OBJECTIVES
We sought to investigate the relationship between target organ damage (TOD) in hypertension and a prothrombotic/hypercoagulable state, using a new technique of "platelet lysis" to quantify the amount of P-selectin per platelet (pP-sel), and to correlate it with other platelet markers (e.g., mass, volume and granularity, soluble P-selectin [sP-sel], and beta-thromboglobulin [beta-TG]).

BACKGROUND
The increased risk of TOD in hypertension may be related to a prothrombotic/hypercoagulable state, with abnormalities in platelets, such as increased expression of P-selectin.

METHODS
We studied 199 patients (mean age 68 years, 75% men) with hypertension. Of these, 125 had TOD (e.g., stroke, previous myocardial infarction, angina, left ventricular hypertrophy). Values obtained were compared with those from 59 healthy normotensive control subjects (mean age 68 years, 58% men).

RESULTS
Hypertensive patients had a higher mean platelet volume, mass, pP-sel, sP-sel, and beta-TG and lower platelet granularity (all p < 0.01), but a similar platelet count, as compared with controls. Within the hypertensive group, those with evidence of TOD had significantly larger platelets with greater mass but had lower granularity, sP-sel, and pP-sel levels than those without TOD, possibly reflecting increased aspirin use. On multivariate analysis, aspirin use was a determinant of pP-sel (p = 0.03) and sP-sel (p = 0.01), but the use of other drugs or other co-morbidity (e.g., diabetes, smoking) did not influence either P-selectin value.

CONCLUSIONS
Patients with hypertension have evidence of changes in platelet physiology, as reflected by a higher level of pP-sel. Patients with TOD also had larger platelets, with greater mass, and the use of aspirin lowered pP-sel and sP-sel levels. These changes may have implications for the pathophysiology of cardiovascular and cerebrovascular disease in hypertension. (J Am Coll Cardiol 2004;44:415–22) © 2004 by the American College of Cardiology Foundation

Despite advances in the understanding of hypertension and its treatment, the precise mechanisms by which hypertension acts as a cardiovascular risk factor are not fully understood. In recent years, it has become evident that markers of coagulation (e.g., fibrinogen) are predictors of cardiovascular events. Many such abnormalities are present in hypertensive patients, indicating that hypertension may confer a prothrombotic or hypercoagulable state; indeed, despite the blood vessels in hypertension being exposed to high pressures, the complications of hypertension are paradoxically thrombotic rather than hemorrhagic (1,2). In addition to severe thrombotic events such as stroke and myocardial infarction (MI), patients with long-standing hypertension also show evidence of damage to other organs, such as left ventricular hypertrophy, collectively referred to as target organ damage (TOD).

More recently, attention has been directed toward the role of platelets in the pathogenesis of the complications of hypertension, and raised plasma P-selectin is an example of this activity (3,4). P-selectin (CD62P), an adhesion molecule facilitating the adhesion of platelets to leukocytes and to the endothelium, is a component of the membrane of the endothelial Weibel-Palade body and the membrane of the platelet alpha and dense granules. During activation and adhesion, platelets mobilize their alpha granules so that P-selectin appears at the surface and is subsequently shed into the plasma (5). This shed P-selectin is measured as soluble P-selectin (sP-sel), and it is now believed that most, if not all, of this sP-sel in the plasma is of platelet origin and, to some extent, parallels levels of plasma beta-thromboglobulin (beta-TG), a more established platelet marker (6,7).

Plasma levels of sP-sel are becoming recognized as a marker of platelet activation in various conditions, such as ischemic heart disease (8,9), atrial fibrillation (10,11), and hypertension (12,13). However, the amount of P-selectin in a particular platelet (pP-sel) has not been extensively studied in hypertension, because, until recently, the main method of
estimating expression of P-selectin has been by flow cytometry (14) or whole platelet enzyme-linked immunosorbent assay (ELISA) (15). We have recently reported a novel method of quantifying total pP-sel levels by lysing a set number of platelets with the detergent Triton X-100 and measuring P-selectin by ELISA in the resultant lysate (16).

Finally, advances in flow cytometry have enabled the development of additional measures of platelet biology, not only mean platelet volume (MPV), but also platelet mass and component/granularity, and although the precise physiologic implications of these three indexes is unclear, they may have a role in unstable angina and acute MI (17).

Due to the increased expression of surface membrane P-selectin by platelets on activation, we hypothesized that the amount of pP-sel would be elevated in hypertensive patients compared with healthy age- and gender-matched control subjects, and that this, in turn, would vary depending on the presence or absence of TOD. We also hypothesized that other platelet indexes (e.g., platelet granularity, mass, and volume) would differ between the various groups. To test this hypothesis, we examined platelet samples from patients with hypertension with and without TOD.

**METHODS**

**Patients.** The study was part of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), which compares hypertensive regimens: overall rationale, methods, and inclusion criteria have been previously described in detail (12,18). Briefly, the inclusion criteria were patients age 40 to 80 years with either untreated hypertension (systolic blood pressure [SBP] ≥160 mm Hg and/or diastolic blood pressure [DBP] ≥100 mm Hg) or treated hypertension (SBP ≥140 mm Hg and/or DBP ≥90 mm Hg). In addition, patients were required to have three or more of the following risk factors: 1) left ventricular hypertrophy; 2) other electrocardiographic abnormalities; 3) diabetes; 4) history of cerebrovascular disease, including transient ischemic attack; 5) male gender; 6) age ≥55 years; 7) microalbuminuria/proteinuria; 8) smoking; 9) plasma total/high-density lipoprotein cholesterol ratio ≥6; 10) history of a coronary artery disease event occurring in a first-degree relative before the age of 55 years in males or 60 years in females; or 11) peripheral vascular disease, as per the Edinburgh claudication questionnaire (19). Patients were excluded if they had a history of malignant or secondary hypertension, congestive cardiac failure, fasting serum triglycerides >4.5 mmol/L, or major concomitant noncardiovascular disease or were taking warfarin. Target organ damage was defined as a previous cardiovascular event (stroke [cerebrovascular accident], transient ischemic attack, MI, left ventricular hypertrophy, or renal failure [serum creatinine >140 mmol/L]). The ASCOT patients were recruited into this cross-sectional study after stabilization on ASCOT trial drug therapy, all after being two or more years into the trial.

We also recruited 59 healthy normal subjects from the hospital staff, relatives of the patients, or those attending the hospital for routine cataract or hernia surgery. The subjects were not taking any regular medication and were nonsmokers, with no clinical evidence of vascular, metabolic, neoplastic, or inflammatory disease by a careful history, examination, and routine laboratory tests. These subjects were normotensive (SBP/DBP ≤140/90 mm Hg) and in sinus rhythm.

**Laboratory.** Blood was drawn from an antecubital with atraumatic venipuncture into vacutainers containing citrate, theophylline, adenosine, and dipyridamole (CTAD) for estimating beta-TG, as well as citrate for pP-sel and sP-sel. The blood samples collected in the CTAD tubes were immediately placed on ice, and plasma was separated within 1 h of collection. Aliquots were stored at −70°C to facilitate batch analysis. Levels of beta-TG were determined by ELISA (Asserachrom, Diagnostica Stago, Asniere sur Seine, France). P-selectin in citrated plasma and platelet lysate was also determined by ELISA (R&D Systems, Abingdon, United Kingdom), standardized by recombinant human P-selectin. The intra-assay coefficient of variation for ELISA was 2.8% at 60 ng/ml, 3.8% at 6 ng/ml, and 5.0% at 3 ng/ml (n = 64). The inter-assay coefficient of variation for ELISA was 6.7% at 60 ng/ml, 8.5% at 5.5 ng/ml, and 7.8% at 3.0 ng/ml (n = 12). The lower limit of sensitivity of the assay was 0.8 ng/ml.

Levels of pP-sel were measured by a lysate technique, as previously described in detail (20). Briefly, platelet-rich plasma was obtained by centrifugation of venous blood at 200g for 10 min. From this, 10° platelets were pelleted by centrifugation at 1,000g for 20 min, washed in phosphate-buffered saline, and lysed by a small volume (250 μl) of 0.1% Triton X-100 (Sigma, Poole, United Kingdom). The total amount of P-selectin in an aliquot of this lysate is determined by ELISA and is reported as ng/cell after adjustment.

Platelet parameters—total platelet count, MPV, mean platelet mass (MPM), and mean platelet granularity (MPG, also known as component)—were measured using flow cytometry by an ADVIA 120 (Bayer, Newbury, Berks, United Kingdom). These indexes are obtained from histograms of two-dimensional, light-scatter signals that are converted into volume and refractive index values; MPV...
(femtoliter [fl]) is directly measured, but both MPG (g/dl) and MPM (pg) are derived (17,21).

**Power calculations.** We based our power calculation on our previous reports of raised sP-sel in other hypertensive patients from this trial (12), in atherosclerosis (7), and in atrial fibrillation (20). By hypothesizing an increase in sP-sel in TOD, compared with patients free of TOD, of ~20% (0.5 SD after log transformation), we needed at least 60 patients per group for two-tailed $p < 0.01$ with a $1 - \beta$ power of 0.9 (22). The same power calculation was used for the case-control aspect. The main post hoc analysis (i.e., on aspirin versus not on aspirin) is also powered for this case-control aspect. The main post hoc analysis (i.e., on aspirin versus not on aspirin) is also powered for this difference.

**Statistics.** The Anderson–Darling test was applied to data of continuous variables to define distribution. Results are expressed as the mean value ± SD or as the median value with interquartile range for normally distributed data and skewed data, respectively. Data between patients and controls were analyzed by the unpaired $t$ test or Mann–Whitney $U$ test, as appropriate. Multivariate logistic regression analyses were performed to seek relationships between categorical data (e.g., on/off aspirin, on/off statin, with/without TOD) and the research indexes. Correlations were performed by Spearman’s correlation method. Differences between categorical data were sought using the chi-square test. All statistical calculations were performed on a microcomputer using a commercially available statistical package (Minitab release 12, Minitab Inc., State College, Pennsylvania). A $p$ value of $<0.05$ was considered statistically significant.

## RESULTS

As our recruitment numbers have exceeded our power calculation (i.e., ability to determine, with high confidence, a difference of 20%/0.5 SD), we are confident of having minimized type 1 and type 2 errors (22).

### Case-control aspect

The demographic, clinical, and platelet parameters of the control and hypertensive subjects are shown in Table 1. Of the hypertensive patients, 49% were taking a calcium channel blocker, 44% beta-blocker, 42% angiotensin-converting enzyme inhibitor, 37% alpha-blocker, 44% diuretic, and 9% angiotensin receptor blocker. A further 52% were taking aspirin and 33% a statin (all were taking 10 mg atorvastatin, as per the ASCOT protocol), and 72 (36%) had diabetes. The hypertensive patients had a significantly higher mean SBP, but not DBP, as compared with controls. Despite similar age, gender, and mean platelet counts, every platelet index was higher in the hypertensive group compared with the control group, except MPG, which was lower.

### Analyses within the hypertensive population

Of the 199 patients with hypertension, 125 (63%) had evidence of TOD (stroke in 25%, transient ischemic attack in 16%, previous MI in 24%, angina in 20%, evidence of left ventricular hypertrophy in 11%, and mild renal failure in 20%). Patients with TOD had a significantly higher MPV and MPM but lower MPG. However, median levels of plasma beta-TG were not significantly different, whereas sP-sel and pP-sel were significantly lower in the hypertensive patients with TOD (Table 2).

Aspirin, an established antiplatelet agent, was being taken regularly by 105 patients at a dose of 75 mg/day in a standardized manner when studied. We therefore analyzed the data with respect to the use of this drug (Table 3). Unsurprisingly, patients taking aspirin were more likely to have cardiovascular disease and, thus, to be taking beta-blockers, but there were fewer diabetics. The use of aspirin was also associated with a higher MPM and MPV but lower sP-sel, pP-sel, and beta-TG values. There were no significant differences in research indexes between patients who were taking a statin and those who were not (data not shown).
Correlations. In the 59 healthy controls (i.e., in “normal” physiology), there was a strong positive correlation between MPM and MPV (i.e., large platelets have greater mass), but a strong inverse relationship between MPV and MPG (i.e., large platelets have a lower concentration of granules). There were no correlations with the platelet count. Levels of sP-sel significantly (but weakly) correlated with pP-sel values (Fig. 1). Unsurprisingly, sP-sel correlated strongly with beta-TG, but less so with MPG, but neither pP-sel nor sP-sel did so.

Within the 199-strong hypertensive patient group (i.e., in “pathology”), the positive correlation between platelet mass and size was still present, albeit weaker, but the correlation between size and granularity disappeared. There were, however, no significant correlations between sP-sel and pP-sel in the hypertensive group as a whole, although, again unsurprisingly, sP-sel correlated with beta-TG, but less strongly than in the controls. Interestingly, pP-sel correlated with MPG.

In the 74 patients free of TOD, the only significant correlations were between sP-sel and beta-TG, MPG, and MPV, as well as between MPM and MPV.

Similarly, in the 125 patients with TOD, there was a significant correlation between sP-sel and beta-TG, and, in addition, MPG correlated with pP-sel. However, the correlations between MPG and MPV and between MPM and MPV were no longer significant, although a new correlation between MPG and MPM appeared. Principal correlations are summarized in Table 4.

Multivariate analysis. Stepwise multiple regression analysis showed that among the hypertensive patients, the use of aspirin was an independent factor affecting (reducing) the levels of sP-sel and pP-sel. Therefore, this seems to explain the potential anomaly whereby patients with TOD have lower levels of these platelet activation markers. No other factors (including smoking and diabetes, both known to influence sP-sel, or the use of drugs such as statins, beta-blockers, or calcium channel blockers or nitrates) affected either of the P-selectin values.

DISCUSSION

A growing mass of data implies that the platelet is important in hypertension (23,24). For example, we, as well as others, have noted raised sP-sel in hypertension (12,13,25) and have also shown abnormalities in other indexes of platelet physiology: increased pP-sel, MPV, and MPG, but lower mean platelet (component) granularity (MPG), despite similar platelet counts. Platelets activated by thrombin...
have lower densities and reduced MPG (21). It follows that low MPG may be consistent with (but does not conclusively demonstrate) platelet activation. Indeed, patients with acute MI have lower MPG than those with unstable angina (17). However, as MPM and MPG are not derived directly (26,27), some degree of caution in interpretation is required, as inter-relationships may be more mathematic than physiologic. The inverse correlation between MPG (granularity) and MPV (volume) in the controls (i.e., in health) implies that large platelets have reduced granularity, and notably, this relationship is not present in the entire patient cohort. However, the relationship reappears in the 74 patients free of TOD, not in the 125 with TOD, implying the effect is dependent not on hypertension but on TOD. Similarly, the positive relationship between mass and volume holds for all groups, except the patients with TOD, implying differing platelet physiology in the latter. This is the reverse of the mass-granularity correlation, present only in the patients with TOD. Finally, pP-sel correlated with granularity in the entire group of patients and in those with TOD alone, again implying an effect due to TOD and not simply to hypertension.

Many investigators have shown platelet activation in hypertension, as reflected by increases in plasma markers such as beta-TG (23) and platelet factor-4 (24,28,29), and our present data support this work. Increased MPV has been described (30), although not all studies confirm this (31). Raised MPV is also a risk factor for MI (32) and, in addition, is a marker of platelet activation (33–35). However, the link between other aspects of platelet physiology in hypertension and the presence of TOD has not been previously documented (i.e., raised MPV and MPM and lower MPG). Flow cytometry is a popular method for assessing platelet activation (25,36), but detects only the P-selectin that is expressed on the cell surface, not the P-selectin present as part of the granule membrane and not (yet) expressed on the cell surface. Our method (20) of lysing platelets with a detergent and then performing ELISA on the lysate bypasses this potential problem.

The reason(s) for increased pP-sel in hypertension are unclear but may reflect changes in megakaryocyte processing and/or thrombopoietin in response to changes in vascular function. P-selectin per platelet correlated with MPG, suggesting to us that the more granular platelets contain more P-selectin. However, the correlation in the subgroup

Table 3. Analysis of Data Based on Utilization of Aspirin

<table>
<thead>
<tr>
<th></th>
<th>Patients Not on Aspirin (n = 93)</th>
<th>Patients on Aspirin (n = 105)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>69 ± 9</td>
<td>68 ± 9</td>
<td>0.7</td>
</tr>
<tr>
<td>Males</td>
<td>73 (78)</td>
<td>77 (73)</td>
<td>0.5</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>147 ± 21</td>
<td>147 ± 24</td>
<td>0.9</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>81 ± 13</td>
<td>79 ± 10</td>
<td>0.2</td>
</tr>
<tr>
<td>Smoking (% admitting)</td>
<td>7.5</td>
<td>16.7</td>
<td>0.131</td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>3 (3%)</td>
<td>55 (52%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVA/TIA</td>
<td>17 (18%)</td>
<td>34 (32%)</td>
<td>0.03</td>
</tr>
<tr>
<td>DM</td>
<td>39 (42%)</td>
<td>33 (32%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>31 (33%)</td>
<td>58 (53%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>46 (49%)</td>
<td>53 (50%)</td>
<td>0.8</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>32 (34%)</td>
<td>49 (46%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Diuretics</td>
<td>49 (53%)</td>
<td>40 (30%)</td>
<td>0.04</td>
</tr>
<tr>
<td>A-II receptor antagonist</td>
<td>11 (12%)</td>
<td>8 (7%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Platelet indexes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPV (fl)</td>
<td>7.3 (6.7–7.9)</td>
<td>7.8 (6.9–8.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>MPM (pg)</td>
<td>1.8 ± 0.19</td>
<td>1.9 ± 0.2</td>
<td>0.01</td>
</tr>
<tr>
<td>MPG (g/dl)</td>
<td>27.2 ± 2.5</td>
<td>27.1 ± 2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Soluble P-selectin (ng/ml)</td>
<td>160 (120–220)</td>
<td>130 (100–195)</td>
<td>0.01</td>
</tr>
<tr>
<td>Platelet P-selectin (&gt; 10^-6 ng/cell)</td>
<td>105 (85–150)</td>
<td>95 (60–125)</td>
<td>0.01</td>
</tr>
<tr>
<td>Beta-TG (IU/ml)</td>
<td>310 (220–340)</td>
<td>300 (200–360)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SD, median value (interquartile range) or number (%) of subjects. Comparisons using unpaired t test, Mann-Whitney U test, or the chi-square test, as appropriate.

Abbreviations as in Tables 1 and 2.

Figure 1. Relationship between soluble P-selectin and platelet P-selectin in normal control subjects. Spearman correlation coefficient, r = 0.317, p < 0.001.
of hypertensive patients with TOD was slightly stronger, suggesting the effect is more likely to be related to TOD and less so to hypertension. In the controls, sP-selectin correlated with beta-TG, sP-selectin correlated with pP-selectin, and pP-selectin correlated with beta-TG. However, only the beta-TG/sP-selectin correlation remained in the patients, regardless of TOD. This further emphasizes the differences between beta-TG (a soluble component of the matrix of the alpha granule) and P-selectin (a component of granule membranes). One possible explanation for this is that platelets in the patients have reduced granularity simply because they are larger than normal platelets. Nonetheless, this alone does not explain raised pP-selectin. We therefore suggest that granules in patients’ platelets have more P-selectin than the granules from controls—a hypothesis that explains raised sP-selectin and beta-TG (both resulting from degranulation) and raised pP-selectin (an index independent of mass and volume), as well as the positive correlation between pP-selectin and granularity, strongest in the patients with TOD. Platelets are known to be affected by smoking (37–39). However, it is unlikely that the presence of smokers in our hypertensive group accounted for the differences in the two groups, as the numbers are small; indeed, there was no significant difference in the research indexes between the smokers and nonsmokers within the hypertensive group in the present study (data not shown).

Studies with aspirin have shown variable results on P-selectin (40–43). More recently, aspirin alone or aspirin plus clopidogrel failed to influence sP-selectin in patients with acute coronary syndromes (44), and, in health, sP-selectin seems to be uninfluenced by aspirin (45,46). We add to this debate by showing that the use of aspirin was associated with lower sP-selectin and pP-selectin and higher MPV and MPM, but no difference in MPG, despite similar blood pressure (Table 3). Although these differences may be causal, we acknowledge that an intervention study in these patients would provide better data than the present cross-sectional design.

Nonetheless, our data do imply that the cyclooxygenase pathway influences the metabolic and/or signalling aspects of P-selectin, maybe in the megakaryocyte (47). Aspirin use was also associated with greater use of beta-blockers, and we acknowledge the possible influence of this class of drug on platelets (48). However, we cannot propose a clear mechanism by which aspirin use leads to larger and heavier platelets at the same time as reduced sP-selectin, pP-selectin, and beta-TG, which is compatible with our other explanations. Therefore, differences may be spurious or simply due to the greater degree of cardiovascular disease and its risk factors in those patients taking aspirin.

The findings of this study have some important implications for the minimization of TOD and cardiovascular events in hypertensive patients. Despite the modulating use of aspirin and other therapies (although directed at blood pressure), patients with TOD still have abnormal platelet indexes as compared with healthy age- and gender-matched controls. Notably, P-selectin expression on platelets determines the size and stability of platelet aggregates (49), and (in an animal model) a procoagulant state results from high levels of sP-selectin in blood (50). These lend support to the argument that all high-risk hypertensive patients should be treated with antiplatelet agents such as aspirin and/or clopidogrel. Indeed, the Hypertension Optimal Treatment (HOT) study has shown that adding an antiplatelet agent to prevent platelet activation translates into clinical benefits (51).

The present analysis primarily assesses the relation of our research indexes to TOD, but is limited by its cross-sectional comparison. We are well powered to show that patients with hypertension have evidence of abnormalities in platelets, as reflected by a higher level of pP-selectin, and that most of this can be explained by additional TOD. The low platelet granularity in hypertension, with or without TOD, may represent those activated cells that have degranulated and are still circulating (52) (having shed their sP-selectin, which then appears in the plasma) or may alternatively simply (mathematically) reflect increased platelet volume and mass.

Table 4. Principal Correlations

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>All Patients With HT</th>
<th>HT Patients With No TOD</th>
<th>HT Patients With TOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet volume and granularity</td>
<td>-0.669</td>
<td>-0.072</td>
<td>-0.597</td>
<td>0.027</td>
</tr>
<tr>
<td>Platelet volume and mass</td>
<td>&lt;0.001</td>
<td>0.316</td>
<td>&lt;0.001</td>
<td>0.772</td>
</tr>
<tr>
<td>Platelet mass and granularity</td>
<td>0.699</td>
<td>0.260</td>
<td>0.770</td>
<td>0.178</td>
</tr>
<tr>
<td>Platelet P-selectin and granularity</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.051</td>
</tr>
<tr>
<td>Soluble P-selectin and platelet P-selectin</td>
<td>0.053</td>
<td>0.106</td>
<td>0.038</td>
<td>0.194</td>
</tr>
<tr>
<td>Beta-thromboglobulin and soluble P-selectin</td>
<td>0.760</td>
<td>0.141</td>
<td>0.746</td>
<td>0.033</td>
</tr>
<tr>
<td>Beta-thromboglobulin and platelet P-selectin</td>
<td>0.048</td>
<td>0.228</td>
<td>0.169</td>
<td>0.234</td>
</tr>
</tbody>
</table>

Data are presented as the Spearman correlation coefficient and p value.

HT = hypertension; TOD = target organ damage.
However, if activated platelets do shed P-selectin and continue to circulate (52), one would expect to see greater levels of plasma sP-sel in patients with TOD, in contrast to the present study. Furthermore, because of the case-control methodology used, we cannot be certain of causality (i.e., cause or effect of the disease), nor that the medications are not responsible for a component of the changes in our research indexes.

Conclusions. Patients with hypertension have evidence of changes in platelet physiology, as reflected by a higher level of pP-sel. Patients with TOD also have larger platelets, with greater mass, and the use of aspirin did lower pP-sel and sP-sel levels. These changes may have implications for the pathophysiology of cardiovascular and cerebrovascular disease in hypertension.

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REFERENCES