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 untoward, by and of themselves or as a resultant, depending upon the mechanisms involved in their genesis and the circumstances in which they occur.2,3 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.4 No study has disclosed that reducing serum uric 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.4 For all the preceding reasons, speculation on the significance of increases in serum uric acid for cardiovascular prognosis must be particularly thorough and circumspect.5 I was glad to note that Ruggiero et al.6 have impressed these qualities upon the discussion of the results of their timely analysis.

References


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Prasugrel, clopidogrel, and combining Swedish apples with American oranges

I read with interest the paper by Jernberg et al.1 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 JUMBO (TIMI-26) trial.2 The team should be acknowledged for the effort, clean data, and some critical insights beyond the initial objective. In fact, this is the first study ever to provide the convincing evidence that therapy with clopidogrel resulted in a mild but rapid >30% inhibition of platelet aggregation (IPA), as early as 2 h after loading with 300 mg (Table 2), but not after 3–4 h as we thought before. These data challenge the unjustified loading dose increases and the perceived shortcoming of the delayed clopidogrel action, indirectly supporting the early absolute mortality benefit of no-load clopidogrel observed in the COMMIT trial.3 Also, the identification of the detailed time course of IPA with prasugrel is indeed important and is obviously instrumental for the dose selection in JUMBO.

There is one major limitation of the study. The patient enrolment was performed in two independent sites in Sweden and the USA. Unfortunately, the pieces of the platelet work were not well coordinated, when different models of aggregometers were used (BioData vs. Chronolog), and/or obvious patient selection bias occurs. It also seems that the US site have more relevant experience in this type of research and monitor their patients more closely, at least in terms of compliance. Indeed, the data presented in Figure 3A and B suggest that the American patients (open squares) exhibited highly significantly more potent IPA than their Swedish (close circles) counterparts. The criticality of this discrepancy is much more serious and harmful for the assessment of the combined study results than ‘variation in aggregation responses’ mentioned in Limitations.

Considering that the degree of platelet inhibition and the controversial issue of ‘non-responders’ after clopidogrel represent the cornerstones of the paper ideology, these data cannot be combined and should be analysed separately. For example, even after accepting the questionable and way too liberal definition 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 is 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/and 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.4 Non-compliance is probably the major realistic cause of non-response, and this hypothesis was later confirmed in one of the prasugrel-treated patient.5

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 data1 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 dosing what is in agreement with the more recent data.5 Therefore, even if the dominant hypothesis that a higher degree

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