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The association of elevated plasma renin activity and myocardial infarction in hypertensive subjects also might have been found to be more significant in the study of Meade et al. if plasma renin activity had not been routinely measured in plasma that had been chilled, which might have resulted in unpredictable cryoactivation of prorenin — a methodologic flaw recognized only after the blood samples were collected for their study.⁴ This event would inevitably mute the association between a high profile and infarction by misclassifying subjects with truly low plasma renin activity in higher categories. Short of drawing more blood samples, there is no post hoc statistical approach to correct for this methodologic error.⁵

Finally, we do not believe the renin assay used by Meade et al. is a "standard method" for measuring plasma renin activity. In fact, when renin incubation is carried out at pH 6 most renin assays routinely add a serine protease inhibitor, such as diisopropyl fluorophosphate or phenylmethylsulfonyl fluoride, to inhibit angiotensinases that are not blocked at this pH by the inhibitors used by Meade et al.

MICHAEL H. ALDERMAN, M.D.
Bronx, NY 10461 Albert Einstein College of Medicine

JEAN E. SEALEY, D.Sc.
JOHN H. LARAGH, M.D.
New York Hospital—
Cornell Medical Center
New York, NY 10021

1. Meade TW, Cooper JA, Peart WS. Plasma renin activity and ischemic heart disease. *N Engl J Med* 1993;329:616-9.
2. Alderman MH, Madhavan S, Ooi WL, Cohen H, Sealey JE, Laragh JH. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. *N Engl J Med* 1991;324:1098-104.
3. Sealey JE, Blumenfeld JD, Bell GM, Pecker MS, Sommers SC, Laragh JH. On the renal basis for essential hypertension: nephron heterogeneity with discordant renin secretion and sodium excretion causing a hypertensive vasoconstriction-volume relationship. *J Hypertens* 1988;6:763-77.
4. Sealey JE. Plasma renin activity and plasma prorenin assays. *Clin Chem* 1991;37:1811-9.
5. Mertens TE. Estimating the effects of misclassification. *Lancet* 1993;342:418-21.

The authors reply:

To the Editor: The comments by Alderman and colleagues are ambivalent, in that they claim that our findings support their conclusions while at the same time they question the laboratory method on which our results were based.

In our analyses we had the advantage of considerably more episodes of myocardial infarction than Alderman et al.,¹ and none of our analyses confirmed an association between plasma renin activity and ischemic heart disease. We drew attention to some findings suggesting that the results of the two studies are not necessarily incompatible, although these came from subgroup analyses to be interpreted only cautiously, as we ourselves pointed out. We referred to the nonsignificant ($P = 0.32$) relation between levels of renin activity and the occurrence of myocardial infarction according to interval between entry and event. There was,

however, a marginally significant trend ($P = 0.04$) for systolic blood pressure. Table 3 of the study by Alderman et al.¹ shows the rate ratio for their high-renin and low-renin groups (accounting for about 11 percent and 31 percent of the person-years of follow-up, respectively). A similar analysis of our data gave the nonsignificant results we referred to. We reiterate, however, that the most appropriate analyses are those based on all available data rather than data from subgroups, and none of these showed relations between plasma renin activity and ischemic heart disease. In other studies, the elevated levels of renin activity expected in patients taking thiazide diuretics are associated with a reduction in the incidence of stroke and ischemic heart disease.^{2,3}

As we also pointed out, our laboratory method establishes the same association between plasma renin activity and a range of characteristics, such as age, sex, ethnic group, and blood pressure, as the assay used by Alderman et al.,¹ so that any differences between the two methods cannot account for the differences between the results of the two studies.

T.W. MEADE, D.M.

J.A. COOPER, M.Sc.

W.S. PEART, M.D.

London EC1M 6BQ,
United Kingdom

Medical College of
St. Bartholomew's Hospital

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WARFARIN AND ASPIRIN AFTER HEART-VALVE REPLACEMENT

To the Editor: In a recent paper (Aug. 19 issue), Turpie et al. report a beneficial effect of adding aspirin to warfarin treatment for heart-valve recipients.¹ We question the interpretation of this study.

The risk of major embolism among patients who received both aspirin and warfarin was 1.6 percent per year, a figure higher than those from the literature for treatment with oral anticoagulants only. Bloomfield et al.² found a 12-year cumulative risk of 8.8 percent, which corresponds to an annual incidence of about 0.8 percent (and not, as stated by Turpie et al., of 2 to 3 percent, which was apparently recalculated from the figures for total embolism). In a meta-analysis combining all literature we found a risk of 1.0 percent per year.³ In our own center, which provides routine care to unselected patients, we found an incidence of major embolism of 0.6 percent per year.⁴

The risk of major bleeding was also higher than expected. The authors reported an incidence rate of major bleeding of 8.5 percent per year in the aspirin group and 6.6 percent per year in the placebo group (both aspirin and placebo were added to warfarin treatment). Recently, we have reported on bleeding complications in our anticoagulation clinic.⁵ Here, in a routine situation, there was a much lower incidence rate of 2.7 percent per year. The figure that Turpie et al. report is exceptionally high, especially when one also considers that their study excluded 8 percent of patients because they had a contraindication to anticoagulants (which would not occur that frequently in a routine situation).

The high incidence of both embolic and bleeding compli-

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T.W. MEADE, D.M.
J.A. COOPER, M.Sc.
W.S. PEART, M.D.
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The high incidence of both embolic and bleeding compli-

cations in this study may not be surprising, however, when the poor anticoagulant control is taken into account. The intensity of anticoagulation was within the target range for only 40 percent of the time. This contrasts sharply with the situation in our center, in which this proportion was 77 percent.⁵

Thus, with well-monitored anticoagulant treatment, it is possible to achieve better results than Turpie et al. did with the addition of aspirin. We would therefore argue that physicians should first achieve the optimal level of anticoagulation, instead of adding aspirin to poorly controlled warfarin treatment, since the number of complications in the latter situation is unacceptably high.

S.C. CANNEGIETER, M.D.
F.J.M. VAN DER MEER, M.D.
E. BRIËT, M.D.

NL-2300 RC Leiden,
the Netherlands

F.R. ROSENDAAL, M.D.
Leiden University Hospital

1. Turpie AGG, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. *N Engl J Med* 1993;329:524-9.
2. Bloomfield P, Wheatley DJ, Prescott RJ, Miller HC. Twelve-year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. *N Engl J Med* 1991;324:573-9.
3. Cannegieter SC, Rosendaal FR, Briët E. Thrombo-embolic and bleeding complications in patients with mechanical heart valve prostheses: review and meta-analysis. *Circulation* (in press).
4. Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJM, Briët E. The optimal intensity of oral anticoagulation therapy in patients with prosthetic heart valves. *Thromb Haemostasis* 1993;69:2363. abstract.
5. van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briët E. Bleeding complications in oral anticoagulant therapy: an analysis of risk factors. *Arch Intern Med* 1993;153:1557-62.

To the Editor: The use of a wide range of values for the international normalized ratio (INR) by Turpie et al. raises two important questions. First, was the benefit or risk of aspirin limited to certain INR ranges? Second, do the data indicate the appropriate level of anticoagulation for valve recipients? These questions might be answerable if the data were presented as incidence rates (number of events per number of patient-years) at different levels of anticoagulation. If this is not feasible, presenting the distribution of events according to the INR range might be helpful.

Since the INRs were below the desired range 49 percent of the time, aspirin may have been beneficial only when a "subtherapeutic" INR posed a high risk of thromboembolism. Alternatively, the increased risk of bleeding may have been limited to patients with INRs greater than 4.5 (which occurred 11 percent of the time). Such information may be useful in selecting candidates for combination therapy. Presenting incidence rates according to anticoagulation level could help resolve the controversy about the intensity of anticoagulation in such patients.

HENRY I. BUSSEY, PHARM.D.
University of Texas
San Antonio, TX 78284-6220 Health Science Center

WILLIAM D. LINN, PHARM.D.
Audie Murphy Veterans Affairs
San Antonio, TX 78284 Medical Center

To the Editor: The benefits of combining oral aspirin and warfarin were well demonstrated in the recent report by Turpie et al. Although the risks were low, gastrointestinal hemorrhage still occurred twice as often in the aspirin group

as in the placebo group. Furthermore, 7 percent of patients considered eligible for this study were excluded because of their inability to take aspirin.

We have recently observed that aspirin can be absorbed through the skin and cause marked and selective suppression of thromboxane biosynthesis.¹ The peak plasma aspirin level at three hours was 0.2 µg per milliliter, considerably lower than levels obtained with a low-dose oral aspirin tablet.²

The gastrointestinal toxicity of aspirin is dose-related, and gastrointestinal ulceration and bleeding probably represent a direct effect on the gastric mucosa. By circumventing the gastrointestinal tract and providing a high degree of platelet selectivity, the use of this route may avoid gastrointestinal bleeding. The advantages of combining warfarin and transdermal aspirin deserve further study.

RUDOLPH M. KEIMOWITZ, M.D.
La Crosse, WI 54601 Gundersen Clinic

DESMOND J. FITZGERALD, F.R.C.P.I.
Dublin, Ireland Center for Cardiovascular Science

1. Keimowitz RM, Pulvernacher G, Mayo G, Fitzgerald DJ. Transdermal modification of platelet function: a dermal aspirin preparation selectively inhibits platelet cyclooxygenase and preserves prostacyclin biosynthesis. *Circulation* 1993;88:556-61.
2. Clarke RJ, Mayo G, Price P, Fitzgerald GA. Suppression of thromboxane A₂ but not of systemic prostacyclin by controlled-release aspirin. *N Engl J Med* 1991;325:1137-41.

The authors reply:

To the Editor: Cannegieter and colleagues state that the rates of major systemic embolism and hemorrhage in our study were higher than reported elsewhere. We disagree. Our rate of major systemic embolism (1.6 percent per patient-year) is well within the range (0.0 to 4.6 percent per patient-year) reported for embolic events in patients with mechanical valves who are treated with anticoagulants.¹

It is difficult to compare bleeding rates across studies, because the criteria used to define major bleeding often differ and the published rates are highly variable. Our rate for major bleeding — 6.6 percent per year in the patients treated with anticoagulants alone — is consistent with the rates reported in a recent review of long-term anticoagulant therapy (e.g., 1.6 and 9.3 percent).² In addition, it is unlikely that major bleeding in our study can be attributed to poor anticoagulant control, since only 11 percent of the patients had INRs above the target therapeutic range. Furthermore, the mean of the INRs immediately before the episodes of major bleeding was 3.4, as compared with an overall mean INR of 3.1.

In our study, the efficacy of adding aspirin to warfarin was dramatic, with a 65 percent reduction in the risk of major systemic embolism; such an effect is unlikely to be achieved with better anticoagulant control.

Some of the comments by Bussey and Linn are addressed above. In addition, it is worth noting that the mean of the INRs immediately before the occurrence of major systemic embolism was 2.8. The appropriate level of anticoagulation for valve recipients cannot be determined from our study. We are currently performing a trial in similar patients, all receiving 100 mg of aspirin daily, who have been randomly assigned to one of two intensities of anticoagulation (target INR, 2.0 to 2.5 or 3.0 to 3.5) to address this question. We agree with Keimowitz and