Letters to the Editor must not exceed 400 words in length and may be subject to editing or abridgment. Letters must be limited to three authors and five references. They should not have tables or figures and should relate solely to an article published in Circulation within the preceding 12 weeks. Only some letters will be published. Authors of those selected for publication will receive prepublication proofs, and authors of the article cited in the letter will be invited to reply. Replies must be signed by all authors listed in the original publication.

**Correspondence**

**Platelet Activation With Unfractionated Heparin at Therapeutic Concentrations and Comparison With Low-Molecular-Weight Heparin and With a Direct Thrombin Inhibitor**

To the Editor:

We read with interest the article by Xiao and Theroux1 on “Platelet Activation With Unfractionated Heparin at Therapeutic Concentrations and Comparisons With a Low-Molecular-Weight Heparin and a Direct Thrombin Inhibitor.” They found that platelets of patients with unstable angina were hyperresponsive during treatment with unfractionated heparin (UFH). Moreover, aggregation to ADP and thrombin receptor agonist peptide (TRAP) was enhanced after addition of UFH ex vivo to blood of normal volunteers. In contrast, when a low-molecular-weight heparin (LMWH) or a direct thrombin inhibitor (argatroban) was added, platelet aggregation induced by TRAP had no detectable effects. However, argatroban reduced maximum platelet aggregation induced by ADP.

We performed similar studies ex vivo and in vitro on platelet aggregation in platelet-rich plasma (PRP) induced by ADP and collagen in the presence of commercial heparin (Liquemin, Roche), LMWHs (LMWH Hepar Laboratory; Enoxaparin, Rhone-Poulenc Rorer), and the direct thrombin inhibitor hirudin (Boehringer Mannheim).2–4 In agreement with Xiao and Theroux, UFH added to PRP at therapeutic concentration or after injection of healthy volunteers with a bolus of 5000 IU induced enhanced platelet aggregation by ADP at different final concentrations (0.8 to 2 μmol/L). Such an effect was still present 60 minutes after the bolus injection. Moreover, LMWH, either injected as a bolus or added in vitro, minimally affected or did not affect platelet aggregation induced by ADP. In contrast, when collagen was the aggregating agent, both UFH and LMWH showed an inhibitory effect, although UFH seemed to be more powerful.2,3

Finally, and more importantly, hirudin at a final concentration of 2 μg/mL reduced ADP-induced aggregation by 50% and did not have any effect when collagen was the aggregating agent. Moreover, when we added 2 thrombolytic agents, urokinase and recombinant tissue plasminogen activator, to PRP, this pattern was not modified.4

Powerful direct antithrombin agents like hirudin or argatroban could play a role in preventing the reocclusion of coronary arteries in the early phase of reperfusion, during thrombolytic therapy, by inhibiting both thrombin released by the residual thrombus and ADP-induced platelet activation. In contrast, the heparins could have a more important action in the subsequent phase after successful thrombolysis, when platelets interact with exposed subendothelial collagen. However, because platelets play a crucial role in the failure of thrombolysis, the new antiplatelet inhibitors could be better drugs for increasing the speed of reperfusion and preventing reocclusion.5

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**Paradoxical Embolism**

To the Editor:

I read with interest the excellent article on patent foramen ovale in major pulmonary embolism by Konstantinides et al.1 Unfortunately, neither the title nor the key words of the article included the term “paradoxical embolism.” Since the latter is a well-established clinical entity, has important diagnostic and therapeutic implications, and is what the article was really about, I wish to draw this to the attention of both your readers and medical librarians for indexing purposes.

**Tsung O. Cheng, MD**  
Professor of Medicine  
Division of Cardiology  
George Washington University  
Washington, DC


**Response**

We greatly appreciate Dr Cheng’s comments on our study. In the key words of our article,1 “embolism” stands both for pulmonary and paradoxical embolism. We certainly agree with Dr Cheng that paradoxical embolism was the crucial event and the main determinant of prognosis in our patients.

**Stavros Konstantinides, MD**  
Department of Cardiology  
University Clinic of Goettingen  
Goettingen, Germany


**RAPPORT?**

To the Editor:

Recently, Brener and colleagues,1 on behalf of the ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) Investigators, reported their data on the use of abciximab with primary angioplasty in patients with acute myocardial infarction.
I have been following closely the revelation that platelet glycoprotein IIb/IIIa blockade has brought to the field of interventional cardiology. While reading the above-cited article, I realized that the authors listed the study by the EPIC Investigators as 2 separate references (references 3 and 20). As indicated in every medical journal, “the accuracy of reference data is the responsibility of the author.” I do not have any knowledge that such duplication of references is allowed in Circulation. A point well made or minor details?

Heidar Arjomand, MD
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Response
We appreciate Dr Arjomand’s careful review of our article. Indeed, as Dr Arjomand pointed out, the EPIC trial was inadvertently referenced twice. We regret the mistake.

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Myocardial Bridging
To the Editor:
In the article on myocardial bridging by Lauer and Carlson, the patient was evaluated by an adenosine thallium SPECT study. This showed a fairly small, reversible anterior wall perfusion defect. Adenosine causes vasodilation and actually decreases intramural myocardial pressure. The reason a reversible defect appears is that more time is spent in systole per minute owing to the adenosine-caused heart rate increase. I would suggest that either exercise or dobutamine stress would have been more appropriate, because by raising intramural pressure (as well as heart rate), the submerged segment would more likely be compressed, giving a more sensitive quantification of the amount of myocardium at risk.

Shia H. Elson, MD
Atlanta, GA

Response
We appreciate Dr Elson’s insightful comments on our article. To the best of our knowledge, there have been no published studies comparing the use of stress modalities in myocardial bridging. Because she was unable to tolerate exercise, our patient was stressed with the use of adenosine as a preoperative evaluation without knowledge of her bridging a priori. We agree that when possible, an exercise stress study is preferable, because it provides functional data and correlates perfusion defects with physiological stress.

Within a bridged coronary segment, intravascular ultrasound and intracoronary Doppler have shown that there is not only a systolic luminal diameter reduction, but also a persistent diastolic diameter reduction with delayed relaxation in diastole and a subsequent prominent peak in coronary flow velocities in early diastole. With an increase in heart rate, a decrease in diastolic filling time, or an increase in contractility, there is a decrease of flow through the bridge segment (for example, with exercise or dobutamine). Furthermore, short-term β-blocker therapy has been demonstrated to significantly decrease diameter reductions during both systole and diastole.

Adenosine, by its dilation of intramyocardial resistance vessels and a slight increase in heart rate, may theoretically decrease flow across a bridge segment by a “steal” phenomenon similar to that seen in significant fixed stenoses. However, because of the dynamic nature of a bridged segment stenosis within the cardiac cycle, adenosine may, in fact, underestimate perfusion defects compared with exercise.
Physician Noncompliance With the 1993 National Cholesterol Education Program (NCEP-ATPII) Guidelines

To the Editor:

We read with interest the intriguing study by Frolkis et al,1 regarding frequency of risk factor evaluation, lipid testing, and treatment of hypercholesterolemia in patients admitted to the coronary care unit of a large university hospital. We2 and others3 have recently reported similarly disappointing rates in outpatients that underscore the authors’ sobering findings.1 The recognized limitations of their study notwithstanding, Frolkis et al have made an important contribution toward increasing awareness of the need for vigilance in coronary risk factor assessment and modification, and we applaud their efforts. We have, however, several comments that may be of value in clarifying the authors’ findings.

In particular, we suggest a degree of caution regarding the authors’ conclusions concerning appropriate evaluation and initiation of lipid-lowering therapy in the setting of an acute coronary event. The National Cholesterol Education Program—Adult Treatment Panel II (NCEP-ATPII) guidelines offer recommendations for outpatient therapy that are longitudinal in nature and require serial evaluation of lipid profiles as patients move toward their goal. They emphasize repeated testing and a graded approach to therapy. As the authors recognize, the stress of an acute event can be so overwhelming that, if anything, physicians have been too zealous in initiating therapy. The main points of emphasis in NCEP-ATPII is the identification or the framework suggested by the 27th Bethesda Conference, there is an evolving consensus that in high-risk patients the use of the NCEP guidelines in a high-risk sample like the one we describe seems quite appropriate.

Dania and Silverman point out that acute hospitalization can lower serum lipid levels, an issue we address explicitly in our article. At no point, however, do we state or imply that “deferral of cholesterol testing during an acute hospitalization is necessarily a misguided approach.” In fact, we agree with others4 that to obtain a valid lipid panel in the acute setting, the specimen must be collected within 24 hours of admission. Our point was that even allowing for this effect, clinical decision making based on lipid values that may have been spuriously low remained strikingly inadequate. By lowering lipid levels, in other words, the effect of the “acute phase response” would have been, if anything, to inflate the measured physician performance; our results may have been even more discouraging if such a mechanism was not operating.

Finally, Dania and Silverman appear to have misunderstood our intent regarding the risk factors of sex (not just male sex, as they state) and age. One of the goals of the study was to evaluate how thoroughly physicians and nurses elicited key risk factors for CHD. Since gender was immediately observable and age (as they state) and age. One of the goals of the study was to evaluate how thoroughly physicians and nurses elicited key risk factors for CHD. Since gender was immediately observable and age (as they state) and age.


Response

We appreciate the comments of Dania and Silverman concerning our article on physician noncompliance and welcome the opportunity to respond. They voice concern that application of the NCEP guidelines in an acute setting may violate the ambulatory and longitudinal intention of the recommendations. We submit that whether one uses the NCEP guidelines, the Framingham risk scores, or the framework suggested by the 27th Bethesda Conference, there is an evolving consensus that in high-risk patients the use of the NCEP guidelines in a high-risk sample like the one we describe seems quite appropriate.

Dania and Silverman point out that acute hospitalization can lower serum lipid levels, an issue we address explicitly in our article. At no point, however, do we state or imply that “deferral of cholesterol testing during an acute hospitalization is necessarily a misguided approach.” In fact, we agree with others4 that to obtain a valid lipid panel in the acute setting, the specimen must be collected within 24 hours of admission. Our point was that even allowing for this effect, clinical decision making based on lipid values that may have been spuriously low remained strikingly inadequate. By lowering lipid levels, in other words, the effect of the “acute phase response” would have been, if anything, to inflate the measured physician performance; our results may have been even more discouraging if such a mechanism was not operating.

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Physician Noncompliance With the 1993 National Cholesterol Education Program (NCEP-ATPII) Guidelines

To the Editor:

We read with interest the intriguing study by Frolkis et al,1 regarding frequency of risk factor evaluation, lipid testing, and treatment of hypercholesterolemia in patients admitted to the coronary care unit of a large university hospital. We2 and others3 have recently reported similarly disappointing rates in outpatients that underscore the authors’ sobering findings.1 The recognized limitations of their study notwithstanding, Frolkis et al have made an important contribution toward increasing awareness of the need for vigilance in coronary risk factor assessment and modification, and we applaud their efforts. We have, however, several comments that may be of value in clarifying the authors’ findings.

In particular, we suggest a degree of caution regarding the authors’ conclusions concerning appropriate evaluation and initiation of lipid-lowering therapy in the setting of an acute coronary event. The National Cholesterol Education Program—Adult Treatment Panel II (NCEP-ATPII) guidelines offer recommendations for outpatient therapy that are longitudinal in nature and require serial evaluation of lipid profiles as patients move toward their goal. They emphasize repeated testing and a graded approach to therapy. As the authors recognize, the stress of an acute hospitalization may significantly decrease the serum cholesterol level for multiple reasons.4,5 Accordingly, we disagree with the authors’ assertion that deferral of cholesterol testing during an acute hospitalization is necessary a misguided approach. In fact, we agree with others4 that to obtain a valid lipid panel in the acute setting, the specimen must be collected within 24 hours of admission. Our point was that even allowing for this effect, clinical decision making based on lipid values that may have been spuriously low remained strikingly inadequate. By lowering lipid levels, in other words, the effect of the “acute phase response” would have been, if anything, to inflate the measured physician performance; our results may have been even more discouraging if such a mechanism was not operating.

Finally, Dania and Silverman appear to have misunderstood our intent regarding the risk factors of sex (not just male sex, as they state) and age. One of the goals of the study was to evaluate how thoroughly physicians and nurses elicited key risk factors for CHD. Since gender was immediately observable and age automatically printed in the hospital chart, no independent effort was required for their ascertainment; hence, we excluded them when assessing screening performance. However, when we constructed the statistical algorithms that were used to judge compliance with NCEP guidelines, sex and age were both incorporated per NCEP criteria.

The comments of Dania and Silverman do point to an issue of considerable interest and importance. Precisely because of results like the ones we, they,2 and others’ report, there is an evolving consensus that in high-risk, secondary-prevention patients, lipid-lowering therapy should perhaps be started before hospital discharge. Although some authors would limit such an intervention to patients whose LDL levels exceed desirable (NCEP-based) cutoffs,5 others recommend treatment in this setting even without screening, because patients have demonstrated by their disease that their levels are too high.5 Until outpatient implementation of recommendations such as the NCEP-ATPII
guidelines improves, this may emerge as a key hedge against physician noncompliance.

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Platelet Activation With Unfractionated Heparin at Therapeutic Concentrations and Comparison With Low-Molecular-Weight Heparin and With a Direct Thrombin Inhibitor
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