would provide valuable information on the potential effect of coronary angioplasty on the progression and/or regression of coronary artery disease in dilated and nondilated arteries.

Jacques Bonnet, MD
Daniel Benchimol, MD
Jean François Dartigues, MD, PhD
Pessac, France
18 February 1996

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Bias in Case-Control Studies of Calcium Antagonists

We agree with Kaplan's argument[1] that patients prescribed calcium antagonists in a recent case-control study by Psaty and colleagues[2] had a higher baseline risk for acute myocardial infarction than patients prescribed β blockers or diuretics. Controlling for differences in clinical characteristics that influence choice of drug and risk of acute myocardial infarction is critical to assuring the validity of risk estimates in any study, not just case-control studies.

Kaplan overemphasizes the need for comparability between cases and controls. Case-control differences arise naturally as a result of the higher incidence of disease in people who possess predisposing characteristics. Enforced comparability, through matching of cases and controls, is an excellent technique for rectifying possible biases, as are methods of statistical adjustment. Both matching and adjustment require that the prognostic information that was available to prescribing physicians be incorporated into the study. The real question is whether the quality of information from the medical record in the study by Psaty and colleagues was sufficiently high to control confounding. Analogous considerations apply to prospective cohort studies.

Dr. Kaplan defers a decision on the safety of calcium channel blockers until the results of randomized controlled trials are available. Unfortunately, public apprehension about calcium channel blockers[3] may affect the success of patient recruitment and retention in trials such as The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT).[4] Rather than dismiss data from observational studies as "flawed" because of potential bias, it seems preferable to explore the bias empirically and account for it in the interpretation of study results.

Alexander M. Walker, MD
Eric S. Johnson, MD
Newton Lower Falls, Massachusetts
20 February 1996

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Long QT Syndrome Associated With Syndactyly in a Female

We read with great interest the report by Marks et al[1] of 2 female patients with the new association of syndactyly with the long QT syndrome. The same authors[2] had described similar cases originally, but only in males. Their patients were also noted to have intermittent 2:1 atrioventricular block as well as congenital cardiac abnormalities. We wish to draw attention to the fact that our observation of syndactyly of the hands and feet associated with the long QT syndrome in a black female infant had already been published in 1992.[3] This child also had a patent ductus arteriosus, which was the cardiac lesion noted in the 3 males and in 1 of the 2 females documented by Marks et al.[1,2] There was no evidence of 2:1 atrioventricular block in the electrocardiogram and Holter recordings in our patient. However, she did have episodes of sinus bradycardia (50 to 55 beats/min). The final outcome of our patient is unknown, as she was lost to follow-up.

Solomon E. Levin, MD
Johannesburg, Republic of South Africa
3 April 1996

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Considerations About Plasma Fibrinogen Concentration and the Cardiovascular Risk: Combined Evidence from the GRIPS and ECAT Studies

According to findings from the recently published European Concerted Action on Thrombosis and disabilities (ECAT) study[1] fibrinogen is strongly and independently associated with the risk of myocardial infarction and sudden death, particularly in patients with preexisting coronary artery disease (CAD). In this group of patients, the relationship of plasma fibrinogen levels to the incidence of acute coronary syndrome was stronger than that of low-density lipoprotein cholesterol, which seems to be in contrast to the findings of other prospective stud-

ies.[2,3] However, these studies[2,3] were performed on subjects without clinically overt cardiovascular diseases at study entry. This may indicate that fibrinogen is effective in promoting mechanisms for acute coronary occlusions on the basis of otherwise induced preexisting coronary sclerosis rather than on the chronic process of coronary atherosclerosis itself.

We tried to support this hypothesis by considering some recent findings from the Goettingen Risk Incidence and Prevalence Study (GRIPS),[3] a prospective cohort study of 5,790 men aged 40 to 59.9 years without cardiovascular diseases at baseline.

Based on 5- and 10-year follow-up investigations (response rate 97.4%), the relation between fibrinogen and the incidence of acute coronary events (fatal and nonfatal myocardial infarction as well as sudden coronary death; n = 299) was characterized by the following findings: (1) The annual incidence of acute coronary events was markedly increased from 14/year in the earlier part of the follow-up period to 27/year in the latter half of the follow-up period for subjects from the lower 4 quintiles of the fibrinogen distribution (<432 mg/dl). In contrast, for subjects from the fifth quintile, it decreased from 10 events/year during the first to 9 events/year during the later 5 years of the observation period. Accordingly, the event-free survival curves (Figure 1) in subjects with normal and elevated fibrinogen levels are nearly the same during the second half of the follow-up period. (2) The adjusted odds ratio per each increase of 1 SD in the fibrinogen level was 1.40 (95% confidence interval [CI] 1.17 to 1.69) during the first 5 years in subjects without CAD at baseline (GRIPS). A very similar odds ratio of 1.30 (95% CI 1.07 to 1.61) was found in patients with preexisting CAD studied in ECAT after the 2-year follow-up of this study. In the GRIPS cohort, however, the independent association between fibrinogen and the incidence of acute coronary events was lost during the second half of follow-up (years 6 to 10) (odds ratio 1.03; 95% CI 0.87 to 1.21). (3) No significant association between fibrinogen and the development of chronic CAD without acute myocardial infarction was found in the GRIPS study population.

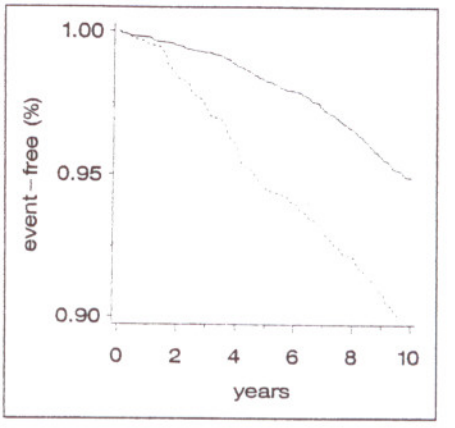

FIGURE 1. GRIPS 10-year follow-up: Event-free survival curves for fatal or nonfatal myocardial infarction or sudden coronary death (acute coronary events) in the fifth (*broken line*) or first to fourth (*solid line*) quintile of the plasma fibrinogen distribution related to the duration of follow-up. *Solid line*, fibrinogen <432 mg/dl; *broken line*, fibrinogen >432 mg/dl.

In accordance with recently published pathophysiologic findings,[4] these epidemiologic and clinical data from ECAT[1] and GRIPS[3] give support to the hypothesis that fibrinogen is a particularly important risk factor for acute coronary events in patients with overt CAD or asymptomatic but already existing coronary lesions. This may infer that inflammatory processes are involved in atherogenesis, as was also suggested by a significantly increased risk of acute coronary events at higher serum concentrations of C-reactive protein in the ECAT study.[1] Thus, plasma fibrinogen concentrations merit particular attention in standard diagnostic and therapeutic strategies for secondary prevention of myocardial infarction to come.

Peter Cremer, MD
Dorothea Nagel, PhD
Dietrich Seidel, MD
Munich, Germany

Juergen C.W. van de Loo, MD
Jochen Kienast, MD
Muenster, Germany

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Avoiding Unnecessary Radionuclide Exercise Stress Testing

The recent article by Stein et al,[1] calling attention to the high proportion of "not-indicated" radionuclide exercise stress tests (RnEST), provided a timely illustration of the overuse of expensive medical technology. Their suggestion, however, that patients referred for RnEST by non-cardiologists first undergo cardiology consultation, is by no means the most cost-effective strategy for reducing the overuse of the procedure. Screening of *all* RnEST requests by a dedicated cardiologist charged with the task of making sure that approved requests conform to an established practice guideline would reduce the overall proportion of not-indicated tests from the 52% found by Stein et al to 0%. Because 36% of the cardiologists' referrals were not-indicated, the strategy of prior cardiology consultation would reduce the proportion only to 36%, and the cost of cardiology consultation is far greater than the cost of the expert screening of a request form according to a guideline.