

# Effects of Lifestyle on Hemostasis, Fibrinolysis, and Platelet Reactivity

## A Systematic Review

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**T**he 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.<sup>1,2</sup> 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.<sup>3</sup>

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.<sup>4-6</sup> Conversely, improvements of these cardiovascular risk factors have been associated with a lower prothrombotic tendency.<sup>7-10</sup> 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 reduction<sup>11</sup> and improved mortality by diets rich in oily fish. In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione (GISSI Prevenzione)<sup>12</sup> trial and the Diet and Reinfarction Trial (DART),<sup>13</sup> 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.<sup>14</sup> However, many instances of sudden death have a thrombotic basis,<sup>15</sup> 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

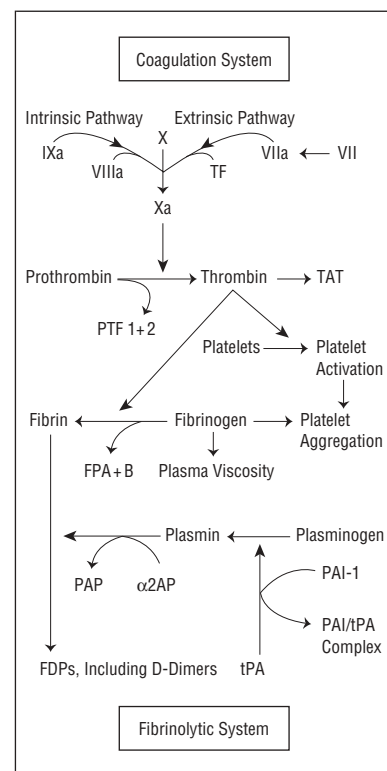
of fibrin within the thrombus, disintegrating clots and hence maintaining vascular patency. Fibrin degrades into soluble fibrin degradation products, including D-dimers. The primary inhibitor of the fibrinolytic process is the plasminogen activator inhibitor type 1 (PAI-1), which inhibits plasminogen 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.<sup>16</sup>

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.<sup>17</sup> 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 subjects<sup>18-22</sup> and those with cardiovascular risk factors<sup>23,24</sup> or established coronary heart disease (CHD).<sup>25</sup> In addition, platelet hyperaggregation,<sup>26,27</sup> plasma viscosity,<sup>28-30</sup> and PAI-1 levels<sup>31-34</sup> 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;  $\alpha$ 2AP,  $\alpha$ 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.<sup>35,36</sup> 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.<sup>37-39</sup>

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 infusion<sup>40</sup> or exercise<sup>37</sup> 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  $\beta$ -blocker therapy but not by aspirin, further support of the important role of sympathoadrenal activation.<sup>41</sup>

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.<sup>62,63</sup> 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.<sup>64</sup> 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.<sup>59</sup>

### 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.<sup>52,66</sup> 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   |
|--|--|--|---|---|
| <b>Regular Exercise or Training</b>    |  |  |   |   |
| Zanettini et al, <sup>42</sup> 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, <sup>43</sup> 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, <sup>44</sup> 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, <sup>45</sup> 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, <sup>46</sup> 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, <sup>47</sup> 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, <sup>48</sup> 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, <sup>49</sup> 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   |
| <b>Acute Exercise</b>                  |  |  |   |   |
| Hegde et al, <sup>50</sup> 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, <sup>51</sup> 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, <sup>52</sup> 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  |
|--------------------------------------|---|--|---|--|
| <b>Acute Exercise (cont)</b>         |   |  |   |  |
| Prisco et al, <sup>53</sup> 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, <sup>54</sup> 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, <sup>55</sup> 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, <sup>56</sup> 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, <sup>57</sup> 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, <sup>58</sup> 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, <sup>59</sup> 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, <sup>60</sup> 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 dysfunction or platelet activation |
| Gibbs et al, <sup>61</sup> 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,  $\alpha$ -linolenic acid;  $\alpha$ 2AP,  $\alpha$ 2-antiplasmin; APTT, activated prothrombin time; AT, antithrombin;  $\beta$ -Tbg,  $\beta$ -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 dysfunction, 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  $\alpha$ 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.<sup>50,51</sup>

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 MI<sup>67</sup> and in older men with hypertension when compared with normotensive subjects.<sup>68</sup>

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,<sup>54,69,70</sup> but others using different protocols have shown either no significant effects<sup>52,71,72</sup> or even a reduction in plasma fibrinogen level after short-term, intense physical exercise.<sup>53</sup> It is possible that the changes in coagulation markers depend on the type of physical exercise to which subjects are subjected. Cerneca et al<sup>54</sup> 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 al<sup>70</sup> 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  $\beta$ -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 al<sup>73</sup> 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.<sup>46,47,72,74-76</sup> One study<sup>77</sup> 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<sup>43,50,51,69,78-80</sup> 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,<sup>45,48,55,81</sup> although 4 weeks of physical training has been shown to lower resting levels of FVIII activity and antigen in post-MI patients.<sup>82</sup> 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.<sup>46,76,83-85</sup> 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.<sup>42</sup> Similarly, 6 months of intensive endurance training reduced plasma fibrinogen in elderly men but not in young men.<sup>46</sup> On the other hand, Schuit et al<sup>47</sup> reported a significant increase in plasma fibrinogen levels in elderly males after a same duration of intensive training, whereas Ponjee et al<sup>48</sup> 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.<sup>65</sup>

†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<sup>80,83,86-88</sup> 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. Studies<sup>89-93</sup> 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.<sup>59,94-96</sup>

#### Exercise Effects on Platelet Reactivity

The effects of exercise on platelet aggregation and activation have been extensively studied, but the results are highly variable.<sup>97,98</sup> It is noteworthy that measurements of platelet reactivity either in vitro or ex vivo aggregability assays or in vivo platelet secretory products (mainly  $\beta$ -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.<sup>99,100</sup> 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.<sup>56,101</sup>

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.<sup>102,103</sup> 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.<sup>37,38</sup> 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.<sup>101</sup>

#### 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.<sup>60</sup> 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.<sup>61</sup>

#### 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.<sup>104,105</sup> 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.<sup>106</sup>

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.<sup>107</sup> 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.<sup>108</sup> 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).<sup>107</sup> In addition, high fibrinogen and plasma viscosity have also been found to be associated with increasing BMI,<sup>107,109,110</sup> although, overall, there is only little evidence that weight reduction reduces plasma fibrinogen or viscosity levels.<sup>106,111</sup> 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,<sup>33,112</sup> 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.<sup>122,123</sup> 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.<sup>117</sup> 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.<sup>106</sup>

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.<sup>124-126</sup> In fact, dietary intervention with a low-saturated-fat diet<sup>127</sup> or gemfibrozil treatment<sup>128</sup> 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, <sup>113</sup> 2001        | 51 Obese women (mean age, 44 y; BMI, 36 kg/m <sup>2</sup> )                                     | 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, <sup>114</sup> 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%; FVIlc, 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, <sup>115</sup> 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, <sup>116</sup> 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, <sup>117</sup> 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, <sup>118</sup> 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, <sup>76</sup> 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, <sup>119</sup> 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, <sup>120</sup> 1998         | 324 Nondiabetic patients with central obesity (aged 35-65 y; mean BMI, 32.5 kg/m <sup>2</sup> ) | 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, <sup>121</sup> 1996 | 19 Elderly obese subjects (aged 60-70 y; BMI >32 kg/m <sup>2</sup> )                            | 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 fibrinolysis 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.<sup>129</sup> The recent Lyon Diet Heart Study<sup>130</sup> 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,  $\alpha$ -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,<sup>12,13</sup> 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.<sup>131</sup>

The experimental group in the Lyon Diet Heart Study had higher plasma levels of oleic acid,  $\alpha$ -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.<sup>132,133</sup> 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.<sup>134,135</sup> Data from the Coronary Artery Risk Development in Young Adults<sup>136</sup> study showed that usual intake of fish or dietary supplementation with  $\alpha$ -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,<sup>137</sup> which showed no relationships between fatty acids and fibrinogen, vWf, PAI-1, or FVII levels. By contrast, results from another cross-sectional study<sup>138</sup> 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  $\alpha$ -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.<sup>140,147,157,158,161-163</sup> One study<sup>164</sup> 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,<sup>156,165,166</sup> although others have yielded little effects.<sup>167-169</sup> 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 author<sup>170</sup> has reported reduced levels of FVIII with n-3 supplements, but most authors<sup>145,171-176</sup> 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<sup>136,171,172,174,177,178</sup> have not been able to show an effect with these fatty acids. In addition, few studies have even suggested that n-3 PUFA, including  $\alpha$ -linolenic acid, may have antithrombotic effects by enhancing protein C activity,<sup>171,174</sup> increasing tissue factor pathway inhibitor,<sup>175</sup> 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, <sup>138</sup> 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, <sup>137</sup> 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, <sup>139</sup> 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, <sup>140</sup> 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, <sup>141</sup> 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, <sup>142</sup> 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, <sup>143</sup> 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, <sup>144</sup> 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, <sup>145</sup> 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, <sup>146</sup> 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, <sup>147</sup> 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, <sup>148</sup> 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, <sup>149</sup> 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.<sup>179</sup>

### 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,<sup>153</sup> 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,<sup>145,148,180</sup> and few even reported significant increased in PAI-1 activity.<sup>146,160,181,182</sup> Moreover, data available on tPA activity also seem contradictory.<sup>145,148,176,183</sup> 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).<sup>137</sup> This is in agreement with a large intervention study<sup>184</sup> 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.<sup>185</sup>

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

| Source                              | Subjects   | Design   | Summary   |
|-------------------------------------|--|--|---|
| Li et al, <sup>150</sup> 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, <sup>151</sup> 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, <sup>152</sup> 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, <sup>153</sup> 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, <sup>154</sup> 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, <sup>155</sup> 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, <sup>156</sup> 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, <sup>157</sup> 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, <sup>158</sup> 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, <sup>159</sup> 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, <sup>160</sup> 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 diet<sup>127</sup> or gemfibrozil treatment<sup>128</sup> 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,<sup>146</sup> 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 al<sup>146</sup> 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.<sup>184,186</sup>

## 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.<sup>187</sup> Although few studies<sup>144,174,188</sup> 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.<sup>189-195</sup> It seems that platelet aggregation induced by low-dose collagen was the most commonly reported index to be influenced. One study<sup>152</sup> has demonstrated no significant difference between supplemented  $\alpha$ -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  $\beta$ -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  $\alpha$ -linolenic acid diet has no significant effect on thromboxane production and platelet aggregation with collagen.<sup>185</sup> Notably, data from studies<sup>195</sup> 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.<sup>150,151,196-198</sup> Novel, well-validated methods for measuring platelet aggregation are desperately needed to solve current controversies.<sup>195</sup>

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.<sup>199,200</sup> 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.<sup>201</sup>

## 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.<sup>202</sup> 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.<sup>203,204</sup> Increasing evidence has indicated that thrombogenic factors may play an important role in mediating such a complex association independent of HDL-C levels.<sup>205,206</sup>

### 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.<sup>107,207</sup> 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.<sup>205,208</sup> 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.<sup>20,209</sup> 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 al<sup>212</sup> 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 al<sup>210</sup> 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-analysis<sup>223</sup> 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, <sup>210</sup> 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, <sup>211</sup> 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, <sup>212</sup> 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, <sup>213</sup> 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, <sup>214</sup> 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, <sup>215</sup> 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, <sup>216</sup> 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, <sup>217</sup> 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, <sup>218</sup> 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, <sup>219</sup> 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, <sup>220</sup> 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, <sup>221</sup> 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 <sub>2</sub> . tPA activity ↓ and PAI ↑ only postprandially and predominantly affect older age group   |
| Lacoste et al, <sup>222</sup> 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.<sup>211,212,216,217,220,221</sup> Notably, a recent study<sup>217</sup> 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,<sup>216</sup> 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 al<sup>221</sup> and Hendriks et al<sup>218</sup> 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 study<sup>211</sup> 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.<sup>224</sup> 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)<sup>225</sup> and loss of the normal circadian periodicity of the hemostatic system is observed.<sup>219</sup> This may explain the increased ischemic strokes or sudden deaths that are known to occur after episodes of binge or heavy drinking.<sup>226</sup> 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,<sup>222</sup> 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.<sup>204,227</sup> 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,<sup>205</sup> 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.<sup>107,228,229,244</sup>

## 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,<sup>229,245</sup> although a decrease in fibrinogen levels follows quickly after cessation of smoking.<sup>246</sup> 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, <sup>228</sup> 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, <sup>229</sup> 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, <sup>230</sup> 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, <sup>231</sup> 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, <sup>232</sup> 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, <sup>233</sup> 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, <sup>234</sup> 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, <sup>235</sup> 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.<sup>107</sup>

### Fibrinolysis

Impaired fibrinolytic potential has been found in smokers with CHD<sup>247</sup> and peripheral vascular disease,<sup>248</sup> 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.<sup>231</sup> 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.<sup>232,233,249</sup> 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.<sup>236</sup> Plasma PAI-1 antigen seems to correlate with cumulative smoking in pack-years,<sup>230,236</sup> and on the other

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

| Source                                  | Methods   | Main Results   | Conclusion  |
|---|---|--|---|
| Haire et al, <sup>236</sup> 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, <sup>237</sup> 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. PAgr assays performed in parallel also showed no differences   | In habitual smokers, PHC and the agonists-induced PAgr assays are not significantly influenced or ↑ compared with healthy nonsmokers. An immediate effect of smoking cannot be excluded   |
| Modesti et al, <sup>238</sup> 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, <sup>239</sup> 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, <sup>240</sup> 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: PAgr to thrombin and ADP, plasma nicotine, β-Tbg, and CECs all ↑ significantly after smoking, but PAgr 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, <sup>241</sup> 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, <sup>242</sup> 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-PAgr ↑ 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, <sup>243</sup> 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 PAgr ratios were 0.80 and 0.65, 0.81, and 0.78, respectively   | Much greater effects of tobacco smoking on ET cell counts and PAgr 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 studies<sup>75</sup> 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,<sup>250</sup> 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,<sup>235</sup> but others have shown no differences in various agonist-induced platelet aggregations in

vitro compared with nonsmokers.<sup>237</sup> 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).<sup>241</sup> 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.<sup>239</sup> 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.<sup>239</sup> 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.<sup>251</sup> Smoking cessation for 6 weeks, however, has resulted in a 29% reduction of circulating P-selectin

plasma levels in healthy smokers<sup>252</sup> and a decrease in platelet count 2 weeks after cessation.<sup>253</sup> Furthermore, aspirin abolished the major cigarette smoke-induced endothelial damage and platelet hyperactivity in the presence of high plasma nicotine levels.<sup>240</sup> 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.<sup>254</sup>

### 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.<sup>255-257</sup> The increased cardiovascular risk may be secondary to excessive cardiovascular reactivity to stress<sup>258</sup> 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,<sup>259,260</sup> and enhances fibrinolysis with increased activity of tPA within a physiological range in healthy subjects.<sup>260,261</sup> 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.<sup>262,263</sup> 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.<sup>264</sup> 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.<sup>265</sup> High job demands have also been significantly related to decreases in tPA activity (ie, lower fibrinolytic capacity, independent of other traditional cardiovascular risk factors)<sup>266</sup> 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.<sup>262</sup>

#### 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<sup>37,267</sup> 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.<sup>267</sup>

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.<sup>37,38,41,268,269</sup> 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 thrombogenic factors might be relevant. However, limited data from intervention study are currently available.

#### Coagulation

Two well-described randomized controlled trials<sup>270</sup> 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 study<sup>271</sup> seems to support such observations, but another cross-sectional study<sup>272</sup> 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 shortened<sup>273</sup> and PAI-1 levels are decreased, whereas tPA activity increases<sup>274</sup> after consumption of coffee and such effects are blunted during caffeine abstinence. However, one study<sup>271</sup> 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<sup>275,276</sup> have reported increased

platelet activation and release after coffee consumption, but others have found the opposite effects.<sup>271,272,277</sup> 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-analysis<sup>278</sup> 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 vivo<sup>279</sup> and to inhibit platelet aggregation in vitro.<sup>280-282</sup>

However, recent randomized controlled trials<sup>283-285</sup> 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 CHD<sup>286</sup> and on in vitro platelet aggregation in healthy subjects<sup>257</sup> 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%.<sup>287</sup> 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.<sup>288</sup>

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' thrombotic 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.<sup>292</sup> Although the increase of fibrinolytic capacity may be counterbalanced by an increase in blood coagulability and platelet activity during short-term exercise,<sup>91</sup> 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.<sup>82,83</sup>

#### 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 thrombotic 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, <sup>92</sup><br>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, <sup>82</sup><br>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, <sup>83</sup><br>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, <sup>289</sup><br>1998 | 13 Post-MI patients   | 2 Maximal exercise on treadmill and BE. Blood drawn before and after each test             | VO <sub>2max</sub> , 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, <sup>77</sup><br>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, <sup>290</sup><br>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, <sup>291</sup><br>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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## REFERENCES

1. Fuster V, Badimon JJ, Chesebro JH. Atherothrombosis: mechanisms and clinical therapeutic approaches. *Vasc Med*. 1998;3:231-239.
2. Davies MJ. The pathophysiology of acute coronary syndromes. *Heart*. 2000;83:361-366.
3. Lip GY, Blann AD. Thrombogenesis and fibrinolysis in acute coronary syndromes: important facets of a prothrombotic or hypercoagulable state? *J Am Coll Cardiol*. 2000;36:2044-2046.
4. Makris TK, Tsoukala C, Krespi P, et al. Haemostasis balance disorders in patients with

- essential hypertension. *Thromb Res.* 1997;88:99-107.
5. Woodward M, Lowe GD, Rumley A, et al. Epidemiology of coagulation factors, inhibitors and activation markers: The Third Glasgow MONICA Survey, II: relationships to cardiovascular risk factors and prevalent cardiovascular disease. *Br J Haematol.* 1997;97:785-797.
  6. Lip GY, Blann AD, Jones AF, Lip PL, Beevers DG. Relation of endothelium, thrombogenesis, and hemorheology in systemic hypertension to ethnicity and left ventricular hypertrophy. *Am J Cardiol.* 1997;80:1566-1571.
  7. Colwell JA. Treatment for the procoagulant state in type 2 diabetes. *Endocrinol Metab Clin North Am.* 2001;30:1011-1030.
  8. Osende JJ, Badimon JJ, Fuster V, et al. Blood thrombogenicity in type 2 diabetes mellitus patients is associated with glycemic control. *J Am Coll Cardiol.* 2001;38:1307-1312.
  9. Makris TK, Stavroulakis GA, Krespi PG, et al. Fibrinolytic/hemostatic variables in arterial hypertension: response to treatment with irbesartan or atenolol. *Am J Hypertens.* 2000;13:783-788.
  10. Ernst E, Resch KL. Therapeutic interventions to lower plasma fibrinogen concentration. *Eur Heart J.* 1995;16(suppl A):47-52.
  11. Sacks FM, Svetkey LP, Vollmer WM, et al. DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med.* 2001;344:3-10.
  12. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet.* 1999;354:447-455.
  13. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet.* 1989;2:757-761.
  14. Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation.* 2002;105:1897-1903.
  15. Davies MJ. The investigation of sudden cardiac death. *Histopathology.* 1999;34:93-98.
  16. Wiman B. Predictive value of fibrinolytic factors in coronary heart disease. *Scand J Clin Lab Invest Suppl.* 1999;230:23-31.
  17. Lip GY. Fibrinogen and cardiovascular disorders. *Q J Med.* 1995;88:155-165.
  18. Lowe GD, Rumley A, Sweetnam PM, Yarnell JW, Rumley J. Fibrin D-dimer, markers of coagulation activation and the risk of major ischaemic heart disease in the caerphilly study. *Thromb Haemost.* 2001;86:822-827.
  19. Rumley A, Lowe GD, Sweetnam PM, Yarnell JW, Ford RP. Factor VIII, von Willebrand factor and the risk of major ischaemic heart disease in the Caerphilly Heart Study. *Br J Haematol.* 1999;105:110-116.
  20. Smith FB, Lee AJ, Fowkes FG, Price JF, Rumley A, Lowe GD. Hemostatic factors as predictors of ischemic heart disease and stroke in the Edinburgh Artery Study. *Arterioscler Thromb Vasc Biol.* 1997;17:3321-3325.
  21. Meade TW, Mellows S, Brozovic M, et al. Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. *Lancet.* 1986;2:533-537.
  22. Ridker PM, Vaughan DE, Stampfer MJ, Manson JE, Hennekens CH. Endogenous tissue-type plasminogen activator and risk of myocardial infarction. *Lancet.* 1993;341:1165-1168.
  23. Juhan-Vague I, Pyke SD, Alessi MC, Jespersen J, Haverkate F, Thompson SG, European Concerted Action on Thrombosis and Disabilities. Fibrinolytic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. *Circulation.* 1996;94:2057-2063.
  24. Junker R, Heinrich J, Schulte H, Erren M, Assmann G. Hemostasis in normotensive and hypertensive men: results of the PROCAM study. *J Hypertens.* 1998;16:917-923.
  25. Thompson SG, Kienast J, Pyke SD, Haverkate F, van de Loo JC, European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. *N Engl J Med.* 1995;332:635-641.
  26. Thaulow E, Erikssen J, Sandvik L, Stormorken H, Cohn PF. Blood platelet count and function are related to total and cardiovascular death in apparently healthy men. *Circulation.* 1991;84:613-617.
  27. Trip MD, Cats VM, van Capelle FJ, Vreken J. Platelet hyperreactivity and prognosis in survivors of myocardial infarction. *N Engl J Med.* 1990;322:1549-1554.
  28. Koenig W, Sund M, Lowel H, Doring A, Ernst E. Association between plasma viscosity and all-cause mortality: results from the MONICA-Augsburg Cohort Study 1984-92. *Br J Haematol.* 2000;109:453-458.
  29. Sweetnam PM, Thomas HF, Yarnell JW, Bewick AD, Baker IA, Elwood PC. Fibrinogen, viscosity and the 10-year incidence of ischaemic heart disease. *Eur Heart J.* 1996;17:1814-1820.
  30. Lowe GD, Lee AJ, Rumley A, Price JF, Fowkes FG. Blood viscosity and risk of cardiovascular events: the Edinburgh Artery Study. *Br J Haematol.* 1997;96:168-173.
  31. Thogersen AM, Jansson JH, Boman K, et al. High plasminogen activator inhibitor and tissue plasminogen activator levels in plasma precede a first acute myocardial infarction in both men and women: evidence for the fibrinolytic system as an independent primary risk factor. *Circulation.* 1998;98:2241-2247.
  32. Nordt TK, Peter K, Ruef J, Kubler W, Bode C. Plasminogen activator inhibitor type-1 (PAI-1) and its role in cardiovascular disease. *Thromb Haemost.* 1999;82(suppl 1):14-18.
  33. Juhan-Vague I, Alessi MC. Fibrinolysis and risk of coronary artery disease. *Fibrinolysis.* 1996;10:127-136.
  34. Meade TW, Ruddock V, Stirling Y, Chakrabarti R, Miller GJ. Fibrinolytic activity, clotting factors, and long-term incidence of ischaemic heart disease in the Northwick Park Heart Study. *Lancet.* 1993;342:1076-1079.
  35. Wallen NH, Goodall AH, Li N, Hjerdahl P. Activation of haemostasis by exercise, mental stress and adrenaline: effects on platelet sensitivity to thrombin and thrombin generation. *Clin Sci (Lond).* 1999;97:27-35.
  36. von Kanel R, Dimsdale JE. Effects of sympathetic activation by adrenergic infusions on hemostasis in vivo. *Eur J Haematol.* 2000;65:357-369.
  37. Wallen NH, Held C, Rehnqvist N, Hjerdahl P. Effects of mental and physical stress on platelet function in patients with stable angina pectoris and healthy controls. *Eur Heart J.* 1997;18:807-815.
  38. Hurlen M, Seljeflot I, Arnesen H. Increased platelet aggregability during exercise in patients with previous myocardial infarction: lack of inhibition by aspirin. *Thromb Res.* 2000;99:487-494.
  39. Willich SN, Lewis M, Lowel H, Arntz HR, Schubert F, Schroder R, Triggers and Mechanisms of Myocardial Infarction Study Group. Physical exertion as a trigger of acute myocardial infarction. *N Engl J Med.* 1993;329:1684-1690.
  40. Larsson PT, Wallen NH, Hjerdahl P. Norepinephrine-induced human platelet activation in vivo is only partly counteracted by aspirin. *Circulation.* 1994;89:1951-1957.
  41. Kawano TA, Aoki N, Homori M, et al. Mental stress and physical exercise increase platelet-dependent thrombin generation. *Heart Vessels.* 2000;15:280-288.
  42. Zanettini R, Bettega D, Agostoni O, et al. Exercise training in mild hypertension: effects on blood pressure, left ventricular mass and coagulation factor VII and fibrinogen. *Cardiology.* 1997;88:468-473.
  43. El Sayed MS, Lin X, Rattu AJ. Blood coagulation and fibrinolysis at rest and in response to maximal exercise before and after a physical conditioning programme. *Blood Coagul Fibrinolysis.* 1995;6:747-752.
  44. El Sayed MS. Effects of high and low intensity aerobic conditioning programs on blood fibrinolysis and lipid profile. *Blood Coagul Fibrinolysis.* 1996;7:484-490.
  45. van den Burg PJ, Hospers JE, van Vliet M, Mosterd WL, Bouma BN, Huisveld IA. Effect of endurance training and seasonal fluctuation on coagulation and fibrinolysis in young sedentary men. *J Appl Physiol.* 1997;82:613-620.
  46. Stratton JR, Chandler WL, Schwartz RS, et al. Effects of physical conditioning on fibrinolytic variables and fibrinogen in young and old healthy adults. *Circulation.* 1991;83:1692-1697.
  47. Schuit AJ, Schouten EG, Kluff C, de Maat M, Menheere PP, Kok FJ. Effect of strenuous exercise on fibrinogen and fibrinolysis in healthy elderly men and women. *Thromb Haemost.* 1997;78:845-851.
  48. Ponjee GA, Janssen GM, van Wersch JW. Prolonged endurance exercise and blood coagulation: a 9 month prospective study. *Blood Coagul Fibrinolysis.* 1993;4:21-25.
  49. Vaisanen SB, Humphries SE, Luong LA, Penttila I, Bouchard C, Rauramaa R. Regular exercise, plasminogen activator inhibitor-1 (PAI-1) activity and the 4G/5G promoter polymorphism in the PAI-1 gene. *Thromb Haemost.* 1999;82:1117-1120.
  50. Hegde SS, Goldfarb AH, Hegde S. Clotting and fibrinolytic activity change during the 1 h after a submaximal run. *Med Sci Sports Exerc.* 2001;33:887-892.
  51. Lin X, El Sayed MS, Waterhouse J, Reilly T. Activation and disturbance of blood haemostasis following strenuous physical exercise. *Int J Sports Med.* 1999;20:149-153.
  52. Rankinen T, Vaisanen S, Penttila I, Rauramaa R. Acute dynamic exercise increases fibrinolytic activity. *Thromb Haemost.* 1995;73:281-286.
  53. Prisco D, Panizza R, Bandinelli B, et al. Evaluation of clotting and fibrinolytic activation after protracted physical exercise. *Thromb Res.* 1998;89:73-78.
  54. Cerneca F, Crocetti G, Gombacci A, Simeone R, Tamaro G, Mangiarotti MA. Variations in hemostatic parameters after near-maximum exercise and specific tests in athletes. *J Sports Med Phys Fitness.* 1999;39:31-36.

55. Watts EJ. Haemostatic changes in long-distance runners and their relevance to the prevention of ischaemic heart disease. *Blood Coagul Fibrinolysis*. 1991;2:221-225.
56. Wang JS, Jen CJ, Chen HI. Effects of exercise training and deconditioning on platelet function in men. *Arterioscler Thromb Vasc Biol*. 1995;15:1668-1674.
57. Li N, Wallen NH, Hjemdahl P. Evidence for prothrombotic effects of exercise and limited protection by aspirin. *Circulation*. 1999;100:1374-1379.
58. Andreotti F, Lanza GA, Sciahbasi A, et al. Low-grade exercise enhances platelet aggregability in patients with obstructive coronary disease independently of myocardial ischemia. *Am J Cardiol*. 2001;87:16-20.
59. Mustonen P, Lepantalo M, Lassila R. Physical exertion induces thrombin formation and fibrin degradation in patients with peripheral atherosclerosis. *Arterioscler Thromb Vasc Biol*. 1998;18:244-249.
60. Li-Saw-Hee FL, Blann AD, Edmunds E, Gibbs CR, Lip GY. Effect of acute exercise on the raised plasma fibrinogen, soluble P-selectin and von Willebrand factor levels in chronic atrial fibrillation. *Clin Cardiol*. 2001;24:409-414.
61. Gibbs CR, Blann AD, Edmunds E, Watson RD, Lip GY. Effects of acute exercise on hemorheological, endothelial, and platelet markers in patients with chronic heart failure in sinus rhythm. *Clin Cardiol*. 2001;24:724-729.
62. Eliasson M, Asplund K, Evrin PE. Regular leisure time physical activity predicts high activity of tissue plasminogen activator: The Northern Sweden MONICA Study. *Int J Epidemiol*. 1996;25:1182-1188.
63. El Sayed MS. Effects of exercise on blood coagulation, fibrinolysis and platelet aggregation. *Sports Med*. 1996;22:282-298.
64. Rydzewski A, Sakata K, Kobayashi A, et al. Changes in plasminogen activator inhibitor 1 and tissue-type plasminogen activator during exercise in patients with coronary artery disease. *Haemostasis*. 1990;20:305-312.
65. Imhof A, Koenig W. Exercise and thrombosis. *Cardiol Clin*. 2001;19:389-400.
66. Szymanski LM, Pate RR. Effects of exercise intensity, duration, and time of day on fibrinolytic activity in physically active men. *Med Sci Sports Exerc*. 1994;26:1102-1108.
67. Fernhall B, Szymanski LM, Gorman PA, Milani J, Paup DC, Kessler CM. Fibrinolytic activity is similar in physically active men with and without a history of myocardial infarction. *Arterioscler Thromb Vasc Biol*. 1997;17:1106-1113.
68. DeSouza CA, Dengel DR, Rogers MA, Cox K, Macko RF. Fibrinolytic responses to acute physical activity in older hypertensive men. *J Appl Physiol*. 1997;82:1765-1770.
69. Arai M, Yorifuji H, Ikematsu S, et al. Influences of strenuous exercise (triathlon) on blood coagulation and fibrinolytic system. *Thromb Res*. 1990;57:465-471.
70. Montgomery HE, Clarkson P, Nwose OM, et al. The acute rise in plasma fibrinogen concentration with exercise is influenced by the G-453-A polymorphism of the beta-fibrinogen gene. *Arterioscler Thromb Vasc Biol*. 1996;16:386-391.
71. Bartsch P, Haeberli A, Straub PW. Blood coagulation after long distance running: antithrombin III prevents fibrin formation. *Thromb Haemost*. 1990;63:430-434.
72. De Paz JA, Lasierra J, Villa JG, Vilades E, Martin Nuno MA, Gonzalez-Gallego J. Changes in the fibrinolytic system associated with physical conditioning. *Eur J Appl Physiol Occup Physiol*. 1992;65:388-393.
73. Szymanski LM, Pate RR, Durstine JL. Effects of maximal exercise and venous occlusion on fibrinolytic activity in physically active and inactive men. *J Appl Physiol*. 1994;77:2305-2310.
74. De Paz JA, Lasierra J, Villa JG, Vilades E, Gonzalez-Gallego J. Effects of aerobic and anaerobic physical conditioning on fibrinolysis. *J Sports Med Phys Fitness*. 1995;35:263-267.
75. Gris JC, Schved JF, Feugeas O, et al. Impact of smoking, physical training and weight reduction on FVII, PAI-1 and hemostatic markers in sedentary men. *Thromb Haemost*. 1990;64:516-520.
76. Lindahl B, Nilsson TK, Jansson JH, Asplund K, Hallmans G. Improved fibrinolysis by intense lifestyle intervention: a randomized trial in subjects with impaired glucose tolerance. *J Intern Med*. 1999;246:105-112.
77. Speiser W, Langer W, Pschaick A, et al. Increased blood fibrinolytic activity after physical exercise: comparative study in individuals with different sporting activities and in patients after myocardial infarction taking part in a rehabilitation sports program. *Thromb Res*. 1988;51:543-555.
78. van den Burg PJ, Hospers JE, Mosterd WL, Bouma BN, Huisveld IA. Aging, physical conditioning, and exercise-induced changes in hemostatic factors and reaction products. *J Appl Physiol*. 2000;88:1558-1564.
79. Rock G, Tittler P, Pipe A. Coagulation factor changes following endurance exercise. *Clin J Sport Med*. 1997;7:94-99.
80. Hansen JB, Wilsyard L, Olsen JO, Osterud B. Formation and persistence of procoagulant and fibrinolytic activities in circulation after strenuous physical exercise. *Thromb Haemost*. 1990;64:385-389.
81. Boman K, Hellsten G, Bruce A, Hallmans G, Nilsson TK. Endurance physical activity, diet and fibrinolysis. *Atherosclerosis*. 1994;106:65-74.
82. Suzuki T, Yamauchi K, Yamada Y, et al. Blood coagulability and fibrinolytic activity before and after physical training during the recovery phase of acute myocardial infarction. *Clin Cardiol*. 1992;15:358-364.
83. Wosornu D, Allardyce W, Ballantyne D, Tansey P. Influence of power and aerobic exercise training on haemostatic factors after coronary artery surgery. *Br Heart J*. 1992;68:181-186.
84. Vanninen E, Laitinen J, Uusitupa M. Physical activity and fibrinogen concentration in newly diagnosed NIDDM. *Diabetes Care*. 1994;17:1031-1038.
85. Ernst E. Regular exercise reduces fibrinogen levels: a review of longitudinal studies. *Br J Sports Med*. 1993;27:175-176.
86. Gill JM, Frayn KN, Wootton SA, Miller GJ, Hardman AE. Effects of prior moderate exercise on exogenous and endogenous lipid metabolism and plasma factor VII activity. *Clin Sci (Lond)*. 2001;100:517-527.
87. van den Burg PJ, Hospers JE, van Vliet M, Mosterd WL, Huisveld IA. Unbalanced haemostatic changes following strenuous physical exercise: a study in young sedentary males. *Eur Heart J*. 1995;16:1995-2001.
88. Connelly JB, Cooper JA, Meade TW. Strenuous exercise, plasma fibrinogen, and factor VII activity. *Br Heart J*. 1992;67:351-354.
89. Prisco D, Paniccia R, Guarnaccia V, et al. Thrombin generation after physical exercise. *Thromb Res*. 1993;69:159-164.
90. Weiss C, Welsch B, Albert M, et al. Coagulation and thrombomodulin in response to exercise of different type and duration. *Med Sci Sports Exerc*. 1998;30:1205-1210.
91. Weiss C, Seitel G, Bartsch P. Coagulation and fibrinolysis after moderate and very heavy exercise in healthy male subjects. *Med Sci Sports Exerc*. 1998;30:246-251.
92. Weiss C, Velich T, Niebauer J, et al. Activation of coagulation and fibrinolysis after rehabilitative exercise in patients with coronary artery disease. *Am J Cardiol*. 1998;81:672-677.
93. Bartsch P, Welsch B, Albert M, Friedmann B, Levi M, Kruihof EK. Balanced activation of coagulation and fibrinolysis after a 2-h triathlon. *Med Sci Sports Exerc*. 1995;27:1465-1470.
94. Grant PJ. Hormonal regulation of the acute haemostatic response to stress. *Blood Coagul Fibrinolysis*. 1990;1:299-306.
95. Chandler WL, Veith RC, Fellingham GW, et al. Fibrinolytic response during exercise and epinephrine infusion in the same subjects. *J Am Coll Cardiol*. 1992;19:1412-1420.
96. El Sayed MS, Davies B. Effect of two formulations of a beta blocker on fibrinolytic response to maximum exercise. *Med Sci Sports Exerc*. 1989;21:369-373.
97. Davis RB, Boyd DG, McKinney ME, Jones CC. Effects of exercise and exercise conditioning on blood platelet function. *Med Sci Sports Exerc*. 1990;22:49-53.
98. Rauramaa R, Salonen JT, Seppanen K, et al. Inhibition of platelet aggregability by moderate-intensity physical exercise: a randomized clinical trial in overweight men. *Circulation*. 1986;74:939-944.
99. Kestin AS, Ellis PA, Barnard MR, Errichetti A, Rosner BA, Michelson AD. Effect of strenuous exercise on platelet activation state and reactivity. *Circulation*. 1993;88:1502-1511.
100. Wang JS, Jen CJ, Kung HC, Lin LJ, Hsiue TR, Chen HI. Different effects of strenuous exercise and moderate exercise on platelet function in men. *Circulation*. 1994;90:2877-2885.
101. Wang JS, Jen CJ, Chen HI. Effects of chronic exercise and deconditioning on platelet function in women. *J Appl Physiol*. 1997;83:2080-2085.
102. Bartsch P. Platelet activation with exercise and risk of cardiac events. *Lancet*. 1999;354:1747-1748.
103. Streiff M, Bell WR. Exercise and hemostasis in humans. *Semin Hematol*. 1994;31:155-165.
104. Rao SV, Donahue M, Pi-Sunyer FX, Fuster V. Results of expert meetings: obesity and cardiovascular disease: obesity as a risk factor in coronary artery disease. *Am Heart J*. 2001;142:1102-1107.
105. Vega GL. Results of expert meetings: obesity and cardiovascular disease: obesity, the metabolic syndrome, and cardiovascular disease. *Am Heart J*. 2001;142:1108-1116.
106. Van Gaal LF, Wauters MA, De Leeuw IH. The beneficial effects of modest weight loss on cardiovascular risk factors. *Int J Obes Relat Metab Disord*. 1997;21(suppl 1):S5-S9.
107. Yarnell JW, Sweetnam PM, Rumley A, Lowe GD. Lifestyle and hemostatic risk factors for ischemic heart disease: the Caerphilly Study. *Arterioscler Thromb Vasc Biol*. 2000;20:271-279.
108. Landin K, Stigendal L, Eriksson E, et al. Abdominal obesity is associated with an impaired fibrinolytic activity and elevated plasminogen activator inhibitor-1. *Metabolism*. 1990;39:1044-1048.

109. Eliasson M, Evrin PE, Lundblad D. Fibrinogen and fibrinolytic variables in relation to anthropometry, lipids and blood pressure: The Northern Sweden MONICA Study. *J Clin Epidemiol*. 1994; 47:513-524.
110. Ernst E, Resch KL. Fibrinogen as a cardiovascular risk factor: a meta-analysis and review of the literature. *Ann Intern Med*. 1993;118:956-963.
111. Ernst E, Resch KL. Therapeutic interventions to lower plasma fibrinogen concentration. *Eur Heart J*. 1995;16(suppl A):47-52.
112. Charles MA, Morange P, Eschwege E, Andre P, Vague P, Juhan-Vague I. Effect of weight change and metformin on fibrinolysis and the von Willebrand factor in obese nondiabetic subjects: the BIGPRO1 Study. *Diabetes Care*. 1998; 21:1967-1972.
113. Rissanen P, Vahtera E, Krusius T, Uusitupa M, Rissanen A. Weight change and blood coagulability and fibrinolysis in healthy obese women. *Int J Obes Relat Metab Disord*. 2001;25:212-218.
114. Marckmann P, Toubro S, Astrup A. Sustained improvement in blood lipids, coagulation, and fibrinolysis after major weight loss in obese subjects. *Eur J Clin Nutr*. 1998;52:329-333.
115. Folsom AR, Qamhi HT, Wing RR, et al. Impact of weight loss on plasminogen activator inhibitor (PAI-1), factor VII, and other hemostatic factors in moderately overweight adults. *Arterioscler Thromb*. 1993;13:162-169.
116. Primrose JN, Davies JA, Prentice CR, Hughes R, Johnston D. Reduction in factor VII, fibrinogen and plasminogen activator inhibitor-1 activity after surgical treatment of morbid obesity. *Thromb Haemost*. 1992;68:396-399.
117. Berntorp E, Berntorp K, Brorson H, Frick K. Liposuction in Dercum's disease: impact on hemostatic factors associated with cardiovascular disease and insulin sensitivity. *J Intern Med*. 1998;243:197-201.
118. Sudi KM, Gallistl S, Trobinger M, et al. The influence of weight loss on fibrinolytic and metabolic parameters in obese children and adolescents. *J Pediatr Endocrinol Metab*. 2001;14: 85-94.
119. Mavri A, Stegnar M, Krebs M, Sentocnik JT, Geiger M, Binder BR. Impact of adipose tissue on plasma plasminogen activator inhibitor-1 in dieting obese women. *Arterioscler Thromb Vasc Biol*. 1999;19:1582-1587.
120. Charles MA, Morange P, Eschwege E, Andre P, Vague P, Juhan-Vague I. Effect of weight change and metformin on fibrinolysis and the von Willebrand factor in obese nondiabetic subjects: the BIGPRO1 Study. *Diabetes Care*. 1998; 21:1967-1972.
121. Calles-Escandon J, Ballor D, Harvey-Berino J, Ades P, Tracy R, Sobel B. Amelioration of the inhibition of fibrinolysis in elderly, obese subjects by moderate energy intake restriction. *Am J Clin Nutr*. 1996;64:7-11.
122. Loskutoff DJ, Samad F. The adipocyte and hemostatic balance in obesity: studies of PAI-1. *Arterioscler Thromb Vasc Biol*. 1998;18:1-6.
123. Lundgren CH, Brown SL, Nordt TK, Sobel BE, Fujii S. Elaboration of type-1 plasminogen activator inhibitor from adipocytes: a potential pathogenetic link between obesity and cardiovascular disease. *Circulation*. 1996;93:106-110.
124. Hamsten A, De Faire U, Walldius G, et al. Plasminogen activator inhibitor in plasma: risk factor for recurrent myocardial infarction. *Lancet*. 1987;2:3-9.
125. Juhan-Vague I, Vague P, Alessi MC, et al. Relationships between plasma insulin triglyceride, body mass index, and plasminogen activator inhibitor 1. *Diabetes Metab*. 1987;13:331-336.
126. Mehta J, Mehta P, Lawson D, Saldeen T. Plasma tissue plasminogen activator inhibitor levels in coronary artery disease: correlation with age and serum triglyceride concentrations. *J Am Coll Cardiol*. 1987;9:263-268.
127. Elkeles RS, Chakrabarti R, Vickers M, Stirling Y, Meade TW. Effect of treatment of hyperlipidaemia on haemostatic variables. *BMJ*. 1980;281: 973-974.
128. Andersen P, Smith P, Seljeflot I, Brataker S, Arnesen H. Effects of gemfibrozil on lipids and haemostasis after myocardial infarction. *Thromb Haemost*. 1990;63:174-177.
129. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
130. de Lorgeril M, Salen P, Martin JL, Monjaud I, Boucher P, Mamelle N. Mediterranean dietary pattern in a randomized trial: prolonged survival and possible reduced cancer rate. *Arch Intern Med*. 1998;158:1181-1187.
131. Kris-Etherton P, Eckel RH, Howard BV, St Jeor S, Bazzarre TL. AHA science advisory: Lyon Diet Heart Study: benefits of a Mediterranean-style, National Cholesterol Education Program/American Heart Association step I dietary pattern on cardiovascular disease. *Circulation*. 2001; 103:1823-1825.
132. Kristensen SD, Iversen AM, Schmidt EB. n-3 polyunsaturated fatty acids and coronary thrombosis. *Lipids*. 2001;36(suppl):S79-S82.
133. Hornstra G. Influence of dietary fat type on arterial thrombosis tendency. *J Nutr Health Aging*. 2001;5:160-166.
134. Hoak JC. Fatty acids in animals: thrombosis and hemostasis. *Am J Clin Nutr*. 1997;65:1683S-1686S.
135. Nobukata H, Ishikawa T, Obata M, Shibutani Y. Long-term administration of highly purified eicosapentaenoic acid ethyl ester prevents diabetes and abnormalities of blood coagulation in male WBN/Kob rats. *Metabolism*. 2000;49:912-919.
136. Archer SL, Green D, Chamberlain M, Dyer AR, Liu K. Association of dietary fish and n-3 fatty acid intake with hemostatic factors in the coronary artery risk development in young adults (CARDIA) study. *Arterioscler Thromb Vasc Biol*. 1998;18:1119-1123.
137. Scarabin PY, Aillaud MF, Luc G, et al. Haemostasis in relation to dietary fat as estimated by erythrocyte fatty acid composition: the PRIME study. *Thromb Res*. 2001;102:285-293.
138. Shahar E, Folsom AR, Wu KK, et al. Associations of fish intake and dietary n-3 polyunsaturated fatty acids with a hypo-coagulable profile: the Atherosclerosis Risk in Communities (ARIC) Study. *Arterioscler Thromb*. 1993;13:1205-1212.
139. Iacoviello L, Amore C, De Curtis A, et al. Modulation of fibrinolytic response to venous occlusion in humans by a combination of low-dose aspirin and n-3 polyunsaturated fatty acids. *Arterioscler Thromb*. 1992;12:1191-1197.
140. Oosthuizen W, Vorster HH, Jerling JC, et al. Both fish oil and olive oil lowered plasma fibrinogen in women with high baseline fibrinogen levels. *Thromb Haemost*. 1994;72:557-562.
141. Boberg M, Pollare T, Siegbahn A, Vessby B. Supplementation with n-3 fatty acids reduces triglycerides but increases PAI-1 in non-insulin-dependent diabetes mellitus. *Eur J Clin Invest*. 1992;22:645-650.
142. Radack K, Deck C, Huster G. The comparative effects of  $\omega$ -3 and n-6 polyunsaturated fatty acids on plasma fibrinogen levels: a controlled clinical trial in hypertriglyceridemic subjects. *J Am Coll Nutr*. 1990;9:352-357.
143. Prisco D, Paniccia R, Filippini M, et al. No changes in PAI-1 levels after four-month n-3 PUFA ethyl ester supplementation in healthy subjects. *Thromb Res*. 1994;76:237-244.
144. Myrup B, Rossing P, Jensen T, et al. Lack of effect of fish oil supplementation on coagulation and transcapillary escape rate of albumin in insulin-dependent diabetic patients with diabetic nephropathy. *Scand J Clin Lab Invest*. 2001;61: 349-356.
145. Toft I, Bona KH, Ingebretsen OC, Nordoy A, Jenssen T. Fibrinolytic function after dietary supplementation with omega3 polyunsaturated fatty acids. *Arterioscler Thromb Vasc Biol*. 1997; 17:814-819.
146. Hansen J, Grimsgaard S, Nordoy A, Bona KH. Dietary supplementation with highly purified eicosapentaenoic acid and docosahexaenoic acid does not influence PAI-1 activity. *Thromb Res*. 2000;98:123-132.
147. Nilsen DW, Dalaker K, Nordoy A, et al. Influence of a concentrated ethylester compound of n-3 fatty acids on lipids, platelets and coagulation in patients undergoing coronary bypass surgery. *Thromb Haemost*. 1991;66:195-201.
148. Hellsten G, Boman K, Saarem K, Hallmans G, Nilsson TK. Effects on fibrinolytic activity of corn oil and a fish oil preparation enriched with omega-3-polyunsaturated fatty acids in a long-term study. *Curr Med Res Opin*. 1993;13:133-139.
149. Rogers S, James KS, Butland BK, Etherington MD, O'Brien JR, Jones JG. Effects of a fish oil supplement on serum lipids, blood pressure, bleeding time, haemostatic and rheological variables: a double blind randomised controlled trial in healthy volunteers. *Atherosclerosis*. 1987;63: 137-143.
150. Li XL, Steiner M. Fish oil: a potent inhibitor of platelet adhesiveness. *Blood*. 1990;76:938-945.
151. Andrioli G, Carletto A, Guarini P, et al. Differential effects of dietary supplementation with fish oil or soy lecithin on human platelet adhesion. *Thromb Haemost*. 1999;82:1522-1527.
152. Freese R, Mutanen M. Alpha-linolenic acid and marine long-chain n-3 fatty acids differ only slightly in their effects on hemostatic factors in healthy subjects. *Am J Clin Nutr*. 1997;66:591-598.
153. Barcelli U, Glas-Greenwalt P, Pollak VE. Enhancing effect of dietary supplementation with omega-3 fatty acids on plasma fibrinolysis in normal subjects. *Thromb Res*. 1985;39:307-312.
154. Mehta J, Lawson D, Saldeen T. Reduction in plasminogen activator inhibitor-1 (PAI-1) with omega-3 polyunsaturated fatty acid (PUFA) intake. *Am Heart J*. 1988;116:1201-1206.
155. Schmidt EB, Varming K, Ernst E, Madsen P, Dyerberg J. Dose-response studies on the effect of n-3 polyunsaturated fatty acids on lipids and haemostasis. *Thromb Haemost*. 1990;63:1-5.
156. Miller ME, Anagnostou AA, Ley B, Marshall P, Steiner M. Effect of fish oil concentrates on hemorheological and hemostatic aspects of diabetes mellitus: a preliminary study. *Thromb Res*. 1987;47:201-214.

157. Schmidt EB, Lervang HH, Varming K, Madsen P, Dyerberg J. Long-term supplementation with n-3 fatty acids. I: effect on blood lipids, haemostasis and blood pressure. *Scand J Clin Lab Invest*. 1992;52:221-228.
158. Smith P, Arnesen H, Opstad T, Dahl KH, Eritsland J. Influence of highly concentrated n-3 fatty acids on serum lipids and hemostatic variables in survivors of myocardial infarction receiving either oral anticoagulants or matching placebo. *Thromb Res*. 1989;53:467-474.
159. Li D, Sinclair A, Wilson A, et al. Effect of dietary alpha-linolenic acid on thrombotic risk factors in vegetarian men. *Am J Clin Nutr*. 1999;69:872-882.
160. Emeis JJ, van Houwelingen AC, van den Hoogen CM, Hornstra G. A moderate fish intake increases plasminogen activator inhibitor type-1 in human volunteers. *Blood*. 1989;74:233-237.
161. Nordoy A, Hatcher L, Goodnight S, FitzGerald GA, Conner WE. Effects of dietary fat content, saturated fatty acids, and fish oil on eicosanoid production and hemostatic parameters in normal men. *J Lab Clin Med*. 1994;123:914-920.
162. Saynor R, Gillott T. Changes in blood lipids and fibrinogen with a note on safety in a long term study on the effects of n-3 fatty acids in subjects receiving fish oil supplements and followed for seven years. *Lipids*. 1992;27:533-538.
163. Goodnight SH Jr, Harris WS, Connor WE. The effects of dietary omega 3 fatty acids on platelet composition and function in man: a prospective, controlled study. *Blood*. 1981;58:880-885.
164. Solomon SA, Cartwright I, Pockley G, et al. A placebo-controlled, double-blind study of eicosapentaenoic acid-rich fish oil in patients with stable angina pectoris. *Curr Med Res Opin*. 1990;12:1-11.
165. Bach R, Schmidt U, Jung F, et al. Effects of fish oil capsules in two dosages on blood pressure, platelet functions, haemorheological and clinical chemistry parameters in apparently healthy subjects. *Ann Nutr Metab*. 1989;33:359-367.
166. Cartwright IJ, Pockley AG, Galloway JH, Greaves M, Preston FE. The effects of dietary omega-3 polyunsaturated fatty acids on erythrocyte membrane phospholipids, erythrocyte deformability and blood viscosity in healthy volunteers. *Atherosclerosis*. 1985;55:267-281.
167. Blonk MC, Bilo HJ, Nauta JJ, Popp-Snijders C, Mulder C, Donker AJ. Dose-response effects of fish-oil supplementation in healthy volunteers. *Am J Clin Nutr*. 1990;52:120-127.
168. Harris WS, Windsor SL, Dujovne CA. Effects of four doses of n-3 fatty acids given to hyperlipidemic patients for six months. *J Am Coll Nutr*. 1991;10:220-227.
169. Rillaerts EG, Engelmann GJ, Van Camp KM, De Leeuw I. Effect of omega-3 fatty acids in diet of type I diabetic subjects on lipid values and hemorheological parameters. *Diabetes*. 1989;38:1412-1416.
170. Nelson GJ, Schmidt PC, Corash L. The effect of a salmon diet on blood clotting, platelet aggregation and fatty acids in normal adult men. *Lipids*. 1991;26:87-96.
171. Allman-Farinelli MA, Hall D, Kingham K, Pang D, Petocz P, Favaloro EJ. Comparison of the effects of two low fat diets with different alpha-linolenic:linoleic acid ratios on coagulation and fibrinolysis. *Atherosclerosis*. 1999;142:159-168.
172. Muller AD, van Houwelingen AC, Dam-Mieras MC, Bas BM, Hornstra G. Effect of a moderate fish intake on haemostatic parameters in healthy males. *Thromb Haemost*. 1989;61:468-473.
173. Sanders TA, Oakley FR, Miller GJ, Mitropoulos KA, Crook D, Oliver MF. Influence of n-6 versus n-3 polyunsaturated fatty acids in diets low in saturated fatty acids on plasma lipoproteins and hemostatic factors. *Arterioscler Thromb Vasc Biol*. 1997;17:3449-3460.
174. Conquer JA, Cheryk LA, Chan E, Gentry PA, Holub BJ. Effect of supplementation with dietary seal oil on selected cardiovascular risk factors and hemostatic variables in healthy male subjects. *Thromb Res*. 1999;96:239-250.
175. Berrettini M, Parise P, Ricotta S, Iorio A, Peirone C, Nenci GG. Increased plasma levels of tissue factor pathway inhibitor (TFPI) after n-3 polyunsaturated fatty acids supplementation in patients with chronic atherosclerotic disease. *Thromb Haemost*. 1996;75:395-400.
176. Hansen JB, Olsen JO, Wilsgard L, Osterud B. Effects of dietary supplementation with cod liver oil on monocyte thromboplastin synthesis, coagulation and fibrinolysis. *J Intern Med Suppl*. 1989;225:133-139.
177. Marckmann P, Bladbjerg EM, Jespersen J. Dietary fish oil (4 g daily) and cardiovascular risk markers in healthy men. *Arterioscler Thromb Vasc Biol*. 1997;17:3384-3391.
178. Schmidt EB, Nielsen LK, Pedersen JO, Kornerup HJ, Dyerberg J. The effect of n-3 polyunsaturated fatty acids on lipids, platelet function, coagulation, fibrinolysis and monocyte chemotaxis in patients with hypertension. *Clin Chim Acta*. 1990;189:25-32.
179. Tremoli E, Eligini S, Colli S, et al. n-3 fatty acid ethyl ester administration to healthy subjects and to hypertriglyceridemic patients reduces tissue factor activity in adherent monocytes. *Arterioscler Thromb*. 1994;14:1600-1608.
180. Takimoto G, Galang J, Lee GK, Bradlow BA. Plasma fibrinolytic activity after ingestion of omega-3 fatty acids in human subjects. *Thromb Res*. 1989;54:573-582.
181. Marckmann P, Sandstrom B, Jespersen J. Fasting blood coagulation and fibrinolysis of young adults unchanged by reduction in dietary fat content. *Arterioscler Thromb*. 1992;12:201-205.
182. Eritsland J, Arnesen H, Seljelot I, Kierulf P. Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coagul Fibrinolysis*. 1995;6:17-22.
183. Marckmann P, Jespersen J, Leht T, Sandstrom B. Effect of fish diet versus meat diet on blood lipids, coagulation and fibrinolysis in healthy young men. *J Intern Med*. 1991;229:317-323.
184. Dunstan DW, Mori TA, Puddey IB, et al. A randomised, controlled study of the effects of aerobic exercise and dietary fish on coagulation and fibrinolytic factors in type 2 diabetics. *Thromb Haemost*. 1999;81:367-372.
185. Armstrong RA, Chardigny JM, Beaufreere B, et al. No effect of dietary trans isomers of alpha-linolenic acid on platelet aggregation and haemostatic factors in European healthy men: the TRANSLinE study. *Thromb Res*. 2000;100:133-141.
186. Almendingen K, Seljelot I, Sandstad B, Pedersen JI. Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on hemostatic variables in men. *Arterioscler Thromb Vasc Biol*. 1996;16:375-380.
187. Kristensen SD, Schmidt EB, Dyerberg J. Dietary supplementation with n-3 polyunsaturated fatty acids and human platelet function: a review with particular emphasis on implications for cardiovascular disease. *J Intern Med Suppl*. 1989;225:141-150.
188. Nelson GJ, Schmidt PS, Bartolini GL, Kelley DS, Kyle D. The effect of dietary docosahexaenoic acid on platelet function, platelet fatty acid composition, and blood coagulation in humans. *Lipids*. 1997;32:1129-1136.
189. Mezzano D, Kosiel K, Martinez C, et al. Cardiovascular risk factors in vegetarians: normalization of hyperhomocysteinemia with vitamin B(12) and reduction of platelet aggregation with n-3 fatty acids. *Thromb Res*. 2000;100:153-160.
190. Pirich C, Gaszo A, Granegger S, Sinzinger H. Effects of fish oil supplementation on platelet survival and ex vivo platelet function in hypercholesterolemic patients. *Thromb Res*. 1999;96:219-227.
191. Vericel E, Calzada C, Chapuy P, Lagarde M. The influence of low intake of n-3 fatty acids on platelets in elderly people. *Atherosclerosis*. 1999;147:187-192.
192. Mori TA, Beilin LJ, Burke V, Morris J, Ritchie J. Interactions between dietary fat, fish, and fish oils and their effects on platelet function in men at risk of cardiovascular disease. *Arterioscler Thromb Vasc Biol*. 1997;17:279-286.
193. Prisco D, Filippini M, Francalanci I, Paniccia R, Gensini GF, Serneri GG. Effect of  $\omega$ -3 fatty acid ethyl ester supplementation on fatty acid composition of the single platelet phospholipids and on platelet functions. *Metabolism*. 1995;44:562-569.
194. Tremoli E, Maderna P, Marangoni F, et al. Prolonged inhibition of platelet aggregation after n-3 fatty acid ethyl ester ingestion by healthy volunteers. *Am J Clin Nutr*. 1995;61:607-613.
195. Mutanen M, Freese R. Polyunsaturated fatty acids and platelet aggregation. *Curr Opin Lipidol*. 1996;7:14-19.
196. Owens MR, Cave WT Jr. Dietary fish lipids do not diminish platelet adhesion to subendothelium. *Br J Haematol*. 1990;75:82-85.
197. Berg KJ, Skaga E, Skjaeggstad O, Stormorken H. Effect of linseed oil on platelet adhesiveness and bleeding-time in patients with coronary heart-disease. *Lancet*. 1965;2:980-982.
198. Natvig H, Borchgrevink CF, Dedichen J, Owren PA, Schiøtz EH, Westlund K. A controlled trial of the effect of linolenic acid on incidence of coronary heart disease: the Norwegian vegetable oil experiment of 1965-66. *Scand J Clin Lab Invest Suppl*. 1968;105:1-20.
199. Christensen JH, Schmidt EB. n-3 fatty acids and the risk of sudden cardiac death. *Lipids*. 2001;36(suppl):S115-S118.
200. Siscovick DS, Raghunathan T, King I, et al. Dietary intake of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *Am J Clin Nutr*. 2000;71(1 suppl):208S-212S.
201. Connor SL, Connor WE. Are fish oils beneficial in the prevention and treatment of coronary artery disease? *Am J Clin Nutr*. 1997;66(4 suppl):1020S-1031S.
202. Beaglehole R, Jackson R. Alcohol, cardiovascular diseases and total mortality: the epidemiological evidence. *N Z Med J*. 1991;104:249-251.
203. Suh I, Shaten BJ, Cutler JA, Kuller LH, The Multiple Risk Factor Intervention Trial Research Group. Alcohol use and mortality from coronary heart disease: the role of high-density lipoprotein cholesterol. *Ann Intern Med*. 1992;116:881-887.

204. Gaziano JM, Hennekens CH, Godfried SL, et al. Type of alcoholic beverage and risk of myocardial infarction. *Am J Cardiol*. 1999;83:52-57.
205. Ridker PM, Vaughan DE, Stampfer MJ, Glynn RJ, Hennekens CH. Association of moderate alcohol consumption and plasma concentration of endogenous tissue-type plasminogen activator. *JAMA*. 1994;272:929-933.
206. Hendriks HF, van der Gaag MS. Alcohol, coagulation and fibrinolysis. *Novartis Found Symp*. 1998;216:111-120.
207. Mukamal KJ, Jadhav PP, D'Agostino RB, et al. Alcohol consumption and hemostatic factors: analysis of the Framingham Offspring cohort. *Circulation*. 2001;104:1367-1373.
208. Lee AJ, Flanagan PA, Rumley A, Fowkes FGR, Lowe GDO. Relationship between alcohol intake and tissue-plasminogen activator antigen and other hemostatic factors in the general population. *Fibrinolysis*. 1995;9:49-54.
209. Ridker PM, Hennekens CH, Stampfer MJ, Manson JE, Vaughan DE. Prospective study of endogenous tissue plasminogen activator and risk of stroke. *Lancet*. 1994;343:940-943.
210. Gorinstein S, Zemser M, Lichman I, et al. Moderate beer consumption and the blood coagulation in patients with coronary artery disease. *J Intern Med*. 1997;241:47-51.
211. Dimmitt SB, Rakic V, Puddey IB, et al. The effects of alcohol on coagulation and fibrinolytic factors: a controlled trial. *Blood Coagul Fibrinolysis*. 1998;9:39-45.
212. Pellegrini N, Pareti FI, Stabile F, Brusamolino A, Simonetti P. Effects of moderate consumption of red wine on platelet aggregation and hemostatic variables in healthy volunteers. *Eur J Clin Nutr*. 1996;50:209-213.
213. Elmer O, Goransson G, Zoucas E. Impairment of primary hemostasis and platelet function after alcohol ingestion in man. *Haemostasis*. 1984;14:223-228.
214. Pikaar NA, Wedel M, van der Beek EJ, et al. Effects of moderate alcohol consumption on platelet aggregation, fibrinolysis, and blood lipids. *Metabolism*. 1987;36:538-543.
215. El Sayed MS, Nieuwenhuizen W. The effect of alcohol ingestion on the exercise-induced changes in fibrin and fibrinogen degradation products in man. *Blood Coagul Fibrinolysis*. 2000;11:359-365.
216. van de WA, van Golde PM, Kraaijenhagen RJ, dem Borne PA, Bouma BN, Hart HC. Acute inhibitory effect of alcohol on fibrinolysis. *Eur J Clin Invest*. 2001;31:164-170.
217. Johansen KM, Skorpe S, Olsen JO, Osterud B. The effect of red wine on the fibrinolytic system and the cellular activation reactions before and after exercise. *Thromb Res*. 1999;96:355-363.
218. Hendriks HF, Veenstra J, Velthuis-te Wierik EJ, Schaafsma G, Klufft C. Effect of moderate dose of alcohol with evening meal on fibrinolytic factors. *BMJ*. 1994;308:1003-1006.
219. Numminen H, Syrjala M, Benthin G, Kaste M, Hillbom M. The effect of acute ingestion of a large dose of alcohol on the hemostatic system and its circadian variation. *Stroke*. 2000;31:1269-1273.
220. McConnell MV, Vavouranakis I, Wu LL, Vaughan DE, Ridker PM. Effects of a single, daily alcoholic beverage on lipid and hemostatic markers of cardiovascular risk. *Am J Cardiol*. 1997;80:1226-1228.
221. Veenstra J, Klufft C, Ockhuizen TH, vd Pol H, Wedel M, Schaafsma G. Effects of moderate alcohol consumption on platelet function, tissue-type plasminogen activator and plasminogen activator inhibitor. *Thromb Haemost*. 1990;63:345-348.
222. Lacoste L, Hung J, Lam JY. Acute and delayed antithrombotic effects of alcohol in humans. *Am J Cardiol*. 2001;87:82-85.
223. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ*. 1999;319:1523-1528.
224. Renaud SC, Ruf JC. Effects of alcohol on platelet functions. *Clin Chim Acta*. 1996;246:77-89.
225. Ruf JC. Wine and polyphenols related to platelet aggregation and atherothrombosis. *Drugs Exp Clin Res*. 1999;25:125-131.
226. Puddey IB, Rakic V, Dimmitt SB, Beilin LJ. Influence of pattern of drinking on cardiovascular disease and cardiovascular risk factors—a review. *Addiction*. 1999;94:649-663.
227. Marques-Vidal P, Arveiler D, Evans A, Amouyel P, Ferrieres J, Ducimetiere P. Different alcohol drinking and blood pressure relationships in France and Northern Ireland: The PRIME Study. *Hypertension*. 2001;38:1361-1366.
228. Eliasson M, Asplund K, Evrin PE, Lundblad D. Relationship of cigarette smoking and snuff dipping to plasma fibrinogen, fibrinolytic variables and serum insulin: The Northern Sweden MONICA Study. *Atherosclerosis*. 1995;113:41-53.
229. Meade TW, Imeson J, Stirling Y. Effects of changes in smoking and other characteristics on clotting factors and the risk of ischaemic heart disease. *Lancet*. 1987;2:986-988.
230. Simpson AJ, Gray RS, Moore NR, Booth NA. The effects of chronic smoking on the fibrinolytic potential of plasma and platelets. *Br J Haematol*. 1997;97:208-213.
231. Enderle MD, Pfohl M, Kellermann N, Haering HU, Hoffmeister HM. Endothelial function, variables of fibrinolysis and coagulation in smokers and healthy controls. *Haemostasis*. 2000;30:149-158.
232. Newby DE, Wright RA, Labinjoh C, et al. Endothelial dysfunction, impaired endogenous fibrinolysis, and cigarette smoking: a mechanism for arterial thrombosis and myocardial infarction. *Circulation*. 1999;99:1411-1415.
233. Newby DE, McAleod AL, Uren NG, et al. Impaired coronary tissue plasminogen activator release is associated with coronary atherosclerosis and cigarette smoking: direct link between endothelial dysfunction and atherothrombosis. *Circulation*. 2001;103:1936-1941.
234. Allen RA, Klufft C, Brommer EJ. Effect of chronic smoking on fibrinolysis. *Arteriosclerosis*. 1985;5:443-450.
235. Belch JJ, McC Ardle BM, Burns P, Lowe GD, Forbes CD. The effects of acute smoking on platelet behaviour, fibrinolysis and haemorrhage in habitual smokers. *Thromb Haemost*. 1984;51:6-8.
236. Haire WD, Goldsmith JC, Rasmussen J. Abnormal fibrinolysis in healthy male cigarette smokers: role of plasminogen activator inhibitors. *Am J Hematol*. 1989;31:36-40.
237. Brockmann MA, Beythien C, Magens MM, Wilckens V, Kuehn P, Gutensohn K. Platelet hemostasis capacity in smokers: in vitro function analyses with 3.2% citrated whole blood. *Thromb Res*. 2001;104:333-342.
238. Modesti PA, Abbate R, Gensini GF, Colella A, Neri Serneri GG. Platelet thromboxane A2 receptors in habitual smokers. *Thromb Res*. 1989;55:195-201.
239. Pernerstorfer T, Stohlawetz P, Stummvoll G, et al. Low-dose aspirin does not lower in vivo platelet activation in healthy smokers. *Br J Haematol*. 1998;102:1229-1231.
240. Blache D, Bouthillier D, Davignon J. Acute influence of smoking on platelet behaviour, endothelium and plasma lipids and normalization by aspirin. *Atherosclerosis*. 1992;93:179-188.
241. Blann AD, Kirkpatrick U, Devine C, Naser S, McCollum CN. The influence of acute smoking on leucocytes, platelets and the endothelium. *Atherosclerosis*. 1998;141:133-139.
242. Gleerup G, Winther K. Smoking further increases platelet activity in patients with mild hypertension. *Eur J Clin Invest*. 1996;26:49-52.
243. Davis JW, Shelton L, Eigenberg DA, Hignite CE, Watanabe IS. Effects of tobacco and non-tobacco cigarette smoking on endothelium and platelets. *Clin Pharmacol Ther*. 1985;37:529-533.
244. Simpson AJ, Booth NA, Moore NR, Gray RS. Does chronic smoking influence fibrinolytic potential in type 1 diabetes mellitus? *Diabet Med*. 1998;15:683-687.
245. Yarnell JW, Sweetnam PM, Rogers S, et al. Some long term effects of smoking on the hemostatic system: a report from the Caerphilly and Speedwell Collaborative Surveys. *J Clin Pathol*. 1987;40:909-913.
246. Feher MD, Rampling MW, Brown J, et al. Acute changes in atherogenic and thrombogenic factors with cessation of smoking. *J R Soc Med*. 1990;83:146-148.
247. ECAT angina pectoris study: baseline associations of hemostatic factors with extent of coronary arteriosclerosis and other coronary risk factors in 3000 patients with angina pectoris undergoing coronary angiography. *Eur Heart J*. 1993;14:8-17.
248. Smith FB, Lee AJ, Rumley A, Fowkes FG, Lowe GD. Tissue-plasminogen activator, plasminogen activator inhibitor and risk of peripheral arterial disease. *Atherosclerosis*. 1995;115:35-43.
249. Chia S, Newby DE. Atherosclerosis, cigarette smoking, and endogenous fibrinolysis: is there a direct link? *Curr Atheroscler Rep*. 2002;4:143-148.
250. Hung J, Lam JY, Lacoste L, Letchacovski G. Cigarette smoking acutely increases platelet thrombus formation in patients with coronary artery disease taking aspirin. *Circulation*. 1995;92:2432-2436.
251. Davis JW, Hartman CR, Shelton L, Ruttinger HA. A trial of dipyridamole and aspirin in the prevention of smoking-induced changes in platelets and endothelium in men with coronary artery disease. *Am J Cardiol*. 1989;63:1450-1454.
252. Blann AD, Steele C, McCollum CN. The influence of smoking on soluble adhesion molecules and endothelial cell markers. *Thromb Res*. 1997;85:433-438.
253. Bain BJ, Rothwell M, Feher MD, Robinson R, Brown J, Sever PS. Acute changes in haematological parameters on cessation of smoking. *J R Soc Med*. 1992;85:80-82.
254. Davis JW, Shelton L, Watanabe IS, Arnold J. Passive smoking affects endothelium and platelets. *Arch Intern Med*. 1989;149:386-389.
255. Williams JE, Nieto FJ, Sanford CP, Tyroler HA. Effects of an angry temperament on coronary heart disease risk: The Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 2001;154:230-235.
256. Whiteman MC, Deary IJ, Fowkes FG. Personality and social predictors of atherosclerotic pro-

- gression: Edinburgh Artery Study. *Psychosom Med.* 2000;62:703-714.
257. Everson SA, Lynch JW, Chesney MA, et al. Interaction of workplace demands and cardiovascular reactivity in progression of carotid atherosclerosis: population based study. *BMJ.* 1997;314:553-558.
  258. Everson SA, Lynch JW, Kaplan GA, Lakka TA, Sivenius J, Salonen JT. Stress-induced blood pressure reactivity and incident stroke in middle-aged men. *Stroke.* 2001;32:1263-1270.
  259. Patterson SM, Krantz DS, Gottdiener JS, Hecht G, Vargot S, Goldstein DS. Prothrombotic effects of environmental stress: changes in platelet function, hematocrit, and total plasma protein. *Psychosom Med.* 1995;57:592-599.
  260. Jern C, Eriksson E, Tengborn L, Risberg B, Wadenvik H, Jern S. Changes of plasma coagulation and fibrinolysis in response to mental stress. *Thromb Haemost.* 1989;62:767-771.
  261. Urano T, Cho M, Takahashi S, et al. Changes of parameters in fibrinolytic system caused by mental stress. *Thromb Res.* 1990;60:501-507.
  262. Raikkonen K, Lassila R, Keltikangas-Jarvinen L, Hautanen A. Association of chronic stress with plasminogen activator inhibitor-1 in healthy middle-aged men. *Arterioscler Thromb Vasc Biol.* 1996;16:363-367.
  263. Vrijkotte TG, van Doornen LJ, De Geus EJ. Work stress and metabolic and hemostatic risk factors. *Psychosom Med.* 1999;61:796-805.
  264. Wamala SP, Murray MA, Horsten M, et al. Socioeconomic status and determinants of hemostatic function in healthy women. *Arterioscler Thromb Vasc Biol.* 1999;19:485-492.
  265. Frimerman A, Miller HI, Laniado S, Keren G. Changes in hemostatic function at times of cyclic variation in occupational stress. *Am J Cardiol.* 1997;79:72-75.
  266. Ishizaki M, Tsuritani I, Noborisaka Y, Yamada Y, Tabata M, Nakagawa H. Relationship between job stress and plasma fibrinolytic activity in male Japanese workers. *Int Arch Occup Environ Health.* 1996;68:315-320.
  267. Grignani G, Pacchiarini L, Zucchella M, et al. Effect of mental stress on platelet function in normal subjects and in patients with coronary artery disease. *Haemostasis.* 1992;22:138-146.
  268. Li N, Wallen NH, Hjerdahl P. Evidence for prothrombotic effects of exercise and limited protection by aspirin. *Circulation.* 1999;100:1374-1379.
  269. Larsson PT, Wallen NH, Hjerdahl P. Norepinephrine-induced human platelet activation in vivo is only partly counteracted by aspirin. *Circulation.* 1994;89:1951-1957.
  270. Bak AA, van Vliet HH, Grobbee DE. Coffee, caffeine and hemostasis: results from two randomized studies. *Atherosclerosis.* 1990;83:249-255.
  271. Naismith DJ, Akinyanju PA, Szanto S, Yudkin J. The effect, in volunteers, of coffee and decaffeinated coffee on blood glucose, insulin, plasma lipids and some factors involved in blood clotting. *Nutr Metab.* 1970;12:144-151.
  272. Happonen P, Salonen JT, Seppanen K, Rauramaa R. Association of coffee consumption with plasma lipoprotein, fibrinogen and platelet aggregability in middle-aged men. In: Proceedings of the Meeting of the International Epidemiological Association; August 8-13, 1987; Helsinki, Finland.
  273. Samarrae WA, Truswell AS. Short-term effect of coffee on blood fibrinolytic activity in healthy adults. *Atherosclerosis.* 1977;26:255-260.
  274. Wojta J, Kirchheimer JC, Peska MG, Binder BR. Effect of caffeine ingestion on plasma fibrinolytic potential. *Thromb Haemost.* 1988;59:337-338.
  275. Ammatturo V, Perricone C, Canazio A, et al. Caffeine stimulates in vivo platelet reactivity. *Acta Med Scand.* 1988;224:245-247.
  276. Paoletti R, Corsini A, Tremoli E, Fumagalli R, Catapano AL. Effects of coffee on plasma lipids, lipoproteins and apolipoproteins. *Pharmacol Res.* 1989;21:27-38.
  277. Bydlowski SP, Yunker RL, Rymaszewski Z, Subbiah MT. Coffee extracts inhibit platelet aggregation in vivo and in vitro. *Int J Vitam Nutr Res.* 1987;57:217-223.
  278. Peters U, Poole C, Arab L. Does tea affect cardiovascular disease? a meta-analysis. *Am J Epidemiol.* 2001;154:495-503.
  279. Yoshida H, Ishikawa T, Hosoi H, et al. Inhibitory effect of tea flavonoids on the ability of cells to oxidize low density lipoprotein. *Biochem Pharmacol.* 1999;58:1695-1703.
  280. Neiva TJ, Morais L, Polack M, Simoes CM, D'Amico EA. Effects of catechins on human blood platelet aggregation and lipid peroxidation. *Phytother Res.* 1999;13:597-600.
  281. Kang WS, Lim IH, Yuk DY, et al. Antithrombotic activities of green tea catechins and (-)-epigallocatechin gallate. *Thromb Res.* 1999;96:229-237.
  282. Janssen K, Mensink RP, Cox FJ, et al. Effects of the flavonoids quercetin and apigenin on hemostasis in healthy volunteers: results from an in vitro and a dietary supplement study. *Am J Clin Nutr.* 1998;67:255-262.
  283. Vorster H, Jerling J, Oosthuizen W, et al. Tea drinking and haemostasis: a randomized, placebo-controlled, crossover study in free-living subjects. *Haemostasis.* 1996;26:58-64.
  284. de Maat MP, Pijl H, Klufft C, Princen HM. Consumption of black and green tea had no effect on inflammation, haemostasis and endothelial markers in smoking healthy individuals. *Eur J Clin Nutr.* 2000;54:757-763.
  285. Hodgson JM, Puddey IB, Mori TA, Burke V, Baker RI, Beilin LJ. Effects of regular ingestion of black tea on haemostasis and cell adhesion molecules in humans. *Eur J Clin Nutr.* 2001;55:881-886.
  286. Duffy SJ, Vita JA, Holbrook M, Swerdlow PL, Keaney JF Jr. Effect of acute and chronic tea consumption on platelet aggregation in patients with coronary artery disease. *Arterioscler Thromb Vasc Biol.* 2001;21:1084-1089.
  287. Jolliffe JA, Rees K, Taylor RS, Thompson D, O'driddle N, Ebrahim S. Exercise-based rehabilitation for coronary heart disease. *Cochrane Database Syst Rev.* 2001;1:CD001800.
  288. Lavie CJ, Milani RV. Benefits of cardiac rehabilitation and exercise training. *Chest.* 2000;117:5-7.
  289. Fernhall B, Szymanski LM, Gorman PA, Milani J, Paup DC, Kessler CM. Fibrinolytic activity is not dependent upon exercise mode in post-myocardial infarction patients. *Eur J Appl Physiol Occup Physiol.* 1998;78:247-252.
  290. Estelles A, Aznar J, Tormo G, Sapena P, Tormo V, Espana F. Influence of a rehabilitation sports programme on the fibrinolytic activity of patients after myocardial infarction. *Thromb Res.* 1989;55:203-212.
  291. Paramo JA, Olavide I, Barba J, et al. Long-term cardiac rehabilitation program favorably influences fibrinolysis and lipid concentrations in acute myocardial infarction. *Haematologica.* 1998;83:519-524.
  292. Hamouratidis ND, Pertsinidis TE, Bacharoudis GP, Papazachariou GS. Effects of exercise on plasma fibrinolytic activity in patients with ischaemic heart disease. *Int J Cardiol.* 1988;19:39-45.