

Accuracy, reproducibility and clinical utility of the CoaguChek S portable international normalized ratio monitor in an outpatient anticoagulation clinic

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Summary

The accuracy and reproducibility of the CoaguChek S, and its clinical agreement with conventional laboratory international normalized ratio (INR) determination, were evaluated in an outpatient anticoagulation clinic setting. Forty-three patients provided 248 paired INR measurements for analysis. The paired results were highly correlated ($r = 0.90$). The mean coefficient of variation for the CoaguChek S for a random sample of 21 patients with three repeated tests each, was 4%. Clinical applicability was also measured by discrepant INR values, as defined in the literature by expanded and narrow agreement, and by INR values resulting in a different clinical decision by a blinded haematology registrar. Expanded agreement and narrow agreement between the two INR values occurred 90 and 88% of the time, respectively. The stricter criteria set down by the clinician resulted in 73% of paired results producing the same dosage decision. The CoaguChek S displayed good correlation with laboratory determination of INR and compared relatively well with expanded and narrow clinical agreement criteria.

Keywords

Warfarin, international normalized ratio, point-of-care, monitor, clinical agreement

Introduction

Warfarin use is increasing internationally at a rate of about 10% per year (Tripodi, Chantarangkul & Mannucci, 2001). The main reason for the increase in use is that it has been conclusively demonstrated that long-term anticoagulation therapy can reduce the risk of stroke by approximately 68%, or from 4.5 to 1.4% per year, in patients with nonvalvular atrial fibrillation (AF), (Ezekowitz & Levine, 1999; Hart *et al.*, 1999) with little increase in the

frequency of major bleeding or intracranial haemorrhage (Petersen *et al.*, 1989; Ezekowitz & Levine, 1999).

The effectiveness and safety of warfarin is maximized by the maintenance of a target international normalized ratio (INR) range, below which effectiveness is lost, and above which the bleeding risk is unacceptably high (Gallus, 1999). Point-of-care INR testing could improve the outcomes of warfarin therapy. The key objective of point-of-care testing is to provide a fast, accurate result so that appropriate treatment can be commenced, leading to an improved clinical state or economic benefits (Price, 2001). A study by the authors found that general practitioners suggested the availability of portable INR monitors would assist with the management of their patients with AF and perhaps increase their prescribing of warfarin for AF (Peterson *et al.*, 2002). The objective of

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this study was to assess the accuracy, reproducibility and clinical agreement of the CoaguChek S monitor in the Australian outpatient setting, prior to its evaluation in general medical practice.

Materials and methods

Clinic participants and point of care procedure

The study was undertaken at the anticoagulation outpatient clinic at the Royal Hobart Hospital, a 400-bed acute care teaching hospital and the only major public hospital in the southern region of Tasmania, Australia (serving a population of approximately 240 000). This small clinic is conducted weekly and mainly manages patients whose anticoagulant control has been difficult in the community setting. Over a 16-month period, patients who attended the clinic gave informed consent to undergo fingerprick testing with the CoaguChek S INR monitor, in addition to having a normal laboratory INR test. Patients with the lupus anticoagulant were excluded, as some of these patients are known to produce errant INR values with phospholipid-based tests (Sanfelippo, Sennet & McMahon, 2000).

The CoaguChek S is a portable, laser coagulometer that measures the INR using whole blood obtained by fingerprick (Tripodi *et al.*, 1993). It has been specifically designed for use by nonhealth professionals. The procedure comprises insertion of a test strip into the monitor and the application of a drop of blood onto the test strip. The surface of the test strip is coated with a mixture of iron oxide particles and rabbit brain thromboplastin. An INR result is provided within 1 min of application of the blood sample to the CoaguChek S (Douketis *et al.*, 1998). All tests were performed by two operators with basic training in the use of the monitor. The result from the CoaguChek S was recorded for later comparison with the patient's corresponding laboratory INR value.

Laboratory procedure

Phlebotomist nurses drew the venous blood samples by standard techniques into 0.129 M (3.8%) sodium citrate tubes. Centrifuged samples were then analysed by the ICA6000 (Sysmex, Kobe, Japan, distributed by Dade Behring in Australia) within 1 h of the venipuncture. The thromboplastin reagent used by the laboratory was Innovin (Dade International Inc., Miami, FL, USA) and then RecombiPlasTin (Ortho-Clinical Diagnostic Systems, Bucks, UK) when the Innovin was discontinued about

two-thirds way through the project. The International Sensitivity Index (ISI) of the Innovin thromboplastin was 1.13, and the RecombiPlasTin 1.10.

Comparison of techniques

Clinical agreement was measured by discrepant INR values and by INR values resulting in a different clinical decision. Discrepant values were defined as the percentage of INR results from the CoaguChek S that was different from the laboratory in the categorization of the individual patient's INR value. The INR categories were nominated as 1.0–1.9, 2.0–3.0, 3.1–3.9 and ≥ 4.0 .

The number of INR values that would have resulted in a different therapeutic decision was based upon clinician decision to leave the warfarin dose the same, or to increase or decrease the dose based upon clinical judgment. This was achieved by giving the attending haematology registrar a list of patients with the two INR readings. The clinician was blinded as to which INR was the CoaguChek S or laboratory value. The clinician indicated whether to maintain the same anticoagulant dose, or to increase or decrease it based on each of the values and the patient's history. The usual therapeutic ranges were 2.0–3.0 for AF and other thromboembolic disorders, and 2.5–3.5 for patients with mechanical heart valves (Ansell *et al.*, 2001).

Published criteria for clinical agreement (expanded and narrow) (Douketis *et al.*, 1998) were also assessed. Expanded agreement was achieved if both the CoaguChek S and the laboratory INR were within, above or below the patient's targeted range, or the difference between the CoaguChek S and the laboratory INR when one of the pair was within the targeted range was no more than 0.5 U. Narrow agreement was achieved if both the CoaguChek S and the laboratory INR were within the patient's targeted range, both the CoaguChek S and the laboratory INR were above the targeted range and the values were within 0.8 U, both the CoaguChek S and the laboratory INR were below the therapeutic range and the values were within 0.4 U, or the difference between the CoaguChek S and the laboratory INR when one of the pair was within the targeted range was no more than 0.5 U.

Statistical methods

Accuracy of the CoaguChek S was determined by comparing the INRs from the monitor and the laboratory values on a linear regression analysis. A Bland–Altman plot (Bland & Altman, 1995) was utilized to assess the magnitude of disagreement between the monitor and the

laboratory INRs. A paired *t*-test ($P < 0.05$ considered significant) was used to compare the INR values with the CoaguChek S and laboratory methods. Reproducibility was defined by the coefficient of variation with three repeated tests performed in a random subset of clinic patients ($n = 21$).

The project had been approved by the Royal Hobart Hospital Research Advisory Committee and the Southern Tasmania Health and Medical Human Research Ethics Committee.

Results

A total of 248 paired samples were obtained from 43 different patients. The mean INR values for the laboratory and CoaguChek S, and the status of the anticoagulant control, are listed in Table 1. The CoaguChek S INR values were significantly correlated with the laboratory INR values ($r = 0.90$, $P < 0.0001$; Figure 1). The mean difference in INR (laboratory minus CoaguChek S) was 0.19 (95% confidence interval: 0.14–0.25; paired $t = 6.7$, $df = 247$, $P < 0.0001$). The mean coefficient of variation for 21 individual patients with the CoaguChek S INR was 4%, with a range of 0–9.1%.

The Bland–Altman style plot is shown in Figure 2. The CoaguChek S showed only slight variation compared with laboratory testing for INR values < 3.5 , with increased scatter around zero as the INR increased to > 3.5 . The CoaguChek S was more likely to underestimate the INR, relative to the laboratory, particularly at values > 3.5 .

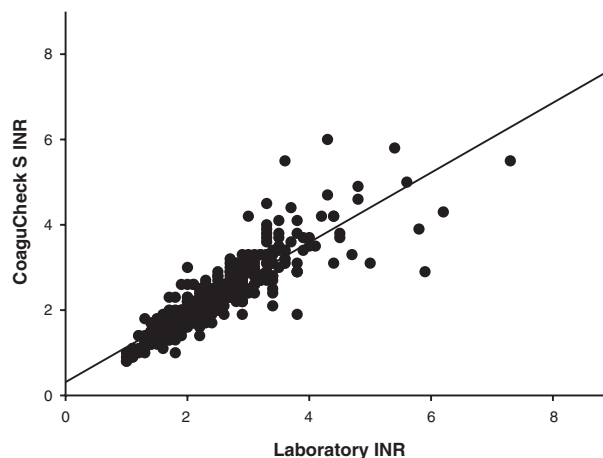


Figure 1. Relationship between CoaguChek S and laboratory international normalized ratio values.

The categorization of laboratory and CoaguChek S INRs is shown in Table 2. There was a significant relationship between the two methods (chi-square = 261, $df = 9$, $P < 0.0001$). Discrepant categorization of the INR value between the laboratory and CoaguChek S occurred in 31% of the samples. That is, 69% (170/248) of CoaguChek S values were placed in the same nominal category as the laboratory INR. Twenty-four per cent were falsely lowered with the CoaguChek S (corresponded to a higher laboratory reading) and 8% were falsely elevated (corresponded to a lower laboratory result).

An analysis of the warfarin dosage decisions of the blinded haematology registrar is shown in Table 3. The

Table 1. Comparison of CoaguChek S and laboratory international normalized ratio (INR) results

Parameter	CoaguChek S	Laboratory
INR (mean \pm SD)	2.44 \pm 0.82	2.64 \pm 1.03
Mean difference \pm SD	-0.19 \pm 0.46	
Percentage within 0.5 INR units	82.5	
Percentage within 10% of laboratory INR	44.0	
INR value, <i>n</i> (%)	248 (100)	248 (100)
≤ 1.9	69 (27.8)	52 (21)
Mean INR \pm SD	1.67 \pm 0.26	1.69 \pm 0.26
Mean difference \pm SD	-0.02 \pm 0.23	
Percentage within 0.5 INR units	92.2	
Percentage within 10%	53.9	
2.0–3.5	155 (62.5)	162 (65.3)
Mean INR \pm SD	2.51 \pm 0.38	2.56 \pm 0.43
Mean difference \pm SD	-0.16 \pm 0.37	
Percentage within 0.5 INR units	81.1	
Percentage within 10%	42.6	
≥ 3.6	24 (9.7)	34 (13.7)
Mean INR \pm SD	4.25 \pm 0.90	4.44 \pm 1.48
Mean difference \pm SD	-0.67 \pm 0.70	
Percentage within 0.5 INR units	50.0	
Percentage within 10%	35.3	

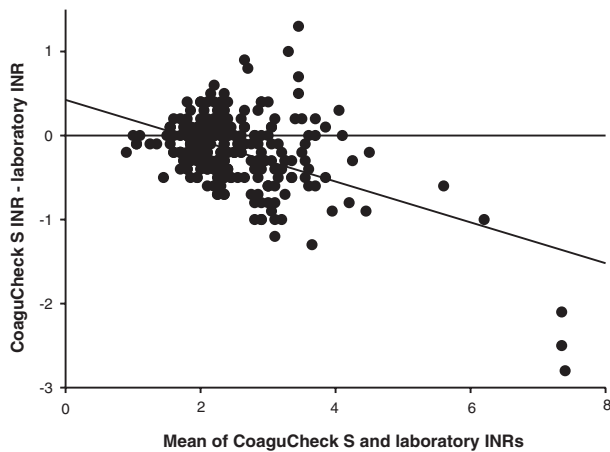


Figure 2. Bland–Altman style bias plot for CoaguChek S and laboratory international normalized ratio values.

relationship between decisions based on the CoaguChek S and those based on laboratory INRs was statistically significant (chi-square = 154, $df = 4$, $P < 0.0001$). It can be seen from this figure that 73% of CoaguChek S readings would have prompted the same clinical decision as the corresponding laboratory value – 42% for a decision to decrease anticoagulant dosage based on the laboratory result, 80% for a decision to increase dosage of anticoagulant and 80% for a decision to leave the dose of anticoagulant the same. The mean laboratory INR for dose decreases that were not in agreement was 3.6. Expanded and narrow agreement (Douketis *et al.*, 1998)

between the two INR values occurred 90 and 88% of the time, respectively.

Discussion

When comparing the accuracy of the CoaguChek S to the laboratory method for INR measurement, one problem is the lack of a gold standard for comparison. The true gold standard for the INR value is a test using the manual tilt-tube technique with the use of a World Health Organisation IRP thromboplastin (Havrda, Hawk & Marvin, 2002). It is important to note that the laboratory analysis is therefore not infallible, and that aberrant results may have been a combination of over or underestimation by the CoaguChek S and vice versa by the laboratory analysis. For instance, previous studies have found that the variation between portable coagulometers and laboratory was not larger than the variation encountered between different laboratories measuring a single sample (Kaatz *et al.*, 1995). However, as the comparison to the true gold standard was not available, the laboratory must be treated as the gold standard for the purposes of this evaluation.

In a study designed to test the accuracy of CoaguChek S INR readings compared with laboratory-tested INR values, we found the CoaguChek S to be 90% accurate against expanded agreement criteria and 88% accurate against narrow agreement criteria (Douketis *et al.*, 1998). This compares favourably with data from other

		CoaguChek S			
		1.0–1.9 ($n = 68$)	2.0–3.0 ($n = 135$)	3.1–3.9 ($n = 34$)	≥ 4.0 ($n = 11$)
Laboratory	1.0–1.9 ($n = 51$)	82	18	0	0
	2.0–3.0 ($n = 131$)	20	73	6	1
	3.1–3.9 ($n = 51$)	0	53	45	2
	≥ 4.0 ($n = 15$)	0	13	27	60

Table 2. Comparison of international normalized ratio (INR) categories for CoaguChek S and laboratory results (values given as percentage of laboratory readings)

Warfarin dosage decision		CoaguChek S		
		Decrease ($n = 24$)	Same ($n = 157$)	Increase ($n = 67$)
Laboratory	Decrease ($n = 45$)	42	58	0
	Same ($n = 152$)	3	80	17
	Increase ($n = 51$)	0	20	80

Table 3. Analysis of clinician decisions based on CoaguChek S compared with laboratory international normalized ratio (INR) result (values given as percentage of laboratory readings)

previously published studies where the older model of CoaguChek monitor was found to be 90% accurate against expanded agreement criteria (Anderson, Harrison & Hirsh, 1993) and 86% accurate against narrow agreement criteria (Douketis *et al.*, 1998). A recent study showed 98 and 97% agreement against expanded and narrow criteria, respectively, with the CoaguChek (Shiach *et al.*, 2002).

Using the clinician-defined agreement criteria for warfarin dosing, the CoaguChek S was found to be accurate 73% of the time for all decisions. It is important to note that a decision to increase the anticoagulant dose based on the CoaguChek S value never resulted in a clinical decision to decrease the anticoagulant dose based on the laboratory value. Similarly, the clinician would not have decreased the anticoagulant dose based on the CoaguChek S when they actually increased the dose based on the laboratory value. The CoaguChek S performed well for dose increases and when no change was made to therapy, however it performed less adequately when dose decreases were compared. The definition of agreement used in this analysis was based on the clinician decision to maintain, lower, or increase the dose of anticoagulant based on each of the paired samples, and took into account factors such as prior INR values, patient factors and trends in INR. This method of comparison is more relevant to actual practice than the arbitrary expanded and narrow agreement criteria used in prior evaluations. In a recent study analysing the CoaguChek S (Havrda *et al.*, 2002) agreement was found 75.5% of the time. The agreement criteria in this case were stricter than any previously used in the literature. The criteria for discrepancy was defined as 1 INR outside of the therapeutic range and the other value within the range, or both INR values outside of the therapeutic range and differing by ≥ 0.5 INR units.

The CoaguChek S produced reproducible INR results, with a mean coefficient of variation below 5%. This study found that the CoaguChek S had a similar correlation ($r = 0.90$) with laboratory INRs as those seen in prior studies of the CoaguChek and the CoaguChek S ($r = 0.91-0.97$) (Gosselin *et al.*, 2000). Regression analysis is only a measure of correlation, not accuracy; a far superior measure is the Bland-Altman analysis (Bland & Altman, 1995). Both of these analyses indicated a general underestimation of the INR, which needs to be factored in to the interpretation of INR results given by the CoaguChek S monitor. Eighty-three per cent of all dual measurements were within 0.5 INR units in this study, which compares with the figure of 79% reported by (Douketis *et al.*, 1998).

As with prior evaluations, the CoaguChek S was most accurate when within the bounds of therapeutic INRs. This finding has also been observed with other portable INR monitors (McCurdy & White, 1992; Tripodi *et al.*, 1993; Kaatz *et al.*, 1995). The proportion of dual INR measurements within 0.5 INR units for laboratory INR ranges of <2.0 , $2.0-3.0$, $3.1-4.0$ and >4.0 was found by Douketis *et al.* (1998) to be 98, 87, 57 and 21%, respectively. These data closely match our data for similar ranges of <1.9 , $2.0-3.5$ and ≥ 3.5 , giving values of 92, 81 and 50%, respectively, within 0.5 INR units. Douketis *et al.* (1998) concluded from the results of their study that the CoaguChek monitor 'achieved a clinically acceptable level of accuracy when compared with the traditional laboratory method and provides a suitable alternative method of monitoring the INR in patients receiving warfarin'. Vacas *et al.* (2001) also confirmed in a study involving capillary, plasma and whole blood samples, that the CoaguChek could be used as a new method for oral anticoagulant monitoring and is in best agreement with the capillary blood prothrombin time (PT) system. However, it was noted that clinicians should be aware that differences do exist between INR values from point-of-care monitors and laboratory values, especially when the INR is elevated (Gosselin *et al.*, 2000). It has also been noted that 'as with any method of measuring the INR, if a high value is found that is not consistent with what was expected, a repeat test with an alternative method may be considered' (Havrda, Hawk & Marvin, 2002).

This and most other studies have shown that the CoaguChek and CoaguChek S devices produce INR values that are highly correlated with laboratory INR values ($r = 0.91-0.97$) and agree with the laboratory INR in therapeutic decisions or dosage alterations in 81-92% of cases (Kaatz *et al.*, 1995; Kapiotis, Quehenberger & Speiser, 1995; Douketis *et al.*, 1998; Chapman *et al.*, 1999; Hobbs *et al.*, 1999; Gosselin *et al.*, 2000). A recent study by Reiss *et al.* (2002) has been the only study that has found that the CoaguChek system showed relatively poor agreement with the laboratory method. The findings of this study were that mean differences in paired INR values were small, but 95% CIs were wide (-1.08 to 1.36), and the r^2 value was found to be only 0.512 ($r = 0.72$).

Overall, the CoaguChek S INR monitor has the potential to lessen the burden on health services, either in the hospital or community setting. The ease of use, accuracy and rapid availability of INR results have the potential to minimize errors and adverse events associated with warfarin therapy. The CoaguChek S INR monitors could become a part of everyday practice for general

practitioners and be used in an inpatient setting in the hospital, where INR results are needed quickly. As a result of the relative inaccuracy of the CoaguChek S at INR values above 3.5, the development of guidelines for the use of the monitor would be paramount in the implementation of the monitor into routine practice. However, any potential problems with the monitor are far outweighed by the capacity of the monitor to provide a fast and accurate INR when the INR is within the therapeutic range, especially for rural and remote patients, where a laboratory result could take days for a result to be known. The use of point-of-care testing for anticoagulation has the potential to revolutionize the management of patients on warfarin therapy. As noted by Bhavnani and Shiach (2002) the remaining issue to be addressed is how we can best offer high quality external quality assurance. In the meantime we must be ready to embrace this technology while still appreciating its limitations.

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References

- Anderson D.R., Harrison L. & Hirsh J. (1993) Evaluation of a portable prothrombin time monitor for home-use by patients who require long-term oral anticoagulant-therapy. *Archives of Internal Medicine* **153**, 1441–1447.
- Ansell J., Hirsh J., Dalen J., Bussey H., Anderson D., Poller L., Jacobson A., Deykin D. & Matchar D. (2001) Managing oral anticoagulant therapy [Review]. *Chest* **119**, 22S–38S.
- Bhavnani M. & Shiach C.R. (2002) Patient self-management of oral anticoagulation. *Clinical and Laboratory Haematology* **24**, 253–257.
- Bland J.M. & Altman D.G. (1995) Comparing methods of measurement – why plotting difference against standard method is misleading. *Lancet* **346**, 1085–1087.
- Chapman D.C., Stephens M.A., Hamann G.L., Bailey L.E. & Dorko C.S. (1999) Accuracy, clinical correlation, and patient acceptance of two handheld prothrombin time monitoring devices in the ambulatory setting. *Annals of Pharmacotherapy* **33**, 775–780.
- Douketis J.D., Lane A., Milne J. & Ginsberg J.S. (1998) Accuracy of a portable international normalization ratio monitor in outpatients receiving long-term oral anticoagulant therapy: comparison with a laboratory reference standard using clinically relevant criteria for agreement. *Thrombosis Research* **92**, 11–17.
- Ezekowitz M.D. & Levine J.A. (1999) Preventing stroke in patients with atrial fibrillation. *JAMA* **281**, 1830–1835.
- Gallus A. (1999) Towards the safer use of warfarin I: an overview. *Journal of Quality in Clinical Practice* **19**, 55–59.
- Gosselin R., Owings J.T., White R.H., Hutchinson R., Branch J., Mahackian K., Johnston M. & Larkin E.C. (2000) A comparison of point-of-care instruments designed for monitoring oral anticoagulation with standard laboratory methods. *Thrombosis and Haemostasis* **83**, 698–703.
- Hart R.G., Benavente O., McBride R. & Pearce L.A. (1999) Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Annals of Internal Medicine* **131**, 492–501.
- Havrdá D.E., Hawk T.L. & Marvin C.M. (2002) Accuracy and precision of the CoaguChek S versus laboratory INRs in a clinic. *Annals of Pharmacotherapy* **36**, 769–775.
- Hobbs F.D., Fitzmaurice D.A., Murray E.T., Holder R., Rose P.E. & Roper J.L. (1999) Is the international normalised ratio (INR) reliable? A trial of comparative measurements in hospital laboratory and primary care settings. *Journal of Clinical Pathology* **52**, 494–497.
- Kaatz S.S., White R.H., Hill J., Mascha E., Humphries J.E. & Becker D.M. (1995) Accuracy of laboratory and portable monitor International Normalized Ratio determinations – comparison with a criterion standard. *Archives of Internal Medicine* **155**, 1861–1867.
- Kapiotis S., Quehenberger P. & Speiser W. (1995) Evaluation of the new method CoaguChek(R) for the determination of prothrombin time from capillary blood – comparison with Thrombotest(R) on Kc-1. *Thrombosis Research* **77**, 563–567.
- McCurdy S.A. & White R.H. (1992) Accuracy and precision of a portable anticoagulation monitor in a clinical setting. *Archives of Internal Medicine* **152**, 589–592.
- Petersen P., Boysen G., Godtfredsen J., Andersen E.D. & Andersen B. (1989) Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet* **1**, 175–179.
- Peterson G.M., Boom K., Jackson S.L. & Vial J.H. (2002) Doctors' beliefs on the use of antithrombotic therapy in atrial fibrillation: identifying barriers to stroke prevention. *Internal Medicine Journal* **32**, 15–23.
- Price C.P. (2001) Regular review – point of care testing [Review]. *British Medical Journal* **322**, 1285–1288.
- Reiss R.A., Haas C.E., Griffis D.L., Porter B. & Tara M.A. (2002) Point-of-care versus laboratory monitoring of patients receiving different anticoagulant therapies. *Pharmacotherapy* **22**, 677–685.
- Sanfelippo M.J., Sennet J. & McMahon E.J. (2000) Falsely elevated INRs in warfarin-treated patients with the lupus anticoagulant. *WMJ* **99**, 62–64.
- Shiach C.R., Campbell B., Poller L., Keown M. & Chauhan N. (2002) Reliability of point-of-care prothrombin time testing in a community clinic: a randomized crossover comparison with hospital laboratory testing. *British Journal of Haematology* **119**, 370–375.
- Tripodi A., Arbini A.A., Chantarangkul V., Bettega D. & Mannucci P.M. (1993) Are capillary whole-blood coagulation monitors suitable for the control of oral anticoagulant treatment by the International Normalized Ratio. *Thrombosis and Haemostasis* **70**, 921–924.

Tripodi A., Chantarangkul V. & Mannucci P.M. (2001) Near-patient testing devices to monitor oral anticoagulant therapy [Review]. *British Journal of Haematology* **113**, 847–852.

Vacas M., Fernandez M.A., Martinez-Brotons F., Lafuente P.J., Ripoll F., Alvarez C. & Iriarte J.A. (2001) Comparative study of a portable prothrombin time monitor employing three different systems in oral anticoagulant units. *Haemostasis* **31**, 18–25.

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