Association of Mean Platelet Volume With Risk of Stroke Among 3134 Individuals With History of Cerebrovascular Disease

Philip Bath, MD, FRCP; Charles Algert, MPH; Neil Chapman, MRCP; Bruce Neal, MRCP(UK), PhD; for the PROGRESS Collaborative Group

Background and Purpose—Mean platelet volume (MPV) is positively associated with measures of platelet activity and may be a useful indicator of the risk of vascular events in a variety of patient groups.

Methods—The association of MPV with the risk of stroke was assessed in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS). All participants had a history of cerebrovascular disease at baseline, and analyses were adjusted for the effects of potential confounders.

Results—The study followed 3134 individuals for an average of 3.9 years (mean age, 65 years; 71% male; average MPV, 10.0 fL). Three hundred eighty-three individuals had 402 stroke events, and 160 had major coronary events. MPV was positively associated with the risk of stroke, with an 11% increased relative risk (95% CI, 3% to 19%) of stroke per femtoliter greater MPV. There was no clear association of MPV with the risk of major coronary events (9% decreased relative risk; 95% CI, −23% to 7%). Perindopril did not alter MPV.

Conclusions—MPV is an independent predictor of the risk of stroke among individuals with a history of stroke or transient ischemic attack. The measurement of MPV may add useful prognostic information for clinicians managing patients with a history of cerebrovascular disease. (Stroke. 2004;35:622-626.)

Key Words: myocardial infarction ▪ platelets ▪ stroke, hemorrhagic ▪ stroke, ischemic

Platelet size, measured as mean platelet volume (MPV), is a marker of platelet function and is positively associated with indicators of platelet activity, including aggregation and release of thromboxane A2, platelet factor 4, and β-thromboglobulin.1,2 Previous studies have documented above average levels of MPV among patients with acute stroke,3–6 myocardial infarction,7,8 chronic vascular disease,9,10 or vascular risk factors.11,12 In addition, there is evidence that an elevated MPV is associated with a poor outcome among survivors of myocardial infarction13,14 and stroke15 and with an increased risk of restenosis after coronary angioplasty.16

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) recruited 6105 individuals with a history of cerebrovascular disease and demonstrated that a blood pressure–lowering regimen, involving an angiotensin-converting enzyme (ACE) inhibitor and diuretic, reduced the risks of stroke and major vascular events.16 We report here a substudy investigating the association of MPV with the risk of stroke and major coronary events among a cohort of 3134 participants.

Subjects and Methods

PROGRESS Trial

A total of 6105 participants were enrolled within 5 years of stroke and/or transient ischemic attack from 172 collaborating centers in 10 countries (Australia, Belgium, China, France, Italy, Japan, New Zealand, Republic of Ireland, Sweden, United Kingdom).16–18 After giving written informed consent and successful completion of a 4- to 6-week run-in period on perindopril, eligible participants were randomized to either continued blood pressure lowering with a perindopril-based regimen or matching placebo. Double-blind follow-up continued for a mean of 3.9 years.

Participants

The MPV substudy was approved by the local research ethics committee of King’s College Hospital, London (No. 1995-0183). Individuals registered in the 5 countries (Australia, China, Japan, New Zealand, Sweden) participating in the MPV substudy were eligible for inclusion, dependent on (1) collection of a blood sample before any outcome event and (2) inclusion in the double-blind follow-up phase of the trial. For analysis of the effect of randomized study treatment on MPV, eligibility further required that (3) the baseline measurement was made on a sample collected before the start of the active run-in treatment and (4) the follow-up sample was collected at least 180 days after randomization.
Blood Collection and Measurement of MPV
Nonfasting venous blood samples were collected into EDTA tubes and transported at 4°C for analysis 24 to 48 hours after venipuncture at a central laboratory in each country. Second blood samples were sought 1 year after randomization from 10% of individuals selected at random from participating countries except China. The repeated blood samples enabled assessment of (1) the effect of perindopril on MPV and (2) errors in the baseline measurements of MPV (regression dilution bias). The hematology analyzers used were as follows: Australia (Sysmex SE9000, BML, Tokyo), New Zealand (Technicon H1 or H1ACTS, Greenlane Hematology, Auckland), and Sweden (Coulter StkK, Centrum for Laboratorie Medicin, Uppsala).

Quality Control
A quality control program was run by the United Kingdom National External Quality Assessment Scheme for Hematology (UK NEQAS/H). Identical pairs of blood samples were sent to each participating laboratory on 12 occasions throughout the study.

Outcomes
The primary outcome was stroke. Secondary outcomes were stroke subtype (ischemic, hemorrhagic, unknown type) and major coronary events (nonfatal myocardial infarction and death from coronary heart disease, including sudden death). All events were reviewed and validated by an adjudication committee. Only the first event of each type was included in the analyses.

Statistical Analysis
The association of MPV with the risk of an event during follow-up was done in 2 ways: (1) by estimating the absolute event rates (95% CIs) defined by fifths of baseline MPV with stratification by country and testing of the trend across the groups by \( \chi^2 \) test and (2) by calculating the percent risk of an event for each unit increase in MPV ([hazard ratio–1]×100) with the use of Cox proportional hazards regression to estimate hazard ratios. Analyses were adjusted for country and for random error in the measurement of baseline MPV (see below). Multivariable analyses included the following baseline characteristics: treatment allocation (active, placebo), age, sex, systolic blood pressure, smoking status, history of diabetes, atrial fibrillation, myocardial infarction, prior stroke, platelet count, red cell count, red cell volume, white cell count, and medications at baseline (including a history of aspirin or other antiplatelet therapy). Covariates were included on the basis of their known effects on the risk of vascular disease or an observed effect on the \( \beta \)-coefficient for the association of MPV with stroke risk. For sensitivity analysis, the association of MPV with the risk of stroke was made for subgroups defined by (1) time of blood sample collection (before/at, after registration visit) and (2) delay between blood sample collection and testing of the trend across the groups by \( \chi^2 \) test and (2) by \( \chi^2 \) test for trend across fifths of MPV. Results for MPV were available for every country for 1 round: New Zealand 6.3 fL, Sweden 9.3 fL, Australia 10.9 fL, Japan 11.7 fL, China 12.3 fL. The principal difference was between New Zealand, in which the autoanalyzer used an optical measurement method, and the other countries, in which measurement was based on electric impedance. Too few samples were returned for reliable assessment of the stability of the autoanalyzers over time.

Blood Collection and Analysis
MPV measurements were made at different times after enrollment: before active run-in treatment, \( n = 1694 \); before randomization, \( n = 890 \); after randomization, \( n = 550 \). The median time between collection of the blood sample and measurement of MPV was 25 hours (interquartile range, 12 to 30 hours). Forty-one percent of samples were assayed within 24 hours of collection, and 16% of samples were assayed >48 hours after collection. Information on blood collection was missing for 27 participants.

Association of MPV With Risk of Stroke
Four hundred two strokes were recorded among 383 individuals during the follow-up period: 301 ischemic strokes, 59 intracerebral hemorrhages, 42 strokes of unknown type (Table 2). Nineteen individuals experienced >1 type of stroke event, and 43 of the strokes were fatal. Stroke rates were greater among individuals with higher measurements of MPV, both overall (\( P \) for trend across fifths of MPV = 0.01) and for ischemic stroke alone (\( P = 0.01 \)) (Figure 2). There was no evidence of an association of MPV with the rates of either intracerebral hemorrhage (\( P = 0.1 \)) or stroke of unknown type (\( P = 0.5 \)). With adjustment for country of recruitment and measurement error, the strength of the overall association was
such that each 1-fL increase in usual MPV was associated with a 12% (95% CI, 4% to 20%) increased relative risk of stroke. Inclusion of other potential confounders in the statistical model had little effect on the estimate (Table 2). This association did not differ among subgroups of participants defined by either the time of baseline measurement ($P_{\text{homogeneity}}=0.4$) or the delay between blood collection and measurement of MPV ($P_{\text{homogeneity}}=0.8$).

Association of MPV With Risk of Major Coronary Events

One hundred sixty individuals had a major coronary event: nonfatal myocardial infarction, $n=93$; coronary heart disease death, $n=54$; sudden death, $n=13$ (Table 2). Coronary event rates were not associated with MPV ($P=0.2$) (Figure 3, Table 2).

Effects of Randomized Treatment on MPV

Two hundred eighty-one participants (130 active, 151 placebo) had baseline and follow-up measurements of MPV. The

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics of Participants Overall and by Country of Recruitment</th>
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<tr>
<td>Country</td>
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<td>---------</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Male, %</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
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<td>Diastolic blood pressure, mm Hg</td>
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<td>Smoker, %</td>
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<tr>
<td>Mean platelet volume, fL</td>
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<td>Platelet count, $\times 10^{11}$/L</td>
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<td>White cell count, $\times 10^{12}$/L</td>
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<td>Red cell count, $\times 10^{12}$/L</td>
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<tr>
<td>Mean red cell volume, fL</td>
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<td>Prior ischemic stroke, %</td>
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<td>Prior hemorrhagic stroke, %</td>
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<td>Prior stroke of unknown type, %</td>
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<td>Prior myocardial infarction, %</td>
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<tr>
<td>Diabetes at baseline, %</td>
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<td>Antiplatelet use at baseline, %</td>
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<td>Assigned active treatment, %</td>
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Values are mean (SD) or frequency (%). *Participants may have had more than one type of prior event.

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<tr>
<th>TABLE 2. Percent Increases in the Risks of Stroke and Major Coronary Events for Each Femtoliter Above the Usual Mean Platelet Volume*</th>
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<tbody>
<tr>
<td>No. of Events†</td>
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<td>Adjusted for Country</td>
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<table>
<thead>
<tr>
<th>Event</th>
<th>No. of Events</th>
<th>Adjusted for Country</th>
<th>Adjusted for Multiple Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any stroke</td>
<td>383</td>
<td>12 (4 to 20)</td>
<td>11 (3 to 19)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>301</td>
<td>16 (7 to 25)</td>
<td>15 (6 to 25)</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>59</td>
<td>8 (6 to 27)</td>
<td>9 (6 to 31)</td>
</tr>
<tr>
<td>Stroke of unknown type</td>
<td>42</td>
<td>-6 (29 to 23)</td>
<td>-14 (35 to 14)</td>
</tr>
<tr>
<td>Major coronary event</td>
<td>160</td>
<td>-11 (24 to 4)</td>
<td>-9 (23 to 7)</td>
</tr>
</tbody>
</table>

*Adjusted for regression dilution bias.
†The first event alone contributes to the analysis.
‡Age, sex, systolic blood pressure, smoking status, history of diabetes, history of atrial fibrillation, history of myocardial infarction, history of prior stroke, country of recruitment, platelet count.

Figure 2. Incidence rates of any stroke (top) and ischemic stroke and intracerebral hemorrhage (bottom) in participant groups defined by fifths of MPV level at baseline.
Mean Platelet Volume and Stroke Recurrence

Figure 3. Incidence rates for major coronary events in participants defined by fifths of MPV level at baseline.

The antiplatelet effects of perindopril and other ACE inhibitors appear to be small. In this study there was no evidence of an effect of the randomized treatment on subsequent platelet parameters. Other studies of the ACE inhibitor
quinapril and the angiotensin receptor blocker losartan similarly have shown little effect on MPV. The findings of this study therefore make it unlikely that perindopril had any effects on platelet production or that this could have been a mechanism by which long-term use of a perindopril-based blood pressure-lowering regimen prevented recurrent stroke in the participants of PROGRESS. Similarly, antiplatelet effects of ACE inhibitors are unlikely to have contributed importantly to the effects observed in the many other trials of ACE inhibitors that have demonstrated beneficial effects on the risks of major vascular outcomes.

In summary, this study identified MPV as an independent predictor of the risk of stroke among high-risk individuals with a history of prior cerebrovascular disease and largely excluded effects on platelet production as a blood pressure–independent mechanism by which ACE inhibitors afford vascular protection. The measurement of MPV may add useful prognostic information for clinicians managing patients with a history of cerebrovascular disease.

Acknowledgments

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References


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