deed, there are likely to be disparate mechanisms responsible for different aspects of arterial stiffening which may be separate from medial calcification. Yuce et al. are proposing that, in CKD, the associated chronic inflammatory state leads to bone resorption and decreased fetuin-A levels, thereby providing a trigger for valvular calcification, presumably through a loss of inhibitory activity. This hypothesis may well have merit, but we do not feel that the evidence for this is as yet overwhelming.

The possible link between vascular calcification and osteoporosis may be dependent on the type and location of dystrophic mineralization. Indeed, the histology of neointimal and valvular calcifications is quite distinct from other vascular calcifications. This may reflect important mechanistic and pathophysiological differences, and although it is the case that these changes often occur simultaneously, this does not necessarily imply a shared causality.

Contrary to the argument of Yuce et al., low bone mass has been associated with increased, not decreased, serum fetuin-A concentrations [2]. It could therefore be hypothesized that, in a state of negative bone balance, there is reduced incorporation of fetuin into bone matrix with a consequent shift into the circulating plasma pool. Increased bone resorption would result in the liberation of fetuin-A into plasma.

Pro-inflammatory cytokines are also likely to be involved in an atherosclerotic calcification and independently linked to poor outcome. Evidence from cell culture and cross-sectional studies suggest that pro-inflammatory cytokines suppress fetuin-A synthesis [3], but the data, particularly in patients with stage 3–4 CKD, are conflicting [1].

Fetuin-A-deficient mice do not spontaneously develop significant vascular calcification or bone loss; therefore, fetuin-A is unlikely to be the sole factor in its pathogenesis. Polymorphisms of the fetuin-A gene have been associated with differences in transcriptional activity and cardiovascular risk [4], but the effect of these variants on bone has not, to the best of our knowledge, been studied. In rat bone marrow cell culture, fetuin-A antagonizes TGF-β osteogenic activity. However, TGFβ action on bone is bimodal with relatively low doses promoting bone growth and high doses suppressing it [5], thus depending on the prevailing TGFβ concentration, fetuin may potentially inhibit or promote bone re-modelling. It is therefore, difficult to predict the impact of the low levels of fetuin-A seen in patients with moderate renal impairment.

We certainly agree that further study is indicated.

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The evidence for sodium bicarbonate therapy for contrast-associated acute kidney injury: far from settled science

Sir,

We read with interest the meta-analysis by Hoste et al. [1] as well as the editorial by Drs Wiedermann and Joannidis [2]. The commentators point out the highly significant benefit in patients undergoing procedures for acute coronary procedures. However, this result is on the basis of only 25 events in 170 patients from two trials. Furthermore, one of these two trials was terminated early [3]. In the other, the subjects in the sodium bicarbonate group received an initial bolus followed by a higher rate of hydration and were also given intravenous N-acetylcysteine compared with controls who were not given an initial bolus of saline and were treated with a lower rate of saline hydration as well as a lower dose of oral N-acetylcysteine [4]. Because this trial is testing a multiple hypothesis, not just the effect of sodium bicarbonate hydration, it is reasonable to exclude it from the meta-analysis [5]. In fact, subleties such as these provide insight into the observed heterogeneity and help the reader better understand the robustness of the findings. In this context, the highly significant benefit of sodium bicarbonate in patients with acute coronary procedures can hardly be considered a robust finding. Another source of heterogeneity that goes largely unrecognized is the relationship of trial size and outcome (Figure 1). The power curve shows the relationship between study size, outcome and power. It is apparent that all positive trials to date, published or unpublished, are considerably underpowered. In contrast, all the negative
trials have tended to be the largest studies to date. Therefore, the positive results of meta-analysis of sodium bicarbonate have been largely driven by a small number of positive trials with extreme treatment effects [5]. We have suggested that the magnitude of benefit is so small (RR 0.85) that a definitive trial with 90% power would require 9918 subjects [5].

The title of the comment, which suggests that there is a little role of unpublished studies, also strikes us as being disingenuous. The importance of unpublished studies has been well recognized, and purposeful omission of such studies may lead to biased results [6,7]. The lower quality of unpublished studies is also a result of the lack of information about the study methodology in the abstract version of the unpublished study. Hence, it is the assessed quality which is low, rather than the true quality per se, as pointed out in our systematic review [5].

There are three more recent meta-analyses [8–10] done on the same subject which bring the total number of meta-analysis in this area to 11, which is equal to the number of published trials in this field. As suggested earlier [11], a proliferation of meta-analyses does not widen the evidence base and cannot resolve the uncertainty engendered by small randomized controlled trials with heterogenous results for a surrogate outcome (change in creatinine rather than requirement for dialysis or mortality).

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Editorial Note: Dr Hoste et al. had been invited to reply to this letter, but we did not receive a response.

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Fig. 1. Power curve: the relationship between trial size and power.
Sir,

In their letter, Swapnil and Brar correctly point at additional reasons such as co-medication potentially contributing to heterogeneity, an observation that was practically found in all meta-analyses performed until now. However, as recent investigations [1,2] as well as a meta-analysis addressing this issue specifically [3] indicate, adding NAC to bicarbonate does not significantly alter bicarbonate's effect on contrast-induced AKI. Consequently, excluding an investigation using different doses of NAC might not be necessary. The power of a study actually addresses the probability of overlooking existing differences rather than finding a difference by chance, the type I error of usual statistics in any published trial. In short of that, truly, we cannot find any disingenuousness by demonstrating in our comment [4] that even inclusion of all studies (published and unpublished) known to that point did not get rid of excess variability among study results. We are well aware of the importance of unpublished studies with regard to publication bias [5,6], but as we have demonstrated, this does not help the case with regard to contrast-induced AKI studies, and consequently, publication bias does not also appear to be the major source of heterogeneity in this context. Finally, this ongoing discussion just even clearer demonstrates the urgent requirement of additional large adequately powered multicentre trials investigating on clinical end points and the effects of bicarbonate in preventing contrast-induced AKI.

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Vascular calcification is not an independent predictor
of mortality in pre-dialysis adult patients

To the Editor:

It has been established that vascular calcification is predictive of mortality in haemodialysis patients [1]. Among pre-dialysis patients, in a study recently published in Nephrol Dial Transplant, Hanada et al. have stated that aortic calcification is associated with an increased risk of cardiovascular events [2]. Furthermore, positive associations between coronary calcification with both cardiovascular events and mortality risk have been reported in the pre-dialysis setting [3]. However, these latter studies were limited by the fact that either mortality was not evaluated [2] or adjustment for possible confounders was not performed [3]. To further investigate this issue, we performed a prospective study of a cohort of 92 pre-dialysis patients (mean ± SD age: 68 ± 12 years) at different chronic kidney disease (CKD) stages (12.5% at stage 2, 37.5% at stage 3, 41% at stage 4 and 9% at stage 5). Abdominal aortic and coronary calcifications were evaluated by multi-slice spiral computed tomography. Eighteen patients died during the follow-up period (mean ± SD duration: 794 ± 244 days). In crude survival analyses, a coronary calcification score >259 AU and an aortic calcification score >1.53 predicted overall mortality (P = 0.01 and P = 0.04, respectively). These cut-off values were estimated by maximizing sensitivity and specificity in ROC curves for predicting mortality. However, the associations were no longer statistically significant after adjustment for age in multivariate Cox regression analyses. In conclusion, vascular calcification was not an independent predictor of mortality in pre-dialysis adult patients. Other factors such as endothelial dysfunction [4] may prevail over vascular calcification in early-stage CKD. Further investigation in a prospective study with a larger sample size is required to address this issue.

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