Reply

Sir,

We are writing in response to Dr Shaldon’s remarks on our recent Editorial Comment [1]. Unfortunately, Dr Shaldon detracts from the main focus of this article that was questioning whether a new set of guidelines should be developed in Europe following the publication of the KDOQI Anaemia Guidelines, and our personal recommendation was that this was unnecessary; this recommendation was recently reiterated by an international group of guideline experts who recommended that the next set of anaemia guidelines should be developed by KDIGO once significant new data are available. The efforts of KDIGO to coordinate guideline development will promote better use of resources, and stop the fruitless repetition of guidelines that has long been supported and fostered by industry.

The KDOQI guidelines reflect a huge effort to interpret the available evidence in the best possible and objective way, including external review. Although Dr Shaldon may disagree with the conclusions of the Anaemia Work Group, we would advise him to carefully read these guidelines. There he will find an in-depth discussion of the risks and benefits of ESA therapy, including the effects on health-related quality-of-life, the methodology available to measure this parameter, as well as a discussion on the limitations of current trials. When he studies this document carefully, he will also notice that there is no evidence that ‘over-swings’ of haemoglobin levels in patients treated to the recommended targets put them at increased risk. Dr Shaldon may also be aware of the recent post hoc analysis of the CHOIR study that showed no risks in patients who actually reached their haemoglobin target, with the extra risk only evident for those patients who did not reach the target and who received high doses of epoetin.

Finally, Dr Shaldon alludes to the current hot topic of guideline development in groups of individuals who have potential conflicts of interest. This subject was intensely debated in the ‘Controversies in Nephrology’ section of the January 2007 issue of CJASN, and will therefore not be further elaborated here. Suffice to say that we agree with the reasons propagated by Dr Van Wyck and colleagues [2] why it is unrealistic to propose that guideline development be carried out only by ‘intelligent physician-scientists with no conflict of interest’. Most importantly in this context, there should be full disclosure of all authors or participants in this process. This also applies to the authorship of the current article, which Dr Shaldon has clearly taken great pleasure in criticising.

Conflict of interest statement: All authors have received consulting fees, honoraria, and lecture fees from Amgen, Ortho Biotech, Roche, Shire, and Affymax.

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Sir,

We read with great interest the article by Grudzinski et al. [1], demonstrating the benefits of sodium citrate 4% locking solution for central venous catheters. The authors concluded that citrate locking improves reliability of international normalized ratio (INR) measurement compared to standard heparin locking. Unfortunately, the study was not designed specifically to assess this question. In addition, the authors reported a surprisingly low incidence (0.8%) of falsely elevated INR due to heparin contamination following heparin locking. They also reported an absence of falsely elevated INR following citrate locking. Such findings are unexpected, given that INR may be clearly overestimated when the blood is contaminated with either heparin [2] or citrate [3–5].

We performed a pilot study with 19 haemodialysis (HD) patients at our centre to assess the reliability of INR measurement when blood samples are drawn directly from central catheters locked with either sodium citrate 4% or standard heparin. INRs were measured simultaneously prior to dialysis from both a peripheral vein and the HD catheter standard heparin locking. Unfortunately, the study was not designed specifically to assess this question. In addition, the authors reported a surprisingly low incidence (0.8%) of falsely elevated INR due to heparin contamination following heparin locking. They also reported an absence of falsely elevated INR following citrate locking. Such findings are unexpected, given that INR may be clearly overestimated when the blood is contaminated with either heparin [2] or citrate [3–5].

We performed a pilot study with 19 haemodialysis (HD) patients at our centre to assess the reliability of INR measurement when blood samples are drawn directly from central catheters locked with either sodium citrate 4% or standard heparin. INRs were measured simultaneously prior to dialysis from both a peripheral vein and the HD catheter after discarding 5 cc of blood from the arterial port. The INR values obtained following citrate or heparin locking were compared using ANOVA.

We found that INR values were falsely elevated in all patients with heparin lock. The mean INR was falsely elevated by 56% ± 28% (INR catheter: 1.7 ± 0.3; INR peripheral vein: 1.1 ± 0.04) in patients without warfarin (n = 7), whereas the mean INR was overestimated by 114% ± 51% (INR catheter: 4.8 ± 1.4; INR peripheral vein: 2.1 ± 0.15) in patients with warfarin (n = 12). In contrast, INRs drawn from citrate-locked catheters were not or were only minimally elevated compared to samples drawn from peripheral venipuncture. In patients without warfarin, the mean INR was increased by 0.04% ± 0.7% (INR catheter: 1.06 ± 0.02; INR peripheral vein: 1.06 ± 0.03) whereas in patients with warfarin, the mean INR was
increased by 1.9% ± 0.6% (INR catheter: 2.20 ± 0.16; INR peripheral vein: 2.19 ± 0.16).

These results clearly demonstrate that sodium citrate catheter locking minimally interferes with INR measurements when blood is drawn directly from the catheter prior to dialysis treatment. They also demonstrate that the overestimation of INR with heparin locking is more frequent than reported by Grudzinski et al. [1]. Hence, the use of citrate catheter locking improves INR measurement reliability and thus facilitates the management of anticoagulation in HD patients.

Conflict of interest statement. None declared.

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3. Chantarangkul V, Tripodi A, Clerici M et al. Assessment of the influence of citrate concentration on the international normalized ratio (INR) determined with twelve reagent-instrument combinations. Thromb Haemost 1998; 80: 258–262
doi: 10.1093/ndt/gfm905
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Reply

Sir,

We would like to thank Dr Rioux et al. for reinforcing our statement that heparin falsely increases INR and this is reversed by the use of sodium citrate 4%, as a catheter locking solution. It seems that our approach was misinterpreted by the correspondents. We purposefully did not include all the cases of false increase in INR associated with heparin contamination. We only included the cases with the most blatant effect (INR > 3.0 and PTT > 100), which usually leads to an inappropriate clinical decision by the treating physician (decrease in the dose or discontinuation of warfarin). Despite this low sensitivity, high specificity approach, the improvement with citrate was seen and cannot be attributed to anything else than to the change in the locking solution. We agree with the correspondents that we included only the tip of the iceberg.

Conflict of interest statement. None declared.

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