further suppress hepcidin, and potentially worsen iron overload in β-thalassemia.

The authors examine the consequences of knockout of erythroid *Tfr2* on erythropoiesis in β-thalassemia by performing a bone marrow transplant of *Tfr2*$^{-/-}$ thalassemic (*Hbb*$^{th3/+}$) cells into *Hbb*$^{th3/+}$ mice.[2] The results demonstrate significantly elevated hemoglobin in *Tfr2*$^{-/-}$ *Hbb*$^{th3/+}$ relative to *Hbb*$^{th3/+}$ mice between 9 and 22 weeks following bone marrow transplant, with a decrease in serum Epo, fewer reticulocytes, and an increased proportion of mature erythroid precursors in the bone marrow. The increased hemoglobin is associated with a decrease in circulating Epo and modestly decreased expression of Epo-responsive genes (including ERFE). Spleen size is unchanged. Furthermore, the authors iron-restrict *Tfr2*$^{-/-}$ *Hbb*$^{th3/+}$ bone marrow–transplanted mice to inquire whether the mechanism of improved hematologic parameters is iron deficiency–driven or whether *Tfr2* loss works by an alternative mechanism. The authors propose that the improvement in hematologic parameters in *Tfr2*$^{-/-}$ *Hbb*$^{th3/+}$ bone marrow–transplanted mice is not the result of limitated available iron.

There are inherent complexities in the relationship between *Tfr2* and EpoR that require accounting for the circulating ligand for *Tfr2* (ie, transferrin isoforms) and for EpoR (ie, Epo concentration). Assessing Epo responsiveness in this setting is challenging, given the change in circulating Epo levels in the *Tfr2*$^{-/-}$ *Hbb*$^{th3/+}$ bone marrow–transplanted mice. Additional experiments are required to fully clarify the expected proportionality between circulating Epo levels and Epo-responsive gene expression. Although RNAseq analysis from spleen identify changes that might be expected with Epo-mediated increased erythropoietic activity, as pointed out by the authors, the analysis is confounded by differences in spleen iron. As such, the conclusion that erythroid parameter improvements in β-thalassemic mice with loss of erythroid *Tfr2* are entirely the result of enhanced Epo-sensitivity will likely require further study.

Based on these interesting findings, the authors suggest a potentially translatable approach by manipulating *Tfr2* in β-thalassemic erythroblasts. However, the therapeutic application of decreased *Tfr2* in erythroblasts may prove to be challenging. The beneficial effect on erythropoiesis in β-thalassemic mice dissipates at 37 weeks posttransplant, possibly as a consequence of critical iron deficiency for erythropoiesis. A better understanding of the basis for this effect, and the effect of transferrin and Epo on the functional properties of erythroid *Tfr2* are needed. Nonetheless, results of *Tfr2* haplo-insufficient *Hbb*$^{th3/+}$ mice suggest the possibility of partial *Tfr2* inhibition using antisense oligonucleotide or small interfering RNA technology. Last, investigating the consequences of *Tfr2* loss in mouse models of β-thalassemia major, rather than intermedia, would be informative.

Conflict-of-interest disclosure: Y.Z.G. serves as a consultant for La Jolla Pharmaceutical Company and has received funding from ApoPharma; R.E.F. serves on the Medical Advisory Board of Protagonist Therapeutics. ■

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DOI 10.1182/blood-2018-10-876110

THROMBOSIS AND HEMOSTASIS

Comment on Amin et al, page 2298

Postthrombotic syndrome: simple prevention

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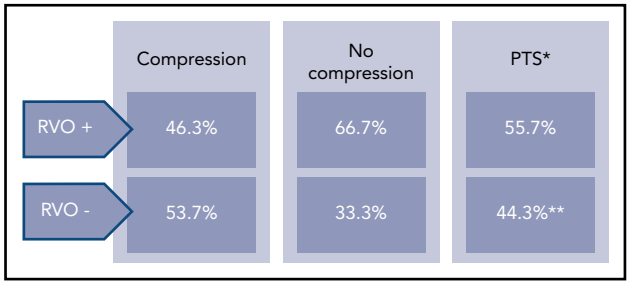
In this issue of *Blood*, Amin et al provide data showing early compression therapy post–venous thromboembolism (VTE) to be effective in reducing the incidence of postthrombotic syndrome (PTS) by achieving reduced residual vein obstruction (RVO) on follow-up ultrasound.[1]

PTS is a significant, disabling,[2] and costly[3] complication in up to 50%[4] of patients with VTE. Given that other PTS treatment interventions, such as the use of elastic compression stockings,[5] or early thrombolysis[6] provide limited benefit or are controversial in reducing the incidence of this morbidity, the current findings are potentially of great clinical interest. The scale of benefit appears comparable to the effect of well-controlled anticoagulation therapy on risk reduction of the incidence of PTS.[7]

Variable in incidence, and in severity, PTS is a common and potentially disabling



Results summary. Asterisk (*) indicates measured at 6 months. Double asterisks (**) indicate odds ratio, 0.66; 95% confidence interval, 0.46-0.96.

longer-term complication of deep vein thrombosis (DVT). Symptoms can range from pain, swelling, skin changes, and heaviness of the limb to venous claudication and development of venous ulcers in the most severe cases. The cost in terms of medical care and loss of quality of life are well documented and considerable.[1-4] The impact of PTS on health is comparable to that associated with major chronic diseases.[2,3] Prevention of the development of PTS should be optimized, as treatment options for symptom control are of limited benefit. Standardized diagnostic criteria, and clinical risk factors associated with the occurrence of PTS are now better understood.[4,5] The pathophysiology of PTS is thought to be related to venous hypertension and its detrimental effects on vascular integrity, venous insufficiency, and the inflammatory response.[4] Clot burden and vein obstruction are associated with venous hypertension. Residual vein obstruction as evaluated on follow-up ultrasound is associated with the risk of PTS.[8] Efforts to reduce clot burden and obstruction by means of early thrombolysis or interventional stents and recanalization procedures have shown success in reducing PTS in some patients.[6] Both approaches are, however, invasive, associated with potential complications, and depend on specialized resources. Amin et al have used a simple, noninvasive treatment, early external compression by bandages or stockings applied 24 hours post-DVT diagnosis, for a duration of 4 weeks. Their data show a 20% absolute risk reduction in the incidence of residual vein obstruction measured 1 week prior to discontinuing anticoagulation. The benefit of vein recanalization also translates to an 11% absolute risk reduction in the development of PTS measured at 6 months post-DVT diagnosis (see figure).

These findings thus corroborate the pathophysiologic role of residual clot in the development of PTS and provide data to suggest that a simple, noninvasive treatment intervention of early compression has a role in promoting clot resolution and reducing the incidence of postthrombotic complications. The use of early compression was not randomized in this study but reflected local practice. Anticoagulant treatment was mostly with vitamin K antagonists but did include the use of low-molecular-weight heparin and direct oral anticoagulants in the minority of the study patients. Anticoagulation control was optimal for both early compression and noncompression groups. All patients subsequently wore elastic compression stockings for a minimum of 6 months. The 2 patient groups did differ in some baseline characteristics, which were adjusted for on statistical analysis. A subgroup analysis of patients with ileofemoral DVT showed a lack of therapeutic effect in the compression group, thus remaining a challenging patient population for PTS prevention. The large sample size and long-term follow-up of the overall patient group strengthen the conclusions of the current study.

The simplicity of the early compression should make this intervention easily available in all health care institutions and should be strongly considered for implementation. Further studies to refine the application and risk stratify patients for greatest potential benefit, along with the evaluation of other interventions to reduce the incidence of PTS, are awaited with interest.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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DOI 10.1182/blood-2018-10-877076