

Effects of Lifestyle on Hemostasis, Fibrinolysis, and Platelet Reactivity

A Systematic Review

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The pathophysiology of atherothrombosis in cardiovascular disease is complex and multifactorial. No doubt, lifestyle habits such as exercise, smoking, diet, and alcohol consumption may have significant influence on cardiovascular disease. As the hemostatic system is assuming an increasingly prominent role in the pathogenesis and progression of atherosclerotic diseases, this review evaluates the effects of lifestyle habits (or lifestyle modifications) on blood coagulation, fibrinolysis, and platelet reactivity.

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The process of initiation, progression, and complication of atherothrombosis in cardiovascular disease is complex and can be influenced by multiple factors. Ischemic coronary syndromes such as unstable angina, myocardial infarction (MI), and sudden ischemic death share common pathophysiologic processes characterized by coronary plaque rupture with superimposed thrombus formation.^{1,2} Indeed, there is substantial experimental and clinical evidence that blood hypercoagulability or thrombogenicity promotes thrombus formation in the circulation, systemically and locally at the exposed atherogenic surface of the disrupted plaque.³

A wide range of factors has been identified in prospective epidemiologic studies to have a systemic effect on blood thrombogenicity. Certainly, there is increasing evidence of a close relationship between the traditional cardiovascular risk factors such as diabetes mellitus, hypertension or hyperlipidemia, and the increased thrombogenicity, which is characterized by hypercoagulability, hypofibrinolysis, or increased platelet reactivity.⁴⁻⁶ Conversely, improvements of these cardiovascular risk factors have been associated with a lower prothrombotic tendency.⁷⁻¹⁰ However, the associa-

tions and the effects of exercise or physical activity, psychosocial stress, diet, and other lifestyle habits on plasma indicators of thrombogenesis are less well established.

Further evidence of the influence of lifestyle changes on cardiovascular risk factors and clinical outcomes is illustrated by data from salt restriction and blood pressure reduction¹¹ and improved mortality by diets rich in oily fish. In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione (GISSI Prevenzione)¹² trial and the Diet and Reinfarction Trial (DART),¹³ there was a significant reduction in mortality after MI by increasing dietary n-3 polyunsaturated fatty acids (n-3 PUFA) and fish intake, respectively, and the mortality reduction has been partly attributed to a reduction in sudden cardiac death. Indeed, the recent reanalysis of the course of appearance of the effects of n-3 PUFA has showed an early and highly significant reduction of sudden cardiac death.¹⁴ However, many instances of sudden death have a thrombotic basis,¹⁵ with evidence of thrombus in the left main coronary artery, and sudden death is not simply an arrhythmogenic phenomenon. The aim of this review is to evaluate the effects of lifestyle habits (or lifestyle modifications) on the plasma indices of the 3 main systems of thrombosis: blood coagulation, fibrinolysis, and platelet reactivity.

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SEARCH STRATEGY

We performed a search using electronic databases (MEDLINE, EMBASE, and DARE), and additionally, abstracts from national and international cardiovascular meetings were reviewed to identify unpublished studies. Relevant authors of these studies were contacted to obtain further data.

BASIC PATHOPHYSIOLOGY AND CLINICAL PERSPECTIVES

The process of hemostasis and thrombus formation depends on the fine balance between the coagulation and fibrinolysis systems (**Figure**). The slower intrinsic clotting pathway depends on circulating coagulation factors, such as factors IXa and VIIIa. The more rapid extrinsic pathway is activated when blood is exposed to an extravascular factor such as tissue factor. Factor VII (FVII) plays a key role in the initiation of this coagulation mechanism when it forms complexes with tissue factor from a disrupted atheromatous plaque. Activation of the coagulation system induces the formation of thrombin from prothrombin. Thrombin converts fibrinogen into (insoluble) fibrin and induces platelet activation.

The binding of fibrinogen to platelet glycoprotein IIb/IIIa receptor leads to platelet aggregation. Fibrinogen is also the major determinant of blood and plasma viscosity, explaining 50% of the latter. Hence, increased tendency of hemostasis and thrombosis may be reflected in high levels of plasma fibrinogen, FVII, factor VIII (FVIII), thrombin generation, platelet reactivity, and high plasma viscosity. Increased thrombin generation may be indicated by high activation markers, such as prothrombin activation fragment 1+2 (F1+2) and thrombin-antithrombin complex (TAT), associated with a decrease in clotting time.

On the other hand, activation of the fibrinolytic system induces the conversion of plasminogen to plasmin by plasminogen activators. Tissue plasminogen activator (tPA) is the main fibrinolytic stimulator. Plasmin promotes the degradation

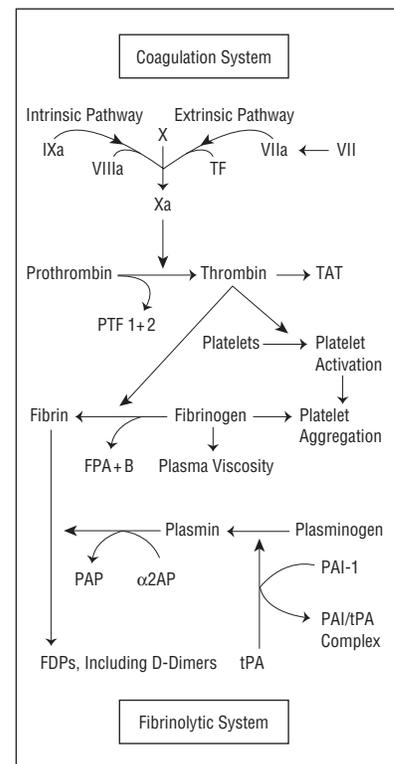
of fibrin within the thrombus, disintegrating clots and hence maintaining vascular patency. Fibrin degrades into soluble fibrin degradation products, including D-dimers. The primary inhibitor of the fibrinolytic process is the plasminogen activator inhibitor type 1 (PAI-1), which inhibits plasminogen activation by binding with tPA to form the PAI/tPA complexes. Therefore, impaired fibrinolytic function may be reflected in high plasma levels of PAI-1 or tPA antigen (which evaluates mainly the inactive PAI-1/tPA complexes) and/or indicated by low plasma levels of tPA activity or activation products such as D-dimer and plasmin-2-antiplasmin complex. Reduced plasmin generation leads to suppression of fibrinolytic activity, thus favoring fibrin persistence and thrombosis.

Most of these variables in the coagulation and fibrinolytic systems can be readily assayed using the enzyme-linked immunosorbent assay (ELISA) technique. It is important to distinguish the difference between the measurement of activity and antigen levels of these molecules. Although the antigen levels refer to the total amount of the circulating proteins (both bound and free), activity levels refer to the functionally active portions of the proteins. Thus, elevated antigen levels of a particular molecule do not necessarily reflect an increase in its functional activity. For example, elevated tPA antigen levels are often a reflection of high levels of circulating PAI-1, resulting in a large portion of tPA antigens being bound to PAI-1 and thereby rendering it inactive.¹⁶

Many of these systemic thrombogenic factors may be involved in the initiation of early atherosclerotic lesions and contribute to the progression of coronary thrombosis, plaque growth, and its clinical sequelae. For example, plasma fibrinogen has been shown to stimulate vascular smooth muscle migration and proliferation, promote platelet aggregation, and contribute to blood viscosity and thrombi.¹⁷ Many of these indices, including fibrinogen, FVII, von Willebrand factor (vWf, a marker of endothelial damage or dysfunction), D-dimer

antigen (a marker of cross-linked fibrin turnover), and tPA antigen, have been identified as independent predictors of subsequent cardiovascular events in prospective studies in both healthy subjects¹⁸⁻²² and those with cardiovascular risk factors^{23,24} or established coronary heart disease (CHD).²⁵ In addition, platelet hyperaggregation,^{26,27} plasma viscosity,²⁸⁻³⁰ and PAI-1 levels³¹⁻³⁴ have also been associated with cardiovascular morbidity and mortality in both men and women in prospective studies. Thus, the potential modifications of these hemostatic or thrombogenic factors by simple lifestyle changes as both primary and secondary prevention have attracted considerable interest from the public health perspective.

The recognition that the onset of cardiovascular events is frequently triggered by physical exertion or mental stresses has led to a possible link between neurohormonal activation and coronary ath-



Summary of the coagulation and fibrinolysis pathways. TF indicates tissue factor; TAT, thrombin-antithrombin complex; PTF, prothrombin fragments; FPA+B, fibrinopeptides A and B; PAP, plasmin-antiplasmin complex; α_2 AP, α_2 -antiplasmin; PAI-1, plasminogen activator inhibitor 1; tPA, tissue plasminogen activator; and FDPs, fibrinogen degradation products. Solid arrowhead denotes activation.

erothermogenesis. The increase in sympathoadrenal activation may not only trigger plaque rupture but also directly induce a hypercoagulable state, leading to a rapid propagation of occlusive coronary thrombus and, hence, sudden death. Typically, an intravenous infusion of epinephrine is used to mimic sympathetic activation and to examine the adrenergic effects on thrombogenic markers.^{35,36} The literature suggests a dose-dependent stimulation of FVIII clotting activity, vWf antigen, tPA activity, and platelets within a 15- to 40-minute infusion of norepinephrine. Although in healthy individuals the increase in coagulability may be counteracted by a rapid rise in fibrinolytic activity, such hemostatic balance between coagulation and fibrinolysis may be impaired in subjects with atherosclerotic disease or risk factors, and hence, catecholamine surge may trigger a hypercoagulable state and enhance the odds of overt thrombosis.³⁷⁻³⁹

The precise mechanisms underlying the hemostatic changes with sympathetic activation remain unclear. The lack of inhibition by aspirin in the increase of platelet aggregability and platelet secretory activity during norepinephrine infusion⁴⁰ or exercise³⁷ suggests that platelets are not being stimulated through the cyclooxygenase-dependent pathway. Furthermore, exercise and mental stress induced in platelet-dependent thrombin generation is suppressed by β -blocker therapy but not by aspirin, further support of the important role of sympathoadrenal activation.⁴¹

It should be emphasized, however, that lifestyle modifications rarely involve a single component; for example, an increase in exercise activity may accompany concomitant improvement in diet, which may in turn lead to weight loss and better psychological well-being. In addition, such efforts may also modify other known independent cardiovascular risk factors, such as lipid levels or hypertension. It is therefore difficult to separate the effects of these various factors in clinical studies, especially in observational studies, although coincidental confounding variables can be statistically controlled, at least to some

extent, with a large sample size and adequate statistical power. Furthermore, differences in aptitudes toward motivation and compliance between studied subjects are difficult to control and may confound the data. These may account for some of the conflicting results seen among studies that investigate the effects of exercise or dietary changes on thrombogenic factors.

EXERCISE AND THROMBOGENESIS

Many long-term epidemiologic studies have demonstrated an unequivocal and strong relationship of increased fitness, exercise, or physical activity during leisure time with reduced cardiovascular risk. Regular exercise is known to lower body weight and blood pressure and improve lipid profile (with a decrease in serum cholesterol levels and an increase in high-density lipoprotein-cholesterol [HDL-C] levels). In addition, regular exercise enhances functional capacity and psychological well-being, as well as quality of life. The underlying biological mechanisms through which these beneficial effects are mediated must be interrelated.

There are many reports on the effects of exercise on coagulation, fibrinolysis, and platelet activation. These mainly consist of intervention studies, prospective randomized controlled trials (**Table 1**), and numerous large, population-based, cross-sectional studies.

Several cross-sectional studies have consistently shown a positive effect toward an antithrombotic state, especially in lowering plasma levels of fibrinogen and improving fibrinolytic capacity by long-term regular exercise.^{62,63} However, it should be noted that most intervention or randomized controlled trials lack a comprehensive evaluation of both the hemostatic and fibrinolytic variables and thus provide only fragmentary data on the potential changes in hemostasis attributable to physical exercise. Indeed, some studies have yielded conflicting data, and this may be due to variations in exercise protocol or training programs used, populations studied (age, sex, CHD), seasonal factors,

and the lack of standardization in the analytical methods used for the assessment of various hemostatic factors, particularly in the assessment of platelet reactivity.

Health vs Disease

The available evidence from the intervention or randomized controlled trials would suggest that exercise or physical training evokes multiple effects on blood hemostasis in healthy individuals and in patients with atherosclerotic disease. For example, patients with atherosclerotic disease have higher basal levels of PAI-1 and lack a similar degree of increase in tPA activity after exercise when compared with healthy subjects.⁶⁴ In addition, higher thrombin generation has been found in patients with peripheral vascular disease in response to exercise, whereas no such increase was detected in healthy controls.⁵⁹

Effects of Short-term vs Regular Exercise on Coagulation and Fibrinolysis

While bearing in mind the considerable inconsistency of the results of various exercise studies due to methodologic variations, there are important differences between the effects of moderate endurance physical training and short-term strenuous exercise on both the hemostatic and fibrinolytic variables (**Table 2**). By and large, regular physical activities of moderate intensity in training programs enhance blood fibrinolytic capacity and possibly also reduce blood coagulation, although the latter remains disputable. Conversely, short-term strenuous exercise seems to induce a hypercoagulable state simultaneously with an increase in fibrinolytic capacity as evidenced by increased levels of fibrinogen, FVIII coagulant, and platelet activities, higher thrombin generation and hemoconcentration, markedly increased tPA activity, and possibly also decreased PAI-1 and tPA antigen levels. The rise in tPA activity is most apparent and seems to be directly proportional to the level of exercise intensity.^{52,66} However, the increased level of fibrinolytic activity seems to fall sharply dur-

Table 1. Intervention or Controlled Randomized Clinical Trials of Exercise on Thrombogenic Factors

Source	Subjects	Exercise	Main Results	Summary
Regular Exercise or Training				
Zanettini et al, ⁴² 1997	14 Sedentary subjects with mild HT	12 Weeks of aerobic exercise; 8 resumed sedentary lifestyle and were reexamined 2 mo later	Exercise ↓ resting and 24-h BP, LVM (echo), and Fg; FVIII unchanged; 2 mo after detraining, all indices returned to baseline except LVM	Regular exercise ↓ BP, LVM, and Fg, improves coronary risk
El Sayed et al, ⁴³ 1995	25 Young subjects randomized: active exercise or control	12 Weeks of exercise (30 min, 3 times per week at 70% [6 wk] and 80% [6 wk] of maximum HR)	No significant differences in the ↑ of APTT, TCT, FVIII antigen and activity, and tPA activity after exercise in both groups	Maximum exercise transiently ↑ coagulation and fibrinolysis. Physical conditioning appears not to influence coagulation and fibrinolysis at rest or at max exercise
El-Sayed, ⁴⁴ 1996	18 healthy subjects; 2 groups: high- vs low-intensity exercise	12 Weeks of preconditioned exercise: exercise on BE for 20 min, 3 times per week at 80% or 30% $\dot{V}O_{2max}$	No difference in resting tPA antigen and activity or PAI antigen and activity; no significant change in tPA antigen and activity and PAI antigen after training; PAI activity ↓ significantly with high-intensity exercise	High intensity exercise conditioning significantly ↓ resting PAI activity. This may be a favorable effect of exercise conditioning
Van den Burg et al, ⁴⁵ 1997	20 Young sedentary men vs 19 nontraining controls	12 Weeks of submaximal training	Posttraining, FVIII activity ↑, with APPT ↓ during maximum exercise. PAI antigen and activity and basal and exercise-induced tPA antigen were ↓, and tPA activity/antigen ratio ↑ in the training group. Controls had ↑ basal PAI antigen and activity, with ↑ basal and exercise-induced tPA antigen; basal and exercise-induced tPA activity were unchanged, but tPA activity/antigen ratio ↓	Training promotes both coagulation and fibrinolysis during exercise and may reverse unfavorable seasonal effects on fibrinolysis
Stratton et al, ⁴⁶ 1991	10 Young (aged 24-30 y) and 13 older men (aged 60-82 y)	6 Months of intensive endurance exercise training	Posttraining, $\dot{V}O_{2max}$ ↑ by 18% in the young group and by 22% in the older group. The older group had ↑ tPA activity by 39%, tPA in active form ↑ by 141%, PAI activity ↓ by 58%, and Fg ↓ by 13% posttraining. The young group had no significant changes in any of the measured indices	Intensive training ↑ resting tPA activity and ↓ Fg and PAI activity in older men
Schuit et al, ⁴⁷ 1997	Elderly (aged 60-80 y); active exercise or controls	6 Months of intensive training program	↑ tPA activity and Fg in exercise but not in controls. The ↓ in PAI antigen was significantly associated with ↓ in TGs and insulin. ↑ Fg coincided with ↑ CRP	Training ↑ fibrinolysis, but may cause chronically ↑ plasma levels of acute phase proteins in the elderly
Ponjee et al, ⁴⁸ 1993	20 Sedentary males and 15 sedentary females	9 Months of intensity training, 3-4 times per week; all ran a 15- and 21-km race after 24 and 36 wk, respectively. Blood drawn before training and 5 d before and 5 d after both races	No significant change in FVIII activity, vWf, and TAT during training. In both groups, no change in Fg after 24 wk but ↑ before the 21-km race and still ↑ significantly 5 d later	Exercise induces physical stress, which has significant effects on Fg, even at rest. In contrast to acute postexercise effects, regular exercise does not induce a long-term activation of the coagulation system
Vaisanen et al, ⁴⁹ 1999	132 Males (aged 52-62 y) randomized to exercise or control group	3 Years of regular low-to-moderate intensity exercise	Aerobic threshold ↑ by 8.8% in exercise but ↓ by 1.1% in controls. PAI activity unchanged in either group but 4G allele homozygotes in exercise group had a 36% ↓ in PAI	PAI activity unchanged by regular exercise in the whole group over the 3 y but may ↑ in 4G allele homozygotes
Acute Exercise				
Hegde et al, ⁵⁰ 2001	10 Healthy men	Ran at 70-75% $\dot{V}O_{2max}$ or walked at 1.2 mph for 30 min. Blood drawn at rest, after exercise, and every 20 min for 1-h recovery	Exercise ↑ FVIII activity by 66% and ↓ APPT and remained the same on recovery. tPA activity and D-dimers ↑ after run. D-dimers remained ↑ but tPA ↓↓ at 1-h recovery	Exercise ↑ coagulation and fibrinolysis but coagulation sustained during a time when fibrinolysis ↓, thus ↑ prothrombic risk in the first hour of recovery time
Lin et al, ⁵¹ 1999	11 Moderately active young men	Blood drawn at rest, immediately after, and 2, 6, and 24 h after BE	Exercise ↑ FVIII activity, ↓ APPT. Exercise ↑ tPA antigen and activity, ↑ total fibrin/Fg DPs, but ↓ PAI activity. FVIII activity ↑ persisted 2 and 6 h into recovery while fibrinolytic activity ↓ sharply	↑ Fibrinolysis during exercise seems to counterbalance the ↑ in coagulation but this hemostatic balance is not maintained during recovery
Rankinen et al, ⁵² 1995	9 Healthy men (aged 23-37 y)	Maximum and 2 randomized submaximum (30 min at 50% [aerobic threshold] and 78% [anaerobic threshold] $\dot{V}O_{2max}$) BE separated by 7 d	Baseline Fg, tPA, and PAI activity similar in each exercise. tPA activity ↑ after each exercise. PAI ↓ in maximum and anaerobic exercise but not aerobic exercise. All 24 h postexercise activity was similar to baseline levels. Fg unchanged in any exercise	Acute exercise ↑ fibrinolysis, which normalized 24 h later. Fg unchanged

(continued)

Table 1. Intervention or Controlled Randomized Clinical Trials of Exercise on Thrombogenic Factors (cont)

Source	Subjects	Exercise	Main Results	Summary
Acute Exercise (cont)				
Prisco et al, ⁵³ 1998	12 Male marathon runners (aged 35 ± 7 y)	Marathon; blood drawn day before, immediately after, and 24 and 48 h after run	Immediately after the race, Fg ↓, but ↑ in PTF F1 + 2, TAT, and ECLT, and ↑ tPA and PAI antigen, D-dimer, and ↑↑ Fg DPs. All indices unchanged at 24 h, but returned to baseline at 48 h	Persistence of coagulation and fibrinolysis activation up to 24 h after the end of the race
Cerneca et al, ⁵⁴ 1999	7 Rowers, 12 marathon runners, 7 weightlifters, and 7 healthy controls	Before and after near-maximum exercise: rowing machine, treadmill, own exercise equipment and BE, respectively	Significant ↓ basal protein C in rowers that ↓ further after exercise. Significantly ↑ basal ATIII, protein C, and protein S activity in runners vs rowers. A high percentage of weightlifters had ↓ in tPA and ↑ PAI after exercise. Controls showed ↑ fibrinolytic activity and all anticoagulants after exercise	Physical activity benefits the coagulation system, particularly fibrinolysis, but certain subjects may be at risk of thrombosis
Watts et al, ⁵⁵ 1991	100 Athletes vs 25 nonexercise controls	10- To 26.2-mile race. Blood drawn before and after races	No difference in baseline Fg, FVII, FVIII, or vWf between the 2 groups but athletes showed ↑ fibrinolytic activity and ↓ adrenaline-PAggr. Immediately posttrace, ↑ platelet count and FVIII clotting but no evidence of consumption or thrombin modification of FVIII clotting. Adrenaline-PAggr ↓ and fibrinolysis ↑ after the race	A hypocoagulable rather than a hypercoagulable state during running in athletes
Wang et al, ⁵⁶ 1995	23 Healthy men (mean age, 21 y) randomized to control or training group	BE at 60% $\dot{V}O_{2max}$ for 30 min/d, 5 d/wk for 8 wk, then deconditioned for 12 wk	PAggr and adhesiveness ↑ by short-term strenuous exercise in both groups, but ↓ after exercise in the trained subjects. Deconditioning reversed the resting and postexercise effects to the pretraining state	PAggr and adhesiveness may be ↓ by training but reversed to the pretraining state after deconditioning
Li et al, ⁵⁷ 1999	15 Healthy men with and without 1 week of pretreatment with aspirin	Exercise to exhaustion by BE, initial workload of 30 W and increments of 10 W/min	Exercise ↑ sP-sel expression and levels, ↑ platelet and leukocyte interaction, platelet-platelet and platelet-leukocyte Aggr, and PTF F1 + 2. Aspirin had no effects on all these indices	Exercise ↑ platelet and leukocyte activation and Aggr in vivo and ↑ responsiveness in vitro. Aspirin did not attenuate the prothrombic effects of exercise
Andreotti et al, ⁵⁸ 2001	27 CHD patients on aspirin vs 12 healthy controls	Blood drawn at rest, immediately after, and 0.5 and 3 h after mild exercise (≤stage III modified Bruce)	Exercise induced myocardial ischemia in 14 patients. PAggr ↑ in all CHD patients at peak exercise but return to baseline at 3 hr. No changes in controls. vWf was similar in both groups	Mild exercise transiently ↑ PAggr in patients with CHD. The effect is independent of myocardial ischemia, occurs despite aspirin
Mustonen et al, ⁵⁹ 1998	15 PVD patients vs 15 healthy controls	Blood drawn before and after submaximum treadmill test	Exercise ↑ tPA antigen and activity, D-dimer, PAP, and catecholamines in both groups but higher levels in patients, both at rest and after exercise. TAT ↑ in patients but not in controls after exercise. PAI antigen unchanged	Sudden catecholamine release and local ischemia during exercise may ↑ the preexisting prothrombic potential of the atherosclerotic vessel wall
Li-Saw-Hee et al, ⁶⁰ 2001	20 Patients with chronic AF vs 2 groups of matched controls in SR	Blood drawn before, after, and at 20 min post-standard Bruce exercise	Basal vWf and Fg ↑ in AF. Significant ↑ in Fg and ↓ in PAI after exercise but no changes in vWf or sP-sel in AF patients. All indices unchanged in controls, despite longer duration and greater workload of exercise	Acute exercise induced a hypercoagulable state in chronic AF, and possible ↑ in fibrinolysis. No significant effect on ET dysfn or platelet activation
Gibbs et al, ⁶¹ 2001	20 Patients with stable CHF vs 2 groups of matched controls	Blood drawn before, after, and at 20 min post-standard Bruce exercise	Basal vWf and sP-sel ↑ in CHF. Significant ↑ in plasma viscosity, Fg, and hematocrit after exercise and positive correlation between exercise workload and plasma viscosity	Acute exercise induced a hypercoagulable state in CHF. Moderate exercise should be encouraged in CHF patients but vigorous exercise should be avoided

Abbreviations: ACA, arachidonic acid; ADP, adenosine diphosphate; Aggr, aggregation; ALA, α -linolenic acid; α 2AP, α 2-antiplasmin; APTT, activated prothrombin time; AT, antithrombin; β -Tbg, β -thromboglobulin; BE, bicycle ergometer; BMI, body mass index; BP, blood pressure; BT, bleeding time; CABG, coronary artery bypass grafting; CECs, circulating endothelial cells; CHD, coronary heart disease; CRP, C-reactive protein; DBR, double-blind randomized; DDAVP, 1-desamino-8-D-arginine vasopressin; DHA, docosahexaenoic acid; DPs, degradation products; ECLT, euglobulin lysis time; EPA, eicosapentaenoic acid; ET dysfn, endothelial dysfunction; F1 + 2, fragments 1 + 2; Fg, fibrinogen; FMD, flow-mediated vasodilation; FPA, fibrinopeptide A; FVII, factor VII; FVIII, factor VIII; HDL, high-density lipoprotein; HR, heart rate; HT, hypertension; HUVECs, human umbilical vein endothelial cells; IGT, impaired glucose tolerance; IMT, carotid intimal media thickness; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; LDL, low-density lipoprotein; LV, left ventricle; LVM, LV mass; MI, myocardial infarction; n-3 and n-6, omega-3 and omega-6 polyunsaturated fatty acid; PAggr, platelet aggregation; PAI, plasminogen activator inhibitor; PAP, plasmin α 2-antiplasmin; PF, platelet factor; PHC, platelet hemostasis capacity; PL, phospholipid; PTF, prothrombin fragment; RBCs, red blood cells; rehab, rehabilitation; SNP, sodium nitroprusside; sP-sel, soluble P-selectin; suppl, supplementation; TAT, thrombin-antithrombin complex; Tbx, thromboxane; TCT, thrombin clotting time; TGs, triglycerides; tPA, tissue plasminogen activator; vWf, von Willebrand factor; WBCLT, whole blood clot lysis time; WHR, waist-hip ratio; ↓, decrease; ↑, increase.

ing the recovery period, whereas activation of the coagulation cascade is persistent.^{50,51}

This phenomenon has been thought to possibly precipitate acute coronary thrombosis, leading to sud-

den cardiac death in susceptible sedentary individuals or patients with preexisting atherosclerotic disease

who may not sustain their fibrinolytic capacity (perhaps due to endothelial dysfunction) when they are exposed to unaccustomed, short-term, strenuous physical exertion. However, recent studies have suggested that functional fibrinolytic activity was similar in physically active men with and without a history of MI⁶⁷ and in older men with hypertension when compared with normotensive subjects.⁶⁸

Although the results of the studies that investigated the effects of short-term exercise on fibrinolytic markers are more consistent, studies that investigated plasma fibrinogen concentration have produced conflicting data. Several studies have reported a significant increase in plasma fibrinogen after strenuous exercise,^{54,69,70} but others using different protocols have shown either no significant effects^{52,71,72} or even a reduction in plasma fibrinogen level after short-term, intense physical exercise.⁵³ It is possible that the changes in coagulation markers depend on the type of physical exercise to which subjects are subjected. Cerneca et al⁵⁴ demonstrated that this might be the case, since rowers, marathon runners, and healthy controls revealed a significant increase in plasma fibrinogen levels after near-maximum exercise tests, whereas weightlifters showed no significant change.

Interestingly, genetic factors might also explain the different effects of exercise on hemostatic or fibrinolytic factors. For example, Montgomery et al⁷⁰ investigated the effects of long-term physical training and short-term, intensive exercise on plasma fibrinogen levels in 156 men in the British Army and found that subjects carrying the A allele of the G453A polymorphism in the β -fibrinogen gene showed a higher increase in plasma fibrinogen than men with the GG genotype.

Endurance Exercise or Physical Training and Fibrinolysis

Various studies have consistently reported a significant improvement in fibrinolytic capacity following regular exercise or physical training. The increase in fibrinolysis is indicated

by a decrease in PAI-1 levels and also a rise in tPA activity. Indeed, Szymanski et al⁷³ demonstrated that persons who are habitually active have the lowest basal PAI-1 activity but the highest increase of tPA activity in response to exercise when compared with inactive subjects. This effect has been repeatedly demonstrated using various exercise intensity and duration.^{46,47,72,74-76} One study⁷⁷ reported lower PAI-1 levels in those participating in regular sporting activities than the respective age-matched sedentary individuals or elderly athletes and post-MI patients, but tPA activities were significantly higher after exercise in those with lower pretest PAI-1 level.

Endurance Exercise or Physical Training and Coagulation

Most exercise studies^{43,50,51,69,78-80} of varying degrees of intensity and duration have been found to induce a significant increase in FVIII coagulant activity. However, others have demonstrated that regular training exercise does not seem to induce significant effect on resting or postexercise levels of FVIII activity and antigen in normal healthy and sedentary subjects,^{45,48,55,81} although 4 weeks of physical training has been shown to lower resting levels of FVIII activity and antigen in post-MI patients.⁸² Although high levels of plasma fibrinogen are usually found in patients with CHD or cardiovascular risk factors, randomized controlled trials have found mixed results in fibrinogen levels in response to regular physical activity.^{46,76,83-85} For example, 12 weeks of aerobic exercise training in sedentary hypertensive subjects lowered blood pressure, left ventricular mass, and plasma fibrinogen levels, but changes returned to baseline values (except left ventricular mass) at 2 months after detraining.⁴² Similarly, 6 months of intensive endurance training reduced plasma fibrinogen in elderly men but not in young men.⁴⁶ On the other hand, Schuit et al⁴⁷ reported a significant increase in plasma fibrinogen levels in elderly males after a same duration of intensive training, whereas Ponjee et al⁴⁸ reported no change in plasma fibrino-

Table 2. Summary of the Effects of Exercise on Thrombogenic Factors*

Thrombogenic Markers	Physical Exercise	
	Regular	Acute
Fibrinogen	↓	↑
Factor VII	↓	↔
Plasma viscosity	↓	↑
tPA	↑	↑†
PAI-1	↓	↓
Platelet activation	↓	↑
Fibrinopeptide A	Unknown	↑
Thrombin generation‡	Unknown	↑

Abbreviations: PAI-1, plasminogen activator 1; tPA, tissue plasminogen activator.

*Adapted from Imhof and Koenig.⁶⁵

†In healthy subjects.

‡A rise in thrombin generation is indicated by elevated levels of thrombin-antithrombin III complex and prothrombin fragments 1 + 2.

gen levels in both males and females after 24 weeks of training.

Only a few reports^{80,83,86-88} on the effects of exercise on FVII are available and, again, with mixed results. Moderate exercise has no significant influence on FVII or at the most the effect is only relatively short-lived. Studies⁸⁹⁻⁹³ on the effects of exercise on fibrinopeptide A (a marker of thrombin activity and fibrin formation) have again produced conflicting results, although raised plasma markers of thrombin generation (TAT and F 1+2) with short-term exercise had been reported. The overall mechanisms underlying these changes in coagulation or fibrinolysis, in response to short-term or long-term endurance exercise, are poorly understood and still remain speculative, but interactions involving neurohormonal pathways are very likely.^{59,94-96}

Exercise Effects on Platelet Reactivity

The effects of exercise on platelet aggregation and activation have been extensively studied, but the results are highly variable.^{97,98} It is noteworthy that measurements of platelet reactivity either in vitro or ex vivo aggregability assays or in vivo platelet secretory products (mainly β -thromboglobulin and platelet factor 4) are associated with considerable methodologic difficulties and thus may

account for the discrepancies of results reported in the literature.

By and large, short-term, strenuous exercise induces a transient increase in agonist-induced platelet aggregation both *in vitro* and *ex vivo* and an increase in platelet counts, adhesiveness, and *in vivo* platelet secretory activity. Overall, these effects seem to be more pronounced in sedentary than healthy subjects.^{99,100} In contrast, long-term endurance physical training (preconditioned) in men and women at moderate intensity (50%-55% of peak oxygen consumption) seems to suppress platelet adhesiveness and aggregation both at rest and after short-term, strenuous exercise. However, the effects reversed back to the pretraining state after a period of deconditioning and hence the importance of regular moderate exercise to maintain such potential benefits.^{56,101}

Thus, as with fibrinolytic response, platelet reactivity in response to exercise also seems to be both duration and intensity dependent. However, the underlying mechanisms remain unclear. Increases in catecholamine concentrations and shear stress are probably important.^{102,103} Perhaps the short-term response may be related to the release of tPA from endothelial cells associated with higher catecholamine release during exercise. Interestingly, the fact that aspirin treatment had no significant influence on platelet activation induced by heavy exercise in patients with stable angina pectoris and matched healthy controls suggests that the response may not be cyclooxygenase-pathway dependent.^{37,38} This implies that aspirin may have a limited antithrombotic effect during physical exercise and probably also in other situations with increased catecholamine levels such as during acute psychological stress. The chronic platelet response, however, may be related to nitric oxide release as a consequence of regular low-to-moderate exercise training.¹⁰¹

Effects of Exercise in Specific Patient Groups on Coagulation and Fibrinolysis

There is increasing evidence that patients with chronic atrial fibrilla-

tion are associated with a prothrombotic or hypercoagulable state. We demonstrated that short-term exercise to exhaustion significantly increased plasma fibrinogen and lower PAI-1 levels but had no influence on vWf or soluble P-selectin levels in patients with atrial fibrillation when compared with age- and sex-matched patients in sinus rhythm.⁶⁰ In another similar exercise study in patients with stable congestive heart failure, we also found that plasma viscosity, fibrinogen, and hematocrit levels were significantly increased, both immediately after exercise and at 20 minutes into the recovery period.⁶¹

WEIGHT REDUCTION

Overweight and obesity, assessed either by body mass index (BMI), a measure of weight in kilograms divided by the square of height in meters, or waist-to-hip circumference ratio (WHR), are associated with increased cardiovascular morbidity and mortality.^{104,105} Indeed, there is increasing evidence that moderate weight loss could result in regression of coronary arterial lesions and significantly reduces cardiac events and total mortality.¹⁰⁶

Most of the present data on thrombotic profile in overweight or obese persons relate to PAI-1 and tPA antigens. For example, both BMI and WHR correlate strongly and positively with hemostatic factors but negatively with fibrinolytic activity.¹⁰⁷ It has been shown that women with high WHR have significantly higher fibrinogen and PAI-1 levels compared with obese women with a low WHR or with lean women.¹⁰⁸ Similarly, after adjusting for other lifestyle variables, obese men (BMI >30) had 50% higher PAI-1 activity and 30% higher tPA antigen when compared with men of "ideal" BMI (<25).¹⁰⁷ In addition, high fibrinogen and plasma viscosity have also been found to be associated with increasing BMI,^{107,109,110} although, overall, there is only little evidence that weight reduction reduces plasma fibrinogen or viscosity levels.^{106,111} On the other hand, there is plenty of evidence that weight reduction by regular exercise and dietary changes

reduces PAI-1 and tPA antigen levels,^{33,112} suggesting a causal relation (**Table 3**).

Recent evidence has shown that elevated plasma PAI-1 activity seen in obese individuals may be caused by increased PAI-1 release from visceral adipose tissue.^{122,123} However, a liposuction procedure that removes visceral adipose tissue and achieves a weight reduction of 5% after 3 months without change in lifestyle does not seem to significantly reduce plasma levels of vWf, fibrinogen, or PAI-1.¹¹⁷ In contrast, surgical removal of adipose tissue in 19 patients with morbid obesity with a mean body weight reduction of 50 kg at 6 months and 64 kg at 12 months has led to a significant reduction in FVII, fibrinogen, and PAI-1 activity and a slight increase in tPA activity. Therefore, it seems that a large amount of adipose tissue may need to be removed artificially before an improvement of hemostatic and fibrinolytic profiles could be detected, or it might be that a change in lifestyle, including increased exercise and dietary control leading to weight reduction, is a prerequisite for improvement in coagulation and fibrinolysis. The latter seems more likely the case, since there is evidence that limited weight loss (<7 kg) by lifestyle modifications alone could lead to a reduction of hemostatic factors, FVII, and PAI-1 levels, while increasing the tPA activity.¹⁰⁶

Indeed, obesity and syndrome of insulin resistance are inextricably linked with hypertriglyceridemia, hyperinsulinemia, hypo-HDL-cholesterolemia, glucose intolerance, and hypertension. It is known that both triglyceride and insulin resistance correlate strongly and positively with PAI-1.¹²⁴⁻¹²⁶ In fact, dietary intervention with a low-saturated-fat diet¹²⁷ or gemfibrozil treatment¹²⁸ that lowers serum triglyceride levels has been accompanied by improvement and even normalization of the fibrinolytic activity. Thus, it is plausible that weight reduction improves fibrinolytic capacity via modifications in both lipids and insulin resistance profiles. However, data on the interactions between physical activity and diet and hemostasis are scarce, and it is likely that moderation in both

Table 3. Weight Reduction and Thrombogenic Factors

Source	Subjects	Design	Main Results	Conclusion
Rissanen et al, ¹¹³ 2001	51 Obese women (mean age, 44 y; BMI, 36 kg/m ²)	DBR, 12-mo weight ↓ trial of placebo and orlistat, plus hypoenergetic diet adjusted for actual body weight at 6 mo. Measurements at 3- to 6-mo intervals	Weight ↓ similar in orlistat and placebo groups. Orlistat did not influence coagulation factors beyond its effect on weight ↓. PAI and FVII ↓ in first 3 mo and correlated with ↓ weight. Between 6 and 12 mo, changes of PAI and FVII paralleled changes of weight; activities ↑ with weight rebound but remained below the 6-mo values if weight ↓ continued. Serum insulin correlated with PAI and FVII at 6 mo and with PAI at 12 mo. No changes in Fg at any time	Maintenance of modest weight ↓ is associated with ↓ in PAI and FVII in obese women. Change of serum insulin is associated with changes of PAI. Fg is not affected by modest weight ↓
Marckmann et al, ¹¹⁴ 1998	36 Obese patients in a 2-stranded randomized intervention study	Randomized: very-low-energy diet (8 wk) or low-energy diet (17 wk), both given anorectic compound, then rerandomized to 24-wk maintenance diets	Mean weight ↓ of 13.6 kg. After 24-wk weight maintenance, PAI antigen ↓ by 34%; TGs, 30%; FVIIc, 12%; cholesterol, 9%; Fg, 6%; but HDL-C ↑ by 5%. All changes highly significant. No differences between slimming or maintenance regimens	Major weight ↓ is associated with sustained and marked improvements in lipids and coagulation profile, irrespective of the tested slimming and maintenance regimens
Folsom et al, ¹¹⁵ 1993	90 Men and 88 women; moderately overweight	Randomized to 1 of 4 weight loss treatment groups or controls. Measurements at baseline and 6 mo	Treatment ↓ weight 9.4 kg in men and 7.4 kg in women and significantly ↓ PAI, tPA antigen, and FVII. ↓ In these variables correlated with the ↓ in weight and TGs. No change in D-dimer, Fg, or protein C with weight ↓	Weight ↓ can improve abnormalities in hemostatic factors associated with obesity
Primrose et al, ¹¹⁶ 1992	19 Patients underwent surgery for obesity	Blood drawn before and at 6 and 12 mo after operation	Surgery ↓ mean weight of 50 kg at 6 mo and 64 kg at 12 mo. At 12 mo, significant ↓ in TC, FVII, Fg, and PAI. tPA activity ↑ slightly. No changes in APPT, FVIII, vWf, α2AP, TAT, protein C, β-Tbg, PF 4, FPA, or platelet count	Surgical treatment of morbid obesity may have a long-term beneficial effect on mortality from atherosclerotic disease
Berntorp et al, ¹¹⁷ 1998	53 Patients with Dercum disease	Blood drawn preoperatively, 2 and 4 wk, and 3 mo postoperatively	Weight ↓ of 4 kg sustained during follow-up. Slight ↑ in coagulation factors 2 and 4 wk postoperatively. At 3 mo the values ↓ to preoperative levels except for PAI, which still slightly ↑	Surgical removal of adipose tissue, without change in lifestyle, does not seem to improve coagulation and fibrinolysis
Sudi et al, ¹¹⁸ 2001	20 Obese boys and 40 obese girls (mean age, 12 y)	Blood drawn before and after 3 wk of low-caloric diet and exercise. Body composition assessed by bioelectrical impedance	Estimates of adiposity, insulin, and TGs correlated with PAI and tPA antigen. WHR correlated with fibrinolytic indices only in girls. Insulin and tPA antigen contributed to PAI, whereas percent fat mass and TGs contributed to tPA antigen. Weight loss ↓ adiposity, abdominal adiposity, fibrinolytic, and metabolic indices. Initial PAI and changes in body mass contributed to ↓ in PAI. Initial tPA antigen contributed to changes in tPA antigen	Fibrinolytic indices associated with body mass ↓ but can occur independently of a concomitant ↓ in fatness. Initial PAI and tPA antigen predict changes of fibrinolytic indices
Lindahl et al, ⁷⁶ 1999	186 Obese subjects with IGT	Randomized to active program 1-y intensified dietary and exercise or usual-care controls	Active group ↓ weight (5.4 kg vs 0.5 kg), ↑ oxygen consumption by 10% (↓ by 1% in controls), ↓ PAI (31% vs 12%), and ↓ tPA antigen (14% vs 6%)	Intense lifestyle program has sustained beneficial effects on fibrinolysis
Mavri et al, ¹¹⁹ 1999	52 Healthy, premenopausal, obese women (33 completed the study)	Weight ↓ program with a hypocaloric diet. Blood drawn at entry, 1 wk, end of program, and 5 mo follow-up	At end of program, PAI antigen and activity ↓. Leptin ↓ but no change in adiponin. PAI associated with BMI, body fat, leptin, and insulin. At 5 mo, PAI remained ↓ in 14 women who maintained weight ↓ but ↑ in 16 women who regained weight. ↑ In PAI correlated with ↑ in body fat and leptin. BMI was the major determinant of PAI level	Weight loss with hypocaloric diet ↓ PAI, which is more closely related to changes in adipose tissue than to changes in metabolic variables, suggesting a significant role for adipose tissue in regulating plasma PAI
Charles et al, ¹²⁰ 1998	324 Nondiabetic patients with central obesity (aged 35-65 y; mean BMI, 32.5 kg/m ²)	DBR 1 y: placebo or metformin groups, in addition to diet and exercise	PAI activity and antigen ↓ significantly but similarly in both groups. This ↓ mainly in subjects who lost weight. tPA antigen and vWf ↓ significantly more in the metformin group	Weight ↓ associated with ↓ in PAI. Metformin may have effect on production or metabolism of tPA antigen and vWf
Calles-Escandon et al, ¹²¹ 1996	19 Elderly obese subjects (aged 60-70 y; BMI >32 kg/m ²)	11 Weeks of energy-restricted diet by 3700-4600 kJ/d deficit	Initially elevated PAI ↓ by 50%, with a ↓ in tPA/PAI complexes but no change in tPA. PAP complex ↑ by 20%. The ↓ in PAI and the ↑ in PAP complexes correlated with weight and fat mass ↓s. No correlation between fibrinolytic variables and baseline substrates or insulin, but change in PAI correlated with change in plasma triacylglycerols	Energy restriction induces moderate weight ↓ and leads to diminution of ↑ plasma PAI and relief of inhibition of fibrinolysis in elderly, obese subjects

Abbreviations: For an explanation of abbreviations, see footnote to Table 1.

efforts would yield a more powerful impact on coagulation and fibrinolytic systems than either lifestyle modification alone. Clearly, more studies are needed to dissect such complex interactions.

DIETARY LIPIDS ON THROMBOGENESIS

Outcome Studies With n-3 PUFA

The role of dietary changes in modifying CHD risk has been well established.¹²⁹ The recent Lyon Diet Heart Study¹³⁰ reported a 50% to 70% lower risk of recurrent heart disease as measured by different combinations of outcome measures, including cardiac death and nonfatal myocardial infarctions in survivors of first-MI patients who received a Mediterranean diet (with more fish, more fiber, but less fat) supplemented with the precursor of n-3 PUFA, α -linolenic acid (18:3n-3, derived mainly from vegetable or seed oil) when compared with controls who received usual care. The study is in parallel with the results of other secondary prevention dietary trials, namely, the DART and GISSI Prevenzione trials,^{12,13} which similarly used a diet with low intake of total and saturated fats and/or increased intake of oily fish rich in n-3 PUFA. Indeed, at least 2 servings of fish per week, especially fatty fish, equivalent to an intake of n-3 PUFA approaching 1 g/d have been recommended by the American Heart Association.¹³¹

The experimental group in the Lyon Diet Heart Study had higher plasma levels of oleic acid, α -linolenic acid, and eicosapentaenoic acid (EPA, 20:5n-3). In the GISSI Prevenzione trial, patients received daily doses of n-3 PUFA as 1 gelatin capsule containing EPA and docosahexaenoic acid (DHA, 22:6n-3) as ethyl esters. In the DART study, at least 3 servings of fatty fish or approximately 15 fish oil capsules per week led to a significant 29% reduction in both cardiac and total mortality within 4 months. The low incidence of cardiovascular disease among Greenland Eskimos and coast land Japanese has been related to high intake of the marine n-3 PUFA: EPA and DHA. However, how particular

lipid constituents in these diets contribute to coronary risk is unknown. The rapidity of onset of the beneficial effects seen in these studies suggests that the diet might have anti-inflammatory, antithrombotic, and even membrane stabilizing and hence antiarrhythmic effects besides lowering the rate of progression of atherosclerosis. Indeed, the effects of dietary manipulations or supplementation with individual or complex dietary lipids on thrombogenic variables have attracted considerable interest with a particular emphasis on n-3 PUFA, although the interplay between these lipid constituents and the coagulation system remains largely unclear.

Epidemiologic Studies

Thus far, only indirect evidence links dietary saturated fatty acids with enhanced thrombogenesis in humans.^{132,133} When unsaturated fatty acids of the n-9, n-6, or n-3 families replace saturated fatty acids in the diet of experimental animals, the development of atherothrombosis was inhibited, but the doses supplemented tended to be much higher than in human clinical studies.^{134,135} Data from the Coronary Artery Risk Development in Young Adults¹³⁶ study showed that usual intake of fish or dietary supplementation with α -linolenic acid, EPA, and DHA was not associated with levels of FVIII, fibrinogen, or vWf and, hence, suggests that usual customary intakes of fish and n-3 PUFA in populations that generally do not consume large amounts of these food items are not associated with these hemostatic factors. Similar results were also found in the PRIME (Prospective Epidemiological Study of Myocardial Infarction) sub-study,¹³⁷ which showed no relationships between fatty acids and fibrinogen, vWf, PAI-1, or FVII levels. By contrast, results from another cross-sectional study¹³⁸ suggest that increases in dietary n-3 PUFA intake from fish is negatively associated with fibrinogen, FVIII, and vWf and positively associated with protein C levels. Such differences have been attributed to higher EPA and DHA intakes in the latter study.

Intervention Studies

There are a large number of intervention studies on the effect of n-3 PUFA in the form of fish oil capsules, fishmeals, or its precursor α -linolenic acid on various hemostatic factors (**Table 4**). We discuss its effects on coagulation, fibrinolysis, and platelet reactivity.

Coagulation and Rheology

The effect of n-3 PUFA on fibrinogen and blood rheology has been extensively studied. Reductions in fibrinogen (the largest contributor to plasma viscosity) and increased erythrocyte flexibility (a major component of whole-blood viscosity) would be desirable for vascular benefit. By and large, however, many studies have shown no or little improvement in fibrinogen levels after giving n-3 PUFA supplements to different types of patients.^{140,147,157,158,161-163} One study¹⁶⁴ has reported an increase in erythrocyte flexibility but an unaltered fibrinogen level. Indeed, n-3 PUFA has been linked to improvement in erythrocyte flexibility with lower whole-blood viscosity in few studies,^{156,165,166} although others have yielded little effects.¹⁶⁷⁻¹⁶⁹ Simply measuring erythrocyte infiltration might be an inadequate method for detecting small but significant differences in erythrocyte flexibility, and this may account for the inconsistency of results among studies.

There is also little agreement on the effects of n-3 PUFA on clotting factors, such as FVII or FVIII. One author¹⁷⁰ has reported reduced levels of FVIII with n-3 supplements, but most authors^{145,171-176} have found either no influence on or an increase in FVII or FVIII by fish oil ingestion or n-3 PUFA diet. Studies on the intake of n-3 PUFA and vWf concentration have also been similarly conflicting. Most studies^{136,171,172,174,177,178} have not been able to show an effect with these fatty acids. In addition, few studies have even suggested that n-3 PUFA, including α -linolenic acid, may have antithrombotic effects by enhancing protein C activity,^{171,174} increasing tissue factor pathway inhibitor,¹⁷⁵ or reducing the expression of procoagulant tis-

Table 4. Intervention and Cross-sectional Studies of n-3-Polyunsaturated Fatty Acids on Thrombogenic Markers

Source	Subjects	Design	Summary
Shahar et al, ¹³⁸ 1993	15 000 Subjects of the ARIC Study	Cross-sectional analysis adjusted for sex, race, age, BMI, smoking, alcohol, diabetes, and field center. Usual dietary intake assessed by a food frequency questionnaire	Dietary intake of n-3 negatively associated with Fg, FVIII, and vWF (black and white patients) and positively associated with protein C (white patients only). ↑ In n-3 intake from fish may modify several coagulation factors
Scarabin et al, ¹³⁷ 2001	283 Subjects of the PRIME study	Cross-sectional analysis adjusted for age, center, and BMI	Only tPA antigen inversely associated with marine n-3. FVII, Fg, PAI, D-dimer, and vWf were not associated with n-3. D-dimer was positively associated with ACA and eicosamonoenoic acid. Marine n-3 may favorably influence tPA antigen
Iacoviello et al, ¹³⁹ 1992	6 Healthy volunteers (aged 24-37 y)	DBR, cross-over study: 5.3 g EPA and DHA or n-6 (control) daily for 29 d. Aspirin (40 mg/d) then added for another 14 d; 2-mo washout before cross-over	Aspirin plus n-3 ↓ tPA antigen and the fibrinolytic response to venous occlusion in all subjects. PAI activity before stasis ↑ by n-3 suppl, but not affected by aspirin
Oosthuizen et al, ¹⁴⁰ 1994	20 Healthy young volunteers	DBR, cross-over study: 6 g fish oil or olive oil (placebo) daily suppl for 6 wk	Fish oil independently ↓ TGs, Fvc, and FVIIc. Both groups significantly ↑ PAI and ↓ FXc and Fg in women, who had higher initial levels than men
Boberg et al, ¹⁴¹ 1992	14 Diabetic patients vs healthy controls	DBR, cross-over study: 10 g maximum EPA (3 g n-3) or olive oil (placebo) daily for 2 consecutive 8-wk periods	PAI activity ↑ in diabetic patients compared with controls. Despite a ↓ in TG and unchanged insulin levels, there was a significant ↑ in PAI activity after maximum EPA. In diabetic patients given n-3 suppl, PAI activity ↑ though TG ↓
Radack et al, ¹⁴² 1990	10 Patients with hyperlipoproteinemia type IIb or IV	DBR, cross-over study: n-3 fish oil vs n-6 corn oil suppl	Fg ↓ in both groups. No significant changes in tPA activity, PAI, protein C antigen, ATIII activity, BT, and platelet counts
Prisco et al, ¹⁴³ 1994	20 Normolipemic healthy men (aged 27-41 y)	DBR study: n-3 (4-g capsules) or placebo (4-g olive oil capsules) daily for 4 mo	No significant changes in plasma Fg, PAI antigen or activity, PT F1 + 2, lipids, and Lp(a) in both groups though there was trend of ↓ in Fg, TG, and Lp(a) with n-3 during treatment and wash-out
Myrup et al, ¹⁴⁴ 2001	29 Insulin-dependent diabetic patients with nephropathy	DBR study: fish oil (4.6 g n-3) or placebo (olive oil) daily suppl for 1 y	No change in n-3 platelet lipids, transcapillary escape rate of albumin, PT F1 + 2, TAT, fibrinolytic indices, Fg, FVII antigen and activity, thrombomodulin, vWf, PF 4, and β-Tbg after 1 y of fish oil suppl compared with olive oil
Toft et al, ¹⁴⁵ 1997	78 Untreated hypertensive patients	DBR study: 4 g EPA and DHA or corn oil (placebo) daily suppl for 16 wk	PAI activity changed similarly in fish oil and corn oil groups, as did tPA, FVIIc, and platelet count. Fg levels ↑ with fish oil and corn oil suppl
Hansen et al, ¹⁴⁶ 2000	224 Healthy men (aged 36-56 y)	DBR study: EPA or DHA, or corn oil (placebo) daily suppl for 7 wk	The ↑ in PAI activity was not different between groups. No correlation between change in TGs or PL n-3 and PAI activity. PAI associated with BMI, apoB100, TGs, and n-6 but not with n-3. Only 21% of the variation in PAI activity is attributable to these variables
Nilsen et al, ¹⁴⁷ 1991	20 Accepted for CABG	DBR study: n-3 (3.15 g EPA and 1.89 g DHA) or corn oil (controls) daily for 5-6 mo. Surgery performed mid-intervention	No significant changes in BT, collagen-PAggr, and TxB2 production. Indices of extrinsic coagulation, including phospholipase C-sensitive FVII and extrinsic pathway inhibitor, unchanged in both groups. TG with n-3 ↓ and Fg ↓ in controls
Hellsten et al, ¹⁴⁸ 1993	40 Healthy subjects	DBR, parallel trial: 6 g cod fish liver oil (2 g n-3) or 6 g corn oil daily suppl for 5 mo	PAI unchanged with fish oil but ↓ with corn oil. tPA activity and mass unchanged in both groups
Rogers et al, ¹⁴⁹ 1987	60 Male volunteers	Randomized: maximum EPA fish oil or olive oil daily suppl for 3-6 wk	Fish oil ↓ TG by 54% and ↓ diastolic BP by 7%. BT ↑ by 12%, but not significant. Heparin thrombin clotting time ↑ by 14% but thrombin time, Fg, or PF 4 unchanged. Fish oil also ↓ RBC pore transit time by 23%, but not significantly. No differences between the 2 groups in TC, HDL, blood counts, or PAggr

(continued)

sue factor activity on monocyte ex vivo.¹⁷⁹

Fibrinolysis

The data available on the effects of n-3 PUFA on fibrinolytic activity are also inconsistent. Since the initial study by Barcelli et al,¹⁵³ which suggested that n-3 PUFA may enhance plasma fibri-

nolysis, others had found no change in PAI-1 level or in tPA antigen after dietary intervention,^{145,148,180} and few even reported significant increased in PAI-1 activity.^{146,160,181,182} Moreover, data available on tPA activity also seem contradictory.^{145,148,176,183} However, a study has reported that tPA antigen level was inversely related to n-3 PUFA derived mostly from fish oil

(EPA, docosapentaenoic acid, and DHA) but not with n-3 PUFA from vegetable origin (α-linolenic acid).¹³⁷ This is in agreement with a large intervention study¹⁸⁴ in diabetic subjects that showed a decrease in tPA antigen after fish supplementation but no effect on PAI-1 activity with high α-linolenic acid diet intake in a double-blind intervention trial.¹⁸⁵

Table 4. Intervention and Cross-sectional Studies of n-3-Polyunsaturated Fatty Acids on Thrombogenic Markers (cont)

Source	Subjects	Design	Summary
Li et al, ¹⁵⁰ 1990	8 Healthy subjects	Randomized: fish oil (6 g EPA) or vegetable oil daily suppl for 25 d	In fish oil group, ACA, ADP, and collagen-PAGgr ↑ but platelet adhesion to Fg and collagen I at low shear rates ↓ by 60%-65%. No changes in platelet adhesiveness in 5 subjects who had vegetable oil suppl
Andrioli et al, ¹⁵¹ 1999	60 Healthy volunteers	Randomized into 3 groups: 20 mL fish oil (0.3 g n-6; 3.6 g n-3; n-6/n-3 ratio 0.1) or 25 g soy lecithin (1.5 g n-6; 0.5 g n-3; n-6/n-3 ratio 3) daily suppl or usual diet (control) for 15 d	Fish oil significantly ↓ stimulated adhesion with ADP and thrombin. Soy lecithin ↑ platelet adhesion in all test conditions with ADP and thrombin. No changes in controls. Platelet adhesion correlated to changes in the platelet n-6/n-3 ratio caused by the different suppl. Fish oil rich in n-3 inhibit stimulated platelet adhesiveness and soy lecithin rich in n-6 ↑ adhesion in all test conditions. n-6/n-3 Ratio is a determinant of platelet adhesion
Freese et al, ¹⁵² 1997	29 Female and 17 male healthy subjects (aged 20-44 y)	Randomized: fish oil plus sunflower oil (EPA plus DHA: 5.2 g/d) or linseed oil (ALA: 5.9 g/d) daily for 4 wk	No differences between the 2 groups in collagen-PAGgr and Tbx production, Aggr to the TbxA2 mimic I-BOP, urinary excretion of 11-dehydro-TbxB2, and β-Tbg, BT, Fg, ATIII activity, FVIIc activity, or PAI activity. Suppl of ALA from vegetable oil and EPA plus DHA from a marine source have similar effects on hemostatic factors
Barcelli et al, ¹⁵³ 1985	9 Healthy subjects	Maximum EPA fish oil (5 g n-3) daily suppl for 2 wk	Vascular plasminogen activator ↑. Inhibitors of vascular plasminogen activator, of plasmin, and of PAP ↓. No significant changes in TCI, TGs, HDL, or LDL levels
Mehta et al, ¹⁵⁴ 1988	8 Patients with CHD and 4 healthy subjects	Maximum EPA fish oil daily suppl for 4 wk	In both groups, TG and PAI ↓ significantly but tPA antigen was unaltered. The magnitude of ↓ in TGs was dependent on baseline TG. PAI ↓ correlated with ↓ TGs ($r = 0.79$)
Schmidt et al, ¹⁵⁵ 1990	10 Healthy males	Dose ranging: 1.3 g, 4 g, or 9 g of n-3 daily suppl for 6 wk	BT, PAI, and HDL ↑, while Fg and TGs ↓ in a dose-dependent fashion. Highest daily dose (9 g) ↓ TGs, Fg, and vWf, while BT, tPA antigen, PAI, and HDL:TC ratio ↑
Miller et al, ¹⁵⁶ 1987	5 Insulin-dependent diabetics and 5 healthy volunteers	Maximum EPA fish oil given without other diet modification for 8 wk	ACA and collagen-PAGgr ↓ equally in both groups, but TG, lipids, glucose, HbA1c, platelet count, and osmotic fragility of RBC were unchanged. Whole blood viscosity ↑ in diabetic patients at baseline, but ↓ in both groups at 8 wk. Diabetic patients ↑ vWf at baseline but ↓ in both groups at 6 wk. Addition of EPA or crude fish oil to HUVEC cultures did not change vWF in the supernatant
Schmidt et al, ¹⁵⁷ 1992	24 Healthy volunteers	4 g n-3 Daily suppl for 9 mo	BT and Fg ↑, while vWf and fibrinolysis ↓. TGs ↓ and a trend of ↑ HDL, while no changes in TC, LDL, and apolipoproteins A1 and B after 9 mo. Systolic and diastolic BP ↓ with n-3 suppl
Smith et al, ¹⁵⁸ 1989	40 Patients with previous MI	1 g Fish oil capsules (3.4 g EPA and DHA) daily suppl for 4 wk; 22 of 40 subjects had concomitant long-term oral anticoagulants	TG ↑ by 25%, TC ↑ by 5%, and HDL unaltered. Ivy BT also ↑. Blood glucose and PAI and FVII-PL complex showed a ↓ trend. Fg ↑ significantly, but clotting time in the combined PT test ↓ in patients who had oral anticoagulants
Li et al, ¹⁵⁹ 1999	17 Male vegetarians	All had a low-ALA diet for 14 d; then randomized to either a moderate- or a high-ALA diet for 28 d	EPA, DHA, total n-3, and n-3:n-6 ratio significantly ↑, whereas ACA:EPA ratio ↓ in platelet PLs, plasma PLs, and triacylglycerols after moderate-ALA or high-ALA diet compared with the low-ALA diet. No differences in thrombotic markers. ALA from vegetable oils (canola and linseed) has a beneficial effect on n-3 concentrations of platelet PLs and plasma lipids in vegetarian males
Emeis et al, ¹⁶⁰ 1989	76 Healthy males	Fish (mackerel) or meat (control) paste with daily main meal for 6 wk	No changes in plasminogen, PAP, tPA antigen, and euglobulin tPA activity in both groups. In the fish group, total PAI activity ↑ by 45% due to a 71% ↑ in PAI-1. This ↑ could not be ascribed to a diet-induced acute-phase reaction and changes in serum TGs or insulin. No change of PAI activity in controls

Abbreviations: For an explanation of abbreviations, see footnote to Table 1.

Many studies have reported a positive correlation between serum triglycerides and PAI-I activity. Dietary interventions, such as a low-saturated-fat diet¹²⁷ or gemfibrozil treatment¹²⁸ to lower serum triglyceride levels, have been accompanied by improvement and even normalization of the fibrinolytic activity.

However, dietary intervention with n-3 PUFA, which is well known for its ability to lower triglyceride levels, has not been shown to be parallel with a decrease in PAI activity,¹⁴⁶ indicating that a causal relationship is unlikely between levels of triglycerides and PAI-I activity during dietary supplementation

with n-3 PUFAs. In fact, by pooling data from all these studies, Hansen et al¹⁴⁶ were able to calculate that approximately a 17% increase in PAI-I activity during intervention could be attributed to the fish oil supplement. Notably, there are few data on the effect of n-3 PUFA on D-dimer.^{184,186}

Platelet Reactivity

The effects of n-3 PUFA on platelet reactivity have been extensively investigated. Studies of Greenland Eskimos have shown that very high intake of marine n-3 PUFA markedly inhibited platelet reactivity, lowered platelet count, prolonged bleeding time, decreased the ratio of proaggregatory thromboxanes to antiaggregatory prostacyclins, and caused favorable changes in lipid and lipoprotein profiles. These findings are of importance for their low incidence of CHD.¹⁸⁷ Although few studies^{144,174,188} have shown no significant influence on platelet reactivity with n-3 PUFA supplementation, most other intervention studies have demonstrated significant inhibition in platelet reactivity of one sort or another but with conflicting combinations of effects with different agonists in vitro or ex vivo.¹⁸⁹⁻¹⁹⁵ It seems that platelet aggregation induced by low-dose collagen was the most commonly reported index to be influenced. One study¹⁵² has demonstrated no significant difference between supplemented α -linolenic acid from vegetable oil and n-3 PUFA from a marine source (EPA and DHA) in their effects on collagen-induced platelet aggregation and thromboxane production, aggregation to the thromboxane A2 mimic, urinary excretion of 11-dehydrothromboxane B2 and β -thromboglobulin, bleeding time, plasma fibrinogen concentration, anti-thrombin III activity, FVII coagulant activity, or PAI-1 activity. However, another study has shown that a high α -linolenic acid diet has no significant effect on thromboxane production and platelet aggregation with collagen.¹⁸⁵ Notably, data from studies¹⁹⁵ on other fatty acids (mainly n-6 PUFA), such as linoleic acid on platelet reactivity, were highly variable, especially in the in vitro assessment of platelet aggregations. Similarly, there was also lack of agreement on the effect of n-3 PUFA on platelet adhesiveness.^{150,151,196-198} Novel, well-validated methods for measuring platelet aggregation are desperately needed to solve current controversies.¹⁹⁵

Thus far, it seems that there is little evidence to support the hypothesis that changes in coagulation, platelet reactivity, or fibrinolysis systems could account for, at least, some of the beneficial effects afforded by a Mediterranean diet with n-3 PUFA supplementation in the secondary prevention trials mentioned herein. The major effect of n-3 PUFA may be antiarrhythmic rather than antithrombotic.^{199,200} It remains unsettled whether the diverse effects of n-3 PUFA supplementation on thrombogenic indices are due to different time of supplementation, patient type, or separate effects of EPA and DHA in a mixture of fish oils. It is likely that fish oil and n-3 PUFA have multifaceted actions in the secondary prevention of cardiovascular disease.²⁰¹

ALCOHOL

Light-to-moderate alcohol consumption (<30 g/d, ie, 1 to 2 drinks per day) is associated with 10% to 40% lower risks of MI and cardiovascular death compared with abstinence. However, heavy alcohol consumption or binge drinking increases such cardiovascular risks, including stroke.²⁰² The reduction in cardiovascular risks with moderate alcohol intake has mainly been attributed to an increase of HDL-C levels, but this only accounts for 50% of the protective effect.^{203,204} Increasing evidence has indicated that thrombogenic factors may play an important role in mediating such a complex association independent of HDL-C levels.^{205,206}

Epidemiologic Studies: Coagulation and Fibrinolysis

The mass of the previously published data on alcohol consumption and hemostasis comes from epidemiologic studies, with only few experimental data reported. Generally, most cross-sectional studies have shown that light-to-moderate alcohol intake is associated with a more favorable coagulation and fibrinolytic profiles as indicated by lower levels of fibrinogen, white blood cell count, plasma viscosity, FVII, and vWf, as well as lower plate-

let count and activity.^{107,207} However, heavy or binge alcohol intake is associated with lower fibrinolytic capacity with relatively greater increase in PAI-1 and tPA antigen than tPA activity.^{205,208} In addition, heavy alcohol consumption also seems to shift the pendulum toward a more procoagulant state, with a rise in the plasma levels of FVII, fibrinogen, and viscosity. Indeed, this may sufficiently predispose individuals to thrombosis, and in the presence of an impaired fibrinolytic state, this may contribute to the increased incidence of ischemic stroke seen in heavier or binge drinkers.^{20,209} Thus, the results from these studies seem to partly explain the complex relationship between level of alcohol consumption and cardiovascular risk seen in large epidemiologic outcome studies on alcohol.

Experimental Studies: Coagulation

The results from experimental studies on the effects of moderate alcohol consumption in both healthy subjects and subjects with CHD are contradictory (**Table 5**). In particular, the alcohol effects on fibrinogen are variable. For example, Pellegrini et al²¹² found a decrease in fibrinogen level after consumption of 30 g of alcohol that consisted of red wine and alcohol diluted in fruit juice for 4 weeks but found no change in fibrinogen level after consumption of dealcoholized red wine. Because alcohol diluted in fruit juice had an effect similar to that of red wine, it seems that alcohol is the effective mediator in alcoholic drinks. On the other hand, Gorinstein et al²¹⁰ studied the effect of beer (20 g/d of alcohol) over 30 days and found no change in fibrinogen levels. It could be argued that there may be other substances in beer that inhibit the beneficial effect of alcohol on fibrinogen. However, this may also be due to differences in study design, timing of blood samplings, quantity or regularity of intake (besides type of beverage used), and inpatient and outpatient variability in alcohol metabolisms. A recent meta-analysis²²³ of all experimental studies that assessed the effects of moderate alcohol intake on lipid lev-

Table 5. Experimental Studies: Effects of Alcohol on Thrombogenic Markers

Source	Study Design	Alcohol	Main Results
Gorinstein et al, ²¹⁰ 1997	28 Patients with CHD. 22 Had alcohol for 4 wk, the other 6 as controls	330 mL/d of beer (20 g alcohol)	Alcohol ↓ FVII activity and antigen and ↓ PAI. Fg and PT factor unchanged
Dimmitt et al, ²¹¹ 1998	55 Men (aged 21-65 y); 4 wk cross-over	Predominantly beer; 13 to 58 mL/d	Alcohol ↓ Fg and platelet count, but ↑ FVII, tPA antigen, and PAI
Pellegrini et al, ²¹² 1996	11 Men (aged 20-45 y); 4 wk randomized cross-over with 4 wk washout	Alternating 30 g/d red wine, 30 g/d clear fruit juice, and dealcoholized red wine	Alcohol in either red wine or alcoholic juice similarly ↓ Fg and collagen-PAGgr. No effects on ADP-PAGgr, tPA antigen, vWF, or plasminogen levels
Elmer et al, ²¹³ 1984	7 Men and 3 women; blood drawn 1 and 2 h after alcohol intake	2 mL/kg weight of 40% alcohol (average 53.5 g for 70 kg of weight)	No effects on factors V, VII VIII, XII, plasminogen, or Fg. BT and PAGgr ↓ at 1- and 2-h after alcohol intake
Pikaar et al, ²¹⁴ 1987	12 Men (aged 21-29 y); 5-wk randomized cross-over; blood drawn after overnight fast	4 Different amounts of red wine: 0, 23, and 46 g/d of alcohol and in "binge drinking"	Dose-response ↓ in tPA activity and collagen-PAGgr. Slight ↑ in plasminogen but no effects on Fg and ADP-PAGgr
El-Sayed et al, ²¹⁵ 2000	11 Men (mean age, 22.8 y). Randomized cross-over, 1-wk washout; blood drawn 45 min after alcohol intake	0.5 g/kg alcohol or nonalcoholic drink	No difference in tPA activity, Fg, fibrin, or Fg DPs
van de Wiel et al, ²¹⁶ 2001	50 Men (mean age, 26 y). 2 Experiments: (1) low vs high alcohol intake vs controls; (2) moderate vs binge vs controls	All consumed red wine 12.5% volume. Controls had mineral water. Low, 2 glasses (250 mL, 20 g ethanol); moderate, 4 glasses; high, 6 glasses; binge, 8 glasses	2 Glasses had no significant disturbance on the circadian rhythm, whereas intake ≥4 glasses inhibited fibrinolysis significantly with a dramatic ↑ PAI antigen and PAI activity; tPA antigen also ↑, but tPA activity and PAP complexes ↓. In binge drinkers, the WBCLT ↑ the following morning indicated continued inhibition of fibrinolysis
Johansen et al, ²¹⁷ 1999	9 Healthy students (aged 23-28 y). Randomized cross-over; 1 of 3 regimens: control, low-dose wine, and high-dose wine	Low-dose, loading dose of red wine to obtain 0.5/mL (0.40 g/kg ethanol); high-dose, 1/mL (0.80 g/kg ethanol) within 1 h. Followed by 0.13 g/kg ethanol per hour for 3 h	Red wine impaired fibrinolysis shown by ↑ WBCLT (3.6%, 20.7%, and 55.7% for control, low-, and high-dose wine, respectively) due to ↑ in PAI antigen (-0.8, 4.8, and 11 ng/mL, respectively). No effect of red wine on fibrinolytic system the next morning. Strong correlation observed between WBCLT and PAI antigen
Hendriks et al, ²¹⁸ 1994	8 Men (aged 45-55 y); 4 treatments randomized controlled order on 4 d over a period of 11 d	40 g (Red wine, beer, or spirits) or mineral water	PAI ↑ at 1, 3, 5, and 9 h; tPA antigen ↑ at 3, 5, and 9 h; tPA activity ↓ at 1, 3, and 5 h but ↑ at 13 h after meal. Similar changes for each beverage type except ↑ in PAI and in 13-h tPA activity were slightly stronger for spirits than for other beverages
Numminen et al, ²¹⁹ 2000	20 Healthy men. Randomized cross-over; 1-wk washout period	Ethanol in fruit juice or fruit juice alone	Acute ingestion of a large but tolerable dose of alcohol transiently ↑ Tbx-mediated platelet activation. A 7-fold ↑ in PAI activity after both morning and evening intakes of alcohol
McConnell et al, ²²⁰ 1997	11 Men and 9 women (aged 23-51 y)	Beer, 13.5 g/d (low-dose alcohol)	No significant ↑ in tPA antigen and activity or PAI antigen and activity or PT factor and TAT. vWf ↓ but not significant
Veenstra et al, ²²¹ 1990	2 Age groups, 20-30 y and 45-55 y; 8 men each	30 g In red port and wine	ADP-PAGgr ↑ postprandially but ↓ in overnight fast. No effects on Tbx B ₂ . tPA activity ↓ and PAI ↑ only postprandially and predominantly affect older age group
Lacoste et al, ²²² 2001	6 Men and 6 women (mean age, 31 y). At 20 min and 6 h after alcohol consumption, blood drawn was infused into a validated ex vivo Badimon superfusion system to examine platelet-thrombus formation on arterial media strips under arterial flow conditions simulating vessel stenosis	2 oz of 40% alcohol (cognac, 24 g of alcohol)	Compared with baseline, platelet thrombus formation at both the low and high shear rate flow was significantly ↓ at 20 min and 6 h. Men and women showed equal benefit. Moderate alcohol intake significantly inhibited platelet thrombus deposition under low and high shear rates of arterial flow conditions

Abbreviations: For an explanation of abbreviations, see footnote to Table 1.

els and hemostatic factors has concluded that moderate alcohol intake of 30 g/d is causally related to an overall 24.7% lower risk of CHD

through favorable changes in lipids (higher HDL-C level) and hemostatic profile (lower plasma fibrinogen levels). However, the precise

mechanism(s) by which moderate alcohol intake decreases fibrinogen and increases HDL-C levels is not known.

Experimental Studies: Fibrinolysis

Most reports seem to indicate that short-term alcohol ingestion leads to inhibition of the fibrinolytic system through a rise in circulating PAI-1 levels.^{211,212,216,217,220,221} Notably, a recent study²¹⁷ has shown an acute, dose-dependent rise in PAI-1 antigen level with a parallel prolongation of whole blood clot lysis time after intake of the high dose of red wine. In addition, there was also a tendency for tPA antigen to increase dose dependently, although this was only significant for the high-dose wine group. In the case of binge drinking, this inhibition in fibrinolysis effect persists into the morning following the evening of alcohol consumption,²¹⁶ and when it coincides with the physiologic morning dip in fibrinolytic activity, this may predispose susceptible individuals to sudden cardiac death. However, the exact reason for decreased fibrinolysis after short-term alcohol intake is still unresolved. Indeed, several studies have discussed whether it is the ethanol component itself or other mediators in red wine (or beer) that induce acute changes in tPA or PAI-1. Veenstra et al²²¹ and Hendriks et al²¹⁸ have pointed out that the red wine effect on t-PA and PAI-1 antigen levels is probably caused by the effect of ethanol but not the effects of other mediators, such as the phenolic compounds in red wine or port wine, although these constituents might contribute to the effects on platelet function. However, it is difficult to distinguish between the effects of red wine and alcohol per se. Notably, in a study²¹¹ with longer-term consumption of beer (4 weeks), the tPA antigen and PAI-1 levels were increased markedly.

Experimental Studies: Platelet Reactivity

Alcohol has also been thought to reduce CHD risk by decreasing platelet reactivity. Indeed, several studies in humans and animals have demonstrated that the immediate effect of light-to-moderate alcohol, either added in vitro to platelets or 10 to 20 minutes after ingestion, can

inhibit platelet aggregation to most specific agonists (adenosine diphosphate [ADP], thrombin, collagen, epinephrine) in platelet-rich plasma. This platelet inhibitory effect seems to persist for several hours after alcohol intake.²²⁴ However, such beneficial effect is not seen in binge drinkers or in individuals with alcoholism after alcohol withdrawal; instead, a rebound phenomenon of platelet hyperaggregability (especially toward thrombin agonist in vitro)²²⁵ and loss of the normal circadian periodicity of the hemostatic system is observed.²¹⁹ This may explain the increased ischemic strokes or sudden deaths that are known to occur after episodes of binge or heavy drinking.²²⁶ Intriguingly, such a rebound phenomenon is not observed after moderate red wine consumption in humans and, in fact, this protection afforded by red wine has been duplicated in rats by alcohol with grade tannins added, which contain the polyphenolic compounds with which red wines are richly endowed. However, it is still unclear how red wine or wine phenolics in particular could significantly inhibit platelet aggregation.

In an interesting study by Lacoste et al,²²² rather than evaluating platelet function and platelet inhibition, the authors assessed the effect of alcohol directly on platelet-dependent thrombosis in 12 healthy subjects in an ex vivo model that simulates a deep arterial wall injury exposed to shear forces typical of flow at sites of stenosed arteries, reflecting the in vivo situation of coronary thrombosis. The study demonstrated for the first time that moderate alcohol consumption (24 g of alcohol) in humans had a potent extracorporeal antithrombotic effect both at the time of peak alcohol concentration and 6 hours after alcohol ingestion when blood alcohol level has returned to baseline.

Overall, the balance of anticoagulant, procoagulant, and fibrinolytic effects in any individual in response to alcohol intake may vary, depending on quantity and type of alcoholic beverage ingested and other variables.^{204,227} The lower level of plasma fibrinogen with moderate alcohol intake may well contrib-

ute to the apparent protection alcohol confers against ischemic coronary and cerebral events. On the other hand, consistent evidence suggests that the relatively greater increase in PAI-1 and tPA antigen than tPA activity and the rebound phenomenon of platelet hyperaggregability with short-term alcohol (binge) intake may attenuate this benefit, resulting in a net antifibrinolytic effect of ethanol consumption,²⁰⁵ predisposing individuals to coronary thrombosis and contributing to the increased incidence of ischemic stroke.

SMOKING

The direct effects of smoking on atherothrombogenesis are still unclear. This may be mediated by its many adverse effects on endothelial function, vascular tone, hemostasis, lipid profile, and inflammatory cells. Much of the data regarding the effects of smoking on thrombogenic factors have been derived from epidemiologic and cross-sectional studies. However, intervention studies are accumulating and have reported an increase in blood coagulability but impaired fibrinolysis in habitual smokers when compared with nonsmoking controls (**Table 6**). It seems that higher plasma levels of fibrinogen and viscosity are the main contributors to higher coagulability found in smokers, whereas the lower fibrinolytic potential is mainly attributed to an increase in PAI-1 activity and possibly also a decrease in tPA activity and lower plasminogen levels.^{107,228,229,244}

Coagulation

In cross-sectional epidemiological studies, lifetime duration of smoking is a strong determinant of initial plasma fibrinogen levels. The effects of smoking on the hemostatic system remain for many years before an exsmoker reverts to a plasma level similar to that of a lifetime nonsmoker,^{229,245} although a decrease in fibrinogen levels follows quickly after cessation of smoking.²⁴⁶ In prospective data, smoking cessation and the adoption or resumption of smoking are associated with a decrease or

Table 6. Effect of Smoking on Thrombogenic Factors

Source	Methods	Main Results	Conclusion
Eliasson et al, ²²⁸ 1995	Cross-sectional study; 604 men and 662 women (aged 25-64 y): smokers, ex-smokers, snuff dippers, and nonsmokers	Male smokers had 0.34 g/L ↑ Fg than nonsmokers. Numbers of cigarettes smoked correlated with Fg. Fg not affected by snuff dipping. Tobacco use had no relationship with tPA or PAI activity and no influence on glucose and postload insulin levels	Cigarette smoking is associated with ↑ Fg, unaltered fibrinolysis, and normal glucose tolerance and insulin levels. Moist oral snuff does not seem to affect these cardiovascular risk factors
Meade et al, ²²⁹ 1987	Cross-sectional; 2023 white men	Duration of smoking is a determinant of initial Fg level, which ↓ soon after cessation but returned to normal levels only after 5 years. Smoking cessation and the adoption or resumption of smoking associated with a ↓ or an ↑, respectively, of -0.15 g/L in plasma Fg equivalent to a ↓ or an ↑ in the risk of IHD by ~20%	A substantial part of the relation between smoking and IHD seems to be mediated through the Fg concentration
Simpson et al, ²³⁰ 1997	Cross-sectional study; 54 healthy individuals; current, ex-smokers, or nonsmokers (aged 25-40 y)	PAI antigen ↑ in smokers vs nonsmokers with intermediate levels in ex-smokers. tPA and platelet pool PAI were not different in the 3 groups. tPA:PAI ratio similar in ex-smokers and nonsmokers but ↓ in smokers. PAI antigen and activity correlated with pack-years of cigarettes smoked. PAI correlated strongly with tPA and TGs. tPA correlated strongly with TGs	Smokers associated with ↓ fibrinolysis as reflected by ↑ PAI. Smoking cessation seems to normalize fibrinolysis. Platelet pool of PAI not quantitatively affected by smoking. Effect of chronic smoking on PAI may be mediated by TGs and insulin resistance
Enderle et al, ²³¹ 2000	30 Healthy smokers (mean age, 40.6 y) vs nonsmokers. FMD as marker of ET dysfn	FMD significantly ↓ and IMT tended to be ↑ in smokers. TAT, Fg, PAP, tPA, and PAI activity did not differ between smokers and controls	Peripheral ET dysfn is common in smokers even without major alterations in markers of coagulation and fibrinolysis
Newby et al, ²³² 1999	12 Smokers (5-20 cigarettes per day) and 12 nonsmokers (aged 25-55 y). Forearm blood flow assessed by venous occlusion plethysmography following infusions of substance P	Substance P caused a dose-dependent ↑ in blood flow and local release of tPA antigen and activity in smokers and nonsmokers, but the ↑ was significantly lower in smokers that the release of tPA antigen and activity ↓ by 51% and 53%, respectively. PAI did not change	Smoking caused marked inhibition of substance P-induced tPA release in vivo. ET dysfn may ↑ the risk of atherothrombosis through a ↓ in the acute fibrinolytic capacity
Newby et al, ²³³ 2001	15 Ex-smokers or current smokers vs 10 nonsmokers (mean age, 56 y). Saline, substance P, or SNP infused into LAD; blood flow measured by IVUS and with arterial and coronary sinus sampling.	Substance P and SNP ↑ LAD blood flow, but ↑ coronary sinus tPA antigen and activity only with substance P. Release of active tPA strongly inversely correlated with LAD plaque burden. Smoking associated with ↓ coronary release of active tPA	Coronary plaque burden and smoking are associated with ↓ acute local fibrinolytic capacity. There may be a direct link between endogenous fibrinolysis, ET dysfn, and atherothrombosis in the coronary circulation
Allen et al, ²³⁴ 1985	30 Healthy men (aged 30-40 y): smokers (≥20 cigarettes per day) vs nonsmokers. Fibrinolysis was studied at rest and after infusion of DDAVP	Smokers had ↓ baseline fibrinolytic activity as indicated by dilute blood clot lysis, euglobulin-fibrin plate assay, and tPA activity. No differences between the groups in various fibrinolytic inhibitors or in the intrinsic fibrinolytic activation pathways. The ↑ levels of tPA activity and FVIII R antigen in response to DDAVP also ↓ in smokers	Smokers have ↓ fibrinolytic capacity both at rest and in response to DDAVP compared with nonsmokers
Belch et al, ²³⁵ 1984	10 Habitual smokers vs nonsmokers. Blood drawn before and 10 min after smoking 3 cigarettes over 30 min	Smokers had ↑ plasma Fg and viscosity but ↓ plasminogen and tPA. After smoking 3 cigarettes, smokers had an ↑ in ADP-PAGgr and ↑ in α2M and FVIII antigen but plasma viscosity and red cell deformability ↓	↑ Hypercoagulability in smokers compared with controls, which becomes more pronounced immediately after smoking 3 cigarettes

(continued)

an increase, respectively, of approximately 0.15 g/L in plasma fibrinogen. There is evidence to suggest that these changes are not due to concurrent changes in other lifestyle variables.¹⁰⁷

Fibrinolysis

Impaired fibrinolytic potential has been found in smokers with CHD²⁴⁷ and peripheral vascular disease,²⁴⁸ with higher levels of PAI-1 activity and tPA antigen than in nonsmok-

ers or light smokers. However, other groups have reported no difference in markers of fibrinolysis and coagulation, although endothelial function has been found to be significantly impaired in healthy smokers compared with nonsmoking controls.²³¹ Interestingly, smokers may have markedly impaired acute substance P-induced endothelial release of active tPA in vivo from coronary and brachial arteries and was closely related to impaired endothelial function in the correspondence

arterial beds, which suggests a possible direct link among impaired endogenous fibrinolysis, endothelial dysfunction, and arterial atherothrombosis in smokers.^{232,233,249} However, although the basal level of PAI-1 activity is higher in long-term smokers, rapid smoking of 2 cigarettes in these patients neither stimulated fibrinolysis nor changed levels of tPA or PAI-1 activities.²³⁶ Plasma PAI-1 antigen seems to correlate with cumulative smoking in pack-years,^{230,236} and on the other

Table 6. Effect of Smoking on Thrombogenic Factors (cont)

Source	Methods	Main Results	Conclusion
Haire et al, ²³⁶ 1989	5 Healthy male smokers (aged 35-45 y)	TPA antigen release in response to venous occlusion was intact at both 8 am and 3 pm. Rapid smoking of 2 cigarettes neither ↑ fibrinolysis nor changed tPA or PAI. Functional PAI and ECLT ↑ in smokers vs matched controls. Plasma and platelet PAI were similar in both groups	Smoking did not acutely alter fibrinolysis in chronic smokers, but they had abnormal fibrinolysis with ↑ PAI activity. Abnormal fibrinolysis may contribute to the thrombotic diathesis of smokers
Brockmann et al, ²³⁷ 2001	54 Healthy subjects into 4 groups: nonsmoking and smoking males and females. Effect of smoking on PHC with an in vitro analyser was examined within 4 h of blood sampled	Smokers had ↑ Fg vs nonsmokers. No differences between smokers and nonsmokers in PHC, for neither the collagen/epinephrine nor the collagen/ADP cartridges. PAggr assays performed in parallel also showed no differences	In habitual smokers, PHC and the agonists-induced PAggr assays are not significantly influenced or ↑ compared with healthy nonsmokers. An immediate effect of smoking cannot be excluded
Modesti et al, ²³⁸ 1989	8 Male healthy smokers (>20 cigarettes per day) vs 9 healthy controls (aged 30-55 y). Platelet TxA2 receptors assessed by a radioligand binding method	Smokers had a significantly ↑ number of TbxA2 platelet receptors vs nonsmokers. No differences in the receptor affinity between the 2 groups	Changes could contribute to the ↑ responsiveness of platelet from smokers to external aggregating stimuli
Pernerstofer et al, ²³⁹ 1998	20 Healthy smokers (>20 cigarettes per day) vs 20 healthy nonsmokers (mean age, 30 y). DBR; aspirin (100 mg/d) or placebo; cross-over; 2 wk wash-out period	Smokers had ↑ sP-sel expression on platelets than nonsmokers. sP-sel expression on platelets and circulating sP-sel unchanged by aspirin	P-sel expression on platelets ↑ in smokers but low-dose aspirin does not ↓ platelet activation in smokers
Blache et al, ²⁴⁰ 1992	12 Fasting smokers. Blood drawn before and at 10 min after inhaled smoke 1 cigarette. Experiment repeated 1 wk later except that subjects had aspirin (650 mg) 10-14 h before blood sampling.	Before aspirin: PAggr to thrombin and ADP, plasma nicotine, β-Tbg, and CECs all ↑ significantly after smoking, but PAggr ratio ↓. After aspirin: except for plasma nicotine, all smoking-induced changes were abolished by ingestion of aspirin	Data indicate an interrelationship between platelet hyperactivity and ET injury. Aspirin inhibits smoking-induced changes. Aspirin may offset several of the deleterious acute effects of smoking. Long-term effects of both smoking and aspirin treatment remain unclear
Blann et al, ²⁴¹ 1998	20 Smokers vs 10 nonsmoker controls (aged 21-55 y). Blood drawn before, immediately after, and at 10 and 30 min after rapid smoking of 2 cigarettes in sequence	Smokers had a transient ↑ in leukocyte count and neutrophil activation, but vWf ↑ steadily at each time point. No changes in neutrophil elastase, sICAM-1, Fg, platelet count, or sP-sel	Rapid smoking of 2 cigarettes in succession activates leukocytes and causes ET cell damage but will not immediately influence platelet activity
Gleerup et al, ²⁴² 1996	10 Smokers and 11 nonsmokers, all with mild HT (diastolic BP, 90-110 mm Hg). Successive measurements after erect posture for 10 min and after a 5-min exercise test	ADP-PAggr ↑ in smokers at rest vs nonsmokers and persisted both in upright posture and after exercise. β-Tbg also ↑ in smokers. No difference of ECLT and PAI between the 2 groups	Smoking adds a further element of ↑ platelet activity to that inherently present in HT
Davis et al, ²⁴³ 1985	20 Healthy nonsmokers. Smoked 2 tobacco cigarettes in 20 min and at cross-over 1 wk later smoked 2 cigarettes made from wheat, cocoa, and citrus plants	Mean ET cell counts before and after tobacco cigarettes were 2.3 and 4.8; before and after nontobacco cigarettes were 2.5 and 3.0. The corresponding mean PAggr ratios were 0.80 and 0.65, 0.81, and 0.78, respectively	Much greater effects of tobacco smoking on ET cell counts and PAggr ratios suggest that nontobacco smoking may be less harmful to the cardiovascular system than tobacco smoking.

Abbreviations: For an explanation of abbreviations, see footnote to Table 1.

hand, other studies⁷⁵ have suggested that smoking cessation of at least 6 months was associated with a decrease in plasma PAI-1 activity.

Platelet Reactivity

Smoking is also known to be associated with increased platelet thrombus formation,²⁵⁰ but studies on the effects of smoking on platelet reactivity have produced conflicting data. For example, rapid smoking of 3 cigarettes in habitual smokers increased ADP-induced platelet aggregation in vitro in one study,²³⁵ but others have shown no differences in various agonist-induced platelet aggregations in

vitro compared with nonsmokers.²³⁷ Certainly, no immediate influence in platelet activity (as indicated by platelet count and soluble P-selectin) occurs after rapid smoking of 2 cigarettes in sequence compared with nonsmoking controls, despite evidence of endothelial damage (indicated by elevated vWf level).²⁴¹ On the other hand, increased P-selectin expression on platelets has been demonstrated in young, healthy, habitual smokers compared with nonsmokers, underlining the increased platelet activation in nicotine-abusing subjects.²³⁹ Importantly, 100 mg/d of aspirin did not reduce platelet activation as measured by un-

changed P-selectin expression on platelets and circulating P-selectin plasma levels. This could indicate that enhanced thromboxane A2 production may not be the primary mechanism for increased P-selectin expression in smokers.²³⁹ Similarly, dipyridamole alone or in combination with aspirin did not have any significant effect on plasma concentrations of β-thromboglobulin, platelet factor 4, the circulating endothelial cell count (indicates endothelial damage), and the platelet aggregate ratio in habitual, male smokers with CHD.²⁵¹ Smoking cessation for 6 weeks, however, has resulted in a 29% reduction of circulating P-selectin

plasma levels in healthy smokers²⁵² and a decrease in platelet count 2 weeks after cessation.²⁵³ Furthermore, aspirin abolished the major cigarette smoke-induced endothelial damage and platelet hyperactivity in the presence of high plasma nicotine levels.²⁴⁰ Notably, passive exposure to tobacco smoke also seems to raise the endothelial cell count and platelet aggregate ratio in a manner similar to that previously observed with active smoking.²⁵⁴

PSYCHOSOCIAL STRESS

The increase in mental stress, demands at work, anger, or low socioeconomic strain has been associated with an increased risk of atherosclerotic disease.²⁵⁵⁻²⁵⁷ The increased cardiovascular risk may be secondary to excessive cardiovascular reactivity to stress²⁵⁸ but may also involve activation of the coagulation and fibrinolysis systems.

Coagulation and Fibrinolysis

Indeed, an association between psychological factors and several of the coagulation and fibrinolysis variables related to atherosclerosis has provided a plausible psychobiological link to CHD. The characteristic patterns of coagulation and fibrinolysis activation in response to various psychological stressors seem to follow closely that of physical or exercise-induced changes in markers of thrombogenesis. Accordingly, as in short-term, strenuous exercise, acute mental stress simultaneously activates the coagulation system, with increased levels of fibrinogen, total plasma protein, hematocrit, FVII, and FVIII,^{259,260} and enhances fibrinolysis with increased activity of tPA within a physiological range in healthy subjects.^{260,261} In patients with atherosclerosis and impaired endothelial anticoagulant function, however, procoagulant responses to acute stressors may outweigh anticoagulant mechanisms and thereby promote a hypercoagulable state.

Similarly, long-term psychosocial stressors, such as prolonged job stress or low socioeconomic strain that provoked a state of vital exhaustion, have been independently associated with hypofibrinolysis, with an

increase in PAI-1 and a decrease in tPA activities.^{262,263} In addition, such long-term mental stress is also independently related to an increase in prothrombotic tendency, with increased levels of fibrinogen, FVII antigen, and activity.²⁶⁴ Changes in hemostatic variables in response to psychosocial job stress are particularly interesting. Significant elevation in coagulation FVII and FVIII levels, fibrinogen level, thrombocyte count, thrombin level, and ADP-induced platelet aggregation has been reported during a period of increased workload compared with a calm work period.²⁶⁵ High job demands have also been significantly related to decreases in tPA activity (ie, lower fibrinolytic capacity, independent of other traditional cardiovascular risk factors)²⁶⁶ and hence increase the likelihood of fibrin deposition. The mechanism(s) underlying these changes is unknown, but impaired fibrinolysis in people with long-term psychosocial stress has been linked to insulin resistance, obesity, and triglyceride levels.²⁶²

Platelet Reactivity

Platelet reactivity also seems to be affected by a variety of psychosocial stressors. Acute mental stresses significantly induce all platelet reactivity variables, such as platelet activation or secretion and *in vitro* or *in vivo* platelet aggregation, in parallel to a concomitant incremental increase of various hemodynamic indices that follow during mental-stress testing. Such a response has been consistently shown in almost every study. Furthermore, these changes seem to be more pronounced in patients with atherosclerotic disease^{37,267} compared with healthy controls. Hence, such a response may precipitate acute ischemic coronary events in patients at high risk of cardiovascular events, including individuals with sedentary lifestyle. One group has reported that dipyridamole attenuated the platelet hyperreactivity in post-MI patients but had no effect on stress-induced increase of hemodynamic variables and epinephrine levels.²⁶⁷

Aspirin has only a minimal effect on physical, psychosocial, or norepinephrine stress-induced

platelet activation, which suggests that platelets are not being stimulated through the cyclooxygenase-dependent pathway.^{37,38,41,268,269} However, the mechanism(s) responsible for the increased of prothrombotic tendency secondary to psychosocial stress may be related to the sympathoadrenal pathways, but clearly this needs further exploration.

COFFEE, TEA, OR CAFFEINE CONSUMPTION ON THROMBOGENESIS

Coffee

The possible link between coffee or caffeine consumption and the risk of CHD is far from settled, but its effects on various thrombotic factors might be relevant. However, limited data from intervention study are currently available.

Coagulation

Two well-described randomized controlled trials²⁷⁰ have reported that brewed or boiled coffee, caffeine-containing drinks, and decaffeinated drinks did not have any effects on hemostatic variables, such as fibrinogen level, FVII activity, FVIII antigen, and protein C and S levels. Another experimental study²⁷¹ seems to support such observations, but another cross-sectional study²⁷² reported an increased in plasma fibrinogen levels with increased coffee consumption.

Fibrinolysis

The available evidence seems to suggest that coffee enhances fibrinolytic potential as whole blood fibrinolysis time is shortened²⁷³ and PAI-1 levels are decreased, whereas tPA activity increases²⁷⁴ after consumption of coffee and such effects are blunted during caffeine abstinence. However, one study²⁷¹ did not find an effect of abstinence from caffeine on blood clot lysis time.

Platelet Reactivity

The effects of caffeine intake on platelet activity are more variable. Several *in vitro* and *in vivo* studies^{275,276} have reported increased

platelet activation and release after coffee consumption, but others have found the opposite effects.^{271,272,277} Again, this may be due to the lack of standardization in the analysis methods used to assess platelet reactivity.

Tea: Coagulation, Fibrinolysis, and Platelet Reactivity

Previous epidemiologic studies have suggested that tea consumption is associated with a decreased risk of cardiovascular events, but a recent meta-analysis²⁷⁸ has reported no significant association and, in contrast, the risk may be even increased for CHD in the United Kingdom and for stroke in Australia with increasing tea consumption. Indeed, the antioxidative polyphenolic flavonoids found in tea have been shown to prevent oxidation of low-density lipoproteins both in vitro and in vivo²⁷⁹ and to inhibit platelet aggregation in vitro.²⁸⁰⁻²⁸²

However, recent randomized controlled trials²⁸³⁻²⁸⁵ of black or green tea or tea extracts have found no effects on both hemostatic and fibrinolytic variables (eg, fibrinogen, vWF, or FVII and PAI-1, tPA, or urokinase-type plasminogen activator) or on inflammatory markers such as C-reactive protein. Similarly, no significant difference was found from black tea consumption on ex vivo platelet aggregation in patients with CHD²⁸⁶ and on in vitro platelet aggregation in healthy subjects²⁵⁷ when compared with drinking hot water. Interestingly, in the same study, the latter group had found significantly lower (15%) soluble P-selectin levels (but not other adhesion molecules) in those who drank black tea; however, whether such a finding is of any clinical significance is unclear. Thus, it seems that the putative protective effect of tea against development of CHD may not be mediated through effects of tea consumption on hemostasis, fibrinolysis, or platelet activity.

CARDIAC REHABILITATION AND THROMBOGENESIS

A recent Cochrane Systematic Review has concluded that cardiac re-

habilitation with either exercise alone or exercise as part of a comprehensive rehabilitation program in post-MI and postrevascularization patients significantly reduced all-cause or total cardiac mortality by at least 26% to 31%.²⁸⁷ In addition to the reduction of cardiovascular morbidity and mortality, cardiac rehabilitation also significantly improves functional capacity and quality of life and lipid profile and blood pressure.²⁸⁸

Thus, given all the evidence discussed herein, it is highly plausible that lifestyle modifications through a program that incorporates stepwise increment of physical training or exercise, patient education and advice, dietary modifications, and psychosocial stress management would have a significant impact on patients' thrombogenic profile and hence may beneficially influence the overall cardiovascular risk.

However, so far, to our knowledge, no study has been reported on the overall effects of such a comprehensive cardiac rehabilitation program on changes of the various variables of hemostasis, fibrinolysis, and platelet reactivity. Previous studies have mainly focused on the effects of short-term or regular physical activities on fibrinolytic responses in post-MI or post-coronary artery bypass grafting patients who participated in cardiac rehabilitation exercise programs (**Table 7**).

In keeping with epidemiologic data, patients with CHD have higher basal levels of PAI-1 and tPA antigen, suggesting impaired fibrinolytic activity compared with healthy subjects. Although healthy subjects tended to have a marked fibrinolytic response to exercise, patients with CHD have a lower increase in the fibrinolytic potential as evidenced by changes in tPA activity and PAI-1 levels after regular physical training.²⁹² Although the increase of fibrinolytic capacity may be counterbalanced by an increase in blood coagulability and platelet activity during short-term exercise,⁹¹ lower plasma fibrinogen level has in fact been found in both post-MI and post-coronary bypass grafting patients who engage in regular aerobic exercise during cardiac rehabilitation.^{82,83}

CONCLUSIONS

The hemostatic system is assuming an increasingly prominent role in the pathogenesis and progression of atherosclerotic diseases. Human lifestyle or physical activities have diverse effects on coagulation, fibrinolysis, and platelet reactivity. There have been abundant studies of the effects of exercise, weight loss, dietary lipids (especially n-3 PUFA), smoking, alcohol, and psychosocial stress on the 3 main systems of thrombogenesis. The data from intervention and randomized clinical trials are largely fragmented, rarely complete, and inconsistent, mainly due to the differences in study design and the inherent complexity of subjects' confounders and the lack of standardization of the various analytical methods used in the assessment of coagulation, fibrinolysis, and platelet function. The in vivo significance of examining one portion of the complex overall system is unclear. How much could one correlate the in vitro or ex vivo findings to the true in vivo biological activities in many of the human biological systems is largely unknown. Nevertheless, these data have provided us with important preliminary explanations for the relative contribution of the various thrombogenic markers in relation to lifestyle habits to clinical outcomes reported in epidemiologic studies. Available evidence from these studies support lifestyles that adopt strategies to lose weight, stop cigarette smoking, engage in regular moderate exercise and relaxation, and regularly consume light-to-moderate alcohol and fatty fish should significantly lower coagulability, promote fibrinolysis, and reduce platelet reactivity. The overall effects ought to translate into an improved cardiovascular or other beneficial clinical outcome in healthy individuals, those with cardiovascular risk factors, or those with established CHD. It follows that a cardiac rehabilitation program that incorporates a stepwise increment of physical training or exercise, patient education and advice, dietary and personal habit modifications, and psychosocial

Table 7. Controlled or Intervention Clinical Trials of Cardiac Rehabilitation Exercise on Thrombogenic Factors

Source	Subjects	Exercise	Main Results	Conclusions
Weiss et al, ⁹² 1998	12 Males with CHD without MI within the preceding 6 mo (aged 55 ± 9 y) vs 12 healthy male controls (aged 52 ± 7 y)	Blood drawn before and after rehab group exercise session lasting 1 h	CHD patients had ↓ PTF F1 + 2 and remained unchanged after exercise, whereas a significant ↑ occurred in controls. Postexercise platelet count, β-Tbg, TAT, and FPA ↑ in both groups but was more pronounced in controls. Exercise ↑ PAP complexes in both groups. Repeated experiments after aspirin given to controls did not alter results	Patients and controls similarly ↑ coagulation and fibrinolysis induced by exercise. Rehab exercise in CHD patients beyond the immediate post-MI period has no detrimental effects on thrombin, fibrin, and plasmin formation
Suzuki et al, ⁸² 1992	56 Active exercise post-MI patients vs 30 post-MI patients without training	Blood drawn before and after 1 mo of systematic physical training	Training ↓ Fg, FVIII, vWf, TAT, plasminogen activity, hematocrit, platelet counts, and α2AP. APTT prolonged with training. In 20 patients with training, resting α2AP, TAT, protein C, PAI, and FVII significantly ↓ after 1 mo, but tPA activity unchanged	Training ↓ coagulation in post-MI patients: ↓ in Fg, FVIII, vWf, FVII, and TAT. The ↓ in plasminogen, tPA antigen, α2AP, PAI, and protein C after training may result from the ↓ coagulation
Wosornu et al, ⁸³ 1992	55 Men (aged 32-70 y) within 12 mo of CABG randomized to aerobic or power exercise or controls	6 Months of aerobic or power exercise on treadmill (3 times per week) in training patients	Both trained groups ↑ exercise capacity at 6 mo. Aerobic exercise improved earlier at 3 mo. Fg ↓ with aerobic exercise but ↓ slightly with power exercise. Gradual ↑ in FVII activity in aerobic and control groups but small ↓ in the power group. No consistent changes in FPA	Aerobic training post-CABG improves exercise capacity and ↓ Fg, which is maintained with further training. Power exercise causes delayed benefit in treadmill performance and a small ↓ in Fg. These changes may ↓ cardiovascular morbidity
Fernhall et al, ²⁸⁹ 1998	13 Post-MI patients	2 Maximal exercise on treadmill and BE. Blood drawn before and after each test	VO _{2max} , uptake, HR, and ventilation greater on treadmill than BE. Blood lactate similar between the 2 modes. tPA activity ↑ but a trend in ↓ PAI activity with exercise	Fibrinolysis ↑ similarly in both modes. Exercise intensity, but not the mode, seemed to be the primary determinant of fibrinolytic response to acute exercise
Speiser et al, ⁷⁷ 1988	71 Males: 2 pairs of age-matched groups. (1) Athletes, (2) not engaged in any sports, (3) regularly practicing sports, and (4) post-MI patients in a rehab sports program	BE exercise	At baseline, those doing regular sporting activities showed ↓ PAI vs the respective age-matched controls. During exercise tPA antigen similar between the age-matched groups but tPA activities ↑ after exercise in groups with lower pretest PAI. No change on D-dimer in any group	(1) Regular vigorous exercise ↑ fibrinolysis by ↓ PAI in healthy individuals; (2) rehab sport does not ↓ PAI in post-MI patients compared with age-matched healthy subjects regularly exercise; and (3) activation of fibrinolysis during exercise has no systemic fibrinolytic effect
Estelles et al, ²⁹⁰ 1989	Post-MI patients, active exercise vs controls	Rehab program with BE. Blood drawn at end of hospitalization and at 3 and 6 mo	At 6 mo, tPA activity ↓ in controls but slightly ↑ in active group. PAI ↑ in controls but remained constant or ↓ slightly in active group	Patients in rehab program showed a slight ↑ in fibrinolytic capacity but ↓ significantly in controls
Paramo et al, ²⁹¹ 1998	30 (M/F, 22/8; mean age, 47 y) Survivors of a first MI vs 30 healthy controls	9 Months of cardiac rehab. Blood drawn before and at 3 and 9 mo after program	Marked ↓ in functional PAI after 3 and 9 mo in MI patients. Also significant ↑ of HDL-C and ↓ of Lp(a) after the program	Cardiac rehab improved fibrinolysis and lipid profile in post-MI patients

Abbreviations: For an explanation of abbreviations, see footnote to Table 1.

stress management would have a significant impact on patients' hemostatic profiles and hence beneficially influence the overall cardiovascular risk.

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