Cardiovascular Surgery

Association between Plasma Fibrinogen Level and Saphenous Vein Graft Patency

Sinan Cersit,[1] Serkan Cay,[1] Yavuzer Koza,[2] Sadik Kadri Acikgoz,[1] Gizem Cabuk,[1] Bihter Senturk[1] and Pinar Dogan[1]

Background: Fibrinogen is related to the pathogenesis of atherosclerosis. The inflammatory process in atherosclerosis may cause an increase in plasma fibrinogen level. Therefore, in this study we proposed to investigate whether plasma fibrinogen is associated with the patency of saphenous vein graft in patients at least 1 year after coronary artery bypass graft (CABG) surgery.

Methods: Patients who had undergone CABG surgery at least 1 year previously with at least one saphenous vein graft were included in the study. Patients were directed to cardiac catheterization for stable anginal symptoms or positive stress test results. Before coronary angiography, all patients underwent routine blood tests including assessment of plasma fibrinogen levels.

Results: Saphenous vein grafts were found to be patent in 199 patients and occluded in 132 patients. Plasma fibrinogen levels were significantly different between the two groups (2.85 ± 0.49 g/L vs. 3.62 ± 0.82 g/L, $p < 0.001$, respectively). Although the time duration after CABG operation differs significantly between the two groups ($p = 0.004$), multiple logistic regression analysis showed that plasma fibrinogen levels were found to be significantly associated with the patency of vein graft (odds ratio = 0.27, 95% confidence internal: 0.16-0.48, $p < 0.001$).

Conclusions: Our results demonstrated that plasma fibrinogen levels were higher in patients with an occluded saphenous vein graft. To conclusively prove the relationship between plasma fibrinogen values and saphenous vein graft patency, additional investigation would be necessary.

Key Words: Atherosclerosis • Coronary artery bypass graft • Fibrinogen • Saphenous vein

INTRODUCTION

Coronary artery bypass graft (CABG) surgery is effective for treatment of coronary artery disease (CAD). The autologous saphenous vein is widely used as a conduit to bypass significant lesions. However, the long term patency rates of saphenous veins are low due to atherosclerosis. Inflammation plays an important role during all stages of atherosclerosis, from its initiation to progression.[1,2]

Saphenous vein graft (SVG) disease is composed of three discrete processes; thrombosis (first month after CABG), intimal hyperplasia (between 1 month and 1 year), and atherosclerosis (> 1 year after CABG).[3,4]

The relationship between the body's coagulation system and atherosclerosis has long been recognized. Plasma fibrinogen is an acute phase reactant with known inflammatory markers, but it also affects platelet aggregation and blood viscosity.[5] Several trials have demonstrated that high plasma fibrinogen concentration is associated with CAD.[6-9]

Therefore, increased plasma fibrinogen level may be related to SVG patency after CABG. In this study we aimed to investigate whether there was a relationship between SVG disease and plasma fibrinogen level in

METHODS

The study population was composed of 331 patients (198 male, 133 female, mean age 63.5 ± 10.0 years) who underwent coronary angiography more than 1 year after CABG surgery with at least one saphenous vein graft. All patients had stable anginal symptoms and/or positive stress test results. Exclusion criteria were determined to be acute coronary syndrome, decompensated heart failure, idiopathic dilated or hypertrophic cardiomyopathy, active chronic infection, connective tissue disease, congenital heart disease, renal or hepatic dysfunction (creatinine > 2.0 mg/dl, liver transaminases (AST, ALT) > 3 times upper limit of normal, respectively), recent history of blood transfusion, and malignant neoplasm. Complete medical history including coronary heart disease risk factors was obtained from each patient. Laboratory parameters were specified with standard methods. Blood samples were obtained following an overnight fasting period before coronary angiography. No smoking, exercising and drug use were permitted and at least 30 minutes of resting was achieved before venous puncture. Blood samples taken once from each patient for measurement of plasma fibrinogen were analyzed by CA-7000 coagulation device (Sysmex, Kobe, Japan) using thromborel S reagent kit. Normal plasma fibrinogen levels range from 1.5 to 4.0 g/L. Left ventricular ejection fraction was calculated by modified Simpson's method on transthoracic echocardiography.

Coronary angiographies were performed via femoral artery using the standard Judkins technique after all patients gave informed consent. Saphenous vein grafts were displayed with appropriate catheters in at least two different projections. Aortagraphy was performed in case the SVG could not be visualized. Angiographic data were interpreted by at least two experienced cardiologists who were unaware of the patients' clinical information. Occluded grafts were defined as a luminal stenosis ≥ 70% or absence of distal TIMI 3 flow.

Statistical analysis

Data analyses were performed using SPSS 17.0 statistical software. Continuous variables were tested with the Kolmogorov-Smirnov method. Parametric variables were expressed as the mean ± standard deviation and categorical variables as percentage (%). Student's t-test and Mann-Whitney U test assessed continuous variables with and without normal distribution, respectively, while the categorical variables were evaluated by $\chi 2$ test. Analysis of variance was used to determine the relationship between the number of occluded SVG and the plasma fibrinogen level. Receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cut-off value of plasma fibrinogen level (at which sensitivity and specificity would be maximal) for the prediction of saphenous vein graft disease. The odds ratios and 95% confidence intervals were estimated with a logistic regression model to evaluate the independent predictors of occluded SVGs. A p value < 0.05 was considered as statistically significant.

RESULTS

Saphenous vein grafts were found to be patent in 199 patients (60.2%) and occluded in 132 patients (39.8%). Table 1 shows baseline characteristics of patients with occluded and patent grafts. There were no significant differences between the two groups with respect to age, sex, prevalence of hypertension and diabetes mellitus, and left ventricular ejection fraction. The mean time between CABG and coronary angiography was longer in the occluded group. Serum levels of total cholesterol, triglyceride, low-density lipoprotein cholesterol, hemoglobin, hematocrit, and red blood cell distribution width (RDW) were similar between the two groups. However, serum high-density lipoprotein cholesterol, sedimentation rate, mean platelet volume (MPV) values, and serum uric acid levels were significantly different between the patent and occluded graft groups. Although salicylate use was similar between the two groups, lipid-lowering drug use was significantly higher in patients without stenosis.

Plasma fibrinogen levels were significantly higher in patients with SVG stenosis than in patients without stenosis (3.62 ± 0.82 g/L vs. 2.85 ± 0.49 g/L, p < 0.001, respectively) (Figure 1).

There was a significant elevation in fibrinogen levels

Table 1. Baseline characteristics of patients with patent and occluded saphenous vein graft

	Patent group (n = 199)	Occluded group (n = 132)	p value
Age (years)	62 ± 10	63 ± 10	0.379
Male sex (n/%)	124/62	74/56	0.256
Hypertension (n/%)	122/61	78/59	0.686
Diabetes mellitus (n/%)	79/40	50/38	0.740
Smoking (n/%)	40/20	39/30	0.048
Time after CABG surgery (years)	5.8 ± 3.7	7.6 ± 4.9	0.004
Time stratification (years)			0.002
1-5 years (n/%)	106/53	53/40	
> 5-10 years (n/%)	71/36	44/33	
> 10-15 years (n/%)	17/9	24/18	
> 15-20 years (n/%)	5/3	11/8	
Ejection fraction (%)	56 ± 4	56 ± 4	0.485
Number of SVGs	1.7 ± 0.7	1.5 ± 0.6	0.055
LAD (n/%)	6/3	4/3	
Cx (n/%)	42/21	31/24	
RCA (n/%)	45/23	53/40	
Cx + RCA (n/%)	39/20	27/21	
LAD + RCA (n/%)	3/2	1/1	
LAD + Cx (n/%)	2/1	0/0	
LAD + Cx + RCA (n/%)	3/2	0/0	
Diagonal + Cx (n/%)	14/7	4/3	
LAD + Diagonal + Cx (n/%)	1/1	0/0	
Diagonal + RCA (n/%)	11/6	2/2	
Diagonal (n/%)	24/12	7/5	
LAD + Diagonal + RCA (n/%)	1/1	0/0	
Diagonal + Cx + RCA (n/%)	8/4	3/2	
Number of occluded SVGs	0	1.3 ± 0.6	< 0.001
Hemoglobin (g/dL)	14.5 ± 1.1	14.5 ± 1.1	0.718
MCV (fL)	89 ± 4	88 ± 5	0.296
Hematocrit (%)	43 ± 3	43 ± 4	0.388
RBC (× 1.000.000/uL)	4.9 ± 0.4	4.9 ± 0.4	0.912
MCH (pg)	30 ± 2	30 ± 2	0.910
MCHC (g/dL)	33 ± 1	33 ± 1	0.543
RDW (%)	13.9 ± 0.9	14.0 ± 0.9	0.258
Platelet (× 1.000/uL)	243 ± 59	244 ± 56	0.649
MPV (fL)	7.9 ± 0.9	9.0 ± 0.8	< 0.001
Sedimentation rate (mm/hour)	11 ± 6	14 ± 8	< 0.001
Total cholesterol (mg/dL)	181 ± 43	184 ± 46	0.501
HDL cholesterol (mg/dL)	42 ± 11	39 ± 9	0.011
LDL cholesterol (mg/dL)	107 ± 38	113 ± 39	0.222
Triglyceride (mg/dL)	153 ± 71	168 ± 94	0.565
Urea (mg/dL)	38 ± 17	36 ± 9	0.188
Creatinine (mg/dL)	0.94 ± 0.19	0.95 ± 0.18	0.650
Uric acid (mg/dL)	5.4 ± 1.2	5.9 ± 1.3	0.001
Aspirin use	158 (79%)	94 (71%)	0.087
Statin use	155 (78%)	54 (41%)	< 0.001

CABG, coronary artery bypass graft; Cx, left circumflex artery; HDL, high-density lipoprotein; LAD, left anterior descending artery; LDL, low-density lipoprotein; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; RBC, red blood cell; RCA, right coronary artery; SVG, saphenous vein graft.

with an increasing number of occluded SVGs, such that 1-vessel (n = 94), 2-vessel (n = 31) and 3-vessel (n = 7) occlusions had mean fibrinogen levels of 3.54 ± 0.78 g/L, 3.76 ± 0.93 g/L and 4.11 ± 0.59 g/L, respectively (p < 0.001).

Table 2 presents the adjusted odds ratios for risk of development of saphenous vein graft disease in univariate regression analysis. Other than smoking, mean time after CABG surgery, MPV level, sedimentation rate, HDL cholesterol level, uric acid, statin use, and fibrinogen level were predictors of saphenous vein graft disease. In multivariate regression analysis, the time interval of saphenous vein graft, MPV level, high density lipoprotein (HDL) cholesterol level, and plasma fibrinogen level were found to be independently associated with the patency of saphenous vein graft (Table 3).

In addition, a plasma fibrinogen value > 3.45 g/L was determined to predict saphenous graft vein disease with a sensitivity of 57% and a specificity of 91% [AUC (area under the curve) = 0.784] (Figure 2).
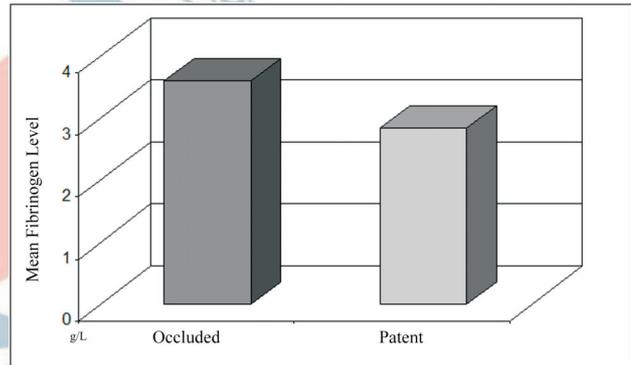

Figure 1. *Comparison of mean fibrinogen levels in both patient groups.*

Table 2. Univariate logistic regression analysis for predictors of saphenous vein graft disease

	Odds ratio	95% confidence interval	p value
Smoking	0.60	0.36-1.00	0.05
Time after CABG surgery	0.91	0.86-0.96	< 0.001
MPV	0.20	0.14-0.29	< 0.001
Sedimentation rate	0.94	0.91-0.97	0.001
HDL cholesterol	1.03	1.01-1.06	0.003
Uric acid	0.73	0.60-0.87	0.001
Statin use	5.09	3.14-8.24	< 0.001
Fibrinogen	0.17	0.11-0.26	< 0.001

CABG, coronary artery bypass graft; HDL, high-density lipoprotein; MPV, mean platelet volume.

Table 3. Multivariate regression analysis showing independent predictors of saphenous vein graft occlusion

	Odds ratio	95% confidence interval	p value
Time after CABG surgery	0.93	0.87-0.99	0.04
MPV	0.26	0.17-0.39	< 0.001
HDL cholesterol	1.04	1.01-1.08	0.012
Fibrinogen	0.27	0.16-0.48	< 0.001

CABG, coronary artery bypass graft; HDL, high-density lipoprotein; MPV, mean platelet volume.

DISCUSSION

CABG is of great importance with respect to treatment of CAD despite the fact that saphenous vein graft patency has poor prognosis in the long term.[1-4] There are many risk factors for SVG disease including smoking, longer intervals after CABG, hyperlipidemia, and diabetes which may cause thrombosis, intimal hyperplasia and then atherosclerosis.[10,11] One major problem of graft failure can be atherosclerosis after one year from the index operation.[7,12] In our study, patients with occluded SVG have significantly higher fibrinogen levels than patients with patent SVG.

Diabetes, hyperlipidemia and atherosclerosis were strongly associated with graft failure in patients who underwent coronary angiography after CABG operation. We found that patients with occluded saphenous vein graft had significantly lower HDL-cholesterol levels. Total cholesterol, low density lipoprotein (LDL) cholesterol and triglyceride levels were not significantly different, and age, gender, diabetes, and hypertension were similar between the two groups.

The study in which 192 patients with CABG were included reported that elevated serum uric acid levels have been associated with saphenous vein graft disease.[13] In another study, increased levels of MPV were correlated with damage to the saphenous graft.[14] In our study, the group with an occluded saphenous vein graft had significantly higher MPV. In addition, in the regression analysis, it was found to be a risk factor to predict saphenous vein graft occlusion. Serum uric acid levels were significantly higher in the group with an occluded saphenous vein graft.

In a study investigating reasons of early saphenous vein graft failure, patients with multiple saphenous vein
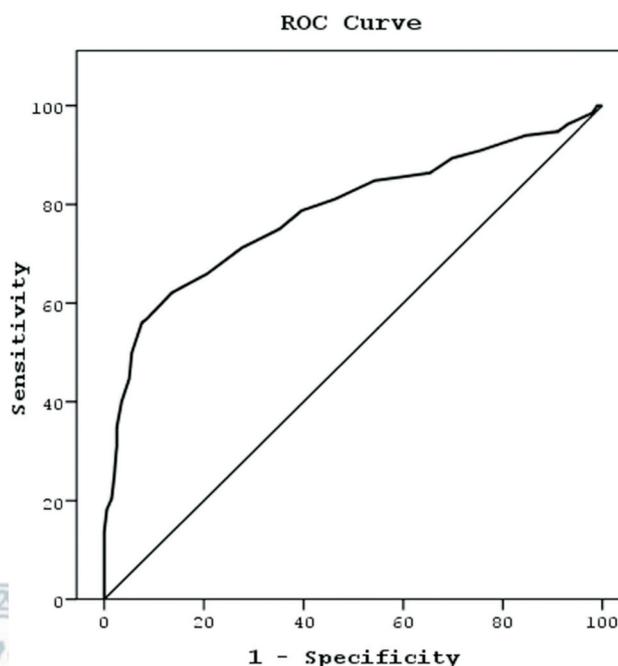

Figure 2. *ROC (receiver operator characteristic) curve for fibrinogen level to predict saphenous vein graft patency.*

grafts needed additional revascularization procedures during subsequent years.[15] We observed that the number of saphenous vein grafts were significantly higher in the patent group.

Due to the fact that control of traditional risk factors including hypertension, diabetes, smoking, and hyperlipidemia do not prevent coronary artery disease, this has led to a search for new risk factors. One of these new risk factors, fibrinogen, is a marker of inflammation.[16-20] Observational and epidemiological studies including National Cholesterol Education Program (NCEP) and Adult Treatment Panel III Guidelines Manual (ATP III) have drawn attention to the role of fibrinogen that may potentially predict total cardiovascular risk in addition to classical risk factors.[21,22] Fibrinogen levels increased the risk of coronary artery disease by 1.8-fold. Additionally, smoking cessation, exercise, weight loss, and fibrates reduce the level of fibrinogen. Fibrinogen is an important part of the coagulation pathway and plasma viscosity, as well as the basic substance as an acute-phase reactant. High plasma fibrinogen concentration in studies has consistently been found to be associated with an increased risk of cardiovascular events.[6] Fibrinogen levels were associated with several traditional risk factors.[23,24] In multivariate analysis, when

these factors are included all together, it continued to be statistically significant in spite of the weakening of the relationship between fibrinogen and cardiovascular disease.[25] In the largest meta-analysis, plasma fibrinogen concentration in healthy middle-aged subjects has been found to be a strong risk factor for coronary artery disease, stroke and other vascular mortality. 1 g/L higher fibrinogen level was correlated to increased risk of coronary disease with a 2.42 ratio.[26]

In our study, higher levels of fibrinogen were found in occluded SVG patients, although the mean values were within the normal range. Clinical conditions affecting and causing very abnormal fibrinogen levels were excluded from the study. Although epidemiological studies have demonstrated that elevated fibrinogen levels are an independent risk factor for atherosclerosis, the strength of the causal association needs to be addressed. One explanation can be genetic variation in the gene encoding fibrinogen, such that subjects with genetic polymorphism have been shown to be associated with elevated levels of fibrinogen compared to control subjects.[27]

To the best of our knowledge, this was the first study to demonstrate a relationship between SVG disease and plasma fibrinogen level in patients with CABG surgery examined > 1 year after the index operation.

There are some limitations to be considered when evaluating the results of the study. First, laboratory data including particularly plasma fibrinogen levels before the CABG were not available. Therefore, it was not possible to make comparisons of baseline and follow-up values. Second, we only examined the patients with stable angina or positive stress test result > 1 year after CABG surgery. Time factor is crucial for saphenous vein graft failure. Third, although the coronary angiogram is the gold standard used to document the extent of graft stenosis/occlusion, it is difficult to delineate the nature of the lesion − which can be demonstrated by cardiac computer tomography angiography as intimal hyperplasia and atherosclerosis. However, no computer tomography data were present in our study. Fourth, unfortunately, no high-sensitivity C-reactive protein data was available to make any comparison between groups and association with fibrinogen levels. Finally, our study is retrospective in nature. Therefore, prospective randomized studies with larger sample sizes are

needed to consider fibrinogen as a risk marker for graft patency.

In our study, only the relationship between plasma fibrinogen level and saphenous vein graft patency has been shown. It is difficult to prove whether or not increased plasma fibrinogen levels cause saphenous vein graft occlusion, or vice versa.

CONCLUSIONS

This study demonstrated for the first time that saphenous vein graft occlusion in patients undergoing CABG surgery was significantly associated with plasma fibrinogen level. Plasma fibrinogen in these patients may be an independent risk factor in predicting late saphenous vein graft disease. Further studies with larger sample size are required to evaluate plasma fibrinogen and bypass grafts.

REFERENCES

1. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2011;58:e123-210.
2. Motwani JG, Topol EJ. Aortocoronary saphenous vein graft disease: pathogenesis, predisposition, and prevention. *Circulation* 1998;97:916-31.
3. Halabi AR, Alexander JH, Shaw LK, et al. Relation of early saphenous vein graft failure to outcomes following coronary artery bypass surgery. *Am J Cardiol* 2005;96:1254-9.
4. Davies MG, Hagen PO. Reprinted article "Pathophysiology of vein graft failure: a review". *Eur J Vasc Endovasc Surg* 2011;42:S19-29.
5. Hamsten A. The hemostatic system and coronary heart disease. *Thromb Res* 1993;70:1-38.
6. Cook NS, Ubben D. Fibrinogen as a major risk factor in cardiovascular disease. *Trends Pharmacol Sci* 1990;11:444-51.
7. Libby P, Ridker PM, Hansson GK, Leducq Transatlantic Network on Atherothrombosis. Inflammation in atherosclerosis: from pathophysiology to practice. *J Am Coll Cardiol* 2009;54:2129-38.
8. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2010;122:e584-636.

9. Hansson GK, Nilsson J. Pathogenesis of Atherosclerosis. In: Crawford MH, DiMarco JP, Paulus WJ, eds. Cardiology. 3rd Ed. Philadelphia: Mosby Elsevier; 2010, pp. 3-15.

10. Knatterud GL, Rosenberg Y, Campeau L, et al. Long-term effects on clinical outcomes of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation in the post coronary artery bypass graft trial. Post CABG Investigators. *Circulation* 2000;102:157-65.

11. Kulik A, Ruel M. Statins and coronary artery bypass graft surgery: preoperative and postoperative efficacy and safety. *Expert Opin Drug Saf* 2009;8:559-71.

12. van Brussel BL, Plokker HW, Voors AA, et al. Progression of atherosclerosis after venous coronary artery bypass graft surgery: a 15-year follow-up study. *Cathet Cardiovasc Diagn* 1997; 41:141-50.

13. Tavil Y, Sen N, Hizal F, et al. Relationship between elevated levels of serum uric acid and saphenous vein graft disease. *Turk Kardiyol Dern Ars* 2008;36:14-8.

14. Tavil Y, Sen N, Yazici HU, et al. Relationship between elevated platelet volume and saphenous vein graft disease. *Clin Invest Med* 2010:E161-7.

15. FitzGibbon GM, Leach AJ, Keon WJ, et al. Coronary bypass graft fate. Angiographic study of 1,179 vein grafts early, one year, and five years after operation. *J Thorac Cardiovasc Surg* 1986;91: 773-8.

16. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med* 2007; 356:2388-98.

17. Wijeysundera HC, Machado M, Farahati F, et al. Association of temporal trends in risk factors and treatment uptake with coronary heart disease mortality, 1994-2005. *JAMA* 2010;303:1841-7.

18. Toth PP. An urgent matter-identifying your patients' cardiovascular risk and improving their outcomes. Atherosclerosis: the underlying disease. *J Fam Pract* 2009;58:S19-25.

19. Lukkarinen H, Hentinen M. Treatments of coronary artery disease improve quality of life in the long term. *Nurs Res* 2006; 55:26-33.

20. Nascetti S, Elosua R, Pena A, et al. Variables associated with fibrinogen in a population-based study: interaction between smoking and age on fibrinogen concentration. *Eur J Epidemiol* 2001;17:953-8.

21. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227-39.

22. National Cholesterol Education Program Expert Panel on Detection Evaluation, Treatment of High Blood Cholesterol in Adutls. 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) final report. *Circulation* 2002;106:3143-421.

23. Berger JS, Jordan CO, Lloyd-Jones D, Blumenthal RS. Screening for cardiovascular risk in asymptomatic patients. *Am Coll Cardiol* 2010;55:1169-77.

24. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Lowe G, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010;375:132-40.

25. Fibrinogen Studies Collaboration, Kaptoge S, White IR, Thompson SG, et al. Associations of plasma fibrinogen levels with established cardiovascular disease risk factors, inflammatory markers, and other characteristics: individual participant meta-analysis of 154,211 adults in 31 prospective studies: the fibrinogen studies collaboration. *Am J Epidemiol* 2007;166:867-79.

26. Nascetti S, Elosua R, Pena A, et al. Variables associated with fibrinogen in a population-based study: interaction between smoking and age on fibrinogen concentration. *Eur J Epidemiol* 2001;17:953-8.

27. van der Bom JG, de Maat MP, Bots ML, et al. Elevated plasma fibrinogen: cause or consequence of cardiovascular disease? *Arterioscler Thromb Vasc Biol* 1998;18:621-5.