Hypercholesterolemia, Abnormal Coronary Vasomotion, and Calcium Antagonists

To the Editor:

I was fascinated by the recent article by Kaufmann et al on the reversal by calcium antagonists of the abnormal coronary vasomotion associated with hypercholesterolemia. Teleologically, this observation is quite logical, and it also explains some of the clinical observations made about coronary artery disease. Let me explain.

Studies in experimental animals have shown that the entry of cholesterol into the endothelial lining of the aorta is dependent on the concentration of cholesterol in the perfusing solution, the pulse pressure, and the number of pulses per minute. These very early abnormalities are noted at the ultrastructural level well before there is any grossly visible modification of the vessel wall (such as the fatty streak). Because the initial injury that starts the long process of formation of the atherosclerotic plaque is very dependent on cholesterol entry into the endothelial cells, it is teleologically reasonable that the greater the level of serum cholesterol, the more the normal increase in pulse pressure with exercise should be constrained.

Also, it is now well accepted that the higher the serum cholesterol level, the greater the development of soft plaques that are more easily ruptured or fissured. Thus, it makes sense that with the higher serum cholesterol, the greater decrease in pulse pressure with exercise would in part protect against such sudden acute events in hypercholesterolemic patients.

There has been a great controversy brewing with regard to the effect of calcium channel blockers on the progression of coronary artery disease. This has especially been noted in the long-term treatment of hypertensives. Some of this has been attributed to the rebound vasoconstriction that occurs with the shorter-acting calcium channel blockers. However, the observation by Kaufmann et al that calcium channel blockers will dilate the coronary arteries with exercise irrespective of the level of serum cholesterol may be another explanation for the greater progression of coronary artery disease in patients on long-term therapy with calcium channel blockers. Thus, this observation by Kaufmann et al would predict that even long-acting calcium channel blockers would have an adverse effect on the development and progression of coronary artery disease in hypertensives, although not as great as the effect of short-acting calcium channel blockers.

It may be that calcium channel blockers should not be used in hypertensives who are free of coronary artery disease unless their cholesterol levels are first lowered to the levels suggested by the American Heart Association. Also, calcium channel blockers should probably be used in patients with well-documented coronary artery disease only after their LDL cholesterol level has been decreased to below 100 mm Hg.

Response

We appreciate Dr David’s interest in our article and his thoughts on clinical observations and the possible effects of calcium channel blockers on the progression of coronary artery disease, with special emphasis on hypertensive patients. However, for the following reasons we do not believe that our results can entirely be extrapolated to Dr David’s conclusions. First, we found beneficial effects of calcium channel blockers on the abnormal coronary vasomotion in patients with hypercholesterolemia in our acute intervention study, but we have not studied long-term effects, precluding any statement in this regard. However, we would expect the pulse pressure to decrease after calcium channel blocker-induced coronary dilation, and according to Dr David, this is thought to protect against sudden acute events rather than being unfavorable. Second, we did not address the issue of the effect of calcium channel blockers on progression or regression of coronary lesions or on morbidity and mortality. Third, hypertensive patients were excluded from the study because hypertension has been shown to be an important determinant of coronary vasomotion, as we stressed in the Methods section. However, we previously reported on the beneficial effects of calcium channel blockers in patients with hypertension, challenging Dr David’s conclusion about adverse effects in this important group of patients.

In summary, we were very cautious to restrict our statements on conclusions based on findings of the study, although we appreciate that many of our findings might stimulate further thoughts and personal interpretation.

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Antibiotic Prophylaxis and Treatment of Cardiovascular Disease

To the Editor:

A recent article by Pasceri et al suggested a significantly higher prevalence of Helicobacter pylori infections in patients with ischemic heart disease compared with matched controls. Two editorials in the same issue of Circulation critically evaluated existing knowledge regarding the association between chronic inflammation and atherosclerosis and the potential use of antibiotic therapy. Although there appears to be increasing evidence that low-grade

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inflammation induced by prior exposure to infective agents such as *Chlamydia pneumoniae, cytomegalovirus, or H pylori* might play a role in the development of atherosclerotic lesions, there is controversy regarding a proven pharmacological rationale for antibiotic therapy for atherosclerotic vascular disease. Pasceri et al conclude that eradication of *H pylori* may play a future role in the prevention of ischemic heart disease.

In our opinion, macrolide antibiotics have many properties that should be considered in the design and evaluation of clinical trials in ischemic heart disease. First, macrolides appear to exert potent anti-inflammatory effects. In the lung, erythromycin seems to ameliorate neutrophil-induced endothelial cell injury by affecting not only neutrophil functions but also the release of nitric oxide from endothelial cells through the action of cAMP-dependent protein kinase. Erythromycin has also been reported to modulate bleomycin-induced pulmonary fibrosis, possibly through suppression of tumor necrosis factor-α (TNF-α) and platelet-derived growth factor (PDGF), while reducing accumulation of inflammatory cells in the lung.* In the treatment of chronic sinusitis, macrolides may affect interactions between antigen-presenting cells such as macrophages and CD4-positive T lymphocytes.* Treatment of human pulmonary artery endothelial cells with erythromycin also appears to attenuate endothelial cell injury induced by activated neutrophils, partially via inhibition of free radicals/superoxide.*

These potent anti-inflammatory effects might contribute to a beneficial effect of macrolide therapy in ischemic heart disease*–*10 independently of a complete eradication of infective organisms from atherosclerotic lesions. In the ROXIS pilot study,*9 patients with unstable angina or non–Q-wave myocardial infarction were randomized to treatment with roxithromycin independently of *C pneumoniae IgG baseline titers. A significant reduction in primary clinical end points was seen after 1 month in the roxithromycin group. The authors suggested that anti-inflammatory action of roxithromycin may have contributed to plaque stabilization. Future trials should not neglect the anti-inflammatory actions of macrolides as urgently needed scientific studies are initiated.

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Response

We appreciate the comment of Zellner and Chou about the possible therapeutic implications of our study. Several recent studies have shown an association between ischemic heart disease and various chronic infections, including *Chlamydia pneumoniae, cytomegalovirus, and Helicobacter pylori.* Although these evidences come merely from case-control studies and may be also due to several confounding factors, we found that the association between *H pylori* infection and ischemic heart disease was due only to a more virulent strain of *Helicobacter,* thus supporting the hypothesis that the association is secondary to the chronic inflammatory response induced by this strain.*2 Whether appropriate drug treatment against these agents may be effective in primary or secondary prevention of ischemic heart disease is still unknown. Two recent small, secondary prevention trials have suggested a beneficial effect of short-term macrolide antibiotic treatment (designed as an anti-*Chlamydia* treatment) in patients with ischemic heart disease.*3,4

As outlined by Zellner and Chou, macrolides, in particular roxithromycin, also have important immunomodulatory effects.*2 Because there is consistent evidence that inflammation plays an important role both in acute coronary syndromes and in the chronic evolution of atherosclerosis, the immunomodulatory effects of macrolides should be taken into account in interpreting the results of clinical trials. Yet, although long-term treatment with macrolides has been associated consistently with immunosuppression, short-term treatment, such as that used in one of the trials,*3 may actually enhance immunologic and inflammatory responses in ex vivo experiments.*5 Furthermore, it is difficult to distinguish between the anti-inflammatory and antibacterial effects of macrolides because there is no strong relationship between serum antibodies and the actual presence of *C pneumoniae.* Conversely, the presence of specific serum antibodies is usually associated with gastric infection by *H pylori.* Because the incidence of new infection after eradication is negligible, a simple 1- to 2-week treatment might yield effects even after many years, and subjects might be chosen according to the presence of the germ. Thus, studies on eradication of *H pylori* could easily distinguish the antibacterial effect from other possible effects of the treatment (anti-inflammatory but also antioxidant or antiithrombotic).

It is worth noting that we did not find any specific association between *H pylori* infection and acute coronary syndromes or severity and number of coronary lesions.*2 Because *H pylori* infection is long lasting (often lifelong) and is usually acquired during childhood, it might have a more important role in the early stages of atherosclerosis than in its late complications. Finally, *H pylori* infection (as well as *Chlamydia* or cytomegalovirus infections) is quite prevalent among individuals without ischemic heart disease and absent in many of those with ischemic heart disease. Therefore, it appears essential to establish the specific mechanisms that confer individual vulnerability or protection toward ischemic heart disease before large clinical trials are required.


Estimation of Risk Reduction

To the Editor:

The recent editorial by Greenland and colleagues highlights the utility of cardiac risk prediction algorithms and points to several important advantages and disadvantages of existing risk equations based on the Framingham Heart Study. Although the excellent observational data obtained from Framingham may be useful for absolute risk estimation, it may not be the best source of information to estimate risk reduction. We propose that better models for estimating the benefits of an intervention can be derived from the vast pool of data found in recently published interventional trials.

These studies have demonstrated both the safety and efficacy of HMG-CoA reductase inhibitors in tens of thousands of subjects followed up for years and include all relevant risk factor profiles. In these studies, the risk factor distributions were expanded by design to enhance their generalizability. A key feature of these large trials is that they provide reasonable numbers of clinically relevant events so that the cardioprotective effect of the therapeutic intervention can be accurately estimated.

This last issue highlights a limitation in the estimation of risk reduction from observational cohort data. Existing models assume that the risk associated with a population-based level of some risk factor (eg, LDL cholesterol) is the same as the risk in an individual who achieves that level via therapy. This assumption may be incorrect. For instance, application of the Framingham equations to estimate risk reduction due to LDL change in the WOSCOPS (West of Scotland Coronary Prevention Study) population underestimates the observed risk reduction due to statin therapy.

This study and a related one also demonstrated that baseline risk in WOSCOPS placebo subjects was comparable to Framingham-predicted risk. This suggests that prediction models based on interventional trials can be used both for estimation of baseline risk and for estimation of risk reduction due to therapy. Risk equations from the large clinical trials can represent a significant advance in determining the risks and benefits of treatment.

Unexplained Acronyms

To the Editor:

In the excellent editorial on low-molecular-weight heparins by Antman and Handin, the authors had a boxed glossary of selected abbreviations and acronyms at the beginning of their article. But, for reasons unfathomable to me, the list did not contain any of the acronyms of trials mentioned in the text, eg, FRISC, FRIC, ESSENCE, TIMI, ENTICES, ATLAST, and HART. Similarly, in another article in the same issue by the French investigators of the ESSENCE trial, no explanation of the acronym ESSENCE was given either.

For those readers who are not acronymophilic and might feel very frustrated by all these unexplained acronyms, I wish to come to their aid:

FRISC=FRagmin during InStability in Coronary artery disease
FRIC=FRagmin In unstable Coronary artery disease
ESSENCE=Efficacy Safety Subcutaneous Enoxaparin in Non–Q-wave Coronary Events study
TIMI=Thrombolysis In Myocardial Infarction
ENTICES=ENoxaparin and Ticlopidine after Elective Stenting
ATLAST=Antiplatelet Therapy versus Lovenox plus Antiplatelet therapy for patients with increased risk of Stent Thrombosis, or Aspirin/Ticlopidine versus Low molecular weight heparin/Aspirin/ticlopidine Stent Trial
HART II=Heparin And Refperfusion Therapies

All of the above definitions could be found in the table of acronyms of clinical trials in cardiology that was published in 1996 and has been updated in 1998. Once again, I wish to make a Plea to Let Each Acronym be Spelled out Every time (PLEASE).
Increased Risk of Myocardial Infarction in Men With Both Hypertriglyceridemia and Elevated HDL Cholesterol

To the Editor:

By the use of a sophisticated statistical method, Jeppesen and colleagues have confirmed that hypertriglyceridemia is an independent risk factor for coronary events in the general male population.\(^1\)\(^-\)\(^^5\) In addition, they made the interesting observation that hypertriglyceridemia increased the risk of myocardial infarction even in the presence of high levels of HDL cholesterol that are considered cardioprotective. Because hypertriglyceridemia in most cases is associated with low HDL cholesterol levels, the coincidence of hypertriglyceridemia and high HDL cholesterol had a low prevalence (3.6%). As a result, the number of myocardial infarctions in this group was also very low (13). Due to the low number of observations, it is important to verify this interesting finding in another study.

We investigated the cooperative effects of hypertriglyceridemia and HDL cholesterol in an 8-year follow-up of 4849 male participants (aged 40 to 64 years) of the Prospective Cardiovascular Münster (PROCAM) study.\(^5\) During this time, 181 definite nonfatal myocardial infarctions, 49 fatal myocardial infarctions, and 28 sudden cardiac deaths were observed. Forty-one men suffered nonfatal stroke, and 179 men died of stroke or noncardiovascular diseases. In addition, 4381 men survived the 8-year follow up without any coronary event or stroke. In men with triglyceride levels below 150 mg/dL, the incidence of coronary events decreased from 10.1% if HDL cholesterol was below 35 mg/dL (24 events among 237 case subjects) to 6.1% if HDL cholesterol levels ranged between 35 and 55 mg/dL (82/1918) and to 1.3% if HDL cholesterol exceeded 55 mg/dL (8/642). In men with triglyceride levels between 150 and 200 mg/dL, the incidences of coronary events in the respective HDL ranges were 12.1% (19/157), 4.3% (25/578), and 4.6% (3/65). Triglyceride levels higher than 200 mg/dL were associated with increased incidences of coronary events both in men with HDL cholesterol levels below 35 mg/dL (58/371, 15.6%) and in men with HDL cholesterol levels above 55 mg/dL (7/58, 12.1%) compared with men with intermediate HDL cholesterol levels (32/613, 5.2%). Compared with the entire unaffected population, the risk for coronary events was increased by a factor of 2.2 in hypertriglyceridemic men with high HDL cholesterol (95% CI, 1.04 to 4.67). Together, the observations in the Copenhagen Male Study and the PROCAM study suggest that the coincidence of hypertriglyceridemia and elevated HDL cholesterol increases the risk for myocardial infarction.

Women Versus Men Regarding Outcome of CABG or PTCA

To the Editor:

It is very gratifying to read from the report from the Bypass Angioplasty Revascularization Investigation (BARI)\(^1\) that women who undergo coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) fare as well as men. However, this conclusion seems to be at odds with another report\(^2\) published at about the same time and based on a much larger number of patients (344 913 compared with 1829 in BARI). The registry from the Society of Thoracic Surgeons\(^2\) reported that women clearly have a higher mortality rate within 30 days of a procedure (4.52% in women versus 2.61% in men; \(P<0.001\)). The report, after adjusting the data for more than 50 potential risk factors, still found a statistically significant higher death rate for women.\(^3\)

Conventional wisdom tells us that women are at higher risk than men for CABG and PTCA because women have smaller, more technically challenging coronary arteries; there is less frequent use of internal mammary artery grafting in women; women develop symptoms from coronary artery disease at an older age than men owing to protection from estrogen; and women are more likely as a result to have such comorbid conditions as diabetes mellitus and renal disease that increase the operative risks.

The issue of whether men do better than women or women do equally well as men in outcomes with CABG and PTCA remains debatable. But the most important message from BARI\(^1\) is that it is reassuring that women do not seem to do worse and therefore gender of the patient should not influence a physician’s decision to recommend medical versus surgical treatment of coronary artery disease.

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References


Response

We appreciate the comments of Dr Cheng, who notes that the finding of a similar outcome in women and men undergoing CABG within the Bypass Angioplasty Revascularization Investigation (BARI)\(^1\) is not corroborated in a large registry of patients in the Society of Thoracic Surgeons National Cardiac Surgery Database.\(^2\)

As stated in the Discussion, interpretation of our results in BARI should take into account that the data are from a randomized clinical trial with specific inclusion and exclusion criteria, and hence, the BARI population is not representative of all patients undergoing coronary revascularization. However, when we examined BARI screening data, we found that women were not disproportionately excluded from the trial population. In addition, data from an ancillary BARI study that conducted a survey of all hospitals in the United States performing CABG and coronary angioplasty during the same time period indicated that the proportion of women undergoing revascularization procedures at BARI sites was similar to the proportion of women undergoing revascularization at a random sample of hospitals around the country (between 26% and 27% of patients and similar to the 26.7% of women in the trial).\(^3\) Thus, there does not appear to be a sex bias for selection into BARI. Similar to other observational studies, women in BARI were older and had a higher risk profile and more comorbid disease than men. However, the detailed inclusion criteria, most notably that the coronary anatomy had to be amenable to both CABG and coronary angioplasty, suggest that the BARI population represents a subset of all patients treated with CABG.

We agree with Dr Cheng that it is unclear whether women do as well as men when undergoing CABG and coronary angioplasty. However, what is important is that the outcome of women undergoing coronary revascularization appears to be improving, as suggested in 2 recent preliminary reports that noted a similar adjusted mortality in women and men undergoing percutaneous coronary intervention within the NHLBI Dynamic Registry\(^4\) and the Northern New England Cardiovascular Disease Study Group registry.\(^5\) These data should be disseminated to clinicians to ensure optimal management of women in need of a coronary revascularization procedure.

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