thrombosis rates to decrease a syndrome, which affects only 1–8% of the accesses, seems to have an unfavorable risk benefit profile.

The MILLER measured, standardized banding procedure is successful because it allows for precise application of resistance into a system.[2] This procedure is minimally invasive and can be performed multiple times just as easily as it can be undone by simply dilating the band with an angioplasty balloon. Ligation of the perforating vein definitely seems to be a good idea in helping the superficial veins to mature. However, it is unlikely to achieve a high level of success in the treatment and prevention of DASS. Although it is a feasible treatment, limited precision of flow volume reduction and irreversibility lead to the same problems that made traditional banding procedures unsuccessful.

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The effect of epoetin dose on hematocrit

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To the Editor: Cotter *et al.*[1] used United States Renal Data System data from 14,001 incident patients to estimate the dose–response relationship between epoetin (EPO) and hematocrit. The authors used their analysis to infer the maximum effective EPO dose and suggested that this should inform Federal reimbursement policy. However, the analytic approach used is inconsistent with FDA guidance and the inferred maximum dose is not likely to be generalizable to the US dialysis population. We think it is inadvisable to support reimbursement policies based on inferential information without careful consideration of the potential clinical consequences.

When there is a time delay in clinical response (for example, hemoglobin) following dosing, FDA recommends parallel dose–response studies where patients receive constant doses over fixed time periods with no target ceiling, such as that proposed by Eschbach *et al.*[2] However, Cotter *et al.*[3] used observational data containing frequent EPO dose titrations, analyzed with marginal structural modeling. In studies of flexible dosing, FDA recommends employing mixed-effects regression, which accounts for interpatient variability in EPO responsiveness. This is important because a broad range of EPO doses (~40-fold) are required to achieve target hemoglobin levels in individuals.[4] The application of unconventional analytics using observational data should not supplant knowledge gained by the established approach of controlled clinical trials designed to estimate dose–response. Inferring a maximum effective dose from an estimated mean might result in inadequate dosing for many patients. Any new EPO policy should be based on the most rigorous data and analyses, with careful assessment of the potential impact.

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Response to 'Regarding "the effect of epoetin dose on hematocrit"'

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Critchlow *et al.*[1] state that 'the application of unconventional analytics using observational data should not supplant knowledge gained via the established approach of controlled clinical trials designed to estimate dose–response.' We agree. However, controlled trials might not provide a generalizable dose–response curve if more sick patients who require higher doses of erythropoiesis stimulating agents are under-represented because of restricted enrollment criteria, patient's underlying disease burden, etc. Therefore, controlled trials based on such restrictions are likely to underestimate the range of erythropoiesis stimulating agent dose required in the general hemodialysis population.

In contrast, our analysis of dose–response uses data from an unselected medicare population and over the dose range currently used by clinicians. We would encourage Amgen and others to attempt to resolve the dose–response issue with appropriately designed clinical trials in a heterogeneous population. In the absence of such trials,