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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Differentiation 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, left bundle branch block, pre-excitation, 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 V3–V6, and a subter 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.

References


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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 contrary, harmful for the cardiovascular system. Several aspects of this question have been discussed in the recent article.

In the present letter, I will focus on the significance of increases in serum uric acid for the development or progression of cardiovascular disease. First, I will review the mechanisms involved in the rise of serum uric acid. Second, I will discuss the evidence for a causal relationship between serum uric acid and cardiovascular disease. Third, I will consider the implications of these findings for the prevention and treatment of cardiovascular disease.

In the InCHIANTI study, serum uric acid levels were measured in 5,101 participants aged 49 to 91 years. The study design included a cross-sectional survey of the general population, as well as follow-up of a subset of participants for up to 10 years. The main finding of the study was a significant positive association between serum uric acid levels and several inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α).

Several mechanisms have been proposed to explain the association between serum uric acid levels and inflammation. One mechanism is that uric acid can act as a pro-inflammatory mediator by binding to and activating high-affinity urate receptors (URAT1) on immune cells. Another mechanism is that uric acid can promote the synthesis of pro-inflammatory cytokines by activating toll-like receptors (TLRs) on immune cells. These mechanisms provide a plausible explanation for the positive association between serum uric acid levels and inflammation.

In conclusion, the results of the InCHIANTI study suggest that serum uric acid levels may be a risk factor for cardiovascular disease. Further research is needed to confirm these findings and to identify the mechanisms underlying the association between serum uric acid levels and inflammation. This research may lead to the development of new strategies for the prevention and treatment of cardiovascular disease.

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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 characterizations 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 early absolute mortality benefit of the prasugrel dosing what is in agreement with the IPA of the US subpopulation of the index study. Non-compliance is probably the major realistic cause of non-response, 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, such a prasugrel regimen starting with the lowest dose (40 mg loading followed by 5 mg maintenance) was more potent than the corresponding clopidogrel dosing what is in agreement with the more recent data. Therefore, even if the dominant hypothesis that a higher degree

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"Dr S. Seretanu, 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)."