The introduction of the international normalized ratio as a breakthrough event in the history of thrombosis

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Very few among the youngest readers of this Journal would think about the introduction of the international normalized ratio (INR) as a breakthrough event in the history of thrombosis. This editorial is meant to give a brief account of the work that has been done over the years to develop this scale, which was instrumental for millions of patients worldwide who benefited from oral anticoagulation to treat or prevent thrombosis in many cardiovascular diseases. Young physicians now dealing with direct oral anticoagulants (DOAC) that do not require laboratory assistance to guide dose-adjustment hardly believe how the INR was important until few years ago when vitamin K antagonists (VKAs) were the mainstay of anticoagulation worldwide.

As a matter of fact, the INR should be considered as a landmark in the history of oral anticoagulation. After the initial experiments on the development of VKAs that is very well known to most, VKAs have been used first to treat the President of the USA Dwight Eisenhower who, while undergoing his electoral campaign for the second term, wanted to be sure of averting recurrent myocardial infarction.[1] From that time, VKAs have been increasingly used to treat patients with cardiovascular diseases in nearly 2% of the general population worldwide. At the very beginning VKA treatment was not free of adverse events such as hemorrhage, simply because dosages were empirically determined by testing prothrombin time (PT) in patients' plasma by means of thromboplastins that were poorly responsive to VKAs. Hence, in most cases the PT (patient-to-normal) clotting time ratio targeted at 2.0 or more, was achieved with an excess of the drug and was therefore burdened with an increased risk of hemorrhage.[2] Clinical researchers such as Drs. L. Poller from Manchester (UK) and J. Hirsh from Hamilton (Canada) were among the first to realize that dosages of VKAs should have been reduced, or better, that thromboplastins more responsive to VKAs should have been adopted to safely tailor VKA dosages in individual patients. Attempts were made to develop standardized thromboplastins from human origin (Manchester Comparative Reagent, MCR) that were distributed to the most important reference laboratories across the world.[3] MCR had a responsiveness to VKAs that was higher than that of rabbit thromboplastins and treated patients had been safely managed for many years based on the PT ratio results obtained with these thromboplastins. It was however recognized that MCR was not enough to cope with the increasing demand of patients on treatment and a new scale of PT ratio values was steadily and successfully introduced. Difficult to follow the precise history of this development to which researchers like Drs. R. Biggs, K.W. Denson in the UK and E.A. Loeliger in the Netherlands, have contributed.[4] Upon the acceptance among the scientific community that the idea of the standardized PT ratio was a valid alternative to the simple PT ratio, Dr. T. Kirkwood[5] from the UK developed a mathematical model, whereby the PT ratio obtained with any given thromboplastin could be translated into a standardized new scale called INR. In addition to the mathematical model this system of standardization requires the provision of an international thromboplastin standard against which all the commercial thromboplastins could be calibrated to determine the international sensitivity index (ISI). This numerical index represents a measure of the responsiveness of commercial thromboplastins relatively to the international thromboplastin standard used as reference. By definition an ISI value equal to 1.0 means that the working thromboplastin possesses a responsiveness to the coagulation defect induced by VKAs equal to that of the international standard, set by definition at 1.0. An ISI higher than 1.0 means that the working thromboplastin is less responsive to VKAs than the international standard and vice versa. Once the ISI of any given commercial thromboplastin is determined, the PT results obtained with cali-

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brated testing systems (i.e., thromboplastin/coagulometer) are linked together as they refer to the same standard. For the PT values (seconds) to be translated into INR, the Kirkwood model requires the application of a simple equation:

$$INR = (PTpatient/MNPT)^{ISI}$$

where the MNPT represents the geometric mean PT of 20 or more non-anticoagulated healthy subjects.

The ISI is calculated from the log-transformed plot of PT (seconds) for 60 patients on stable anticoagulation with VKAs and a group of 20 healthy non-anticoagulated subjects both tested with the international standard (vertical axis) and with the thromboplastin to be calibrated (working thromboplastin). The best-fit orthogonal regression line is calculated and the ISI represents the slope of best-fit orthogonal regression line. Scatter points around the regression line are used to estimate the precision of the calibration (Figure 1).

Following the establishment of the INR scale, numerous clinical trials have been carried out. These studies were not possible before the adoption of the INR because the results of PT ratio were heavily dependent on the thromboplastins used for testing. The above studies allowed to establish the *"universal"* therapeutic interval, now known as 2.0-3.0 INR for most VKAs indications. The outcome of the above studies showed that patients with an INR higher that 3.0 are likely to bleed and patients with INR lower than 2.0 are likely to develop recurrent thrombosis. The INR was adopted by the scientific community and endorsed by the World Health Organization (WHO) in 1980s. From that time, there were many attempts trying to refine the model to which many researchers like L. Poller, T. van den Besselaar and myself have contributed. Guidelines on thromboplastin calibration have been developed and issued by WHO[6] and new international standards have been established to replace those that have been dismissed.[9-12] More recently, a group of laboratories with personnel expert in running the manual (tilt-tube) technique that is needed to test PT with the international standard, have been trained and established and will be in charge to replace future international thromboplastin standards.[12] The INR model is flexible and can also be used to standardize the PT ratio when measured by point of care devices[13] or when the PT is used in conditions other than VKA treatment such as chronic liver disease to prioritize patients for liver transplantation.[14]

In conclusion, from the above brief history the youngest readers of the Journal may appreciate how INR has been a paradigmatic example of effective and impactful research and development, leading to a previously unimaginable management of millions of individuals on anticoagulation worldwide. I apologize for not mentioning many valuable researchers that have contributed to this development. Detailed historical information can be found in other publications.[4,15]

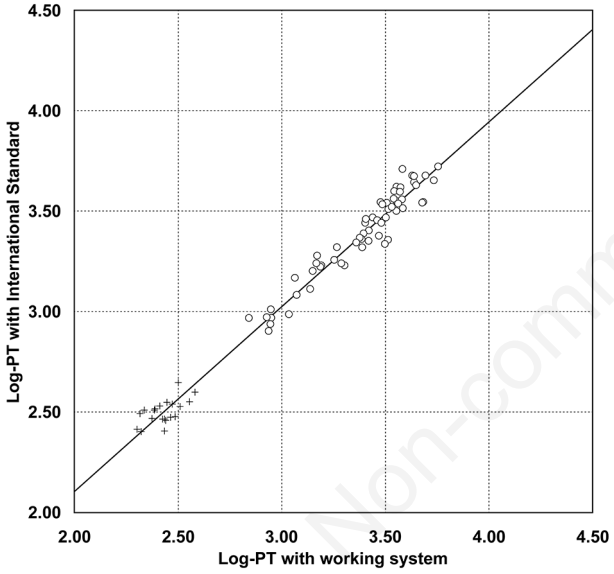

Figure 1. Schematic representation of the calibration of a working prothrombin time (PT) system (thromboplastin/coagulometer). According to WHO guidelines,[6] 60 patients stabilized on anticoagulation with VKAs (open circles) and a group of 20 healthy subjects are tested for their PT (seconds) with the international standard for thromboplastin (vertical axis) and with the working PT system to be calibrated. PT with the international standard is measured by a standardized manual (tilt-tube technique)[7] and the PT with the working system is measured by either manual technique or by any of the commercial coagulometers. Paired PT values are plotted on a double log-scale and the best-fit orthogonal regression line is drawn through the data points. The slope of the orthogonal regression line [multiplied by the international sensitivity index (ISI) of the international standard] represents the ISI of the working PT system. The estimated ISI and the resultant international normalized ratio (INR) calculated thereafter is valid for the batch of working thromboplastin and the coagulometer used for calibration. Furthermore, the resultant INR is valid for patients on VKAs, in the range of INR 1.5- 4.0[8] and for patients on stabilized anticoagulation.

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