Methylenetetrahydrofolate Reductase Mutation and Coronary Artery Disease

To the Editor:

The article by Kluijtmans and colleagues \(^1\) (Circulation, Oct 21, 1997) adds to the growing literature on the relationship between the common thermolabile variant of methylenetetrahydrofolate reductase (MTHFR) and risk of vascular disease. In an angiographically assessed cohort of subjects with coronary artery disease (CAD) participating in a statin regression trial (REGRESS), significantly increased homocysteine concentrations were found in subjects homozygous (+/+) or heterozygous (+/-) for the thermolabile variant compared with those carrying only the normal variant (-/-). Median levels were 2.8 and 0.8 \(\mu\)mol/L higher in the +/+ and +/− subjects, respectively. Compared with population-based controls, there was trend toward higher risk of CAD in subjects carrying the thermolabile variant, but this did not reach significance (OR for +/+ versus -/-: 1.21 [0.87 to 1.68]; +/− versus -/-: 1.14 [0.94 to 1.38]). However, when the results were combined with those of 6 other studies, including our own,\(^2\) in a meta-analysis, there was a significant increase in relative risk in subjects with the +/+ genotype (OR, 1.22; 95% CI, 1.10 to 1.47).

The data of Kluijtmans et al in a large cohort of well-characterized CAD patients are welcome. However, I am concerned by their meta-analysis. They have pooled together data from studies that have examined different phenotypes. For example, in our study,\(^2\) we recruited subjects with myocardial disease (CAD) participating in a statin regression trial (REGRESS), significantly increased homocysteine concentrations were found in subjects homozygous (+/+), or heterozygous (+/-) for the thermolabile variant compared with those carrying only the normal variant (-/-). Median levels were 2.8 and 0.8 \(\mu\)mol/L higher in the +/+ and +/− subjects, respectively. Compared with population-based controls, there was trend toward higher risk of CAD in subjects carrying the thermolabile variant, but this did not reach significance (OR for +/+ versus -/-: 1.21 [0.87 to 1.68]; +/− versus -/-: 1.14 [0.94 to 1.38]). However, when the results were combined with those of 6 other studies, including our own,\(^2\) in a meta-analysis, there was a significant increase in relative risk in subjects with the +/+ genotype (OR, 1.22; 95% CI, 1.10 to 1.47).

The data of Kluijtmans et al in a large cohort of well-characterized CAD patients are welcome. However, I am concerned by their meta-analysis. They have pooled together data from studies that have examined different phenotypes. For example, in our study,\(^2\) we recruited subjects with myocardial infarction. Although there is, of course, a relationship between angiographic CAD and myocardial infarction, the 2 are not synonymous, and each has distinct determinants. This is likely to extend to genetic causes. Indeed, analysis of different phenotypes may explain at least some of the discrepancies that have been reported not only in relation to the thermolabile MTHFR mutation but also to other genetic factors. Meta-analysis, even when restricted to a single phenotype, has several well-recognized limitations.\(^3\) When added to by heterogeneity in the phenotype, its validity is highly questionable. The meta-analysis carried out by Kluijtmans et al adds little to their primary data. Although positive, it should not be interpreted as strong evidence in support of a role for the MTHFR thermolabile mutation as a determinant of coronary risk. As discussed by Wilcken et al\(^4\) in a detailed letter in the same issue of Circulation, the jury is still out on its relevance.

N.J. Samani, MD, FRCP
Department of Cardiology
University of Leicester
Leicester, UK


Response

Since the characterization of the common 677C→T variant in the methylenetetrahydrofolate reductase (MTHFR) gene, many efforts have been made to study its contribution to hyperhomocysteinemia and to the risk of various forms of vascular disease.

In our study published in the October 21, 1997, issue of Circulation,\(^1\) we analyzed the frequency of this mutation in angiographically proven coronary artery disease (CAD) patients selected from the Dutch Regression Growth Evaluation Statin Study (REGRESS) and in a meta-analysis in which we combined 8 studies to estimate the relative risk of the homozygous (+/+), heterozygous (+/-), and normal (-/-) genotype in CAD. In REGRESS, a study that included patients with clinical evidence of CAD severe enough to be a reason for invasive analysis, we were able to demonstrate that homoygotes and heterozygotes for this 677C→T variant had significantly elevated homocysteine concentrations. Furthermore, the relative risk for this MTHFR variant equaled the risk that could be calculated on the basis of differences in homocysteine concentrations between MTHFR genotypes. Thus, the thermolabile MTHFR variant most likely exerts its proarteriosclerotic effects via an elevation of plasma homocysteine. In the meta-analysis, patients with either CAD or myocardial infarction were included. As correctly indicated by Dr Samani, CAD and myocardial infarction are not identical and may have their distinct determinants, but both phenotypes are strongly correlated. In almost every patient, myocardial infarction originates from a progressively extended coronary arteriosclerosis. Because mild hyperhomocysteinemia has been identified as a risk factor for both CAD\(^2,3\) and myocardial infarction,\(^4,5\) the combination of both phenotypes to study the effects of this MTHFR variant in the risk of coronary heart disease seems to be justified.

L.J. Kluijtmans, MSc
H.J. Blom, PhD
Department of Pediatrics
G.H.J. Boers, MD, PhD
Department of Internal Medicine
F. Willems, MD
Department of Cardiology
University Hospital Nijmegen
Nijmegen, Netherlands


Response
Dr Samani makes relevant comments about the article by Kluijtmans and colleagues. He points out that it remains unresolved whether or not mild elevation of circulating homocysteine, which is frequently associated with the presence of vascular disease, contributes independently to cardiovascular risk or, as discussed in our previous letter, a fellow traveler.

In their carefully studied patients, Kluijtmans et al show that those homozygous and heterozygous for the 677C→T mutation in the MTHFR gene have increases in median homocysteine levels; but the increases are indeed small (2.8 and 0.8 μmol/L, respectively). And, for the reasons set out in Dr Samani’s letter, their meta-analysis, which includes a limited number of studies, does not provide convincing evidence that homocysteoygosity for the MTHFR mutation increases coronary risk.

The somewhat lower MTHFR (+/+ ) prevalence in the Netherlands compared with that of other white populations is also perhaps worth noting. Kluijtmans et al comment that this may vary between different populations, but in other white populations in which substantial numbers of subjects have been assessed, the population prevalence has been about 11.5%. Thus, the 9.5% in patients and 8.5% in controls in the Dutch study may reflect a lower prevalence of the genotype in Holland.

D.E.L. Wilcken
The University of New South Wales
Department of Cardiovascular Medicine
The Prince of Wales Hospital
Sydney, New South Wales, Australia


Safety of Calcium Channel Blockers in Cardiovascular Disease

To the Editor:
I read with interest the report by Michels et al and the accompanying editorial and wondered about reversed bias in publication when the research is newsworthy. As is the case with many observational studies, the quality of data is diminished by lack of ascertainment for drug exposure and confounding bias.

On the basis of the results of Table 3A, the authors conclude that there is an increased risk of myocardial infarction (MI) among those exposed to calcium channel blockers. However, covariate adjustment does not appear to include adjustment for previous MI, even though Table 2 clearly demonstrates an increased prevalence of previous MI among these subjects. Furthermore, casual inspection of Table 3A suggests a similar increase in risk of MI among those exposed to β-blockers, with a statistically significant increase in those taking diuretics and β-blockers. The group with the highest risk consists of those subjects taking a combination of diuretics, β-blockers, and calcium channel blockers. Not surprisingly, when the history of previous cardiovascular disease is removed (Table 3B), no association with increased risk of MI is found. The observation that the risk of calcium channel blocker therapy is mostly imparted from the groups of subjects treated with combination therapy with diuretics and β-blockers (Tables 3A and 3B) highlights the complexity and unreliability of these analyses.

The only conclusion that can be reliably reached is that calcium channel blockers are prescribed more frequently in sicker individuals. Because of the strength of this association, reliable adjustment to remove confounding bias cannot be completed. Given the lack of knowledge as to which of the calcium channel blockers was taken, if any, the results of this large observational study are rendered nongeneralizable to the current standard of practice.

Anatoly Langer, MD
Director, Canadian Heart Research Center
Division of Cardiology
St. Michael’s Hospital
Toronto, Ontario Canada


Response
We agree with Dr Langer—and, in fact, began our discussion section with the statement—that in our cohort, a greater proportion of women prescribed calcium channel blockers had risk factors for cardiovascular disease. Furthermore, we also stated that residual confounding by indication is likely to remain, and results from observational studies on these issues have to be interpreted with considerable caution. Specifically, it remains unclear whether any observed increased risks are real, are due to chance, or represent residual confounding by indication.

We also wish to clarify our analytical strategy, which may have been unclear due to a typographical error in that in our cohort, a greater proportion of women prescribed calcium channel blockers had risk factors for cardiovascular disease. Furthermore, we also stated that residual confounding by indication is likely to remain, and results from observational studies on these issues have to be interpreted with considerable caution. Specifically, it remains unclear whether any observed increased risks are real, are due to chance, or represent residual confounding by indication.

We also wish to clarify our analytical strategy, which may have been unclear due to a typographical error that occurred in typesetting our article: in Tables 1 and 3A, the symbols “↑” and “↑” were erroneously exchanged. When read correctly, the footnote for Table 3A indicates that 296 women with prior myocardial infarction (MI) were excluded from the analysis for the end point of MI. We only presented results on first events. The 296 women excluded from the analysis of MI had been confirmed by medical records to have suffered a prior MI. As described in the Methods section, women who reported a prior MI but for whom this diagnosis could not be confirmed were not excluded from the analysis presented in Table 3A, but their self-report of MI was adjusted for in the analysis. The analysis presented in Table 3B excluded all women with self-reported MI and, additionally, all women who reported stoke, CABG/PTCA, or angina pectoris.

Karin B. Michels, ScD
Bernard A. Rosner, PhD
JoAnn E. Manson, MD, DrPH
Meir J. Stampfer, MD, DrPH
Alexander M. Walker, MD, DrPH
Walter C. Willett, MD, DrPH
Charles H. Hennekens, MD, DrPH
Harvard University
Boston, Mass

Pravastatin and Coronary Heart Disease

To the Editor:
In the April 21, 1998, edition of Circulation, the WOSCOPS study group (West of Scotland Coronary Prevention Study) report that the benefit achieved by administration of pravastatin in WOSCOPS was essentially independent of the percentage by which LDL cholesterol was lowered by treatment and greater than that which could be attributed to lowering of LDL cholesterol alone.
With unexpected findings of this nature, it is important to exclude bias, especially when the results are derived from post hoc subgroup analysis. In the case at hand, a potential source of bias lies in the selection procedure. WOSCOPS included only men with an LDL cholesterol level of 174 to 232 mg/dL. However, individuals with a history of severe illness, ECG abnormalities or arrhythmias, or severe arterial hypertension, some of which are statistically associated with raised LDL cholesterol levels, were excluded.2 This may have led to a gradient of non–LDL-related risk of coronary heart disease (CHD), ie, men at the high end of the LDL distribution may have had fewer non-LDL risk factors than men at the low end. This might explain why event rates with pravastatin treatment at a given LDL concentration were less than those with placebo at the same LDL concentration: the treated men in WOSCOPS might have been otherwise healthier than men with an identical LDL cholesterol level at baseline. Such a bias would also explain the lack of correlation between extent of LDL cholesterol lowering and reduction in event rate. This conjecture is supported by the finding that event rates in the upper and lower parts of the LDL distribution in the placebo group of WOSCOPS were almost identical (8.3 events per 100 in 5 years at LDL cholesterol ≥189 mg/dL versus 7.6 events per 100 in 5 years at LDL cholesterol <189 mg/dL).2

Most epidemiological and intervention studies point to a semilogarithmic relationship between CHD risk and LDL cholesterol levels, including those obtained with statin treatment.3 This means that the benefit of cholesterol reduction diminishes at low LDL levels, but it does not mean that there is no relationship between on-treatment LDL and CHD risk. In our view, dissemination of the message that minimal lowering of LDL cholesterol (eg, by 12%) by pravastatin is sufficient for primary prevention of CHD would be potentially hazardous and even ethically problematical. The results of this WOSCOPS analysis should be seen as a preliminary hypothesis-generating exercise and not as a guide for treatment decisions.

Gerd Assmann, MD, FRCP
Helmut Schulte, PhD
Paul Cullen, MD, FRCP
Institut für Arterioskleroseforschung
an der Universität Münster
Münster, Germany


Response

We thank Drs Assmann, Schulte, and Cullen for their comments and respond as follows.

It is suggested that selection bias may have confounded our analysis. Specifically, the question is asked whether subjects at the high end of the LDL distribution had fewer non-LDL risk factors. When the subjects were divided into those with LDL >189 or <189 mg/dL at baseline, we found a virtually identical distribution of nonlipid risk factors; eg, age was 55.2 versus 55.2 years, diastolic blood pressure was 84 versus 84 mm Hg, incidence of smoking was 46% versus 42%, and incidence of hypertension was 16% versus 16%, respectively. Minor manifestations of coronary heart disease (CHD) at baseline were, if anything, more prevalent in the group with LDL >189 mg/dL; nitrate use/angina was present in 6.8% versus 4.7% and ECG abnormalities in 8.9% versus 7.3% of the high and low LDL groups, respectively. When baseline LDL was divided into quintiles, an association with CHD risk (as shown in Figure 1) was observed. Thus, it is clear that the subjects with higher LDL levels at baseline were not healthier than those with lower levels.

Furthermore, as stated in Methods, adjustment for all baseline risk factors was made in the multivariate models used to examine the difference in risk for subjects taking placebo versus pravastatin for a given on-treatment LDL level (in fact, no substantive differences were present between the 2 groups).

With respect to the relationship between LDL change and risk reduction, we believe that attention should be drawn to the marked attenuation in absolute risk reduction that accompanies increasing degrees of LDL lowering. We did not say that “minimal lowering of LDL is sufficient for primary prevention.” Rather, we suggested that the additional clinical benefit obtained by lowering LDL beyond 20% to 25% may be small. We were very careful also to point out that “the results are derived from post hoc analysis and, therefore, must be viewed cautiously.” It was of great interest to learn that the observations of the CARE investigators closely paralleled our own findings with pravastatin.

Because clinical benefit is now believed to come largely from plaque stabilization rather than regression, and there is increasing recognition that atherosclerosis is not fully reversible, the result of an intervention cannot be predicted accurately by recourse to epidemiological data alone. The abundance of clinical event data now available for a number of statins can be used to address the questions raised by epidemiology.

Chris J. Packard, DSc
James Shepherd, FRCP
Department of Pathological Biochemistry
Stuart M. Cobbe, FRCP
Peter W. Macfarlane, FRSE
A. Ross Lorimer, FRCP
Department of Medical Cardiology
James H. McKillop, FRCP
University Department of Medicine
Glasgow Royal Infirmary
Glasgow, Scotland

Ian Ford, PhD
John Norrie, MSc
Robertson Center for Biostatistics
University of Glasgow
Glasgow, Scotland

Christopher G. Isles, FRCP
Department of Medicine
Dumfries and Galloway Royal Infirmary
Dumfries, Scotland


Extended Mortality Benefit of Early Postinfarction Reperfusion

To the Editor:

Ross et al1 (April 28, 1998) report that in the GUSTO-1 angiographic substudy, successful reperfusion produced mortality benefits that were amplified beyond the first 30 days. This extended mortality benefit has been reported previously in the Grampian Region Early Anistreplase Trial (GREAT).2 In this randomized, double-blind, controlled clinical trial, 311 patients with suspected acute myocardial infarction either received anistreplase prehospital
at 105 minutes (median) after symptom onset or in hospital at 240 minutes. At 30 days, there was a trend in favor of prehospital thrombolysis (≈6 lives saved per 100), but this did not reach statistical significance (log rank=3.4, \( P<0.10 \)). Between 30 days and 2 years, however, there was a significant additional survival benefit of ≈10 lives per 100 (log rank=6.3, \( P<0.025 \)).

An “open artery” is the common pathway for several different mechanisms of benefit, with significant myocardial salvage and recovery of function only within the first 2 hours. By 4 to 6 hours, myocardial necrosis is irreversible, but reperfusion of the infarct-related artery is still beneficial because it confers electrical stability on the infarct and minimizes infarct expansion. Myocardial salvage would be expected to give extended benefit, whereas the other mechanisms would not.

GUSTO-I had a short median time to treatment of 2.8 hours, so many patients would have benefited from myocardial salvage. The extended mortality benefit described by Ross et al\(^1\) is more closely related to left ventricular ejection fraction than to TIMI 3 flow, suggesting that it results from myocardial salvage rather than patency of the infarct-related artery itself. In GREAT, 64\% of patients in the prehospital group were treated within 2 hours compared with <1\% in the hospital group. The extended mortality benefit in this trial is also likely to be a consequence of myocardial salvage.

In ISIS-2, in which there was no significant additional mortality benefit from streptokinase (or aspirin) after 35 days, only 15\% of patients were randomized within 2 hours, the median time of randomization was 5 hours, and there was an additional delay between randomization and treatment. GUSTO-I and GREAT therefore differ from ISIS-2 not only in their use of thrombolytic agents that have higher and therefore faster patency rates than streptokinase, but also in having a much higher proportion of patients treated within 2 hours. The extended benefit demonstrated in both these trials is very likely to be due to myocardial salvage, which would not have been the mechanism of benefit for most patients in ISIS-2 nor, indeed, in other hospital trials in which randomization was >4 hours after onset.

John Rawles, FRCP, FRCPE
Medicines Assessment Research Unit
University of Aberdeen
Foresterhill, Aberdeen, Scotland


Response

We agree with Dr Rawles that myocardial salvage and consequent preservation of ventricular function is likely the dominant mechanism underlying the long-term augmented survival benefits we reported. However, we wish to point out that when evaluated by multivariate analysis that tested both time to treatment and convalescent left ventricular function, the achievement of early TIMI grade 3 flow in the infarct-related artery was shown to be an independent predictor of increasing survival benefit between 30 days and 2 years after infarction.\(^1\)

Conor F. Lundergan, MD
Allan M. Ross, MD
The Cardiovascular Research Institute
The George Washington University
Washington, DC

Methylenetetrahydrofolate Reductase Mutation and Coronary Artery Disease
N. J. Samani

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