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Potential Role of Recombinant Erythropoietin and Intravenous Iron Preparations in Target Vessel Re-Stenosis Following Coronary Stent Insertions in Hemodialysis Patients

Key words: ESRD, atherosclerosis, cardiovascular disease, anemia, oxidative stress, inflammation

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To the Editor In an article published in the November issue of the Journal, Dr. Takeuchi and colleagues (1) reported on the incidence of target lesion re-stenosis in a cohort of 165 consecutive patients with coronary artery disease who had undergone 231 paclitaxel-eluting stent placements in their facility between May 2007 and August 2009. All patients had been treated with two types of anti-platelet agents (aspirin and Clopidogrel or Ticlopidine) and 90% of the subjects had received follow-up coronary angiogram 6 months later. The underlying diseases in the study population included hypertension in 75%, hyperlipidemia in 78%, diabetes mellitus in 60% and end-stage renal disease treated with intermittent hemodialysis in 14%. Overall target lesion revascularization rate within 6 months following stent placement was 14.6%. The rate of target lesion re-stenosis in hemodialysis patients (43%) was far greater ($p=0.0001$, odds ratio: 6.61, 95% C.I.: 2.34-18.6) than in those with hypertension (15.0%), hyperlipidemia (12.4%), and diabetes mellitus, treated with either oral medications (12.5%) or insulin (12.0%). Based on these observations the authors concluded that hemodialysis confers the greatest risk of target lesion re-stenosis after a coronary artery drug-eluting stent placement procedure. In fact comparison of outcomes among patients with chronic kidney disease undergoing coronary artery stent placement has revealed a significantly greater incidence of target vessel revascularization in the dialysis than in non-dialysis patients (2-5). The increased risk of target lesion re-stenosis in hemodialysis patients has been attributed to chronic vascular inflammation and poor vessel dilation (6) due to medial calcification commonly present in these patients (7-9). It is noteworthy however, that using intravascular ultrasonography or angiography Takeuchi et al (1) found no difference in the minimal stent area or minimal stent lumen diameter between patients who did and those who did not experience target lesion re-stenosis, thus excluding technical factors such as poor dilation as the cause of increased risk of stent re-stenosis in their hemodialysis-dependent patients. Exposure of blood to artifi-

cial surfaces such as tubing and dialyzer membrane, mechanical stress induced by the roller pump and influx of impurities from the dialysate compartment are known to result in activation of leukocytes and release of pro-inflammatory mediators in patients undergoing hemodialysis. The recurrent hemodialysis-induced inflammatory response is thought to, in part, contribute to target vessel re-stenosis following stent placement by stimulating neo-intimal expansion in hemodialysis-dependent patients (10).

The author wishes to suggest that two additional factors can, in part, contribute to the high incidence of target vessel re-stenosis in patients maintained on chronic hemodialysis treatment. These include recombinant erythropoietin products collectively referred to as erythropoiesis-stimulating agents (ESAs) and intravenous iron preparations which are used to treat anemia in nearly all dialysis-dependent patients with end-stage renal disease. ESAs have been shown to cause vasoconstriction-dependent hypertension and vascular smooth muscle cell proliferation, increase endothelin, thromboxane and reactive oxygen species (ROS) production, reduce prostacyclin and nitric oxide generation and up-regulate vascular tissue rennin-angiotensin system (reviewed in Ref. (11, 12)). These effects of ESAs particularly when administered in high doses to overcome ESA-resistant anemia in highly inflamed patients can contribute to target vessel re-stenosis following coronary stent placement. In addition, by stimulating platelet production, increasing platelet activity (via augmentation of platelet calcium signaling), raising E-selectin and P selectin expression and release of plasminogen activator inhibitor-1 and von Willebrand factor, ESAs can promote thrombosis (reviewed in Ref. (11-14)). Together via these non-erythropoietic actions, the use of ESAs in dialysis patients can, at least, in part, account for the observed high incidence of target vessel re-stenosis and thrombosis in this population. In fact, the use of these agents has been linked to vascular access stenosis and thrombosis in dialysis patients and to accelerated tumor growth and thrombotic complications in cancer patients (15, 16).

In addition to ESAs, intravenous iron preparations which are commonly used to replenish iron stores in hemodialysis patients can intensify oxidative stress, stimulate monocyte activation and adhesion and promote vascular remodeling (17, 18), events that can potentially facilitate target vessel re-stenosis following stent placement.

Given the universal use of ESAs and intravenous iron preparations in dialysis-dependent ESRD patients and the well-known effects of these agents on vascular tissue and the blood coagulation system, careful assessment of the po-

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tential impact of the dosage and duration of treatment with these agents would be warranted in patients undergoing coronary stent placement procedure.

The authors state that they have no Conflict of Interest (COI).

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