinfarction patients. Superimposed is the isoprevalence contour line (red line) at 0.19 that divides high-risk patients (open circles) from low-risk patients (filled circles). Estimated prevalences are: dark green (0.10), light green (0.15), yellow-orange (0.20), and red (0.25).

corresponding contour plot with the isoprevalence line at 0.19 superimposed showing the high-risk subgroup as a triangular region containing 149 patients. The 618 remaining patients were designated as a low-risk patient subgroup. For reference, Fig. 3 gives Adult Treatment Panel III (ATP III) cut-points for cholesterol and CRP as well as lowest concentrations of the markers in the high-risk subgroup.

To validate high risk in the subgroup, Kaplan–Meier and Cox regression analyses were performed on the high-risk subgroup ( $N=149$ ) versus low-risk subgroup ( $N=618$ ). Fig. 4 gives Kaplan–Meier curves corresponding to the presumptive high-risk subgroup and lower risk subgroup. The curves are statistically significantly different (log-rank statistic,  $p=0.024$ ). Additionally, Cox regression analysis adjusted

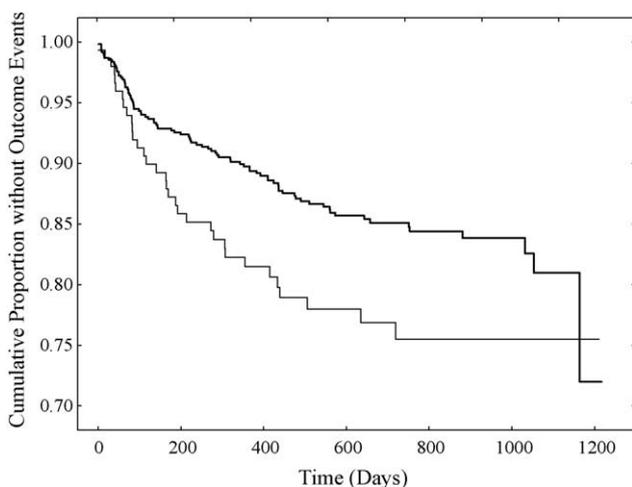


Fig. 4. Kaplan–Meier curves of patients in presumptive high-risk subgroup (lower curve,  $N=149$ ) vs. lower risk subgroup (upper curve,  $N=618$ ) (log-rank statistic,  $p=0.024$ ).

for clinical covariates previously shown to be significant in the total population (prior MI, ejection fraction, and myocardial index) [6], gave for the high-risk subgroup a hazard ratio for recurrent coronary events of 1.55 (95% CI; 1.04, 2.31;  $p=0.033$ ) versus the lower risk subgroup. Thus there was a 55% greater chance for recurrent coronary events for patients in the high-risk subgroup relative to patients in the lower risk subgroup.

### 2.3. High-risk subgroup characterization

Table 1 gives clinical and laboratory characteristics of low- and high-risk subgroups. Both groups demonstrated similar clinical characteristics except for more females in the high-risk subgroup. In addition to the expected higher cholesterol and CRP, there were significantly higher values in the high-risk subgroup for other markers of the lipoprotein–cholesterol factor (apoB, apoAI) and inflammation factor (fibrinogen, d-dimer, vWF). Additionally, the high-risk subgroup had higher values of triglycerides, PAI-1, and factor VII.

We further characterized the high-risk subgroup with regard to recurrent coronary events, by comparing clinical and laboratory results for patients without and with outcome

Table 1  
Clinical and laboratory characterization of low-risk and high-risk subgroups

Characteristic	Low-risk, $N=618$ (mean $\pm$ S.D.)	High-risk, $N=149$ (mean $\pm$ S.D.)
Outcome event rate (%)	14.4	22.1
Age (years)	58.4	58.0
Males (%)	80.3	63.8
Race (% white)	79.9	72.5
Prior MI (%)	16.9	16.3
Statins (%)	42.7	30.2
Beta blockers (%)	78.2	75.8
Aspirin (%)	83.1	77.2
Ca channel blockers (%)	20.6	16.8
Nitrates (%)	32.4	38.9
ACE-inhibitors (%)	31.4	41.6
Oral anticoagulants (%)	16.2	24.8
Chol (mmol/l)	4.86 $\pm$ 1.02	6.10 $\pm$ 1.07*
CRP (mg/l)	2.90 $\pm$ 4.50	10.3 $\pm$ 10.7*
apoB (g/l)	1.18 $\pm$ 0.26	1.42 $\pm$ 0.27*
apoA1 (g/l)	1.16 $\pm$ 0.24	1.27 $\pm$ 0.25*
HDL (mmol/l)	0.98 $\pm$ 0.28	1.03 $\pm$ 0.29
Trig (mmol/l)	2.13 $\pm$ 1.22	2.71 $\pm$ 1.49*
PPD (nm)	26.3 $\pm$ 0.83	26.17 $\pm$ 0.80
Glucose (mmol/l)	4.94 $\pm$ 1.08	5.16 $\pm$ 1.50
Insulin (pmol/l)	119 $\pm$ 178	124 $\pm$ 117
BMI (kg/m <sup>2</sup> )	27.4 $\pm$ 4.66	28.2 $\pm$ 5.70
PAI-1 ( $\mu$ g/l)	25.4 $\pm$ 22.8	31.7 $\pm$ 30.6*
Lp(a) (mmol/l)	0.62 $\pm$ 0.58	0.65 $\pm$ 0.62
vWF (%)	137 $\pm$ 58.6	163 $\pm$ 70.0*
Fibr (g/l)	3.31 $\pm$ 0.67	4.14 $\pm$ 1.00*
d-dim ( $\mu$ g/l)	457 $\pm$ 411	537 $\pm$ 428*
FVII (%)	99.1 $\pm$ 39.2	116.5 $\pm$ 54.2*
FVIIa ( $\mu$ g/l)	2.44 $\pm$ 1.53	2.87 $\pm$ 2.23
HDLMed (nm)	8.79 $\pm$ 0.29	8.79 $\pm$ 0.27

\* Significant differences by Mann–Whitney  $U$  ( $p<0.05$ ).

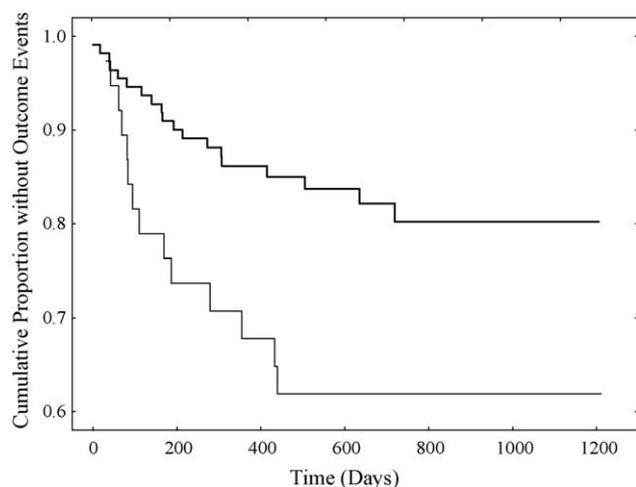


Fig. 5. Kaplan–Meier curves of patients in high-risk subgroup ( $N=149$ ) divided into two groups based on HDL cholesterol concentration with one group having values of HDL levels within the combined three quartiles of lowest HDL ( $N=111$ ) and the other having values of HDL levels within the highest HDL quartile ( $N=38$ ). Curves are: lowest three HDL quartiles—upper line and highest HDL quartile—lower line (log-rank statistic,  $p=0.012$ ).

events. Both groups showed similar clinical and laboratory characteristics with the only difference being higher levels of HDL in event positive patients ( $1.14 \pm 0.38$  mmol/l versus  $1.01 \pm 0.25$  mmol/l;  $p < 0.05$ , Mann–Whitney  $U$ ).

#### 2.4. Additional risk within high-risk subgroup

To elucidate risk within the high-risk subgroup, especially in view of finding higher HDL levels in event positive patients, Cox regression and Kaplan–Meier analyses were performed as a function of the original 17 laboratory parameters within the high-risk subgroup. For Cox analyses, laboratory parameters were dichotomized in three ways as described in Section 1. Of the eight clinical covariates, only pulmonary congestion gained entry ( $p < 0.1$ ). Adjusting for pulmonary congestion, single entry into the model of each of the 17 laboratory parameters was performed separately for each of the three dichotomization schemes. Results showed only one marker to enter the model and in only one way. This was HDL dichotomized as quartile with highest concentration versus combined three quartiles with lowest concentrations. Results gave for elevated HDL a hazard ratio of 2.24 (95% CI; 1.12, 4.49;  $p = 0.023$ ). Subsequent single entry of medications demonstrated no effect. The corresponding Kaplan–Meier curves for highest HDL concentration quartile versus combined three lowest quartiles are given in Fig. 5 which shows higher rate of outcome events for patients in the highest HDL quartile (log-rank statistic,  $p = 0.012$ ). Interestingly, this effect seems essentially complete within 1 year. To further characterize patients of the highest HDL quartile in comparison to patients in the combined three lowest quartiles of HDL, the highest quartile HDL patients demonstrated statistically significant differences in blood mark-

ers including higher apoA1 levels ( $1.48 \pm 0.23$  g/l versus  $1.20 \pm 0.22$  g/l), and larger HDL particles ( $8.98 \pm 0.30$  nm versus  $8.73 \pm 0.23$  nm).

As a control experiment, we assessed the role of blood markers, especially HDL, in the low-risk subgroup ( $N = 618$ ) using Cox regressions adjusted for significant clinical covariates (prior MI and myocardial index) and the blood markers dichotomized in the same three ways. Only BMI, dichotomized as quartile with highest values versus combined three quartiles with lowest values, entered the model giving hazard ratio of 1.63 (95% CI; 1.05, 2.51;  $p = 0.028$ ). There were no significant medication effects. Although HDL did not enter the model, closest approach ( $p = 0.105$ ) gave hazard ratio for elevated HDL of 0.64 suggesting high levels of HDL trend towards protection against recurrent coronary event risk in this subgroup.

### 3. Discussion

This study demonstrated the presence of a subgroup of patients at high risk for recurrent coronary events in a population of non-diabetic postinfarction patients. The high-risk subgroup was characterized by concomitantly high levels of CRP and total cholesterol. High risk in the subgroup was a manifestation of the interaction of the risks associated with inflammation and hypercholesterolemia. Further analysis within the high-risk subgroup demonstrated only HDL to be an independent and significant predictor of risk within the subgroup from a collection of metabolic, inflammatory, and thrombogenic blood markers. Furthermore, HDL-associated risk within the subgroup was associated with high, not low, levels of HDL. Additionally, patients with the higher levels of HDL were found to have larger diameter HDL particles as well as higher levels of apoA1.

Results indicate that determination of both CRP and total cholesterol levels together identify high-risk postinfarction patients. This is consistent with the known poor correlation of CRP and blood lipid levels seen in other work in populations at risk for a first myocardial infarction [8,9] and in the present study as demonstrated by the presence of CRP and total cholesterol in separate factors that are actually formulated in a way so as to minimize inter-factor correlations. Poor correlation between CRP and atherogenic lipid levels makes possible individual contributions to total risk that may be more than multiplicative [8]. With particular regard to postinfarction patients as recently reviewed [10], evidence for CRP-associated risk of recurrent events is less consistent than in the setting of primary prevention. Our results indicate that inflammatory processes in postinfarction patients as represented by increased CRP levels are indeed important in predicting risk. Lack of similar findings in other studies of postinfarction patients may relate to use of traditional risk factor stratification. The graphical screening approach used in our study for identification of high-risk subgroups allowed delineation of a subgroup with high levels of CRP

and total cholesterol that because of its shape in the outcome prevalence map could not be characterized by single cut-point values for CRP and cholesterol. As recently reviewed [10,11], our results are consistent with many previous studies supporting the role of inflammation as represented by CRP in the atherogenic process.

Results regarding additional risk for recurrent coronary events within the high-risk subgroup defined by high cholesterol and CRP levels singled out only HDL as a statistically significant predictor of risk within the subgroup, and surprisingly, risk was associated with higher rather than lower levels of HDL. Further, higher risk patients within the subgroup had larger HDL particles and higher apoA1 concentrations than lower risk patients having the lower concentrations of HDL. This finding may indicate for the presumably cholesteryl ester-rich HDL particles in higher risk patients, relative inability to effectively support reverse cholesterol transport. As in our study, various manifestations of CVD risk have been previously associated with high HDL levels [12–16]. Recent reports of such include patients with genetic variants of several enzymes involved in lipoprotein metabolism including cholesterol ester transfer protein [17], paraoxonase [18], endothelial lipase [19–21], and possibly hepatic lipase [22,23].

The high-risk subgroup identified in our study has, as one of its defining characteristics, an inflammatory component as demonstrated by elevated CRP levels. Additionally, there is further within-subgroup risk associated with high levels of HDL. CVD risk in association with high HDL levels is thought to be connected with the role of HDL in inflammation, or more specifically, with changing function of HDL from an anti-inflammatory agent to a pro-inflammatory agent. As recently reviewed [24–27], this change is believed to arise from inflammation-induced alterations in HDL particles by displacement and/or modification of multiple protein constituents of HDL including apoA1, lecithin:cholesterol acyltransferase, paraoxonase, and lipoprotein-associated phospholipase A<sub>2</sub> (platelet-activating factor acetylhydrolase). These changes are thought to affect anti-atherogenic HDL functionality regarding its usual roles in reverse cholesterol transport and HDL-mediated inhibition of oxidative degradation of LDL [24]. Recent reports demonstrate oxidative modifications in apoA1 as playing a significant role in transforming HDL from anti-inflammatory to pro-inflammatory [28–30]. apoA1 oxidation was shown to be mediated by preferential nitration and chlorination of apoA1 tyrosine residues by the enzyme, myeloperoxidase (MPO), present in atheroma macrophages with apoA1 as a selective target of MPO action [28]. These oxidative changes of apoA1 in HDL result in selective inhibition of ATP-binding cassette transporter A1 (ABCA1)-dependent cholesterol efflux from macrophages [29]. In further support of these alterations as pro-atherogenic, markedly higher levels of serum apoA1 content of nitrotyrosine and chlorotyrosine were found in patients with CVD in comparison to those without [30]. We speculate that such results likely play a role

in the findings of our study regarding HDL-associated risk.

There were several limitations in our study that restricted the extent of conclusions. One was the number of patients in the study population that limited statistical power especially in the high-risk subgroup and its further subdivisions that may have prevented identification of additional risk markers and correlations. Additionally, although we adjusted for multiple clinical and medication covariates in the analyses, it would have been desirable to have patient information on exercise, diet, social support, depression, and ethanol use. Further, it would be useful for elucidation of pathophysiologic mechanisms to have determined additional blood markers associated with atherogenic lipoproteins and inflammation, especially regarding HDL and apoA1 alterations. These considerations could be addressed in specifically focused future studies. With regard to the outcome prevalence mapping approach of our study, it should be stressed that this is a technique, like other data exploratory techniques, that is used to ascertain relationships, associations, and structure in large collections of data. In our case, we use the mappings, simply put, to stratify patients. In this regard it parallels exactly traditional approaches where the first step in analysis is stratification of the data, and this most often is on the basis of percentile partitions. In the traditional approach, risk is most often ascertained from results of previous studies while exploratory approaches ascertain risk from the specific data at hand. For both approaches, however, subsequent rigorous statistical analysis is required for confirmation of hypotheses.

In conclusion, we identified a subgroup of patients at high risk for recurrent coronary events in a study population of non-diabetic postinfarction patients by using an exploratory graphical approach to map outcome event prevalence. The subgroup derived from interaction of atherogenic lipoprotein-associated risk, in this case—hypercholesterolemia, and inflammation-associated risk as manifested by high levels of CRP. Additionally, within the high-risk subgroup and from a set of lipoprotein, metabolic, inflammatory, and thrombogenic blood markers, only high HDL was found to be a significant and independent predictor of risk. Clearly, further studies are needed to confirm these findings in additional postinfarction populations and in other patient populations as well.

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