Von Willebrand Factor, Soluble P-Selectin, and Target Organ Damage in Hypertension
A Substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

Charles G.C. Spencer, David Gurney, Andrew D. Blann, D. Gareth Beevers, Gregory Y.H. Lip

Abstract—To investigate the relationship between soluble markers of platelet, endothelial and rheological function, and target organ damage and their response to intensified management in a population of middle-age hypertensive patients at high risk of cardiovascular complications, we studied 382 consecutive patients (308 men; mean age, 63 years, SD 8) along with 60 normotensive controls free of cardiovascular disease. Patients were divided into those with target organ damage (TOD; n=110) and those free of end-organ damage. Plasma levels of soluble P-selectin (sP-sel), a marker of platelet activation, and von Willebrand factor (vWF), an index of endothelial damage/dysfunction (both enzyme-linked immunosorbent assay), and the rheological indices fibrinogen, plasma viscosity, hematocrit, platelet, and white cell count were measured. In 53 patients, variables were further measured after 6 months of intensified cardiovascular risk management. Patients with TOD had significantly higher vWF, 137 (SD 33) versus 125 (SD 33) IU/dL (P=0.002,) and a greater proportion of smokers, 31% versus 16% (P=0.002). There were no statistically significant differences in plasma viscosity, fibrinogen, hematocrit, white blood cell count, platelet count, or sP-sel between the 2 subgroups. In multivariate analysis, vWF was a significant independent predictor for TOD. After 6 months of intensified management in 53 patients who entered the trial, there were significant reductions in systolic blood pressure, total cholesterol, hematocrit, plasma viscosity, sP-sel, and vWF (all P<0.01) but no significant change in fibrinogen. In conclusion, there is a relationship between TOD and endothelial damage/dysfunction in hypertension. Intensified management results in improvements in hemorheology, endothelial and platelet function. (Hypertension. 2002;40:61-66.)

Key Words: target organ damage □ endothelium □ von Willebrand factor □ fibrinogen □ soluble P-selectin □ rheology

Hypertensive patients with target organ damage (TOD) are at high risk of adverse cardiovascular events, particularly myocardial infarction and stroke. For example, in the Framingham study,1 increasing left ventricular mass was associated with an increased incidence of cardiovascular events, including cardiovascular death. Similarly, patients with a history of stroke or transient ischemic attack (common complications of hypertension) are at increased risk of not only another stroke but also coronary artery disease. Increased cardiovascular mortality and coronary heart disease have also been noted in hypertensive subjects with severe symptomatic and asymptomatic peripheral arterial disease.2,3 Many of these complications (stroke, coronary disease) are thrombosis related.

A number of hemorheological and thrombotic markers have been shown to be elevated in hypertensive subjects that are significantly related to, and predictive of, thrombotic cardiovascular events.4 For example, von Willebrand factor is widely regarded as a marker of endothelial cell damage/dysfunction, and elevated plasma levels are related to adverse cardiovascular outcomes.5 Platelets are important in the process of both atherosclerosis and thrombosis,6 and soluble P-selectin is a plasma marker of platelet activation that has been related to adverse cardiovascular prognosis.7,8

Blood rheology is also important, as abnormalities of flow constitute 1 component of Virchow’s triad of thrombogenesis. Plasma viscosity, an index of blood rheology, is positively correlated with blood pressure (BP)9 and has been related to future cardiovascular events in a number of prospective studies.10,11 Likewise, plasma fibrinogen, which is a clotting factor and an important determinant of plasma viscosity, has been found to be related to BP,12 although this has not been consistent across all studies.13 An extensive body of evidence also indicates a relationship between fibrinogen and incident cardiovascular disease.14 Another index of blood rheology, the hematocrit, has been related to adverse cardiac events.15

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In view of the relationship between TOD and thrombosis-related adverse cardiovascular outcomes in hypertension, we hypothesized that there would be a relationship between indices of endothelial damage/dysfunction (von Willebrand factor, platelet activation (soluble P-selectin), hemorheology (fibrinogen, plasma viscosity, hematocrit and white cell count), and TOD in hypertensive subjects. To test this hypothesis, we measured these indices in hypertensives with numerous risk factors, and provide data from healthy controls to provide a perspective.

Methods

Patients

We recruited from hypertensive patients age 40 to 79 years, both treated and untreated, who were identified from general practitioner records or a hospital hypertension clinic and were invited for screening for the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trial.16 The hypertensive patients were assessed for their future cardiovascular risk, requiring ≥3 risk factors to be included into ASCOT. Risk factors included (1) left ventricular hypertrophy (LHV) according to Cornell voltage duration product (>2440) or Sokolow Lyon criteria (>38 mV), (2) other ECG abnormalities (left ventricle strain pattern, abnormal Q waves, left bundle branch block, ST-T changes compatible with ischemic heart disease), (3) history of diabetes mellitus according to World Health Organization criteria, (4) past medical history of cerebrovascular event, including transient ischemic attack, (5) male sex, (6) age ≥55 years, (7) microalbuminuria/proteinuria, (8) smoking, (9) plasma total cholesterol/HDL cholesterol, (10) family history of first degree relative before the age of 55 (men) or 60 (women), and (11) peripheral vascular disease according to Edinburgh claudication questionnaire.17

Volunteers were interviewed by a specialist nurse, who took a detailed medical history, and an ECG was performed. BP was measured after the patient was seated for 10 minutes in a quiet room, using the OMRON 705CP, as per the ASCOT protocol; a minimum of 3 readings were performed, and the average of the last 2 readings were used. Patients were excluded from the substudy if they had a history of coronary artery disease, treated angina, or major concomitant noncardiovascular disease or were taking warfarin.

All patients were given lifestyle advice regarding diet, smoking, alcohol, and exercise in both verbal and written forms. Smoking cessation was strongly encouraged. Patients with diabetes mellitus, the target BP was <130 mm Hg systolic and <80 mm Hg diastolic. The ‘healthy control’ group consisted of 60 healthy normotensive controls (43 men, 17 women; mean age, 63 years, SD 8) recruited from well patients in the community, healthy hospital staff, relatives of the patients, and those attending the hospital for routine cataract surgery. The subjects were without clinical evidence of vascular, metabolic, neoplastic, or inflammatory disease by careful history, examination, and routine laboratory tests. These subjects were normotensive and in sinus rhythm.

On the day of randomization and after a median of 6 months of treatment, blood was drawn after an 8-hour fasting period with minimal trauma from the antecubital vein. Samples were centrifuged at 3000 rpm for 20 minutes within 30 minutes of collection, and the citrated plasma stored at −80°C until analysis.

Laboratory

Von Willebrand factor was measured by an established enzyme-linked immunosorbsent assay using commercial antisera from Dako (Ely) and reference von Willebrand factor from the National Institute for Biological Standards and Control (Potters Bar). Soluble P-selectin was measured in citrated plasma by enzyme-linked immunosorbsent assay using commercial reagents (R&D Systems). The intraassay coefficient of both assays was <5%; interassay variation was <10%. Fibrinogen was measured by a modified Clauss technique using a coagulometer and thrombin from Pacific Hemostasis. Hematocrit and white blood cells were measured using an automated blood count machine (Advia 120, Bayer Diagnostics). Plasma viscosity was measured using a Coulter viscometer II (Coulter Electronics Ltd).

Power Calculations and Statistical Analyses

We based our power calculation on levels of von Willebrand factor, a molecule known to be increased in cardiovascular disease and also to be predictive of poor prognosis.6 We hypothesized that patients with TOD would have levels of von Willebrand factor >0.25 of a SD higher than patients free of TOD. To achieve this with a 1-β power of 0.80 and P<0.05, 100 subjects per group are demanded. However, to improve our power, we aimed to recruit approximately twice as many subjects free of TOD. To test the hypothesis that a package of cardiovascular risk factor treatments will reduce levels of von Willebrand factor by one third of a SD, good paired data from 50 subjects are required.18

BP, cholesterol glucose, von Willebrand factor, and hematocrit were normally distributed and are presented as mean (SD). Body mass index, plasma viscosity, white blood cells, soluble P-selectin, and fibrinogen were nonnormally distributed and are thus presented as median with interquartile range. Data between the 2 groups were compared using unpaired t tests or the Mann-Whitney U test as appropriate for continuous variables and the χ2 test for categorical variables. Correlations between the measured indices and BP were performed using Spearman’s rank correlation method. A stepwise multiple regression analysis was undertaken with the research indices (von Willebrand factor, soluble P-selectin, etc) as dependent variables, and clinical factors (eg, age, sex, presence of TOD, diabetes, smoking status, etc) as predictors. A value of P<0.05 was considered statistically significant. All analyses were performed using SPSS version 10 software (SPSS Inc).

Results

Cross-Sectional Data

Clinical, demographic, and laboratory data are presented in Table 1. Of the 382 patients, 341 (89%) were taking antihypertensive therapy (with either amlopidine±perindopril or atenolol±bendroflumethiazide), and previous antihypertensive medication was withdrawn. Of these, 138 (41%) were taking an ACE inhibitor, 23 (7%) an α-adrenoreceptor blocker, 111 (32%) a β-blocker, 12 (4%) an angiotensin II receptor blocker, 124 (3%) a calcium channel blocker, and 118 (35%) a diuretic. As expected, these patients had various abnormalities in risk factors and laboratory indices compared with those of the controls. In particular, reanalysis of the data comparing research indices in diabetics versus nondiabetics in the hypertensive cohort did not show any significant differences (data not shown).

Target Organ Damage Versus No Target Organ Damage

The 108 patients with TOD were compared with 274 patients without TOD (Table 2). The only significant differences were

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the proportion of smokers and levels of von Willebrand factor. As smoking is a known influence on various laboratory indices, including von Willebrand factor, soluble P selectin, and fibrinogen, we performed a subanalysis on 300 nonsmokers, which provides sufficient power to detect a difference of 0.28 of a SD. This analysis (Table 3) showed that von Willebrand factor was 0.41 of a SD higher than in those with TOD (\(P < 0.0001\)). The smaller number of 77 smokers (33 with TOD) does not provide sufficient power for such an analysis. In 5 patients, smoking status was not defined.

Correlations and Stepwise Multiple Regression Analysis
There were significant correlations between hematocrit (HCT) and diastolic BP (\(R = 0.139, P = 0.01\)) and between von Willebrand factor and pulse pressure (ie, the difference between systolic and diastolic blood pressures) (\(R = 0.133, P = 0.01\)).

Stepwise multiple regression analysis demonstrated that the presence of TOD was a significant predictor for von Willebrand factor (\(P < 0.05\)) but not any other marker. Age was a predictor for von Willebrand factor, HCT, and fibrinogen. Male sex was a predictor for hematocrit, whereas current smoking was a predictor for soluble P-selectin, white blood cells, HCT, and fibrinogen. Finally, cholesterol/HDL cholesterol ratio was a predictor for von Willebrand factor, soluble P-selectin, white blood cells, and HCT (all, \(P \leq 0.05\)).

Effect of Treatment
The results of BP and, when indicated, cholesterol treatment in 53 patients with TOD is presented in Table 4. After 6 months of treatment the mean systolic BP, total cholesterol, HCT, plasma viscosity, soluble P-selectin, and von Willebrand factor all fell. However, despite this intensified management, systolic BP, glucose, fibrinogen, von Willebrand factor, and soluble P-selectin all remained significantly higher after 6 months than levels in the healthy control group (Table 4).

Discussion
As well as confirming the presence of endothelial, platelet, and hemorheological abnormalities in hypertension, the present study shows a relationship between TOD and the endothelial marker von Willebrand factor, but not soluble P-selectin and conventional hemorheological markers, in hypertensive patients. The exact mechanisms by which this occurs or, indeed, whether TOD promotes endothelial damage or vice versa is unclear. It is of note that there were no significant differences in blood pressure between the 2 groups, but as the majority of patients were treated, it may be the case that those with TOD had been treated more aggressively to achieve similar blood pressures than those without. This is probably unlikely as further analysis of our data found no significant difference in the number of drugs patients were taking between the 2 groups. Furthermore, previous work in our department has demonstrated no difference in plasma prothrombotic markers between uncontrolled hypertensives receiving medication and untreated patients.

When dividing our patients into those with and without TOD, we chose simply to divide a group of patients who are already at
TABLE 2. Von Willebrand Factor, Soluble P-Selectin, and Haemorheology in Relation to Target Organ Damage in Hypertensive Subjects and Healthy Controls

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hypertensives</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TOD (n=108)</td>
<td>No TOD (n=274)</td>
<td>P (TOD vs No TOD)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>64 (8)</td>
<td>63 (8)</td>
<td>0.388</td>
<td></td>
</tr>
<tr>
<td>Gender, M:F</td>
<td>83:24</td>
<td>224:50</td>
<td>0.860 ($\chi^2$)</td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>166 (18)</td>
<td>164 (17)</td>
<td>0.560</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>88 (11)</td>
<td>90 (10)</td>
<td>0.060</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>27.7 (25.4–31.5)</td>
<td>28.7 (26.5–32.2)</td>
<td>0.071</td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>24 (22)</td>
<td>67 (24)</td>
<td>0.645 ($\chi^2$)</td>
<td></td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>33 (31)</td>
<td>44 (16)</td>
<td>0.002 ($\chi^2$)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>6.1 (1.1)</td>
<td>6.1 (1.1)</td>
<td>0.691</td>
<td></td>
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<tr>
<td>HDL cholesterol, mol/L</td>
<td>1.3 (0.4)</td>
<td>1.3 (0.4)</td>
<td>0.966</td>
<td></td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>6.8 (2.9)</td>
<td>6.5 (1.9)</td>
<td>0.392</td>
<td></td>
</tr>
<tr>
<td>Number of drugs, n</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>0.217</td>
<td></td>
</tr>
<tr>
<td>Soluble P-selectin, ng/mL</td>
<td>66 (49–87)</td>
<td>60 (49–75)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Von Willebrand factor, U/dL</td>
<td>137 (33)</td>
<td>125 (33)</td>
<td>&lt;0.002</td>
<td></td>
</tr>
<tr>
<td>Plasma viscosity, mpa</td>
<td>1.80 (1.72–1.89)</td>
<td>1.80 (1.74–1.88)</td>
<td>0.897</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.12 (2.67–3.77)</td>
<td>3.02 (2.62–3.47)</td>
<td>0.134</td>
<td></td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>44.1 (4.1)</td>
<td>44.2 (3.7)</td>
<td>0.847</td>
<td></td>
</tr>
<tr>
<td>White blood count, $\times 10^9$/L</td>
<td>6.4 (5.5–7.9)</td>
<td>6.6 (5.3–7.4)</td>
<td>0.292</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>245 (69)</td>
<td>243 (57)</td>
<td>0.801</td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%), mean (SD), or median (interquartile range), and compared by unpaired t test or Mann-Whitney test, as appropriate.

TABLE 3. Von Willebrand Factor, Soluble P-Selectin, and Hemorheology in Relation to Target Organ Damage in Hypertensive Subjects and Healthy Controls

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hypertensives</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TOD (n=75)</td>
<td>No TOD (n=225)</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Soluble P-selectin, ng/mL</td>
<td>61 (48–87)</td>
<td>61 (49–74)</td>
<td>0.741</td>
<td></td>
</tr>
<tr>
<td>Von Willebrand factor, U/dL</td>
<td>140 (36)</td>
<td>126 (32)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Plasma viscosity, mpa</td>
<td>1.81 (1.72–1.89)</td>
<td>1.80 (1.74–1.87)</td>
<td>0.978</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.03 (2.64–3.60)</td>
<td>2.98 (2.58–3.47)</td>
<td>0.293</td>
<td></td>
</tr>
<tr>
<td>Haematocrit, %</td>
<td>43.8 (3.9)</td>
<td>43.8 (3.6)</td>
<td>0.984</td>
<td></td>
</tr>
<tr>
<td>White cell count, $\times 10^9$/L</td>
<td>1.81 (0.26)</td>
<td>1.80 (0.25)</td>
<td>0.886</td>
<td></td>
</tr>
<tr>
<td>Platelets, $\times 10^9$/L</td>
<td>243 (69)</td>
<td>241 (54)</td>
<td>0.802</td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%), mean (SD), or median (interquartile range), and compared by unpaired t test or Mann-Whitney test, as appropriate.
between those with and without TOD. This concurs with earlier work in our department which found no difference in these variables between patients with echocardiographic LVH.19 Both soluble P-selectin and white blood cells have previously been found to be elevated in hypertensives compared with controls,19 and it may be that there is a plateau effect with no further increase in those with TOD above levels found in our relatively high risk comparator group.

Our finding of no difference in fibrinogen or plasma viscosity between the 2 groups contrasts with our earlier work, which found higher fibrinogen and plasma viscosity in hypertensive patients with LVH, although in that study, LVH was diagnosed by echocardiography.19 The difference may be owing to the different populations studied, as the earlier study is likely to have included patients at a lower overall cardiovascular risk reflected in lower plasma fibrinogen levels in the group free of LVH. It is also possible that plasma fibrinogen is raised in patients with multiple cardiovascular risk factors, but not further elevated if they develop TOD. Secondly, patients with LVH by echocardiography may be a very different group from the patients with TOD in the present study.

Our findings that management of hypertension produces a significant reduction in several of our markers including von Willebrand factor, soluble P-selectin, plasma viscosity, and HCT, and a near significant reduction in white blood cells is important. Despite effective control of blood pressure, many27 but not all28 reports have found antihypertensive medication does not reduce cardiovascular risk back to the levels found in the normotensive population. Failure to improve hemorheological abnormalities may be one reason for this difference, and our findings in the present study add to a number of previous (small) studies conducted in this area. Many of these found no change in hemorheological markers but used patients at low cardiovascular risk followed up for short periods of time. For example, in hypertensives with no abnormalities of coagulation or endothelial function compared with controls, treatment with either quinapril or nifedipine produced no change in fibrinogen or von Willebrand factor.29 Similarly, in low-risk, previously untreated patients, losartan or enalapril had no significant impact on hemorheological parameters, von Willebrand factor, or soluble P-selectin.30 However, a number of studies mainly involving subjects at somewhat higher cardiovascular risk have found reductions in plasma viscosity with a variety of agents, including ACE inhibitors,31 calcium antagonists,32 and α-adrenoreceptor blockers.33 One study also found a reduction in HCT.31 Reductions in fibrinogen have also been demonstrated with doxazosin,33 urapidil,34 and perindopril but not with losartan.35 A small number of studies have investigated the effect of blood pressure reduction on von Willebrand factor. Blann and Waite36 found a significant reduction in 15 patients treated with a variety of drugs, and another study has demonstrated reductions with doxazosin.37 One study has found a nonsignificant reduction in soluble P-selectin with quinalapril and nifedipine.38 The importance of our study is that we have demonstrated that in subjects at particularly high cardiovascular risk by virtue of having TOD, significant reductions in hemorheological, platelet, and endothelial markers (with the exception of fibrinogen) may be achieved by intensified BP control and risk factor management.

The present analysis primarily assesses the relation of our research indices to TOD, but is limited by its cross-sectional comparison. Furthermore, as this substudy is part of the main ASCOT clinical trial, the investigations and treatment regimes allowed are very much protocol-driven, and the substudy was secondary to the main ASCOT trial. The patients in the present analysis were consecutive patients over the initial period of the trial recruitment at the Birmingham study site, and we accept that men were overrepresented (as with many clinical trials). The paired data on 53 patients are also presented as a whole, in fulfillment of our power calculation, after completing a “package of care” of general cardiovascular risk management, which includes education, lifestyle advice, dietary advice, antihypertensive treatment, and statin use. Further planned analyses from this substudy would occur at the end of 5 years (on completion of the main ASCOT study), at which we would hope to present complete data from the Birmingham center on these research indices in relation to the full duration of followup, study

### Table 4. Effect of Treatment in Patients With Target Organ Damage

<table>
<thead>
<tr>
<th>Parameters</th>
<th>At Baseline (n=53)</th>
<th>After 6 Months of Treatment (n=53)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64 (7)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.1 (1.2)</td>
<td>5.4 (1.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.3 (0.45)</td>
<td>1.4 (0.45)</td>
<td>0.778</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>6.9 (3.0)</td>
<td>6.6 (1.9)</td>
<td>0.189</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>167 (15)</td>
<td>156 (22)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>89 (11)</td>
<td>86 (16)</td>
<td>0.172</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>44.4 (4.3)</td>
<td>42.5 (7.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>White blood count, ×10⁶/L</td>
<td>6.6 (5.3–8.2)</td>
<td>6.3 (4.9–7.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Platelet count, ×10⁹/L</td>
<td>245 (67)</td>
<td>242 (62)</td>
<td>0.574</td>
</tr>
<tr>
<td>Plasma viscosity, mpa</td>
<td>1.81 (1.74–1.89)</td>
<td>1.76 (1.67–1.84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrogen, g/L</td>
<td>2.74 (3.25–3.87)</td>
<td>2.65 (3.20–3.66)</td>
<td>0.45</td>
</tr>
<tr>
<td>Soluble P-selectin, ng/mL</td>
<td>67.0 (49.0–86.5)</td>
<td>53.0 (40.5–61.0)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Von Willebrand factor, U/dL</td>
<td>143 (35)</td>
<td>131 (32)*</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*p=0.001 vs control; †P<0.0001 vs healthy controls.
endpoints, grades of blood pressure reduction, effects of different drug regimes (including statins), etc.

**Perspectives**

Our study suggests that there is a relationship between TOD and endothelial activation in hypertension. Given the critical role of the endothelium in arterial thrombosis, this is likely to be of significance in the pathogenesis of hypertensive complications and raises the possibility that von Willebrand factor may be of use in identifying a “high-risk” group of hypertensives. Furthermore, intensified management results in significant improvements in hemorheological, platelet, and endothelial parameters.

**Acknowledgments**

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**References**


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