The Continued Yin and Yang of Uric Acid
To the Editor:

We read with interest the recent research letter by Amaro et al. Their analysis adds to the growing literature on uric acid (UA) and vascular disease. However, their review of this nascent literature was unbalanced, and we must challenge certain of their statements of “fact”.

The “positive” effect of UA claimed by Amaro et al must be balanced against established data suggesting a link between increasing serum UA and cardiovascular disease. We have previously shown that small increments in admission serum UA are associated with significantly worse 90-day outcome. However, their group have previously suggested very different findings—that increasing serum UA is associated with favorable outcome at 7 days. This difference is intriguing. We do not agree with the author’s comment that “confounders” may have biased our results; if anything, our analysis is more robust, and at the very least highly similar in technique to their own. We thoroughly explored univariate differences in clinical features between outcome groups and used multiple logistic regression to control for factors known to influence outcome: including baseline National Institutes of Health Stroke Scale score. We also performed a further analysis where fully adjusted multiple Cox proportional-hazards ratios revealed an increased risk of recurrent vascular events with increasing serum uric acid. We chose an objective, reliable 90-day outcome (alive, placed in own home or dead), which recent data suggest is closely related to 90-day modified Rankin scale score. They used day-7 Mathew scale score—this eponymous scale is poorly validated and has been all but abandoned in the modern stroke literature.

We completely agree that the potential antioxidant properties of serum UA are of interest, and we hope that they investigate this further. Their data concerning lower-lipid peroxidation after administration of UA are of particular interest. However, it is important to acknowledge that the case for a pure antioxidant property of serum UA is not completely made. Considerable data suggest that UA is a conditional pro-oxidant. Also, although animal data suggest that administration of serum UA can reduce infarct volume, we must recall the dangers of direct extrapolation from animal to human where neuroprotectant therapy is concerned. This may particularly apply here: UA metabolism and serum levels differ widely between species dependent on the presence of the uricase enzyme, which is lacking in humans.

The increasingly conflicting data, where some suggest benefit and others suggest harm from elevated serum UA, demand thorough and thoughtful debate. It is entirely plausible that chronic elevations in serum UA convey harm via detrimental effects on endothelial function and smooth-muscle cell proliferation but that the potential antioxidant effects of UA itself can be harnessed in acute ischemia and oxidative stress. In summary, their data are promising; we hope to see further study, but it must be acknowledged that more data concerning the effect of serum UA on accepted “clinical trial standard” outcomes such as 90-day modified Rankin Scale are required. Equally, the STAIR criteria, or perhaps the “New Roadmap for Neuroprotection” must be followed.

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Jesse Dawson, MRCP
Terry Quinn, MRCP
Kennedy Lees, MD, FRCP
Matthew Walters, MD, FRCP
Department of Cardiovascular and Medical Sciences
Western Infirmary Hospital
Glasgow, UK

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Jesse Dawson, Terry Quinn, Kennedy Lees and Matthew Walters

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