

Latest US KDOQI Anaemia Guidelines update—what are the implications for Europe?

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In medicine, large randomized controlled trials are powerful entities; not only do they influence clinical practice and impact on clinical practice guidelines, but they also have the ability to confuse the medical and non-medical community by producing surprising or alarming results that question current concepts of clinical management. Examples of this in the non-nephrological literature include the Women's Health Initiative trial of hormone replacement therapy for cardiovascular protection in post-menopausal women [1]. This very large placebo-controlled randomized trial in over 16 000 post-menopausal women showed beyond doubt that combined oestrogen and progesterone replacement did not reduce cardiovascular risk, but in fact increased it. Similarly, in the CAST trial (Cardiac Arrhythmia Suppression Trial), the hypothesis was that anti-arrhythmic drugs such as flecainide and encainide would reduce the incidence of ventricular arrhythmias post-myocardial infarction [2]. In fact, mortality was increased with the use of such agents. Closer to home, in nephrological practice, the results of the HEMO study countermanded the previous belief that more dialysis was better, and that high-flux dialysis was better than low-flux dialysis [3]. Similarly, the 4D (*Die Deutsche Diabetes Dialyse*) study of atorvastatin in diabetic haemodialysis patients confused the issue regarding the cardiovascular protective role of statin therapy in this patient population [4].

In the renal anaemia field, the US Normal Hematocrit Trial by Besarab and colleagues [5] began to discredit the hypothesis that aiming for

normalization of haemoglobin in dialysis patients with symptomatic cardiovascular disease was better than aiming for incomplete correction of anaemia by epoetin therapy. Although this addressed patients with severe cardiac disease only [6], a subsequent randomized double-blind trial in dialysis patients without symptomatic cardiac disease, reported by Parfrey *et al.* [7], also showed no benefit of a haemoglobin target within the normal range, in comparison with partial anaemia correction, on left ventricular hypertrophy. More recently, we have seen the publication of the CREATE and CHOIR studies in the same issue of the *New England Journal of Medicine* [8,9]. Both of these studies yielded useful data addressing the issue of optimal target haemoglobin ranges in chronic kidney disease patients not on dialysis, an area that previously lacked high-quality evidence to support clinical practice recommendations. The CREATE study suggested that early and complete correction of anaemia does not improve cardiovascular outcomes compared with later and incomplete correction of anaemia [8]. Moreover, the number of patients starting chronic dialysis was higher in the higher haemoglobin arm. The main limitation of the CREATE study was that it ended up under-powered, due to a lower annual event rate incidence of 6% compared with the 15% used for the sample size calculation.

Of even greater concern, however, were the data from the CHOIR study [9]. This large prospective randomized trial in the United States suggested that aiming for a target haemoglobin of 13.5 g/dl is harmful compared to targeting a haemoglobin of 11.3 g/dl, in terms of the composite end-point of death, myocardial infarction, stroke and hospitalization for cardiac failure. Although the CHOIR data are important and informative, one should be aware of the features of this study, which may limit the generalizability and the strength of its results. These have been extensively discussed elsewhere [10,11], but in short, these include: 50% of the patient population, diabetic, imbalances in the patient groups at baseline [the higher

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haemoglobin group had significantly more hypertension ($P=0.03$) and coronary artery bypass grafting ($P=0.05$), the high ESA doses administered (initial dose 10 000 IU every week; maximum maintenance dose 20 000 IU per week), the censoring of patients not experiencing an event at the time of study termination, and the fact that patients were not followed beyond the initiation of dialysis.

These latter findings have generated considerable scientific discussion and commentary in both the nephrological and the general medical literature, and further discussion and controversy was generated by the publication of a large meta-analysis in the *Lancet* [12]. A major concern with this meta-analysis has been the pooling of results from very heterogeneous CKD populations, including both dialysis and non-dialysis patients. In addition, one must bear in mind that, since the CHOIR study is so large, any conclusions from this meta-analysis will be strongly influenced by this single study, and likewise any flaws will be perpetuated.

The accompanying editorial to this meta-analysis by Strippoli *et al.* [13] stated quite dogmatically that we have got target haemoglobins 'wrong' for years, and it is time that we now changed. While it would take a very brave nephrologist to argue completely against the viewpoints expressed in this editorial, some of the sweeping statements have since been challenged, notably the comment that the TREAT study should now be stopped before completion, since we now have all the answers to the questions we need. TREAT is the largest randomized controlled trial ever to be conducted in the field of renal anaemia management, being within a few months of completing the recruitment target of 4000 patients. Patients enrolled in TREAT are randomized equally to two treatment arms, the first involving correction of anaemia with darbepoetin alfa to a target haemoglobin of 13 g/dl vs the placebo control arm with darbepoetin alfa rescue therapy if the haemoglobin falls below the 9 g/dl level. Although there are some similarities between the CREATE, CHOIR and TREAT studies, there are notable differences also. Differences between CHOIR and TREAT include the study population (exclusively type II diabetics in TREAT), the sample size (nearly three times greater in TREAT), the fact that TREAT compares treatment with no treatment (while CHOIR compared two target haemoglobin levels), the slightly lower 'upper Hb target' in TREAT (13.0 g/dl vs 13.5 g/dl), the expected difference between achieved haemoglobin levels in both treatment arms (the target ranges were 13.5 g/dl vs 11.3 g/dl for CHOIR and are 13.0 g/dl with a rescue protocol aiming to maintain Hb levels >9.0 g/dl for TREAT), as well as the fact that TREAT is a blinded study [14]. The arguments put forward by the chairman of the TREAT Executive Committee, Dr Marc Pfeffer, supporting continuation of TREAT are persuasive [15], and even more importantly, the Data Safety and Monitoring Board for this study has carefully examined the safety data, finding no reason to recommend termination of the

study at this point, although considerably more events have already occurred in TREAT than in CHOIR. Thus, at the present time, it looks as if TREAT can continue, hopefully until study completion.

In addition, the CHOIR study has arguably aroused more political emotions in the United States than has any previous randomized controlled trial in nephrology, and this has had implications for clinical practice guidelines, regulatory authorities and health insurance schemes such as Medicare. The implications for Medicare are obvious. This health insurance scheme spent over 4 billion US dollars on erythropoiesis-stimulating agents in 2006, and even a modest reduction in the ceiling target haemoglobin beyond which no reimbursement will be provided, has huge financial implications. Since the CREATE and CHOIR data became public in the middle of 2006, even before full publication of these studies in November 2006, the US Food and Drug Administration (FDA) was initiating discussions with the ESA-producing pharmaceutical companies, to determine whether any changes should be made to the label of their products. Various statements from the FDA have appeared on their website over the last few months, the latest one (released on 9 March 2007) being the most stringent yet. Several 'Dear Doctor' letters had already produced some warnings about haemoglobin concentration in patients receiving erythropoiesis-stimulating agents, but this latest 'black box' warning stated that physicians should 'use the lowest dose of erythropoiesis-stimulating agent that will gradually increase the haemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion'. This recommendation thus limits the benefits of anaemia therapy to a reduction in blood transfusions and does not take into account any potential benefit to quality-of-life. The question now arises as to whether this FDA mandate is appropriate, in the light of CHOIR and CREATE, or whether the FDA has now over-reacted to the data from these trials.

At the same time as the FDA deliberations, the National Kidney Foundation in the United States elected to re-convene the US KDOQI Anemia Guidelines Work Group, to discuss the implications of CHOIR, CREATE and four small randomized controlled trials on the target haemoglobin issue. All but one of these trials had been published following the cut-off from the previous evidence review that had culminated in the May 2006 revision of the US KDOQI Anemia Guidelines [16]. The six additional randomized controlled trials had expanded the evidence on clinically important outcomes, doubled the number of all chronic kidney disease patients examined and increased the number of non-dialysis chronic kidney disease patients from 497 to 3432 [17]. In keeping with criteria for updating a systematic review and guidelines prior to a scheduled revision, the Work Group undertook a re-examination of the available evidence on haemoglobin treatment targets. This re-examination included both the new studies

and those appraised previously. Thus, following an extensive review conducted by the Tufts-New England Medical Center Evidence Review Team in Boston, the Anemia Work Group met in Dallas in early February 2007. After a period of public consultation and review, the final conclusions of the Work Group have just been published in the September issue of *American Journal of Kidney Diseases* [17]. This is a comprehensive document with numerous evidence-weighting tables, a new meta-analysis of all published trials and an extensive commentary, but in a nutshell, the three updated statements in relation to haemoglobin targets appeared as follows:

- 2.1.1 In the opinion of the Work Group, selection of the Hb target and selection of the Hb level at which ESA therapy is initiated in the individual patient should include consideration of potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events). (Clinical Practice RECOMMENDATION)
- 2.1.2 In the opinion of the Work Group, in dialysis and nondialysis patients with CKD receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dl. (Clinical Practice RECOMMENDATION)
- 2.1.3 In dialysis and nondialysis patients with CKD receiving ESA therapy, the Hb target should not be greater than 13.0 g/dl. (Clinical Practice GUIDELINE - MODERATELY STRONG EVIDENCE)

Note that statements 2.1.1 and 2.1.2 are opinion-based clinical practice recommendations, while statement 2.1.3 is an evidence-based clinical practice guideline. What are the implications of these latest clinical practice recommendations and the guideline statement for Europe, not to mention Australia, Canada and the rest of the world? The European Renal Association—European Dialysis and Transplant Association (ERA-EDTA) previously commissioned a review of the original European Best Practice Guidelines on Anaemia Management, which was published in May 2004 [18], and which is now also slightly outdated. Similarly, the CARI Guidelines produced by Australia [19], and the Canadian Guidelines produced by the Canadian Society of Nephrology [20] may also now be inappropriate in the light of the latest evidence. Clearly, Europe, Australia, Canada and other geographical regions could all form new Anaemia Guidelines Work Groups to revisit the evidence base, but there has already been too much duplication of effort in generating different guidelines around the world. This was the thinking behind the formation of KDIGO (Kidney Disease—Improving Global Outcomes) [21,22], and it now seems appropriate for KDIGO to take the lead in co-ordinating the timing and conduct of any subsequent review on anaemia management recommendations/guidelines. Given that the KDOQI

Anemia Guidelines Work Group has already just completed an extensive review of the literature, is there really a place for this to be repeated in Europe or elsewhere? It is the opinion of the authors of this Editorial Comment that the answer is 'no'. Instead of duplicating the enormous amount of time and effort that has already been expended in generating this latest US KDOQI Anemia Guidelines update, resources should rather be used to implement these recommendations and, if possible, generate new evidence to address the many open questions that remain. This recommendation follows one of the fundamental processes of the KDIGO initiative: 'globalize the evidence' and 'localize the implementation'.

There is one final point of relevance for the practising nephrologist, be it in the United States or Europe, and that is the apparent conflict between drug regulatory authorities and evidence-based clinical guidelines. Whereas in the past, the discrepancies between the FDA-regulated labels for the ESAs were fairly small, and did not present a major problem for practising nephrologists in the United States, the latest FDA warning and the US KDOQI Anemia Guidelines show a greater discrepancy. The US physician now has to make a choice as to whether he follows evidence-based clinical practice guidelines or alternatively obeys the FDA label. Many nephrologists in the United States will interpret the latest FDA label as being over-cautious to the detriment of patient care and quality-of-life, and it is notable that several patient groups in the United States have already voiced strong opinions against this latest FDA warning. Clearly, if a US nephrologist disobeys the FDA 'black box' warning, and follows the Anemia recommendations, he/she is opening himself to litigation if anything goes wrong. This concern is additional to whether or not they will actually be reimbursed for the cost of the ESA!

The reaction in Europe has not been quite as panicked so far. Thus, at the time of writing, the European Agency for the Evaluation of Medicinal Products (EMA) has provided no guidance or recommendation, none of the Summaries of Product Characteristics have been altered and, waiting for a KDIGO initiative, the European Best Practice Guidelines have not been updated. The EMA is indeed looking closely at the implications of CHOIR and CREATE, and is expected to announce their opinions and recommendations within the next couple of months. In the meantime, several clear messages have recently emerged from the fog surrounding the issue of target haemoglobin in CKD patients. According to Hippocrates, a physician's first responsibility is to 'do no harm'. The evidence base for CKD anaemia management now suggests that aiming for haemoglobin targets >13.0 g/dl in patients receiving ESAs runs the risk of causing harm. Generally aiming for a haemoglobin of 11–12 g/dl would seem to provide the best compromise, in terms of gaining benefit and minimizing the risks of using ESAs, recognizing that this target range is very narrow and there will be a Gaussian distribution of Hb

values actually achieved by the patients. It still leaves us with the two 'woolly' areas on either side of this haemoglobin range: do patients with haemoglobin levels of 10–11 g/dl really fare less well than those whose haemoglobin is >11 g/dl? Secondly, although deliberately targeting haemoglobin levels >13 g/dl may increase the likelihood of causing harm, there is no evidence to suggest that transient fluctuations into this haemoglobin range should cause either the nephrologist or the patient any concern. One must be mindful that the adverse data from CHOIR were generated from a group of patients who were deliberately targeting a haemoglobin of 13.5 g/dl and using very large doses of epoetin alfa to overcome patient hyporesponsiveness. This situation is likely to differ from that of a patient who is targeted to a haemoglobin between 11 and 12 g/dl, but who occasionally (through normal biological variability) develops a haemoglobin of 12–13 g/dl or above. Although it is noteworthy that the mean haemoglobin concentration in the higher Hb arm in CHOIR was 12.6 g/dl, this does not imply that targeting patients into this range confers harm. Since many observational studies have in fact shown that patient outcome improves with higher Hb levels, it is possible that the concept of a single optimal target Hb for all patients is not correct and that both EPO resistance (the amount of ESA needed to increase the Hb concentration by 1 g/dl) as well as the absolute ESA dose required to achieve a certain Hb level are also important for anaemia management.

Finally, when a nephrologist is making a decision about the appropriate target haemoglobin concentration, he/she is often doing this for an individual patient who is sitting in front of him/her at the outpatient clinic. There may be individual factors that influence this decision, and although clinical practice guidelines are essential, one of the major limitations of clinical practice guidelines is that the available evidence usually does not allow separate recommendations to be created for specific patient subgroups. Two quotations have become common in our language of today: 'Guidelines are for the population, while the doctor is for the patient' and 'one size cannot fit all'. To quote also from Dr Uhlig and her colleagues' excellent Editorial Comment in *NDT* a year ago [23] under the subsection 'What guidelines are and are not': 'Clinical Practice Guidelines cannot be followed like book recipes. They cannot be detailed enough to spell out an individualized approach, that takes into account all potentially important factors, such as patient needs, preferences, available resources, and limitations unique to an institution or type of practice'. And further on in the review: 'Guidelines need to be applied to unique patient settings, and healthcare providers have the final responsibility—and therefore must also have the final authority—to follow the recommendations or not. This decision-making process requires incorporation of patient preferences

and weighing whether exemptions or deviations from recommendations are justified'.

Conflict of interest statement. Dr Macdougall has served as a Work Group member for the revised US KDOQI Anemia Guidelines, as well as for both the original (1999) and the revised (2004) versions of the European Best Practice Guidelines on CKD Anaemia Management. He has received research grants, honoraria and lecture fees from Amgen, Ortho Biotech, Roche, Shire and Affymax. Dr Eckardt has served as a co-chair of the US KDOQI Anemia Guidelines Work Group, was a member of the EBPAG Anaemia Working Group and serves on the Executive Committee of TREAT. He has received lecture honoraria and consulting fees from Amgen, Ortho Biotech, Roche, Shire and Affymax. Francesco Locatelli has served as a Work Group member for the revised US KDOQI Anemia Guidelines, and was Chairman of the revised EBPAG Anaemia Working Group; he is a member of Advisory Boards for Roche, Amgen, Dompé and Shire.

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Sevelamer: a promising but unproven drug

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Sevelamer hydrochloride, a synthetic phosphate binder, licensed for treatment of calcium–phosphorus abnormalities in chronic kidney disease (CKD), is one of many high-cost pharmaceuticals (lanthanum carbonate, calcimimetics, vitamin D analogues) targeted specifically at patients with the CKD-Mineral and Bone Disorder (CKD-BMD) [1]. Phosphate binders, traditionally containing calcium or aluminium, improve metabolic abnormalities in CKD by reducing absorption of dietary phosphorus. Altered mineral metabolism occurs universally in people with stage 4 and 5 CKD [2], due to impaired excretion of phosphorus, reduced activation of vitamin D and a compensatory increase in parathyroid hormone (PTH) secretion [3]. These metabolic features of CKD are associated with deleterious clinical consequences,

including muscle dysfunction [4], fracture [5], cardiovascular and soft tissue calcification [6] and death. Hyperphosphataemia and treatment-related hypercalcaemia have, in large-scaled cohort studies, been powerfully, consistently and independently associated with the excess all-cause and cardiovascular mortality in CKD [7,8]. Such observational research, however, is at best hypothesis-forming, and does not elucidate the mechanisms for cause of death in these patients, and more importantly, whether reversing such metabolic disturbances prevents death. The pivotal question remains—is cardiovascular calcification on the causal chain between calcium–phosphorus–PTH imbalance and cardiovascular morbidity and mortality? Are these valid surrogate outcomes for clinical research?

Administration of sevelamer, a non-aluminium and non-calcium containing phosphate binding polymer, has a potential advantage over traditional calcium-based binders, in reducing both circulating phosphorus and calcium levels, and ameliorating vascular calcification. However, the translation of these drug-specific effects into improved survival in people with CKD has not yet been demonstrated [9]. Sevelamer is not alone in this respect. Other therapies

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