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A Prospective Study of Fibrinogen and Risk of Myocardial Infarction in the Physicians' Health Study

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OBJECTIVES We examined the association of baseline plasma fibrinogen with future risk of myocardial infarction (MI) in the Physicians' Health Study.

BACKGROUND Elevated plasma fibrinogen increases and low dose aspirin decreases risk of MI. However, prospective data are limited about their interrelationships.

METHODS Blood samples were prospectively collected at baseline from 14,916 men in the Physicians' Health Study, aged 40 to 84 years, who were randomly assigned to take aspirin (325 mg every other day) or placebo for 5 years. We measured baseline plasma fibrinogen among 199 incident cases of MI and 199 age- and smoking-matched control subjects free of cardiovascular disease at the time of the case's diagnosis.

RESULTS Cases had significantly higher baseline fibrinogen levels (geometric mean: 262 mg/dl) than did control subjects (245 mg/dl, $p = 0.02$). Those with high fibrinogen levels (≥343 mg/dl, the 90th percentile distribution of the control subjects) had a twofold increase in MI risk (age- and smoking-adjusted relative risk = 2.09, 95% confidence interval = 1.15 to 3.78) compared with those with fibrinogen below 343 mg/dl. Adjustment for lipids and other coronary risk factors as well as randomized aspirin assignment did not materially change the result. Furthermore, we observed no interaction between fibrinogen level and aspirin treatment.

CONCLUSIONS Among these apparently healthy U.S. male physicians, fibrinogen is associated with increased risk of future MI independent of other coronary risk factors, atherogenic factors such as lipids and antithrombotics such as aspirin. (J Am Coll Cardiol 1999;33:1347–52) © 1999 by the American College of Cardiology

Fibrinogen, an acute phase protein and a clotting factor, appears to be an independent risk factor for cardiovascular disease (1), but the mechanism(s) are still uncertain. As a key determinant of plasma and red cell viscosity, elevated levels of fibrinogen may decrease blood flow, particularly through stenotic vessels (2). Through conversion to fibrin, fibrinogen may promote thrombus formation. Fibrinogen appears to directly enhance atherogenesis by its conversion to fibrin, which binds low density lipoprotein and stimulates proliferation of vascular smooth muscle (3–5). In addition, fibrinogen may bind to platelet membrane glycoprotein IIb/IIIa (fibrinogen receptor), which in turn is a precondition for platelet aggregation in vivo (6). Also, platelets have been proposed as a link between fibrinogen levels and the development of cardiovascular disease, both during the early stages of vascular lesion development and subsequently as platelet aggregation on occluding thrombus. The Northwick Park Heart Study found that platelet aggregatability (defined as the median effective dose for aggregation by adenosine diphosphate) significantly correlated with plasma fibrinogen in men even within its normal physiologic range (7,8).

Fibrinogen has been extensively investigated in epidemiologic studies, and some pharmacologic approaches, including aspirin, bezafibrate, pentoxyfyline and ticlopidine administration, have been suggested to counteract some of the pathologic effects of elevated fibrinogen, including increased viscosity, platelet aggregation and red blood cell rigidity (9–12). However, no randomized trial data have been available to demonstrate whether such measures have applications for primary prevention of cardiovascular disease.

The Physicians' Health Study, a randomized, double-blind, placebo-controlled trial of low dose aspirin among healthy male physicians, showed a 44% reduction in the risk

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Abbreviations and Acronyms

EDTA	= ethylenediaminetetraacetic acid
MI	= myocardial infarction
RR	= relative risk
TC/HDL	= total to high density lipoprotein cholesterol ratio
95% CI	= 95% confidence interval

of first myocardial infarction (MI) in the aspirin group (13). In the present study, using a nested case–control design, we sought to examine the association of plasma fibrinogen with future risk of MI among these apparently, healthy middle-aged U.S. male physicians. This aspirin trial also provides us a unique opportunity to examine the primary preventive effect of aspirin on the relation between fibrinogen and the incidence of MI.

METHODS

Population and specimen collection. The subjects and methods of the Physicians' Health Study are described in detail elsewhere (13). Briefly, this was a randomized, double-blind, placebo-controlled 2 × 2 factorial trial of low dose aspirin (Bufferin, Bristol-Myers Products, 325 mg every other day) and beta-carotene (Lurotin, BASF, 50 mg on alternate days) (13). A total of 22,071 U.S. male physicians, aged 40 to 84 years in 1982, were enrolled. Men were excluded if they had a prior history of myocardial infarction, stroke or transient ischemic attack, cancer (except nonmelanoma skin cancer), current renal or liver disease, peptic ulcer or gout, contraindication to aspirin or current use of aspirin, other platelet active agents or vitamin A supplements. The aspirin component of the trial was terminated on January 25, 1988, principally because of a 44% reduction in the incidence of first myocardial infarction among the aspirin group.

Between August 1982 and December 1984, during the run-in period when all men were taking aspirin, we sent kits for blood sampling to participants who were instructed to have their blood drawn into ethylenediaminetetraacetic acid (EDTA) vacutainer tubes, to centrifuge them and to return the plasma in the polypropylene cryopreservation vials by prepaid overnight courier. The kit included a cold pack to keep the specimens cool (but not frozen) until receipt at Channing Laboratory the following morning, when they were aliquoted and stored at −80°C. During storage, no specimen thawed or warmed substantially. We received specimens from 14,916 (68%) of the randomized physicians, over 70% between September and November 1982.

Ascertainment and confirmation of end points. Cases of nonfatal myocardial infarction were reported on questionnaires mailed to participants every six months. Deaths were usually reported by the families or postal authorities. Persistent nonresponders to the questionnaires were telephoned. Follow up for nonfatal events was 99.7% complete, and for fatal outcomes, 100%. Medical records were reviewed by the End Points Committee without knowledge of treatment assignment. All cases of myocardial infarction included in this analysis met the World Health Organization criteria (14), which require symptoms plus either enzyme elevations or diagnostic electrocardiographic changes. For fatal cases, we also accepted diagnoses based on autopsy, or confirmation by records that the death was due to coronary heart disease (International Classification of Diseases codes 411–414). Silent infarcts discovered on routine examination were not included, because they could not be assigned an accurate date. Sudden deaths in individuals with no history of coronary disease were not included, because coronary disease could not be confirmed as the cause of death.

Selection of control subjects. Each case was matched to one control subject free from MI at the time of the case's diagnosis. Control subjects were randomly selected from participants who met the matching criteria of age (±1 year), smoking habit (current, past or never smoker) and time from randomization in six-month intervals. Aliquots from cases and control subjects were paired, with the positions varied at random within the pairs. The pairs were handled together and identically throughout processing and analysis.

Laboratory analyses. After five years of follow up, samples from 204 men who subsequently developed myocardial infarction were analyzed for fibrinogen levels together with matched control samples. The paired, blinded plasma samples were shipped on dry ice to the Department of Laboratory Medicine, University of Washington for analyses. Fibrinogen in plasma was measured with a polymerization method as originally described by Clauss (15). Blind paired quality-control samples (n = 10 pairs) were interspersed at random among the specimens. The quality-control samples were aliquots of a large, well mixed plasma pool from healthy volunteers that were treated identically to the samples collected from the participants. The mean within-pair coefficient of variation for plasma fibrinogen levels in these paired quality-control specimens was 17%. We also measured plasma levels of total and high density lipoprotein (HDL) cholesterol (16).

We compared fibrinogen levels in split samples of plasma collected with EDTA or sodium citrate vacuum tubes among nine young volunteers. Plasma treated with EDTA had lower fibrinogen levels (mean ± SD: 219 ± 55 mg/dl) than citrated plasma (232 ± 68 mg/dl), but the levels of the two treatments were highly correlated ($r = 0.95$, $p < 0.01$).

Statistical analysis. From 204 paired cases and control subjects, we excluded five with missing data for other coronary risk factors. Because of the skewed distribution of fibrinogen levels, we used natural log transformed fibrinogen for the paired *t* test. We used conditional logistic regression methods for the main effect analyses. To estimate

Table 1. Characteristics of 199 Men With Myocardial Infarction (Case Subjects) and 199 Matched Control Subjects in the Physicians' Health Study

Risk Factor	Case Subjects	Control Subjects	p Value
Fibrinogen (mg/dl)*	262	245	0.02
Fibrinogen ≥343 mg/dl† (%)	19 (n = 37)	10 (n = 20)	0.02
Age (yr)	60.3 ± 8.5	60.3 ± 8.5	Matching factor
Quetelet index (wt[kg]ht[m]^2)	25.6 ± 3.2	24.8 ± 2.7	0.003
Total cholesterol (mg/dl)	218 ± 38	213 ± 34	0.26
HDL cholesterol (mg/dl)	44 ± 11	49 ± 12	0.0001
TC/HDL (ratio)	5.3 ± 1.5	4.6 ± 1.2	0.0001
Alcohol consumption (drinks/day)	0.48 ± 0.44	0.54 ± 0.46	0.18
Cigarette smoking (%)			
Never	37	37	Matching factor
Past	47	47	Matching factor
Current	16	16	Matching factor
History of diabetes (%)	8	4	0.08
History of angina (%)	6	2	0.03
History of hypertension (%)	32	20	0.006
Aspirin assignment (%)	32	46	0.005

*Geometric means, p value based on nature log-transformed values. †The 90th percentile of the control distribution. TC/HDL = total to high density lipoprotein cholesterol ratio.

whether there was a linear association between fibrinogen levels and risk of myocardial infarction, we defined quintile and decile cut points based on the distribution among control subjects and examined the age- and smoking-adjusted relative risk (RR) (estimated by the odds ratios) using the lowest quintile or decile as the reference group. We then defined fibrinogen levels ≥343 mg/dl (the 90th percentile among the control subjects) as abnormally high values, those below this level as normal. Unconditional logistic regression models were used for testing of interactions adjusting for the matching variables and for further simultaneous adjustment for other coronary risk factors. Interactions were assessed using the product of both exposures as continuous variables in the model. We also used dichotomized variables to assess interaction by comparing the log likelihood statistics of the main effect model with the joint effect model. To estimate the joint effect of aspirin and fibrinogen on the risk of myocardial infarction, four groups were formed based on the cross classification by the two fibrinogen levels (normal and high) and aspirin or placebo assignment. We then calculated the RR comparing each group with the reference group of men with normal fibrinogen levels and aspirin assignment. Because aspirin use modifies the association of total to HDL cholesterol (TC/HDL) ratio with MI risk (the protective effect of aspirin is more pronounced among those with a low TC/HDL ratio) (16), and to avoid three-way interaction, we estimated the joint effect of fibrinogen and TC/HDL ratio only among those who were assigned to placebo. We defined the highest tertile of TC/HDL as high ratio and the two lower tertiles of TC/HDL ratio (to avoid very small numbers in some of the subgroups) as normal and formed four groups by cross-classifying the two categories of fibrinogen and TC/HDL ratio. All p values are two tailed, and statistical significance is based on the 0.05 level. The analyses were done using SAS (17).

RESULTS

Among these apparently healthy U.S. physicians, men who subsequently developed MI had higher baseline plasma fibrinogen levels, and a larger proportion of them had fibrinogen values above the 90th percentile of the distribution among control subjects (Table 1). Age and smoking were matching variables and hence distributed identically between cases and control subjects. As expected, cases had a higher mean body mass index, lower HDL cholesterol, higher, TC/HDL ratio and greater prevalence of angina, diabetes and hypertension (Table 1). Table 2 shows the Spearman correlation coefficients between fibrinogen and these risk factors according to case or control status. Among control subjects, fibrinogen was slightly but significantly correlated with age, HDL cholesterol, TC/HDL ratio, cigarette smoking and history of hypertension (Table 2). We did not observe any significant seasonal variations of fibrinogen levels.

We assessed the association of plasma fibrinogen levels and risk of future MI based on the quintile distribution of the control group and observed a nonsignificant and nonlinear positive association. The RRs (95% confidence interval [95% CI]) for the second to the fifth quintiles compared with the lowest were: 1.08 (0.59 to 1.99), 0.95 (0.50 to 1.83), 1.27 (0.65 to 2.47) and 1.50 (0.77 to 2.90) controlling for age and smoking status. However, when fibrinogen levels were further divided into deciles, we observed a significant increased risk of MI only among those in the

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Table 2. Spearman Correlation Coefficients Between Fibrinogen Levels and Coronary Risk Factors Among 199 Men With Myocardial Infarction (Case Subjects) and 199 Matched Control Subjects in the Physicians' Health Study

Risk Factor	Case Subjects	Control Subjects	Total
Age	0.15*	0.19†	0.17†
Quetelet index	0.02	0.08	0.06
Total cholesterol	0.03	0.13	0.09
HDL cholesterol	0.003	−0.15*	−0.08
TC/HDL	0.03	0.25†	0.15†
Alcohol consumption (drinks/day) (n = 198 pairs)	−0.09	−0.02	−0.06
Cigarette smoking	0.06	0.17*	0.12*
History of diabetes	0.01	0.05	0.03
History of angina	−0.13	−0.08	−0.10
History of hypertension	0.02	0.16*	0.09
Aspirin assignment	0.12	−0.01	0.05

*$p < 0.05$. †$p < 0.01$.
TC/HDL = total to high density lipoprotein cholesterol ratio.

90th percentile (RR = 2.34, 95% CI = 1.17 to 4.67 compared with the lower 50th percentile, Fig. 1). We then combined all those up to the 90th percentile (normal level, <343 mg/dl) as the reference group, and those in the highest decile of fibrinogen as high level (≥343 mg/dl). We observed an approximate twofold increase in risk of MI among those with high fibrinogen levels compared with those with normal levels (RR = 2.09, 95% CI = 1.15 to 3.78). Adding aspirin assignment (using placebo as the reference group) into the model did not change the results for fibrinogen (RR = 2.09, 95% CI = 1.15 to 3.78); men assigned to aspirin had a 45% reduction in risk (RR = 0.55, 95% CI = 0.36 to 0.84). Further adjustment for other coronary risk factors (including the ratio of total to HDL cholesterol, alcohol consumption, body mass index, homocysteine levels and history of diabetes, hypertension and angina) had no effect on this relationship (RR = 2.02, 95% CI = 1.06 to 3.84). Stratified analyses by years of follow-up (the first two years and the third to fifth year) did not materially alter the results.

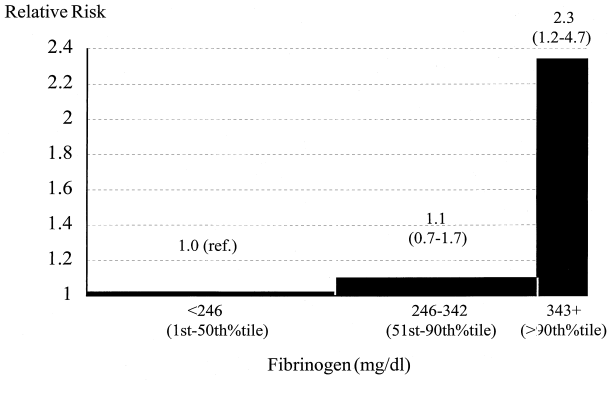

Figure 1. Age- and smoking-adjusted relative risk (95% confidence interval) of future myocardial infarction associated with baseline plasma fibrinogen levels in the Physicians' Health Study. Numbers of cases/control subjects were: 89/99 in the 1st to 50th percentile, 73/80 in the 51st to 90th percentile and 37/20 in the >90th percentile.

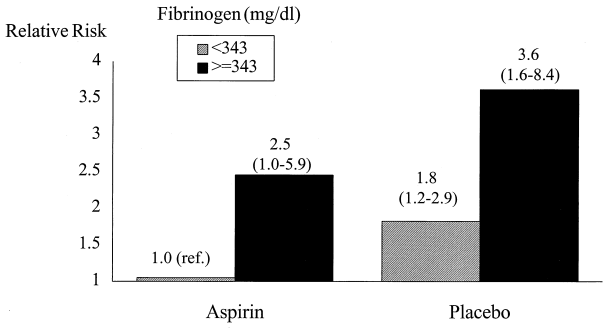

Figure 2. Age- and smoking-adjusted relative risk (95% confidence interval) of future myocardial infarction according to fibrinogen levels and aspirin assignment in the Physicians' Health Study. Numbers of cases/control subjects were: in aspirin group, 50/80 for fibrinogen <343 mg/dl, 15/10 for fibrinogen ≥343 mg/dl; in placebo group, 112/99 for fibrinogen <343 mg/dl, 22/10 for fibrinogen ≥343 mg/dl.

Because this study is nested in the randomized aspirin trial, we assessed whether the association of baseline fibrinogen level with the risk of MI was different among those assigned to aspirin or placebo. We conducted a stratified analysis according to normal and high fibrinogen level and aspirin and placebo assignment. In both treatment groups, men with high fibrinogen levels had twice the risk of those with normal levels (<343 mg/dl). Men with high fibrinogen levels and in the placebo group had 3.6-fold higher risk (RR = 3.62, 95% CI = 1.57 to 8.36) compared with those with normal fibrinogen who were on aspirin (Fig. 2). Conversely, aspirin treatment reduced MI risk from 32% among men with high fibrinogen levels to 45% among those with normal levels. There was no significant interaction between aspirin assignment and fibrinogen level ($p_{interaction} = 0.46$).

Assmann et al. (18) and Thompson et al. (19) proposed that the effect of fibrinogen varied according to the atherogenic lipid profile. We assessed the joint effect of elevated fibrinogen level and TC/HDL ratio on the risk of myocardial infarction adjusted for age and smoking status among those who were assigned to placebo (134 cases and 109 control subjects). We excluded those assigned to aspirin, because aspirin treatment interacts with the TC/HDL ratio; aspirin was less protective among those with TC/HDL ratios in the higher two quintiles (16). We reported the TC/HDL ratio results because it was a better predictor of future risk of MI than TC and HDL assessed separately (16). In contrast to the two previous studies (18,19), we found no significant interaction between fibrinogen and TC/HDL ratio using either continuous variables or dichotomized variables ($p_{interaction} = 0.48$). Compared with men

with normal fibrinogen and in the low and medium tertiles of TC/HDL (52 cases and 66 control subjects), the RRs were 2.67 (95% CI = 0.84 to 8.48) for those with high fibrinogen and in the low and medium tertiles of TC/HDL ratio (10 cases and five control subjects). Among men in the highest tertile of TC/HDL ratio, the RRs were: 2.39 (95% CI = 1.35 to 4.22) for those with normal fibrinogen (60 cases and 33 control subjects) and 3.59 (95% CI = 1.13 to 11.40) for those with high fibrinogen levels (12 cases and five control subjects). Further adjustment of other coronary risk factors did not materially change the results. This finding suggests that the effect of fibrinogen is not substantially modified by lipid levels.

DISCUSSION

Plasma fibrinogen levels predict MI risk. In these apparently healthy U.S. male physicians, those who developed myocardial infarction within five years had significantly higher baseline fibrinogen levels than their age- and smoking-matched control subjects. This association seems to be nonlinear after controlling for age and cigarette smoking. The increased risk was most evident among men with abnormally high fibrinogen level (above the 90th percentile, 343 mg/dl), who had an approximately, twofold increase in risk compared with those with plasma fibrinogen levels below 343 mg/dl. There was no evidence of interaction by aspirin use or atherogenic lipid profile.

The prospective design of the Physicians' Health Study minimized the possibility that this association can be explained as an effect of selection bias. The average fibrinogen levels were lower and the within-pair coefficient of variation of the measurement was higher (17%) in our study than those reported in other studies (20–25). It is likely that the EDTA tubes we used for collecting blood samples may cause low fibrinogen concentrations and high measurement variation. However, the Caerphilly and Speedwell Studies (20) also collected their blood samples in EDTA tubes, and the men in these studies had higher fibrinogen levels (409 mg/dl and 366 mg/dl for men with ischemic heart disease and disease-free men, respectively) than the men in our study. Another possibility is that the male physicians in our study had generally low coronary risk profiles, thus their fibrinogen levels would be lower than those of the other study populations. Lee et al. (25) found that individuals in the highest socioeconomic class tended to have lower fibrinogen levels, even after adjusting for smoking status. Nevertheless, because the samples from cases and control subjects were stored for the same duration and were handled together and identically throughout processing, it is unlikely that the methods of blood sample collection and storage or measurement would cause any biases. Any random errors in sample processing or measurement, or random within-person day-to-day variability would attenuate the differences, yielding an underestimate of the apparent effect.

Our findings from the Physicians' Health Study further support the conclusion from other prospective studies that fibrinogen is a strong and independent predictor for ischemic heart disease (1,20–27). This was true even after controlling for other conventional coronary risk factors including TC/HDL ratio and aspirin use. We observed no material change in the risk between the first two years of follow-up and the third to fifth year follow-up, which is consistent with the findings that elevated fibrinogen levels may also relate to preclinical nonsymptomatic atherosclerosis (5). Although we observed a weaker and nonlinear association compared with most of the reported studies, some showed a threshold effect of fibrinogen similar to that which we observed (20,23). Another likely explanation may stem from our presentation of age- and smoking-adjusted RR, which would be lower than the univariate results reported in most studies. Smoking represents the strongest known environmental influence on fibrinogen levels (1), and a dose-dependent increase in fibrinogen with smoking has been confirmed (28). Part of the effect of cigarette smoking on risk of ischemic heart disease is probably mediated through its effect of raising fibrinogen (9,20). One study showed that adjusting for smoking and preexistent ischemic heart disease decreased the RR by 40% compared with an analysis adjusted for age alone (20).

No effect modification by aspirin or lipids. The randomized, double-blind, placebo-controlled design of the study provides unique evidence on the primary preventive efficacy of aspirin on the risk of future MI by level of plasma fibrinogen. Although small numbers in some of the subgroup analyses limit the power to detect statistically, significant interactions, we observed no apparent interaction between plasma fibrinogen levels and aspirin treatment. Elevated fibrinogen levels were associated with about 2–2.5-fold increased risk of MI regardless of aspirin treatment, and aspirin treatment was associated with 32% to 45% reduction in risk across all fibrinogen levels. We previously reported that, among these healthy U.S. physicians, the TC/HDL was a powerful predictor of myocardial infarction and that the protective effect of aspirin was significantly more pronounced among those with a lower TC/HDL ratio (16). In the present study, among men assigned to placebo, we observed no interaction between fibrinogen and TC/HDL ratio; both elevated fibrinogen levels and high TC/HDL ratio were independently associated with increased risk. In contrast, the PROCAM study, a prospective study of healthy men with an eight-year follow up, found that elevated fibrinogen levels were associated with risk only among men whose LDL cholesterol was in the higher two tertiles, but not in the lowest (18). The ECAT study found that elevated fibrinogen levels were associated with increased risk of MI even at the lowest tertile of total cholesterol among angina patients (19). However, unlike our study, the ECAT study found that increased total cholesterol levels were not associated with increased risk among those with low fibrinogen levels (19). Taken to-

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gether, the totality of evidence suggests these are independent noninteractive risk factors.

Summary. In summary, our prospective data from apparently healthy U.S. physicians are consistent with previous findings that plasma fibrinogen is associated with risk of coronary heart disease, independent of other risk factors including total to HDL cholesterol ratio and aspirin treatment. Our results suggest that aspirin can reduce the risk of MI by 32% to 45% through the whole range of fibrinogen levels.

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