Unfractionated Heparin Dosing in the FRIC Study
To the Editor:
In the recent FRIC study,\textsuperscript{1} the subheading on page 65 states “Anti–Factor Xa Activity and aPTT Values in the Acute Phase,” but no activated partial thromboplastin time (aPTT) values were provided. Because one of the measures of performance of unfractionated heparin (UFH) dosing is the aPTT achieved, the reader cannot interpret the degree of anticoagulation achieved with UFH if no aPTT values are provided. Because aPTT measurement was mandated per protocol at 6 and 12 hours as well as daily through 48 hours, these median aPTT values should be reported as well as the percentages of patients below and above the target of aPTT of 1.5 times the control value. If dalteparin at a dose of 120 IU/kg twice daily is as good as poorly dosed UFH with no safety advantages, why would one use the more expensive dalteparin?

A separate issue relating to all multicenter studies of anticoagulants that use one mandated range for aPTT measurement (such as 1.5 times control) relates to the lack of standardization of the aPTT ranges to target UFH concentrations as well as variability among reagents used for aPTT measurement at individual centers when the target range is only expressed in seconds (eg, 60 to 85 seconds). Both inconsistencies with aPTT measurement could lead to uninterpretable results with UFH. If all new, more expensive anticoagulants are to be compared with UFH, closer scrutiny of dosing is warranted.

Sarah A. Spinler, PharmD
Associate Professor of Clinical Pharmacy
Philadelphia College of Pharmacy and Science
Adjunct Assistant Professor of Pharmacy in Medicine
Cardiovascular Division
University of Pennsylvania
Philadelphia, Pa


Response
The median aPTT values in the acute phase of the FRIC trial were as follows (Table 1):

<table>
<thead>
<tr>
<th>TABLE 1. Median aPTT Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Seconds</td>
</tr>
<tr>
<td>n</td>
</tr>
</tbody>
</table>

Therefore the median aPTT was \(\approx60\) seconds for days 1 to 3 and maintained to around 45 seconds for days 4 to 7. The median length of the heparin infusion was 51 hours and the median total length of heparin treatment (intravenous only or intravenous plus subcutaneous) was 6 days. From a clinical perspective this must be considered sufficient heparin treatment with aPTT levels as a tool for monitoring. This is also reflected in a rather low number of ischemic events after 48 hours in the heparin arm of the FRIC trial.

In addition, we have calculated how many patients were within (1.5 to 2.0 times the local reference value), below, or above these limits. The results are shown in Table 2:

| TABLE 2. Patients Below, Within, and Above Limits |
|--------------------|----------------|----------------|----------------|
| Time               | Below          | Within         | Above          |
| 6 Hours            | 102            | 231            | 192            | 36.6 |
| 12 Hours           | 90             | 226            | 151            | 32.3 |
| Day 2              | 99             | 296            | 156            | 28.3 |
| Day 3              | 94             | 265            | 132            | 26.9 |

Approximately 50% of the patients achieved the desired target range during days 1 to 7. However, during days 1 to 3, 20% were below the desired range and levels were maintained below an average of 40% for days 4 to 7.

Finally, it should be mentioned that the use of low-molecular-weight heparin by the subcutaneous route provides the potential of simple, effective delivery of anticoagulation with enhanced convenience without the costs of staff, infusion equipment, and aPTT monitoring associated with intravenous unfractionated heparin. The simplicity of dosing and lack of toxicity of subcutaneous low-molecular-weight heparin allow unstable patients to be treated in a low-cost environment while infarction is ruled out, such as in accident or emergency holding wards or general medical wards rather than in a coronary care unit setting only.

Werner W. Klein, MD
Medizinische Universitätsklinik Graz
Graz, Austria

How Should We Define Inadequate Coronary Arterial Remodeling?
To the Editor:
After our report\textsuperscript{1} showing the contribution of “inadequate compensatory enlargement” to the development of coronary narrowing, Mintz et al\textsuperscript{2} in their recently published report confirmed this concept in a larger study population by using a different definition of “inadequate arterial remodeling.” However, the assessment of the relative importance of “inadequate arterial remodeling” is highly dependent on the definition used.

As pointed out by Mintz et al, the assessment of the true effect of vessel remodeling on the progression of coronary narrowing would require serial or longitudinal intravascular ultrasound studies (IVUS) over a long time period. However, such longitudinal, serial studies are time consuming and impractical. Consequently, we compared the size of the external elastic lamina (EEL) area (the area within the outer border of the sonoluent zone considered to represent EEL) at the lesion site with those at the reference sites. The proximal and distal reference sites were defined as the sites with...
minimal narrowing by angiography and the largest lumen area and \(<50\%\) area stenosis as determined by IVUS. In our study, the EEL area of all arteries was larger at the proximal reference sites than at the distal reference sites, and “inadequate compensatory enlargement” was defined when there was a smaller EEL area at the lesion site than at the distal reference site. This definition is based on two factors: (1) nonatherosclerotic coronary arteries taper from the proximal to the distal portion of the coronary artery and (2) "adequate arterial remodeling" at the lesion site should result in the same or more prominent compensatory enlargement of the vessel compared with the distal reference site that has less luminal narrowing. Our definition resulted in a frequency of “inadequate compensatory enlargement” of 26% or approximately 1 in 4 patients.

Mintz et al defined “inadequate arterial remodeling” as a ratio of the lesion EEL area over the proximal reference EEL area \(\leq 0.78\) and found that 15% of the lesions they studied met this criteria. By applying these criteria to our study population, we found that 14% of the coronary lesions (1 in 7 patients) had “inadequate arterial remodeling,” which reflects an excellent agreement between our studies. Hence the apparent discrepancy between the studies (1 in 4 [26\%] versus 1 in 7 [14\%]) concerning the relative importance of “inadequate arterial remodeling” seems to be due to different definitions. We, like Pasterkamp et al, Mintz et al, and others, hypothesize that a substantial proportion of arterial stenoses are due to not only plaque accumulation but also to the failure to develop compensatory arterial enlargement. In this context we believe that it is essential to carefully assess the rationale behind the definitions of this new entity. Mintz et al based their definition of normal tapering of the coronary artery on their previous study, in which among 146 coronary arteries with focal, hemodynamically significant stenoses, no artery developed EEL area tapering exceeding 21% over a 10-mm arterial length from the proximal to the distal reference site. However the proximal and the distal reference sites used for the definition of normal tapering also had atherosclerosis and exhibited an area stenosis of \(\approx 50\%\), and these “normal sites,” as pointed out by the authors, may be affected by a variable type and degree of vessel remodeling. Moreover, the significance lesion located between both reference sites may have also influenced coronary remodeling at the reference sites. Hence the prevalence of “inadequate coronary arterial remodeling,” suggested by the data presented by Mintz et al are hampered by the fact that they did not use “ideal” reference segments in their definition. Our definition is not based on idealized segments either; rather, we use the coronary artery being imaged as its own “control.” Our criteria use on-line assessment and require no complex calculations or assumptions. IVUS imaging is used to directly assess whether “inadequate compensatory enlargement” at the lesion site is present in the specific coronary artery being assessed for intervention. Should “inadequate compensatory enlargement” have an impact on which coronary interventions are preferable in a given clinical situation, we believe our definition may serve as an appropriate and practical tool for the coronary interventionalist.

Toshihiko Nishioka, MD
Division of Cardiology
Self-Defense Forces Central Hospital
Tokyo, Japan

Hans Berglund, MD
Hual Luo, MD
Tomoo Nagai, MD
Robert J. Siegel, MD
Division of Cardiology
Cedars-Sinai Medical Center
Los Angeles, Calif


Response

The reports from Nishioka et al, Pasterkamp et al, and our laboratory confirm that inadequate arterial remodeling contributes importantly to the process of atherosclerotic stenosis formation in some lesions.

We agree with Nishioka and colleagues that the definition used in our report required a number of assumptions and was, perhaps, cumbersome. However, all of the studies (including ours) had flaws. Either the sample size was small, the results were potentially biased by lesion selection, or the prevalence was definition dependent.

In the report by Nishioka et al, the lesion was compared with a distal reference segment. This comparison also has limitations. First, the ultrasound catheter must be advanced far enough past the lesion into the distal vessel to identify a distal reference segment, something not always possible. Second, the authors did not define the axial distal between their lesion image slice and their distal reference segment. (Because vessels taper, distal reference segment selection will also affect identification of inadequate remodeling.) Third, it has been our experience that crossing a stenosis with the ultrasound catheter, especially a tight stenosis (ie, stenoses most likely to require intervention), causes the distal vessel to become underperfused. (1) making identification of the distal reference segment difficult and (2) causing the cross-sectional measurements to be unreliably small. Fourth, the distal reference must contain enough of a plaque burden with positive remodeling.

We believe that remodeling is a spectrum and that many stenoses fitting none of the definitions in these three studies may also have an element of inadequate remodeling. Also, none of these studies adequately address whether these findings are present during the early stages of lesion formation in some vessels or whether plaque and arterial shrinkage are late events.

Finally, we believe that the pathologic concepts outlined in all three of these studies are more important than the exact prevalence of the findings and the definitions used.

Gary S. Mintz, MD
Martin B. Leon, MD
Intravascular Ultrasound Imaging and Cardiac Catheterization Laboratories
Washington Hospital Center
Washington, DC
Factor V Leiden and Thromboembolism

To the Editor:

In an excellent study, Ridker et al.\(^1\) recently demonstrated that the risk of thrombosis is greatly increased when the factor V Leiden mutation and hyperhomocysteinemia, which alone are only moderate risk factors for thrombosis, occur together. As stated in the accompanying editorial by Phillips,\(^2\) a potential weakness of this study is that the activity of other anticoagulant and fibrinolytic proteins was not specifically reported. We present a case of a 33-year-old man with factor V Leiden, increased plasminogen activator inhibitor 1 (PAI-1) activity, and a history of multiple thromboembolic events.

At the age of 18 years, the patient had pulmonary embolism of unknown origin when he was hospitalized for urologic surgery. At the age of 24 years, he developed a deep venous thrombosis without evidence of trauma complicated also on this occasion by pulmonary embolism. Warfarin was administered for 6 months. However, detailed investigations of the hypercoagulable state were not performed. At the age of 29 years, the patient was admitted with chest pain and acute inferior myocardial infarction diagnosed by ECG. Despite thrombolysis, the patient developed a maximum creatinine kinase level of 515 U/L with an MB fraction of 15%. Coronary angiography was performed 3 weeks after the myocardial infarction and revealed normal coronary arteries (see Figure), suggesting that the infarction had been caused by a thrombotic occlusion and not by rupture or dissection of an atheromatous plaque. Six months after the infarction, the patient was referred to our institution for assessment of potential risk factors. He was a nonsmoker, had normal blood pressure, and was overweight (body mass index, 31.3 kg/m\(^2\)). Lipid levels were normal (total cholesterol, 114 mg/dL; triglycerides, 80 mg/dL; LDL cholesterol, 51 mg/dL; HDL cholesterol, 47 mg/dL; lipoprotein(a), 11 mg/dL). Investigation for a hypercoagulable state showed normal values of fibrinogen (260 mg/dL), antithrombin III activity (84%), plasminogen (101%), protein C activity (91%), and protein S activity (96%). The activity of PAI-1 was increased (5.1 U/mL; reference range: 0.3 to 3.5 U/mL). In addition, the patient showed activated protein C (APC) resistance (APC ratio, 1.8; reference limit >2.0) associated with heterozygosity for factor V Leiden. A family history revealed that the sister of the patient had died at the age of 36 years from sudden cardiac death. The patient’s mother had a history of six venous thromboses, four of which occurred during pregnancy and the remaining two of which occurred without obvious precipitating factors. She was identified as a carrier of factor V Leiden and had an increased fibrinogen of 475 mg/dL. PAI-1 and all other laboratory parameters were normal. The following relatives who had only one risk factor interfering with the coagulation system had no history of thromboembolism: The patient’s father had an increased fibrinogen (476 mg/dL) and no other risk factors. The patient’s sister and brother both showed an increased fibrinogen of 394 and 402 mg/dL, respectively, but no other risk factors. The risk profile of the patient’s 5- and 9-year-old daughters was normal except for heterozygosity for the factor V mutation in the 5-year-old daughter.

These data support the concept that increased thrombotic risk arises from the synergistic interaction of a number of risk factors. The occurrence of a myocardial infarction in our index patient was unexpected because epidemiologic studies did not show a higher prevalence of factor V Leiden in patients after myocardial infarction.\(^3,4\) However, it cannot be excluded entirely that factor V Leiden, in rare instances, causes not only venous but also arterial thrombosis. It is possible that such patients suffer from myocardial infarction at a very young age and have therefore been missed in the cohort studies performed up to now.

Michael Walter, MD
Holger Reinecke, MD
Günter Breithardt, MD, FESC, FACC
Gerd Assmann, MD
Institute for Arteriosclerosis Research
Institute of Clinical Chemistry and Laboratory Medicine
Department of Cardiology and Angiology
University Hospital of Münster, Germany

Jürgen Heinrich, PhD
Community Hospital Solingen, Germany

Coronary angiography was performed 3 weeks after myocardial infarction. A, Left coronary artery; B, right coronary artery.


Response

My colleagues and I appreciate the kind words of Drs Walter, Reinecke, Heinrich, Breithardt, and Assmann concerning our description of markedly increased risks of venous thromboembolism among individuals with both factor V Leiden and hyperhomocysteinemia.\(^1\) Indeed, as discussed elsewhere, the evolving epidemiology of hemostasis and thrombosis clearly indicates that thromboembolism is more likely to occur among those with...
multiple defects of the anticoagulation and fibrinolytic systems. Such defects can be permanent (genetic), acquired (antibody related), or transient (pregnancy).

With specific regard to PAI-1 antigen and tissue plasminogen activator antigen, we note that prior work from our group found no evidence of association between these parameters and risks of venous thrombosis. On the other hand, we and others have found PAI-1 antigen and/or tissue plasminogen activator antigen to be strong markers of risk for arterial thrombosis.4,5 Thus the observation of acute myocardial infarction in the patient described with both factor V Leiden and evidence of hypofibrinolysis is intriguing. From a clinical perspective, evaluations for such hypercoagulable interactions should generally be performed with the patient discontinued from warfarin therapy.

It is of importance that a careful distinction be made between venous and arterial thrombosis. Specific defects of hemostasis tend to be risk factors only for venous thrombosis or only for arterial thrombosis, but not both. Hyperhomocysteinemia appears to be one of the few factors with substantial effects on clinical events in both the arterial and venous systems.

Paul M. Ridker, MD
Division of Cardiovascular Diseases
Brigham and Women’s Hospital
Boston, Mass


Sulfonylureas and Cardiovascular Mortality in Diabetes: A Class Effect?

To the Editor:

In a recent issue of Circulation, Cleveland and coworkers1 provided excellent evidence that in diabetic patients, chronic inhibition of the K<sub>ATP</sub> channel with oral sulfonylureas abolishes ischemic preconditioning of explanted myocardium. The authors conclude that this phenomenon might contribute to the increased cardiovascular mortality in sulfonylurea-treated diabetic patients, as found in the University Group Diabetes Programme (UGDP).2 This extension of their findings in mainly glibenclamide-treated patients (6 and 1 glipizide) to sulfonylureas as a class, however, must be seen with some limitations because neither experimental nor clinical data suggest a uniform effect of different sulfonylureas on the cardiovascular system.

In experimental animals, inhibition of the cardiac K<sub>ATP</sub> channel with glibenclamide has been shown to increase ischemia-reper-

fusion damage, whereas glipizide, a sulfonylurea with pronounced in vivo antioxidative properties, prevented such damage.3 In studies in the human forearm, significant interaction with the vascular K<sub>ATP</sub> channel was found for glibenclamide, whereas the effect was much less pronounced for tolbutamided and even absent for the new drug glipepiride.7 For tolbutamide (the sulfonylurea used in the UGDP), further evidence of an increased cardiovascular morbidity in comparison to glibenclamide or glipizide was recently reported,2 and a possible substance-specific cardiotoxicity was suggested. Tolbutamide, as a first-generation sulfonylurea, is used in the highest dose (up to 3000 mg) of all currently available sulfonylureas (for review, see Reference 9). In a recent survey from Australia, neither glibenclamide- nor glipizide-treated patients with myocardial infarction had higher mortality rates than insulin-treated diabetic patients.10 In the same survey, glibenclamide-treated patients, on the other hand, had significantly less ventricular fibrillation than those receiving gliclazide or insulin.

Taken together, these data suggest that sulfonylureas, despite their comparable actions on the pancreatic beta-cell K<sub>ATP</sub> channel, strongly differ in their ability to interfere with vascular or cardiac K<sub>ATP</sub> channels. As a result, different effects on preconditioning, arrhythmias, and reperfusion damage are reported. Therefore I suggest that based on our current knowledge, a class effect of sulfonylureas with regard to an increased cardiovascular risk must not be hypothesized, and the effect described by Cleveland and coworkers must be restricted to the substance(s) investigated.

Thomas C. Wascher, MD
Department of Internal Medicine
Diabetes and Metabolism Unit
University of Graz
Graz, Austria


Response

We appreciate the interest of Dr Wascher in our recently published work concerning chronic oral sulfonylurea ingestion.
and the inhibition of myocardial preconditioning in human tissue. Dr Wascher offers a very insightful hypothesis to explain our findings. He astutely notes that the patients reported in our series were taking either glibenclamide or glipizide, and he questions whether our results can be uniformly extrapolated to suggest that all sulfonylureas inhibit ischemic preconditioning in human myocardium.

We agree with Dr Wascher that a uniform consistency of cardiovascular K\textsubscript{ATP} channel inhibition with differing oral sulfonylureas is not evident. Nevertheless, his hypothesis that our results may only apply to glibenclamide- or glipizide-treated patients can neither be supported nor refuted on the basis of our data. We argue that it remains unknown whether other sulfonylurea agents could inhibit ischemic preconditioning in human myocardium because we did not encounter any patients who were taking agents other than glibenclamide or glipizide. We certainly believe, however, that Dr Wascher’s observations are valid, and he raises a critically important question of whether we can conclude that all sulfonylureas could produce the same inhibitory effect on ischemic preconditioning.

We believe that one other comment is important. In our opinion, it is increasingly evident that the K\textsubscript{ATP} channel plays a central role in ischemic preconditioning in human myocardium. Although our study associates chronic K\textsubscript{ATP} channel blockade with inhibition of human preconditioning, it also questions whether chronic inhibition of the K\textsubscript{ATP} channel could explain the increased cardiovascular mortality observed in the UDGP study. While the particular sulfonylureas that were studied may provide further insights into agent specific cardiovascular mortality, we think the potential significance of our data lies in the linking of the K\textsubscript{ATP} channel to cardioprotection of ischemic preconditioning in human myocardium.

Insightful questions by investigators such as Dr Wascher are enlightening and extraordinarily valuable to properly interpret our data. We think his hypothesis is plausible, and we await further experience with other sulfonylurea agents in human myocardial preconditioning to answer these relevant and valid questions.

Joseph C. Cleveland, Jr, MD  
Daniel R. Meldrum, MD  
Brian S. Cain, MD  
Anirban Banerjee, PhD  
Alden H. Harken, MD

University of Colorado Health Sciences Center  
Department of Surgery  
Denver, Colo


Unfractionated Heparin Dosing in the FRIC Study
Sarah A. Spinler

Circulation. 1998;97:1424
doi: 10.1161/01.CIR.97.14.1424

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/97/14/1424