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Thrombogenic Factors and Recurrent Coronary Events

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Background—Thrombosis is a pivotal event in the pathogenesis of coronary disease. We hypothesized that the presence of blood factors that reflect enhanced thrombogenic activity would be associated with an increased risk of recurrent coronary events during long-term follow-up of patients who have recovered from myocardial infarction.

Methods and Results—We prospectively enrolled 1045 patients 2 months after an index myocardial infarction. Baseline thrombogenic blood tests included 6 hemostatic variables (D-dimer, fibrinogen, factor VII, factor VIIa, von Willebrand factor, and plasminogen activator inhibitor-1), 7 lipid factors [cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, lipoprotein(a), apolipoprotein (apo)A-I, and apoB], and insulin. Patients were followed up for an average of 26 months, with the primary end point being coronary death or nonfatal myocardial infarction, whichever occurred first. The hemostatic, lipid, and insulin parameters were dichotomized into their top and the lower 3 risk quartiles and evaluated for entry into a Cox survivorship model. High levels of D-dimer (hazard ratio, 2.43; 95% CI, 1.49, 3.97) and apoB (hazard ratio, 1.82; 95% CI, 1.10, 3.00) and low levels of apoA-I (hazard ratio, 1.84; 95% CI, 1.10, 3.08) were independently associated with recurrent coronary events in the Cox model after adjustment for 6 relevant clinical covariates.

Conclusions—Our findings indicate that a procoagulant state, as reflected in elevated levels of D-dimer, and disordered lipid transport, as indicated by low apoA-I and high apoB levels, contribute independently to recurrent coronary events in postinfarction patients. (*Circulation*. 1999;99:2517-2522.)

Key Words: thrombosis ■ coagulation ■ apolipoproteins ■ coronary disease ■ myocardial infarction

Thrombosis is a pivotal event in the pathogenesis of coronary occlusion and acute myocardial infarction.¹ Several prothrombotic factors, including factor V Leiden,² coagulation defects resulting from polymorphisms of factor II and factor VII genes,^{3,4} and elevated levels of factor VII,^{5,6} have been associated with an increased risk of myocardial infarction. In the Physicians' Health Study, an increased concentration of D-dimer, a degradation product of heightened fibrinolysis, was found to be a marker, but not an independent risk predictor, for future myocardial infarction among initially healthy men.⁷ These studies suggest that enhanced thrombogenesis may contribute to coronary thrombotic events.

Intravascular thrombogenesis is influenced by a complex interplay of procoagulant, anticoagulant, and fibrinolytic factors. In 1993, our multicenter research group hypothesized that in patients who survive an acute myocardial infarction, the presence of circulating blood parameters that reflect increased thrombogenic activity would be associated with an increased risk of recurrent coronary events during long-term follow-up. During a 4-year period (1994–1998), we enrolled 1045 patients after recovery from an index myocardial infarction in our thrombogenic risk-factor study. Special blood tests performed on these patients included the measurement of 5 coagulation factors, 1 marker of fibrin degradation

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(D-dimer), insulin, and several lipid parameters that can influence the thrombogenic process and plaque stability. This report describes the results of this prospective study.

Methods

Population

Patients of either sex who were ≥ 21 years of age and had been admitted to coronary care units of the 13 participating hospitals with a documented myocardial infarction were eligible for enrollment. Between October 1, 1994, and June 30, 1997, 5916 patients were screened during their coronary care unit admission, 2407 met the eligibility requirements, 1161 agreed to participate in the study at the time of hospital discharge, and 1045 patients were enrolled and signed the consent for participation at the 2-month postinfarction (baseline) visit. The demographic characteristics of the enrolled patients and the eligible nonenrolled patients were similar. The enrolled patients were followed up to a common termination date (March 31, 1998), with an average follow-up of 26 months. Eighteen patients were lost to follow-up and were censored from analysis at the time of their last contact date.

The diagnosis of myocardial infarction required enzyme confirmation, with MB isoenzyme fraction $>4\%$ of the total creatine kinase and symptoms or ECG changes consistent with an acute myocardial infarction. Patients were excluded from enrollment if they had coronary bypass graft surgery during the hospital phase of the index event; if they had significant comorbidity, such as malignancy or severe hepatic, renal, or cerebral disease; if they were receiving heparin-type anticoagulant therapy; for logistical reasons; or if they refused to consent for participation.

The patients were treated at the discretion of their attending physicians. The therapy rendered during the index infarction and the medications the patients were receiving at the time of baseline enrollment were identified and recorded.

Data Acquisition

Definitions for all clinical variables were specified in a manual of operations in advance of the start-up of the study. The clinical variables included demographic information, medical and cardiac history, course in the coronary care unit, and ejection fraction and chest roentgenogram when ordered by the attending physician. ECGs from the index coronary event were used to determine the type of infarction (Q-wave or non-Q-wave) according to the Manhattan criteria.⁸ Routine clinical data were missing in $<0.5\%$ of patients. Ejection fraction and chest roentgenogram studies were not obtained in 11.0% and 9.1% of patients, respectively.

Thrombogenic Factors

Blood (55 mL) was drawn in the fasting state at the baseline clinic visit 2 months after the index acute myocardial infarction. Plasma and serum samples were each separated, frozen, and sent to Rochester, NY, for central storage in a -70°C freezer. The hemostatic factor analyses included measurement of factor VII,⁹ factor VIIa,¹⁰ fibrinogen,¹¹ von Willebrand factor,¹² and plasminogen activator inhibitor-1.¹³ D-Dimer was measured by an ELISA technique (Asserachrom D-Di, Diagnostica Stago).¹⁴ Colorimetric assays were used to measure total cholesterol, HDL cholesterol, and triglycerides (all by Vitros Chemistry Products); apolipoprotein (apo)A-I and apoB were measured by Beckman Immunochemistry Systems; lipoprotein(a) was measured by immunoassay (Macra, Strategic Diagnostics); and insulin was measured by radioimmunoassay (Coat-A-Count Diagnostic Products). The concentration of LDL cholesterol was calculated by the Friedewald formula.¹⁵ Blood samples were analyzed in all but 1 patient. Analyses were run according to the manufacturers' specifications, and quality control was within the recommended precision for each test.

End-Point Data

The prespecified end points were death due to coronary heart disease or nonfatal myocardial infarction occurring on or before March 31, 1998. A 2-member committee reviewed information on the end-point events

from appropriate medical records. The criteria for diagnosing nonfatal myocardial infarction were the same as those applied to the index coronary event. The Hinkle-Thaler criteria¹⁶ were used to categorize the cause of death. The end point was defined as death due to coronary heart disease or recurrent nonfatal myocardial infarction, whichever occurred first. The end-point data were closed to the investigators until after the prespecified primary analyses were carried out.

Statistical Procedures

We planned to enroll 1300 patients to provide 80% power to detect a relative risk of ≥ 1.63 in the coronary event rate over 2.5 years for those with versus those without ≥ 1 thrombogenic risk variables, with a 2-sided significance level of $<5\%$. The concentrations of the hemostatic factors, lipids, and insulin were recorded in their continuous form. In advance of the completion of the study, it was prespecified that each of these variables would be dichotomized into their top and lower 3 risk quartiles for use in the planned survival analyses. The effects of the dichotomized thrombogenic variables on time to end point were examined graphically by the Kaplan-Meier method,¹⁷ and the log-rank statistic was used when comparing the difference in survival between each pair of curves.

The primary analysis was performed with the Cox proportional-hazards survivorship model¹⁸ (SAS PHREG computer program).¹⁹ Patients who died of causes other than coronary heart disease were censored at the time of their death. A stepwise forward selection procedure was used to identify important clinical risk predictors for the time to end point from 11 preselected covariates (age, sex, race, prior myocardial infarction, prior stroke, history of diabetes mellitus, index infarct type by ECG [Q-wave versus non-Q-wave], thrombolytic therapy, pulmonary congestion by chest roentgenogram, and ejection fraction during the index coronary event, and smoking status at enrollment), with enrolling hospitals ($n=13$) and hematology laboratory technicians ($n=2$) entered as stratification factors. Diabetes mellitus was coded as a 3-level variable: no diabetes, diabetes treated with oral hypoglycemic agents (type II), or diabetes treated with insulin (type I). Radiographic pulmonary congestion was coded as absent, present, or roentgenogram not obtained. Ejection fraction was coded as >0.30 , ≤ 0.30 , or not obtained. Cigarette smoking status was coded as never smoked, ex-smoker, or current smoker. A significance level of $P<0.10$ was used for entering a variable into the basic clinical model. The additional contributions of the thrombogenic variables to the basic clinical model were evaluated in a forward selection procedure, with $P<0.05$ for entering a variable. The contribution of 2-factor interactions to the model were evaluated for thrombogenic variables that showed significant ($P<0.05$) main effects. The effects of 7 cardiac medications (acetylsalicylic acid, ACE inhibitors, β -adrenergic blockers, calcium channel blockers, diuretics, oral anticoagulants, and statin lipid-lowering drugs that the patients were receiving at the time the baseline blood samples were drawn) on the final model were evaluated by adding these therapies singly to the model to determine whether the results could be partially explained by the use of any one of these therapies.

A comparison of end-point event rates between 2 levels of identified risk variables is reported in terms of the hazard ratio, ie, the ratio of the risk of the end-point event per unit time for patients in the top risk quartile to patients in the lower 3 risk quartiles. The significance of a linear trend in the hazard ratios over the 4 quartiles of each risk variable was also determined. Interactions of prespecified clinical, hemostatic, lipid, and insulin variables with the identified thrombogenic risk variable(s) were also assessed by the Cox model. Interaction was considered to exist if the ratio of the hazard ratios for the thrombogenic risk factor(s) was not proportional ($P<0.01$) across patient subsets. The reported analyses used version 1.0 of the analytic database released on June 5, 1998.

Results

Study Population

The clinical characteristics of the entire study population as well as those with and without coronary events during follow-up are presented in Table 1. During an average

TABLE 1. Baseline Characteristics According to Outcome

Characteristic	All Patients (n=1045)	Without Coronary Events (n=964)	With Coronary Events (n=81)
Age \geq 60 y	48	47	59*
Male	76	75	83
Race, white	74	74	75
History			
Prior myocardial infarction	19	17	39*
Treated hypertension	44	44	46
Diabetes mellitus	19	17	41*
Stroke	3	2	6*
Cigarette smoking status			
Never smoked	33	34	28
Ex-smoker	43	42	49
Current smoker	24	24	22
Index myocardial infarction			
Type of infarction new Q-wave	35	35	40
Pulmonary congestion	19	18	38*
Ejection fraction			
Mean	0.48 \pm 0.12	0.48 \pm 0.12	0.43 \pm 14*
\leq 0.30	12	11	24*
Thrombolytic therapy	34	35	26
Medications at enrollment			
Acetylsalicylic acid	82	82	75
ACE inhibitors	37	36	44
β -Blockers	76	77	64*
Calcium channel blockers	20	20	31*
Diuretics	17	15	35*
Oral anticoagulants†	18	18	14
Statin hypolipidemic drugs	38	39	35
Hemostatic factors			
D-Dimer, ng/mL	522 \pm 637	477 \pm 449	913 \pm 1573*
Factor VII, %	103 \pm 43	103 \pm 43	112 \pm 48
Factor VIIa, ng/mL	2.55 \pm 1.71	2.54 \pm 1.70	2.65 \pm 1.74
Fibrinogen, mg/dL‡	353 \pm 88	350 \pm 85	387 \pm 112*
PAI-1, ng/mL	28 \pm 28	29 \pm 28	25 \pm 18
von Willebrand factor, U/dL	149 \pm 69	148 \pm 68	158 \pm 74
Lipid and metabolic factors			
Apolipoprotein A-I, mg/dL	119 \pm 25	119 \pm 25	117 \pm 24
Apolipoprotein B, mg/dL	123 \pm 28	123 \pm 28	126 \pm 32
Cholesterol, mg/dL‡	197 \pm 44	197 \pm 44	199 \pm 47
HDL-cholesterol, mg/dL‡	39 \pm 12	39 \pm 11	40 \pm 17
LDL-cholesterol, mg/dL‡	120 \pm 38	120 \pm 38	123 \pm 43
Lipoprotein(a), mg/dL	25 \pm 23	25 \pm 23	23 \pm 23
Triglyceride, mg/dL‡	201 \pm 117	201 \pm 118	202 \pm 110
Insulin, IU/mL	19 \pm 29	19 \pm 29	20 \pm 20

PAI indicates plasminogen activator inhibitor. Values are percentage; plus-minus values are mean \pm SD.

* P <0.05 difference between those with vs without cardiac events.

†Oral anticoagulants: dicumarol or warfarin.

‡To convert cholesterol to mmol/L, multiply by 0.02586; to convert triglycerides to mmol/L, multiply by 0.01129; to convert fibrinogen to μ mol/L, multiply by 0.02933.

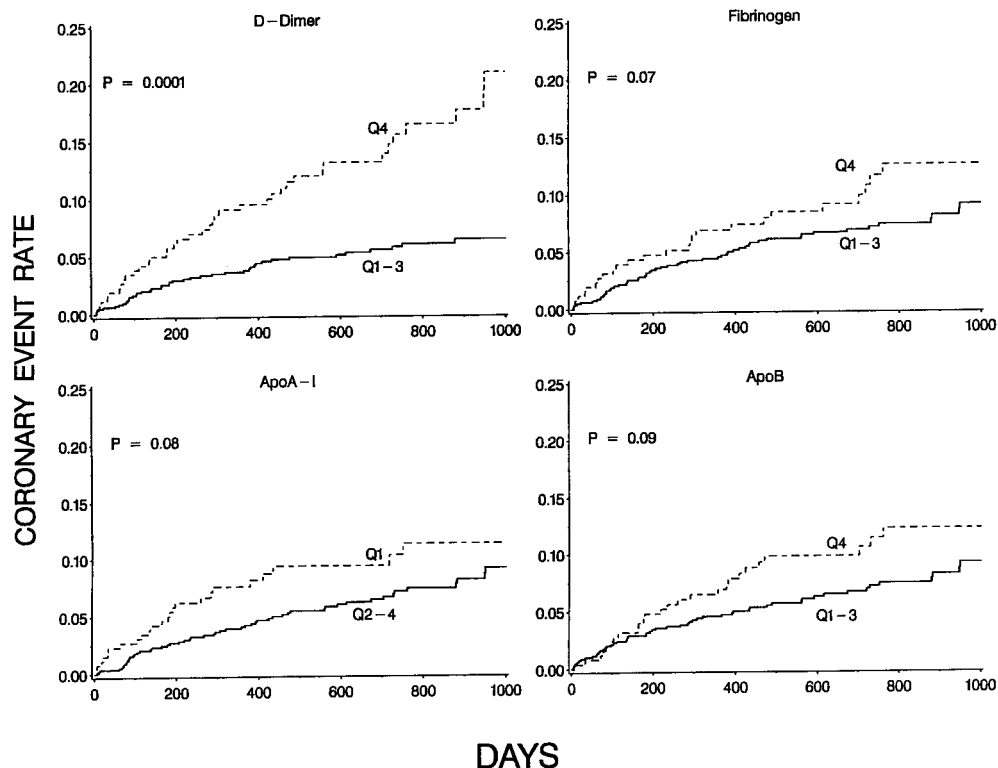


Figure 1. Cumulative rates of first cardiac event for 4 thrombotic factors. Kaplan-Meier cumulative cardiac event rates for top risk quartile (dashed line) vs lower 3 risk quartiles (solid line) are shown for D-dimer, fibrinogen, apoA-I, and apoB. Q₄ is top risk quartile for D-dimer (>650 ng/mL), fibrinogen (>398 mg/dL), and apoB (>140 mg/dL); Q₁ is top risk quartile for apoA-I (≤ 101 mg/dL). Probability value by log-rank statistic.

follow-up of 26 months (range, 7 to 42 months), 81 patients experienced a first recurrent coronary event, including 56 patients with a nonfatal myocardial infarction and 25 patients with a fatal coronary event. The baseline concentrations of D-dimer and fibrinogen were the only continuously distributed thrombotic factors that were significantly ($P < 0.05$) elevated in those with recurrent coronary events (Table 1).

Univariate Survival Analyses

The hemostatic, lipid, and insulin variables were dichotomized into their top and lower 3 risk quartiles, and Kaplan-Meier cumulative cardiac event curves were constructed for the dichotomized variables. Among these risk variables, only the top risk quartiles of D-dimer, fibrinogen, apoA-I, and apoB were associated with increased coronary event rates ($P < 0.10$) compared with the lower 3 risk quartiles, with the most significant difference ($P < 0.01$) observed with D-dimer (Figure 1).

Multivariate Survival Analyses

A multivariate survivorship model was constructed to determine the independent contribution that the hemostatic, lipid, and insulin variables made to recurrent coronary events in the presence of relevant clinical risk variables. Six clinical variables entered the clinical model at $P < 0.10$ (Table 2). The 6 hemostatic factors, the 7 lipid variables, and insulin were dichotomized (top versus lower 3 risk quartiles) and evaluated for entry into the clinical model. Only D-dimer, apoA-I, and apoB entered the clinical model at $P < 0.05$, with hazard ratios in the 1.82 to 2.43 range (Table 2). Similar hazard ratios were obtained for D-dimer,

apoA-I, and apoB when either total mortality or coronary death was used as the end point. There were no 2-factor interactions among the 3 identified risk factors.

The hazard ratios for D-dimer, apoA-I, and apoB were similar in the subsets involving the dichotomized clinical, hemostatic, and lipid covariates presented in Table 1, with no 2-factor interactions. The contributions of 7 baseline cardiac medications that the patients were receiving at enrollment (Table 1) to the survival model were evaluated one at a time, and none had a significant influence on the survivorship model involving the 3 identified risk factors.

TABLE 2. Contribution of Thrombotic and Lipid Factors to the Survival Model*

Factor	Hazard Ratio†	95% CI	P
D-Dimer (Q ₄ :Q ₁₋₃)	2.43	1.49, 3.97	0.0003
ApoB (Q ₄ :Q ₁₋₃)	1.82	1.10, 3.00	0.018
ApoA-I (Q ₁ :Q ₂₋₄)	1.84	1.10, 3.08	0.018

*The survival model includes adjustment for 6 clinical variables ($P < 0.10$ to enter): diabetes mellitus, prior myocardial infarction, index infarct type by ECG, pulmonary congestion on chest roentgenogram, male sex, and ejection fraction ≤ 0.30 .

†Ratio of the risk of experiencing a cardiac event per unit time for patients in the top risk quartile (Q₄ for D-dimer and apoB; Q₁ for apoA-I) to patients in the lower 3 risk quartiles (Q₁₋₃ for D-dimer and apoB; Q₂₋₄ for apoA-I) of the specified factor. The top risk quartiles were >650 ng/mL for D-dimer, >140 mg/dL for apoB, and ≤ 101 mg/dL for apoA-I.

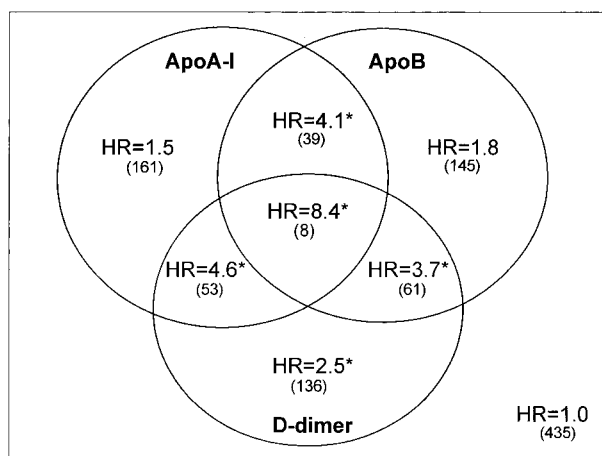


Figure 2. Individual and joint risks for patients in high- and low-risk partitions for D-dimer, ApoA-I, and ApoB. Distribution of numbers of subjects (numbers in parentheses) and hazard ratios (HRs) for recurrent coronary events are presented according to presence or absence of elevated D-dimer, reduced apoA-1, and elevated apoB, separately and in combination. *HRs that significantly exceed unity ($P < 0.05$). Subjects with none of the 3 risk factors form reference group, with HR set to unity by convention. HRs were obtained from a multivariate Cox model including terms representing main effects and interactions for 3 risk factors, with adjustment for 6 clinical variables presented in Table 2.

Because D-dimer, apoA-I, and apoB contribute independent yet equivalent risk, we explored the joint risk for patients in the high- and low-risk partitions for these 3 risk factors. The risks associated with combinations of any 2 or all 3 of the risk factors are, for the most part, multiplicative (Figure 2).

We explored the individual quartile contributions of D-dimer and the 2 apolipoproteins to the risk of recurrent coronary events. Table 3 shows the hazard ratios for recurrent coronary events for each of the 3 higher-risk quartiles relative

TABLE 3. Hazard Ratios for First Cardiac Events for D-Dimer, ApoB, and ApoA-I by Risk Quartile

Quartiles (Q)	D-Dimer		ApoB	
	Hazard Ratio*	95% CI	Hazard Ratio*	95% CI
Q ₁	1.0	...	1.0	...
Q ₂ :Q ₁	0.92	0.39,2.15	1.45	0.77,2.75
Q ₃ :Q ₁	1.39	0.64,2.94	0.76	0.35,1.68
Q ₄ :Q ₁	2.55	1.28,5.07	1.93	1.03,3.62
	ApoA-I			
Q ₄	1.0	...		
Q ₃ :Q ₄	1.17	0.59,2.33		
Q ₂ :Q ₄	0.99	0.48,2.06		
Q ₁ :Q ₄	1.73	0.86,3.46		

*The hazard ratios by quartile (Q₁, Q₂, Q₃, and Q₄) for D-dimer, apoB, and apoA-I were determined with the multivariate survivorship model, which included 6 clinical variables (Table 2), with the lowest risk quartile serving as the reference group. The hazard ratios are the risk of experiencing a cardiac event per unit time for patients in a given risk quartile to patients in the lowest risk quartile of a specified factor. There is a significant linear upward trend ($P < 0.01$) in the hazard ratios for the ordinal quartiles of D-dimer, but not for the ordinal quartiles of apoA-I or apoB. See text for details.

to their lowest risk quartile used as the referent group. D-Dimer and the 2 apolipoproteins have different risk patterns, with a gradient effect in the hazard ratios for the ordinal quartiles of D-dimer ($P < 0.01$ for a linear upward trend), but not for apoA-I or apoB ($P = 0.18$ and 0.10 for a linear upward trend, respectively). The risk for each of the apolipoproteins is concentrated in their highest risk quartile.

Discussion

Three thrombogenic risk factors were identified for recurrent coronary events that were independent of each other and of accepted clinical risk parameters. One thrombogenic factor, D-dimer, is a marker of enhanced in vivo fibrin degradation,²⁰ a finding that suggests the presence of a chronic hypercoagulable state. Two lipid-related factors, low apoA-I and high apoB levels, identified patients with recurrent coronary events in the absence of identified risk with standard lipid parameters. These findings provide a better understanding of the independent procoagulant and disordered lipid-transport mechanisms that contribute to recurrent coronary events in patients with established coronary disease.

Elevated blood levels of D-dimer have been associated with coronary disease in a few retrospective studies. A 4-fold increased risk of coronary events was observed among patients with symptomatic peripheral arterial disease who had high levels of D-dimer.²¹ In a case-control analysis from the Physicians' Health Study, a 2-fold higher risk of subsequent myocardial infarction was found in healthy men with baseline D-dimer exceeding the 95th percentile of the control distribution.⁷ A higher rate of ischemic heart disease was also found during 5-year follow-up of healthy adults with baseline D-dimer in the upper quintile of the normal distribution.²²

Elevated levels of D-dimer may reflect a systemic thrombotic state and possibly focal vessel-wall-related fibrin formation and degradation associated with unstable atherosclerotic-plaque activity.²³ Elevated levels of fibrinogen,²⁴ von Willebrand factor,²⁵ factor VII,^{5,6} and plasminogen activator inhibitor²⁶ have been associated with coronary events, but none of these hemostatic variables entered the multivariate survivorship model in this study (Table 2).

Apolipoproteins are directly involved in lipid mobilization and transport and in the metabolic conversion of different lipoprotein classes. Synthesis of apolipoproteins is under genetic control, but their concentrations can be influenced by diet, hormones, and medications.²⁷ ApoA-I, a key constituent of HDLs, returns cholesterol to the liver from peripheral cells in a process called reverse cholesterol transport.²⁸ ApoA-I also serves as a cofactor in lecithin-cholesterol acyltransferase activity, which is necessary for esterification of cholesterol and its efficient transport to the liver. Thus, apoA-I functions, in part, as a cholesterol scavenger. In the present study, patients with low concentrations of apoA-I had an increased risk of recurrent coronary events, without a similar risk in those with low concentrations of HDL cholesterol.

High concentrations of apoB were associated with recurrent coronary events in the absence of any identified risk from high concentrations of total cholesterol, LDL cholesterol, lipoprotein(a), or triglycerides. Similar findings were recently reported by Westerveld et al.²⁹ ApoB is enriched in small, dense lipopro-

tein particles,³⁰ a component of atherogenic lipoproteins that was not measured in this study. Small dense lipoprotein particles are thought to contribute to the lipid core of atherosclerotic plaques³¹ and may be a factor driving the atherosclerotic plaque to instability, with recurrent coronary events related to consequent plaque deterioration.²³

The finding from this study support the rationale for combined antithrombotic and lipid-lowering therapy in the secondary prevention of recurrent coronary events. The favorable results reported with statin-type drugs in cardiovascular event reduction may be related to improved plaque stability from the beneficial effects of this therapy on apoA-I and apoB levels, but also to the antithrombotic properties of the statins.³²

In conclusion, D-dimer is a uniquely strong predictor of recurrent coronary events, probably reflecting a hypercoagulable state. The risk contributions of low levels of apoA-I and high levels of apoB are consistent with the hypothesis that disordered lipid transport contributes to enhanced lipid deposition in plaques, with a consequent increased probability of plaque deterioration, erosion, and rupture. The combined presence of elevated D-dimer and dysfunctional apolipoprotein concentrations is associated with a superimposed likelihood of recurrent coronary events. These findings have important implications for prevention of secondary coronary events with combined antithrombotic and lipid-lowering therapy, especially in high-risk postinfarction patients.

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