Other Estimation of Blood Losses in Hemodialysis and Formula for Translating Liver Iron Concentration From Iron Balance Calculation Based on Iron Removal by Phlebotomy

To the Editor: In his recent editorial, Daniel Coyne[1] raises concerns regarding iron overload detection in dialysis patients by quantitative magnetic resonance imaging (MRI). Using the equation established by Barry[2] in 1974 (based on the relationship between liver iron content [LIC] and stored iron mobilized by phlebotomy in 12 patients with genetic hemochromatosis, where 30 μmol/g dry liver LIC equals 1 g of iron), Daniel Coyne calculates that the decline in LIC on MRI found by Rostoker *et al.*[3] in their iron-overloaded hemodialysis patients after iron withdrawal (17.9 μmol/g dry liver/month or 215 μmol/g dry liver per year) "cannot match blood losses (7.16 g of iron lost per year with Barry's formula).[2]"

I recently conducted an in-depth review of blood loss in hemodialysis patients; these are related to the hemodialysis procedure itself, to routine blood sampling for laboratory tests, and to occult gastrointestinal bleeding due to uremic enteropathy.[4] In dialysis patients with a native fistula, iron losses are 1340 mg per year compared with 2765 mg per year in patients with a long-lasting double-lumen catheter; these losses are increased by antiplatelet drugs and vitamin K antagonists (703–961 mg of additional iron lost).[4]

With the widely used formula of Brissot *et al.*[5] (based on the relationship between LIC and phlebotomy in 29 cases of genetic hemochromatosis in which 130 μmol/g dry liver LIC equals 1 g of iron), the yearly decrease in LIC found by Rostoker *et al.*[3] (270 μmol/g per year, corresponding to 1680 mg of iron per year) fits fairly well with usual blood losses in hemodialysis patients.

1. Coyne DW. Iron overload in dialysis patients: rust or bust? *Kidney Int Rep*. 2017;2:995–997.
2. Barry M. Liver iron concentration, stainable iron and total body storage iron. *Gut*. 1974;15:411–415.
3. Rostoker G, Griuncelli M, Loridon C, et al. Hemodialysis-associated hemosiderosis in the era of erythropoiesis-stimulating agents: a MRI study. *Am J Med*. 2012;125:991–999.
4. Rottembourg J, Rostoker G. Use of intravenous iron supplementation in chronic kidney disease: interests, limits, and recommendations for a better practice. *Nephrol Ther*. 2015;11:531–542.
5. Brissot P, Bourel M, Henry D, et al. Assessment of liver iron content in 271 patients: a reevaluation of direct and indirect methods. *Gastroenterology*. 1981;80:557–565.

Jacques Rottembourg[1]

[1]Service de Néphrologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, France

Correspondence: Jacques Rottembourg, Hôpital de la Pitié, Service de Nephrologie, 83 Boulevard de l'Hôpital, Paris 75013, France. E-mail: jacques.rottembourg@wanadoo.fr

Received 11 November 2017; accepted 20 November 2017; published online 29 November 2017

Kidney Int Rep (2018) **3,** 220; https://doi.org/10.1016/j.ekir.2017.11.012

The Author Replies: Dr. Rottembourg[1] cites a 1981 paper by Brissot *et al.*[2] stating that liver iron content (LIC) is related to the total body iron (TBI) by approximately each 130 μmol/g dry liver of LIC is equal to 1 g of TBI. Because Rostoker *et al.*[3,4] found a yearly decrease in LIC of 270 μmol/g per year, corresponding to 1.68 g of TBI, they conclude that the magnetic resonance imaging (MRI) estimate of LIC (MRI-LIC) fits well with their calculated annual iron losses in hemodialysis and with the relationship of MRI-LIC to TBI seen in hemochromatosis patients. However, if Rottembourg is correct, this would mean that severe iron overload begins at 1.5 g of iron (200 μmol/g divided by 130 μmol/g = TBI), which is a trivial amount of excess iron in the context of hemochromatosis-induced iron overload.

Rottembourg correctly quotes Brissot *et al.*, but unfortunately, the statement by Brissot *et al.* is a mathematical or typographical error off by a factor of 10, which is easily proven by examining the data and regression equation of Brissot *et al.*[2] provided in their Figure 1 of the same publication. Rostoker *et al.*[4] and Issad *et al.*[5] state that 130 μmol/g dry liver is moderate iron overload, whereas >200 μmol/g dry liver is severe iron overload. Brissot *et al.*[2] present the *Y* axis as LIC in μmol/100 mg of dry liver, so we need to divide the MRI-LIC[4,5] by 10 to graph their results.[2] It is readily apparent based on the figure that an LIC of 13 μmol/100

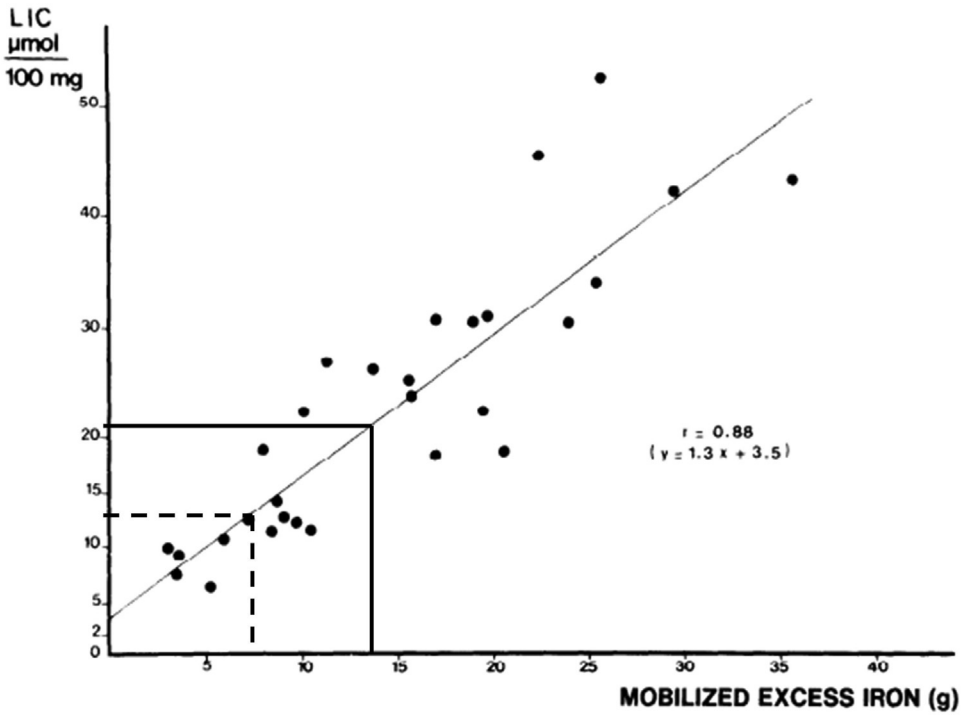

Figure 1. Comparison of liver iron concentration (LIC) values before venosections and mobilized excess iron in 29 cases of idiopathic hemochromatosis. The dotted lines on the graph demonstrate that 13 µmol/100 mg dry liver is 7.3 g of mobilized excess iron, whereas the solid lines demonstrate that 21 µmol/100 mg dry liver is 13.6 g of mobilized excess iron. Adapted with permission from Brissot P, Bourel M, Herry D, et al. Assessment of liver iron content in 271 patients: a reevaluation of direct and indirect methods. *Gastroenterology*. 1981;80:557–565.[1]

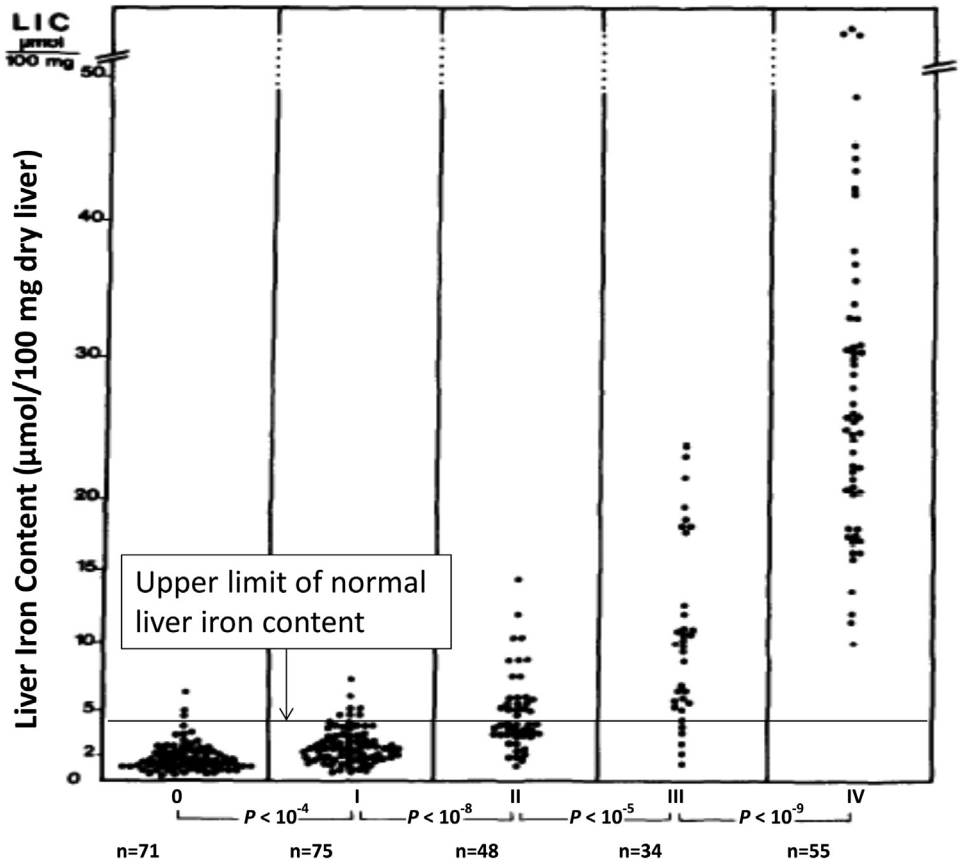

Figure 2. The *Y* axis is the determined liver iron concentration (LIC) from a tissue biopsy, whereas the *X* axis is the estimated LIC based on a histologic estimation system. In groups II and III, all subjects below the line are misclassified by histology because their determined LIC is normal. Also in group III, subjects with between 4 and 10 µmol/100 mg dry liver are overclassified and should be in group II. Adapted from Brissot P, Bourel M, Herry D, et al. Assessment of liver iron content in 271 patients: a reevaluation of direct and indirect methods. *Gastroenterology*. 1981;80:557–565.[1]

mg of dry liver is ~7 g of mobilized excess iron (Figure 1, dashed line), whereas 21 μmol/100 mg dry liver is ~14 g (Figure 1, solid lines). If we solve using the regression equation of Brissot *et al.*[2] (LIC = (1.3 × mobilized excess iron) + 3.5), then the TBI is 7.3 g and 13.6 g, respectively, for these 2 examples. Based on Rottembourg's expected hemodialysis annual blood losses,[3] (1.68 g/yr), patients with severe iron overload by MRI-LIC would take at least 8.0 years to normalize their LIC, and yet Rostoker's group[4] reports that they did this in 10 to 12 months.

Additionally, Figure 2 of Brissot *et al*. demonstrates that semiquantitative histologic estimates of LIC, as Rostoker used in another publication, frequently overestimate the actual LIC.[2,6] At least one-half of the grade 2 LIC estimates had normal actual LIC, whereas ~15% of grade 3 LIC estimates had normal LIC, and many others should have been categorized as grade 2.[2]

In summary, these data indicate that MRI-LIC measurement in dialysis patients overestimates TBI by a factor of 10 when applying Brissot's equation, whereas I conservatively estimated that they were off by a factor of 3 to 6.[2,7] Brissot also demonstrates that histologic assessments of LIC are inferior to actual determinations.[2] I could not have made my points any better.

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2. Brissot P, Bourel M, Herry D, et al. Assessment of liver iron content in 271 patients: a reevaluation of direct and indirect methods. *Gastroenterology*. 1981;80:557–565.
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Daniel W. Coyne[1]

[1]Division of Nephrology, Washington University, St. Louis, Missouri, USA

Correspondence: Daniel W. Coyne, Division of Nephrology, Washington University, St. Louis, Missouri 63110-1093, USA. E-mail: dcoyne@wustl.edu

Received 21 November 2017; accepted 21 November 2017; published online 1 December 2017

Kidney Int Rep (2018) **3,** 220–222; https://doi.org/10.1016/j.ekir.2017.11.011

American Geriatrics Society Beers Criteria and Anticoagulant Use in Older Adults With Renal Impairment

To the Editor: We are writing you regarding the 2015 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.[1] Specifically, this letter is in reference to the use of oral anticoagulants based on creatinine clearance (CrCl) thresholds in this population.

The 2015 criteria provide, for the first time, recommendations on the use of the newer oral anticoagulants (e.g., rivaroxaban, apixaban, edoxaban, dabigatran). The recommendations are provided in Table 6 of the criteria and ultimately direct physicians to either "Avoid" or use a "Reduced dose" for these therapies based on the patient's CrCl. Although most of the recommendations made in these criteria are based on evidence from literature searches, the CrCl thresholds listed for these newer oral anticoagulants are based on the respective Phase 3 clinical trial exclusion criteria, which may not match the actual prescribing direction provided in the labels.

For example, this is evident in the recommendation for rivaroxaban (XARELTO), and patients with atrial fibrillation with a CrCl <30 ml/min. The Beers criteria state that this compound should be avoided in this patient category, whereas the XARELTO package insert, based on clinical trial data, allows for a reduced dose (15 mg) in these patients. It should be noted that the 15-mg dose of rivaroxaban was a dedicated dose for those patients with a CrCl of 30 to 50 ml/min studied in the Phase 3 ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), a dose paradigm that is unique to XARELTO. Although the 15-mg dose was not studied in those patients with a CrCl of ≤30 ml/min, the pharmacokinetic and pharmacodynamic profile