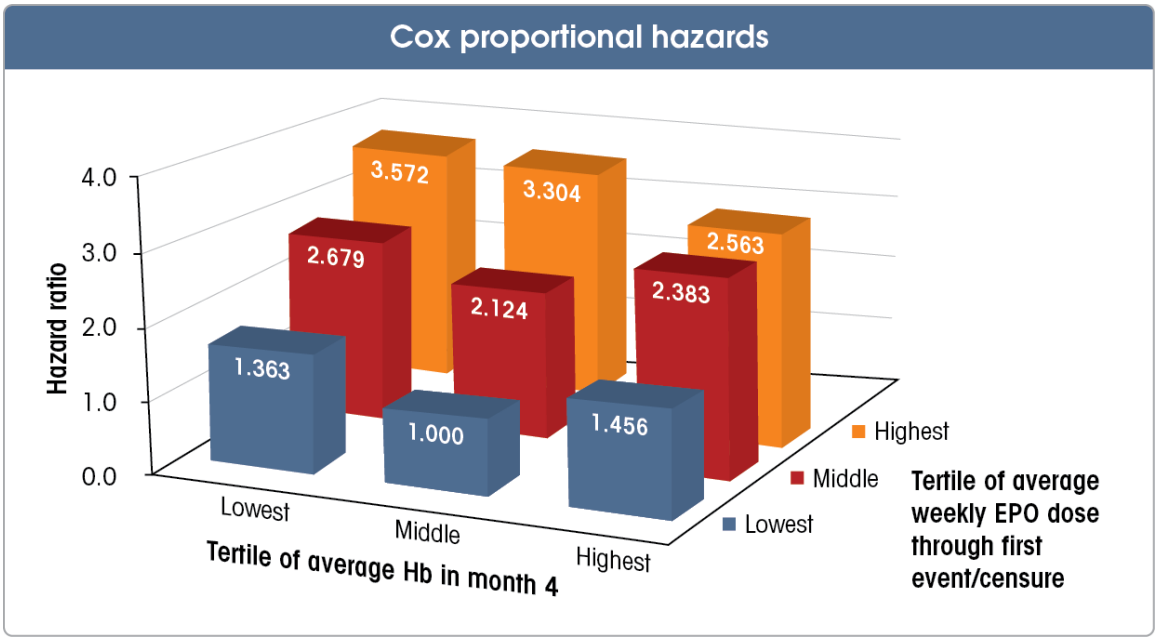
The strongest correlation of adverse outcomes in the post-hoc analyses has been to the level of the recombinant erythropoietin stimulating agent (rESA) dose, not the hemoglobin level achieved.

All of the studies analyzed to date demonstrate that both nondialysis and dialysis-dependent chronic kidney disease (CKD) subjects who achieved normal hemoglobin levels with or without minimal doses of injectable rESAs or supplemental iron had better clinical outcomes than subjects assigned to higher hemoglobin targets who failed to reach the assigned level with increasing doses of injectable rESAs and iron. In addition, CKD patients who are able to achieve and maintain normal hemoglobin levels through means other than the use of injectable rESAs (such as hypoxia or iron supplementation) experienced fewer cardiovascular events and reduced morbidity and mortality. Recent studies of injectable rESA use in various preclinical models (including nonhuman primates) also showed that the frequency of mortality and thrombotic events cannot be explained solely by the achieved higher hemoglobin levels, but is related to the dose, dose frequency, and dose duration of injectable rESAs.

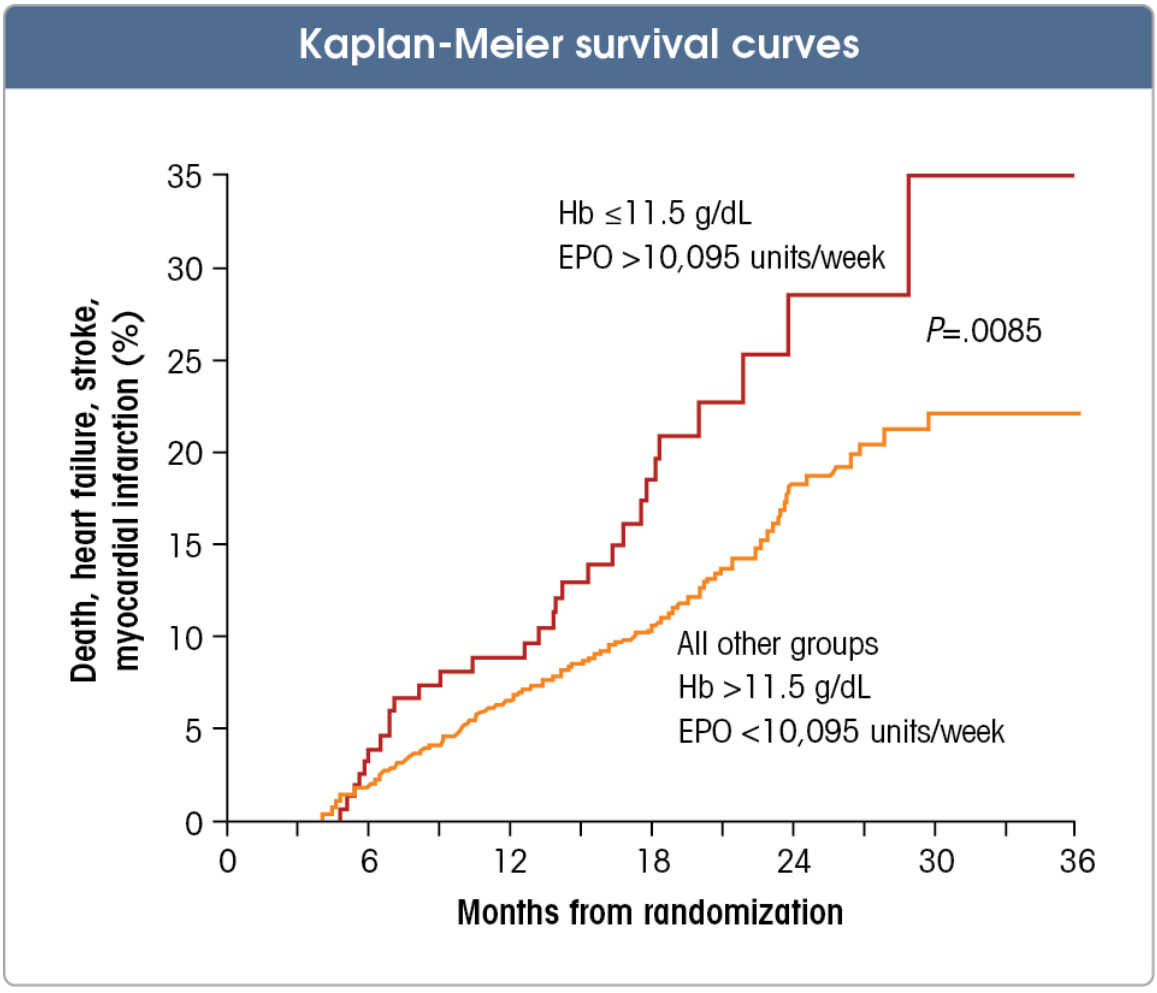
The graphs below highlight these findings. The first chart explores the relative risk of serious cardiovascular adverse events, including death, hospitalization for heart failure, stroke, or myocardial infarction, based upon the hemoglobin achieved during the study as well as the weekly rESA dose. The data clearly show that the risk of adverse cardiovascular events was greatest in those patients receiving the highest rESA doses, regardless of the hemoglobin level that was achieved.



The second graph explores the probability of reaching 1 of several adverse events (death, heart failure, stroke, or myocardial infarction) over time for 2 different groups:

• Patients who achieve the target hemoglobin level with a low rESA dose

• Patients who do not reach the target hemoglobin level, but receive a high rESA dose in an effort to reach the target level



This chart is consistent with the previous chart as it shows that patients with high hemoglobin levels on low rESA doses have better outcomes than patients with high rESA doses and low hemoglobin levels. Therefore, high injectable rESA doses, not high hemoglobin levels, appear to be correlated most strongly with adverse outcomes.