

Influence of Industry on Renal Guideline Development

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Clin J Am Soc Nephrol 2: 3–7, 2007. doi: 10.2215/CJN.02170606

There is ongoing controversy concerning the influence of the pharmaceutical industry on physicians, research publications, medical societies, and disease advocacy groups (1–7). Nowhere is the potential influence of industry more concerning than in development of clinical practice guidelines (8), which are designed to improve and standardize patient care yet also have enormous economic implications. As outlined herein, industry has provided major financial support to the National Kidney Foundation (NKF), the principal organization that develops and promulgates management guidelines in nephrology, and honoraria and/or research support to many participants who are involved in nephrology guideline development. Opinion-based recommendations have benefited some industries and harmed others. If not managed appropriately, then these relationships have the opportunity to undermine the guidelines and harm industry's reputation. They also may reflect poorly on the renal community in general and threaten our independence. Major changes are necessary to limit the influence of conflicts of interest and the appearance of undue influence. The recent 2006 Kidney and Dialysis Outcomes Quality Initiative (KDOQI) anemia guidelines highlight many of these issues.

The New Hemoglobin Target

The recent 2006 KDOQI anemia guidelines increased the target hemoglobin range from 11 to 12 to 11 to 13 g/dl for all patients with chronic kidney disease (CKD) (9). Because of the tight relationship in patients with CKD between target hemoglobin and erythropoietin-stimulating protein (ESP; epoetin or darbepoetin) dosage (Figure 1), this undoubtedly will increase ESP use and cost to the health care system.

Since 1991, the mean hemoglobin and mean epoetin dosage in dialysis patients have risen steadily. Medicare's payments for ESP in patients with ESRD alone have increased from \$843 million in 1998, when the first DOQI guideline set a hemoglobin target of 11 to 12 g/dl, to \$1.55 billion in 2003 after the 2001 KDOQI guidelines reiteration of this target (10). Because mean hemoglobin among dialysis patients now is almost 12.0 g/dl (10), without an increase in the target hemoglobin, mean ESP dosage and ESP expenses per patient might have stabilized finally. According to annual reports, combined Epogen and

Aranesp US sales in 2005 were \$4.56 billion (11), and Procrit and Eprex had worldwide sales of \$3.32 billion (12).

All forms of ESP state in their Food and Drug Administration (FDA)-approved package inserts that target hemoglobin in patients with CKD should not exceed 12 g/dl and that the dosage of ESP should be reduced or held if this level is exceeded. The new anemia guidelines set a higher target hemoglobin by noting that there is insufficient evidence to maintain routinely hemoglobin concentrations ≥ 13.0 g/dl in patients who are treated with ESP. The existence and promotion of guideline recommendations to exceed the hemoglobin level in FDA-approved labeling is likely to increase ESP sales greatly.

Dialysis facilities, which now are owned predominantly by large corporations, also benefit from increased use of ESP. Not unlike other dialysis corporations, DaVita Corp. reported that approximately 25% of 2005 dialysis revenues were from ESP, and "our agreement with Amgen also provides for specific rebates and incentives" (13). Despite the Medicare changes in payments for dialysis services, ESP remain a potential profit center because ESP are reimbursed at 6% above the average sales price, and sales contracts may contain incentives that reward achieving patient outcome targets and volume growth (13). With release of the new guidelines, DaVita has increased its hemoglobin target to 12.5 to 13.0 g/dl (14). This belies the 2006 anemia guideline claim that a "narrow" 1-g/dl target had to be rejected because it "affords neither clarity nor simplicity, is possible to achieve in only a minority of patients, discourages flexibility. . . and likely promotes cycling of hemoglobin" (9).

The NKF certainly receives private sector financial support for the development and promotion of the new anemia KDOQI guidelines. Since 1996, the NKF has received a large amount of corporate support. Dr. Kerry Willis of the NKF communicated that KDOQI received an estimated \$3.3 million in revenue *via* donations from the NKF Board of Directors and 18 corporations in the past 2 yr. Amgen "is the founding and principal sponsor" of the KDOQI guidelines (15). In the 2006 anemia guidelines, Amgen alone has their name and logo in the front of the journal, and the acknowledgments recognize Amgen alone for supporting the guideline development (15). The NKF also has developed the Kidney Learning System, which is intended to teach and promote adherence to the guidelines. This, too, is supported by the pharmaceutical industry.

Many members of the KDOQI work groups, advisory boards, and steering committee also benefit by speaking and writing as experts in the field, serving as consultants to anemia-related pharmaceutical industry, and receiving research funding. As

Published online ahead of print. Publication date available at www.cjasn.org.

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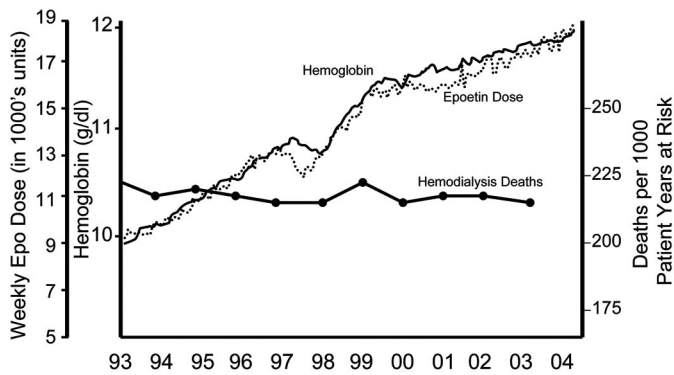


Figure 1. US hemodialysis prevalent patient mean weekly epoetin dosage (dashed line) and hemoglobin (solid line) from 1993 to 2004. Rate of deaths per 1000 patient-years (—●—) in prevalent US hemodialysis patients, adjusted for age, gender, race, and primary renal disease. Adapted from reference (10), pp 16, 26.

experts in the anemia field, it is not surprising that some members of the 2006 anemia work group have potential conflicts of interest (COI) involving ESP producers and/or intravenous iron manufacturers. Of the 16 members, 14 reported receiving consultant fees, speaking fees, and/or research funds from at least one company that potentially is affected by the guidelines; 11 reported potential COI with the ESP industry (15). Studies of members of guideline work groups in other medical fields have noted a similar high incidence of potential COI with affected pharmaceutical companies (16). With completion of new guidelines, experts who are associated with KDOQI often receive honoraria to speak or write to explain and support the guidelines, not uncommonly *via* direct or indirect funding by industry.

It is unclear whether our patients actually will benefit from this latest change in the hemoglobin target, and they may even be harmed. Several studies have compared a lower hemoglobin target (9.5 to 12.0 g/dl) with a higher target (13.0 to 16.0 g/dl). The largest of these trials was in 1233 U.S. dialysis patients and was stopped early by the safety monitoring committee because of a significantly higher fistula and graft thrombosis rate and that “differences in mortality between the groups were recognized as sufficient to make it very unlikely that continuation of the study would reveal a benefit of the normal hematocrit group and the results were nearing the statistical boundary of a higher mortality rate in the normal hematocrit group” (17). This study played a major role in the 2001 KDOQI anemia committee’s retaining the hemoglobin target of 11 to 12 g/dl (18). In the past decade, the mortality rate in dialysis patients has fallen minimally despite the marked increase in mean hemoglobin (Figure 1) (10).

Since the 2001 guidelines, several large trials of lower *versus* higher hemoglobin targets in patients with CKD and dialysis patients have failed to show significant benefit for higher hemoglobin (19–22) and evidence of harm, including increased cerebrovascular events (21). In all of these trials, the lower target and achieved hemoglobin have never exceeded 12 g/dl. An analysis of the 1846 patients in the HEMO study identified

a higher hematocrit as a potential risk factor for stroke, with cerebrovascular deaths significantly greater in the highest quartile with hematocrit >36.3% (relative risk 2.96; 95% confidence interval 1.28 to 6.82; $P = 0.011$ *versus* the lowest quartile with hematocrit <31.1%) (23). Quality of life may improve with higher hemoglobin; however, preexisting comorbidities may affect the achieved hemoglobin and therefore influence this relationship. The cost of one quality-adjusted year gained by targeting hemoglobin to 12 to 12.5 g/dl compared with 11 to 12 g/dl has been estimated at \$613,015 (24). Reports of adverse thrombotic events and deaths in oncology trials (25,26) that have used higher ESP dosages and higher hemoglobin targets led the FDA to require package insert revision for epoetin and darbepoetin in 2004. Other anemia experts with conflicts and two systematic analyses by independent groups have reviewed similar anemia data in CKD and reached conclusions that are different from those of the 2006 anemia work group (27–30).

In addition, two major hemoglobin target trials (Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin [CREATE] and Correction of Hemoglobin and Outcomes in Renal Insufficiency [CHOIR]) in patients with CKD were completed recently. These results were not considered by the KDOQI anemia work group, which was limited by their own rules to only published information. The 600-patient CREATE trial noted significantly higher rate of initiating dialysis and insignificantly higher risk for cardiovascular events among patients who were assigned a hemoglobin target of 13 to 15 g/d, compared with the low-arm target of 10.5 to 11.5 g/dl (31). Aspects of quality of life assessments were better in the higher hemoglobin group. The lead investigator of the CHOIR study (32), a 1432-patient randomized trial of higher (13.5 g/dl) and lower hemoglobin (10 to 12 g/dl) targets in patients with stages 3 and 4 CKD, notified the work group chair that the study was terminated early and the work group should not raise the hemoglobin target without awaiting the results. The CHOIR study results, announced on April 20, 2006, at the NKF annual meeting, showed that the higher hemoglobin arm had a 33.7% higher event rate in the primary end point of cardiovascular events and death. On April 21, 2006, at the same meeting, the new KDOQI anemia guidelines announced a higher hemoglobin range of 11 to 13 g/dl.

NKF, KDOQI, and COI

The NKF guidelines state that the organization “makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group” (33). The 2001 anemia work group biosketches listed few and limited COI statements (18). The draft 2006 guidelines that were released in October 2005 also listed few commercial conflicts of the work group members. The final document lists COI but does not report stock ownership or board positions (15). Work group members and chairs are not restricted from owning or acquiring stock in affected corporations, developing or maintaining consultancy agreements with pharmaceutical firms or dialysis providers, or even assuming board positions with industry during the guideline development process. Al-

though the chairpersons and work group members undoubtedly held themselves to high ethical standards, the existence of financial and business conflicts can undermine the appearance of impartiality when clinical practice recommendations take positions that favor industry.

Failure to outline COI clearly and report how they were managed undermines guidelines in other ways. Work group members commonly are the authors of nondefinitive studies that serve as the basis of opinion-based recommendations. If there are conflicting studies, then it is important to note in the guideline document that the work group member recused him- or herself from critically evaluating his or her own work that serves as the basis of a recommendation, especially when that recommendation has economic implications.

KDOQI Structure and Procedures and the Impact on Guideline Development

The KDOQI development guidelines state, "When the quality of evidence is low, very low, or missing," the work group could develop clinical practice recommendations that are based on consensus of expert opinion (15). Therefore, selection of the chair and work group members will have a huge impact on the nature of the opinion-based clinical practice recommendations. If members have expressed opinions that are supportive of a higher hemoglobin target (34,35) or lower ferritin limit (36), then we should not be surprised when the work group reaches similar conclusions. This is not bias by the committee members, because when scientific data are not definitive, experts will differ in their interpretation. Viewpoints usually will not be altered until definitive studies (which may never come) are provided. However, potential COI increase the likelihood that opinion-based recommendations will favor industry sponsors.

The NKF adopted "a structured intensive evidence review process not previously used" and recommends applying "that process to both newly available literature and literature examined in the development of previous guideline versions. . ." (15). This permitted reassessment of previous recommendations. The chair and co-chair define the scope of work and the specific questions to be addressed. Consider the questions not asked: Is maintaining hemoglobin between 12 and 13 g/dl safer and more beneficial than our present target of 11 to 12 g/dl? Is there sufficient evidence to justify increases in ESP dosage every 2 to 3 wk in dialysis patients as long as hemoglobin is <11 g/dl? Are higher dosages of ESP potentially harmful? Is there sufficient evidence of efficacy to justify extremely high dosages of ESP?

Last, the work group could not consider the unpublished CHOIR and CREATE study data. Similarly, the chair also received from me confidential interim data from the now completed Dialysis Patients Response to IV Iron with Elevated Ferritin (DRIVE) study, which examined iron responsiveness in patients with ferritin >500 ng/ml. The new evidence review process did not permit consideration of unpublished results, although the committee was proposing opinion-based hemoglobin and ferritin targets, not evidence-based guidelines. Was it in our patients' interest not to consider the data? In whose

interest was it not to delay release of the guidelines until the results of these studies were available?

Kidney Disease Improving Global Outcomes, Pharmaceutical Support, and the Appearance of Bias

The initial 2004 KDOQI, bone guidelines were controversial in part because of industry support and the COI of the work group (5). Dr. Marcia Angell, former editor of the *New England Journal of Medicine*, stated that the guidelines "can't be trusted" because of the financial support of industry (5). The opinion-based recommendation to maintain calcium "preferably toward the lower end (8.4 to 9.5 mg/dl)" (37) of the normal range clearly favored use of cinacalcet, an Amgen drug that was nearing approval at the time, a fact certainly noted by at least one biotech stock analyst (5). This recommendation, based on association and inference, also favored use of sevelamer, a non-calcium-based binder and a product of Genzyme. Both corporations were financial supporters of the bone guideline development. Despite the lack of substantive data, the guidelines also opined that active vitamin D compounds in stages 3 and 4 CKD should be avoided when calcium exceeded 9.5 mg/dl (37). This too favored use of cinacalcet.

Kidney Disease Improving Global Outcomes (KDIGO) is an independent organization that is governed by an international board of directors, managed by the NKF, and intended to supplant KDOQI. The group is funded mostly by industry, but the list clearly reflects an attempt to expand the scope of support to neutral corporations or groups. The effectiveness of this attempt is impossible to gauge because KDIGO also refuses to report individual donor amounts.

The *Clinical Guide to Bone and Mineral Metabolism in CKD* (38) is the initial publication of KDIGO and is an opinion-based primer on renal osteodystrophy. Although a well-written and well-edited series of articles, it lacks any COI statements by the authors. It also contains an extensive, up-to-date, and favorable view of the association of lower calcium and phosphorus levels with improved survival in dialysis patients (39). However, the book lacks a substantive discussion of the association of active vitamin D use with improved survival, despite that vitamin D can increase calcium and phosphorus. The text and the figures that outline treatment of hyperparathyroidism in patients with stages 3 and 4 CKD lack mention of oral paricalcitol, a form of active vitamin D and the major competitor to cinacalcet (40). These inclusions and omissions favor the sale of products of Amgen, a sponsor of KDIGO.

The KDOQI and KDIGO guideline recommendations may be entirely correct. However, they overwhelmingly are opinion based, and some offer large economic benefits for drug manufacturers and dialysis corporations. Many of these corporations fund the guideline process, then promote adherence to these recommendations within the nephrology community, frequently employing as speakers the same individuals who wrote the guidelines. None of this may be improper, but these interconnections undoubtedly will lead many to question the integrity and the independence of highly influential practice guidelines.

Recommendations

KDOQI guidelines have been a tremendous asset to the renal community and patients with CKD alike. The improvement and the standardization in care as a result of KDOQI cannot be overstated. Outlined herein are process problems that involve corporate support and transparency, identification and management of COI, ensuring the patient-centeredness of the evaluation of nondefinitive and emerging medical evidence, and the final review and timing of release of new recommendations. All of these process problems can be improved to maintain and enhance the integrity of renal guidelines.

Corporate support for the development of guidelines is considered by many a necessary evil. Neither the NKF nor KDIGO is capable of independently funding guideline development. Given the financial ramifications to the government, guidelines that are developed through the National Institutes of Health, similar to the hypertension and cholesterol guidelines, would be ideal. Despite recent funding limitations, the cost to the government of opinion-based recommendations potentially is immensely greater than the cost of establishing a government-sponsored, conflict-free renal guideline group. Congress can and should demand action.

For the NKF, pairing with other organizations, such as the American Society of Nephrology and International Society of Nephrology, could reduce and diffuse the dependence on and influence of industry support. Permitting a single corporation to provide full support for all stages of the specific guideline's process (development, publication, and distribution) increases the appearance of bias and should be avoided.

The NKF must be forthcoming about all funding sources and the amount received from each source. The full exposure of the amount of funding from each company (both direct and indirect) might demonstrate that there is less influence than perceived or may raise concerns and lead to limitations on support.

A claim that all real experts have conflicts and, therefore, that it is necessary and even ideal to seek these experts despite their conflicts is not supported by evidence. By refusing to prohibit or greatly limit COI, large corporations may try to establish financial connections to experts and create experts by widely promoting individuals who are sympathetic to their positions *via* authorship on manuscripts and regional and national speaking engagements. Work groups largely should prohibit experts with COI from participating in guideline development. If the opinion-based recommendations of experts with COI are so reasonable, then would not intelligent physician-scientists who do not have COI and review the same information make similar recommendations? Work group members should have no ongoing COI. Work group members' historical COI should be published in great detail. Stock ownership or corporate board positions should be unacceptable. Strict rules that exclude or limit experts with COI would create a disincentive among corporations to attempt to influence experts.

Management of other forms of COI is not a passive process (16). The COI of each member should be defined clearly to all members at the beginning of the process. The work group and the advisory board decide how these conflicts will be handled before any data review, including excluding members from

certain decisions or even removing members (41). A complete statement of how specific issues that are related to COI were handled by the work group should be presented in an appendix. COI should be updated throughout the process, and members should not be permitted to use their position to garner COI.

Work groups should reflect exceptional expertise and the broad range of opinions, particularly in controversial areas. The NKF appropriately denies corporations a say in work group membership. The NKF should exclude all national and international expert advocates/speakers for corporations from participating in work groups. These experts often present views in editorials and speeches that indicate that they are likely poor choices for critical reassessment of nondefinitive medical information. When association data or inconclusive studies are the basis of guidelines, work group members should not review their own research.

Last, external reviews and publication of guidelines should not be deadline driven. Every publication should incorporate all relevant information. Bias by omission is just as serious as bias by commission. Revision and publication of guidelines should depend on new science, not arbitrary deadlines.

Disclosures

D.W.C. is a consultant/advisor to Abbott, Amgen, Roche, and Watson; a speaker for Abbott, Amgen, Merck, Watson, and the NKF; a research investigator funded by or for Abbott, Advanced Magnetism, Amgen, Roche, Watson, and the NKF of Eastern Missouri; and a clinical grant reviewer for the NKF.

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