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Does sticky blood predict a sticky end? Associations of blood viscosity, haematocrit and fibrinogen with mortality in the West of Scotland

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Summary. There is increasing evidence that blood viscosity and its major determinants (haematocrit, plasma viscosity and fibrinogen) are associated with an increased risk of incident cardiovascular events; however, their associations with mortality are not established. We therefore studied the associations of these variables with cardiovascular events and total mortality in 1238 men and women aged 25–64 years, followed for 13 years in the first North Glasgow MONICA (MONItoring CArdiovascular disease) survey and West of Scotland centres in the Scottish Heart Health Study. After adjustment for age and sex, increasing whole blood viscosity, plasma viscosity, haematocrit and fibrinogen (analysed by both von Clauss and heat precipitation assays) were significantly associated with mortality. Only the association for fibrinogen (von Clauss assay) remained significant after adjustment for major cardiovascular risk factors. We conclude that clottable fibrinogen may be independently associated with mortality. However, the significance of this association, and the extent to which viscosity is associated with mortality, remain to be established in larger studies and meta-analyses.

Keywords: viscosity, haematocrit, fibrinogen, mortality, heart disease.

Whole-blood viscosity (a global measure of the intrinsic flow resistance of blood in macrovessels) was shown to be a potentially independent predictor of cardiovascular events in a prospective study of a random population sample (Lowe *et al*, 1997) and in a primary prevention trial of a statin for coronary heart disease (Lowe *et al*, 2000), but not in another prospective study of hospital-referred patients with intermittent claudication (Smith *et al*, 1998). Recent meta-analyses of prospective studies of the major haematological determinants of whole-blood viscosity [haematocrit, plasma viscosity, red cell aggregation as measured by the erythrocyte sedimentation rate (ESR), and plasma fibrinogen] found that each was an independent predictor of cardiovascular events, after adjustment for major cardiovascular risk factors (Danesh *et al*, 2000a,b). While increased blood viscosity might play a causal role in cardiovascular disease (CVD), such as by promoting atherosclerosis (Lee *et al*, 1998), thrombosis or ischaemia (Lowe, 1994), this remains to be established by randomized trials of blood viscosity reduction (Lowe, 1998; Danesh *et al*, 2000a).

There is some evidence that increased viscosity may be associated with symptomatic leg ischaemia (claudication), independently of the extent of underlying atherosclerosis (Lowe *et al*, 1993; Lee *et al*, 1996), and that reducing fibrinogen and viscosity improves claudication (Meade *et al*, 2002). It is therefore possible that increased viscosity may cause patients with stenotic arterial disease to present earlier; however, such persons may not necessarily suffer severe consequences of CVD, such as an increased mortality. Only two recent studies have reported on the association of viscosity with total mortality. Koenig *et al* (2000) reported a significant, independent association of plasma viscosity (whole blood viscosity was not measured) with mortality in the prospective Augsburg MONICA cohort. Lowe *et al* (2000) reported a significant association of calculated whole-blood viscosity with mortality in the West of Scotland Coronary Prevention Study; however, only fibrinogen remained associated with mortality after adjustment for baseline CVD and classic cardiovascular risk factors.

We therefore report the association of blood viscosity and its major determinants (haematocrit, viscosity and

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fibrinogen) with total mortality at 13 years follow-up of the first North Glasgow MONICA (MONItoring CArdiovascular disease) study and West of Scotland centres in the Scottish Heart Health Study (Lowe *et al*, 1988). We also prospectively studied the relative associations of two types of fibrinogen assay: the routine Clauss assay based on the clotting rate of fibrinogen (von Clauss, 1957) and a heat precipitation assay (Millar *et al*, 1971). Fibrinogen that can be precipitated by heat has been reported to show a stronger association with incident coronary heart disease than the von Clauss assay in the Caerphilly study (Sweetnam *et al*, 1998).

SUBJECTS AND METHODS

Subjects were selected from two, overlapping, studies: the first Glasgow MONICA survey (MONICA-1) and the west Scotland portion of the Scottish Heart Health Study (SHHS). Both studies used the same questionnaire and clinical investigations, and each involved selection of an age-/sex-stratified general population sample from General Practitioners' lists (Smith *et al*, 1987). MONICA-1 was a sample of 1262 residents of Glasgow living north of the River Clyde aged 20–64 years, surveyed in 1986. SHHS was a sample of 10 369 individuals aged 40–59 years, surveyed between 1984 and 1986, with four of the 22 districts included being considered for this study (Lowe *et al*, 1988). In total, 1254 subjects were selected, of whom 859 were part of SHHS only, 195 were part of MONICA-1 only and 200 were included in both studies.

Participants received questionnaires by post: completed questionnaires were brought to a clinic session, run by trained nurses, for checking. The questionnaire included standard questions about socio-demographic status, medical history and smoking. Rose chest pain questions (Rose *et al*, 1977) were also included. Among other investigations at the clinic, blood pressure measurements were taken, carbon monoxide in expired air was recorded (as an objective measure of smoking), and a 12-lead electrocardiogram (ECG) and blood sample was extracted. From the blood sample, lipid measurements were assayed in serum, as previously described (Smith *et al*, 1987). Venous blood was anticoagulated with dry dipotassium EDTA (final concentration 1·5 mg/ml blood) and kept at 4°C prior to measurement. Whole blood and plasma viscosity were measured at 37°C in a Coulter-Harkness capillary viscometer (Lowe *et al*, 1988). Haematocrit was measured using a Hawksley microhaematocrit centrifuge and reader. Fibrinogen was measured in the microhaematocrit tube using a heat precipitation method (Millar *et al*, 1971). Fibrinogen was also measured as clottable fibrinogen by the von Clauss assay, in a Coag-A-Mate (Organon Teknika) automated coagulometer, in citrated plasma (Woodward *et al*, 1998).

Follow-up. This article presents results of the mortality follow-up of all study participants up to June 2001. Deaths were primarily identified through copies of death certificates, forwarded by the Scottish National Health Service Register. Ancillary information was obtained from enquiries to Scottish health boards and the Information

Table I. Mean values (standard errors) of haematological variables according to sex, smoking status, CVD status at baseline and whether or not death occurred during follow-up.

	Whole blood viscosity (mPa.s)*	Haematocrit (%)	Plasma viscosity (mPa.s)	Fibrinogen-von Clauss (g/l)*	Fibrinogen-Heat (g/l)*
Sex					
Male ($n = 658$)	3·49 (0·019)	45·7 (0·14)	1·33 (0·0035)	2·10 (0·029)	3·89 (0·035)
Female ($n = 596$)	3·14 (0·018)	42·2 (0·15)	1·32 (0·0037)	2·30 (0·034)	3·89 (0·036)
P-value	≤ 0·0001	≤ 0·0001	0·12	≤ 0·0001	0·95
Smoking					
Current ($n = 453$)	3·42 (0·023)	44·9 (0·17)	1·33 (0·0042)	2·37 (0·039)	4·05 (0·043)
Ex ($n = 352$)	3·26 (0·025)	43·5 (0·19)	1·32 (0·0049)	2·17 (0·041)	3·91 (0·048)
Never ($n = 439$)	3·25 (0·022)	43·3 (0·17)	1·32 (0·0043)	2·05 (0·035)	3·71 (0·040)
P-value	≤ 0·0001	0·001	0·46	≤ 0·0001	≤ 0·0001
Baseline CVD					
Yes ($n = 235$)	3·37 (0·032)	44·1 (0·24)	1·35 (0·0059)	2·27 (0·053)	3·96 (0·060)
No ($n = 1019$)	3·30 (0·015)	43·9 (0·11)	1·32 (0·0028)	2·18 (0·024)	3·87 (0·028)
P-value	0·03	0·34	≤ 0·0001	0·14	0·19
Death					
Yes ($n = 184$)	3·44 (0·038)	44·5 (0·28)	1·34 (0·0068)	2·39 (0·066)	4·07 (0·072)
No ($n = 1070$)	3·29 (0·014)	43·8 (0·11)	1·32 (0·0028)	2·17 (0·024)	3·86 (0·027)
P-value	0·0003	0·02	0·03	0·001	0·007

*Analysed via log transformation. Point estimates are after back transformation; standard errors are estimated from confidence intervals after back transformation.

All values adjusted for age and sex.

and Services Division of the Scottish Common Services Agency (Tunstall-Pedoe *et al*, 1997). Death was recorded as due to a cardiovascular cause if the underlying cause was coded between 393 and 451 for International Classification of Disease (ICD) −9 or between I00 and I99 for ICD-10.

Statistical methods. Mean values for each haematological variable at baseline were compared between the sexes, cigarette smoking groups (current/ex/never), those with and without cardiovascular disease at baseline, and those who did and did not die during follow-up using general linear models, adjusting for age and sex. Baseline CVD was judged positive if the subject had a previous doctor diagnosis of angina, myocardial infarction (MI) or stroke; or if they exhibited either angina or MI according to their ECG or their answers to the Rose questions (Woodward *et al*, 1998). Whole blood viscosity and both fibrinogen variables were log transformed to improve approximations to normal distributions. To facilitate interpretation, point estimates of transformed means were back-transformed (by exponentiation) before presentation. Similarly, standard errors on the original scale were estimated as half the width of the 95% confidence interval after back-transformation, divided by 1·96. Haematological variables were related to continuous major cardiovascular risk factors, and each other, using Spearman rank correlation coefficients, again adjusting for age and sex. A P-value of $\leq 0{\cdot}05$ was considered significant.

Cox proportional hazard regression models were used to estimate hazard ratios for all-cause mortality associated with each haematological variable. Values of haematological variables were grouped into three equal parts, taking the lowest third (those below the lowest tertile for their particular sex) as the reference group. Analyses were adjusted for age and sex, and additionally for major cardiovascular risk factors: baseline CVD, smoking status, carbon monoxide in expired air, systolic and diastolic blood pressure, triglycerides, and total and high density lipoprotein (HDL) cholesterol.

RESULTS

Of the 1254 people studied, 48% were women and the mean age was 48·2 years (standard deviation 8·30 years). During a total of 17 549 person-years of follow-up (for live subjects, a mean follow-up of 14·8 years), 184 (15%) died, of whom 70 died of cardiovascular causes. Two were lost to follow-up.

Whole blood viscosity and haematocrit were significantly ($P < 0{\cdot}05$) higher in men and von Clauss fibrinogen (but not heat-precipitated fibrinogen) was significantly higher in women (Table I). Means of all five haematological variables (blood and plasma viscosity, haematocrit, von Clauss fibrinogen and heat-precipitated fibrinogen) were highest among current smokers and those with prevalent CVD at baseline, although not always significantly so. All five were significantly higher among those who subsequently died during follow-up than among those who survived or were lost to follow-up.

Table II. Age/sex-adjusted Spearman rank correlations (number, P-value).

	Whole blood viscosity (mPa.s)	Haematocrit (%)	Plasma viscosity (mPa.s)	Fibrinogen-von Clauss (g/l)	Fibrinogen-Heat (g/l)
Age*	0·15 (1134, ≤ 0·0001)	0·05 (1238, 0·06)	0·21 (1222, ≤ 0·0001)	0·22 (1221, ≤ 0·0001)	0·18 (1204, ≤ 0·0001)
Systolic blood pressure	0·20 (1132, ≤ 0·0001)	0·17 (1236, ≤ 0·0001)	0·19 (1220, ≤ 0·0001)	−0·004 (1219, 0·90)	0·01 (1202, 0·62)
Diastolic blood pressure	0·25 (1132, ≤ 0·0001)	0·22 (1236, ≤ 0·0001)	0·23 (1220, ≤ 0·0001)	0·0005 (1219, 0·99)	0·02 (1202, 0·46)
Triglycerides	0·27 (1122, ≤ 0·0001)	0·15 (1226, ≤ 0·0001)	0·25 (1211, ≤ 0·0001)	0·17 (1209, ≤ 0·0001)	0·09 (1193, 0·002)
Total cholesterol	0·32 (1123, ≤ 0·0001)	0·25 (1227, ≤ 0·0001)	0·31 (1212, ≤ 0·0001)	0·14 (1210, ≤ 0·0001)	0·15 (1194, ≤ 0·0001)
HDL cholesterol	−0·05 (1098, 0·10)	0·04 (1199, 0·13)	−0·05 (1183, 0·07)	−0·11 (1183, ≤ 0·0001)	−0·08 (1165, 0·004)
Carbon monoxide	0·19 (1129, ≤ 0·0001)	0·22 (1233, ≤ 0·0001)	0·02 (1217, 0·49)	0·13 (1217, ≤ 0·0001)	0·18 (1199, ≤ 0·0001)
Whole blood viscosity		0·67 (1120, ≤ 0·0001)	0·50 (1110, ≤ 0·0001)	0·27 (1124, ≤ 0·0001)	0·29 (1089, ≤ 0·0001)
Haematocrit			0·30 (1206, ≤ 0·0001)	0·11 (1205, ≤ 0·0001)	0·25 (1198, ≤ 0·0001)
Plasma viscosity				0·29 (1190, ≤ 0·0001)	0·29 (1174, ≤ 0·0001)
Fibrinogen-von Clauss					0·34 (1171, ≤ 0·0001)

*Adjusted for sex only.

Table III. Number (%) of deaths and hazard ratios (95% confidence intervals) for all-cause mortality by thirds of haematological variables.

Third (male/female upper boundaries)	Deaths (%)	Hazard ratios	
		Age/sex adjusted	Multiple adjusted*
Whole blood viscosity (mPa.s)			
1 (3·288/2·956)	40 (24%)	1	1
2 (3·660/3·264)	43 (26%)	0·96 (0·62–1·48)	0·90 (0·58–1·42)
3	81 (49%)	1·55 (1·06–2·27)	1·29 (0·84–1·96)
Haematocrit (%)			
1 (43/40)	39 (22%)	1	1
2 (46/43)	61 (34%)	1·18 (0·79–1·76)	1·10 (0·73–1·67)
3	79 (44%)	1·48 (1·01–2·17)	1·23 (0·81–1·87)
Plasma viscosity (mPa.s)			
1 (1·280/1·278)	50 (27%)	1	1
2 (1·358/1·346)	45 (25%)	0·72 (0·48–1·08)	0·66 (0·43–1·01)
3	87 (48%)	1·23 (0·86–1·76)	1·07 (0·73–1·59)
Fibrinogen-von Clauss (g/l)			
1 (1·88/2·05)	38 (21%)	1	1
2 (2·38/2·63)	53 (30%)	1·31 (0·86–1·98)	1·23 (0·80–1·90)
3	88 (49%)	1·78 (1·21–2·61)	1·49 (1·01–2·21)
Fibrinogen-Heat (g/l)			
1 (3·55/3·54)	47 (27%)	1	1
2 (4·30/4·28)	45 (26%)	0·86 (0·57–1·29)	0·74 (0·48–1·13)
3	84 (48%)	1·45 (1·01–2·07)	1·10 (0·75–1·62)

*Adjusted for baseline CVD, smoking (current/ex/never), systolic and diastolic blood pressure, triglycerides, HDL and total cholesterol, and carbon monoxide in expired air.

Whole blood viscosity, haematocrit and plasma viscosity were highly, significantly ($P < 0·0001$) and positively correlated with systolic and diastolic blood pressure, triglycerides and serum total cholesterol (Table II). Blood and plasma viscosity but not haematocrit, were positively related to age. Blood viscosity and haematocrit, but not plasma viscosity, were positively related to carbon monoxide (tobacco inhalation). None of these three haematological variables were correlated with HDL cholesterol. Both fibrinogen variables were strongly, positively correlated with age, triglycerides, total cholesterol and carbon monoxide, but slightly less strongly, negatively correlated to HDL cholesterol and were not linearly related to blood pressure. All five haematological variables were strongly correlated with each other.

Table III shows hazard ratios for all-cause mortality by tertiles of haematological variables. Whole-blood viscosity, haematocrit and both assays of fibrinogen (but not plasma viscosity) were significantly associated with mortality, after adjustment for age and sex. After further adjustment for baseline CVD, smoking, blood pressure, lipids and carbon monoxide, all hazard ratios were reduced to non-significance, with the exception of fibrinogen by the von Clauss assay [hazard ratio 1·49 (95% CI 1·01–2·21) for upper tertile versus lower tertile]. Removing baseline CVD from the adjustment set made virtually no difference to the results.

DISCUSSION

This prospective study observed that blood viscosity and two of its major determinants (haematocrit and fibrinogen) were significantly associated with mortality after a follow-up of 13 years, when adjusted only for age and sex. In contrast to two other prospective studies (Koenig *et al*, 2000; Lowe *et al*, 2000), plasma viscosity was not associated with incident mortality. Following adjustment for evidence of baseline CVD, and for classic cardiovascular risk factors (which were associated with baseline levels of blood viscosity determinants: Lowe *et al*, 1988), only fibrinogen (measured as clottable fibrinogen by the von Clauss assay) was significantly associated with mortality. These results are in accordance with the results of the West of Scotland Coronary Prevention Study in men (Lowe *et al*, 2000).

Three prospective studies (the present; and Koenig *et al*, 2000, and Lowe *et al*, 2000) have now shown that measures (or determinants) of blood viscosity are associated with incident mortality. However, the results of the present study, and of another prospective study in West of Scotland men (Lowe *et al*, 2000), show that a major part of this association is due to the mutual associations of blood viscosity and its determinants, baseline evidence of CVD, cardiovascular risk factors and risk of death. In the West of Scotland, CVD is the leading cause of death, and its risk

factors, such as smoking, are thus the major risk factors for all-cause mortality. Therefore, the causal role of increased blood viscosity in increasing the risk of premature mortality remains to be established, for example by large, randomized trials of viscosity reduction. A recent large randomized controlled trial of simvastatin in patients with coronary disease, other occlusive arterial disease or diabetes has shown a significant reduction in total mortality, as well as in cardiovascular events (Heart Protection Study Collaborative Group, 2002). Reduced blood and plasma viscosity by statins (which lower plasma lipoproteins) is one possible mechanism for this effect (Lowe *et al*, 2000).

Clottable fibrinogen, measured using the von Clauss assay, was independently associated with total mortality in the present study. This finding is consistent with the independent association of clottable fibrinogen with total mortality at the 8-year follow-up of the whole Scottish Heart Study cohort (Woodward *et al*, 1998). In the present study, fibrinogen assayed by a heat-precipitation assay showed a weaker association with mortality. In contrast, fibrinogen that could be precipitated by heat was significantly associated with mortality in the West of Scotland Coronary Prevention Study (Lowe *et al*, 2000), and showed a stronger association than the von Clauss assay with incident coronary events in the Caerphilly Study (Sweetnam *et al*, 1998). The relative strength of different fibrinogen assays in the prediction of cardiovascular events and mortality requires further assessment in large, prospective, comparative studies.

What are the clinical implications of the association of fibrinogen levels with mortality? First, this should be confirmed and quantified in a meta-analysis of all prospective studies, such as through the ongoing Fibrinogen Studies Collaboration (Lowe *et al*, 2002). Second, its causal significance should be evaluated in randomized controlled trials of agents which chronically and selectively lower fibrinogen levels by 10–20%; however, no such agent is available at present. Third, lifestyle measures which lower fibrinogen, such as regular exercise (Wannamethee *et al*, 2002) and reduction in smoking habit (Lowe, 2001) should be encouraged, and indeed recommended, as public health policy. Fourth, persons with high fibrinogen should be considered for more intensive treatment for other cardiovascular risk factors, particularly lowering of blood pressure and cholesterol which have recently been shown to be beneficially lowered among a wide range of patients at a high risk of CVD (Perindopril Protection Against Recurrent Stroke Study (PROGRESS) Progress Collaborative Group, 2001; Heart Protection Study Collaborative Group, 2002).

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