tests rely on the assumption of normal distribution, alternative methods such as non-parametric or permutation procedures are needed to derive more accurate *P* values. The trait can also be dichotomized on the basis of a predefined ACR threshold, but this approach generally leads to a significant loss of power. Future studies that examine kidney pathology scores, such as degree of glomerulosclerosis or fibrosis instead of the ACR measurements, may also circumvent this problem by providing more powerful injury-specific phenotypes. Finally, for the purpose of testing for signal concordance in humans, a careful selection of adequately powered human cohorts with disease phenotypes that are closely related to those studied in mice is necessary. Because the susceptibilities of mice to age-related albuminuria and to diabetic nephropathy may have distinctly different genetic determination, one cannot discard the mouse signals that are not observed in the human cohort. Hopefully, with the increasing number of human genome-wide association study data sets, more powerful cohorts will soon become available to make these types of approaches more feasible. Lastly, we must remain aware that significant associations are not a proof of causality but merely represent a screening method for identifying genetic variants that warrant further research.

DISCLOSURE
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Anemia treatment in chronic kidney disease accompanied by diabetes mellitus or congestive heart failure

Steven Fishbane[1] and Nobuyuki Miyawaki[1]

Anemia is common in chronic kidney disease (CKD). The CHOIR study found increased risk of a composite cardiovascular outcome when anemia was treated with epoetin-alfa to a target hemoglobin level of 13.5 as compared with 11.3 g/dl. Whether this increase applies to all patient subgroups equally is unclear. We discuss an analysis by Szczech and colleagues of the effects of the higher hemoglobin target in CKD patients with diabetes mellitus or congestive heart failure.

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In this issue of *Kidney International*, Szczech and colleagues[1] report on a *post hoc* analysis of the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study.[2] The original study was notable for finding increased risk of a composite cardiovascular end point with epoetin-alfa targeted to a hemoglobin (Hgb) level of 13.5 as compared with 11.3 g/dl in patients with chronic kidney disease (CKD). When this is considered together with the CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta) study (CKD patients)[3] and the Normal Hematocrit Cardiac Trial (hemodialysis patients),[4] there was a strong trend in each study for increased risk for mortality with higher Hgb targets during erythropoiesis-stimulating agent (ESA) treatment. As a result, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) anemia guidelines were revised in 2007 to include an evidence-based warning to avoid Hgb targets above 13 g/dl in CKD patients treated with ESAs. Little, however, has been learned about whether higher Hgb targets affect certain sub-populations differently. The current elegant analysis by Szczech *et al.*[1] examines the effect of Hgb target in the CHOIR study on two highly relevant sub-populations, CKD patients with diabetes mellitus and those with congestive heart failure (CHF).

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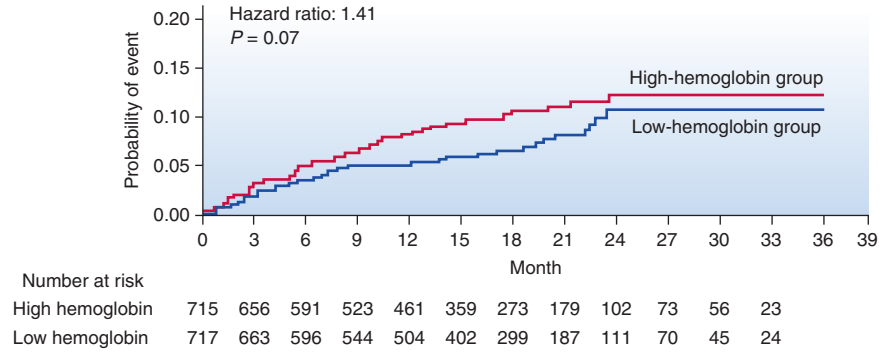

Figure 1 | Hospitalizations for congestive heart failure (without renal replacement therapy) in the CHOIR study. There was a strong trend (hazard ratio 1.41, $P = 0.07$) toward increased risk for hospitalization among patients randomized to the high-hemoglobin-target group. (Adapted with permission from ref. 2.)

Before we consider the interesting findings of this analysis, one thing must be stated clearly. The article by Szczech *et al.*[1] represents a *post hoc* observational analysis and, while interesting, carries little evidentiary weight compared with the three major randomized controlled trials (RCTs) noted above. These studies found trends for increased mortality of 21%–48% with higher Hgb targets in the general CKD population. The novel findings of Szczech and colleagues[1] should stimulate consideration of causal pathways and generate new approaches to RCTs to evaluate anemia Hgb targets in the sub-populations analyzed. But there should be no change at all to current ESA treatment in these patients. The Hgb target during ESA therapy should remain either 10–12 or 11–12 g/dl depending on whether US Food and Drug Administration prescribing instructions or the KDOQI guidelines are used as guidelines.

Szczech *et al.*[1] found that the increased risk found in the CHOIR study with the higher Hgb target did not occur among patients with either diabetes mellitus or CHF. An observation of this type is always worth testing with a question of whether the finding is biologically sensible and plausible. This leads directly to the question of what are the causal pathways that explain the harm found with higher Hgb targets in broader populations. A variety of hypotheses, all difficult to prove, have been suggested, including (1) increased blood viscosity, (2) toxic effects of higher ESA doses, (3) a special vulnerability in ESA-hyporesponsive patients, (4) toxicity of additional iron treatment requirements, (5) increased blood pressure during ESA treatment, (6) platelet effects, and others.[5,6] Whichever of these is the true cause of harm with higher Hgb targets, it is difficult to see why patients with diabetes or CHF would be immune to the harmful effects. There certainly could, however, be some yet-to-be-hypothesized mechanism, and continued research is to be encouraged.

Among patients with diabetes, a highly relevant study is the recently completed TREAT study (Trial to Reduce Cardiovascular Events With Aranesp Therapy). This was a 4000-patient double-blinded RCT that compared darbepoetin treatment to a Hgb target of 13 g/dl with placebo among patients with diabetes mellitus type 2 and CKD. Although not a pure test of ESA-treated Hgb targets, it is yet another study that used ESA therapy to treat to a higher-than-typical Hgb target. The top-line results of this study were announced recently, and, most importantly, there was no statistically significant difference between the groups in cardiovascular outcomes. This would seem to add external validity to the findings of Szczech *et al.*[1] regarding the safety of higher Hgb targets in diabetics. But one reported result raised concern: "Among the elements that formed these composite endpoints, an excess of stroke events (a labeled risk of Aranesp therapy) occurred in the Aranesp-treated patients compared to those receiving placebo."[7] This is not the first time that increased risk for cerebrovascular events has been found to occur with ESA treatment to higher Hgb targets.[8] But the fact that it occurred in a study specifically of patients with diabetes, and with the greater evidentiary value of an RCT, runs counter to the findings of Szczech *et al.*[1]

Treatment of anemia in patients with CKD and coexisting CHF is a particularly interesting area. Early studies suggested significant benefit of ESA and iron treatment in terms of improved symptoms and reduced hospitalization risk.[9] However, the CHOIR study found that among patients randomized to the higher Hgb target there was a strong trend toward increased risk for hospitalization due to CHF (Figure 1). Indeed, this is one of the great paradoxes of the analysis by Szczech *et al.*[1] The higher Hgb target led to increased hospitalization for CHF in the whole study population, yet a baseline history of CHF was not associated with increased cardiovascular risk with the higher Hgb target! This finding defies easy explanation. Although we cannot explain this discrepancy, we would like to comment on the complexity of ESA treatment among patients with concordant CKD and CHF (a large and growing population of patients). Nephrologists are well aware of the oscillating interplay of renal and cardiac function in these patients. Increased diuresis worsens renal function but improves breathing and edema; reduction in diuretic dose does the reverse. Add ESA treatment to this mix and things become even more complicated. During active diuresis, hemoconcentration occurs, and the ESA dose may be reduced despite no change in actual red-cell mass. When diuretics are held or doses reduced, dilution occurs and Hgb decreases, and ESA dose may be increased despite no actual decrease in red-cell mass. There has been little in the way of formal study of this phenomenon. Mancini *et al.*, however, found that anemia in CHF is often due to a combination of true reduction in red-cell mass with dilution.[10] From the management perspective, nephrologists simply need to be sensitive to the effects of volume

shifts on Hgb concentration, and to adjust ESA doses with this additional variable in mind.

In conclusion, the findings of the interesting analysis by Szczech *et al.*[1] should be a stimulus for further study. But there are no immediate clinical implications of this observational analysis. Hgb targets during ESA therapy for patients with CHF or diabetes mellitus should remain consistent with current guidelines. An Hgb target of 10–12 or 11–12 g/dl remains a reasonable target that balances improved quality of life with potential cardiovascular risk.

DISCLOSURE
The authors declared no competing interests.

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Hepatitis B virus infection in hemodialysis populations: progress toward prevention

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Hemodialysis patients are at increased risk of acquiring hepatitis B virus (HBV) infection. Administration of the standard HBV vaccine is suboptimal as a means of prevention because of an impaired seroconversion response in individuals with chronic kidney disease. Surquin and colleagues describe a novel vaccine adjuvant system that increases speed of seroconversion and duration of seroprotection compared with older vaccine formulations. However, its ability to improve overall seroconversion response remains unproven.

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Over the past few decades, there has been a substantial decrease in the incidence of hepatitis B virus (HBV) infection in hemodialysis patients, probably attributable to screening of blood donors, a decline in blood transfusion requirements with increased erythropoietin use, and authoritative guidelines relating to infection control and vaccination. Despite this progress, hemodialysis patients remain at increased risk of acquiring HBV because of increased exposure to blood products, shared hemodialysis equipment, frequent breaching of skin, immunodeficiency, and continuing high prevalence rates of HBV infection among hemodialysis populations. Although acute infection tends to be mild and asymptomatic in dialysis patients, up to two-thirds may progress to chronic carriage, with significant risk of chronic liver disease, premature death from cirrhosis or liver cancer, and nosocomial transmission within hemodialysis units.[1,2]

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When available to healthy individuals, HBV vaccination is an extremely effective means of disease prevention. Administration of three doses of 20 μg of HBV surface antigen (HBsAg) over 6 months achieves seroprotection rates of more than 90%.[2] Alternatively, among chronic kidney disease (CKD) populations, immune responses to HBV vaccination are impaired, proportionally to the degree of kidney failure.[1] Hence, CKD patients experience lower seroconversion rates (32–80%), lower peak antibody titers, and shorter durations of seroprotection (protective antibody titers maintained in 50% of CKD patients compared with 85% of healthy individuals after 1 year).[2,3] Strategies to improve response rates among such patients have included vaccination as early as possible in the course of renal disease, use of double vaccine dose, and a four-dose rather than three-dose schedule.[1,2] These have yielded some, but still suboptimal, improvement, achieving response rates of approximately 70%.[3] Thus, additional strategies to improve vaccination response remain an important and as-yet unmet priority.

The development of protective immunity following administration of vaccine requires the interaction of the innate and adaptive immune systems (Figure 1). Specifically, antigen recognition requires