ISTH considers the results obtained in Sweden and other countries using the Owren type PT assay. We have shown that there are several preanalytical and analytical advantages of the Owren type PT assay compared with the conventional Quick PT assay. We have also described a reproducible way to characterize INR calibrant plasmas based on collection of normal plasma samples and a very simple procedure for direct local INR calibration with highly competitive results. The current situation with many different PT methods and complicated calibration procedures are clearly not an optimal situation. The Swedish experience indicates that it is time to discuss which PT methods should be used in order to improve the current situation. The Owren PT assay allows simplification of standardization procedures [6]. It should be the task of the Subcommittee to take all facets of oral anticoagulation control into consideration, not only primarily for the benefit of patients but also to give the laboratories the optimal tools in order to achieve the goals of improvement of the quality of PT testing.

References

1 Van den Besselaar AMHP, Barrowcliffe TW, Houbouyan-Réveillard LL, Jespersen J, Johnston M, Poller L, Tripodi A. Guidelines on preparation, certification, and use of certified plasmas for ISI calibration and INR determination. *J Thromb Haemost* 2004; **2**: 1946–53.

2 Hillarp A, Egberg N, Nordin G, Stigendal L, Fagerberg I, Lindahl TL. Local INR calibration of the Owren type prothrombin assay greatly improves the intra- and interlaboratory variation. A three-year follow-up from the Swedish national external quality assessment scheme. *Thromb Haemost* 2004; **91**: 300–7.

3 Lindahl TL, Egberg N, Hillarp A, Ødegaard OR, Edlund B, Svensson J, Sandset PM, Rånby M. INR calibration of Owren-type prothrombin time based on the relationship between PT% and INR utilizing normal plasma samples. *Thromb Hemost* 2004; **91**: 1223–31.

4 Horsti J. Agreement of Owren and Quick prothrombin times: effects of citrate and calcium concentrations and international sensitivity index correction. *Clin Chem* 2001; **47**: 940–4.

5 Horsti J. Comparison of Quick and Owren prothrombin time with regard to the harmonisation of the international normalised ratio (INR) system. *Clin Chem Lab Med* 2002; **40**: 399–403.

6 Jackson CM. Monitoring oral anticoagulant therapy – INR values for the Owren prothrombin time. *Thromb Haemost* 2004; **91**: 210–2.

Guidelines on preparation, certification, and use of certified plasmas for ISI calibration and INR determination – reply to a rebuttal

A. M. H .P. VAN DEN BESSELAAR

Haemostasis and Thrombosis Research Center, Leiden University Medical Center, Leiden, The Netherlands

To cite this article: van den Besselaar AMHP. Guidelines on preparation, certification, and use of certified plasmas for ISI calibration and INR determination – reply to a rebuttal. *J Thromb Haemost* 2005; **3**: 2371–2.

See also Egberg N, Fagerberg I, Hillarp A, Lindahl TL, Stigendal L. Guidelines on preparation, certification, and use of the certified plasmas for ISI calibration and INR determination – a rebuttal. This issue, pp 2370–1; van den Besselaar AMHP, Barrowcliffe TW, Houbouyan-Re veillard LL, Jespersen J, Johnston M, Poller L, Tripodi A on behalf of the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the ISTH. Guidelnes on preparation, certification, and use of certified plasmas for ISI calibration and INR determination. *J Thromb Haemost* 2005; **2**: 1946–53.

In their letter to the editor, Egberg *et al*. [1] refer to their recently published method for calibration of so-called Owren-PT-type reagents [2,3]. These reagents are very popular in Scandinavian countries for the control of oral anticoagulant therapy. The Owren-PT-type reagents are similar in composition, i.e., containing rabbit tissue factor and adsorbed bovine plasma. The calibration procedure chosen by the Scandinavian group involved the establishment of a mathematical relation between the Owren PT(%) and INR obtained with the manual Quick method with reagent ISI assigned according to WHO recommendations. The Scandinavian procedure allowed the production of calibrant plasmas with assigned INR values that are traceable to the international reference preparation for thromboplastin. The Scandinavian procedure involved a two-point calibration curve where the local PT in seconds is plotted in a log–log diagram on the *y*-axis and the reference INR values on the *x*-axis.

Egberg *et al*. are disappointed that experiences with Owren-type reagents are not referred to in the 'Guidelines on preparation, certification, and use of certified plasmas for ISI calibration and INR determination' [4] published a few months after the publication of the calibration method by the

Correspondence: A. M. H .P. van den Besselaar, Haemostasis and Thrombosis Research Center, Leiden University Medical Center, Leiden, The Netherlands.
E-mail: a.m.h.p.van_den_besselaar@lumc.nl

Scandinavian group [2]. I would like to emphasize that the 'Guidelines' are intended to cover all types of thromboplastin reagents and methods. In fact, the 'Guidelines' refer to another Owren-PT-type reagent, i.e., OBT/79 which is a batch of Thrombotest. Thrombotest contains bovine brain tissue factor and adsorbed bovine plasma.

The use of a two-point calibration curve is not recommended in the 'Guidelines' for the following reasons. All calibrations performed with more than two plasmas are associated with 'scattering' of the points in the diagram. The scattering is caused not only by imprecision of the measurements, but also by genuine interaction between the coagulation factors in the test plasmas and the thromboplastin reagents. In general, scattering of the points increases with increasing dissimilarity of the reagents being compared with each other. Therefore, a full calibration according to the WHO recommendation involves 20 normal and 60 patient plasmas. By using a large number of individual plasmas an average relation between the reagents is obtained. The 'Guidelines' allow a reduction in the number of plasmas under certain conditions without compromising the reliability of the calibration. A set of one normal and at least three abnormal plasmas is recommended. If only two plasmas are used for the calibration, it is not possible to assess the error in the calibration line and it is not possible to detect any curvature in the relation.

It seems that in the Scandinavian procedure an international reference preparation had been used only once, i.e., for the establishment of the relation between Owren PT% and INR [2]. Ever since, this relation has been used by EQUALIS to certify lyophilized, artificially depleted plasma calibrators. EQUALIS seems to assume that the relation is constant. There is a certain risk associated with this procedure. If the composition of the Owren-PT-type reagent is modified by the manufacturer, the relation between Owren PT% and INR may be changed as well. Therefore, the relation between Owren PT% and INR should be checked regularly.

References

1 Egberg N, Fagerberg I, Hillarp A, Lindahl TL, Stigendal L, Guidelines on preparation, certification, and use of certified plasmas for ISI calibration and INR determination - a rebuttal. *J Thromb Haemost* 2005; **3**: 2370–1.

2 Lindahl TL, Egberg N, Hillarp A, Ødegaard OR, Edlund B, Svensson J, Sandset PM, Rånby M. INR calibration of Owren-type prothrombin time based on the relationship between PT% and INR utilizing normal plasma samples. *Thromb Haemost* 2004; **91**: 1223–31.

3 Hillarp A, Egberg N, Nordin G, Stigendal L, Fagerberg I, Lindahl TL. Local INR calibration of the Owren type prothrombin assay greatly improves the intra- and interlaboratory variation. *Thromb Haemost* 2004; **91**: 300–7.

4 van den Besselaar AMHP, Barrowcliffe TW, Houbouyan-Réveillard LL, Jespersen J, Johnston M, Poller L, Tripodi A. Guidelines on preparation, certification, and use of certified plasmas for ISI calibration and INR determination. *J Thromb Haemost* 2004; **2**: 1946–53.