toxic, or associated with recognized cardiovascular disease in which the degree of myocardial dysfunction is not explained by the abnormal loading conditions or the extent of ischemic damage. Histology is nonspecific. Presentation is usually with heart failure, which is often progressive. Arrhythmias, thromboembolism, and sudden death are common and may occur at any stage. Regarding the need to perform a myocardial biopsy to absolutely exclude the presence of patients with myocarditis, we refer to the 2005 AHA/ACC Guidelines in which no recommendation is reported for the routine use of endomyocardial biopsy for the diagnostic assessment of patients with dilated cardiomyopathy. A recent review on this complex issue concluded that outside scientific studies there is no indication to perform myocardial biopsy in these patients. The lack of a recommendation for the routine use of such an invasive procedure has also safety reasons: the risk of serious complications is around 1%, which is not negligible and should be, therefore, justified and outweighed by a high rate of diagnostic accuracy. But this is not the case because many patients with a non-ischemic cardiomyopathy show non-specific changes on biopsy (including hypertrophy, cell loss, and fibrosis), and it has not been established conclusively how biopsy findings (even when positive) affect patient management.

In relation to the cut-off value employed, 2 is a widely accepted criterion of normality as extensively discussed with review of the existing literature. During the revision process of the manuscript, the ROC analysis we performed was not considered an appropriate approach by the statistical reviewer due to the censored nature of the endpoint. Nonetheless the best cut-off value identified by the ROC analysis was 1.8, which is consistent with our previous results in patients with coronary artery disease.

The nature of the study design did not allow us to perform CFR in the follow-up, but the improvement of CFR in certain diseases with coronary microvascular dysfunction would have a positive impact on prognosis, representing a new therapeutic target. We agree with Tona and with Zamorano and Mateos that this will be an important challenge for future studies in the field.

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Differentialation of aborted myocardial infarction from masquerading myocardial infarction

We read with great interest the article by Verheugt et al., dealing with aborted myocardial infarction (MI) as a new target for reperfusion therapy. The authors emphasize the importance of differentiating between aborted MI and masquerading MI to avoid inappropriate fibrinolysis. The most common differential diagnoses of patients with masquerading MI are given in Table 1 of the article. While we agree that the diseases listed there (acute pericarditis, aortic dissection, previous MI with recurrent myocardial ischaemia in same area, left ventricular aneurysm, left ventricular hypertrophy, early depolarization, Brugada syndrome) can often lead to a potentially false diagnosis of aborted MI (i.e. masquerading MI), we would like to expand this list by including yet another case. In August 2004, we reported a previously unpublished case of reversible myocardial ischaemia following acute upper airway obstruction. The patient was admitted in the emergency department with marked respiratory distress as a result of oropharyngeal and epiglottic swelling. Electrocardiogram revealed pronounced ST-segment elevation in V1–V6 and a subtler one in inferior leads with reciprocal depression in I, aVL, and V5. The ST-segment elevation returns to normal 10 min later with the relief of the upper airway obstruction (intubation was performed), without any evidence of myocardial damage. This is a typical example of masquerading MI and we believe that our experience with this case can benefit clinical practice in the future.

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Significance of uric acid for the heart and vessels

The recent article describing a positive association between serum uric acid and several inflammatory markers in the InCHIANTI study addresses the issue of whether uric acid is an independent cardiovascular risk factor. Uric acid is an antioxidant and appears to contribute to salutary immune reactions, but the cardiovascular significance of rises in its serum level remains poorly understood. I would like to summarize the intricacies of this question. Increases in serum uric acid concentration could be primarily unrelated to the heart and vessels, they could originate in or form part of the processes that account for the development or progress of several cardiovascular conditions, including atherosclerosis, hypertension and heart failure, or they could constitute compensatory reactions to such processes. Mechanistically, elevations in serum uric acid may result from increases in its synthesis, from reductions in its renal excretion, in theory from decrements in its transformation rate (i.e. from diminutions in the rate at which it quenches reactive species), and from combinations thereof. In terms of their effects on cardiovascular structures and functions, rises in serum uric acid could theoretically be inconsequential, beneficial, or, on the other hand, as a resultant, depending upon the mechanisms involved in their genesis and the circumstances in which they occur. Reactive oxygen species are co-generated when the synthesis of uric acid or the formation of its precursor, xanthine from hypoxanthine is catalyzed by the xanthine oxidase form of xanthine oxidoreductase. No study has disclosed that reducing serum uric acid in human beings attenuates the development or progress of any cardiovascular disorder independently of co-changes in other variables. Moreover, decrements in serum uric acid secondary to the inhibition of its synthesis with allopurinol or oxypurinol have failed to benefit patients with heart failure. For all the preceding reasons, speculation on the significance of increases in serum uric acid for cardiovascular prognosis must be particularly thorough and circumspect. I was glad to note that Ruggiero et al. have impressed these qualities upon the discussion of the results of their timely analysis.

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Prasugrel, clopidogrel, and combining Swedish apples with American oranges

I read with interest the paper by Jernberg et al. that compared platelet characteristics after different loading and maintenance doses of prasugrel vs. conventional clopidogrel regimen in stable patients with coronary artery disease. The goal of this Phase 2a study was to explore and justify the future dosing of prasugrel used in the COMMIT trial. The statement in Conclusion that the index study justifies the prasugrel dosing what is in agreement with the index study. Non-compliance is probably the major realistic cause of non-response at <25% IPA, there are no clopidogrel non-responders among the American patients at day 28, while the majority (12/19) of patients from Sweden are non-responders. These differences may be only explained by the quality control failures with the aggregometer calibration or daily routine use, flaws in blood sample drawing and preparation, protocol violation, or non-compliance, especially in the outpatient chronic setting. Our platelet data driven from the small JUMBO subset correspond with the IPA of the US subpopulation of the index study. Non-compliance is probably the major realistic cause of non-response, and this hypothesis was later confirmed in one of the prasugrel-treated patient.

The statement in Conclusion that the index study justifies the prasugrel dosing regimen (60 mg loading, followed by 10 mg daily maintenance) chosen for the Phase 3 TRITON (TIMI-38) trial is not supported by the presented evidence and exaggerates the clinical validity of this quality work. In fact, the index data support the JUMBO trial design, and when the study was over (2003), TRITON was not even planned. Also, every prasugrel regimen starting with the lowest dose (40 mg loading followed by 5 mg maintenance) was more potent than the corresponding clopidogrel regimen what is in agreement with the more recent data. Therefore, even if the dominant hypothesis that a higher degree

Drs V. Serebruany, J. Brandt, and K. Winters are listed as inventors in the US Patent Application ‘Method for treating vascular disease with prasugrel’ assigned to Lilly (P-17232).

References

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