

The possible merits of the president's tax-incentive approach deserve debate, but tax reform is a long-term issue that should not stand in the way of the necessary expansion of SCHIP and its September 30 deadline. We believe that the president is making a serious mistake in holding children hostage for the sake of his personal political agenda. SCHIP, a small block-grant program of inarguable merit, is scarcely a stalking horse for universal health care. It is a shining example of

what is good about our country. We have enormous wealth, and in our best moments we have been willing to share it with the most fragile members of our society. If the president is sincere in his commitment to leave no child behind, he must begin by leaving no child uncovered.

1. Iglehart JK. The battle over SCHIP. *N Engl J Med* 2007;357:957-60.

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## Targeting Anemia with Erythropoietin during Critical Illness

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The overall goals of clinical research in the intensive care unit (ICU) are to improve clinical outcomes through enhanced understanding of how critical illness develops and how such illness is best prevented, diagnosed, treated, or palliated. Several "normal" physiological measurements and laboratory values have been abandoned as therapeutic targets during critical illness, since in some randomized trials, attempts to normalize these measurements and values have shown either harm or no benefit with respect to clinical outcomes.

One such target is the hemoglobin concentration. Anemia is commonly acquired in the ICU owing to hemodilution, blood loss, reduced red-cell production, and enhanced red-cell destruction. Furthermore, critical illness is characterized by decreased erythropoietin production, a blunted cellular response of erythropoietin, disordered iron metabolism, and nutritional deficiencies.

An important contribution to the literature appears in this issue of the *Journal*, with Corwin et al.<sup>1</sup> posing this clinical question: What is the effect of weekly treatment with epoetin alfa on the percentage of critically ill patients receiving a red-cell transfusion? In this randomized, concealed, multicenter trial, 1460 medical, surgical, or trauma patients were assigned to receive epoetin alfa (40,000 U weekly for up to 3 weeks) or placebo between 48 and 96 hours after admission to the ICU. The primary outcome was the percentage of patients receiving any red-cell transfusion — an end point traditionally dependent on the transfusion threshold of individual physicians. Although more liberal transfusion of red-cell units contributed to higher transfusion rates among controls than among treated patients in

previous trials involving critically ill patients,<sup>2</sup> the trial by Corwin et al. used a target hemoglobin concentration of 7 g per deciliter to 9 g per deciliter, consistent with the restrictive transfusion strategy favored by the Transfusion Requirements in Critical Care (TRICC) Investigators.<sup>3</sup> No difference was found in the percentage of patients who received a red-cell transfusion (46.0% in the epoetin alfa group and 48.3% in the placebo group,  $P=0.34$ ) or in the number of red-cell units transfused per patient ( $4.5\pm 4.6$  and  $4.3\pm 4.8$ , respectively;  $P=0.42$ ).

The transparent reporting of the recruitment and retention of patients in this trial is welcome. The reported data underscore the challenges of clinical research in critically ill patients. Of 6168 potentially eligible patients, 3587 (58.2%) patients or surrogates were approached to participate, of whom 2127 (59.3%) did not provide consent. Overall, 109 patients were lost to follow-up, 54 (7.4%) in the epoetin alfa group and 55 (7.6%) in the placebo group.

In this trial, approximately 95% of all patients experienced at least one adverse event, and approximately 44% experienced at least one serious adverse event. These rates reflect the maxim that critical illness is a series of established and acquired evolving, static, or resolving complications. However, such comprehensive reporting of adverse events, while fulfilling regulatory requirements, may induce either inappropriate alarm or a false impression of safety. From a clinical perspective, adverse events are interpreted in the context of the population enrolled. For example, since the physical examination is insensitive for identifying proximal deep-vein thrombosis and pulmonary embolism in semirecumbent patients

receiving mechanical ventilation,<sup>4</sup> venous thromboembolism will be underdiagnosed when objective screening tests are performed only on the basis of clinical suspicion.

As compared with the placebo group, the increased incidence of thrombotic vascular events in the epoetin alfa group (hazard ratio, 1.41; 95% confidence interval [CI], 1.06 to 1.86) was detected in the absence of screening tests and despite the exclusion of patients at high risk for this complication (those with chronic renal failure,<sup>5</sup> previous venous thromboembolism,<sup>5</sup> and cardiac ischemia). The 45 to 55% increase in the relative risk of vascular thrombotic events was independent of dose and is consistent with the higher rates of venous thromboembolism among patients with cancer treated with erythropoietin than among those treated with placebo.<sup>6</sup> Greater rates of arteriovenous access thrombosis and mortality have been found among patients with chronic renal failure who had higher hemoglobin targets than among those who had lower targets (risk ratio for thrombosis, 1.34; 95% CI, 1.16 to 1.54; risk ratio for mortality, 1.17; 95% CI, 1.01 to 1.35).<sup>7</sup> Recently, findings of increased numbers of thrombotic vascular events and deaths and concerns about tumor progression associated with the use of erythropoiesis-stimulating agents have led to black-box warnings from the Food and Drug Administration.

Corwin et al. reported similar mortality in the epoetin alfa group and the placebo group, both at 29 days and at 140 days, on the basis of a Cox regression analysis. This is consistent with a meta-analysis of nine trials involving critically ill patients that showed that the use of erythropoietin does not influence mortality (odds ratio among patients receiving erythropoietin vs. those receiving placebo, 0.86; 95% CI, 0.71 to 1.05).<sup>2</sup> In the trial by Corwin et al., as is often the case in critical care research, it is challenging to balance the benefits and harms observed, given the diverse and complex courses of disease and treatment, potentially including vascular thrombotic events, death, transfusions, loss to follow-up, and discontinuation of the study drug (8.3% of patients in the epoetin alfa group and 10.9% of those in the placebo group).

The concept that erythropoietin saves the lives of trauma patients with hemoglobin concentrations below 12 g per deciliter who have been in the ICU for at least 48 hours and who do not have renal insufficiency or prior venous throm-

boembolism is tantalizing but premature. The interaction between the stratification variables of the admission group and the study group was not significant. In the study by Corwin et al., mortality data for the 793 trauma patients were adjusted for 10 covariates. Twelve more trauma patients had died in the placebo group than in the epoetin alfa group at both day 29 (26 vs. 14 [6.6% vs. 3.5%]) and day 140 (36 vs. 24 [9.2% vs. 6.0%]). This small absolute difference in the number of decedents is insufficient to provide support for the routine use of erythropoietin in practice. Trauma patients have a higher risk of venous thromboembolism than do other ICU patients, which could lower the number of patients "needed to harm." Inferences about subgroups are limited by unclear mechanisms of action, which appear to be exclusive to trauma patients and are not mediated by transfusions averted. Finally, the increased mortality in trials involving other populations receiving more than three doses of erythropoietin remains a concern.<sup>2,6,7</sup> We trust that these hypothesis-generating subgroup results will be tested in a large, rigorous trial to carefully evaluate the use of erythropoietin in trauma patients.

As for other research directions, this intriguing trial should incite some investigators in bedside-to-bench research to explain the potential survival benefits of erythropoietin in trauma patients; others may seek understanding of unanticipated adverse events. Clinical investigators may reexamine the risk-benefit ratio for administering erythropoietin to patients with chronic renal failure in the ICU, given their high prevalence of vascular disease. Large observational studies are needed of anemia, erythropoietin, transfusions, and myocardial ischemia in patients in the ICU, in whom the biomarker troponin is commonly elevated, conferring an increased risk of death.<sup>8</sup> Health services research on behavioral approaches to blood conservation and restrictive transfusion strategies will also advance this field.<sup>9</sup>

As this study illustrates, large, rigorous investigations involving vulnerable, critically ill patients are crucial to help inform clinicians about what to do, what to consider, and what to avoid. Without a clear indication for initiating erythropoietin in all critically ill patients, new prescriptions for this drug should be restricted to randomized trials with independent research oversight carefully examining fatal and nonfatal clinically important outcomes.

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## Maintaining Sinus Rhythm — Making Treatment Better Than the Disease

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Atrial fibrillation affects patients by increasing their risk of stroke and decreasing their quality of life. Unfortunately, even if restoration of sinus rhythm is possible, most patients remain at risk for stroke and need continued protection with anticoagulation therapy.<sup>1,2</sup> Patients with atrial fibrillation usually have shortness of breath, palpitations, and chest pain. An additional and less well appreciated symptom is fatigue, a nonspecific symptom in the elderly population that has a broad differential diagnosis. Since the risk of atrial fibrillation increases with age and since the mean age of Western populations is steadily rising, the well-described projected increase in the incidence of atrial fibrillation will probably continue for the foreseeable future.<sup>3</sup>

The motivation to restore and maintain sinus rhythm is not to obviate the necessity of anticoagulation therapy but to improve the quality of life, as shown in the Sotalol–Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T).<sup>4</sup> Therapies that have been approved by the Food and Drug Administration (FDA) or supported by association guidelines for the maintenance of sinus rhythm in patients with atrial fibrillation have substantial limitations and side effects. Flecainide and propafenone are associated with an increased risk of life-threatening ventricular arrhythmias and are contraindicated in patients with coronary artery disease (approximately 30% of patients with atrial fibrillation) and in those with heart failure or significant left ventricular

hypertrophy.<sup>5</sup> Sotalol and dofetilide need to be initiated in the hospital because of the risk of QT prolongation and torsades de pointes.<sup>6</sup> Amiodarone, which is not FDA-approved for use in atrial fibrillation, does not have the proarrhythmic effects of the other agents but can adversely affect the thyroid, lungs, kidneys, liver, skin, and nervous system, among other effects.<sup>7</sup>

In this issue of the *Journal*, Singh et al.<sup>8</sup> report on two identical studies, one predominantly in Europe and the other in North America, South America, South Africa, and Australia, evaluating the efficacy of dronedarone, a drug with an electropharmacologic profile similar to that of amiodarone but with modifications intended to eliminate the adverse effects attributable to the thyroid. Dronedarone inhibits the potassium currents  $I_{Kr}$ ,  $I_{Kl}$ ,  $I_{KACH}$ , and  $I_{sus}$ , as well as sodium currents and slow L-type calcium currents in isolated cardiomyocytes.<sup>9</sup> In addition, dronedarone has antiadrenergic properties.<sup>10</sup> In vivo, dronedarone has been shown to be as effective as amiodarone in arrhythmia models.<sup>11</sup>

The studies by Singh et al. were placebo-controlled and showed that in patients with a history of atrial fibrillation who were in sinus rhythm at the time of drug initiation, dronedarone significantly prolonged the interval until the first recurrence of arrhythmia.<sup>8</sup> The likelihood of recurrence of atrial fibrillation at 12 months was also significantly reduced.

An important aspect of these two dronedarone