Artificially depleted plasmas are not necessarily commutable with native patient plasmas for International Sensitivity Index calibration and International Normalized Ratio derivation: a rebuttal

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We read with interest the letter by van den Besselar [1] about ISI calibrant plasmas and the ensuing exchange of correspondence with Poller *et al.* [2,3]. We agree with the ECAA colleagues that with the FDA-approved ECAA set of artificially depleted plasmas and the PT/INR line, inter-laboratory INR deviations are significantly reduced with all types of reagents, but we also suspect that, unless fresh native plasmas from patients on warfarin are used for calibration, this may not translate in better laboratory monitoring of patients on warfarin. van den Besselar [1] and Tripodi *et al.* [4] have reported discrepancies in INR between fresh and lyophilized samples with two rabbit thromboplastins and different coagulometers, but, given the advanced explanation of a different clotting factor composition of artificially depleted and native plasmas [3], we are afraid that such a discrepancy may also occur with reagents other than rabbit thromboplastins.

With a STA-R coagulometer and assuming Neoplastin Plus (Stago, Asniere sur Seine, France) as reference thromboplastin (certified coagulometer-specific ISI = 1.31) we have calculated on fresh plasma samples from stable patients on warfarin a coagulometer-specific ISI value of 0.77 (with Tomenson correction = 1.09) for Innovin (Siemens GmbH, Marburg, Germany) [5], which was confirmed in an independent series of 100 patients on warfarin [6].

In a recent multicentre study, Poller *et al.* [7] have validated the PT/INR line for coagulometer-specific ISI derivation. Six participants in that study used Innovin and STA-R as the local reagent/instrument combination. The average stated values of these laboratories for ISI and MNPT before local calibration with either the ECAA set or the PT/INR line were 0.94 and 9.3 s, respectively. Given that no STA-R-specific ISI value for Innovin is provided by the manufacturer, we suspect that the stated ISI values were derived by local ISI calibration with the PT-Multi Calibrator set (Siemens), because using this set for the above-mentioned series of 100 patients on warfarin we have found a very similar STA-R-specific ISI value for Innovin of 0.96 (95% confidence interval, 0.95–0.97) with a derived MNPT of 10.2 s. According to the manufacturer, this set of six calibrator plasmas is obtained by pooling stabilized human plasma samples, some also containing a portion of animal plasma or of pretreated human plasma, followed by lyophilization.

In the Poller *et al.* [7] study, coagulometer-specific ISI values and MNPT after local calibration with the ECAA calibrator set and the PT/INR line were 0.99 and 9.8 s and 1.06 and 10.6 s, respectively. The ECAA colleagues state that coagulometer-specific ISI values 'can be derived for the range of locally used thromboplastins and automated PT systems listed in the published EAA reports and without the need for the demanding WHO ISI calibration' [2]. Accordingly, for the above-mentioned series of 100 patients on warfarin, we have compared the INR values obtained with the STA-R/Innovin combination by WHO ISI calibration (see above) and our local MNPT (9.6 s) as denominator term with the values obtained using ISI and MNPT derived from the PT Multi Calibrator set (derived MNPT = 10.2 s) or using ISI and MNPT reported for the ECAA calibrator set and the PT/INR line. Average INR values were 2.55, 2.74, 2.96 and 2.96, respectively (Fig. 1). While the number of under-anticoagulated patients was similar, the number of apparently over-anticoagulated patients was two times higher with the PT Multi Calibrator set (19% vs. 8%), as previously reported [6], but it was three times higher with both the ECAA set (23%) and the PT/INR line (25%). The data shown in Fig. 1 are based on the assumption of a correct WHO ISI calibration of Neoplastin Plus by Stago. For the same reagent/instrument combination, a slightly lower ISI value of 1.23 was observed by formal ISI calibration using fresh plasma samples from stable patients on warfarin [4]. Assuming 1.23 as the correct coagulometer-specific ISI value for Neoplastin Plus, the fresh plasma-dependent ISI of Innovin would be lower than 0.77 and the number of apparently over-anticoagulated patients with the lyophilized calibrator plasmas would accordingly increase rather than decrease.

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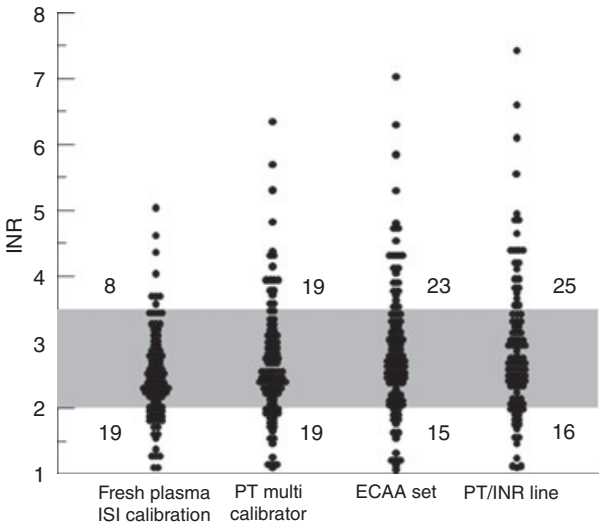

Fig. 1. INRs of 100 patients on warfarin obtained with Innovin and the STA-R coagulometer derived according to the WHO ISI calibration with fresh plasma samples and the local MNPT, or calculated with ISI and MNPT derived from the Siemens (PT Multi Calibrator), ECAA and PT/INR line sets of lyophilized INR calibrator plasmas (see text for explanations). The dashed area encompasses the INR therapeutic range. Numbers refer to over- and under-anticoagulated patients.

Any valid attempt to reduce inter-laboratory variation in INR values is surely welcome. However, use of artificial plasmas for local INR calibration may be not as valid as initially thought.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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