Plasma concentration of von Willebrand factor predicts mortality in patients on chronic renal replacement therapy

Nathalie C. Pékériaux¹, Rob Fijnheer², Eugenie F. Gemen¹, Arjan D. Barendrecht², Friedo W. Dekker³, Raymond T. Krediet⁴, Jaap Beutler⁵, Elisabeth W. Boeschoten⁶ and Mark Roest²

¹Department of Clinical Chemistry and Haematology, Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands, ²Department of Clinical Chemistry and Haematology, University Medical Center, Utrecht, The Netherlands, ³Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands, ⁴Department of Nephrology, Academic Medical Center, Amsterdam, The Netherlands, ⁵Department of Nephrology, Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands and ⁶Hans Mak Institute, Naarden, The Netherlands

Correspondence and offprint requests to: Nathalie C. Pékériaux; E-mail: n.pequeriaux@jbz.nl

Abstract

Background. Traditional cardiovascular risk factors do not explain the high incidence of cardiovascular mortality and morbidity in patients with end-stage renal disease. A prothrombotic state could accelerate the process of vascular disease in these patients.

Methods. In this study, four platelet activation markers (NAP-2, P-selectin, GP1b and RANTES) and two endothelial cell activation markers (von Willebrand factor and its propeptide) were measured in 671 haemodialysis patients and 275 patients on continuous ambulatory peritoneal dialysis (PD). All were long-term dialysis patients. The risk of all-cause and cardiovascular mortality was assessed in relation to these markers after a mean follow-up time of 2.5 years.

Results. The von Willebrand factor showed a positive correlation with total mortality in the haemodialysis patients. In an unadjusted model, the hazard rate (HR) of total mortality was 2.4 [95% confidence interval (95% CI) 1.7–3.4] in the upper quartile of von Willebrand factor compared with the lowest quartile. It remained statistically significant (HR 1.8; 95% CI 1.2–2.6) after adjustment for traditional risk factors. In contrast, no significant correlation was found between von Willebrand factor levels and total mortality in PD patients. Finally, no relationship between platelet activation markers and total mortality was found in either the haemodialysis or the PD patients.

Conclusion. It can be concluded that chronic endothelial cell activation, but not platelet activation, is related to all-cause mortality in end-stage renal disease patients on long-term dialysis.

Keywords: endothelial cell activation; haemodialysis; mortality; platelet activation; von Willebrand

Introduction

Endothelial cells form a natural barrier between circulating blood and the surrounding tissue. In addition to this barrier function, endothelial cells produce several anti-thrombotic factors that prevent haemostasis in the circulation. Damaged endothelial cells lose their anti-thrombotic capacity, which can cause an increase in the risk of cardiovascular disease or other disease complications [1].

Like endothelial cells, platelets are crucial for the maintenance of an adequate haemostatic balance. Hyperreactive platelets play a detrimental role in ischaemic vascular disease [2], while hyporeactive platelets may result in bleeding complications. Large clinical trials studying the effects of platelet inhibitors on cardiovascular disease mortality have shown that inhibition of primary haemostasis reduces the incidence of cardiovascular disease in both high-risk patients and the general population [3].

Clinical studies on the relationship between platelet and endothelial cell activation and cardiovascular disease outcome require specific biomarkers for endothelial cells and platelets. One of the major constituents of Weibel–Palade bodies (storage granules in endothelial cells) is the von Willebrand factor, a large multimeric protein that is required for the capture of platelets in fast-flowing blood. Since large quantities of von Willebrand factor protein and its propeptide are released from the Weibel–Palade bodies of activated endothelial cells [4], both can be used as biomarkers for endothelial cell activation. By measuring the concentrations of the von Willebrand factor and its propeptide, one can estimate acute or chronic endothelial cell activation: the molar excretion of the von Willebrand factor is equal to the molar excretion of its propeptide, while the half-life of the factor in the blood is several fold longer than that of the propeptide [4, 5]. Both elevated levels reflect acute vascular perturbation, while only elevated von Willebrand factor levels indicate chronic endothelial cell activation. Biomarkers
of platelet activation include CXC7 (NAP-2 precursors) and RANTES, which are released from platelet α-granules upon activation. Other biomarkers of platelet activation are soluble P-selectin [6] and soluble GP1b, which are released from the surface of activated platelets by means of proteolytic shedding.

Little is known about the involvement of either endothelial cell activation or platelet activation in relation to mortality in patients with end-stage renal disease. Compared with the general population, patients with end-stage renal disease have accelerated cardiovascular disease development and a pathophysiology that differs in a number of areas [7]. Traditional risk factors of cardiovascular disease, such as male gender, older age, hypertension, smoking, diabetes, obesity and hypercholesterolaemia, however, do not explain the high incidence of cardiovascular mortality and morbidity seen in these patients [8]. Therefore, in the present study, we investigated the relationship between biomarkers of platelet and endothelial cell activation and cardiovascular and all-cause mortality in a cohort study of end-stage renal disease patients who were treated for >12 months with either haemodialysis or continuous ambulatory peritoneal dialysis (PD). As far as the authors know, there are no data from other large cohort studies to establish a relationship between the involvement of either platelet activation markers or endothelial cell activation markers and cardiovascular and all-cause mortality in end-stage renal disease patients.

Materials and methods

Patients

The Netherlands Cooperative Study on the Adequacy of Dialysis is a large, prospective multicentre cohort study in which patients with end-stage renal disease are followed from the initiation of dialysis therapy until transplantation or death. All patients with end-stage renal disease in >40 Dutch dialysis centres were included in the study. Patients had to be at least ≥18 years of age with dialysis as their first renal replacement therapy, and they had to give informed consent before inclusion. The Medical Ethics Committees of all participating dialysis centres approved the study. Patients who were on either haemodialysis or PD, who had been stable on dialysis for 12 months and who had started long-term dialysis treatment between January 1997 and October 2005 were included in the study. All dialysis centres follow the guidelines of the Dutch federation of Nephrology based on the European best practice guidelines (EBPG) on dialysis strategies and the EBPG for PD.

Data collection procedures

Blood and data on demography, primary kidney disease and comorbidity were collected at the time of entry to the study. The dose of dialysis measured, as total Kt/V urea per week, was reported.

Causes of death were recorded over the entire follow-up period and classified according to the coding system of the European Renal Association and European Dialysis and Transplant Association. The following codes were classified as cardiovascular mortality: 0 (cause of death uncertain/not determined); 11 (myocardial ischaemia and infarction); 14 (other causes of cardiac failure); 15 (cardiac arrest and cause unknown); 18 (fluid overload); 22 (cerebrovascular accident); 26 (haemorrhage from ruptured vascular aneurysm) and 29 (mesenteric infarction). All other codes were regarded as deaths of non-cardiovascular origin, of which Codes 31–39 were classified as deaths due to infection.

Blood samples were taken from haemodialysis patients just before the start of the haemodialysis session.

Enzyme-linked immunosorbent assay procedure

Antibodies raised against human NAP-2 (MAB393, BAF393), human soluble P-selectin (DY137, antibody combination) and RANTES (MAB278, AB-278-NA) were all purchased from R&D Systems Europe (Abingdon, UK). A monoclonal antibody against soluble GP1b (6.30) was raised in our own laboratory, while a biotin-labelled secondary anti-GP1b antibody (M1852) was purchased from Sanquin (Amsterdam, the Netherlands). Antibodies raised against von Willebrand factor (A0082 and P0226) were purchased from Dako (Glostrup, Denmark), and von Willebrand propeptide antigen levels were determined using in-house polyclonal rabbit antibodies raised against purified recombinant propeptide [9]. Bovine serum albumin (BSA; A7906) was purchased from Sigma–Aldrich (Zwijndrecht, The Netherlands) and Ampex Red reagent (A36006) from Invitrogen (Breda, The Netherlands).

 Plasma levels of NAP-2, P-selectin, GP1b, RANTES, the von Willebrand factor and the von Willebrand factor propeptide were successfully determined in 671 haemodialysis patients and 271 PD patients, using a semi-automated enzyme-linked immunosorbent assay (ELISA) on a Tecan Freedom EVO robot (Tecan, Mannedorf, Switzerland). Each antigen was measured on a separate Nunc maxisorp ELISA plate (Thermo Fisher Scientific, Roskilde, Denmark). Each plate contained a control sample consisting of a plasma pool of 40 healthy donors to determine the values of each sample in the normal population. Capture antibodies [MAB393 (1 µg/mL), DY137 part 841 154 (1 µg/mL), 0.63 (0.9 µg/mL), MAB278 (0.5 µg/mL), A0082 (0.78 µg/mL)], anti-von Willbrand factor and anti-von Willebrand factor propeptide ELISA were coated on different plates over-night at 4°C. Unbound antibodies were washed away in five steps with phosphate-buffered saline (PBS)0.5% Tween-20. After washing, the plate was blocked with 1% BSA for 2 h at room temperature. Plasma samples were diluted in PBS/1% BSA 1/1000, 1/10, 1/25, 1/50, 1/625 and 1/30 for the NAP-2, P-selectin, GP1b, RANTES, von Willebrand factor and von Willebrand factor propeptide measurements, respectively. Then, after five washes, the plasma samples and calibration curves were added to the plate containing the corresponding capture antibody and incubated for 2 h at room temperature. For the calibration curves of the von Willebrand factor and its propeptide ELISA, we used a dilution range of pooled plasma from healthy donors (N = 40) with known concentrations. For the calibration curves of the NAP-2, RANTES, P-selectin and GP1b ELISAs, we used a dilution range of a standard serum sample with known concentrations. All ELISAs contained two calibration curves (duplex). Dilutions were made in 1% BSA/PBS. Unbound antigens were again removed with five washes using PBS/0.5% Tween. Detection antibodies [BAF393 (50 ng/mL), DY137 (0.01 µg/mL), M1852 (0.25 µg/mL), P0226 (0.28 µg/mL) and peroxidase-labelled anti-propeptide antibodies] were added to the corresponding plates and incubated for 2 h at room temperature. For the detection of NAP-2, P-selectin and GP1b, an additional five-step wash using PBS/0.5% Tween-20 and a 2-h incubation with streptavidin/horseradish peroxidase at room temperature were performed to link peroxidase-conjugated streptavidin to the biotin-labelled antibody. This step was not required for the von Willebrand factor and its propeptide since these were already conjugated with peroxidase. After the five-step wash, Ampex Red reagent was added and, after 1 and 3 h of incubation, fluorescence intensity was measured with a fluorimeter (excitation: 490 nm and emission: 520 nm) (Fluostar Galaxy, Offenburg, Germany).

Statistical analysis

In this paper, continuous data are summarized as means and SD and as medians and interquartile ranges, while categorical data are presented as counts and percentages.

Patients were divided into separate quartiles according to the concentration of each biomarker of endothelial cell and platelet activation and according to the ratio von Willebrand factor/von Willebrand factor. Kaplan–Meier analysis was used to analyse crude mortality according to the quartiles of the endothelial cell and platelet activation markers. A patient’s survival time was censored at the time of transplantation, at withdrawal from the study or at the end of the study period.

Multivariate Cox proportional hazards models were used to study the different biomarker concentrations as independent predictors of mortality. The crude model contained quartiles of the specific biomarkers. Model 1 was unadjusted; Model 2 was adjusted for age and sex; Model 3 was adjusted for age, sex, body mass index, diabetes, smoking at baseline, aspirin use, systolic blood pressure and total cholesterol and Model 4 was adjusted for age, sex, body mass index, diabetes, smoking at baseline, aspirin use, systolic blood pressure, total cholesterol and history of cardiovascular disease. In addition, haemodialysis and PD patients were studied separately to distinguish between the hazard rates (HRs) of the observed associations in the two groups.
Standard descriptive statistics were used to examine differences between haemodialysis and PD patients. Student’s t-tests were applied to analyse the differences in continuous variables, while χ²-tests were used to compare the distributions of dichotomous or categorical data. Regression analysis was used to adjust for confounders. For all analyses, P < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software, version 11.0 (SPSS Inc., Chicago, IL).

**Results**

**Patients**

General characteristics of patients on PD and haemodialysis are presented in Table 1. The median age of patients receiving PD treatment was 12 years younger than that of haemodialysis patients. There were no significant differences in gender distribution, body mass index, systolic blood pressure, smoking at baseline, haemoglobin, haematocrit and use of anti-hypertensive and lipid-lowering therapy between PD and haemodialysis patients. Compared with patients on haemodialysis, those on PD less frequently had a history of cardiovascular disease (P < 0.05), used less aspirin (P < 0.05), used less erythropoietin (P < 0.01) and had higher cholesterol levels (P < 0.05). The frequency of glomerulonephritis was higher in PD patients than in haemodialysis patients (P < 0.01), while the frequency of renal vascular disease was higher (P < 0.01) in haemodialysis patients than in PD patients.

**Platelet and endothelial cell activation markers**

The concentrations of platelet activation markers (NAP-2, P-selectin, GP1b and RANTES) and endothelial cell activation markers (von Willebrand factor and von Willebrand factor propeptide) in the plasma of 271 PD patients and of 671 haemodialysis patients are presented in Table 2. The median value of the plasma pool of 40 healthy donors for NAP-2, P-selectin, GP1b, RANTES, von Willebrand factor and for von Willebrand factor propeptide was 14.88 ng/mL, 0.055 μg/mL, 2.51 μg/mL, 4.49 ng/mL, 12.02 μg/mL, 6.77 nM, respectively. There was no difference in the concentrations of platelet activation markers between PD patients and haemodialysis patients.

All values of platelet activation markers, von Willebrand factor and von Willebrand factor propeptide were elevated in PD patients and in patients on haemodialysis compared with plasma of 40 healthy donors.

The concentrations of von Willebrand factor and those of its propeptide were higher in PD patients than in the predialysis plasma samples of haemodialysis patients (P < 0.01).

**Von Willebrand factor and total mortality**

After a mean follow-up of 2.5 years, 289 of 671 patients on haemodialysis and 72 of 275 patients on PD had died. When the two groups were combined, patients in the highest quartile of von Willebrand factor had a 2.0-fold higher mortality risk than patients in the lowest quartile, while no difference was found with regard to platelet activation markers or the von Willebrand factor propeptide. Also, patients in the highest quartile of the ratio von Willebrand propeptide/von Willebrand factor had a lower mortality risk (HR 0.6; [95% confidence interval (95% CI) 0.5–0.8]).

In the haemodialysis population, there was a dose–effect relationship between increased von Willebrand factor concentrations and increased total mortality (Table 3); the lowest quartile of von Willebrand factor concentration in the plasma was used as reference. The HR of total mortality associated with von Willebrand factor in the upper quartile was 2.4 (95% CI 1.7–3.4). After adjustment for age and sex, the HR was 1.7 (95% CI 1.2–2.5); after adjustment for body mass index, diabetes, smoking at baseline, aspirin use, systolic blood pressure and total cholesterol, the HR was 1.6 (95% CI 1.1–2.3) and after further adjustment for body mass index, diabetes, smoking at baseline, aspirin use, systolic blood pressure, total cholesterol and history of cardiovascular disease, the HR was 1.8 (95% CI 1.2–2.6). Although the HRs were affected by adjustment, they remained statistically significant (P < 0.01).

**Table 1.** Characteristics of 271 patients on PD and 671 patients on haemodialysis who participated to the Netherlands Cooperative Study on the Adequacy of Dialysis multicentre cohort study

<table>
<thead>
<tr>
<th>Determinant</th>
<th>PD (n = 275)</th>
<th>Haemodialysis (n = 671)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>53.1 (20.3)</td>
<td>65.1 (19.1)</td>
</tr>
<tr>
<td>Male, %</td>
<td>65.8</td>
<td>58.3</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.3 (1.7)</td>
<td>4.6* (1.5)</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>12.4</td>
<td>13.1</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.8 (2.5)</td>
<td>24.4 (4.9)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>150 (30)</td>
<td>150 (30)</td>
</tr>
<tr>
<td>Smoking at baseline, %</td>
<td>25</td>
<td>20.3</td>
</tr>
<tr>
<td>Primary kidney disease, %</td>
<td>21.8</td>
<td>10.7**</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>12.7</td>
<td>10.9</td>
</tr>
<tr>
<td>Cystic kidney disease</td>
<td>10.9</td>
<td>12.5</td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>12.0</td>
<td>20.4**</td>
</tr>
<tr>
<td>Other multisystem disease</td>
<td>12.0</td>
<td>16.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Others</td>
<td>22.2</td>
<td>23.2</td>
</tr>
<tr>
<td>Aspirin use, %</td>
<td>14.9</td>
<td>28.5*</td>
</tr>
<tr>
<td>Erythropoietin use, %</td>
<td>73.7</td>
<td>91.6**</td>
</tr>
<tr>
<td>Lipid-lowering therapy, %</td>
<td>36.1</td>
<td>29.0</td>
</tr>
<tr>
<td>Anti-hypertensive therapy, %</td>
<td>79.2</td>
<td>77.4</td>
</tr>
<tr>
<td>Total Kt/V urea</td>
<td>2.19 (0.71)</td>
<td>3.69** (0.98)</td>
</tr>
<tr>
<td>History of CVD, %</td>
<td>19.6</td>
<td>37.7*</td>
</tr>
<tr>
<td>Haemoglobin, mmol/L</td>
<td>7.4 (1.0)</td>
<td>7.1 (1.1)</td>
</tr>
<tr>
<td>Haematocrit, L/L</td>
<td>0.35 (0.04)</td>
<td>0.35 (0.07)</td>
</tr>
</tbody>
</table>

*Data are means (SD), medians (interquartile range) or percentages. CVD, cardiovascular disease.  
*P < 0.05.  
**P < 0.01.

**Table 2.** Platelet and endothelial cell activation markers by PD and haemodialysis treatment in patients who participated to the Netherlands Cooperative Study on the Adequacy of Dialysis multicentre cohort study

<table>
<thead>
<tr>
<th>Determinant</th>
<th>PD (n = 275) Median (IQ range)</th>
<th>Haemodialysis (n = 671) Median (IQ range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAP-2, ng/mL</td>
<td>20.82 (41.26)</td>
<td>18.9 (31.01)</td>
</tr>
<tr>
<td>P-selectin, μg/mL</td>
<td>0.17 (0.09)</td>
<td>0.17 (0.11)</td>
</tr>
<tr>
<td>GP1b, μg/mL</td>
<td>4.18 (2.05)</td>
<td>4.20 (2.11)</td>
</tr>
<tr>
<td>RANTES, ng/mL</td>
<td>9.99 (8.44)</td>
<td>9.93 (9.24)</td>
</tr>
<tr>
<td>vWF, μg/mL</td>
<td>22.54 (15.58)</td>
<td>17.99* (10.63)</td>
</tr>
<tr>
<td>vWF propeptide, nM</td>
<td>12.44 (7.03)</td>
<td>10.07* (6.13)</td>
</tr>
</tbody>
</table>

*vWF, von Willebrand; IQ, interquartile.

*P < 0.01; vWF 10 μg/mL = 100 IU/mL.
The same analysis was performed with data from PD patients (Table 3). The HR of total mortality associated with von Willebrand factor in the upper quartile was 1.6 (95% CI 0.9–3.0). This relationship declined to a non-significant HR of 1.0 (95% CI 0.5–2.2) after adjustment for age, sex, body mass index, diabetes, smoking at baseline, aspirin use, systolic blood pressure, total cholesterol and history of cardiovascular disease. As indicated by the wide CIs, the number of PD patients was too low for reliable comparisons.

Kaplan–Meier survival curves for total mortality in haemodialysis patients are presented by quartiles of von Willebrand factor concentrations in Figure 1. The median follow-up time was 2.5 years.

Von Willebrand factor and cardiovascular mortality

Both groups were analysed for the relationship between increased von Willebrand factor concentrations and increased cardiovascular mortality. The HR of cardiovascular mortality for the highest von Willebrand factor quartile compared to the lowest was 1.8 (95% CI 1.0–3.2). This relationship declined to a non-significant HR of 1.2 (95% CI 0.7–2.2) after adjustment for age, sex, body mass index, diabetes, smoking at baseline, aspirin use, systolic blood pressure, total cholesterol and history of cardiovascular disease. As indicated by the wide CIs, the number of PD patients was too low for reliable comparisons.

Discussion

This multicentre cohort study of 671 haemodialysis and 275 PD patients investigated the relationship between mortality and the von Willebrand factor and its propeptide as markers for endothelial cell activation and between mortality and CXC17 (NAP2 precursors), RANTES, soluble P-selectin and soluble GP1b as biomarkers of platelet activation. This is the first prospective investigation to show that levels of von Willebrand factor predict future mortality in end-stage renal disease patients on haemodialysis and probably also in patients receiving PD.

![Fig. 1. Kaplan–Meier survival curves for total mortality by quartiles of plasma concentrations of von Willebrand factor. Blue line Quartile 1; green line Quartile 2; beige line Quartile 3 and pink line Quartile 4.](image)
Earlier studies have shown that increased levels of von Willebrand factor predict cardiovascular disease in other high-risk populations, e.g. in patients with a history of ischaemic heart disease [10], in those with peripheral and cerebral vascular disease [11], in non-diabetic and diabetic subjects [12] and in patients with atrial fibrillation [13, 14]. However, it is not clear whether an increased von Willebrand factor level was functionally involved in increased mortality risk or if it was just a marker of endothelial cell activation. As far as the authors know, no studies have been conducted on other markers of endothelial cell activation in relation to the prediction of mortality in end-stage renal disease patients.

The present study showed that significantly lower concentrations of von Willebrand factor and its propeptide were observed in patients receiving haemodialysis than in those receiving PD. This was unexpected since patients receiving PD were clearly younger, while significantly more cardiovascular disease was observed in patients on haemodialysis. It cannot be ruled out that PD by itself leads to an increased level of von Willebrand factor. Chronic peritoneal stimulation by fluid exchange, low recurrent infection of the peritoneal cavity or a direct effect of infusion fluids could influence the endothelial cell function and increase the level of the von Willebrand factor. A higher degree of hypercoagulation has been previously reported in patients on PD than in patients on haemodialysis [15]. In addition, a role for albumin loss in the peritoneal dialysate has been suggested as an explanation for the prothrombotic state found in PD patients [16].

Platelets are activated during haemodialysis and can contribute to thrombotic events [17]. In addition, circulating platelet-derived microparticles are elevated in uraemic patients, which may explain the thrombotic tendency seen in these patients [18]. In the present study, markers of platelet activation were not associated with mortality in end-stage renal disease patients. This is in contrast to other studies of patients with cardiovascular and cerebrovascular disease and the general population. Those studies showed that platelet activation was found in patients with acute ischaemic disease [2, 19, 20] and in those with peripheral arterial disease [20]. Furthermore, platelet activation markers could predict the risk of death after an event [13, 21]; and treatment of these patients with platelet inhibitors reduced the recurrence of thrombotic events and the risk of mortality [3, 22, 23]. Anti-platelet therapy to prevent thrombosis of the haemodialysis vascular access, however, is of little benefit [24]. Our findings indicate that in vivo platelet activation markers are not major predictors of mortality in end-stage renal disease patients.

Important strong points of the present study are its prospective design and the way in which samples were collected at baseline by the investigators, i.e. investigators were not aware of the health status of the patients or of their future morbidity or mortality risk. As a result, all forms of selection bias can be excluded. Another strong point of the study is that all patients had been stable on dialysis during the previous 12 months. This reduces the risk that measurements were affected by fluctuations commonly observed at the commencement of dialysis.

The present study has shown that some areas require further comments. Firstly, levels of the von Willebrand factor in the plasma vary widely among individuals. While some conditions are transient, others are longer lasting or constitutional. ABO blood type, for example, is a major genetic modifier of the level of von Willebrand factor in the plasma that is unrelated to endothelial activation. Some studies have shown an association between non-O blood type and thromboembolic diseases, while others revealed that the association between von Willebrand factor and cardiovascular mortality was independent of blood group [12]. Thus, the influence of blood group on von Willebrand factor levels is clear, but its relationship with cardiovascular disease is uncertain. ABO blood type was not registered in the present population. Secondly, the plasma markers used in the present study may have been affected by the handling of the blood. However, it is unlikely that this can explain the increased mortality risk seen in our end-stage renal disease patients with high levels of von Willebrand factor because all samples were collected long before the patients died and the variation in handling conditions was randomly distributed among those patients who died and those who completed follow-up. Handling conditions may, however, influence the in vitro release of platelet activation markers and thereby mimic the concentrations that are released by in vivo activation. We cannot deny that this could be an alternative explanation for the absence of a relationship between platelet activation markers and mortality. Thirdly, another potential bias is the use of aspirin by almost 30% of the patients on haemodialysis. This could have significantly influenced the concentration of platelet activation markers in the study. Finally, biomarkers of endothelial cell activation and biomarkers of platelet activation might be affected by (other) biomarkers of mortality. Although partly excluded by multivariate regression analysis, this could explain the increased risk of mortality in subjects with high levels of von Willebrand factor.

In conclusion, this population-based study showed that chronic endothelial cell activation, but not platelet activation, was related to all-cause mortality in end-stage renal disease patients on long-term dialysis. High levels of von Willebrand factor predicted a 2.4-fold higher mortality risk than low levels of the factor. Although adjustments for age, sex, body mass index, diabetes, smoking at baseline, aspirin use, systolic blood pressure, total cholesterol and history of cardiovascular disease reduced this relationship, a statistically significant difference remained. This study demonstrated that high levels of von Willebrand factor in the plasma are associated with a higher risk of all-cause mortality in patients on haemodialysis and probably also in those receiving PD. The data indicate that chronic endothelial cell activation may be an important indicator of mortality risk.

Conflict of interest statement. None declared.

References
Von Willebrand and mortality in patients on haemodialysis


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