To the Editor:

We read the manuscript by Foubert et al. regarding protamine dosing in 38 adult patients after cardiopulmonary bypass with great interest.(1) We share the opinion of the authors that heparin reversal is an ongoing challenge. The authors evaluated heparin reversal after cumulative 20%-doses of a calculated total protamine dose. For each patient, an individualized heparin dose-response curve was constructed.(2) From this Bull-curve, heparin concentration at end of bypass was deduced, which the authors aimed to reverse using a unit-for-unit protamine to heparin ratio. Complete reversal was defined as an ACT Plus (Medtronic, Minneapolis, USA) returning to a maximum of 1.1 times the patient's baseline measurement. The protamine and heparin employed was of the Leo brand (Leo Pharma, Lier, Belgium). The mean total of administered heparin was 33748 international units (IU) (SD 5518 IU), while the mean protamine total dose was 28930 IU (SD 9479 IU). As the authors state that '1 mg of protamine equals to 100 units of protamine', we infer that a mean dose of 289 mg of protamine was given.

However, the conversion factor used by Foubert et al. to calculate IU from mg of protamine (100:1) differs from the manufacturer's recommendation (140:1). This difference should be considered when interpreting their results. The authors report that the majority of patients showed ACT Plus normalization following administration of as little as 60% of the predicted protamine dose. Our calculations, adjusting for the true potency of the specific brand of protamine used (140:1) indicate that 84 % of the predicted dose (in IU) was needed to achieve ACT Plus normalization. Similarly, the calculated dose of protamine as reported by the authors to be associated with 61.1% ROTEM-diagnosed protamine overdose would in fact correspond to 140% of the required protamine dose, i.e. an excessive amount of protamine, in line with the ROTEM findings.

Obviously, depending on the exact conversion rate used to calculate IU from 1 mg of protamine administered, the clinical message differs considerably: if a 140:1 ratio is respected, as recommended by the manufacturer of the drug, the findings would be in line with the current literature and confirm the widely adopted practice of 1-to-1 IU ratio to neutralize heparin effect with protamine. In the authors interpretation however, i.e. assuming a universal 100:1 ratio regardless of the indicated potency, the findings suggest that the routine practice to use 1 IU of protamine to antagonize 1 IU of heparin leads to overdosing. Importantly, potency of protamine vials varies between manufacturers and may range from 66 IU to 140 IU for 1 mg of protamine (*Exir* vs *Leo* brands). Hence, failure to take manufacturer-specific protamine potency into account may lead to a clear over- or underdosing.

To avoid erroneous conclusions, we advocate all communication concerning heparin and protamine dosages to be described in IU as well as mg, clearly stating brands. Brand-specific conversion ratios should be taken into account. Additionally, detailed information on timing, dilution, additional dosing and autotransfusion is required to allow comparison between different studies. Protamine-to-heparin dosing ratios should be clearly described by referring to initial, total and/or estimated current heparin level at end of cardiopulmonary bypass. More sensitive parameters of low-range heparin activity should be developed and considered to allow

for a more detailed assessment of coagulation status. In this regard, our group has recently been investigating a novel promising Sonoclot-based parameter to estimate low-range heparin activity.(3)

All these considerations should be taken into account to further optimize protamine dosage, which after over sixty years of daily use still proves to be a real conundrum. The brands of the drugs used can have important consequences.

1. Foubert R, Van Vaerenbergh G, Cammu G, Buys S, De Mey N, Lecomte P, et al. Protamine titration to optimize heparin antagonization after cardiopulmonary bypass. Perfusion. 2022 Dec 11.

2. Bull BS, Korpman RA, Huse WM, Briggs BD. Heparin therapy during extracorporeal circulation: I. Problems inherent in existing heparin protocols. J Thorac Cardiovasc Surg. 1975 May 1;69(5):674–84.

3. Vandenheuvel M, Vandewiele K, Van Gompel C, De Kesel PM, Wyffels P, De Somer F, et al. A novel methodology for low-range heparin detection. Eur J Anaesthesiol. 2023 Jan;40(1):57–60.